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(54) Title: QUINONE SUBSTITUTED QUINAZOLINE AND QUINOLINE KINASE INHIBITORS

(57) Abstract: The present invention provides for compounds with the general formula: A compound of formula (1) having the structure (1) wherein Z is a radical selected from the group (a), (b), or (c) as well as methods and compositions containing these compounds useful for treatment of diseases that are characterized, at least in part, by excessive, abnormal, or inappropriate angiogenesis. These disease states, include but are not limited to, cancer, diabetic retinopathy, macular degeneration and rheumatoid arthritis. These compounds inhibit angiogenesis by inhibiting a tyrosine kinase receptor enzyme, specifically KDR, and binding to the KDR in an irreversible manner.

Docket No.: 2200786-WO0

QUINONE SUBSTITUTED QUINAZOLINE AND QUINOLINE KINASE INHIBITORS

This application claims priority from U.S. Provisional Application Serial No. 60/573,251, filed May 20, 2004, the disclosure of which is incorporated herein by reference in its entirety.

1. FIELD OF THE INVENTION

This invention relates to certain substituted quinazoline and quinoline compounds as well as the pharmaceutically acceptable salts thereof. The compounds of the present invention inhibit the action of certain growth factor receptor protein tyrosine kinases (PTK) that regulate blood vessel growth and function as anti-angiogenic agents.

2. BACKGROUND OF THE INVENTION

Growth of most solid tumors is dependent on the angiogenesis involving activation, proliferation and migration of vascular endothelial cells and their subsequent differentiation into capillary tubes. Angiogenesis of tumors allows them access to blood-derived oxygen and nutrients, and also provides them adequate perfusion. Hence inhibiting angiogenesis is an important therapeutic strategy for treating cancer as well as a number of chronic diseases, such as rheumatoid arthritis, psoriasis, diabetic retinopathy and age-related macular degeneration.

Tumor cells produce a number of angiogenic molecules. Vascular Endothelial Growth Factor (VEGF) is one such angiogenic factor. VEGF, a homodimeric disulfide-linked member of the Platelet-Derived Growth Factor (PDGF) family, is an endothelial cell-specific mitogen and is known to cause a profound increase in the vascular endothelial permeability in the affected tissues. VEGF is also a senescence-preventing survival factor for endothelial cells. Almost all nucleated tissues in the body possess the capability to express VEGF in response to various stimuli including hypoxia, glucose deprivation, advanced glycation products and inflammatory cytokines.

Growth-promoting angiogenic effects of VEGF are mediated predominantly via its signaling receptor Kinase insert Domain containing Receptor (KDR). This

receptor is sometimes also referred to as Flk-1 or VEGFR-2. The effects of VEGF are also mediated by the Fms-Like Tyrosine kinase (Flt-1, also known as VEGFR-1).

KDR is a receptor protein tyrosine kinase with an extracellular VEGF-binding domain consisting of seven immunoglobulin-like domains and a cytoplasmic domain containing the catalytic tyrosine kinase domain split by a kinase-insert region. Binding to VEGF causes dimerization of KDR resulting in its autophosphorylation and initiation of signaling cascade. The expression of KDR is low on most endothelial cells. However, activation with angiogenic agents results in a significant upregulation of KDR on endothelial cells. Most angiogenized blood vessels express high levels of KDR. Therefore, compounds that inhibit the tyrosine kinase activity of KDR will also function as anti-angiogenic agents and are useful for the treatment of cancer and other diseases.

There are several benefits to the use of anti-angiogenic therapy for the treatment of cancer. Genetically unstable cancer cells often develop resistance to standard therapy. By targeting untransformed endothelial cells, resistance is less likely to develop. Additionally, slow growing tumors that are resistant to standard cytotoxic cancer therapy may be responsive to a continuous low to moderate dose of anti-angiogenic drugs. Moreover, since the therapeutic target is not the tumor cells itself, the anti-angiogenic drug therapy is effective against tumors from different tissue origins. The growth of solid tumors, such as lung, colorectal, breast and prostate, have been inhibited by targeting KDR in animal models as well as patients.

Neutralizing antibodies to VEGF and KDR have been developed that inhibit primary tumor growth, as well as metastases, *in vivo*. When these neutralizing antibodies are used in combination with standard cytotoxics, such as paclitaxel, efficacy of the cytotoxics is improved. Antisense RNA, ribozymes and DNAzyme technology that specifically diminish VEGR or KDR expression have been demonstrated to be effective in both cellular and animal models.

Some small molecule inhibitors of KDR kinase are also in development. Unlike RNA and antibody strategies, most of the small molecule inhibitors are non-selective and inhibit other related kinases, which may be of benefit since some of these kinases also may be involved in angiogenesis. These agents appear to be most effective when administered orally on a daily basis.

However, despite these benefits, the clinical results of the inhibitor therapy has been mixed. Phase I safety trials of small molecules and antibody monotherapy has shown minimal adverse side effects. However, combination trials with established cytotoxic therapy have resulted in more adverse events, such as vascular effects. In phase II and III clinical trials of solid tumors, some partial regressions have been observed. Some complete regressions, increased time to progression and increased survival time have been reported with the anti-VEGF antibody, alone or in combination therapy.

It is unknown why there is limited success with these agents. However, an alternative method of targeting KDR is to use irreversibly binding inhibitors. A tyrosine kinase, such as KDR, catalyses the transfer of a phosphate group from a molecule of ATP to a tyrosine residue located on a protein substrate. The reversible inhibitors of KDR so far known in the art are usually competitive with either the ATP or the protein substrate of the kinase. Some of these inhibitors can be competitive with both ATP and substrate simultaneously. The 4-anilinoquinazoline and 4-anilinoquinoline inhibitors of KDR known in the art and described below are reversible binding inhibitors that are competitive with ATP. Since the concentration of ATP in a cell is normally very high (millimolar), compounds that are competitive with ATP may show diminished efficacy and duration of action since it would be difficult for such compounds to reach the concentrations within the cell that are necessary to displace the ATP from its binding site for the extended time needed to inhibit tumor growth effectively.

The KDR inhibitors known to date are believed to reversibly bind to the target receptor, but compounds that irreversibly bind to certain other target receptors have been shown to be superior tumor suppressors. For example, Frey *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 95:12022-12027 (1998)) have reported small molecules purported to irreversibly inhibit epidermal growth factor receptor (EGFR) bind irreversibly to the receptor and alkylate a cysteine residue in the ATP binding pocket of the molecule. These compounds are said to be more potent suppressors of tumor growth in animal models. Others have reported that irreversible EGFR kinase inhibitors effectively suppress growth in human tumor cell models (Discafani *et al.*, *Biochem. Biopharmacol.* 57:917-925 (1999)). Hence, the identification of compounds that irreversibly bind KDR offers the ability to identify new therapeutic compounds which

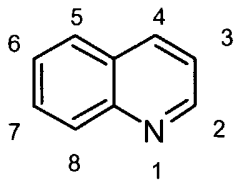
are likely to be superior tumor suppressors compared to the reversible KDR inhibitors that are currently available.

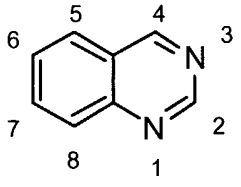
As demonstrated below, many of the quinazoline and quinoline inhibitors of this invention have the unique ability of inhibiting KDR kinase in an irreversible manner or behave as if they are inhibiting in an irreversible manner and are therefore non-competitive with ATP or protein substrate. Thus, the compounds of the present invention would function as superior anti-angiogenic agents that are useful for the treatment of the aforementioned disease states.

For recent reviews on this subject see F. J. Giles, "The Emerging role of Angiogenesis Inhibitor in Hematologic Malignancies" *Oncology Supplement* 16:23-29 (2002); S. J. Boyer, "Small Molecule Inhibitors of KDR (VEGFR-2) Kinase: An Overview of Structure Activity Relationships", *Curr. Top. Med. Chem.* 2:973-1000 (2002); J. Folkman, "Role of Angiogensis in Tumor Growth and Metastasis", *Seminars in Oncology* 29:15-18 (2002); and R. K. Jain, "Tumor Angiogenesis and Accessibility: Role of Vascular Endothelial Growth Factor", *Seminars in Oncology* 29:3-9 (2002).

This invention also relates to the manufacture of said quinazoline and quinolines. In addition to the above utilities, some of the compounds of the present invention are useful for the preparation of other compounds of this invention.

The compounds of this invention are certain substituted quinazoline and quinoline derivatives. Throughout this patent application, these ring systems will be numbered as indicated below:





Unlike many of the quinoline compounds described in the prior art, the quinoline compounds of the present invention are substituted at the 4-position with a quinone moiety. There are reports of quinolines, unsubstituted at the 4-position, that are inhibitors of protein tyrosine kinases (Gazit A. *et al.*, *J. Med. Chem.* 39(11):2170 (1996)). International patent applications WO 96/09294, WO 98/13350, WO 01/55116 and WO 02/12226 describe inhibitors of protein tyrosine kinases that

include 4-anilino quinolines with a large variety of substituents on positions 5-8, but no quinone ring in the 4-position. United States Patent No. 5,480,883 describes quinoline derivatives that are inhibitors of protein tyrosine kinases, but do not have an attached quinone ring. International patent applications WO 98/02434 and WO 98/02438 also describe quinoline derivatives that do not have an attached quinone ring.

3-Cyanoquinolines are also present in the literature. The compounds of the present invention differ from these compounds because of the quinone substitutent at the 4-position. Several patents and patent applications disclose compounds with an expanded anilino moiety at the 4-position. In U.S. Patent No. 6,297,258, WO 00/18740, WO 00/18761, and WO 02/36570, compounds having an ether, thioether or sulfide linkage in addition to the possible aniline at the quinoline 4-position are described. However, none of these compounds have an attached quinone ring. International patent application WO 03/00266 discloses phosphorus-containing 4-anilino-3-cyanoquinolines. This patent application allows for additional substitution of a broad range on the quinoline at the 2, 6, and 7 positions as well as incorporating not just anilines at the 4-position, but also aliphatic amines and other heteroaliphatic or heteroaryl substituents. However, the compounds described do not have an attached quinone ring. International patent application WO 02/72578 describes a piperazine ring, with a urea functionallity, directly linked to the quinazoline at the 4-position. Again, there is no disclosure of compounds with a quinine moiety attached at the 4-position disclosed int his application.

The core structures claimed in international patent applications DE 1990/8567, DE 1001/7539, and WO 00/55141 encompass quinolines, 3-cyanoquinolines and quinazolines with 4-anilino substituent and variations of the substituents at the 5, 6, 7, and 8 positions of the heterocyclic ring. However, none of the compounds described in these applications have an attached quinone ring.

Several patents teach compounds with quinolines and quinazolines in their generic core structures but do not included a quinone substitutent at the 4-position of the corresponding heterocycle like the compounds of the present invention. WO 00/78735, WO 02/18370, WO 02/18376, and WO 02/18372 disclose compounds containing 4-anilinoquinolines and 4-anilinoquinazolines, allowing additional substitution at the heterocycles 6 and 7 positions. Two additional patent applications

(GB 2345486 and WO 99/35132) allow for extensive variation of the aniline moiety at the 4-position of the corresponding heterocycle, such as heterocyclic anilines, but the compounds described do not have an attached quinone ring. These two patent applications also allow for incorporation of an additional heteroatom at either the 6 or 7 positions of the heterocycle. Compounds with a cyclic aliphatic amine incorporated at the quinoline and quinazoline 4-position are disclosed in WO 98/14431 and U.S. Patent No. 6,169,008. International patent application WO 97/17329 teaches compounds that exclude the typical aniline substitution at the 4-position of the corresponding heterocycle yet encompasses phenyl ethers, phenyl thioethers and carbon linkages with simple substitution at the 6 and 7 position of the corresponding heterocycle. This patent application also does not describe compounds that have an attached quinine ring.

In addition to quinolines, certain quinazoline derivatives that are similar in some respects to the compounds of this invention are known to be inhibitors of protein tyrosine kinases. The application WO 98/50370 contains a disclosure of 2,4,5-substituted quinazolines that inhibit serine threonine kinases. These compounds contain different functional groups and substitution pattern than the compounds of the present invention. The key component of the disclosed compounds of application WO 99/10349 is the pyrrolione ring substituted at the quinazoline 4-position, while the compounds of the present invention contain a novel quinone or quinone epoxide ring at the 4-position. International patent application WO 01/66099 teaches a compound containing a urea directly linked to the quinazoline at the 4-position, but again, no disclosure of a quinone moiety at this same position. Similarly other international patent applications (WO 02/16351, WO 02/16360, WO 02/16361, and WO 02/16362) contain a urea (or thiourea) moiety off the quinazoline 4-position. However, in these instances, an essential piperazine ring links the urea to the quinazoline.

While a large portion of the quinazoline patent literature concerns anilinoquinazolines, again the compounds of the present invention are unique because of the quinone or quinone epoxide substitutent at the 4-position of the quinazoline. The application, EP-520722, describes 4-anilinoquinazolines that contain simple substituents such as chloro, trifluoromethyl, or nitro groups at positions 5 to 8. The compounds in application EP-566226 are similar, but with a

much larger variety of allowed substituents at positions 5 to 8. Application WO 96/09294 describes compounds with similar substituents at positions 5 to 8 and with the substituent at the 4-position consisting of some polycyclic ring systems. Some simple substituted quinazolines are also described in applications WO 95/24190, WO 95/21613, WO 95/15758, WO 97/32856, WO 98/13354 and WO 01/32651. The patent applications EP-602851 and WO 95/23141 cover similar quinazoline derivatives where the aryl group attached at position 4 can be a variety of heterocyclic ring structures. The application EP-635498 describes certain quinazoline derivatives that have alkenoylamino and alkynoylamino groups among the substituents at position 6 and a halogen atom at position 7. WO 96/33981 describes 4-anilinoquinazolines where the 6 and 7 position may contain polyether or amino substitution. None of these patent applications disclose or suggest quinazoline compounds with a quinone or quinone epoxide substituent at the 4-position like the quinazoline compounds of the present invention.

There are additional patents and patent applications that describe quinazolines that are inhibitors of various kinases such as WO 96/33978, WO 02/93577, WO 02/92579, WO 02/92578, WO 03/00188, WO 02/30924, WO 02/30926, WO 02/34744, WO 02/18351, WO 97/30044, EP-787722, WO 02/18373, WO 02/50043, WO 02/18375, EP-1230919, WO 02/50043, WO 97/30034, WO 99/01441, WO 02/02552, WO 97/30035, WO 01/77085, WO 00/21955, WO 00/47212, WO 01/21594, WO 01/21596, WO 01/21597, WO 02/85895, and U.S. Patent No. 5,721,237. However, none of these patent documents describe compounds that have an attached quinone or quinone epoxide moiety, like the compound of the present invention.

* * * * * *

The citation and/or discussion of a reference in this section and throughtout the specification is provided merely to clarify the description of the present invention and is not an admission that any such reference is "prior art" to the invention described herein.

3. SUMMARY OF THE INVENTION

The present invention overcomes the problems in the art by providing compounds that irreversibly bind to tyrosine kinase enzymes, specifically KDR, or behave as if they are inhibiting in an irreversible manner and are therefore non-competitive with ATP or protein substrate. The compounds of this invention can function like irreversible binding inhibitors by virtue of the fact that they may form covalent bonds to amino acid residues located at the active site of the enzyme. In this respect, the compounds of the present invention differ from all other KDR inhibitors reported previously. In particular, it is shown that it is the unique nature and combination of substituents contained in the compounds of the present invention that may lead to the irreversible binding of the inhibitor to the enzyme. These unique properties of the compounds of this invention contribute to their ability to function as anti-angiogenic agents.

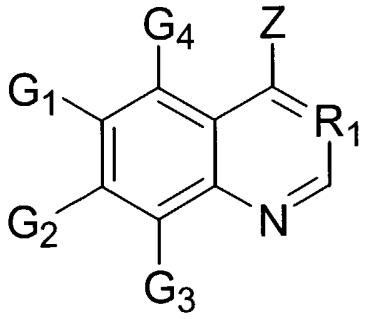
There are many advantages to an irreversible KDR inhibitor. For one, as discussed above, these inhibitors would not compete with ATP.

Secondly, since prolonged suppression of the kinase is most likely necessary for maximum tumor suppression, an irreversibly bound inhibitor provides an advantage by permanently eliminating the existing kinase activity, which should return only when a new receptor is synthesized.

Lower plasma levels of the inhibitor is also an advantage. The irreversible binding inhibitors require that plasma concentrations be attained only long enough to expose the inhibitor to the target. After the irreversible inhibitor binds, no more inhibitor is needed in the plasma in order to maintain inhibition. Thus, there is less likelihood of toxicity, which results from high or prolonged plasma levels.

Lastly, there may be possible cross-reactivity of the irreversible binding inhibitors with other kinases involved in angiogenesis that have homologous amino acids in their active site, *e.g.*, platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor 1 (VEGFR-1).

This invention provides a compound of formula **1**:

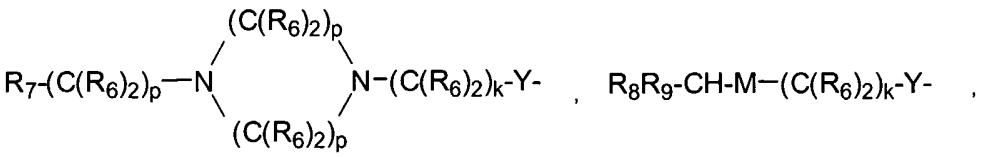


1

wherein:

R_1 is N, C-CN, C-H, C-F, C-Cl, C-Br, or C-I

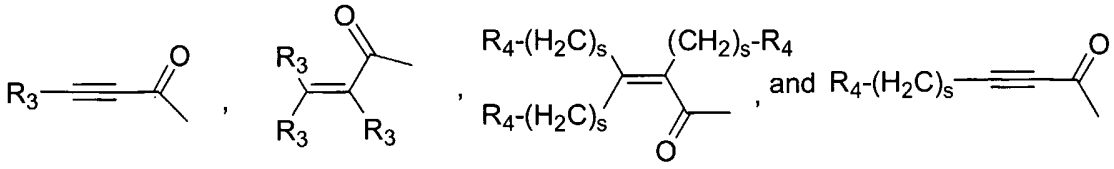
G_1, G_2, G_3, and G_4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, alkylamido of 2-7 carbon atoms, halomethyl, alkyl-N-alkylamido of 4-10 carbon atoms, alkanoyloxy of 2-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, phenylacetyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino, R_2NH,



R_7-$(C(R_6)_2)_g$-Y- , R_7-$(C(R_6)_2)_p$-M-$(C(R_6)_2)_k$-Y- , R_5-$(C(R_6)_2)_q$-W-$(C(R_6)_2)_k$-Y- ,

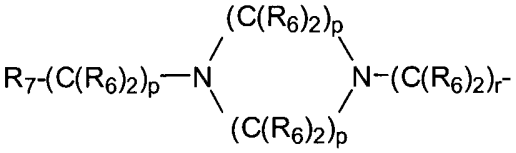
with the proviso that G3 or G4 are not R_2NH;

R_2, is selected from the group consisting of



, and

R_3 is, independently, hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,



,

R_7-$(C(R_6)_2)_s$- , R_7-$(C(R_6)_2)_p$-M-$(C(R_6)_2)_r$- ,

R_8R_9-CH-M-$(C(R_6)_2)_r$- , or R_5-$(C(R_6)_2)_q$-W-$(C(R_6)_2)_r$- ;

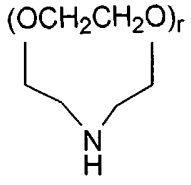
R_4 is Cl, Br, or I;

R_6 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl 2-7 carbon atoms, phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, or alkyl of 1-6 carbon atoms; with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

R_7 is $-NR_6R_6$, $-OR_6$, $-R_4$, $-N(R_6)_3^+$, or $-NR_6(OR_6)$;

M is $>NR_6$, -O-, $>N-(C(R_6)_2)_pNR_6R_6$, or $>N-(C(R_6)_2)_p-OR_6$, or a divalent phenyl radical;

W is $>NR_6$, -O-, a divalent phenyl radical, or is a bond;

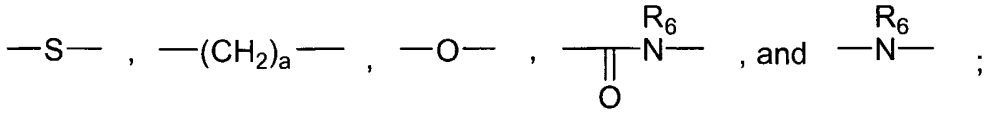
R_5 is a phenyl radical or a heterocyclic radical selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine , tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane , tetrahydropyran, and  ;

wherein the phenyl radical or the heterocylic radical may be optionally mono- or di-substituted on carbon with R_6, hydroxy, $-N(R_6)_2$, $-OR_6$ $-(C(R_6)_2)_sOR_6$, or $-(C(R_6)_2)_sN(R_6)_2$ and

wherein the heterocylic radical may be optionally mono-substituted on nitrogen with R_6 and optionally mono or di-substituted on a saturated carbon with divalent radicals -O- or $-O(C(R_6)_2)_sO-$;

R_8 and R_9 are each, independently, $-(C(R_6)_2)_rNR_6R_6$, or $-(C(R_6)_2)_r OR_6$;

Y is a divalent radical selected from the group consisting of



a = 0-1;

g = 1-6;

k = 0-4;

p = 2-4;

q= 0-4;

r = 1-4;

s = 1-6;

provided that

when R_6 is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

and provided that

when Y is $-NR_6-$ and R_7 is $-NR_6R_6$, $-N(R_6)_3^+$, or $-NR_6(OR_6)$, then g = 2-6;

when M is -O- and R_7 is $-OR_6$ then p = 1-4;

when Y is $-NR_6-$ then k = 2-4;

when Y is -O- and M or W is -O- then k = 1-4;

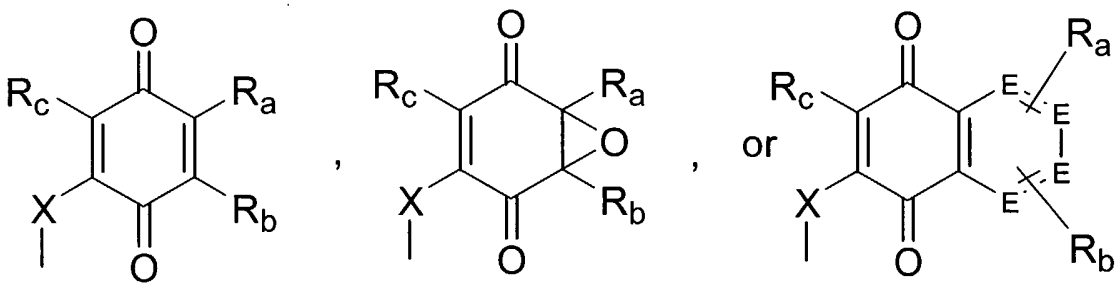
when W is not a bond or a divalent phenyl radical with R_5 bonded through a nitrogen atom then q = 2-4,

when M is a divalent phenyl radical then p = 0-4 and r = 0-4,

when W is a divalent phenyl radical then r = 0-4,

and when W is a bond with R_5 bonded through a nitrogen atom and Y is -O- or $-NR_6-$ then k = 2-4;

Z is a radical selected from the group

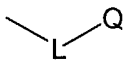
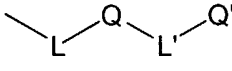


X is a divalent radical selected from the group –NH-, $>NR_{10}$, -O-, and - S-;

R_{10} is an hydrogen, an alkyl group from 1-6 carbon atoms, phenyl or benzyl;

R_a, R_b, R_c are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkanoyloxy of 2-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkylamido of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxyalkyl of 2-14 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms,

phenylacetyl, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, azido, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, benzyloxy, benzylthio, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl of 2 to 6 carbon atoms, N,N-dialkylcarbamoyl of 2 to 12 carbon atoms, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,


, or

;

when attached to a double bond at contiguous carbon atoms, R_a and R_b can be taken together as the divalent radicals $-(C(R_{10})_2)_3-$, $-(C(R_{10})_2)_4-$, $-X-(C(R_{10})_2)_3-$, $-X-(C(R_{10})_2)_2-X-$, $-C(R_{10})_2-X-(C(R_{10})_2)_2-$, or $-C(R_{10})_2-X-C(R_{10})_2-$;

Q and Q' are a phenyl mono or divalent radical which may be optionally substituted with 1-5 halogen atoms, or mono- di- or tri-substituted with a substituent selected from the group consisting of hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, alkylamido of 2-7 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, benzoyl, amino, phenylacetyl, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N-alkylcarbamoyl of 2 to 6 carbon atoms, N,N-dialkylcarbamoyl of 2 to 12 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino, or

Q and Q' are a mono or divalent radical comprising a 3-8-membered heterocyclic ring where the heterocyclic ring contains 1 to 3 heteroatoms selected from N, O, and S; wherein the heterocyclic ring may be optionally substituted with 1-5 halogen atoms, or mono- or di-substituted with a substituent selected from the group

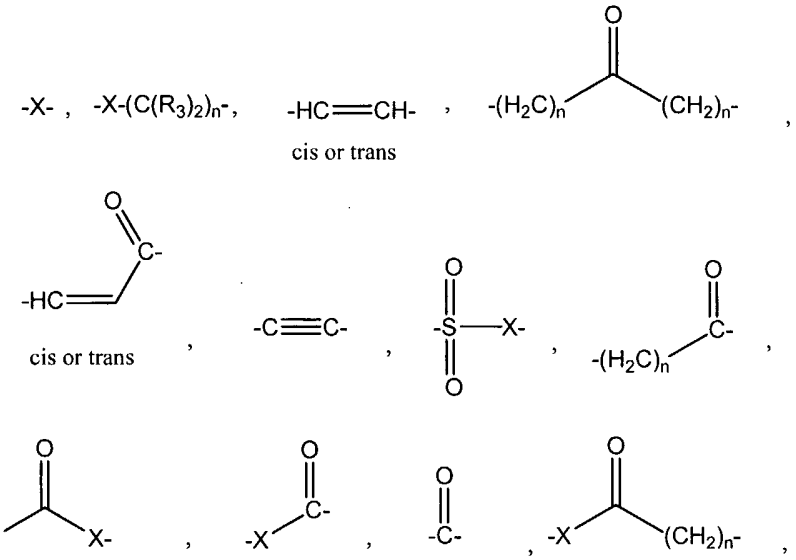
consisting of oxo, thio, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, alkylamido of 2-7 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, phenylacetyl, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylcarbamoyl of 2 to 6 carbon atoms, N,N-dialkylcarbamoyl of 2 to 12 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino, or

Q and Q' are a mono or divalent radical comprising a fused or bridged bicyclic or tricyclic carbocyclic ring system or a fused or bridged bicyclic or tricyclic heterocyclic ring system of 6 to 18 atoms, where the bicyclic or tricyclic heterocyclic ring system contains 1 to 4 heteroatoms selected from N, O, and S; wherein the bicyclic or tricyclic carbocyclic ring system or the bicyclic or tricyclic heterocyclic ring system may be optionally substituted with 1-5 halogen atoms, or mono-, di-, tri-, or tetra-substituted with a substituent selected from the group consisting of oxo, thio, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, alkylamido of 2-7 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenylacetyl, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylcarbamoyl of 2 to 6 carbon atoms, N,N-dialkylcarbamoyl of 2 to 12 carbon

atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino, or

Q and Q' are hydrogen or a mono or divalent radical comprising straight or cyclic alkyl groups of 1 to 10 carbon atoms, both of which can optionally be branched, substituted with 1-6 halogen groups, or contain sites of unsaturation, or be;

L and L' are divalent radicals selected from the group

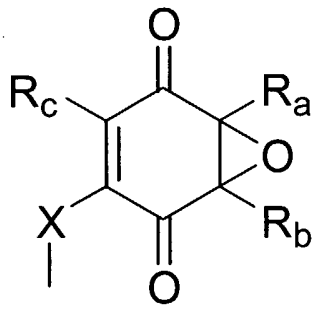


-N—O-, -X-(C(R3)2)n-X-; -(C(R3)2)n- -S(O)2-, -S(O)-, or are bonds;

n is an integer from 1 to 4;

E is CH or N with the proviso that there be no more than 2 ring nitrogen atoms;

it is provided that when Z is the moiety



R_a and R_b are independently hydrogen or are attached to the ring only via carbon atoms;

or a pharmaceutically acceptable salt thereof.

The present invention also provides for compositions containing these compounds and methods of using these compounds and compositions to treat patients in need of treatment, prevention and/or suppression of excessive, abnormal or inappropriate angiogenesis related to such disease states as cancer, including, but not limited to, cancer of the breast, kidney, bladder, mouth, larynx, esophagus, stomach, prostate, colon, ovary and lung, diabetic retinopathy, macular degeneration and rheumatoid arthritis.

4. DETAILED DESCRIPTION OF THE INVENTION

The terms used in this specification generally have their ordinary meanings in the art, within the context of the invention, and in the specific context where each term is used. Certain terms are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner in describing the compounds, compositions, and methods of the invention and how to make and use them. For convenience, certain terms are highlighted, for example using italics and/or quotation marks. The use of highlighting has no influence on the scope and meaning of a term; the scope and meaning of a term is the same, in the same context, whether or not it is highlighted. Moreover, it will be appreciated that the same thing can be said in more than one way. Consequently, alternative language and synonyms may be used for any one or more of the terms discussed herein, nor is any special significance to be placed upon whether or not a term is elaborated or discussed herein. Synonyms for certain terms are provided. A recital of one or more synonyms does not exclude the use of other synonyms. The use of examples anywhere in this specification, including examples of any terms discussed herein, is illustrative only, and in no way limits the scope and meaning of the invention or of any exemplified term. Likewise, the invention is not limited to the preferred embodiments.

As used herein, *"about"* or *"approximately"* shall generally mean within 20 percent, preferably within 10 percent, and more preferably within 5 percent of a given value or range.

The terms "*prevent*" or "*prevention*", as used herein, refer to the partial or complete inhibition of the development of a condition that impairs the performance of a function of the human body. The terms "*treat*" or "*treatment*", as used herein, refer

to an attempt to ameliorate a disease problem. Further, the term "*suppress*" or "*suppression*" refers to a complete or partial inhibition of a condition, *e.g.*, as evidenced by a lessening of the severity of the symptoms associated with that condition.

Still further, the terms "*effective amount*" and "*therapeutically effective amount*" refer to that amount of the compound or composition determined by the skilled artisan to effectively prevent, suppress or treat the targeted condition. The effective amount of a compound or composition will be determined empirically by administering a range of dosages to the patient and observing that dosage which is most effective for the treatment of the condition and best tolerated by the patient. The method of making such a determination will be readily understood by the skilled artisan and will necessarily take into account such factors as, *inter alia*, the route of administration, formulation, and the condition, age, sex, height, and weight of the patient.

The terms "*irreversible*" or "*irreversibly*" are used herein to mean an inhibitor of receptor tyrosine kinase activity that is permanently bound or associated with the receptor tyrosine kinase.

As discussed above, the present invention provides compounds having Formula 1 or pharmaceutically acceptable salts thereof. The preferred pharmaceutically acceptable salts are those derived from such organic and inorganic acids such as acetic, lactic, citric, tartaric, succinic, maleic, malonic, gluconic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids.

Either or all rings of the bicyclic or tricyclic carbocyclic ring systems or the bicyclic or tricyclic heterocyclic ring systems of Formula 1 may be fully unsaturated, partially saturated, or fully saturated. The bicyclic or tricyclic heterocyclic ring can be bound to a carbon atom via either a carbon or nitrogen atom. The bicyclic or tricyclic heterocyclic ring can be bound to a heteroatom via carbon atom. An oxo substituent on the bicyclic or tricyclic carbocyclic ring system or bicyclic or tricyclic heterocyclic ring system means that one of the carbon atoms has a carbonyl group. A thio substituent on the bicyclic or tricyclic carbocyclic ring system or the bicyclic or tricyclic heterocyclic ring system means that one of the carbon atoms has a thiocarbonyl group.

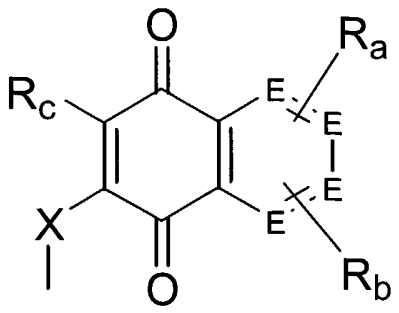
Moreover, when Q or Q' is a 3-8-membered heterocyclic ring, it may be fully unsaturated, partially saturated, or fully saturated. The heterocyclic ring can be bound to a carbon atom via either a carbon or nitrogen atom. The heterocyclic ring can be bound to a heteroatom via carbon atom. An oxo substituent on the heterocyclic ring means that one of the carbon atoms has a carbonyl group. A thio substituent on the heterocyclic ring means that one of the carbon atoms has a thiocarbonyl group.

When a compound of this invention with Formula 1 has a moiety that contains a heterocyclic ring, either mono, bicyclic, or tricyclic, such heterocyclic ring does not contain O-O, S-S, or S-O bonds in the ring.

Preferred bicyclic or tricyclic carbocyclic ring systems and bicyclic or tricyclic heterocyclic ring systems include naphthalene, 1,2,3,4-tetrahydronaphthalene, indane, 1-oxo-indane, 1,2,3,4-tetrahydroquinoline, naphthyridine, benzofuran, 3-oxo-1,3-dihydro-isobenzofuran, benzothiophene, 1,1-dioxo-benzothiophene, indole, 2,3-dihydroindole, 1,3-dioxo-2,3-dihydro-1H-isoindole, benzotriazole, 1H-indazole, indoline, benzopyrazole, naphthyridine, 1,3-benzodioxole, benzooxazole, purine, phthalimide, coumarin, chromone, quinoline, terahydroquinoline, isoquinoline, benzimidazole, quinazoline, pyrido[2,3-b]pyridine, pyrido[3,4-b]pyrazine, pyrido[3,2-c]pyridazine, pyrido[3,4-b]pyridine, 1H-pyrazole[3,4-d]pyrimidine, 1,4-benzodioxane, pteridine, 2(1H)-quinolone, 1(2H)-isoquinolone, 2-oxo-2,3-dihydro-benzthiazole, 1,2-methylenedioxybenzene, 2-oxindole, 1,4-benzisoxazine, benzothiazole, quinoxaline, quinoline-N-oxide, isoquinoline-N-oxide, quinoxaline-N-oxide, quinazoline-N-oxide, benzoxazine, phthalazine, 1,4-dioxo-1,2,3,4-tetrahydro-phthalazine, 2-oxo-1,2-dihydro-quinoline, 2,4-dioxo-1,4-dihydro-2H-benzo[d][1,3]oxazine, carbazole, fluorene, dibenzofurnan, 2,5-dioxo-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepine and cinnoline.

When Q or Q' is a 3-8-membered heterocyclic ring, preferred heterocyclic rings include pyridine, pyrimidine, imidazole, thiazole, aziridine, azetidine thiazolidine, pyrrole, furan, thiophene, oxazole, 1,2,4-triazole, morpholine, thiomorpholine, piperidine, pyrrolidine, oxiran, 1,2,3-triazole, tetrazole, piperazine, tetrahydrothiophene, tetrahydrofuran, triazine, dioxane, 1,3-dioxolane and tetrahydropyran.

The formula for when Z is



indicates that the right hand ring can be optionally substituted at any of the positions that are carbon atoms with R_a and R_b groups.

The alkyl portion of the alkyl, alkoxy, alkanoyloxy, alkylamido, alkoxymethyl, alkanoyloxymethyl, alkylsulphinyl, alkylsulphonyl, alkylsulfonamido, carboalkoxy, carboalkyl, carboxyalkyl, carboalkoxyalkyl, alkanoylamino, N-alkylcarbamoyl, N,N-dialkylcarbamoyl , N-alkylaminoalkoxy, N,N-dialkylaminoalkoxy, or where else it occurs in Formula 1, can include straight chain, cyclic, and branched carbon chains. The N,N-dialkylamino moiety includes cyclic amino radicals where the two alkyl groups form a saturated ring. The alkenyl portion of the alkenyl, alkenoyloxymethyl, alkenyloxy, and alkenylsulfonamido substituents include straight chain, cyclic, and branched carbon chains and one or more sites of unsaturation and all possible configurational isomers. The alkynyl portion of the alkynyl, alkynoyloxymethyl, alkynylsulfonamido and alkynyloxy substituents include both straight chain as well as branched carbon chains and one or more sites of unsaturation. Carboxy is defined as a -CO_2H radical. Carboalkoxy of 2-7 carbon atoms is defined as a -CO_2R" radical, where R" is an alkyl radical of 1-6 carbon atoms. Carboxyalkyl is defined as a HO_2C-R"'- radical where R"' is a divalent alkyl radical of 1-6 carbon atoms. Carboalkoxyalkyl is defined as a R"O_2C-R"'- radical where R"' is a divalent akyl radical and where R" and R"' together have 2-7 carbon atoms. Carboalkyl is defined as a -COR" radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkanoyloxy is defined as a -OCOR" radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkanoyloxymethyl is defined as R"CO_2CH_2- radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkoxymethyl is defined as R"OCH_2- radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkylsulphinyl is defined as R"SO- radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkylsulphonyl is defined as R"SO_2- radical, where R" is an alkyl radical of 1-6 carbon atoms. Alkylsulfonamido,

alkenylsulfonamido and alkynylsulfonamido are defined as R"SO2NH- radical, where R" is an alkyl radical of 1-6 carbon atoms, an alkenyl radical of 2-6 carbon atoms or an alkynyl radical of 2-6 carbon atoms, respectively. N-alkylcarbamoyl is defined as R"NHCO- radical, where R" is an alkyl radical of 1-6 carbon atoms. N,N-dialkylcarbamoyl is defined as R" R'NCO- radical, where R" is an alkyl radical of 1-6 carbon atoms, R' is an alkyl radical of 1-6 carbon atoms and R' and R" may be the same or different. It is preferred that of the substituents G_3 and G_4, at least one is hydrogen, and it is most preferred that both be hydrogen.

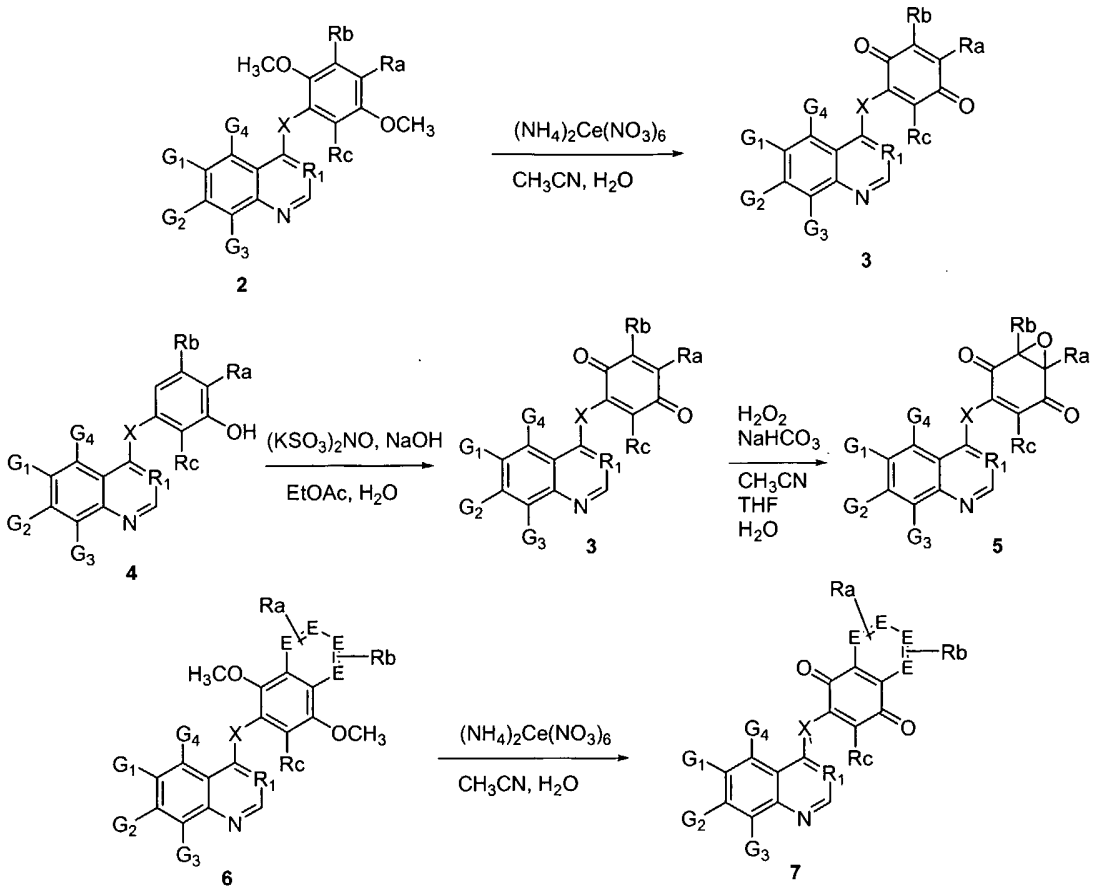
R_5 is a heterocycle, as defined above which may be optionally mono- or di-substituted on a carbon with R_6, optionally mono-substituted on nitrogen with R_6, optionally mono- or di-substituted on a carbon with hydroxy, $-N(R_6)_2$, or $-OR_6$, optionally mono or di-substituted on a carbon with $-(C(R_6)_2)_sOR_6$ or $-(C(R_6)_2)_sN(R_6)_2$ and optionally mono or di-substituted on a saturated carbon with divalent -O- or $-O(C(R_6)_2)_sO-$ (carbonyl and ketal groups, respectively). In some cases when R_5 is substituted with -O- (carbonyl), the carbonyl group can be hydrated. R_5 may be bonded to W when q = 0 via a carbon atom on the heterocyclic ring, or when R_5 is a nitrogen containing heterocycle which also contains a saturated carbon-nitrogen bond. Such a heterocycle may be bonded to carbon, via the nitrogen when W is a bond. When q = 0 and R_5 is a nitrogen containing heterocycle, which also contains an unsaturated carbon-nitrogen bond, that nitrogen atom of the heterocycle may be bonded to carbon when W is a bond and the resulting heterocycle will bear a positive charge. When R_5 is substituted with R_6, such substitution may be on a ring carbon, or in the case of a nitrogen containing heterocycle, which also contains a saturated carbon-nitrogen bond, such nitrogen may be substituted with R_6 or in the case of a nitrogen containing heterocycle, which also contains an unsaturated carbon-nitrogen bond, such nitrogen may be substituted with R_6. In such a case, the heterocycle will bear a positive charge.

The compounds of this invention may contain one or more asymmetric carbon atoms. In such cases, the compounds of this invention include the individual diasteromers, the racemates, and the individual R and S entantiomers thereof. Some of the compound of this invention may contain one or more double bonds. In

such cases, the compounds of this invention include each of the possible configurational isomers as well as mixtures of these isomers. Some of the compounds of this invention may exist as separate tautomers. In such cases, the compounds of this invention include each tautomer and mixtures of these tautomers. When a compound of this invention contain a moiety containing the same substituent more than once (for example, when R_7 is $-NR_6R_6$), each substituent (R_6, in this example) may be the same or different. When the compounds of this invention contain a dialkylamino group (for example, when R_7 is $-NR_6R_6$), this dialkylamino group can also be a cyclic amino group (for example, for $-NR_6R_6$ the two R_6 groups are attached to each other to form a ring).

The compounds of this invention can be prepared from commercially available starting materials or starting materials that can be prepared using literature procedures. More specifically, the preparation of the compounds and intermediates of this invention encompassed by Formulas **3** and **5** is described below in Flowsheet 1 where R_1, G_1-G_4, X, R_a, R_b, and R_c are as described above. Oxidation of the dimethoxy derivatives having Formulas **2** or **6** with an oxidizing agent, such as ceric ammonium nitrate in aqueous acetonitrile, furnishes the quinone compounds **3** or **7**, respectively. Alternatively, oxidation of the phenol derivative **4** with an oxidizing agent, such as Fremy's salt in the presence of base in a mixture of water and ethyl acetate (EtOAc), also furnishes compounds of this invention of formula **3**. In those cases where both R_a and R_b are either hydrogen atoms or are bound to the quinone ring of **3** via carbon atoms, the molecule can be further oxidized to the quinone epoxide using hydrogen peroxide and a mixture of aqueous tetrahydrofurnan (THF) and acetonitrile in the presence of a weak base such as sodium bicarbonate. In those cases where the substituents such as G_1-G_4, X, R_a, R_b, and R_c are not stable to the oxidative reaction conditions, they can be protected using a suitable protecting group which can then be removed after the oxidation. The application of protecting groups is discussed in detail in *Protective Groups in Organic Synthesis* by T. W. Green and P. G. M. Wuts, John Wiley & Sons Inc., New York, 1991.

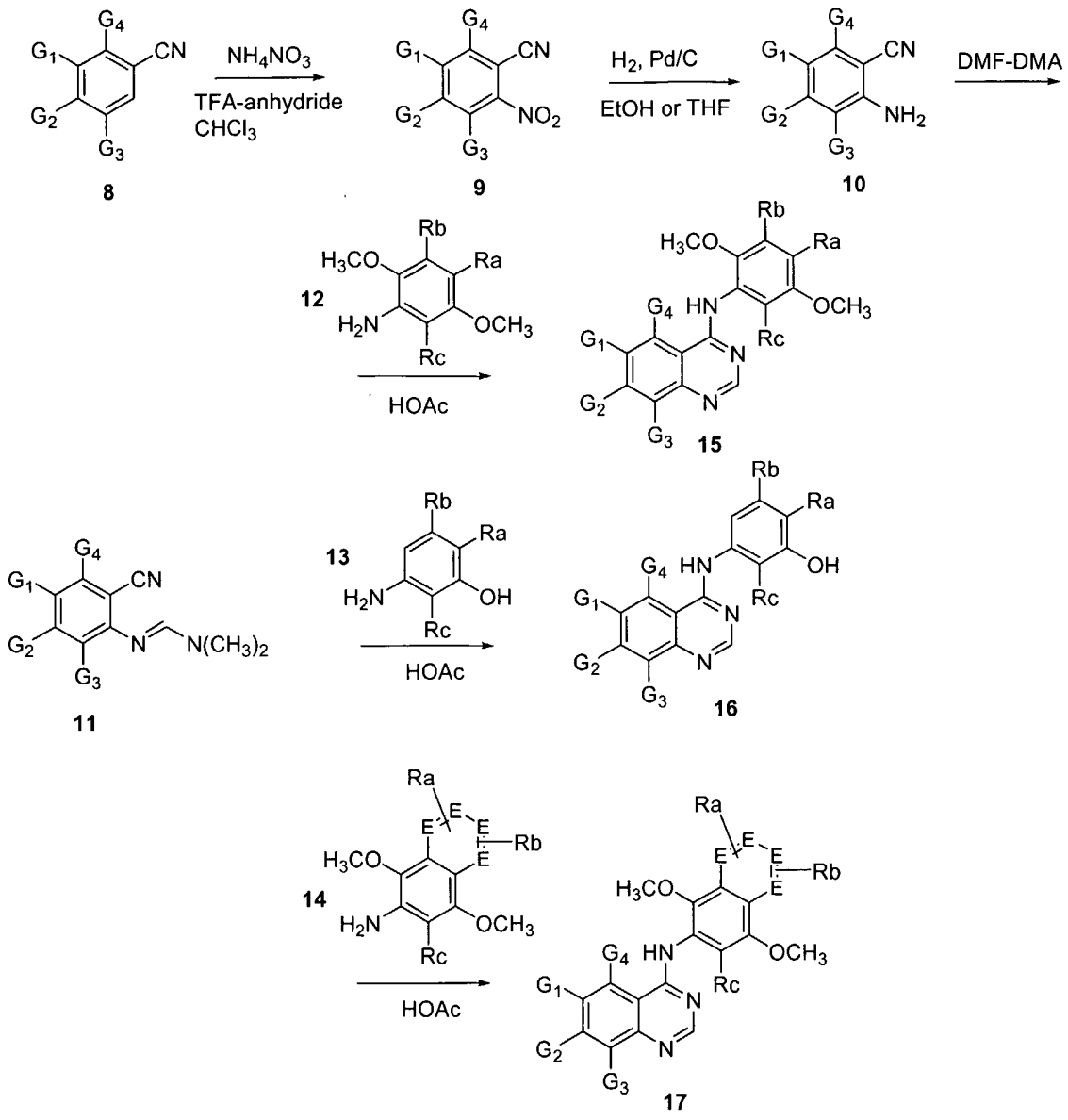
Flowsheet 1


Rb
H3CO
Ra
G4
X
OCH3
G1
Rc
R1
G2
N
G3
2
(NH4)2Ce(NO3)6
CH3CN, H2O
O
3
OH
(KSO3)2NO, NaOH
EtOAc, H2O
4
H2O2
NaHCO3
CH3CN
THF
H2O
5
E
6
7

The starting materials represented by formulas **2**, **4** and **6** and the intermediates needed to prepare these starting materials can be prepared using the methods outlined in the patent applications WO 00/18761, WO 00/18740, EP-93300270, WO 96/15118 and WO 96/09294, and U.S. Patent No. 6,002,008 and the methods described below.

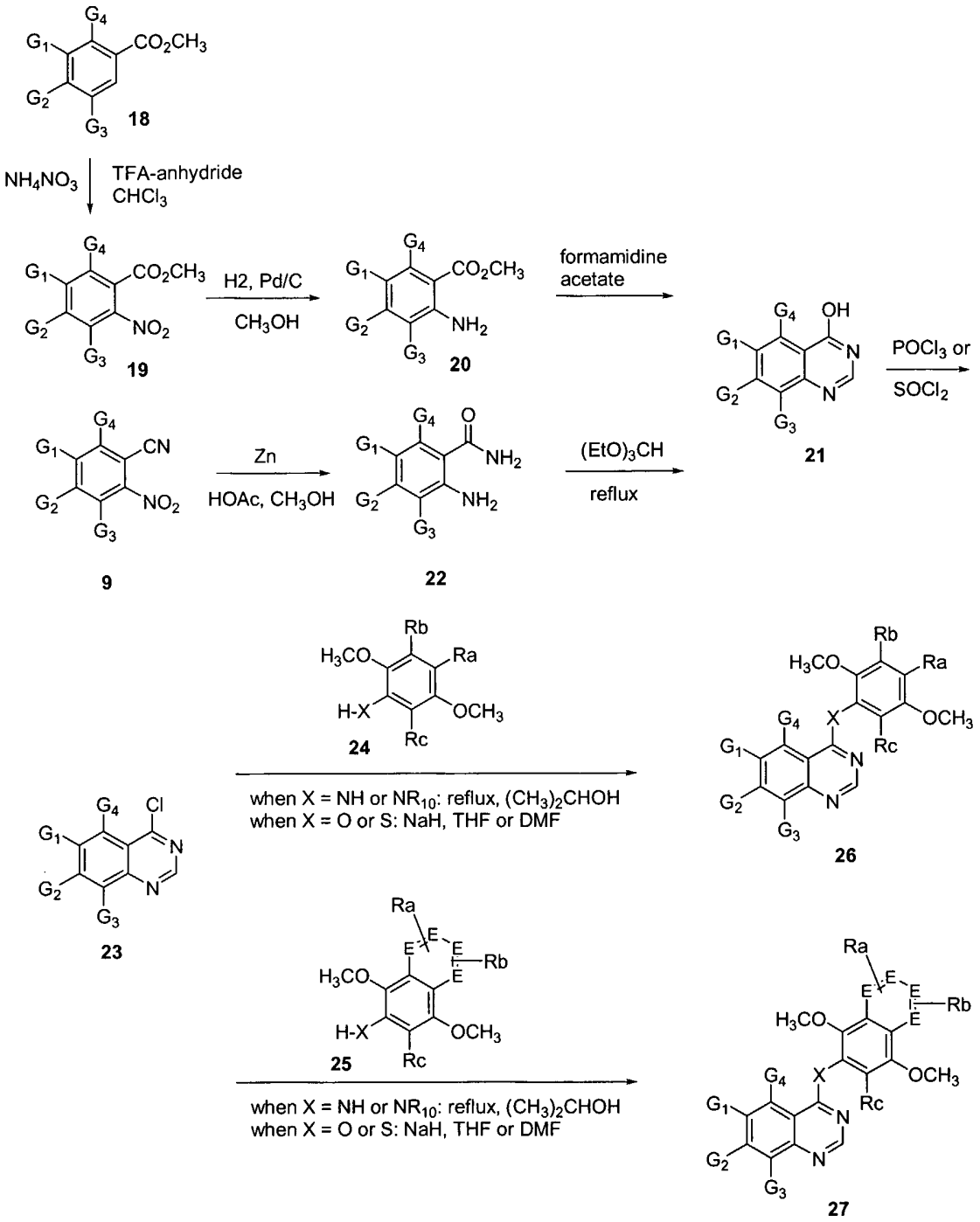
The intermediates represented by formulas **15-17,** necessary for the preparation of some of the compounds of this invention, are prepared as shown below in Flowsheet 2, where E, G_1-G_4, R_a, R_b, and R_c are as described above. A substituted benzonitrile derivative **8** is nitrated using ammonium nitrate in a mixture of trifluoroacetic anhydride and chloroform. Nitration with nitric acid can also be used for this reaction. If the nitration of **8** results in isomers, the desired isomer can be separated by chromatography or fractional recrystallization. The nitro group of compound **9** is reduced by catalytic hydrogenation using a palladium catalyst and hydrogen gas or cyclohexene as the hydrogen source. The aniline **10** is heated with an excess of neat dimethylformamide-dimethylacetal to give the amidine **11**. Refluxing **11** with the anilines **12-14** in acetic acid gives the intermediates **15-17**, respectively.

Flowsheet 2


G4
G1
CN
G2
G3
8
NH4NO3
TFA-anhydride
CHCl3
NO2
9
H2, Pd/C
EtOH or THF
NH2
10
DMF-DMA
Rb
H3CO
Ra
12
H2N
OCH3
Rc
HOAc
HN
15
N(CH3)2
11
13
OH
16
Rc
14
17

Alternatively, these intermediates can be prepared from 4-chloroquinazoline derivatives as shown below in Flowsheet 3 where E, R_{10}, G_1-G_4, X, R_a, R_b, and R_c are as described above. The ester **18** or the corresponding ethyl ester is nitrated using ammonium nitrate in a mixture of trifluoroacetic anhydride and chloroform. Nitration with nitric acid can also be used for this reaction. If the nitration of compound **18** results in isomers, the desired isomer can be separated by chromatography or fractional recrystallization. Catalytic hydrogenation of compound **19** gives compound **20**. This reduction can also be accomplished using metals such as iron powder in refluxing ammonium chloride solution in methanol. Heating **20** with formamidine acetate, either neat or in a solvent such as isopropanol, gives the hydroxyquinazoline **21**. Alternatively, reduction of **9** (from Flowsheet 2) with zinc in a mixture of refluxing acetic acid and methanol results in the reduction of the nitro group and hydrolysis of the nitrile group giving compound **22**. This compound is then reacted with triethylorthoformate at reflux to give compound **21**. In the next step, **21** is chlorinated by refluxing in either phosphorous oxychloride or thionyl chloride and catalytic dimethylformamide resulting in compound **23**. In those cases where compounds **24** and **25** are anilines (X = NH or NR_{10}), heating these with **23** in an inert solvent such as isopropanol or ethoxyethanol results in compounds **26** and **27** (X = NH or NR_{10}), respectively. If needed, this reaction can be catalyzed using a small amount of pyridine hydrochloride. In those cases where **24** and **25** are phenols or thiophenols (X = O or S), they can be reacted with **23** using a base, such as sodium hydride, and an inert solvent, such as tetrahydrofuran, toluene, or dimethylformamide, to give **26** and **27** (X = O or S), respectively. If necessary, the reaction mixture can be heated up to the reflux temperature of the solvent.

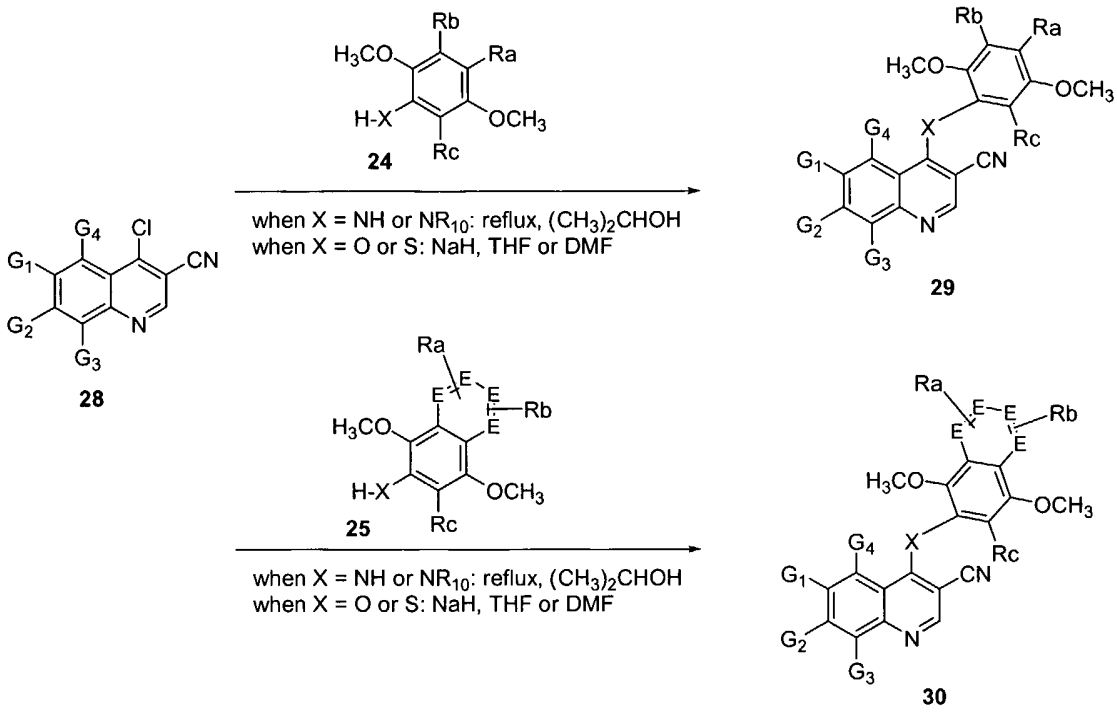
Flowsheet 3



Intermediates needed to prepare the compounds of this invention that are 3-cyanoquinolines are prepared as shown in Flowsheet 4 where E, R_{10}, G_1-G_4, X, R_a, R_b, and R_c are as described above. The methods used to prepare the starting 4-

chloro-3-cyanoquinolines represented by formula **28** are described in detail in international patent applications WO 98/43960, WO 00/18761 and WO 00/18740. In those cases where **24** and **25** are anilines (X = NH or NR_{10}), heating these with **28** in an inert solvent, such as isopropanol or ethoxyethanol, results in compounds **29** and **30** (X = NH or NR_{10}), respectively. If needed, this reaction can be catalyzed using a small amount of pyridine hydrochloride. In those cases where **24** and **25** are phenols or thiophenols (X = O or S), they can be reacted with **28** using a base, such as sodium hydride, and an inert solvent, such as tetrahydrofuran, toluene or dimethylformamide, to give **29** and **30** (X = O or S), respectively. If necessary, the reaction mixture can be heated up to the reflux temperature of the solvent.

Flowsheet 4



5

Certain compounds of this invention can be used as intermediates for the preparation of other compounds of this invention as shown below in Flowsheet 5 where R_1 and G_1-G_4 are as defined above. HO-Q_1 is H–L-Q or H–L-Q-L'-Q' as defined above with L being restricted to –O-, -O-$(CH_2)_n$-, and –O-$(CH_2)_n$-X-. NH_2-Q_2 is H-L-Q or H-L-Q-L'-Q' with L being restricted to –NH-, -NH-$(CH_2)_n$-, and –NH-$(CH_2)_n$-X-. NHR_{10}-Q_3 is H-L-Q or H-L-Q-L'-Q' with L being restricted to –NR_{10}-, -NR_{10}-$(CH_2)_n$-, and –NR_{10}-$(CH_2)_n$-X-. HS-Q_4 is H–L-Q or H–L-Q-L'-Q' with L being restricted to –S-, -S-$(CH_2)_n$-, and –S-$(CH_2)_n$-X-. Q_5 is -Q or -Q-L'-Q' as defined above where Q is a bicyclic, tricyclic heteroaryl, or heteroaryl moiety that has, as the reactive center, a –NH- as part of the heterocyclic ring.

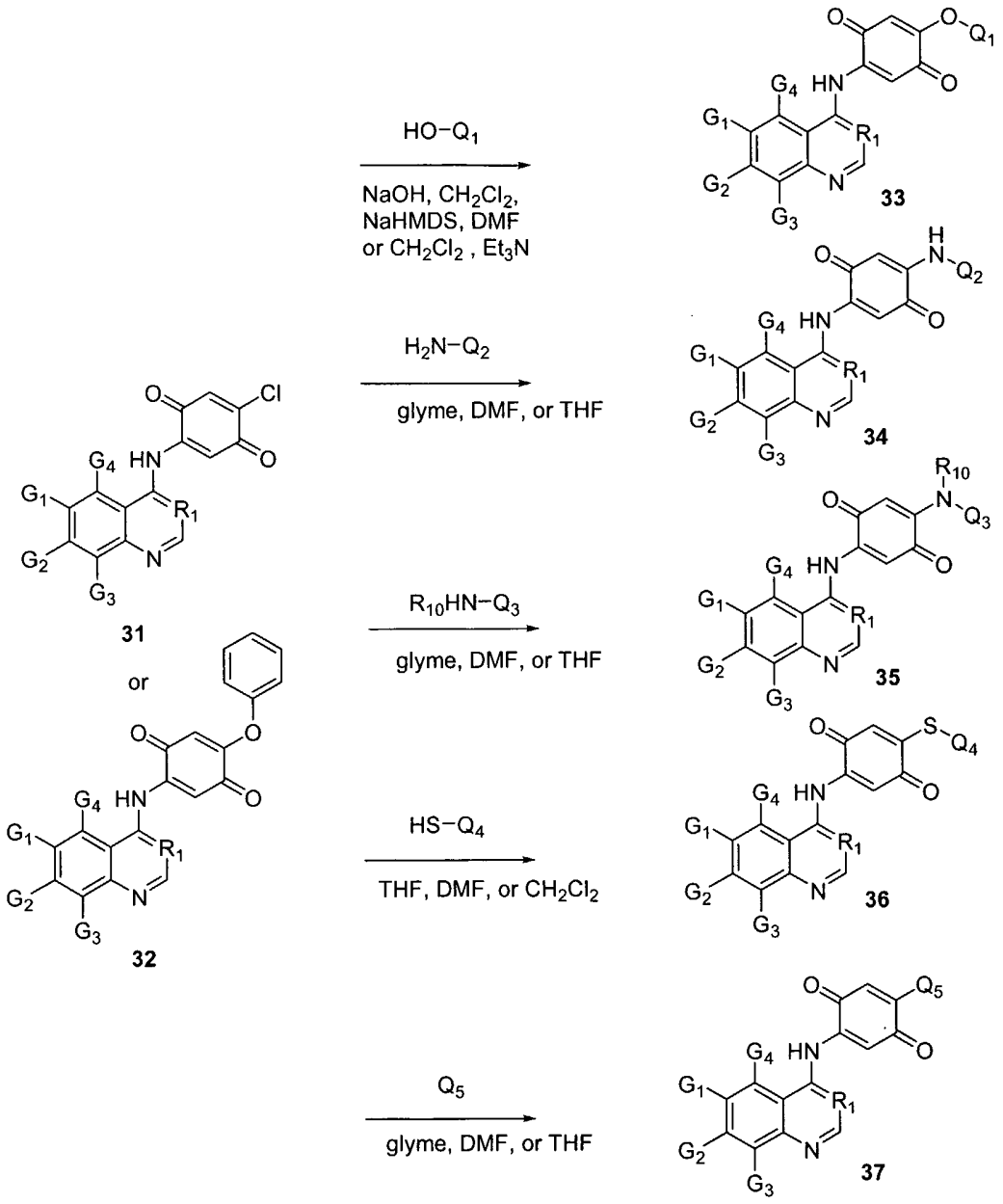
The reaction of the chloroquinone **31** with a substituted phenol or heteroaryl moiety that contains an attached OH group in the presence of base and an inert solvent, such as methylene chloride, DMF or THF, results in displacement of the chlorine atom to give compound **33**. Sometimes it is beneficial to do the displacement in the presence of a phase transfer catalyst, such as tricaprylylmethylammonium chloride. When the moiety HO-Q_1 is an alcohol, the reaction of the phenoxy substituted quinone **32** with an excess of this alcohol in an inert solvent such as methylene chloride in the presence of a base such as triethylamine also furnishes the compound of formula **33**. This reaction proceeds at room temperature or at reflux.

The reaction of NH_2-Q_2 or NHR_{10}-Q_3 with **31** or **32** in an inert solvent such as glyme, DMF or THF results in the compounds **34** and **35**, respectively. This reaction proceeds at room temperature or at reflux.

The reaction of HS-Q_4 with **31** or **32** in an inert solvent such as methylene chloride or THF results in the compound **36**. This reaction proceeds at room temperature or at reflux. The reaction can sometimes be accelerated using base catalyst such as triethylamine. Due to quinone reduction, side products, in addition to **36,** sometimes result in this reaction. These side products can be removed by chromatography.

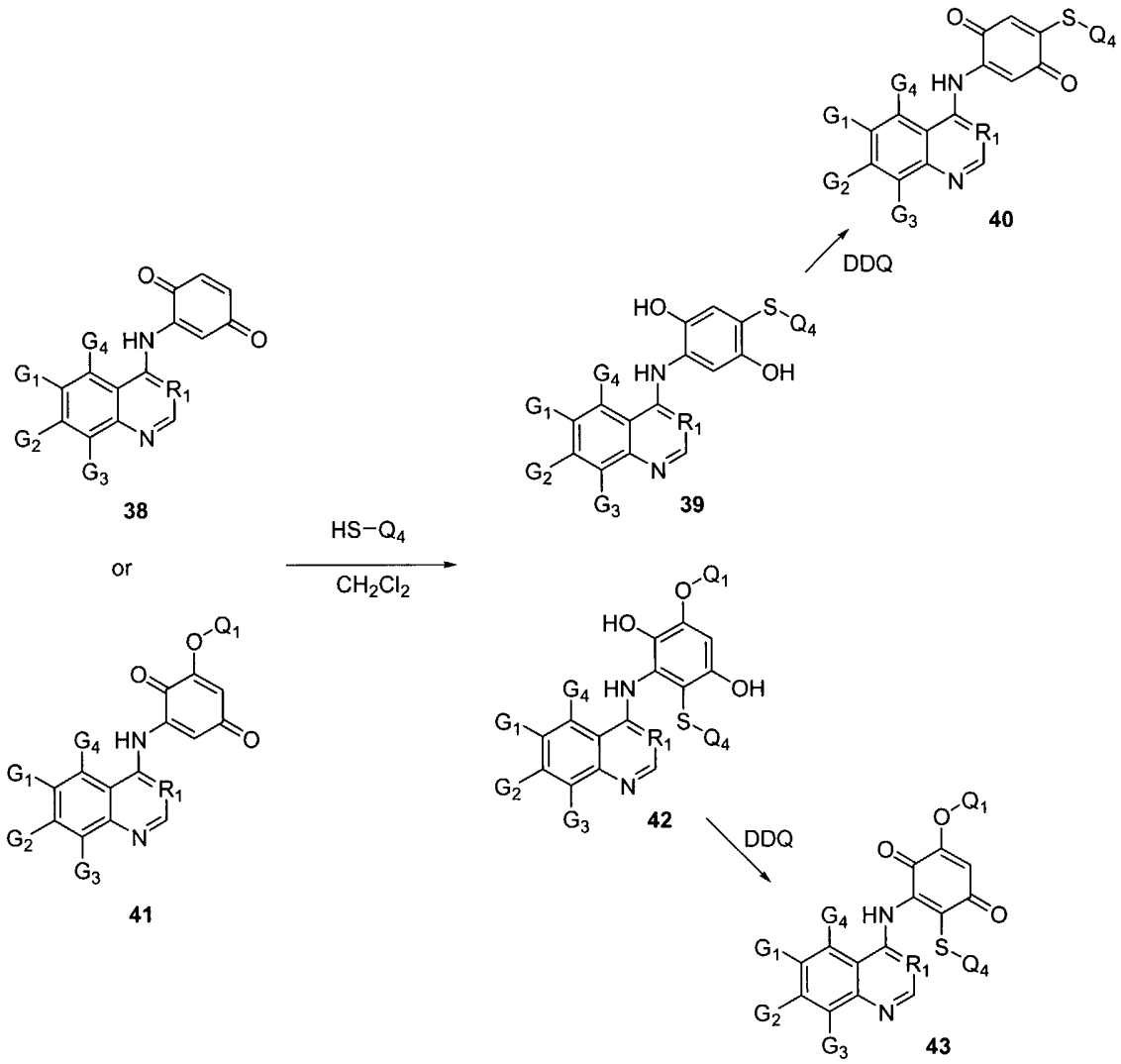
The reaction Q_5 with **31** or **32** in an inert solvent such as glyme, DMF or THF results in the compound **37** where the nitrogen atom of Q_5 is bonded directly to the quinone ring. This reaction proceeds at room temperature or at reflux. Sometimes a base will accelerate this reaction.

Flowsheet 5


HO–Q1
NaOH, CH2Cl2, NaHMDS, DMF or CH2Cl2 , Et3N
H2N–Q2
glyme, DMF, or THF
R10HN–Q3
glyme, DMF, or THF
HS–Q4
THF, DMF, or CH2Cl2
Q5
glyme, DMF, or THF
31
or
32
33
34
35
36
37

Other compounds of this invention can be used to make additional compounds of this invention as shown below in Flowsheet 6 where R_1, G_1-G_4 , -S-Q_4, and –O-Q_1 are as described above. The reaction of a sulfhydryl species such as HS-Q_4 with quinone **38** in an inert solvent, such as methylene chloride or THF, results in reductive addition to give the hydroquinone **39**. This compound can then be oxidized to the quinone **40** using an oxidizing agent such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The reaction of a sulfhydryl species, such as HS-Q_4, with quinone **41** in an inert solvent, such as methylene chloride or THF, results in reductive addition to give the hydroquinone **42**. This compound can then be oxidized to the quinone **43** using an oxidizing agent, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

Flowsheet 6



Additional compounds of this invention are prepared as shown below in Flowsheet 7 where R_1 and G_1-G_4 are as defined above. HO-Q_1 is H–L-Q or H–L-Q-L'-Q' as defined above with L being restricted to –O-, -O-$(CH_2)_n$-, and –O-$(CH_2)_n$-X-. NH_2-Q_2 is H-L-Q or H-L-Q-L'-Q' with L being restricted to –NH-, -NH-$(CH_2)_n$-, and –NH-$(CH_2)_n$-X-. NHR_{10}-Q_3 is H-L-Q or H-L-Q-L'-Q' with L being restricted to –NR_{10}-, -NR_{10}-$(CH_2)_n$-, and –NR_{10}-$(CH_2)_n$-X-. HS-Q_4 is H–L-Q or H–L-Q-L'-Q' with L being restricted to –S-, -S-$(CH_2)_n$-, and –S-$(CH_2)_n$-X-. Q_5 is -Q or -Q-L'-Q' as defined above where Q is a bicyclic, tricyclic heteroaryl, or heteroaryl moiety that has as the reactive center, a –NH- as part of the heterocyclic ring.

Addition of hydrogen chloride to compound **44** in chloroform at room temperature affords the hydroquinone **45**. Oxidation of **45** to the quinone **46** is accomplished using an oxidizing agent, such as DDQ, in an inert solvent, such as chloroform, acetonitrile or methylene chloride.

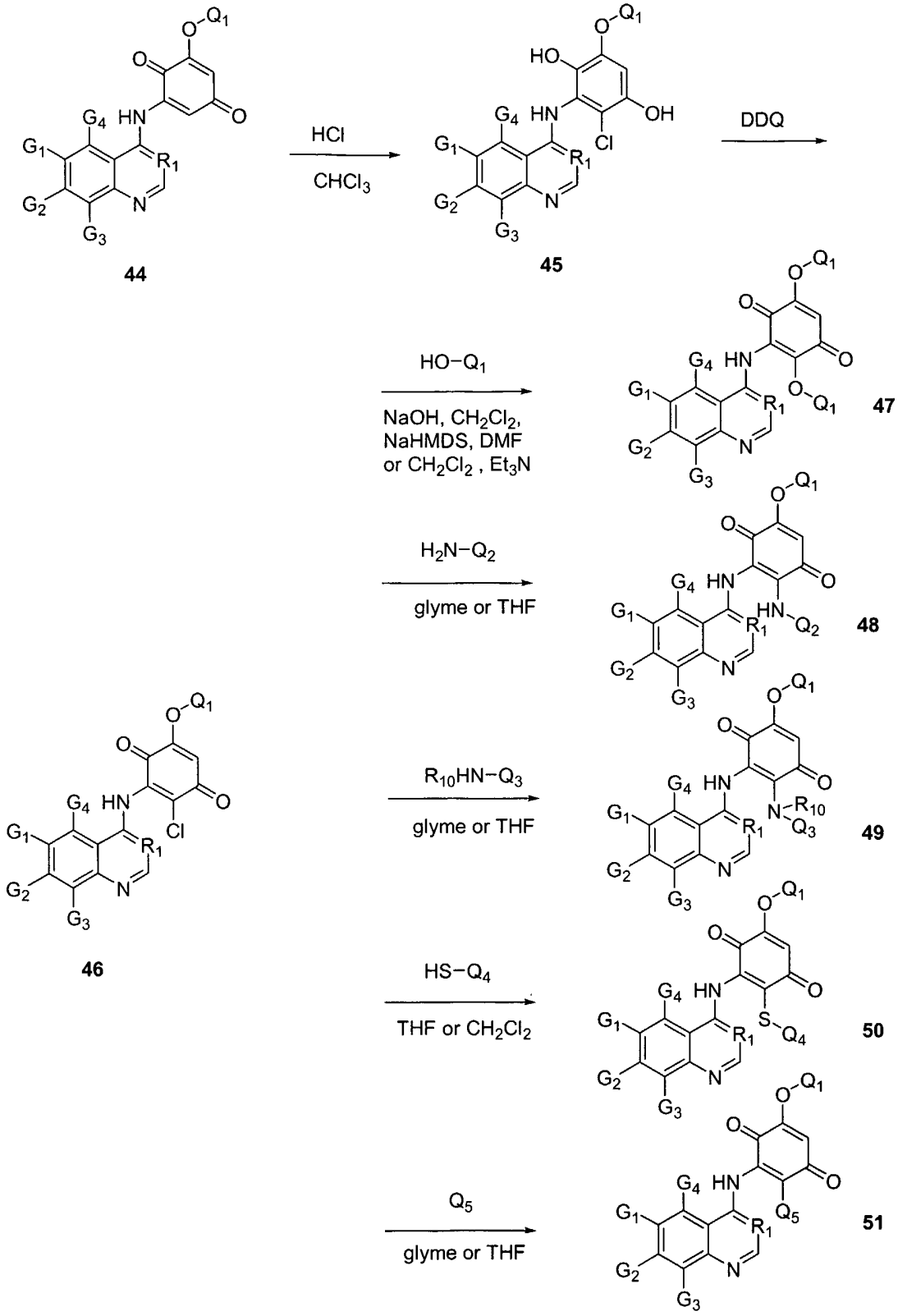
The reaction of the chloroquinone **46** with a substituted phenol or heteroaryl moiety that contains an attached OH group in the presence of base and an inert solvent, such as methylene chloride, DMF or THF, results in displacement of the chlorine atom to give compound **47**. Sometimes it is beneficial to do the displacement in the presence of a phase transfer catalyst such as tricaprylylmethylammonium chloride. This reaction proceeds at room temperature or at reflux.

The reaction of NH_2-Q_2 or NHR_{10}-Q_3 with **46** in an inert solvent, such as glyme or THF, results in the compounds **48** and **49**, respectively. This reaction proceeds at room temperature or at reflux. Sometimes it is beneficial to do this reaction using a base such as potassium carbonate or triethylamine.

The reaction of HS-Q_4 with **46** in an inert solvent, such as methylene chloride or THF, results in the compound **50**. This reaction proceeds at room temperature or at reflux. The reaction can sometimes be accelerated using base catalyst such as triethylamine. Due to quinone reduction, side products, in addition to **50,** sometimes result in this reaction. These side products can be removed by chromatography.

The reaction Q_5 with **46** in an inert solvent, such as glyme, methylene chloride, acetonitrile or THF, results in the compound **51,** where the nitrogen atom of Q_5 is bonded directly to the quinone ring. This reaction proceeds at room temperature or at reflux. Sometimes a base will accelerate this reaction.

Flowsheet 7


HCl
CHCl3
DDQ
44
45
HO–Q1
NaOH, CH2Cl2, NaHMDS, DMF or CH2Cl2 , Et3N
47
H2N–Q2
glyme or THF
48
46
R10HN–Q3
glyme or THF
49
HS–Q4
THF or CH2Cl2
50
Q5
glyme or THF
51

There are certain functional group manipulations that are useful to prepare the compounds of this invention that can be applied to various intermediate quinazoline or quinolines, such as compounds with Formulas **2**, **4**, and **6**. These manipulations refer to the substituents G_1-G_4, which are located on the formulas shown in the above Flowsheets. Some of these functional group manipulations are described below.

Where one or more of G_1-G_4 is a nitro group, it can be converted to the corresponding amino group by reduction using a reducing agent such as iron in acetic acid, or by catalytic hydrogenation.

Where one or more of G_1-G_4 is an amino group, it can be converted to the corresponding dialkyamino group of 2-12 carbon atoms by alkylation with at least two equivalents of an alkyl halide of 1-6 carbon atoms by heating in an inert solvent or by reductive alkylation using an aldehyde of 1-6 carbon atoms and a reducing agent such as sodium cyanoborohydride.

Alternatively, where one or more of G_1-G_4 is an amino group, it can be converted to the corresponding alkylsulfonamido, alkenylsulfonamido or alkynylsulfonamido group of 2-6 carbon atoms by the reaction with an alkylsulfonyl chloride, alkenylsulfonyl chloride or alkynylsulfonyl chloride, respectively, in an inert solvent using a basic catalyst, such as triethylamine or pyridine.

Alternatively, where one or more of G_1-G_4 is an amino group, it can be converted to the corresponding alkyamino group of 1-6 carbon atoms by alkylation with one equivalent of an alkyl halide of 1-6 carbon atoms by heating in an inert solvent or by reductive alkylation using an aldehyde of 1-6 carbon atoms and a reducing agent such as sodium cyanoborohydride, in a protic solvent such as water or alcohol, or mixtures thereof.

Where one or more of G_1-G_4 is hydroxy, it can be converted to the corresponding alkanoyloxy group of 1-6 carbon atoms by reaction with an appropriate carboxylic acid chloride, anhydride, or mixed anhydride in a inert solvent using pyridine or a trialkylamine as a catalyst.

Alternatively, where one or more of G_1-G_4 is hydroxy, it can be converted to the corresponding alkenoyloxy group of 1-6 carbon atoms by reaction with an

appropriate carboxylic acid chloride, anhydride or mixed anhydride in an inert solvent using pyridine or a trialkylamine as a catalyst.

Alternatively, where one or more of G_1-G_4 is hydroxy, it can be converted to the corresponding alkynoyloxy group of 1-6 carbon atoms by reaction with an appropriate carboxylic acid chloride, anhydride or mixed anhydride in a inert solvent using pyridine or a trialkylamine as a catalyst.

Where one or more of G_1-G_4 is carboxy or a carboalkoxy group of 2-7 carbon atoms, it can be converted to the corresponding hydroxymethyl group by reduction with an appropriate reducing agent, such as borane, lithium borohydride or lithium aluminum hydride in a inert solvent. The hydroxymethyl group, in turn, can be converted to the corresponding halomethyl group by reaction in an inert solvent with a halogenating reagent, such as phosphorous tribromide to give a bromomethyl group, or phosphorous pentachloride to give a chloromethyl group. The hydroxymethyl group can be acylated with an appropriate acid chloride, anhydride, or mixed anhydride in an inert solvent using pyridine or a trialkylamine as a catalyst to give the compounds of this invention with the corresponding alkanoyloxymethyl group of 2-7 carbon atoms, alkenoyloxymethyl group of 2-7 carbon atoms or alkynoyloxymethyl group of 2-7 carbon atoms.

Where one or more G_1-G_4 is a halomethyl group, it can be converted to an alkoxymethyl group of 2-7 carbon atoms by displacing the halogen atom with a sodium alkoxide in an inert solvent.

Alternatively, where one or more of G_1-G_4 is a halomethyl group, it can be converted to an aminomethyl group, N-alkylaminomethyl group of 2-7 carbon atoms or N,N-dialkylaminomethyl group of 3-14 carbon atoms by displacing the halogen atom with ammonia, a primary, or secondary amine, respectively, in an inert solvent.

In addition to the methods described herein above, there are a number of patent applications that describe methods that are useful for the preparation of the intermediates used to prepare compounds of this invention. The chemical procedures described in the application WO 96/33981 can be used to prepare the intermediates used in this invention wherein G_1-G_4 are alkoxyalkylamino groups. The chemical procedures described in the application WO 96/33980 can be used to prepare the intermediates used in this invention wherein G_1-G_4 are aminoalkylalkoxy groups. The chemical procedures described in the application WO 96/33979 can be

used to prepare the intermediates used in this invention wherein G_1-G_4 are alkoxyalkylamino groups. The chemical procedures described in the application WO 96/33978 can be used to prepare the intermediates used in this invention wherein G_1-G_4 are aminoalkylamino groups. The chemical procedures described in the application WO 96/33977 can be used to prepare the 3-cyanoquinoline intermediates used in this invention wherein G_1-G_4 are aminoalkylalkoxy groups. Although these applications describe methods for the preparation of certain quinazolines, they are also applicable to the preparation of corresponding substituted quinolines and although they also describe compounds where the indicated functional group have been introduced onto the 6-position of a quinazoline, the same chemistry can be used to introduce the same groups onto positions occupied by any of the G_1-G_4 substituents of the compounds of this invention, represented by compounds with Formulas **2**, **4**, **6**, **15-17**, **26**, **27**, **29**, and **30**.

Methods described in the following publications can also be used to prepare intermediates that are used to prepare the compounds of this invention: Hennequin *et al.*, J. Med. Chem. 42:5369-5389 (1999); Hennequin *et al.*, J. Med. Chem. 45:1300-1312 (2002); Wissner *et al.*, J. Med. Chem. 46:49-63 (2003); Wissner *et al.*, J. Med. Chem., 43:3244-3256 (2002); and Wissner *et al.*, Bioorg. Med. Chem. Lett. 12:2893-2897 (2002).

Representative compounds of this invention were evaluated in several standard pharmacological test procedures that showed that the compounds of this invention possess significant activity as inhibitors of certain tyrosine kinases and function as anti-angiogenic agents. Some of these test procedures are described in patent application, serial no. **(TO BE ASSIGNED)**, entitled "ASSAYS TO IDENTIFY IRREVERSIBLY BINDING INHIBITORS OF RECEPTOR TYROSINE KINASES", by inventors Frank Loganzo, Lee M. Greenberger, Xingzhi Tan and Allan Wissner, filed concurrently herewith.

Based on the activity shown in the standard pharmacological test procedures, the compounds of this invention are therefore useful as antineoplastic agents and as agents for the treatment of other disease states characterized by abnormal, excessive, or otherwise inappropriate blood vessel growth. The test procedures used and results obtained are shown below.

Inhibition of KDR Kinase

Expression of recombinant KDR enzyme

The full cytoplasmic domain of human KDR (VEGF-receptor-2) was cloned by standard reverse transcription / polymerase chain reaction (RT-PCR) using total RNA isolated from human umbilical vein endothelial cells (HUVEC). Total RNA was isolated with the RNAgents Total Isolation System (Promega) and cDNA generated by RT-PCR (SuperScript II RnaseH$^-$ Reverse Transcriptase and Platinum *Pfx* DNA Polymerase, Invitrogen) using primers specific for KDR (GenBank accession NM_002253) beginning at Met-806 [underlined] (5'-ATG GAT CCA GAT GAA CTC CCA TTG) and ending at Val-1356 [underlined] (5'-AAC AGG AGG AGA GCT CAG TGT GGT). Primers were designed with *Hind*III/*Xho*I terminal sites, respectively, to allow for subcloning. The cDNA product was cloned in-frame into the pCMV-Tag4 vector (Stratagene) at the *Hind*III/*Xho*I sites such that a FLAG sequence (DYKDDDDK) is expressed at the C-terminus to allow for protein purification.

Human embryonic kidney (HEK) 293 cells (American Type Culture Collection) were transiently transfected with the KDR-Flag vector and cells were harvested 48 hour post-transfection to confirm protein expression. Stable clones were then selected in geneticin G418 (500 ug/ml) for approximately 3 weeks and used for moderate-scale protein preparations.

Cells (36 x 150 mm dishes of sub-confluent monolayers) were lysed in 72 ml of lysis buffer containing protease inhibitors (50 mM HEPES, 150 mM NaCl, 2 mM EDTA, 1% Igepal CA-630, pH 7.5, 1 mM Na_3VO_4, 1 mM PMSF, 20 KIU/ml aprotinin, 10 ug/ml pepstatin, 10 ug/ml leupeptin) and then centrifuged at 12,000 rpm for 20 minutes at 4°C to remove insoluble debris.

KDR protein was isolated from cell lysate by batch purification on anti-FLAG M2 affinity resin (Sigma) for 2 hour at 4°C followed by sequential washing and centrifugation. Resin was applied to a column and protein eluted with 200 ug/ml FLAG peptide in 50 mM HEPES, 100 mM NaCl, 10% glycerol, 1 mM Na_3VO_4, 1 mM EDTA. Fractions were collected and evaluated for KDR content by SDS-PAGE/ immunoblot analyses using anti-KDR antibody (Dougher, M. and Terman, B.I., *Oncogene* 18: 1619-1627 (1999)) or anti-FLAG M2 antibody (Sigma). KDR purity is typically 20 - 40%. Bovine serum albumin was added to a final concentration of 1

mg/ml and glycerol is added to 50% (v/v). Small-volume aliquots are stored at –70 ° C.

The recombinant cytoplasmic (intracellular) protein product is designated KDR-IC-Flag.

KDR kinase enzyme assay

The kinase activity of KDR-IC-Flag was evaluated using a DELFIA® (dissociation-enhanced lanthanide fluorescent immunoassay) (PerkinElmer Life Sciences, Boston) as described by PerkinElmer and Loganzo, F. and Hardy, C. *American Biotechnology Laboratory* 16:26-28 (1998).

Nunc Maxisorb 96-well plates were coated at room temperature for 1 to 2 hours with 100 µl per well of 25 µg/ml poly(Glu_4-Tyr) peptide (Sigma) in tris-buffered saline (TBS) (25 mM Tris pH 7.2, 150 mM NaCl). Unbound peptide was washed three times with TBS.

KDR-IC-Flag enzyme was diluted (depending on the batch, from 10- to 20-fold) in 0.1% BSA/ 4 mM HEPES. A master mix of enzyme plus kinase buffer was prepared: (per well) 10 µl of diluted enzyme, 10 µl of 5X kinase buffer (5X= 20 mM HEPES, pH 7.4, 5 mM $MnCl_2$, 100 uM Na_3VO_4), and 9 µl of water. Master mix (29 µl) was added to each well and compounds (1 µl) prepared in 100% dimethyl sulfoxide (DMSO) were added to appropriate wells. Test compounds were added as 50X stocks as necessary for single point or dose-response analyses. Controls were done by adding DMSO alone, *i.e.*, no test compound, to wells containing the master mix of enzyme plus kinase buffer.

After 15 minutes at room temperature, ATP/$MgCl_2$ (20 µl of 25 µM ATP, 25 mM $MgCl_2$, 10 mM HEPES, pH 7.4) was added to each well to initiate the reaction. Final concentrations of the assay components were: 10 µM ATP, 10 mM $MgCl_2$, 1 mM $MnCl_2$, 4 mM HEPES, pH 7.4, 20 µM Na_3VO_4, 20 ug/ml BSA, 2% DMSO.

After 40 minutes at room temperature, the liquid was removed and plates were washed three times with TBST (TBS with 0.05% Tween-20). The wells were then incubated for 1 hour at room temperature with 75 µl of approximately 0.1 ug/ml europium-conjugated anti-phosphotyrosine antibody (PT66; PerkinElmer) prepared in Assay Buffer (PerkinElmer). Plates were washed three times with TBST, then incubated for 15 minutes in the dark with 100 µl of Enhancement Solution (PerkinElmer). Plates were read in a Victor-V multi-label counter (PerkinElmer) using

the default europium detection protocol. Percent inhibition or IC_{50} of compounds were calculated by comparison with DMSO-treated control wells. The results are shown in Table 1.

When multiple entries for an inhibitor appear in Table 1, it indicates that the inhibitor was evaluated multiple times using the conditions stated in the table. The data in Table 1 shows that the compounds of this invention are effective inhibitors of KDR kinase and are therefore useful for the treatment of the aforementioned disease states.

Table 1
Inhibition of KDR Kinase

Example	IC50 (nM)	Concentration (nM)	% Inhibition	ATP conc. (μM)
2		100	83	10
2		100	77	10
2		1000	96	10
2		1000	98	1000
2	5.1			10
4		100	3	10
4		100	13	10
4	80.5			10
4	285.2			10
4		1000	15	10
4		1000	12	1000
4	706.5			10
5		100	18	10
5		100	16	10
5		1000	49	10
5		1000	60	1000
7		100	85	10
7		100	83	10
7	2.3			10
7		1000	96	10
7		100	94	10
7		1000	94	10
7		10000	96	10
7		100	96	10
7		1000	96	10
7		10000	97	10
7		100	97	10
7		100	96	10
7		1000	96	10
7		1000	95	10

7		1000	97	1000
7		1000	97	1000
7		1000	97	1000
7	1.3			10
8		1000	82	10
8		100	51	10
8		100	45	10
8		1000	85	10
8	175.1			10
8	199.6			100
8	238.8			1000
8		1000	80	1000
8		1000	76	1000
8	176.7			10
9		1000	58	10
9		100	24	10
9		1000	33	1000
15		100	32	10
15		100	40	10
15	197			10
15	157.2			10
15	154.2			10
15		1000	63	10
15		100	54	10
15		1000	78	10
15	176.6			10
15	321.4			100
15	681.3			1000
15	251.4			1
15	372.8			10
15	789.2			100
15	>1000			
15		1000	42	1000
15		1000	54	1000
15		1000	53	1000
15		100	43	10
15		1000	70	10
17		100	96	10
17		1000	95	10
17		1000	96	1000
18		100	13	10
18		1000	2	10
18		1000	-30	1000
19		100	41	10
19		1000	88	10
19		1000	88	1000
20	17.9			10
20		1000	90	10
20		100	92	10
20		100	80	10

20		1000	94	10
20		1000	97	1000
20		1000	95	1000
22		100	97	10
22		1000	96	10
22		1000	98	1000
24		100	96	10
24		1000	92	10
24		1000	96	1000
25		1000	95	10
25		100	94	10
25		1000	99	1000
25	4.8			10
26		100	83	10
26		100	81	10
26		100	76	10
26		100	70	10
26		100	81	10
26		100	80	10
26		100	82	10
26		100	83	10
26	30			10
26	10			10
26	10			10
26	11.1			10
26	12			10
26	8.1			10
26		1000	96	10
26		1000	95	10
26		1000	96	10
26		1000	95	10
26		1000	93	10
26		1000	94	10
26		1000	93	10
26		100	92	10
26		100	94	10
26		100	91	10
26		100	93	10
26		1000	95	10
26		10000	96	10
26		100	96	10
26		1000	96	10
26		10000	96	10
26	2.3			10
26		100	96	10
26		100	95	10
26		100	97	10
26		1000	95	10
26		1000	95	10
26		1000	95	10

26	5.1			10
26	5.7			100
26	5.2			1000
26	12.7			1
26	7.4			10
26	6			100
26	6.3			1000
26	12.7			1
26	7.4			10
26	6			100
26	6.3			1000
26		1000	97	1000
26		1000	97	1000
26		1000	96	1000
26		1000	96	1000
26		1000	97	1000
26		1000	97	1000
26		1000	98	1000
26		1000	97	1000
26		1000	97	1000
26		1000	97	1000
26		100	93	10
26		1000	96	10
26		100	92	10
26		100	92	10
26		1000	93	10
26		1000	94	10
26	6			10
27		100	63	10
27		100	65	10
27	34.4			10
27		1000	96	10
27		1000	98	1000
28		100	83	10
28		100	84	10
28	12.1			10
28		1000	96	10
28		1000	98	1000
29		100	62	10
29		100	54	10
29	37.7			10
29		1000	92	10
29		1000	95	1000
30		100	83	10
30		100	82	10
30		1000	96	10
30		1000	98	1000
31		100	82	10
31		100	77	10
31		1000	96	10

31		1000	98	1000
32		100	88	10
32		100	83	10
32		1000	96	10
32		100	97	10
32		1000	95	10
32		1000	98	1000
32		1000	97	1000
32	4.8			10
33		100	84	10
33		100	75	10
33		1000	96	10
33		1000	98	1000
34		100	55	10
34		100	37	10
34		1000	95	10
34		1000	97	1000
35		100	87	10
35		100	77	10
35		1000	96	10
35		1000	98	1000
36		100	79	10
36		100	72	10
36		1000	96	10
36		1000	98	1000
37		100	89	10
37		1000	93	10
38		100	93	10
38		1000	95	10
39		100	91	10
39		1000	94	10
39	3.5			10
40		100	92	10
40		1000	94	10
41		100	92	10
41		1000	92	10
41	2			10
42		100	92	10
42		1000	94	10
43		100	45	10
43		1000	89	10
43	121			10
44		100	92	10
44		1000	94	10
45		100	92	10
45		1000	93	10
45	2.6			10
46		100	93	10
46		1000	94	10
47		100	86	10

47		1000	94	10
48		100	86	10
48		1000	93	10
49		100	88	10
49		1000	93	10
49	148.9			10
50		100	93	10
50		1000	94	10
51		100	91	10
51		1000	93	10
52		100	91	10
52		1000	95	10
53		100	90	10
53		1000	94	10
54		100	-2	10
54		1000	10	10
55		100	90	10
55		1000	93	10
55	5.4			10
56		100	69	10
56		1000	81	10
56	62.2			10
71		1000	85	10
71		100	41	10
71		1000	58	1000
71	273.3			10
72	53.7			10
72		1000	93	10
72		100	73	10
72		1000	94	1000
72	72.4			10
73		100	-20	10
73		100	7	10
73	1844			10
73		1000	30	10
73		1000	-2	1000
73	>1000		13	10
74		100	27	10
74		100	37	10
74		1000	89	10
74		1000	84	1000
75		100	47	10
75		100	38	10
75		1000	92	10
75	93			10
75		1000	93	1000
76		100	45	10
76		100	43	10
76		1000	91	10
76		1000	92	10

76		100	60	10
76	75.7			10
76		1000	77	1000
76		1000	97	1000
78	146.5			10
78		1000	90	10
78		1000	62	10
78		100	53	10
78		100	27	10
78	95.9			10
78		1000	74	1000
78		1000	95	1000
78	406.4			10
80		1000	28	10
80		1000	69	10
80		100	11	10
80		100	32	10
80		100	17	10
80		1000	74	10
80		1000	9	1000
80		1000	74	1000
80		1000	67	1000
80	654.2			10
82		1000	30	10
82		100	15	10
82		1000	45	1000
84		100	5	10
84		100	1	10
84		1000	88	10
84		1000	82	1000
85		1000	62	10
85		100	20	10
85		1000	64	1000
86		1000	93	10
86		100	58	10
86	40.7			10
86		1000	96	1000
87		1000	72	10
87		100	19	10
87		1000	85	1000
88		1000	63	10
88		100	28	10
88		1000	48	1000
89		1000	18	10
89		100	11	10
89		1000	-12	1000
90		100	74	10
90		100	82	10
90	30			10
90	7.5			10

90	8.8			10
90		1000	94	10
90		100	92	10
90		100	95	10
90		1000	96	10
90		1000	95	10
90		1000	96	1000
90		1000	97	1000
90		1000	97	1000
91		100	76	10
91		100	85	10
91	18.9			10
91		1000	96	10
91		1000	97	1000
92		1000	93	10
92		100	92	10
92		1000	97	1000
93		100	84	10
93		100	71	10
93		100	89	10
93		100	81	10
93	30			10
93	2.8			10
93	2.8			10
93	4.2			10
93		1000	96	10
93		1000	95	10
93		1000	98	1000
93		1000	95	1000
94		1000	94	10
94		100	93	10
94		1000	96	1000
94	4			10
95		100	85	10
95		100	83	10
95	3.7			10
95		1000	96	10
95		1000	98	1000
96		1000	91	10
96		100	67	10
96		1000	96	1000
96	52.8			10
97		1000	91	10
97		100	38	10
97		1000	95	1000
99		1000	92	10
99		100	93	10
99		1000	96	1000
101		100	30	10
101		100	21	10

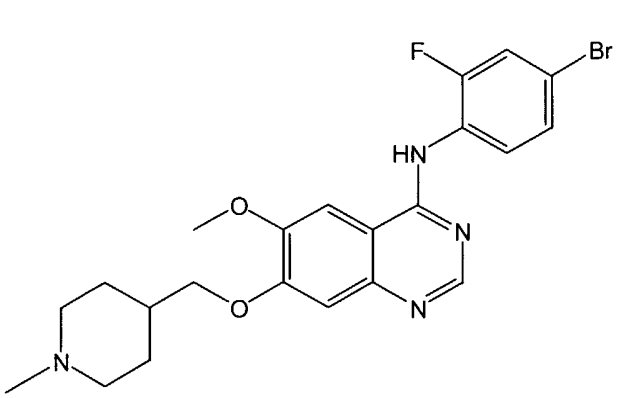
101	492			10
101		1000	66	10
101	375.1			10
101		1000	69	1000
106		100	23	10
106		100	-12	10
106		100	16	10
106		100	20	10
106	339			10
106		1000	69	10
106		1000	77	10
106		1000	70	1000
106		1000	69	1000

Irreversible Inhibition of KDR Kinase

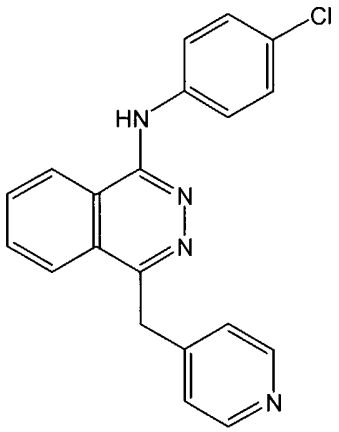
Enzyme assay wash-out experiments

To determine if compounds bound irreversibly to enzyme, plates were washed after the enzyme plus compound pre-incubation step and prior to the addition of ATP. Parallel plates were tested wherein one plate was processed exactly as above while a second plate was washed three times in 100 µl of 4 mM HEPES, pH 7.4, to remove unbound compound. 1X Kinase buffer (30 µl of 1 mM $MnCl_2$, 4 mM HEPES, pH 7.4, 20 µM Na_3VO_4) and 20 µl of ATP/$MgCl_2$ were added to the wash-out plate. Detection of phosphotyrosinylated peptide for both plates was performed as described above. "Irreversible" compounds are considered to be those where the IC_{50} differs by approximately three-fold or less between the unwashed and the wash-out plates. The results are shown in Table 2.

For each inhibitor shown in Table 2, two IC_{50} determinations are shown, one under normal conditions and the other where an intermediate wash-out step is carried out. If there was little change in the IC_{50} value in the wash-out experiment (3-fold or less) compared to the experiment where there was no wash-out, then it was determined that the compound is as an irreversible binding inhibitor or is behaving like an irreversible binding inhibitor. If there was a large increase in the IC_{50} value in the wash-out experiment compared to the experiment where there was no wash-out, then it was determined that the compound was behaving as a conventional reversible binding inhibitor. In order to determine the behavior of conventional reversible binding KDR inhibitors in this test, the reference inhibitors Compound A and Compound B were also tested. Compound A is a quinazoline-based inhibitor reported to be a conventional ATP competitive inhibitor described in Hennequin *et al.*, J. Med. Chem. 42:5369-5389 (1999) and Hennequin *et al.*, J. Med. Chem. 45:1300-1312 (2002). Compound B is a phthalazine-based inhibitor reported to be a conventional ATP competitive inhibitor (Bold *et al.*, J. Med. Chem. 43:2310-2323 (2000).



Compound A



Compound B

For the reference inhibitors Compound A and Compound B, it is evident from the data in Table 2 that there is a large increase in the IC_{50} values in the experiment where there is a wash-out step compared to the experiment with no wash-out step indicating that these compounds are functioning as conventional reversible binding inhibitors. In contrast, for many of the compounds of this invention, there is a minimal change in the IC_{50} values between the wash-out and no wash-out experiments suggesting that these inhibitors function as irreversible binding inhibitors of the enzyme or like irreversible binding inhibitors. Some of the compounds of this invention, such as the compounds of Examples 4 and 15, appear to act like reversible binding inhibitors but are nevertheless potent.

The data in Table 2 again shows that the compounds of this invention are effective inhibitors of KDR kinase that can differ fundamentally from other KDR kinase inhibitors known previously in the art in that they may function as irreversible binding inhibitors of the enzyme or like irreversible binding inhibitors. They therefore are useful for the treatment of the aforementioned disease states.

Table 2
Inhibition of KDR Kinase with and without the addition of a washout step

Example	IC_{50} (nM)	Experiment
4	285.2	no wash
4	>1000	wash out
7	2.3	no wash
7	1.2	wash out
15	154.2	no wash
15	>1000	wash out
93	3.7	no wash

93	5.2	wash out
86	40.7	no wash
86	57.1	wash out
78	146.5	no wash
78	513.5	wash out
78	95.9	no wash
78	150	wash out
90	8.8	no wash
90	18.5	wash out
101	375.1	no wash
101	693.7	wash out
91	18.9	no wash
91	18.9	wash out
76	75.7	no wash
76	155	wash out
75	93	no wash
75	160.9	wash out
95	4.2	no wash
95	6.5	wash out
26	12	no wash
26	27.5	wash out
26	8.1	no wash
26	14.1	wash out
26	2.3	no wash
26	5.3	wash out
20	17.9	no wash
20	33.1	wash out
72	53.7	no wash
72	73.7	wash out
105	483	no wash
105	692.5	wash out
108	59.8	no wash
108	82.6	wash out
153	69.8	no wash
153	119.1	wash out
184	5.9	no wash
184	14.2	wash out
213	4.7	no wash
213	16.9	wash out
221	603.6	no wash
221	832.1	wash out
222	78.6	no wash
222	127.5	wash out
Compound A	122.8	no wash
Compound A	>1000	wash out
Compound B	438.5	no wash
Compound B	>1000	wash out

Inhibition of KDR Kinase Autophosphorylation in KDR15 Cells
Cellular autophosphorylation assay

Human embryonic kidney 293 cells were transfected with full length KDR and designated KDR15 cells. Cells were maintained in 10% fetal calf serum (FCS) in DMEM (LifeTechnologies), penicillin/ streptomycin, plus 0.4 µg/ml puromycin. Cells were plated in 24-well dishes (approximately 4000 cells per well) and allowed to adhere for 1 day. Compounds prepared in DMSO were diluted into cold serum-free DMEM media at appropriate final concentrations. Growth media was aspirated from each well and the cells were washed one time with serum-free DMEM. The serum-free media was replaced with 0.5 ml of compound-containing serum-free media. Cells were incubated for 1 hour on ice, then 55 µl of 500 ng/ml VEGF (final 50 ng/ml; $VEGF_{165}$, R&D Systems) was added to each well and incubated for 30 minutes on ice. Cells were resuspended during VEGF incubation and transferred to 1.5 ml tubes, then centrifuged at 12,000 rpm for 10 minutes and the supernatants discarded. Pellets were lysed in 50 µl of NP40 lysis buffer (150 mM NaCl, 50 mM Tris, pH 7.5, 2 mM EDTA, 1% NP-40 [Ipegal CA-630], 1 mM Na_3VO_4, 1 mM PMSF, 20 KIU/ml aprotinin, 1 µg/ml pepstatin, 0.5 ug/ml leupeptin). Lysates were centrifuged for 10 minutes at 12,000 rpm at 4 °C and the supernatants transferred to fresh tubes and frozen until use.

Equal volumes of lysates were fractionated by SDS-PAGE (7.5% acrylamide or 4-15% gradient) and transferred to PVDF membranes (BioRad). Blots were blocked in 8% BSA/TBST for 1 hour at room temperature, then incubated overnight at 4°C with 1:1000 anti-phospho-KDR-Y996 antibody (specifically detects phosphorylated tyrosine-996 on KDR; Cell Signaling) in 4% BSA/TBST. Blots were washed three times with TBST, followed by incubation with secondary antibody (1:1000 HRP-conjugated goat anti-rabbit IgG) in 5% milk/TBST. Blots were washed six times, 10 minutes each in TBST, then detected with enhanced chemiluminescent reagents (Amersham) and exposed to film. Autoradiographs were quantified by scanning on a FluorS imager (BioRad) and data normalized to untreated controls. To confirm equal loading of protein, blots were occasionally stripped in SDS/Tris at 50°C, followed by immunoblot analysis in 1:1000 anti-KDR antibody in 5% milk/TBST. The results are shown in Table 3.

When multiple entries for an inhibitor appear in Table 3, it indicates that the inhibitor was evaluated multiple times using the conditions stated in the table. The

data in Table 3 shows that the compounds of this invention are effective inhibitors of KDR kinase in intact cells and are therefore useful for the treatment of the aforementioned disease states.

Table 3

Inhibition of KDR Kinase Autophosphorylation in KDR15 Cells

Example	IC50 (nM)	Compound conc. (nM)	% Inhibition
2		1000	18
2		1000	12
4		1000	100
4		1000	106
4	<62.5		
4	<15.6		
5		1000	56
7	250		
7		1000	22
7		1000	41
7		1000	35
7		1000	41
7		1000	38
7		1000	72
7		1000	60
7		1000	114
7		1000	95
7		1000	93
8	172		
8		1000	65
8		1000	54
8		1000	82
8		1000	93
8		1000	45
8		1000	103
8		1000	98
8		1000	97
8		500	25
8		1000	102
8		1000	86
9		1000	55
9		1000	94
15	<15.6		
15	<62.5		
15		1000	108
15		200	61
15		1000	73
15		1000	99
15		1000	100

15		1000	89
15		1000	104
15		1000	103
15		500	89
15		1000	95
15		1000	110
15		1000	69
15		1000	111
15	<62.5		
17		1000	16
18		1000	27
19		1000	-10
20		1000	5
20		1000	-1
20		1000	23
22		1000	31
24		1000	0
25	1000		
25		1000	64
25		1000	49
25		1000	60
26	207		
26	250		
26	221		
26		1000	50
26		1000	138
26		200	84
26		600	94
26		200	36
26		1000	83
26		1000	69
26		1000	90
26		1000	80
26		1000	85
26		1000	87
26		1000	62
26		1000	67
26		1000	31
26		500	57
26		500	63
26		1000	91
26		1000	91
26		1000	68
26		1000	92
26		1000	75
26		1000	29
26		1000	113
26	<62.5		
27		1000	25
28		1000	35

29		1000	30
30		1000	54
30		1000	23
31		1000	37
31		1000	18
32		1000	62
32		1000	32
33		1000	19
34		1000	12
35		1000	39
36		1000	27
36		1000	70
36		1000	25
37		1000	11
38		1000	97
39		1000	140
40		1000	110
41		1000	120
42		1000	64
105		1000	124
44		1000	81
45		1000	99
46		1000	79
47		1000	66
48		1000	74
49		1000	90
50		1000	100
51		1000	105
52		1000	94
53		1000	79
54		1000	-5
71		1000	26
71		1000	2
72		1000	10
72		1000	-6
72		1000	-4
73	<15.6		
73		1000	90
73		1000	143
73		1000	113
74		1000	4
75		1000	45
75		1000	61
76	1000		
76		1000	75
76		1000	42
76		1000	48
76		1000	47
76		1000	31
76		1000	60

78		1000	3
78		1000	61
78		1000	117
78		1000	61
80	<62.5		
80		1000	92
80		1000	52
80		1000	58
80		1000	15
80		1000	52
80		1000	21
80		1000	71
82		1000	12
84		1000	4
86		1000	5
86		1000	-17
88		1000	32
90	236		
90		1000	53
90		1000	84
90		200	29
90		1000	29
90		1000	35
90		1000	52
90		1000	34
90		1000	54
90		1000	75
90		1000	55
90		1000	42
90		1000	73
90	147		
91		1000	55
92		1000	-22
92		1000	29
93	184		
93		1000	49
93		1000	131
93		1000	82
93		1000	40
93		1000	35
94	386		
94		1000	40
96		1000	26
94		1000	54
96		1000	22
94		1000	64
97		1000	44
97		1000	15
99		1000	20
99		1000	29

101		1000	112
101		1000	71
101		1000	36
101	219		
106		1000	78
106		1000	100
106		1000	59
106	1000		
105	4-15	1000	
108		1000	68
153		1000	17
184		1000	0
213	236-400	1000	
221	15	1000	
222	175-210	1000	

Inhibition of Cellular VEGF-dependent HUVEC proliferation

HUVEC proliferation assay

Human umbilical vein endothelial cells (HUVEC), obtained from Clonetics, were maintained at 37°C in EGM2 media (Endothelial Cell Basal Media (EBM) supplemented with components suggested by the distributor: 2% serum, VEGF, hFGFb, EGF, heparin, R3-IGF-1, hydrocortisone, gentamicin sulfate and penicillin/streptomycin). Cells were plated into 96-well dishes (4000 cells per well) and allowed to attach overnight. HUVEC were rinsed one time with 100 µl of EBMc-V (EBM supplemented with all above components except serum or VEGF), then 50 ul of EBMc-V was added to cells. Compounds were prepared at 200X stocks in DMSO, diluted into EBMc-V media as 4X stocks, then 50 ul added to appropriate wells. Finally, 100 µl of 2X VEGF (100 ng/ml prepared in EBMc-V; final 50 ng/ml VEGF) was added to all VEGF-treated wells. EBMc-V (no VEGF) was added to negative control wells. Parallel compound-treated plates were prepared except that 100 µl of EGM2 media containing 2% serum but lacking VEGF (EGMc-V) was added. Cells were incubated for 4 – 5 days at 37°C.

DNA synthesis was assessed by thymidine incorporation. Cells were incubated for 5 hours in 1 µCi of [^{3}H]-thymidine (PerkinElmer) by addition of 10 ul of 0.1 µCi/ul thymidine prepared in PBS to each well. After incubation, media was aspirated and the cells trypsinized and collected onto a mat using a vacuum-based Micro Cell Harvester (Skatron). [^{3}H]-thymidine was counted in a liquid scintillation counter. Compounds evaluated for ability to inhibit VEGF-dependent growth of human umbilical vein endothelial cells (HUVEC). The results are shown in Table 4.

When multiple entries for an inhibitor appear in Table 4, it indicates that the inhibitor was evaluated multiple times using the conditions stated in the table. The data in Table 4 shows that the compounds of this invention are effective inhibitors of VEGF-dependent growth of human umbilical vein endothelial cells (HUVEC) and therefore can function as anti-angiogenic agents and are useful for the treatment of the aforementioned disease states.

Table 4
Inhibition VEGF-dependent Growth of Human Umbilical Vein Endothelial Cells (HUVEC)

Example	Conc. (nM)	% Inhibition
7	100	23
7	1000	79
7	10000	97
7	100	23
7	1000	79
7	10000	97
8	100	-18
8	1000	30
8	10000	87
8	100	35
8	1000	51
8	10000	98
8	100	21
8	1000	37
8	10000	89
8	100	-18
8	1000	30
8	10000	87
8	100	35
8	1000	51
8	10000	98
8	100	21
8	1000	37
8	10000	89
15	100	24
15	1000	86
15	10000	96
15	100	40
15	1000	95
15	10000	98
15	100	42
15	1000	67
15	10000	97
15	100	24
15	1000	86
15	10000	96
15	100	40
15	1000	95
15	10000	98
15	100	42
15	1000	67
15	10000	97
25	100	29
25	1000	51

25	10000	81
25	100	29
25	1000	51
25	10000	81
26	100	-5
26	1000	12
26	10000	89
26	100	10
26	1000	15
26	10000	96
26	100	43
26	1000	61
26	10000	99
26	100	9
26	1000	34
26	10000	95
26	100	10
26	1000	13
26	10000	87
26	100	7
26	1000	20
26	10000	91
26	100	-5
26	1000	12
26	10000	89
26	100	10
26	1000	15
26	10000	96
26	100	43
26	1000	61
26	10000	99
26	100	9
26	1000	34
26	10000	95
26	100	10
26	1000	13
26	10000	87
26	100	7
26	1000	20
26	10000	91
32	100	10
32	1000	41
32	10000	98
32	100	10
32	1000	41
32	10000	98
39	100	18
39	1000	58
39	10000	99
39	100	18

39	1000	58
39	10000	99
41	100	-5
41	1000	42
41	10000	98
41	100	-5
41	1000	42
41	10000	98
105	100	-1
105	1000	36
105	10000	88
105	100	-1
43	1000	36
43	10000	88
55	100	7
55	1000	61
55	10000	99
55	100	7
55	1000	61
55	10000	99
75	100	-22
75	1000	41
75	10000	91
75	100	-22
75	1000	41
75	10000	91
76	100	-30
76	1000	63
76	10000	96
76	100	-30
76	1000	63
76	10000	96
78	100	6
78	1000	71
78	10000	94
78	100	9
78	1000	81
78	10000	99
78	100	9
78	1000	25
78	10000	74
78	100	6
78	1000	71
78	10000	94
78	100	9
78	1000	81
78	10000	99
78	100	9
78	1000	25
78	10000	74

80	100	39
80	1000	85
80	10000	97
80	100	39
80	1000	85
80	10000	97
90	100	22
90	1000	15
90	10000	95
90	100	22
90	1000	15
90	10000	95
91	100	0
91	1000	15
91	10000	93
91	100	0
91	1000	15
91	10000	93
94	100	28
94	1000	60
94	10000	94
94	100	20
94	1000	52
94	10000	78
94	100	28
94	1000	60
94	10000	94
94	100	20
94	1000	52
94	10000	78
101	100	12
101	1000	36
101	10000	94
101	100	12
101	1000	36
101	10000	94

In vivo Evaluation of the Compounds of Examples 26, 105 and 190

The compound described in Example 26 was evaluated *in vivo* using standard pharmacological test procedures which measures the ability to inhibit the growth of human tumor xenografts. Human colon carcinoma DLD-1 cells (American Type Culture Collection, Rockville, Maryland) were grown in tissue culture in DMEM (Gibco/BRL, Gaithersburg, MD) supplemented with 10% FBS (Gemini Bio-Products Inc., Calabasas, CA). Athymic *nu/nu* female mice (Charles River, Wilmington, MA) were injected subcutaneously (SC) in the flank area with 6 x 10^6 DLD-1 cells. When tumors attained a mass of between 75 and 100 mg, the mice were randomly assigned into treatment groups with 5 animals per group. Animals were treated orally (PO) once daily on days 1 through 20 post staging (day zero) with a dose range (50 to 100 mg/kg/dose) of compound prepared in 0.5% Methocel/ 0.5% Tween 80 or 0.5% Methocel/ 0.4% Tween 80 as the vehicle control. Tumor mass was determined every 7 days [(length X width^2)/2] for 21 days post-staging. Relative tumor growth (mean tumor mass on days 7, 14 and 21 divided by the mean tumor mass on day zero) was determined for each treatment group. The results are shown in Table 5.

The results in Table 5 show that after the 21-day course of the experiment the tumors in the drug treated animals are much smaller than those in the animals that did not receive the drug, indicating that the compounds of this invention are useful anti-tumor agents for the treatment of cancer.

Table 5

The Effect of the Compound of Example 26 on the Growth of Human Colon Carcinoma DLD1 in the Nude Mouse Model

a	b	c	d	b	c	d	b	c	d	e
Drug Treat-ment mg/kg/ dose	Day 7	% T/C	(p)	Day 14	% T/C	(p)	Day 21	% T/C	(p)	S/T
Saline (control)	4.99			11.14			17.21			10/10
Ex. 26 (100 PO)	3.36	67	0.09	6.10	55	0.04	8.80	51	0.06	5/5
Ex. 26 (50 PO)	4.21	84	0.25	6.93	62	0.08	10.50	61	0.12	5/5

a) The compound is administered on days 1 through 20.

b) Relative Tumor Growth = Mean Tumor Mass on Day 7, 14, 21 / Mean Tumor Mass on Day 0

c) % T/C = Relative Tumor Growth of Treated Group / Relative Tumor Growth of Placebo Group X 100

d) Statistical Analysis (Student's T-test) of Log Relative Tumor Growth. A p-value ($p \leq 0.05$) indicates a statistically significant reduction in Relative Tumor Growth of Treated Group compared to the Placebo control.

e) S/T = # of Survivors/# of Treated on Day +21 post tumor staging.

The compounds described in Examples 105 and 190 were also tested using the above protocol. The results are shown in Table 6.

The results in Table 6 also show that after the 21-day course of the experiment, the tumors in the drug treated animals are much smaller than those in the animals that did not receive the drug, indicating that the compounds of this invention are useful anti-tumor agents for the treatment of cancer.

Table 6

The Effect of the Compounds of Examples 105 and 190 on the Growth of Human Colon Carcinoma DLD1 in the Nude Mouse Model

a	b	c	d	b	c	d	b	c	d
Drug Treatment mg/kg/dose	Day 7	% T/C	(p)	Day 14	% T/C	(p)	Day 21	% T/C	(p)
0/5% Methocel 0/4% Tween 80	2.58			7.86			14.22		
Ex. 190	1.58	61	0.35	7.41	94	0.48	10.74	76	0.35
Ex.150	1.62	63	0.33	6.45	82	0.39	12.54	88	0.39

a) Compounds were adminstered on days 1 through 20.

b) Relative Tumor Growth = Mean Tumor Mass on Day 7, 14, 21, 28 / Mean Tumor Mass on Day 0

c) % T/C = Relative Tumor Growth of Treated Group / Relative Tumor Growth of Placebo Group X 100

d) Statistical Analysis (Student's T-test) of Log Relative Tumor Growth. A p-value ($p \leq 0.05$) indicates a statistically significant reduction in Relative Tumor Growth of Treated Group compared to the Placebo Control.

The compositions and dosage forms of the invention are administered to a patient in need of treatment or prevention of a condition characterized, at least in part by, excessive, abnormal or inappropriate angiogenesis. The patient may be an animal, and is preferably a mammal, and more preferably, human.

The compounds of this invention may be formulated neat or may be combined with one or more pharmaceutically acceptable carriers for administration, as example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules (including time release and sustained release formulations), dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parentally in the form of sterile injectable solution or suspension containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 0.05 up to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 1000 mg/kg of body weight, optionally given in divided doses two to four times a day, or in sustained release form. The total daily dosage is projected to be from about 1 to 1000 mg, preferably from about 2 to 500 mg. Dosage forms suitable for internal use comprise from about 0.5 to 1000 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The compounds of this invention may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of

the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy injectability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

For the treatment of cancer, the compounds of this invention can be administered in combination with other antitumor substances or with radiation therapy. These other substances or radiation treatments can be given at the same or at different times as the compounds of this invention. These combined therapies may effect synergy and result in improved efficacy. For example, the compounds of this invention can be used in combination with mitotic inhibitors such as taxol or vinblastine, alkylating agents such as cisplatin or cyclophosamide, antimetabolites such as 5-fluorouracil or hydroxyurea, DNA intercalators such as adriamycin or

bleomycin, topoisomerase inhibitors such as etoposide or camptothecin, antiangiogenic agents such as angiostatin, and antiestrogens such as tamoxifen.

The compounds of this invention are tyrosine kinase inhibitors and can be used in combination with other tyrosine kinase inhibitors. The compounds of this invention can be used in combination with antibodies that target deregulated receptors involved in malignancy.

The preparation of representative examples of the compounds of this invention is described below.

Example 1

N-(4-chloro-2,5-dimethoxyphenyl)-6,7-dimethoxy-4-quinazolinamine

A mixture of 15.0 g (84.2 mmol) of 2-amino-4,5-dimethoxy-benzonitrile and 13.3 g (112 mmol) of dimethylformamide dimethylacetal was stirred at 100 °C for 2 hours. The excess reagents were removed at reduced pressure at 100 °C. The residue was dissolved in methylene chloride and the solution was passed through a short column of Magnesol™ eluting with methylene chloride. The solvent was removed and ether was added. After storage in the cold, the ether was decanted from an orange solid that was dried under vacuum giving 17.7 g of amidine intermediate, N'-(2-cyano-4,5-dimethoxy-phenyl)-N,N-dimethyl-formamidine. A 3 g (12.9 mmol) portion of this intermediate and 2.5 (13.5 mmol) of 4-chloro-2,5-dimethoxy-aniline in 12 ml of acetic acid was refluxed for 1.5 hours. The mixture was cooled to room temperature and ether was added. Solid was collected and washed with ether giving 3.9 g of the title compound: mass spectrum (electrospray, m/e): M+H 376.16.

Example 2

2-chloro-5-[(6,7-dimethoxy-4-quinazolinyl)amino]benzo-1,4-quinone

A solution of 2 g (5.32 mmol) of N-(4-chloro-2,5-dimethoxyphenyl)-6,7-dimethoxy-4-quinazolinamine in 70 ml acetonitrile and 10 ml of water was prepared by warming on a steam bath. While still slightly warm, 5.84 g (10.6 mmol) of ceric ammonium nitrate was added over 5 minutes. After stirring 1 hour, the solid was collected and washed several times with water and ether. The solid was refluxed in acetonitrile and the mixture was cooled. Solid was collected giving 1.38 g of the title compound as a red crystalline solid: mass spectrum (electrospray, m/e): M+H 346.07.

Example 3

5-(6,7-dimethoxy-quinazolin-4-ylamino)-2-methyl-phenol

A mixture of 3.0 g of 4-chloro-6,7-dimethoxy-quinazoline (12.9 mmol) and 1.66 g (13.5 mmol) of 3-hydroxy-4-methyl aniline was refluxed in 12 ml of acetic acid for 1.5 hours. The mixture was cooled and diluted with an equal volume of ether. The solid was collected and washed with ether yielding 4.0 g of the title compound.

Example 4

2-[(6,7-dimethoxy-4-quinazolinyl)amino]-5-methylbenzo-1,4-quinone

To a solution of 2.38 g (22.5 mmol) of sodium carbonate and 22.5 ml of 1 N sodium hydroxide in 176 ml of water, 3.5 g (11.2 mmol) of 5-(6,7-dimethoxy-quinazolin-4-ylamino)-2-methyl-phenol and 70 ml of ethyl acetate was added. The mixture was stirred as 9 g of Fremy's salt was added over 10 minutes. The mixture was then stirred overnight. The mixture was neutralized with solid ammonium chloride and extracted with a THF-ethyl acetate mixture. The organic solution was dried over magnesium sulfate and filtered through a short column of Magnesol™. The solvent was removed and the residue was refluxed in 70 ml of acetonitile. The mixture was cooled to room temperature and the solid was collected and washed with ether, yielding 1.8 g of the title compound as a red powder: mass spectrum (electrospray, m/e): M+H 326.10

Example 5

4-[(6,7-dimethoxy-4-quinazolinyl)amino]-1-methyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione

A suspension of 1.2 g (3.7 mmol) of 2-[(6,7-dimethoxy-4-quinazolinyl)amino]-5-methylbenzo-1,4-quinone in 70 ml of acetonitrile and 10 ml of water containing 1.55 g (18.4 mmol) of sodium bicarbonate was stirred as 2.09 g of 30% hydrogen peroxide was added. After 4 hours, the solid was collected via filtration and washed with water and then with ether. The solid was dried under vacuum at 90°C yielding the title compound as a yellow powder: mass spectrum (electrospray, m/e): M+H 342.11.

Example 6

3-[(6,7-dimethoxy-4-quinazolinyl)amino]-5-methylphenol

A mixture of 3.0 g of 5-(6,7-dimethoxy-quinazolin-4-ylamino)-2-methyl-phenol (12.9 mmol) and 1.66 g (13.5 mmol) of 3-hydroxy-5-methyl aniline was refluxed in 12 ml of acetic acid for 1.5 hour. The mixture was cooled and diluted with an equal volume of ether. The solid was collected and washed with dilute sodium bicarbonate and then with water. The solid was boiled in methanol and then cooled and collected giving 1.1 g of the title compound: mass spectrum (electrospray, m/e): M+H 312.16.

Example 7

2-[(6,7-dimethoxy-4-quinazolinyl)amino]-6-methylbenzo-1,4-quinone

To a solution of 1.1 g (10.4 mmol) of sodium carbonate and 8 ml of 1 N sodium hydroxide in 125 ml of water, 2.5 g (8 mmol) of 3-[(6,7-dimethoxy-4-quinazolinyl)amino]-5-methylphenol and 50 ml of ethyl acetate were added. The mixture was stirred as 6.5 g of Fremy's salt was added over 10 minutes. The mixture was then stirred 2 hours. The mixture was neutralized with solid ammonium chloride and extracted with ethyl acetate. The organic solution was dried over magnesium sulfate and filtered through a short column of Magnesol™. The solvent was removed and the residue was refluxed in 70 ml of acetonitile. The mixture was concentrated, cooled to room temperature and diluted with ether. The solid was collected and washed with ether yielding 0.31 g of the title compound as a red powder: mass spectrum (electrospray, m/e): M+H 326.10

Example 8

2-[(6,7-dimethoxy-4-quinazolinyl)amino]-5-ethylbenzo-1,4-quinone

The title compound was prepared from N-(4-ethyl-2,5-dimethoxyphenyl)-6,7-dimethoxy-4-quinazolinamine using the method described above in Example 2. The N-(4-ethyl-2,5-dimethoxyphenyl)-6,7-dimethoxy-4-quinazolinamine is prepared as described above in Example 1: mass spectrum (electrospray, m/e): M+H 340.14

Example 9

2-[(6,7-dimethoxy-4-quinazolinyl)amino]-5-isopropylbenzo-1,4-quinone

The title compound was prepared from N-(4-isopropyl-2,5-dimethoxyphenyl)-6,7-dimethoxy-4-quinazolinamine using the method described above in Example 2. The N-(4-isopropyl-2,5-dimethoxyphenyl)-6,7-dimethoxy-4-quinazolinamine was prepared as described above in Example 1: mass spectrum (electrospray, m/e): M+H 354.0.

Example 10

3-methoxy-4-(2-methoxyethoxy)benzonitrile

To a suspension of 7.5 g (187.7 mmol) of 60% sodium hydride in 100 ml of dimethylformamide (DMF), 24.2 g (174.3 mmol) of 1-bromo-2-methoxy-ethane was added. A solution of 20 g (134.1 mmol) of 4-hydroxy-3-methoxy-benzonitrile in 100 ml DMF was added dropwise over 20 minutes. The mixture was stirred at 70 °C for 5.5 hours and at room temperature overnight. The mixture was poured into water. The solid was collected and washed with water and hexanes yielding 19.5 g of the title compound as a white solid: mass spectrum (electrospray, m/e): M+H 207.00.

Example 11

5-methoxy-4-(2-methoxyethoxy)-2-nitrobenzonitrile

To a stirred solution of 16.7 g (80.6 mmol) of 3-methoxy-4-(2-methoxyethoxy)benzonitrile in 100 ml of trifluoroacetic anhydride and 70 ml of chloroform, 9.7 g (120.9 mmol) of solid ammonium nitrate was added portionwise over 10 minutes. The solid was separated and the mixture was warmed to a gentle boil. After 2 hours, the mixture was diluted with hexanes and the solid was collected. The solid was washed with hexanes, water, dilute sodium bicarbonate solution and then with water. This solid was air dried to yield 18.4 g of the title compound as a light yellow solid : mass spectrum (electrospray, m/e): M+H 251.97

Example 12

2-amino-5-methoxy-4-(2-methoxyethoxy)benzonitrile

To a mixture of 17 g (67.4 mmol) of 5-methoxy-4-(2-methoxyethoxy)-2-nitrobenzonitrile, 83 g (1 mol) of cyclohexene in 180 ml of ethyl acetate, and 180 ml of methanol, 1.7 g of 10% palladium on carbon catalyst was added. The mixture was stirred at reflux for 4 hours. The mixture was filtered and the solvent was evaporated. The residue was boiled in ethanol, cooled to 35°C, and filtered from a

solid that was discarded. The solvent was evaporated from the filtrate and the residue was recrystallized from a mixture of carbon tetrachloride and hexanes yielding 7.5 g of the title compound: mass spectrum (electrospray, m/e): M+H 223.15

Example 13

N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide

A mixture of 7.45 g (33.5 mmol) of 2-amino-5-methoxy-4-(2-methoxyethoxy)benzonitrile and 5.3 g (44.6 mmol) of dimethylformamide dimethylacetal was heated at 100°C for 2 hours. Excess reagent was removed at reduced pressure leaving a solid which was washed with ether-hexanes 1:1 yielding 8.8 g of the title compound: mass spectrum (electrospray, m/e): M+H 278.16

Example 14

5-{[6-methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]amino}-2-methylphenol

A mixture of 3 g (10.82 mmol) of N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide and 1.4 g (11.36 mmol) of 3-hydroxy-4-methyl aniline was heated in 12 ml of acetic acid for 1 hour 15 minutes. The mixture was cooled and diluted with 35 ml of ether. After stirring, solid was collected yielding 3.8 g of the title compound as a light yellow solid: mass spectrum (electrospray, m/e): M+H 356.15.

Example 15

2-{[6-methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]amino}-5-methylbenzo-1,4-quinone

A mixture of 3.7 g (10.4 mmol) of 5-{[6-methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]amino}-2-methylphenol, 1.1 g of sodium carbonate, 13 ml of 1 N sodium hydroxide, and 8.38 g (31.2 mmol) of Fremy's salt was stirred at room temperature for 17 hours. To this mixture, 70 ml of THF was added and the mixture was stirred at 50°C for 2 hours. The organic layer with suspended solid was separated and filtered. The solid was washed with water and ethyl acetate. This was recrystallized from a mixture of ethyl acetate, THF and methanol yielding the title compound as red needles: mass spectrum (electrospray, m/e): M+H 370.14.

Example 16

6-methoxy-7-(2-methoxyethoxy)-N-(2,3,5-trimethoxyphenyl)quinazolin-4-amine

A mixture of 8 g (28.85 mmol) of N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide and 5.8 g (31.7 mmol) of 2,3,5-trimethyloxyaniline (Monatsh Chem. 20:398 (1899) and Chem. Ber. 408 (1948)) was heated in 35 ml of acetic acid for 1 hour. The mixture was cooled and diluted with ether. After stirring, solid was collected and washed with ether yielding 9.05 g of the title compound as a solid: mass spectrum (electrospray, m/e): M+H 416.10.

Example 17

2-methoxy-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 8.65 g (20.8 mmol) of 6-methoxy-7-(2-methoxyethoxy)-N-(2,3,5-trimethoxyphenyl)quinazolin-4-amine in 261 ml acetonitrile and 39 ml of water was prepared by warming on a steam bath. While still slightly warm, 34.24 g (62.5 mmol) of ceric ammonium nitrate was added over 15 minutes. After stirring for 1 hour 10 minutes, the mixture was poured into water and extracted with methylene chloride. The solution was dried over magnesium sulfate and filtered through a short column of Magnesol™. The solvent was evaporated. The solid residue was refluxed in ethyl acetate and the mixture was cooled. Solid was collected giving 2.27 g of the title compound as a red crystalline solid: mass spectrum (electrospray, m/e): M+H 386.10.

Example 18

5-methoxy-3-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-2-(phenylthio)benzo-1,4-quinone

A solution of 0.45 g (1.17 mmol) of 2-methoxy-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone in 62 ml of acetronitrile was prepared by boiling. While still warm, a solution of 0.12 g (1.28 mmol) of thiophenol in 12 ml of acetonitrile was added. After stirring for 1 hour, 0.277 g (1.34 mmol) of DDQ was added. After 30 minutes, the mixture was diluted with 500 ml of methylene chloride. The solution was washed with dilute sodium carbonate and then with water. The solution was dried over magnesium sulfate and passed through a short column

of Magnesol™. The product was eluted from the column using ethyl acetate-methanol 9:1. The solvent was removed from the combined product fractions and recrystallized from acetonitrile-ether to yield 0.51 g of the title compound as an orange solid: mass spectrum (electrospray, m/e): M+H 494.10.

Example 19

2-(benzylthio)-5-methoxy-3-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared from 2-methoxy-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and benzyl mercaptan using the method decribed in Example 18 above using a 2.5 hour initial reaction time. The title compound was obtained as a red powder: mass spectrum (electrospray, m/e): M+H 508.10.

Example 20

3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-2-(1,3-thiazol-5-ylthio)benzo-1,4-quinone

This compound was prepared from 2-methoxy-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and thiazole-2-thiol using the method decribed in Example 18 above using a 10 hr initial reaction time at 100°C. The title compound was obtained as a red powder: mass spectrum (electrospray, m/e): M+H 501.1.

Example 21

N-(3,4-dichloro-2,5-dimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy)quinazolin-4-amine

A mixture of 6.4 g (23 mmol) of N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide, 2.1 g (25.4 mmol) of sodium acetate and 6.56 g (25.4 mmol) of 3,4-dichloro-2,5-dimethoxy aniline hydrochloride was heated in 27 ml of acetic acid for 1 hour. The mixture was cooled and diluted with ether. After stirring, the solid was collected and washed with ether. The solid was boiled in isopropanol, cooled, and collected, yielding 3.9 g of the title compound as a solid: mass spectrum (electrospray, m/e): M+H 454.1, 456.1.

Example 22

2,3-dichloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared from N-(3,4-dichloro-2,5-dimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy)quinazolin-4-amine using the method described above in Example 17. The product was purified by chromatography on silica gel eluting with chloroform: mass spectrum (electrospray, m/e): M+H 424.0, 426.1.

Example 23

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This was prepared from of N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide and 2,5-dimethyoxy aniline using the combined methods described above in Examples 16 and 17: mass spectrum (electrospray, m/e): M+H 356.1, 426.1.

Example 24

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(phenylthio)benzo-1,4-quinone

To a warm solution of 0.33 g (0.93 mmol) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone in 49 ml of acetonitrile, 0.112 g (1 mmol) of thiophenol in 10 ml acetonitrile was added. After stirring 30 minutes, 0.22 g (1.07 mmol) of DDQ was added. The mixture was poured into methylene chloride and the solution washed with dilute sodium carbonate. The solution was filtered through a Magnesol™ plug and solvent was removed from the filtrate. The residue was chromatographed on silica gel eluting product with ethyl acetate. The title compound was obtained (0.097 g) as a brown solid after recrystallization from acetonitrile-ether: mass spectrum (electrospray, m/e): M+H 464.

Example 25

2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared from N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide and 4-chloro-2,5-dimethyoxy aniline using the combined methods described above in Examples 16 and 17.

Example 26

2-[4-(1H-imidazol-1-yl)phenoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

To a solution of 0.0534 g (0.33 mmol) of 4-(imidazol-1-yl)phenol and 0.01 g of the phase transfer catalyst tricaprylylmethylammonium chloride in 4 ml of methylene chloride, 0.3 ml of 1 N sodium hydroxide solution and 0.1 g (0.26 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone were added. The mixture was stirred vigorously for 30 minutes, poured into water and extracted with methylene chloride. The organic layer was dried over magnesium sulfate and poured onto a short column of Magnesol™. The product was eluted with methylene chloride-methanol 4:1 yielding 0.11 g of the title compound as a red solid: mass spectrum (electrospray, m/e): M+H 514.1, $(M+2H)^{+2}$ 257.7; mp = 124-132 °C.

Examples 27-36

100 mg of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 100 mg of a phenol, 100 mg of potassium carbonate and 2.5 ml of acetone were added to a reaction vial. The vials were agitated with a vortex shaker for 16 hours. The contents of the vials were filtered and the solids washed with water. The solids were assayed by LC-MS and those containing the desired products were purified by using a Gilson semi-prep HPLC and a gradient of acetonitrile-water. The fractions from this chromatography were assayed using LC-MS, and those containing the desired individual products in pure form were combined and concentrated to solids. By using this method, the compounds of this invention listed in Table 7 were prepared starting with the indicated phenol.

Table 7

Example	Phenol	Compound Name	MS m/e M+H
27	3-hydroxy-benzonitrile	3-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzonitrile	473.15
28	3-methoxyphenol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(3-methoxyphenoxy)benzo-1,4-quinone	478.16
29	4-phenoxyphenol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(4-phenoxyphenoxy)benzo-1,4-quinone	540.17
30	4-fluorophenol	2-(4-fluorophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	466.14
31	4-hydroxy-benzonitrile	4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzonitrile	473.14
32	4-methoxyphenol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(4-methoxyphenoxy)benzo-1,4-quinone	478.16
33	3-chlorophenol	2-(3-chlorophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	482.11
34	3-hydroxy-acetophenone	2-(3-acetylphenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	490.16
35	4-methylsulfanyl-phenol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(methylthio)phenoxy]benzo-1,4-quinone	494.14
36	4-trifluoromethyl-phenol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(trifluoromethyl)phenoxy]benzo-1,4-quinone	516.14.

Examples 37-56

A phenol (0.152 mmol) and the phase transfer catalyst tricaprylylmethylammonium chloride (0.01 mmol) were treated with an equivalent amount of 1 N NaOH. Methylene chloride (2 ml) and water (1 ml) were added and this mixture was stirred for 15 minutes. The biphasic mixture was then treated with the 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (0.101 mmol) in a methylene chloride solution to give a total volume of 8 ml in the reaction. The reactions were agitated with a vortex shaker for a time ranging from 2 hours to 48 hours. Completion of the reaction was determined by LC-MS. The organic layers were then separated and the aqueous solution was extracted further with methylene choride (2x 2 ml). The organic layers were combined and dried over magnesium sulfate and concentrated. The reactions, which showed only desired quinone as the major component, were purified by either recrystallization from acetonitrile or silica gel chromatography. Some reactions showed a substantial amount of the desired product in reduced form. These reactions were treated with an excess of DDQ in methylene chloride (2 ml) and agitated with a vortex shaker overnight. The reactions were washed with a saturated potassium carbonate solution (3x 2 ml), and the organic layers dried over magnesium sulfate and concentrated. Again, the reactions which showed only desired quinone as the major component were purified by either recrystallization from acetonitrile or silica gel chromatography. By using this method, the compounds of this invention listed in Table 8 were prepared starting with the indicated phenol.

Table 8

Example	Phenol	Compound Name	MS m/e M+H
37	(4-hydroxy-phenyl)-acetic acid ethyl ester	ethyl {4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]phenyl}acetate	534.18
38	4-hydroxy-benzenesulfonamide	4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy] benzenesulfonamide	527.12
39	(4-hydroxy-phenyl)-phenyl-methanone	2-(4-benzoylphenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	552.18

40	3-(4-hydroxy-phenyl)-propionic acid methyl ester	methyl 3-{4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]phenyl}propanoate	534.19
41	9H-carbazol-2-ol	2-(9H-carbazol-2-yloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	537.18
42	4-hydroxy-benzoic acid methyl ester	methyl 4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzoate	506.16
43	3-trifluromethyl phenol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[3-(trifluoromethyl)phenoxy]benzo-1,4-quinone	516.14
44	3-flurophenol	2-(3-fluorophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	466.14
45	5-hydroxy-2-methyl-1H-indole-3-carboxylic acid ethyl ester	ethyl 5-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]-2-methyl-1H-indole-3-carboxylate	573.20
46	4-bromophenol	2-(4-bromophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	526.06
47	2-isoxazol-5-yl-4-methyl-phenol	2-(2-isoxazol-5-yl-4-methylphenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	529.17
48	4-hydroxy-benzoic acid benzyl ester	benzyl 4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzoate	582.19
49	1-(4-hydroxy-phenyl)-2-phenyl-ethanone	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(phenylacetyl)phenoxy]benzo-1,4-quinone	566.19
50	3-ethylamino-phenol	2-[3-(ethylamino)phenoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	491.19
51	6-bromo-naphthalen-2-ol	2-[(6-bromo-2-naphthyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	576.08
52	2-benzyloxy-phenol	2-[2-(benzyloxy)phenoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	554.19
53	9H-fluoren-2-ol	2-(9H-fluoren-2-yloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	536.18
54	4-(2-amino-ethyl)-phenol	2-[4-(2-aminoethyl)phenoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	491.19
55	1-(4-hydroxy-phenyl)-3-phenyl-	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-{4-	578.19

	propenone	[(2E)-3-phenylprop-2-enoyl]phenoxy}benzo-1,4-quinone	
56	4-(1-methyl-1-phenyl-ethyl)-phenol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(1-methyl-1- phenylethyl)phenoxy]benzo-1,4-quinone	566.23

Example 57

3-methoxy-4-[(1-methylpiperidin-4-yl)methoxy]benzonitrile

53.3 ml of 1 N sodium bis(trimethylsilyl)amide was added to a stirred solution of 6.63 g (51.3 mmol) of (1-methyl-piperidin-4-yl)-methanol in 14 ml of THF. After 20 minutes, solid 4-fluoro-3-methoxy benzonitrile was added. The mixture was refluxed for 20 minutes, cooled to room temperature and poured into water. The mixture was extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate. The solvent was removed and the residue was recrystallized from ethyl acetate-hexanes yielding 8.9 g of the title compound as a white solid: mass spectrum (electrospray, m/e): M+H 261.2.

Example 58

5-methoxy-4-[(1-methylpiperidin-4-yl)methoxy]-2-nitrobenzonitrile

To a stirred solution of 8.8 g (33.8 mmol) 3-methoxy-4-[(1-methylpiperidin-4-yl)methoxy]benzonitrile in 34 ml of trifluoroacetic anhydride and 34 ml of chloroform cooled in a ice bath, 4.06 g (50.7 mmol) of solid ammonium nitrate was added portionwise over 15 minutes. The mixture was stirred at room temperature for 30 minutes. The solvent was removed and the residue was diluted with chloroform. The solution was washed with sodium bicarbonate solution until neutral. The mixture was dried over magnesium sulfate, filtered, concentrated and chromatographed on a silica gel column. The product fraction was eluted with a mixture of ethyl acetate, methanol and triethylamine to yield 5.2 g of the title compound as a colored solid : mass spectrum (electrospray, m/e): M+H 306.2.

Example 59

2-amino-5-methoxy-4-[(1-methylpiperidin-4-yl)methoxy]benzonitrile

A solution of 4 g (13.1 mmol) 5-methoxy-4[(1-methylpiperidin-4-yl)methoxy]-2-nitrobenzonitrile in 200 ml of tetrahydrofuran containing 1.2 g of 10% palladium on carbon catalyst was hydrogenated in a Parr apparatus overnight. The mixture was filtered and the solvent evaporated. The product was purified by chromatography on silica gel eluting with ethyl acetate-methanol-triethylamine 80:20:0.5 to give 2.83 g of the title compound as a tan solid: mass spectrum (electrospray, m/e): M+H 276.2.

Example 60

(4-chloro-2,5-dimethoxy-phenyl)-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-4-yl]-amine

To a stirred solution of 32.6 g (118.4 mmol) of 2-amino-5-methoxy-4-[(1-methylpiperidin-4-yl)methoxy]benzonitrile in 100 ml of isopropanol, 25.8 g (148 mmol) of t-butoxy-bis(dimethylamino)methane was added and the mixture heated until the reaction was complete. The solvent and excess reagent were evaporated at reduced pressure give the amidine intermediate. A portion of the intermediate (18.2 g (55.17 mmol)) and 10.9 g (57.9 mmol) of 4-chloro-2,5-dimethoxy-phenylamine in 75 ml of acetic acid was refluxed for 2.5 hour. The solvent was evaporated at reduced pressure at 100 °C. The residue was dissolved in chloroform and the solution was washed with saturated sodium bicarbonate. The colored solution was dried over magnesium sulfate and filtered through a pad of Magnesol™. The solvent was evaporated and the residue purified by chromatography on silica gel eluting with ethyl acetate-methanol-triethylamine mixtures to yield 4.6 g of the title compound as a grey powder: mass spectrum (electrospray, m/e): M+H 473.2.

Example 61

2-chloro-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone

To a warm stirred solution of 7.5 g (15.86 mmol) of (4-chloro-2,5-dimethoxy-phenyl)-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-4-yl]-amine in 200 ml of acetonitrile and 30 ml of water, 26.1 g (47.57 mmol) of ceric ammonium nitrate was added over 40 minutes. After 15 minutes, 100 ml of chloroform and 60 ml of saturated sodium bicarbonate were added. The organic layer was separated, washed with water and dried over magnesium sulfate. This solution was poured onto

a short Magnesol™ column. The product was eluted with chloroform-isopropanol mixtures. The solvent was removed from product fractions giving a brown solid that was extracted many times with ethyl acetate. The solvent was concentrated from the extract and ether was added. The title compound, 0.74 g, was collected as a red powder: mass spectrum (electrospray, m/e): M+H 443.1.

Example 62

methyl 3-methoxy-4-(2-methoxyethoxy)benzoate

A mixture of 101.2 g (0.56 mol) of 4-hydroxy-3-methoxy-benzoic acid methyl ester (methyl vanillate), 77.2 g (0.56 mol) of 2-bromoethyl methyl ether and 102.1 g (0.74 mol) of potassium carbonate was refluxed and stirred in 1 L of acetone for 23 hours. The hot mixture was filtered. The solvent was evaporated and the residue was dissolved in ethyl acetate. The solution was washed with 1 N sodium hydroxide and then with water. The solution was dried over magnesium sulfate, filtered and the solvent evaporated yielding 95.6 g of the title compound as a solid: mass spectrum (electrospray, m/e): M+H 241.

Example 63

methyl 5-methoxy-4-(2-methoxyethoxy)-2-nitrobenzoate

To a stirred solution of 24.0 g (0.1 mmol) of methyl 3-methoxy-4-(2-methoxyethoxy)benzoate in 70 ml of acetic acid, 26 ml of 70% nitric acid was added dropwise. After stirring 2 hours, the mixture was heated to 50°C for 15 minutes. The mixture was poured onto ice water and filtered. The solid was washed with water and dried, yielding 26.3 g of the title compound.

Example 64

methyl 2-amino-5-methoxy-4-(2-methoxyethoxy)benzoate

A mixture of 26.3 g (92 mmol) of methyl 5-methoxy-4-(2-methoxyethoxy)-2-nitrobenzoate, 15.4 g (280 mmol) of iron powder, 44.3 g (829 mmol) of ammonium chloride, 75 ml of water, and 300 ml of ethanol was stirred at reflux for 30 minutes. The mixture was filtered while hot. The solids were washed with additional hot ethanol. The solvent was evaporated from the combined filtrate. The residue was dissolved in methylene chloride and filtered through a short column of Magnesol™.

The solvent was evaporated giving 21.7 g of the title compound as a solid: mass spectrum (electrospray, m/e): M+H 256.4

Example 65

4-hydroxy-6-methoxy-7-(2-methoxy-ethoxy)-quinoline-3-carbonitrile

A mixture of 21.7 g (85.1 mmol) of methyl 2-amino-5-methoxy-4-(2-methoxyethoxy)benzoate and 45 ml of dimethylformamide dimethylacetal was heated at 100 °C for several hours. The excess reagent was removed at reduced pressure. The residue was dissolved in methylene chloride and filtered through a pad of Magnesol™. The solvent was evaporated and the residue was dried in vacuum yielding 26.2 g of the intermediate formamide derivative.

A solution of 10.86 ml of 2.5 M n-butyl lithium in hexanes in 300 ml of dry THF was stirred under nitrogen at –78 °C as 9.25 ml (177 mmol) of acetonitrile in 300 ml of THF was added dropwise. After 30 minutes, a solution of the amidine prepared above in 300 ml of THF was added dropwise. After 1 hour, 24 ml of acetic acid was added and the mixture was allowed to warm to room temperature. The solvent was evaporated and the resulting solid was washed with water and air dried giving the title compound.

Example 66

4-chloro-6-methoxy-7-(2-methoxyethoxy)-quinoline-3-carbonitrile

To a suspension of 11.4 g (41.6 mmol) of 4-hydroxy-6-methoxy-7-(2-methoxy-ethoxy)-quinoline-3-carbonitrile in 200 ml of methylene chloride, 18 ml (208 mmol) of oxalyl chloride and 0.5 ml of dimethylformamide were added with stirring. The mixture was stirred for 4 hours. The solvent was evaporated at reduced pressure and the residue was redissolved in methylene chloride. The solution was passed through a short column of Magnesol™. The solvent was evaporated and the residue washed with ether yielding 10.3 g of the title compound as a solid.

Example 67

4-[(3-hydroxy-4-methylphenyl)amino]-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile

A solution of 2.93 g (10 mmol) of 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile, 1.35 g (11 mmol) of 5-amino-2-methyl-phenol and 1.27 of pyridine hydrochloride in 25 ml of isopropanol was stirred at reflux for 1 hour. The mixture was cooled and the solid was collected as the hydrochloride salt and washed with cold isopropanol and ether. The solid was stirred in a mixture of saturated sodium bicarbonate and methylene chloride overnight. The solid was collected and washed with water and ether giving after drying yielding 3.1 g of the title compound: mp 230-233 °C; mass spectrum (electrospray, m/e, negative mode): M-H 378.2.

Example 68

6-methoxy-7-(2-methoxyethoxy)-4-[(4-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)amino]quinoline-3-carbonitrile

A mixture of 2.96 g (7.8 mmol) of 4-[(3-hydroxy-4-methylphenyl)amino]-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile, 0.83 g of sodium carbonate, 9.75 ml of 1 N sodium hydroxide, 100 ml of water, and 60 ml of ethyl acetate was stirred as 6.3 g (23.4 mmol) of Fremy's salt was added. After stirring overnight at room temperature, 65 ml of THF was added and the mixture was heated to 50 °C for 2 h. A solid was collected by filtration. The filtrate was extracted with methylene chloride and this extract was combined with the solid. Solvent was evaporated. The residue was redissolved in methylene chloride and filtered. The filtrate was chromatographed on silica gel. Product was eluted with methylene chloride-methanol 39:1. The solvent was evaporated from the product fractions and the residue was washed with ether, yielding 0.93 g of the title compound as an orange solid: mp 174-177 °C; mass spectrum (electrospray, m/e): M-H 394.1.

Example 69

4-[(4-chloro-2,5-dimethoxyphenyl)amino]-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile

A solution of 7.3 g (24.9 mmol) of 4-chloro-6-methoxy-7-(2-methoxyethoxy)-3-quinolinecarbonitrile and 4.3 g (24.9 mmol) of 4-chloro-2,5-dimethoxy-phenylamine in 200 ml of methyoxyethanol was stirred at reflux for 3.5 hours and then allowed to stand at room temperature overnight. The solid was collected and washed with ether giving the hydrochloride salt. This was heated in 700 ml of ethyl acetate and sodium hydroxide solution until the solid dissolved. The organic layer was dried over magnesium sulfate. The solvent was evaporated and the product recrystallized from ethyl acetate-hexanes yielding 9.7 g of the title compound: mass spectrum (electrospray, m/e): M-H 444.2.

Example 70

4-[(4-chloro-3,6-dioxocyclohexa-1,4-dien-1-yl)amino]-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile

A solution of 7.7 g (19 mmol) of 4-[(4-chloro-2,5-dimethoxyphenyl)amino]-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile in 322 ml of acetonitrile was prepared by boiling. To this solution, 65 ml of water was added. The mixture was stirred and when the temperature reached 30°C, 19 g (34.7 mmol) of ceric ammonium nitrate was added over 5 minutes. After 45 minutes, the mixture was diluted with dilute sodium bicarbonate. The solid was collected by filtration and washed with water. This solid was suspended in 300 ml of water and 35 ml of concentrated hydrochloride acid was added. After stirring for 15 minutes, the precipitated solid was collected. The solid was stirred with 700 ml of methylene chloride and saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and the solution was passed onto a column of Magnesol™. The product was eluted from the column using ethyl acetate. The solvent was evaporated from the product fractions to give a solid that was washed with ether, yielding 1.8 g of the title compound as a red powder: mass spectrum (electrospray, m/e): M-H 414.2.

Example 71

4-[(3,6-dioxo-4-phenoxycyclohexa-1,4-dien-1-yl)amino]-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile

To a stirred solution of 0.5 g (1.21 mmol) of 4-[(4-chloro-3,6-dioxocyclohexa-1,4-dien-1-yl)amino]-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile in 10 ml of dimethylformamide in an ice bath, 0.43 g (2.54 mmol) of sodium phenoxide was added. The mixture was stirred for 30 minutes at room temperature and then diluted with 200 ml of ether and a blue solid collected. This solid was stirred in 200 ml of methylene chloride containing 0.15 ml of acetic acid until the solids dissolved. The solution was poured onto a silica gel column and the product was eluted with chloroform-methanol mixtures. The solvents were evaporated from product fractions yielding 0.4 g of the title compound as an orange solid: mass spectrum (electrospray, m/e): M-H 472.2.

Example 72

4-({4-[4-(1H-imidazol-1-yl)phenoxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile

This compound was prepared from 4-[(4-chloro-3,6-dioxocyclohexa-1,4-dien-1-yl)amino]-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile and the sodium salt of 4-imidazol-1-yl-phenol using the method described above in Example 71. The title compound was obtained as an orange-brown solid: mass spectrum (electrospray, m/e): M-H 538,2, $(M+2H)^{+2}$ 269.8.

Example 73

2-[(3,4-dimethoxyphenyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 0.49 g (1.25 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and 0.5 ml of N-methyl-3,4-dimethoxy aniline in 10 ml of glyme was stirred at 85°C for 2 hours. The solvent was evaporated and the residue suspended in ether. The solid was collected via filtration and chromatographed on silica gel eluting with ethyl acetate-methanol 49:1 to give 0.29 g of the title compound as a colored solid: mass spectrum (electrospray, m/e): M-H 521.3

Example 74

2-[(3-fluorophenyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared using the method described above in Example 73 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and N-methyl-3-fluoroaniline. The title compound was obtained as a red solid: mass spectrum (electrospray, m/e): M-H 479.29.

Example 75

2-[[4-(dimethylamino)phenyl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared using the method described above in Example 73 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and N,N,N'-trimethyl-benzene-1,4-diamine. The title compound was obtained as a dark solid: mass spectrum (electrospray, m/e): M-H 504.1, $(M+2H)^{+2}$ 252.6.

Example 76

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(phenyl)amino]benzo-1,4-quinone

This compound was prepared using the method described above in Example 73 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and N-methylaniline. The title compound was obtained as the colored acetate salt after recrystallization from acetic acid: mass spectrum (electrospray,m/e): M-H 479.0; mp= 239-243°C.

Example 77

2-[(4-fluorophenyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared using the method described above in Example 73 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and N-methyl-4-fluoroaniline. The title compound was obtained as a dark solid: mass spectrum (electrospray, m/e): M-H 479.0.

Example 78

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(4-methoxyphenyl)(methyl)amino]benzo-1,4-quinone

This compound was prepared using the method described above in Example 73 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and N-methyl-4-methoxyaniline. The title compound was obtained as a brown solid: mass spectrum (electrospray, m/e): M-H 491.3; mp = 197-198 °C.

Example 79

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-morpholin-4-ylbenzo-1,4-quinone

A solution of 1.13 g (2.5 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and 1 ml of morpholine in 30 ml of THF was stirred for 3 hours. The solid was collected via filtration and washed with THF and water to yield, after drying, 1.1 g of the title compound as a red solid: mass spectrum (electrospray, m/e): M-H 441.1; mp = 239-243 °C.

Example 80

2-[cyclohexyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 1.13 g (2.5 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and 1 ml cyclohexyl-methyl-amine in 5 ml of glyme was stirred at 85°C for 4 hours. The solid was collected via filtration and washed with THF to give 0.87 g of the title compound as a red solid: mass spectrum (electrospray, m/e): M-H 467.1; mp = 178-180 °C.

Example 81

2-(dimethylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 0.97 g (2.5 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 0.29 g of pyridine hydrochloride, and 5 ml of 2 M dimethylamine in THF, in 15 ml of THF, was stirred

for 3 hours. The solid was collected via filtration and washed with water to give, after drying, 0.94 g of the title compound as a light brown solid: mass spectrum (electrospray, m/e): M-H 399.2.

Example 82

2-[benzyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared using the method described above in Example 81 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and N-methyl-benzylamine. The title compound was obtained as a red solid: mass spectrum (electrospray, m/e): M-H 475.2.

Example 83

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3-methylbenzyl)amino]benzo-1,4-quinone

This compound was prepared using the method described above in Example 81 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and 3-methyl benzylamine. The title compound was obtained as an orange solid: mass spectrum (electrospray, m/e): M-H 475.2 ; mp = 241-242 °C.

Example 84

2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-morpholin-4-ylbenzo-1,4-quinone

A solution of 1.35 g (4 mmol) of 2-chloro-5-[(6,7-dimethoxy-4-quinazolinyl)amino]benzo-1,4-quinone and 0.696 g (8 mmol) of morpholine in 80 ml of toluene was stirred overnight. The solution is filtered through Magnesol™ using methylene chloride. The resulting solid was collected and washed with ether yielding 0.71 g of the title compound as a red solid: mass spectrum (electrospray, m/e): M-H 397.2 ; mp = 249-250 °C.

Example 85

2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-[methyl(phenyl)amino]benzo-1,4-quinone

This compound was prepared using the method described above in Example 73 from 2-chloro-5-[(6,7-dimethoxy-4-quinazolinyl)amino]benzo-1,4-quinone and N-

methylaniline and THF as the solvent. The title compound was obtained as a red solid: mass spectrum (electrospray, m/e): M-H 417.3 ; mp = 204-206 °C.

Example 86

2-anilino-5-[(6,7-dimethoxyquinazolin-4-yl)amino]benzo-1,4-quinone

This compound was prepared using the method described above in Example 73 from 2-chloro-5-[(6,7-dimethoxy-4-quinazolinyl)amino]benzo-1,4-quinone and aniline and THF as the solvent. The title compound was obtained as a red solid: mass spectrum (electrospray, m/e): M-H 403.1 ; mp = 258-261 °C.

Example 87

2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-piperidin-1-ylbenzo-1,4-quinone

This compound was prepared using the method described above in Example 84 from 2-chloro-5-[(6,7-dimethoxy-4-quinazolinyl)amino]benzo-1,4-quinone and piperidine and THF as the solvent. The title compound was obtained as a red solid: mass spectrum (electrospray, m/e): M-H 395.2 ; mp = 226-227 °C.

Example 88

2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-(dimethylamino)benzo-1,4-quinone

A solution of 1.73 g (5 mmol) of 2-chloro-5-[(6,7-dimethoxy-4-quinazolinyl)amino]benzo-1,4-quinone and 5 ml of 2 M dimethylamine in THF in 20 ml of THF was stirred for 30 hours. The solid was collected via filtration and washed with water to yield, after drying, 1.3 g of the title compound as a light brown solid: mass spectrum (electrospray, m/e): M-H 355.16; mp = 245-250 °C.

Example 89

2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-(methylamino)benzo-1,4-quinone

This compound was prepared using the method described above in Example 88 from 2-chloro-5-[(6,7-dimethoxy-4-quinazolinyl)amino]benzo-1,4-quinone and 2 M methylamine in THF. The title compound was obtained as a brown solid: mass spectrum (electrospray, m/e): M-H 341.2 ; mp = 283-285 °C.

Example 90

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-methylphenoxy)benzo-1,4-quinone

A mixture of 1.03 g (2.5 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 1.05 g (9.7 mmol) of 2-methylphenol and 1 g (7.17 mmol) of postassium carbonate in 20 ml of acetone was stirred for 40 hours. The mixture was filtered and solvent evaporated from the filtrate. The original solid and the residue from the filtrate were extracted with methylene chloride. The solvent was evaporated and the resulting solid washed with ether yielding 0.91 g of the title compound as a brown solid: mass spectrum (electrospray, m/e): M-H 462.2 ; mp 134-137 °C.

Example 91

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(pyridin-3-yloxy)benzo-1,4-quinone

This compound was prepared using the method described above in Example 90 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and 3-hydroxy pyridine. The title compound was obtained as a solid: mass spectrum (electrospray, m/e): M-H 449.1 ; mp = 189-190°C.

Example 92

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(4-methylphenoxy)benzo-1,4-quinone

This compound was prepared using the method described above in Example 90 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and 4-methylphenol. The title compound was obtained as a red solid: mass spectrum (electrospray, m/e): M-H 462.2 ; mp = 171-172°C.

Example 93

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-phenoxybenzo-1,4-quinone

This compound was prepared using the method described above in Example 90 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

and phenol. The title compound is obtained as a red solid: mass spectrum (electrospray, m/e): M-H 448.2 ; mp = 177-180°C.

Example 94

2-(4-chlorophenoxy)-5-[(6,7-dimethoxyquinazolin-4-yl)amino]benzo-1,4-quinone

This compound was prepared using the method described above in Example 90 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and 4-chlorophenol. The product was purified by chromatography using a methylene chloride methanol mixture (99:1). The title compound was obtained as a red solid: mass spectrum (electrospray, m/e): M-H 438.25, 440.26.

Example 95

2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-phenoxybenzo-1,4-quinone

This compound was prepared using the method described above in Example 90 from 2-chloro-5-[(6,7-dimethoxy-4-quinazolinyl)amino]benzo-1,4-quinone and phenol. The title compound was obtained as a red solid: mass spectrum (electrospray, m/e): M-H 404.13 ; mp = 228-234°C.

Example 96

2-(benzyloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 0.67 g (1.5 mmol) of 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-phenoxybenzo-1,4-quinone, 20 ml of benzyl alcohol and 0.5 ml of triethylamine in 20 ml methylene chloride was stirred for 16 hours. The solvent was evaporated and the residue diluted with ether. The solid was collected and washed with ether giving 0.66 g of the title compound as an orange solid: mass spectrum (electrospray, m/e): M-H 462.4 ; mp = 218-220°C.

Example 97

2-(2-methoxyethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared using the method described above in Example 94 from 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-phenoxybenzo-1,4-

quinone, methoxyethanol and triethylamine. The title compound was obtained as a brown solid: mass spectrum (electrospray, m/e): M-H 430.3 ; mp = 211-212°C.

Example 98

N-(2,5-dimethoxy-1,1'-biphenyl-4-yl)-6,7-dimethoxyquinazolin-4-amine

This compound was prepared by the method of Example 1 given above using 2-amino-4,5-dimethoxy-benzonitrile and 2,5-dimethoxy-biphenyl-4-ylamine. The title compound was obtained as an off-white solid: mass spectrum (electrospray, m/e): M-H 418.1 ; mp = 226-229°C.

Example 99

2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-phenylbenzo-1,4-quinone

This compound was prepared by the method of Example 2 given above from N-(2,5-dimethoxy-1,1'-biphenyl-4-yl)-6,7-dimethoxyquinazolin-4-amine and ceric ammonium nitrate. The title compound was obtained as a brown solid: mass spectrum (electrospray, m/e): M-H 388.1 ; mp = 200-205°C.

Example 100

4-[(6,7-dimethoxyquinazolin-4-yl)amino]-1-phenyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione

This compound was prepared from 2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-phenylbenzo-1,4-quinone and hydrogen peroxide using the method described above in Example 5. The title compound was obtained as a yellow solid: mass spectrum (electrospray, m/e): M+H 404.1 ; mp = 252-253°C.

Example 101

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-piperidin-1-yl-benzo-1,4-quinone

This compound was prepared using the method described above in Example 81 from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and piperidine. The title compound was obtained as a solid: mass spectrum (electrospray, m/e): M-H 439.3 ; mp = 197-200°C.

Example 102

(1,4-dimethoxy-naphthalen-2-yl)-[6-methoxy-7-(2-methoxy-ethoxy)-quinazolin-4-yl]-amine

This compound was prepared by the method described above in Example 16 using N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide and 1,4-dimethoxy-naphthalen-2-ylamine (Syn. Comm., 16:81-687 (1986)). The product was recrystallized from isopropanol yielding the title compound as a light grey solid: mass spectrum (electrospray, m/e): M+H 436.2.

Example 103

2-[6-methoxy-7-(2-methoxyethoxy)-quinazolin-4-ylamino]-[1,4]naphthoquinone

This compound was prepared by the method of Example 17 described above using (1,4-dimethoxy-naphthalen-2-yl)-[6-methoxy-7-(2-methoxy-ethoxy)-quinazolin-4-yl]-amine and ceric ammonium nitrate. After passing the solution through Magnesol™, the filtrate was concentrated and the solid collected and washed with ether. The title compound was obtained as an orange solid: mass spectrum (electrospray, m/e): M+H 406.2.

Example 104

2-(2-hydroxyethyl)thio)-3-[6-methoxy-7-(2-methoxyethoxy)-quinazolin-4-ylamino]-[1,4]naphthoquinone

A solution of 0.7 g (1.73 mmol) of 2-[6-methoxy-7-(2-methoxyethoxy)-quinazolin-4-ylamino]-[1,4]naphthoquinone and 0.27 g (3.45 mmol) of mercaptoethanol was stirred at room temperature for 5 days. To the solution, 0.21 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was added. After 10 minutes, the mixture was poured into dilute sodium carbonate and extracted with chloroform. The organic layer was dried over magnesium sulfate and passed through a column of Magnesol™ eluting with a mixture of chloroform and isopropanol. The solvent was evaporated and the residue chromatographed on silica gel eluting with chloroform and then with chloroform-isopropanol mixtures. The solvent was evaporated from product fractions and the residue recrystallized from isopropanol to give 0.47 g of the title compound as an orange solid: mass spectrum (electrospray, m/e): M+H 482.1.

Example 105

2-(methoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared by the method of Example 94 using 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-phenoxybenzo-1,4-quinone, methanol, and triethylamine in methylene chloride. The product was purified on silica gel eluting with methylene chloride-methanol 39:1, to yield the title compound as a red solid.

Example 106

4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]amino}-1-methyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione

This compound was prepared by the method of Example 5 using 2-{[6-methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]amino}-5-methylbenzo-1,4-quinone (Example 15) and hydrogen peroxide. The title compound was obtained as a yellow solid: mass spectrum (electrospray, m/e): M+H 386.13.

Example 107

4-[(6,7-dimethoxy-4-quinazolinyl)amino]-1-isopropyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione

This compound was prepared from N-(4-chloro-2,5-dimethoxyphenyl)-6,7-dimethoxy-4-quinazolinamine and 4-isopropyl-2,5-dimethoxy-phenylamine using the methods of Examples 2, 3 and 5, sequentially. The title compound was obtained as a solid: mass spectrum (electrospray, m/e): M+H 370.21; mp = 188-190 °C.

Example 108

1-benzyl-4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione

This compound was prepared from N-(4-chloro-2,5-dimethoxyphenyl)-6,7-dimethoxy-4-quinazolinamine and 4-benzyl-2,5-dimethoxy-phenylamine using the methods Examples 2, 3 and 5, sequentially. The title compound was obtained as a solid: mass spectrum (electrospray, m/e): M+H 462.2 ; mp = 104-108 °C.

Example 109

4-[(6,7-dimethoxy-4-quinazolinyl)amino]-1-ethyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione

This compound was prepared from N-(4-chloro-2,5-dimethoxyphenyl)-6,7-dimethoxy-4-quinazolinamine and 4-ethyl-2,5-dimethoxy-phenylamine using the methods of Examples 2, 3 and 5, sequentially. The title compound was obtained as a solid: mp = 202-204 °C.

Example 110

2-chloro-5-methoxy-3-[6-methoxy-7-(2-methoxyethoxy)-quinazolin-4-ylamino]-benzo-1,4-quinone

A solution of 2 g of 2-methoxy-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone was prepared by boiling in 50 ml of chloroform. The solution was cooled to room temperature and 2 ml of chloroform saturated with hydrogen chloride was added. This mixture was stirred overnight. The solvent was evaporated giving the hydroquinone as a yellow-brown solid. This solid was dissolved in 50 ml of acetonitrile and 10 ml of water to which 1.2 g of DDQ was added. After 1 hour, the mixture was poured into saturated sodium bicarbonate and extracted several times with methylene chloride. The extract was dried over magnesium sulfate and solvent evaporated. The product was purified by chromatography eluting with ethyl acetate- isopropanol mixtures. Product fractions were combined and solvent evaporated yielding 1.2 g of the title compound as a yellow solid: mass spectrum (electrospray, m/e): M+H 420.0.

Example 111

5-methoxy-3-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-2-(pyridin-2-ylthio)benzo-1,4-quinone

This compound was prepared from 2-methoxy-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and 2-mercaptopyridine using the method described in Example 18 above using a 30 minute initial reaction time. The title compound was obtained as a red powder: mass spectrum (electrospray, m/e): M+H 495.0.

Example 112

2-[ethyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 0.20 g (0.51 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 0.06 g of pyridine hydrochloride and 0.12 g methylethylamine in 2 ml of tetrahydrofuran was sonicated for 0.5 hour at 40°C, then shaken at 40°C for 3 hours. The solid was collected via filtration and washed with water to give, after drying, 0.165 g of the title compound as a light brown solid: mass spectrum (electrospray, m/e): M+H 413.2.

Examples 113-143

The following examples in Table 9 were prepared from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and the appropriate amine using the procedure outlined above in Example 112.

Table 9

Example	Compound Name	MS m/e $(M+H)^+$	MS m/e $(M+2H)^{2+}$
113	2-(diisobutylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	483.3	
114	2-(2,5-dimethylpyrrolidin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	453.2	227.1
115	2-(3,5-dimethylpiperidin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	467.2	
116	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(3-methylpiperidin-1-yl)benzo-1,4-quinone	453.2	
117	2-[(2,3-dihydroxypropyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	459.2	
118	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-methylaziridin-1-yl)benzo-1,4-quinone	411.2	
119	2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	469.2	

120	2-(dipropylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	455.2	
121	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-pyridin-3-ylpiperidin-1-yl)benzo-1,4-quinone	516.2	258.6
122	tert-butyl 1-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)-L-prolinate	525.2	
123	2-azocan-1-yl-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	467.2	
124	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(pentyl)amino]benzo-1,4-quinone	455.2	
125	2-{4-[4-chloro-3-(trifluoromethyl)phenyl]piperazin-1-yl}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	618.2	
126	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]benzo-1,4-quinone	508.2	254.6
127	2-[4-(2-fluoro-4-nitrophenyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	579.2	
128	2-[[(3S)-1-benzylpyrrolidin-3-yl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	544.2	272.6
129	2-(4-benzylpiperidin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	529.2	
130	2-[4-(2-hydroxyethyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	484.2	242.6
131	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(4-pyrazin-2-ylpiperazin-1-yl)benzo-1,4-quinone	518.2	259.6
132	2-[[2-(1H-indol-3-yl)ethyl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	528.2	
133	ethyl 1-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)piperidine-4-carboxylate	511.2	
134	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(2-methoxyphenyl)piperidin-1-yl]benzo-1,4-quinone	545.2	
135	2-(4-benzyl-1,4-diazepan-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	544.2	272.6

136	2-(1,4'-bipiperidin-1'-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	522.3	261.6
137	2-[[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	549.2	
138	tert-butyl N-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)-N-methylglycinate	499.2	
139	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]benzo-1,4-quinone	537.2	269.1
140	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]benzo-1,4-quinone	537.3	269.1
141	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(2-phenylethyl)amino]benzo-1,4-quinone	489.2	
142	2-[4-(ethylsulfonyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	532.1	
143	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-pyrrolidin-1-ylbenzo-1,4-quinone	425.2	

Example 144

2-(2,3-dihydro-1,4-benzooxazepin-4(5H)-yl)-5-[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-benzo-1,4-quinone

A slurry of 0.075 g (0.19 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 0.04 g of pyridine hydrochloride, 0.1 ml of N,N-diisopropylethylamine and 0.14 g of 2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine hydrochloride in 2 ml of tetrahydrofuran was sonicated for 0.5 hour at 40°C, then shaken at 40°C for 3 hours. The solid was collected via filtration, washed with tetrahydrofuran, then water and dried *in vacuo* to give 0.05 g of the title compound as a tan solid: mass spectrum (electrospray, m/e): M+H 503.2.

Examples 145-146

The following examples in Table 10 were prepared from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and the appropriate amine hydrochloride salt using the procedure outlined above for Example 144.

Table 10

Example	Compound Name	MS m/e $(M+H)^+$
145	2-{4-hydroxy-4-[3-(trifluormethyl)phenyl]piperidin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	599.2
146	2-[(1R,4R)-5-(4-chlorophenyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	562.2

Example 147

1-{4-[6-methoxy-7-(2-methoxyethoxy)-quinazolin-4-ylamino]-3,6-dioxo-cyclohexa-1,4-dien-1-yl}-piperidine-4-carboxylic acid

A slurry of 0.10 g (0.26 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 0.001-0.002 g of 4-(dimethylamino)pyridine and 0.105 g of piperidine-4-carboxylic acid in 2 ml of N,N-dimethylformamide was stirred for 24 hours. The reaction mixture was then diluted with water and the precipitated solid was collected by filtration, washed with water and dried in vacuo to give 0.11 g of the title compound as a red-brown solid: mass spectrum (electrospray, m/e): M+H 483.2.

Example 148

1-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)azetidine-3-carboxylic acid

The title compound was prepared from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and azetidine-3-carboxylic acid using the procedure described above in Example 147: mass spectrum (electrospray, m/e): M+H 455.1.

Example 149

2-[[2-(diethylamino)ethyl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 0.12 g (0.31 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and 0.52 ml (3.2 mmol) of N,N-diethyl-N'-methylethylenediamine in 1.5 ml of dioxane was treated with either 0.11 g (0.93 mmol) of pyridine hydrochloride or 0.86 ml (4.9 mmol) N,N-diisopropylethylamine. The mixture was then heated via microwave irradiation at 75 to 125°C for 5 minutes. The crude product was then directly purified by reverse phase chromatography using gradient elution with acetonitrile and water containing 0.05% trifluoroacetic acid to give 0.11 g of the title compound: mass spectrum (electrospray, m/e): M+H 484.3.

Examples 150-173

The following examples in Table 11 were prepared from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and the appropriate amine using the procedure outlined above for Example 149.

Table 11

Example	Compound Name	MS m/e $(M+H)^+$	MS m/e $(M+2H)^{2+}$
150	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[2-(trifluoromethyl)pyrrolidin-1-yl]benzo-1,4-quinone	493.2	
151	N,N-diethyl-1-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)piperidine-3-carboxamide	538.2	269.6
152	ethyl 1-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)piperidine-3-carboxylate	511.2	
153	2-(4-benzylpiperazin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	530.2	265.6
154	2-[(1,3-dioxolan-2-ylmethyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	471.2	
155	2-[[2-(dimethylamino)ethyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	456.2	228.6

156	2-[(cyclopropylmethyl)(propyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	467.2	
157	2-[(2-methoxyethyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	443.2	
158	2-[6-methoxy-7-(3-methoxy-propyl)-quinazolin-4-ylamino]-5-(3-methylamino-pyrrolidin-1-yl)-[1,4]benzoquinone	454.2	227.6
159	2-[isobutyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	441.2	
160	2-(4-ethylpiperazin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	468.2	234.6
161	2-[butyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	441.2	
162	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(1-methylpiperidin-4-yl)amino]benzo-1,4-quinone	482.5	
163	2-[3-(hydroxymethyl)piperidin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	469.2	
164	2-(4-acetylpiperazin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	482.2	
165	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(1-methylpyrrolidin-3-yl)amino]benzo-1,4-quinone	468.5	
166	2-[[3-(dimethylamino)propyl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	470.5	235.7
167	2-(diallylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	451.2	
168	2-[(2-furylmethyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	465.1	
169	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(4-morpholin-4-ylphenyl)amino]benzo-1,4-quinone	532.2	
170	2-[allyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	425.2	
171	2-(2,3-dihydro-1,4-benzodioxin-6-ylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	505.2	

172	2-[(4-isopropylphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	489.5	
173	2-[(2-ethylphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	475.2	

Example 174

2-[(9-ethyl-9H-carbazol-3-yl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 0.10 g (0.26 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 0.095 g (0.77 mmol) of pentafluorophenol, 0.16 g (0.77 mmol) of 3-amino-9-ethylcarbazole and 0.11 g (0.77 mmol) of potassium carbonate in 4.0 ml of acetone was heated to 45°C for 3 hours. The crude product was then diluted with water and extracted three times with methylene chloride. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo*, and purified by reverse phase chromatography to yield 0.04 g of the title compound: mass spectrum (electrospray, m/e): M+H 564.2.

Examples 175-180

The following examples in Table 12 were prepared from 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and the appropriate amine using the procedure outlined above for Example 174.

Table 12

Example	Compound Name	MS m/e $(M+H)^+$
175	2-[ethyl(3-methylphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	489.2
176	2-[(3,5-di-tert-butylphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	559.3
177	2-{[4-(4-chlorophenoxy)phenyl]amino}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	574.2
178	ethyl 5-{4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)amino]phenyl}-2-methyl-3-furoate	599.2
179	2-(4-imidazol-1-yl-phenylamino)-5-[6-methoxy-7-(3-methoxypropyl)-quinazolin-4-ylamino]benzo-1,4-quinone	513.5
180	N-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)-L-valine	471.2

Example 181

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(pentafluorophenoxy)benzo-1,4-quinone

A solution of 0.11 g (0.28 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 0.10 g (0.56 mmol) of pentafluorophenol and 0.11 g (0.83 mmol) of potassium carbonate in 3.0 ml of acetone was heated to 45°C for 1.5 hours. The crude product was then diluted with water and extracted three times with methylene chloride. The combined extracts were dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo*, and purified by chromatography over silica gel to give 0.03 g of the title compound: mass spectrum (electrospray, m/e): M+H 538.1.

Example 182

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(2-methoxypropyl)amino]benzo-1,4-quinone

To 0.05 g (0.12 mmol) of 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-methylaziridin-1-yl)benzo-1,4-quinone, 56 ml each of tetrahydrofuran, methanol, and water were added. After stirring for 18 hours, the solution was concentrated and the aqueous layer extracted three times with methylene chloride. The mixture was dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo*, and the desired product was isolated by chromatography over silica gel using a mixture of methylene chloride and isopropyl alcohol as eluant, to give 0.017 g of the title compound as a red-brown solid: mass spectrum (electrospray, m/e): $M+H^+$ 443.2.

Example 183

2-[(2-hydroxypropyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

To a stirred solution of 0.25 g (0.64 mmol) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-methylaziridin-1-yl)benzo-1,4-quinone in 250 ml tetrahydrofuran and 250 ml water, concentrated hydrochloric acid was added until the reaction mixture reached a pH of 4. After 18 hours, the solution was concentrated and the aqueous layer extracted three times with methylene chloride. The mixture was dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo,* and the product was purified by chromatography over silica gel, using a

mixture of methylene chloride and isopropyl alcohol as eluant, to give 0.19 g of the title compound as a red-brown solid: mass spectrum (electrospray, m/e): $M+H^+$ 429.2.

Example 184

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(5-methyl-2-oxo-1,3-oxazolidin-3-yl)benzo-1,4-quinone

To a solution of 0.13 g (0.30 mmol) 2-[(2-hydroxypropyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 0.49 g 1,1"-carbonyl diimidazole in 10 ml of 1-methyl-2-pyrrolidinone was added. After stirring for 27 hours at 80°C under an atmosphere of nitrogen, the solution was poured into 100 ml of water and extracted three times with ethyl acetate. The mixture was dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo*, and the product was purified by chromatography over silica gel using a mixture of methylene chloride and isopropyl alcohol as eluant, to give 0.06 g of the title compound as a red solid: mass spectrum (electrospray, m/e): $M+H^+$ 455.1.

Example 185

3-iodo-2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-methylbenzo-1,4-quinone

A solution of 1 g (2.71 mmol) of 2-{[6-methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]amino}-5-methylbenzo-1,4-quinone (Example 15) and 0.755 g (2.98 mmol) of iodine in 10 ml of pyridine was stirred for 2 hours. The mixture was poured onto a column of Magnasol™ and product was eluted with chloroform-isopropanol mixtures to give 1.12 g of the title compound as a black powder: mass spectrum (electrospray, m/e): $M+H^+$ 495.9.

Example 186

3-[(2-hydroxyethyl)thio]-2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4- yl]amino}-5-methylbenzo-1,4-quinone.

A solution of 0.625 g (1.26 mmol) of 3-iodo-2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-methylbenzo-1,4-quinone (Example 185) and 0.14 g (1.77 mmol) of mercaptoethanol in 20 ml of methylene chloride was

stirred for 3 hours. To the solution was added 0.34 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). After 15 minutes, the mixture was diluted with methylene chloride and washed with dilute potassium carbonate. The organic solution was dried and passed through a column of silica gel. The product was eluted with ethyl acetate-isopropanol mixtures: mass spectrum (electrospray, m/e): $M+H^+$ 446.1.

Example 187

2-iodo-5-methoxy-3-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 1 g of 2-methoxy-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (Example 17) and .79 g of iodine in 10 ml of methylene chloride was stirred for 7 days. The mixture was poured unto a column of Magnasol™ and product was eluted with ethyl acetate-isopropanol 10:1 giving 0.58 g of an orange powder: mass spectrum (electrospray, m/e): $M+H^+$ 511.9.

Example 188

2-amino-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 0.7 g of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (Example 25) was prepared by warming. After cooling, ammonia was bubbled in for 3 minutes. The mixture was stirred for 20 minutes and diluted with ether. The solid was collected, dissolved in chloroform and poured onto a column of Magnasol™. The product was eluted with chlorform-isopropanol mixtures to yield 0.19 g of product as a orange-brown powder: mass spectrum (electrospray, m/e): $M+H^+$ 371.0.

Example 189

2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared from of N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide and 5-amino-2-chloro-3,4-dimethoxy-phenol using the combined methods described above in Examples 16 and 17: mass spectrum (electrospray, m/e): $M+H^+$ 436.1.

Example 190

2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-6-(methylthio)benzo-1,4-quinone

Methyl mercaptan was bubbled into a solution of 2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (Example 189) in 50 ml of methylene chloride containing 1 drop of triethylamine. After 1.5 hours, the solvent was removed, the residue stirred with ether and the solid collected. The solid was dissolved in hot acetonitrile (50 ml) and 0.3 g of DDC was added. After 10 minutes, the mixture was diluted with chloroform and the solution was passed through a column of Magnasol™. The solvent was removed and the product was purified by chromatography yielding 0.36 g of a blue-black powder: mass spectrum (electrospray, m/e): $M+H^+$ 468.0.

Example 191

5-methoxy-3-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-2-(methylthio)benzo-1,4-quinone

This compound was prepared from 2-methoxy-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (Example 17) and methyl mercaptan using the method described above for Example 190: mass spectrum (electrospray, m/e): $M+H^+$ 432.1.

Example 192

2-bromo-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared from of N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide and 3-bromo-2,5-dimethoxy-aniline using the combined methods described above in Examples 16 and 17: mass spectrum (electrospray, m/e): $M+H^+$ 434.0

Examples 193-211

A phenol (0.152 mmol) and the phase transfer catalyst tricaprylylmethylammonium chloride (0.01 mmol) were treated with an equivalent amount of 1 N NaOH, to which methylene chloride (2 ml) and water (1 ml) were added. This solution was stirred for

15 minutes. The biphasic mixture was then treated with the 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (0.101 mmol) in a methylene chloride solution to give a total volume of 8 ml in the reaction. The reactions were agitated with a vortex shaker for a time ranging from 2 to 48 hours. Completion of the reaction was determined by LC-MS. The organic layers were then separated and the aqueous solution was extracted further with methylene choride (2x 2 ml). The organic layers were combined and dried over magnesium sulfate and concentrated. The reactions, which showed only desired quinone as the major component, were purified by either recrystallization from acetonitrile or silica gel chromatography. Some reactions showed a substantial amount of the desired product in reduced form. These reactions were treated with an excess of DDQ in methylene chloride (2 ml) and were agitated with a vortex shaker overnight. The reactions were washed with a saturated potassium carbonate solution (3x 2 ml) and the organic layers dried over magnesium sulfate and concentrated. Again, the reactions which showed only desired quinone as the major component were purified by either recrystallization from acetonitrile or silica gel chromatography. By using this method, the compounds of this invention listed in Table 13 were prepared starting with the indicated phenol.

Table 13

Example	Phenol	Compound Name	Mass spectrum (M+H)
193	4-hydroxybenzamide	4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzamide	491.5
194	m-cresol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(3-methylphenoxy)benzo-1,4-quinone	462.5
195	4-benzyloxyphenol	2-[4-(benzyloxy)phenoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	554.6
196	3-acetamidophenol	N-{3-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]phenyl}acetamide	505.5
197	5-hydroxyisoquinoline	2-(isoquinolin-5-yloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-	499.5

		yl]amino}benzo-1,4-quinone	
198	2-allylphenol	2-(2-allylphenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	488.5
199	trifluoromethyl-m-cresol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[3-(trifluoromethyl)phenoxy]benzo-1,4-quinone	516.5
200	o-hydroxybenzophenone	2-(2-benzoylphenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	552.5
201	2-bromophenol	2-(2-bromophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	526.4
202	2-chlorophenol	2-(2-chlorophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	482.9
203	2-cyanophenol	2-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzonitrile	473.5
204	6-hydroxylquinoline	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(quinolin-6-yloxy)benzo-1,4-quinone	499.5
205	2'-hydroxy-1'-acetonaphthone	2-[(1-acetyl-2-naphthyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	540.6
206	1'-hydroxy-2'-acetonaphthone	2-[(2-acetyl-1-naphthyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	540.6
207	4-(4-hydroxy phenyl)-2-butanone	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(3-oxobutyl)phenoxy]benzo-1,4-quinone	518.5
208	2-hydroxydibenzofuran	2-(dibenzo[b,d]furan-2-yloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	538.5
209	6-hydro-1,3-benzoxathiol-2-one	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(2-oxo-1,3-benzoxathiol-6-yl)oxy]benzo-1,4-quinone	538.5
210	4-chloro-1-naphthol	2-[(4-chloro-1-naphthyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	532.9
211	methyl 3-hydroxy-2-naphthoate	methyl 3-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]-2-naphthoate	556.6

Examples 212-222

2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone was dissolved in methylene chloride and treated with sodium phenoxide (trihydrate, 2.0 equivalents) and the listed alcohol in a 10-fold excess. The reaction was then agitated with a vortex shaker overnight. The reactions that were determined to be complete by LC-MS were washed with water, saturated sodium carbonate and dried over sodium sulfate. The solutions were concentrated. The resulting residues were purified by either HPLC or crystallization from acetonitrile. By using this method, the compounds of this invention listed in Table 14 were prepared starting with the indicated alcohol.

Table 14

Example	Alcohol	Compound Name	Mass Spectrum (M+H)
212	1,3-difluoro-2-propanol	2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	450.5
213	cyclopropane methanol	2-(cyclopropylmethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	426.5
214	cyclopentanol	2-(cyclopentyloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	440.5
215	cyclohexylmethanol	2-(cyclohexylmethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	468.5
216	2-cyanoethanol	3-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]propanenitrile	425.2
217	2-phenoxyethanol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-phenoxyethoxy)benzo-1,4-quinone	492.6
218	3-methoxybenzyl alcohol	2-[(3-methoxybenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	492.5
219	2,2,2-trifluoroethanol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2,2,2-trifluoroethoxy)benzo-1,4-quinone	454.5
220	3-hydroxy tetrahydrofuran	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(tetrahydrofuran-3-yloxy)benzo-1,4-quinone	442.5
221	3-(hydroxymethyl)	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-	463.1

	pyridine	4-yl]amino}-5-(pyridin-3-ylmethoxy)benzo-1,4-quinone	
222	2-(methylphenyl amino)ethanol	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-{2-[methyl(phenyl)amino]ethoxy}benzo-1,4-quinone	505.5

Example 223

5-({[4-methoxy-3-(2-methoxyethoxy)phenyl]amino}methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione

To a stirred solution of 4-methoxy-3-(2-methoxyethoxy)aniline (16.04 g, 81.41 mmol), Meldrum's acid (12.89 g, 89.55 mmol) and trimethyl ortho formate (11 mL, 97.69 mmol) were added neat and sequentially. The solution was refluxed for 5 hours. The reaction was cooled to room temperature and the resulting solid was collected by vacuum filtration, 19.47 g (68%) of the title compound as a white solid, mass spectrum (electrospray, m/e): M+H 352.2.

Example 224

6-methoxy-7-(2-methoxyethoxy)quinolin-4(1H)-one

To a refluxing solution of dowtherm (10 ml), 5-({[4-methoxy-3-(2-methoxyethoxy)phenyl]amino}methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.5 g, 7.12 mmol) was added neat. The reaction was refluxed for 1 hour. The reaction was then cooled to room temperature. The resulting solid was collected by vacuum filtration and washed with hexanes, yielding 1.68 g of the title compound as a tan solid (94%), mass spectrum (electrospray, m/e): M+H 250.1.

Example 225

4-chloro-6-methoxy-7-(2-methoxyethoxy)quinoline

6-methoxy-7-(2-methoxyethoxy)quinolin-4(1H)-one (1.11 g, 4.47 mmol) was refluxed in $POCl_3$ (30 ml) neat for 5 hours. The reaction was cooled to room temperature and concentrated. The brown residue was cooled 0°C and was partitioned with saturated sodium bicarbonate and ethyl acetate. The layers were separated and the organic layer was washed with saturated sodium bicarbonate. The organic solution was passed through a magnesol plug and was concentrated to yield 583.0 mg of the title compound as a white solid (49%), mass spectrum (electrospray, m/e): M+H 268.07.

Example 226

N-(4-chloro-2,5-dimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy)quinolin-4-amine

4-chloro-6-methoxy-7-(2-methoxyethoxy)quinoline (222.0 mg, 0.83 mmol) and 4-chloro-2,5-dimethoxy-aniline (468.9 mg, 2.49 mmol) were refluxed in methoxyethanol (20 mL) for several hours. The solvent was removed and the residue was partitioned with saturated sodium bicarbonate and ethyl acetate. The layers were separated and the organic layer was washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated to give 228.1 mg (66%) of the title compound, mass spectrum (electrospray, m/e): M+H 419.1.

Example 227

2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinolin-4-yl]amino}benzo-1,4-quinone

N-(4-chloro-2,5-dimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy)quinolin-4-amine (228.3 mg, 0.55 mmol) was refluxed in the presence of ceric ammonium nitrate (658.5 mg, 1.2 mmol) in acetonitrile (10 ml)/water (2 ml) for 1 hour. The aqueous solution was extracted with methylene chloride (3X). The organic layers were combined washed with water, dried over sodium sulfate and concentrated to give 129.5 mg of a red solid (61%), mass spectrum (electrospray, m/e): M+H 389.08.

Example 228

2-{[6-methoxy-7-(2-methoxyethoxy)quinolin-4-yl]amino}-5-[4-(1-methyl-1-phenylethyl)phenoxy]benzo-1,4-quinone

2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinolin-4-yl]amino}benzo-1,4-quinone (205.4 mg, 0.529 mmol) was dissolved in methylene chloride (4 ml), treated with water (2 ml), 1N NaOH (530 µl), a catalytic amount of aliquot and 4-(1-methyl-1-phenyl-ethyl)-phenol (145.9 mg, 0.69 mmol). The biphasic mixture was stirred at room temperature for 2 hours. The phases were separated and the aqueous layer was extracted with methylene chloride (3X). The organic layers were combined and passed through a magnesol plug and concentrated to give 230.7 mg of the title compound as a red solid (77%), mass spectrum (electrospray, m/e): M+H 565.2.

Example 229

2-(dimethylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinolin-4-yl]amino}benzo-1,4-quinone

2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinolin-4-yl]amino}benzo-1,4-quinone (160.6 mg, 0.414 mmol) was dissolved in tetrahydrofuran (5 ml) and was treated with pyridinium hydrochloride (47.83 mg, 0.414 mmol) and a solution of dimethylamine (2.1 ml, 2.0 M, 4.14 mmol) in tetrahydrofuran. The mixture was stirred for 3 hours. The resulting solid was collected by vacuum filtration and washed with water, yielding 128.9 mg (78%) of the title compound as red solid, mass spectrum (electrospray, m/e): M-H 396.15.

Example 230

N-(4-bromo-2,5-dimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy) quinazolin-4-amine

This compound was prepared from N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide (8.32 g, 30 mmol) and 4-bromo-2,5-dimethoxy-phenylamine (7.66 g, 33 mmol) in HOAc (30 mL) using the procedure described above for Example 14 to give 12.17 g (87%) of the title compound as a grey solid: mp 217-221 °C; MS (ESI) *m/z* 464; ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm 3.34 (s, 3 H) 3.71 - 3.77 (m, 5 H) 3.78 - 3.80 (m, 3 H) 3.94 (s, 3 H) 4.22 - 4.28 (m, 2 H) 7.18 (s, 1 H) 7.34 (s, 1 H) 7.37 (s, 1 H) 7.79 (s, 1 H) 8.32 (s, 1 H) 9.18 (s, 1 H).

Example 231

2-bromo-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino} benzo-1,4-quinone

This compound was prepared from N-(4-bromo-2,5-dimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy) quinazolin-4-amine (300 mg, 0.65 mmol) and CAN (0.78 g, 1.43 mmol) in CH_3CN (8.6 mL) and H_2O (1.1 mL) to give 256 mg (90.6%) of the product as a purple red solid: mp 200-210 °C; HRMS: calcd for $C_{18}H_{16}BrN_3O_5$ + H+, 434.03461; found (ESI-FTMS, $[M+H]^{1+}$), 434.03449; ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 3.49 (s, 3 H) 3.88 – 3.90 (m, 2 H) 4.07 (s, 3 H) 4.33 - 4.35

(m, 2 H) 7.03 (s, 1 H) 7.40 (s, 1 H) 8.34 (s, 1 H) 8.46 (s, 1 H) 8.83 (s, 1 H). HPLC purity 84.4% at 215 nm, 10.9 min.; Prodigy ODS3, 0.46 x 15 cm column, 1.0 mL /min, 20min Gradient ACN in H_2O/TFA.

Example 232

2-[benzyl(4-methoxyphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

To a suspension of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino} benzo-1,4-quinone (150 mg, 0.4 mmol) and Et_3N (263 mL, 1.92 mmol) in 3 mL CH_2Cl_2 at 60°C, 4-(2-methoxy-benzyl)piperidine (791.4 mg, 3.86 mmol) was added. The reaction mixture was stirred at 60°C for 2 hours and then filtered through a pad of magnesol with CH_2Cl_2. The solvent was removed *in vacuo*. The residue was triturated with Et_2O. The resulting solid was purified by silica gel column (3% MeOH / CH_2Cl_2) and Gilson HPLC to give 161.4 mg (55%) of the title compound: MS (ESI) *m/z* 567.2; HRMS: calcd for $C_{32}H_{30}N_4O_6$ + H+, 567.22381; found (ESI-FTMS, $[M+H]^{1+}$), 567.2231.

Examples 233-235

To a suspension of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (150 mg, 0.4 mmol) and Et_3N (263 mL, 1.92 mmol) in 3 mL CH_2Cl_2 at 60°C, the appropriate aniline (~3.9 mmol) was added. The reaction mixture was stirred at 60°C for 2 hours and filtered through a pad of magnesol with CH_2Cl_2. The solvent was removed *in vacuo*. The residue was triturated with Et_2O. The resulting solid was purified by silica gel column (3% MeOH / CH_2Cl_2) and Gilson HPLC to give the title compound. The compounds of the invention made by this method are listed in Table 15.

Table 15

Example	Compound Name	MS	HRMS
233	2-[ethyl(4-methylphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 489.2	HRMS: calcd for $C_{27}H_{28}N_4O_5$ + H+, 489.21325; found (ESI-FTMS, $[M+H]^{1+}$), 489.21332
234	2-[butyl(phenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI-FTMS) m/z 503.22849; MS (ESI-FTMS) m/z 503.2289	HRMS: calcd for $C_{28}H_{30}N_4O_5$ + H+, 503.22890; found (ESI-FTMS, $[M+H]^{1+}$), 503.22849
235	2-[ethyl(phenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 475.2	HRMS: calcd for $C_{26}H_{26}N_4O_5$ + H+, 475.19760; found (ESI-FTMS, $[M+H]^{1+}$), 475.19711

Example 236

2-(5-bromo-2,3-dihydro-1*H*-indol-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (150 mg, 0.38 mmol) and 18-crown-6 (10 mg, 0.4 mmol) in 4 mL DMF was stirred at 60°C for 1 hour. 5-bromoindoline (191 mg, 0.96 mmol) in 2 mL DMF was added. The reaction mixture was stirred at 60°C for 3 hours. It was filtered through a pad of magnesol with CH_2Cl_2 / THF. The solvent was removed *in vacuo*. The residue was purified by column eluting with CH_2Cl_2 and 30 % CH_2Cl_2 / THF. The solvent of the product fraction was evaporated to yield 116.9 mg (55%) of the title compound: HRMS: calcd for $C_{26}H_{23}BrN_4O_5$ + H+, 551.09246; found (ESI-FTMS, $[M+H]^{1+}$), 551.09118.

Examples 237-242

A solution of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (150 mg, 0.38 mmol) and 18-crown-6 (10 mg, 0.4 mmol) in 4 mL DMF was stirred at 60°C for 1 hour. The appropriate aniline (~ 1.0 mmol) in 2 mL DMF was added and the reaction mixture was stirred at 60°C for 3 hours and filtered through a pad of magnesol with CH_2Cl_2 / THF. The solvent was removed *in vacuo*. The residue was purified by column eluting with CH_2Cl_2 and 30 % CH_2Cl_2 / THF. The solvent of the product fraction was evaporated to yield the title compound. The compounds of the invention are listed in Table 16.

Table 16

Example	Compound Name	MS	HRMS
237	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(3-methylphenyl)amino]benzo-1,4-quinone	MS (ESI) m/z 475.1	HRMS: calcd for $C_{26}H_{26}N_4O_5$ + H+, 475.19760; found (ESI-FTMS, $[M+H]^{1+}$), 475.19806
238	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[pentyl(phenyl)amino]benzo-1,4-quinone	MS (ESI) m/z 517.2	HRMS: calcd for $C_{29}H_{32}N_4O_5$ + H+, 517.24455; found (ESI-FTMS, $[M+H]^{1+}$), 517.24497
239	2-(2,3-dihydro-1H-indol-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI+) m/z 473.1	HRMS: calcd for $C_{26}H_{24}N_4O_5$ + H+, 473.18195; found (ESI-FTMS, $[M+H]^{1+}$), 473.18255
240	2-[(4-chlorophenyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI+) m/z 495.1	HRMS: calcd for $C_{25}H_{23}ClN_4O_5$ + H+, 495.14297; found (ESI-FTMS, $[M+H]^{1+}$), 495.14368
241	2-[1,3-benzodioxol-5-yl(ethyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI+) m/z 519.1	HRMS: calcd for $C_{27}H_{26}N_4O_7$ + H+, 519.18743; found (ESI-FTMS, $[M+H]^{1+}$), 519.18768
242	2-[ethyl(1-naphthyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 525.2; MS (ESI) m/z 283.6; MS (ESI) m/z 263.1	HRMS: calcd for $C_{30}H_{28}N_4O_5$ + H+, 525.21325; found (ESI-FTMS, $[M+H]^{1+}$), 525.2124

Examples 243-257

A solution of 0.97 g (2.5 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 0.29 g of pyridine hydrochloride, and the appropriate amine or piperazine in THF, in 15 ml of THF, was stirred for 3 hours. The solid was collected via filtration and washed with water and dried to give the title compound. The compounds of the invention made by this method are listed in Table 17.

Table 17

Example	Compound Name	MS	HRMS
243	3-chloro-2-[4-(3-chlorobenzyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 598; MS (ESI) m/z 299.5; MS (ESI) m/z 320	HRMS: calcd for $C_{29}H_{29}Cl_2N_5O_5$ + H+, 598.16185; found (ESI-FTMS, $[M+H]^{1+}$), 598.16231
244	2-[(3-hydroxy-3-phenylpropyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 519.2	HRMS: calcd for $C_{28}H_{30}N_4O_6$ + H+, 519.22381; found (ESI_FTMS, $[M+H]^{1+}$), 519.22376
245	2-[4-(2,4-dimethoxybenzyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 590.1; MS (ESI) m/z 295.6	HRMS: calcd for $C_{31}H_{35}N_5O_7$ + H+, 590.26093; found (ESI-FTMS, $[M+H]^{1+}$), 590.26109
246	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(2-pyridin-2-ylethyl)amino]benzo-1,4-quinone	MS (ESI) m/z 490.2; MS (ESI) m/z 245.6	HRMS: calcd for $C_{26}H_{27}N_5O_5$ + H+, 490.20850; found (ESI_FTMS, $[M+H]^{1+}$), 490.20811
247	4-{[4-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)piperazin-1-yl]methyl}benzonitrile	MS (ESI) m/z 555.3; MS (ESI) m/z 278.2; MS (ESI) m/z 298.7	HRMS: calcd for $C_{30}H_{30}N_6O_5$ + H+, 555.23505; found (ESI-FTMS, $[M+H]^{1+}$), 555.23495
248	2-{4-[4-(dimethylamino)benzyl]piperazin-1-yl}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 573.3	HRMS: calcd for $C_{31}H_{36}N_6O_5$ + H+, 573.28200; found (ESI-FTMS, $[M+H]^{1+}$), 573.28393
249	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-	MS (ESI) m/z 510.2; MS	HRMS: calcd for $C_{27}H_{35}N_5O_5$ + H+,

	yl]amino}-5-[4-(2-methylbutyl)piperazin-1-yl]benzo-1,4-quinone	(ESI) m/z 255.6	510.27110; found (ESI-FTMS, $[M+H]^{1+}$), 510.2696
250	2-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 574.2; MS (ESI) m/z 287.6; MS (ESI) m/z 308.1	HRMS: calcd for $C_{30}H_{31}N_5O_7$ + H+, 574.22963; found (ESI-FTMS, $[M+H]^{1+}$), 574.22908
251	2-[4-(3-fluorobenzyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 548.2; MS (ESI) m/z 274.6; MS (ESI) m/z 295.1	HRMS: calcd for $C_{29}H_{30}FN_5O_5$ + H+, 548.23037; found (ESI-FTMS, $[M+H]^{1+}$), 548.22888
252	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(2-thienylmethyl)piperazin-1-yl]benzo-1,4-quinone	MS (ESI) m/z 536.2; MS (ESI) m/z 268.6; MS (ESI) m/z 289.1	HRMS: calcd for $C_{27}H_{29}N_5O_5S$ + H+, 536.19622; found (ESI-FTMS, $[M+H]^{1+}$), 536.19525
253	2-[4-(3,7-dimethyloct-6-en-1-yl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 578.3; MS (ESI) m/z 289.6	HRMS: calcd for $C_{32}H_{43}N_5O_5$ + H+, 578.33370; found (ESI-FTMS, $[M+H]^{1+}$), 578.33375
254	2-[4-(2-furylmethyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 520.2; MS (ESI) m/z 260.6	HRMS: calcd for $C_{27}H_{29}N_5O_6$ + H+, 520.21906; found (ESI-FTMS, $[M+H]^{1+}$), 520.21863
255	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(pyridin-3-ylmethyl)piperazin-1-yl]benzo-1,4-quinone	MS (ESI) m/z 531.2; MS (ESI) m/z 266.1; MS (ESI) m/z 286.6	HRMS: calcd for $C_{28}H_{30}N_6O_5$ + H+, 531.23505; found (ESI-FTMS, $[M+H]^{1+}$), 531.23518
256	2-[4-(2,4-dimethoxybenzyl)-1,4-diazepan-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 604.2; MS (ESI) m/z 302.6	HRMS: calcd for $C_{32}H_{37}N_5O_7$ + H+, 604.27658; found (ESI-FTMS, $[M+H]^{1+}$), 604.2777

257	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(2-methylbutyl)-1,4-diazepan-1-yl]benzo-1,4-quinone	MS (ESI) m/z 524.2; MS (ESI) m/z 262.6	HRMS: calcd for $C_{28}H_{37}N_5O_5$ + H+, 524.28675; found (ESI-FTMS, $[M+H]^{1+}$), 524.2864

Examples 258-260

A solution of 0.20 g (0.51 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 0.06 g of pyridine hydrochloride and the appropriate amine in 2 ml of THF was sonicated for 0.5 hour at 40°C, then shaken at 40°C for 3 hours. The solid was collected via filtration and washed with water and dried to give the title compound. The compounds of the invention made by this method are listed in Table 18.

Table 18

Example	Compound Name	MS	HRMS
258	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(2-naphthylmethyl)piperazin-1-yl]benzo-1,4-quinone	MS (ESI) m/z 580.1; MS (ESI) m/z 290.6	HRMS: calcd for $C_{33}H_{33}N_5O_5$ + H+, 580.25545; found (ESI-FTMS, $[M+H]^{1+}$), 580.25435
259	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(1-naphthylmethyl)piperazin-1-yl]benzo-1,4-quinone	MS (ESI) m/z 580.2; MS (ESI) m/z 290.6	HRMS: calcd for $C_{33}H_{33}N_5O_5$ + H+, 580.25545; found (ESI-FTMS, $[M+H]^{1+}$), 580.25619
260	2-[4-(3-chlorobenzyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 564.1; MS (ESI) m/z 282.5; MS (ESI) m/z 303.1	HRMS: calcd for $C_{29}H_{30}ClN_5O_5$ + H+, 564.20082; found (ESI-FTMS, $[M+H]^{1+}$), 564.2007

Example 261

2-[4-(2-methoxybenzyl)piperidin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

To a suspension of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (150 mg, 0.4 mmol) and Et_3N (263 mL, 1.92 mmol) in 3 mL CH_2Cl_2 at 60 °C was added the appropriate amine (~3.9 mmol). The reaction mixture was stirred at 60°C for 2 hours. It was filtered through a pad of magnesol with CH_2Cl_2. The solvent was removed *in vacuo*. The residue was triturated with Et_2O. The resulting solid was purified by silica gel column (3% MeOH / CH_2Cl_2) and Gilson HPLC to give the title compound:MS (ESI) *m/z* 559.2; HRMS: calcd for $C_{31}H_{34}N_4O_6$ + H+, 559.25511; found (ESI-FTMS, $[M+H]^{1+}$), 559.25342.

Example 262

5-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-(ethylthio)-2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

To a degassed stirred solution of acetonitrile:deionized (MilliQ) water (1:1, 1000mL) of the quinone (~0.1 mmol, 40 mg) under N_2, ethanethiol (10 equiv., ~0.1 mL) was added. The solution was stirred until starting material was consumed as shown by TLC or LCMS (1 hour-5 days). At the end of the reaction, 2.9 g of 0.7 mmol/g loading maleimide resin (Silicycle, Si-maleimide) was added to scavenge the ethanethiol. The suspension was stirred overnight, then filtered (medium frit) and extracted with 3x150mL EtOAc, dried with Na_2SO_3, and concentrated *in vacuo* (30-40°C). The crude residue was purified by RP-HPLC (C18 Phenomenex Luna 150x30mm, 20-80% MeCN:water 0.02% TFA). NaCl was added to the isolated fractions and extracted into DCM, dried with Na_2SO_3 and concentrated *in vacuo* (30-40° C) giving 3 mg of title compound: MS (ESI) m/z 634.3; MS (ESI) m/z 317.6; MS (ESI) m/z 338.1.

Example 263

N-[2,5-dimethoxy-4-(methylthio)phenyl]-6-methoxy-7-(2-methoxyethoxy) quinazolin-4-amine.

Compound N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide (885 mg, 3.19 mmol) and 2,5-dimethoxy-4-methylsulfanyl-phenylamine (700 mg, 3.51 mmol) (Chem Ber. 1964, 285-294) were heated to 110°C in AcOH (4 mL) for 3 hours. The reaction was partitioned in water / EtOAc, the brown solid precipitates filtered and washed with water and EtOAc. The solids were dissolved in MeOH and purified in silica gel column, eluted with 2.5% MeOH/CH_2Cl_2 to yield 485 mg (35%) of the title compound as pink solids: MS (ESI) m/z 432.1; HRMS: calcd for $C_{21}H_{25}N_3O_5S$ + H+, 432.15877; found (ESI-FTMS, [M+H]1+), 432.15853; 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.44 - 2.47 (m, 3 H) 3.47 - 3.50 (m, 3 H) 3.84 - 3.92 (m, 2 H) 3.97 (s, 6 H) 4.01 - 4.10 (m, 3 H) 4.28 - 4.38 (m, 2 H) 6.93 (s, 1 H) 7.03 (s, 1 H) 7.28 - 7.32 (m, 1 H) 8.55 (s, 1 H) 8.71 (s, 1 H).

Example 264

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(methylthio)benzo-1,4-quinone

This compound was prepared from N-[2,5-dimethoxy-4-(methylthio)phenyl]-6-methoxy-7-(2-methoxyethoxy) quinazolin- 4-amine (130 mg, 0.3 mmol) and CAN (345 mg, 21.0 mmol) in $CHCl_3$ (1.5 mL), CH_3CN (3.0 mL) and H2O (0.6 mL) using the procedure described above for Example 17 to give 102 mg (84%) of the title compound as a red solid: MS (ESI) m/z 402; HRMS: calcd for $C_{19}H_{19}N_3O_5S$ + H+, 402.11182; found (ESI-FTMS, [M+H]1+), 402.11222; 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.39 (s, 3 H) 3.49 (s, 3 H) 3.88 - 3.90 (m, 2 H) 4.08 (s, 3 H) 4.33 - 4.35 (m, 2 H) 6.39 (s, 1 H) 7.07 (s, 1 H) 7.33 (s, 1 H) 8.14 (s, 1 H) 8.72 (s, 1 H) 8.83 (s, 1 H).

Examples 265-292

2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone was dissolved in methylene chloride and treated with sodium phenoxide (trihydrate, 2.0 equivalents) and the appropriate alcohol in a 10-fold excess. The reaction was then agitated with a vortex shaker overnight. The reactions that were determined to be complete by LC-MS were washed with water and saturated sodium carbonate, dried over sodium sulfate and concentrated. The resulting residues were purified by either HPLC or crystallization from acetonitrile. The compounds of the invention made by this method are listed in Table 19.

Table 19

Example	Compound Name	MS	HRMS
265	2-[(2-chlorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 496.1	HRMS: calcd for $C_{25}H_{22}ClN_3O_6$ + H+, 496.12699; found (ESI-FTMS, $[M+H]^{1+}$), 496.12636
266	2-isopropoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 414.1	HRMS: calcd for $C_{21}H_{23}N_3O_6$ + H+, 414.16596; found (ESI-FTMS, $[M+H]^{1+}$), 414.16758
267	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(1-methylbutoxy)benzo-1,4-quinone	MS (ESI) m/z 442.1	HRMS: calcd for $C_{23}H_{27}N_3O_6$ + H+, 442.19726; found (ESI-FTMS, $[M+H]^{1+}$), 442.1989
268	2-(cycloheptyloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 468.1	HRMS: calcd for $C_{25}H_{29}N_3O_6$ + H+, 468.21291; found (ESI-FTMS, $[M+H]^{1+}$), 468.21393
269	2-sec-butoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 428.1	HRMS: calcd for $C_{22}H_{25}N_3O_6$ + H+, 428.18161; found (ESI-FTMS, $[M+H]^{1+}$), 428.18304
270	2-(1-ethylpropoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 442.1	HRMS: calcd for $C_{23}H_{27}N_3O_6$ + H+, 442.19726; found (ESI-FTMS, $[M+H]^{1+}$), 442.19858
271	2-[(1,4-dimethylpentyl)oxy]-5-{[6-methoxy-7-(2-	MS (ESI) m/z 470.2	HRMS: calcd for $C_{25}H_{31}N_3O_6$ + H+,

	methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone		470.22856; found (ESI-FTMS, $[M+H]^{1+}$), 470.22845
272	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(1-methylpiperidin-3-yl)oxy]benzo-1,4-quinone	MS (ESI) m/z 469.1; MS (ESI) m/z 235	HRMS: calcd for $C_{24}H_{28}N_4O_6$ + H+, 469.20816; found (ESI-FTMS, $[M+H]^{1+}$), 469.20801
273	2-[(2-fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 480.1	HRMS: calcd for $C_{25}H_{22}FN_3O_6$ + H+, 480.15654; found (ESI-FTMS, $[M+H]^{1+}$), 480.1564
274	2-[(3-fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 480.2	HRMS: calcd for $C_{25}H_{22}FN_3O_6$ + H+, 480.15654; found (ESI-FTMS, $[M+H]^{1+}$), 480.15514
275	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(tetrahydro-2H-pyran-2-ylmethoxy)benzo-1,4-quinone	MS (ESI+) m/z 470.2	HRMS: calcd for $C_{24}H_{27}N_3O_7$ + H+, 470.19218; found (ESI-FTMS, $[M+H]^{1+}$), 470.19192
276	2-[(4-fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 480.2	HRMS: calcd for $C_{25}H_{22}FN_3O_6$ + H+, 480.15654; found (ESI-FTMS, $[M+H]^{1+}$), 480.15548
277	2-[(4-methoxybenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 492.2	
278	2-(2,3-dihydro-1H-inden-2-yloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 488.2	
279	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-	MS (ESI) m/z	

	yl]amino}-5-(3-phenoxypropoxy)benzo-1,4-quinone	506.2	
280	2-ethoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 400.1	HRMS: calcd for $C_{20}H_{21}N_3O_6$ + H+, 400.15031; found (ESI-FTMS, $[M+H]^{1+}$), 400.15058
281	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2,2,2-trifluoro-1-phenylethoxy)benzo-1,4-quinone	MS (ESI) m/z 530.1	HRMS: calcd for $C_{26}H_{22}F_3N_3O_6$ + H+, 530.15335; found (ESI-FTMS, $[M+H]^{1+}$), 530.15321
282	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3R)-THF-3-yloxy]benzo-1,4-quinone	MS (ESI) m/z 442.1	HRMS: calcd for $C_{22}H_{23}N_3O_7$ + H+, 442.16088; found (ESI-FTMS, $[M+H]^{1+}$), 442.16066
283	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3S)-THF-3-yloxy]benzo-1,4-quinone	MS (ESI) m/z 442.1	HRMS: calcd for $C_{22}H_{23}N_3O_7$ + H+, 442.16088; found (ESI-FTMS, $[M+H]^{1+}$), 442.16092
284	2-{[1-(4-chlorophenyl)cyclopropyl]methoxy}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 536.1	
285	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(pentafluorobenzyl)oxy]benzo-1,4-quinone	MS (ESI) m/z 552.1	HRMS: calcd for $C_{25}H_{18}F_5N_3O_6$ + H+, 552.11885; found (ESI-FTMS, $[M+H]^{1+}$), 552.1169
286	2-(2,2-difluoroethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 436.1; MS (ESI) m/z 871.2	HRMS: calcd for $C_{20}H_{19}F_2N_3O_6$ + H+, 436.13147; found (ESI-FTMS, $[M+H]^{1+}$), 436.13104

287	2-[(2,3,3,4,4,5-hexafluorocyclopentyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 548.1	HRMS: calcd for $C_{23}H_{19}F_6N_3O_6$ + H+, 548.12508; found (ESI-FTMS, $[M+H]^{1+}$), 548.12599
288	2-(1,3-benzodioxol-5-ylmethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 506.1	HRMS: calcd for $C_{26}H_{23}N_3O_8$ + H+, 506.15579; found (ESI-FTMS, $[M+H]^{1+}$), 506.15597
289	2-{[4-(benzyloxy)-3-methoxybenzyl]oxy}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 598.2	HRMS: calcd for $C_{33}H_{31}N_3O_8$ + H+, 598.21839; found (ESI-FTMS, $[M+H]^{1+}$), 598.21829
290	2-{[4-(benzyloxy)benzyl]oxy}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 568.2	HRMS: calcd for $C_{32}H_{29}N_3O_7$ + H+, 568.20783; found (ESI-FTMS, $[M+H]^{1+}$), 568.20692
291	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3-phenylprop-2-yn-1-yl)oxy]benzo-1,4-quinone	MS (ESI) m/z 486.1	HRMS: calcd for $C_{27}H_{23}N_3O_6$ + H+, 486.16596; found (ESI-FTMS, $[M+H]^{1+}$), 486.16532
292	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3-phenoxybenzyl)oxy]benzo-1,4-quinone	MS (ESI) m/z 554.1	HRMS: calcd for $C_{31}H_{27}N_3O_7$ + H+, 554.19218; found (ESI-FTMS, $[M+H]^{1+}$), 554.19197

Examples 293-296

A solution of 0.67 g (1.5 mmol) of 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-phenoxybenzo-1,4-quinone, 0.5 ml of triethylamine, and the appropriate alcohol (~20 mL) in 20 ml methylene chloride was stirred for 16 hours. The solvent was evaporated and the residue diluted with ether. The solid was collected and

washed with ether giving the appropriate compound. The compounds of the invention made by this method are listed in Table 20.

Table 20

Example	Compound Name	MS	HRMS
293	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(tetrahydro-2H-pyran-4-yloxy)benzo-1,4-quinone	MS (ESI+) m/z 456.2	HRMS: calcd for $C_{23}H_{25}N_3O_7$ + H+, 456.17653; found (ESI-FTMS, $[M+H]^{1+}$), 456.17691
294	2-[2-(dimethylamino)-1-methylethoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 457.1; MS (ESI) m/z 229.1	HRMS: calcd for $C_{23}H_{28}N_4O_6$ + H+, 457.20816; found (ESI-FTMS, $[M+H]^{1+}$), 457.20793
295	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(THF-3-ylmethoxy)benzo-1,4-quinone	MS (ESI) m/z 456.1	HRMS: calcd for $C_{23}H_{25}N_3O_7$ + H+, 456.17653; found (ESI-FTMS, $[M+H]^{1+}$), 456.17542
296	2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3-methyloxetan-3-yl)methoxy]benzo-1,4-quinone	MS (ESI+) m/z 456.2	HRMS: calcd for $C_{23}H_{25}N_3O_7$ + H+, 456.17653; found (ESI-FTMS, $[M+H]^{1+}$), 456.17556

Example 297

2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(1-methylpyrrolidin-3-yl)oxy]benzo-1,4-quinone

A solution of 0.97 g (2.5 mmol) of 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone, 0.29 g of pyridine hydrochloride, and 5 ml of the 3-hydroxy-1-methylpyrrolidine in THF, in 15 ml of THF, was stirred for 3 hours. The solid was collected via filtration and washed with water and dried to yield 0.94 g of the title compound as a light brown solid: mass spectrum (electrospray, m/e): M-H 399.2; MS (ESI+) m/z 455.2; HRMS: calcd. for $C_{23}H_{26}N_4O_6$ + H+, 455.19251; found (ESI-FTMS, $[M+H]^{1+}$), 455.19148.

Example 298

2-[(3-fluorobenzyl)oxy]-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

To a suspension of *N*-(4-chloro-2,5-dimethoxyphenyl)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-amine (890 mg, 1.88 mmol) in 45 mL CH_3CN and 22 mL H_2O, ammonium cerium (IV) nitrate (1.84 g, 5.65 mmol) was added. The reaction mixture was diluted with CH_2Cl_2. A saturated solution of Na_2CO_3 was added. The aqueous layer was extracted (3X) with CH_2Cl_2. The solution containing the quinone intermediate (a final volume of 500 mL CH_2Cl_2) was dried over $MgSO_4$. NaOPh($3H_2O$) (595.1 mg, 3.76 mmol) was dissolved in warm 3-fluorobenzyl alcohol (2.85 g, 22.58 mmol) and then added to the solution of quinone. About 150 mL of solvent was removed at 45°C over 15 minutes. The reaction mixture was filtered through a plug of magnesol, eluting with $CHCl_3$, EtOAc, EtOAc / isopropanol and EtOAc / isopropanol / Et_3N = 80:20:1. The solvent was removed from product fractions to yield 0.163 g (16.2 %) of title compound as an orange solid: MS (ESI) *m/z* 533.1; MS (ESI) *m/z* 267; MS (ESI) *m/z* 287.6; ^{1}H NMR (400 MHz, $CDCL_3$) δ ppm 1.80 (s, 4 H) 2.09 - 2.22 (m, 2 H) 2.55 (s, 4 H) 2.68 (t, *J*=7.30 Hz, 2 H) 4.07 (s, 3 H) 4.27 (t, *J*=6.55 Hz, 2 H) 5.12 (s, 2 H) 6.02 (s, 1 H) 7.05 (s, 1 H) 7.07 - 7.11 (m, 1 H) 7.16 (d, *J*=9.06 Hz, 1 H) 7.21 (d, *J*=8.06 Hz, 1 H) 7.33 (s, 1 H) 7.36 - 7.43 (m, 1 H) 8.09 (s, 1 H) 8.71 (s, 1 H) 8.82 (s, 1 H); Anal. ($C_{29}H_{29}FN_4O_5 \cdot 0.5\ H_2O$) C, H, N.

Examples 299-323

To a suspension of *N*-(4-chloro-2,5-dimethoxyphenyl)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-amine (890 mg, 1.88 mmol) in 45 mL CH_3CN and 22 mL H_2O, ammonium cerium (IV) nitrate (1.84 g, 5.65 mmol) was added. The reaction mixture was diluted with CH_2Cl_2. A saturated solution of Na_2CO_3 was added. The aqueous layer was extracted (3X) with CH_2Cl_2. The solution containing the quinone intermediate (a final volume of 500 mL CH_2Cl_2) was dried over $MgSO_4$. NaOPh($3H_2O$) (595.1 mg, 3.76 mmol) was dissolved in the appropriate warm alcohol (~23 mmol) and then added to the solution of quinone. About 150 mL of solvent was removed at 45°C over 15 minutes. The reaction mixture was filtered through a plug of magnesol, eluting with $CHCl_3$, EtOAc, EtOAc / isopropanol and EtOAc / isopropanol / Et_3N = 80:20:1. The solvent was removed from product fractions to yield the title compound. The compounds of the invention made by this method are listed in Table 21.

Table 21

Example	Compound Name	MS	HRMS
299	2-[(2-hydroxyethyl)amino]-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 468.1; MS (ESI) m/z 234.5	
300	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(1-methylprop-2-yn-1-yl)oxy]benzo-1,4-quinone	MS (ESI) m/z 477.2; MS (ESI) m/z 239.1; MS (ESI) m/z 259.6	
301	2-(allyloxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 465.1; MS (ESI) m/z 233.1; MS (ESI) m/z 253.6	
302	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(prop-2-yn-1-yloxy)benzo-1,4-quinone	MS (ESI) m/z 463.1; MS (ESI) m/z 232; MS (ESI) m/z 252.6	
303	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(1-phenylprop-2-yn-1-yl)oxy]benzo-1,4-quinone	MS (ESI) m/z 539.1; MS (ESI) m/z 270.1	
304	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(THF-3-yloxy)benzo-1,4-quinone	MS (ESI) m/z 495.2; MS (ESI) m/z 248.1; MS (ESI) m/z 268.6	HRMS: calcd for $C_{26}H_{30}N_4O_6$ + H+, 495.22381; found (ESI-FTMS, $[M+H]^{1+}$), 495.22402
305	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(2-methylbenzyl)oxy]benzo-1,4-quinone	MS (ESI) m/z 529.2; MS (ESI) m/z 265.1; MS (ESI) m/z 285.6	HRMS: calcd for $C_{30}H_{32}N_4O_5$ + H+, 529.24455; found (ESI-FTMS, $[M+H]^{1+}$), 529.24463

306	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-{[4-(methylsulfonyl)benzyl]oxy}benzo-1,4-quinone	MS (ESI) m/z 593.1; MS (ESI) m/z 297.1	HRMS: calcd for $C_{30}H_{32}N_4O_7S$ + H+, 593.20645; found (ESI-FTMS, $[M+H]^{1+}$), 593.20469
307	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(pentafluorobenzyl)oxy]benzo-1,4-quinone	MS (ESI) m/z 605.1; MS (ESI) m/z 323.5	HRMS: calcd for $C_{29}H_{25}F_5N_4O_5$ + H+, 605.18179; found (ESI-FTMS, $[M+H]^{1+}$), 605.1804
308	2-({4-[(4-fluorobenzyl)oxy]benzyl}oxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 639.2	HRMS: calcd for $C_{36}H_{35}FN_4O_6$ + H+, 639.26134; found (ESI-FTMS, $[M+H]^{1+}$), 639.26041
309	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-{2-[methyl(phenyl)amino]ethoxy}benzo-1,4-quinone	MS (ESI) m/z 558.2; MS (ESI) m/z 279.6	HRMS: calcd for $C_{31}H_{35}N_5O_5$ + H+, 558.27110; found (ESI-FTMS, $[M+H]^{1+}$), 558.27113
310	2-(benzyloxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 515.1; MS (ESI) m/z 278.5; MS (ESI) m/z 278.6	
311	2-[(4-chlorobenzyl)oxy]-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 549.1; MS (ESI) m/z 275; MS (ESI) m/z 295.5	HRMS: calcd for $C_{29}H_{29}ClN_4O_5$ + H+, 549.18992; found (ESI-FTMS, $[M+H]^{1+}$), 549.18971
312	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(pyridin-3-ylmethoxy)benzo-1,4-quinone	MS (ESI) m/z 516.1; MS (ESI) m/z 258.5; MS (ESI) m/z 279.1	HRMS: calcd for $C_{28}H_{29}N_5O_5$ + H+, 516.22415; found (ESI-FTMS, $[M+H]^{1+}$), 516.22542
313	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(pyridin-2-ylmethoxy)benzo-1,4-	MS (ESI) m/z 516.1; MS (ESI) m/z 258.5	

	quinone		
314	3-{[(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]methyl}benzonitrile	MS (ESI) m/z 540.1; MS (ESI) m/z 270.5; MS (ESI) m/z 291.1	
315	2-[2-chloro-1-(fluoromethyl)ethoxy]-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 519.1; MS (ESI) m/z 260; MS (ESI) m/z 280.5	HRMS: calcd for $C_{25}H_{28}ClFN_4O_5$ + H+, 519.18050; found (ESI-FTMS, $[M+H]^{1+}$), 519.1819
316	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(3-phenylprop-2-yn-1-yl)oxy]benzo-1,4-quinone	MS (ESI) m/z 539.1; MS (ESI) m/z 270.1; MS (ESI) m/z 290.6	
317	2-(2-furylmethoxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 505.2	HRMS: calcd for $C_{27}H_{28}N_4O_6$ + H+, 505.20816; found (ESI-FTMS, $[M+H]^{1+}$), 505.2077
318	2-(2,2-difluoroethoxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI+) m/z 489.1	HRMS: calcd for $C_{24}H_{26}F_2N_4O_5$ + H+, 489.19440; found (ESI-FTMS, $[M+H]^{1+}$), 489.1956
319	2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 503.1; MS (ESI) m/z 252; MS (ESI) m/z 272.6	HRMS: calcd for $C_{25}H_{28}F_2N_4O_5$ + H+, 503.21005; found (ESI-FTMS, $[M+H]^{1+}$), 503.21081
320	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(3-phenoxypropoxy)benzo-1,4-quinone	MS (ESI) m/z 559.2; MS (ESI) m/z 280.1; MS (ESI) m/z 300.6	HRMS: calcd for $C_{31}H_{34}N_4O_6$ + H+, 559.25511; found (ESI-FTMS, $[M+H]^{1+}$), 559.2544
321	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-	MS (ESI) m/z 541.2; MS	HRMS: calcd for $C_{31}H_{32}N_4O_5$ + H+,

	{[(2E)-3-phenylprop-2-en-1-yl]oxy}benzo-1,4-quinone	(ESI) m/z 271.1; MS (ESI) m/z 291.6	541.24455; found (ESI-FTMS, $[M+H]^{1+}$), 541.24582
322	2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(2-phenoxyethoxy)benzo-1,4-quinone	MS (ESI) m/z 545.2	HRMS: calcd for C30H32N4O6 + H+, 545.23946; found (ESI-FTMS, [M+H]1+), 545.24125
323	2-methoxy-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 439.1; MS (ESI) m/z 220; MS (ESI) m/z 240.5	HRMS: calcd for C23H26N4O5 + H+, 439.19760; found (ESI-FTMS, [M+H]1+), 439.1995

Example 324

N-(4-chloro-2,5-dimethoxyphenyl)-6-methoxy-7-(3-pyridin-4-ylpropoxy) quinazolin-4-amine

This compound was prepared from *N*-(4-chloro-2,5-dimethoxyphenyl)-7-fluoro-6-methoxy-*N*-(4-methoxybenzyl) quinazolin-4-amine (726 mg, 1.5 mmol), 4-pyridine propanol (0.62 g, 4.5 mmol) and sodium bis(trimethylsilyl)amide (1.0 M in THF) (3.75 mL, 3.75 mmol) in THF (1.5 mL). The residue was purified on a flash column of silica gel (2 x 20 cm), eluting with 10:10:1 CH_2Cl_2/EtOAc/MeOH and 10:1 CH_2Cl_2/MeOH to yield 625 mg (86.8%) of the title compound as a white solid: mp 205-208 °C; MS (ESI) *m/z* 481.1; MS (ESI) *m/z* 241; MS (ESI) *m/z* 261.5; ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 2.11 - 2.18 (m, 2 H) 2.79 - 2.83 (m, 2 H) 3.75 (s, 3 H) 3.80 (s, 3 H) 3.94 (s, 3 H) 4.15 (t, *J*=6.42 Hz, 2 H) 7.15 (s, 1 H) 7.22 (s, 1 H) 7.28 - 7.31 (m, 2 H) 7.38 (s, 1 H) 7.80 (s, 1 H) 8.32 (s, 1 H) 8.47 (dd, *J*=4.53, 1.51 Hz, 2 H) 9.19 (s, 1 H).

Example 325

2-chloro-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino) benzo-1,4-quinone

This compound was prepared from *N*-(4-chloro-2,5-dimethoxyphenyl)-6-methoxy-7-(3-pyridin-4-ylpropoxy) quinazolin-4-amine (4.37 g, 9.23 mmol) and CAN (11.1 g, 20.3 mmol) in CH_3CN (92 mL) and H_2O (37 mL) using the procedure described above for Example 17. The reaction mixture was stirred in $CHCl_3$ and Na_2CO_3 (0.67 M, 100 mL,) and filtered through a pad of Celite. The $CHCl_3$ layer was washed with brine, dried over $MgSO_4$, and concentrated in the presence of hexane at 25°C to yield 4.2 g (100%) of the title compound as a red solid: MS (ESI) *m/z* 443.1; MS (ESI) *m/z* 222.1; MS (ESI) *m/z* 242.6; HRMS: calcd for $C_{22}H_{23}ClN_4O_4$ + H+, 443.14806; found (ESI-FTMS, $[M+H]^{1+}$), 443.14908; ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.90 - 2.10 (m, 5 H) 2.12 - 2.28 (m, 2 H) 2.38 - 2.49 (s, 3 H) 3.09 (s, 2 H) 4.01 - 4.12 (m, 5 H) 7.03 (s, 1 H) 7.10 (s, 1 H) 7.29 (s, 1 H) 8.29 (s, 1 H) 8.49 (s, 1 H) 8.82 - 8.84 (m, 1 H); Anal. ($C_{22}H_{23}ClN_4O_4 \cdot 0.1\ H_2O$) C, H, N.

Examples 326-327

To a suspension of 2-chloro-5-{[6-methoxy-7-(1-methylpiperidin-4-yl)methoxy) quinazolin-4-yl]amino} benzo-1,4-quinone (150 mg, 0.4 mmol) and Et_3N (263 mL, 1.92 mmol) in 3 mL CH_2Cl_2 at 60°C, the appropriate piperidine or piperazine (~3.9 mmol) was added. The reaction mixture was stirred at 60°C for 2 hours and then filtered through a pad of magnesol with CH_2Cl_2. The solvent was removed *in vacuo*. The residue was triturated with Et_2O. The resulting solid was purified by silica gel column (3% MeOH / CH_2Cl_2) and Gilson HPLC to give the title compound. The compounds of the invention made by this method are listed in Table 22.

Table 22

Example	Compound Name	MS	HRMS
326	2-(4-benzylpiperazin-1-yl)-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone	MS (ESI) m/z 583.3; MS (ESI) m/z 292.1; MS (ESI) m/z 222.4	HRMS: calcd for $C_{33}H_{38}N_6O_4$ + H+, 583.30273; found (ESI-FTMS, $[M+H]^{1+}$), 583.30388
327	2-[4-(2-methoxybenzyl)piperidin-1-yl]-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone	MS (ESI) m/z 612.3; MS (ESI) m/z 306.6; MS (ESI) m/z 327.1	HRMS: calcd for $C_{35}H_{41}N_5O_5$ + H+, 612.31805; found (ESI-FTMS, $[M+H]^{1+}$), 612.31905

Examples 328-331

A solution of 0.67 g (1.5 mmol) of 2-{[6-methoxy-7-(1-methylpiperidin-4-yl)quinazolin-4-yl]amino}-5-phenoxybenzo-1,4-quinone, 20 ml of the appropriate alcohol and 0.5 ml of triethylamine in 20 ml methylene chloride was stirred for 16 hours. The solvent was evaporated and the residue diluted with ether. The solid was collected and washed with ether giving the title compound. The compounds of the invention made by this method are listed in Table 23.

Table 23

Example	Compound Name	MS	HRMS
328	2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-({6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinazolin-4-yl}amino)benzo-1,4-quinone	MS (ESI) m/z 532.2; MS (ESI) m/z 287.1; MS (ESI) m/z 266.6	
329	2-ethoxy-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone	MS (ESI) m/z 453.1; MS (ESI) m/z 247.6; MS (ESI) m/z 227	HRMS: calcd for $C_{24}H_{28}N_4O_5$ + H+, 453.21325; found (ESI-FTMS, $[M+H]^{1+}$), 453.21421
330	2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-({6-methoxy-7-[1-methylpiperadin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone	MS (ESI) m/z 503.2; MS (ESI) m/z 272.6; MS (ESI) m/z 252.1	
331	2-methoxy-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone	MS (ESI) m/z 439.2; MS (ESI) m/z 240.6; MS (ESI) m/z 220.1	

Examples 332-334

To a solution of 2-chloro-5-{[6-methoxy-7-(1-methylpiperidin-4-yl)quinazolin-4-yl) quinazolin-4-yl]amino}benzo-1,4-quinone (800 mg, 1.91 mmol) in dichloromethane (115 mL), $CsCO_3$ (800 mg, 1.91 mmol) and the appropriate alcohol (~1.5 mmol) were added. The reaction mixture was stirred at room temperature for 2.5 hours and filtered through a short column of silica gel. The solvent was removed in rotary evaporator. The residue was chromatographed on silica gel, eluting with $CHCl_3$/ EtOAc from 7:3 to 5:5. The product fraction was collected and concentrated in rotary evaporator. The residue was stirred in small amount of CH_3CN. The resulting solid was filtered to yield title compound. The compounds of the invention made by this method are listed in Table 24.

Table 24

Example	Compound Name	MS	HRMS
332	2-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)-5-(2-phenoxyethoxy)benzo-1,4-quinone	MS (ESI) m/z 545.2; MS (ESI) m/z 293.6; MS (ESI) m/z 273.1	HRMS: calcd for $C_{30}H_{32}N_4O_6$ + H+, 545.23946; found (ESI-FTMS, $[M+H]^{1+}$), 545.23931
333	2-(benzyloxy)-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone	MS (ESI) m/z 515.1; MS (ESI) m/z 278.5	HRMS: calcd for $C_{29}H_{30}N_4O_5$ + H+, 515.22890; found (ESI-FTMS, $[M+H]^{1+}$), 515.22821
334	2-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)-5-{2-[methyl(phenyl)amino]ethoxy}benzo-1,4-quinone	MS (ESI) m/z 558.2; MS (ESI) m/z 279.6; MS (ESI) m/z 300.1	HRMS: calcd for $C_{31}H_{35}N_5O_5$ + H+, 558.27110; found (ESI-FTMS, $[M+H]^{1+}$), 558.272

Example 335

2-chloro-5-{[6-methoxy-7-(3-pyridin-4-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 7.7 g (19 mmol) of 4-[(4-chloro-2,5-dimethoxyphenyl)amino]-6-methoxy-7-(3-pyridin-4-ylpropoxy)quinoline-3-carbonitrile in 322 ml of acetonitrile was heated to reflux and to this solution, 65 ml of water was added. The mixture was stirred and when the temperature reached 30°C, 19 g (34.7 mmol) of ceric ammonium nitrate was added over 5 minutes. After 45 minutes, the mixture was diluted with dilute sodium bicarbonate. The solid was collected by filtration and washed with water. This solid was suspended in 300 ml of water and 35 ml of concentrated hydrochloride acid was added. After stirring for 15 minutes, the precipitated solid was collected. The solid was stirred with 700 ml of methylene chloride and saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and the solution was passed onto a column of Magnesol™. The product was eluted from the column using ethyl acetate. The solvent was evaporated from the product fractions to give a solid that was washed with ether, yielding the title compound: MS (ESI+) m/z 451.2; HRMS: calcd for $C_{23}H_{19}ClN_4O_4$ + H+, 451.11676; found (ESI-FTMS, $[M+H]^{1+}$), 451.11643.

Example 336

2-methoxy-5-{[6-methoxy-7-(3-pyridin-4-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 0.67 g (1.5 mmol) of 2-{[6-methoxy-7-(3-pyridin-4-ylpropoxy)quinazolin-4-yl]amino}-5-phenoxybenzo-1,4-quinone, 20 ml of methanol and 0.5 ml of triethylamine in 20 ml methylene chloride was stirred for 16 hours. The solvent was evaporated and the residue diluted with ether. The solid was collected and washed with ether giving title compound: MS (ESI+) m/z 447.1.

Examples 337-338

A solution of 7.7 g (19 mmol) of the appropriate carbonitrile in 322 ml of acetonitrile was heated to reflux and to this solution, 65 ml of water was added. The mixture was stirred and when the temperature reached 30°C, 19 g (34.7 mmol) of ceric ammonium nitrate was added over 5 minutes. After 45 minutes, the mixture was

diluted with dilute sodium bicarbonate. The solid was collected by filtration and washed with water. This solid was suspended in 300 ml of water and 35 ml of concentrated hydrochloride acid was added. After stirring for 15 minutes, the precipitated solid was collected. The solid was stirred with 700 ml of methylene chloride and saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and the solution was passed onto a column of Magnesol™. The product was eluted from the column using ethyl acetate. The solvent was evaporated from the product fractions to give a solid that was washed with ether, yielding the title compound. The compounds of the invention made by this method are listed in Table 25.

Table 25

Example	Compound Name	MS	HRMS
337	2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI+) m/z 400.1	
338	2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-5-chlorobenzo-1,4-quinone	MS (ESI+) m/z 434.1	HRMS: calcd for $C_{20}H_{20}ClN_3O_6$ + H+, 434.11134; found (ESI-FTMS, $[M+H]^{1+}$), 434.11147

Examples 338-340

2-chloro-5-{[6,7-bis(2-methoxyethoxyquinazolin-4-yl]amino}benzo-1,4-quinone was dissolved in methylene chloride and treated with sodium phenoxide (trihydrate, 2.0 equivalents) and the appropriate alcohol in a 10-fold excess. The reaction was then agitated with a vortex shaker overnight. The reactions that were determined to be complete by LC-MS were washed with water and saturated sodium carbonate, and dried over sodium sulfate, then concentrated. The resulting residues were purified by either HPLC or crystallization from acetonitrile. The compounds of the invention made by this method are listed in Table 26.

Table 26

Example	Compound Name	MS	HRMS
338	2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(pyridin-3-ylmethoxy)benzo-1,4-quinone	MS (ESI+) m/z 507.1	
339	2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[2-fluoro-1-(fluoromethyl)ethoxy]benzo-1,4-quinone	MS (ESI) m/z 494.1	HRMS: calcd for $C_{23}H_{25}F_2N_3O_7$ + H+, 494.17333; found (ESI-FTMS, $[M+H]^{1+}$), 494.17237
340	2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-5-methoxybenzo-1,4-quinone	MS (ESI) m/z 430.1	HRMS: calcd for $C_{21}H_{23}N_3O_7$ + H+, 430.16088; found (ESI-FTMS, $[M+H]^{1+}$), 430.16079

Example 341

2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(1*H*-imidazol-1-yl)phenoxy]benzo-1,4-quinone

To a stirred mixture of 2,4-(imidazol-1-yl)phenol (83 mg, 0.52 mmol), aliquot 336 (16 mg, 0.04 mmol), 1*N* NaOH (46 mL, 0.46 mmol) in CH_2Cl_2 at 25°C, 2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-5-chlorobenzo-1,4-quinone (174 mg, 0.40 mmol) was added. The reaction mixture was stirred for 30 minutes and diluted with CH_2Cl_2, washed with H_2O, and dried over $MgSO_4$. The CH_2Cl_2 solution was passed through a pad of magnesol, eluting with CH_2Cl_2, 5:1= CH_2Cl_2 / isopropanol. The product fraction was evaporated. The residue was stirred in 8 mL MeOH and filtered to give 107 mg (48%) of title compound as red solid: mp 109-115°C; MS (ESI+) m/z 558.1.

Example 342

(4-chloro-2,5-dimethoxyphenyl)(4-methoxybenzyl)amine

To a stirred solution of the *p*-anisaldehyde (35.4 g, 260 mmol) in dichloroethane (750 mL), 4-chloro-2,5-dimethoxyaniline (46.9 g, 250 mmol), sodium triacetoxyborohydride (79.5 g, 375 mmol) and acetic acid (21.5 mL, 375 mmol) under nitrogen was added at room temperature. The reaction mixture was stirred at room temperature for 2.5 hours, stirred in CH_2Cl_2 and water, and basified with K_2CO_3 to pH 9-10. The CH_2Cl_2 layer was washed with water, dried, and concentrated. The residue was dissolved in 3:1 hexane-ethyl acetate (500 mL) and passed through a 8.0 x 4.0 cm pad of silica gel. The solvent was evaporated to yield 77.1 g (96%) of the title compound as a white solid: mp 53-63 °C; MS (ESI) *m/z* 308; ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 3.77 (d, *J*=5.54 Hz, 6 H) 3.80 (s, 3 H) 4.26 (s, 2 H) 4.57 (bs, 1 H) 6.25 (s, 1 H) 6.75 (s, 1 H) 6.84 - 6.94 (m, 2 H) 7.24 - 7.34 (m, 2 H).

Example 343

N-(4-chloro-2,5-dimethoxyphenyl)-7-fluoro-6-methoxy-*N*-(4-methoxybenzyl) quinazolin-4-amine

A mixture of (4-chloro-2,5-dimethoxyphenyl)(4-methoxybenzyl)amine (30.8 g, 100 mmol), 4-chloro-7-fluoro-6-methoxyquinazoline (17.0 g, 80 mmol), pyridine (0.65 mL, 8 mmol) and *t*-BuOH (240 mL) under nitrogen was stirred at reflux temperature for 24

hours. The *t*-BuOH was evaporated, and the residue stirred with CH_2Cl_2 and dilute NH_4OH. The insoluble material was filtered and washed with CH_2Cl_2 and water. The CH_2Cl_2 layer of filtrate was washed with brine, dried over $MgSO_4$, and evaporated to give 148.4 g of dark red gum. The gum was dissolved into 40:1 CH_2Cl_2 / EtOAc (30 mL) and chromatographed in a silica gel column (3.6 x 42 cm), eluting with 40 : 1 CH_2Cl_2 / EtOAc, followed by 3:1 CH_2Cl_2 / EtOAc to yield 31 g (80 %) of the title compound as a white amorphous solid: ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm 3.34 (d, *J*=2.01 Hz, 6 H) 3.70 (d, *J*=5.29 Hz, 6 H) 5.27 (s, 2 H) 6.63 (d, *J*=9.57 Hz, 1 H) 6.78 - 6.86 (m, 2 H) 7.12 (s, 1 H) 7.21 (s, 1 H) 7.26 - 7.36 (m, 2 H) 7.56 (d, *J*=12.34 Hz, 1 H) 8.65 (s, 1 H).

Example 344

N-(4-chloro-2,5-dimethoxyphenyl)-6-methoxy-7-(tetrahydro-2*H*-pyran-2-ylmethoxy) quinazolin-4-amine

To a stirred mixture of *N*-(4-chloro-2,5-dimethoxyphenyl)-7-fluoro-6-methoxy-*N*-(4-methoxybenzyl) quinazolin-4-amine (0.725 g, 1.5 mmol), tetrahydropyran-2-methanol (0.35 g, 3.0 mmol) in THF (2.0 mL) under nitrogen at 25°C, sodium bis (trimethylsilyl)amide (1.0 M in THF, 2.5 mL, 2.5 mmol) was added over 30 seconds. The reaction mixture was refluxed for 2 hours, cooled, and partitioned with CH_2Cl_2 and water. The CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$, and evaporated. A solution of the resulting gum in TFA (15 mL) was stirred at 55-60°C for 60 minutes and concentrated to dryness. The residue was partitioned with CH_2Cl_2 and aqueous $NaHCO_3$. The CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified on a flash column of silica gel (2 x 20 cm), eluting with 3:1 CH_2Cl_2 /EtOAc and 25:25:1 CH_2Cl_2/EtOAc/MeOH to yield 313 mg (45%) of the title compound as a white solid: mp 203-209 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm 1.36 - 1.43 (m, 2 H) 1.50 - 1.53 (m, 2 H) 1.67 - 1.72 (m, 1 H) 1.83 - 1.84 (m, 1 H) 3.38 - 3.45 (m, 1 H) 3.72- 3.75 (m, 4 H) 3.80 (s, 3 H) 3.90 (d, *J*=1.26 Hz, 1 H) 3.94 (s, 3 H) 4.06 - 4.10 (m, 2 H) 7.16 (s, 1 H) 7.22 (s, 1 H) 7.38 (s, 1 H) 7.79 (s, 1 H) 8.32 (s, 1 H) 9.18 (s, 1 H).

Example 345

2-chloro-5-{[6-methoxy-7-(tetrahydro-2*H*-pyran-2-ylmethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

This compound was prepared from *N*-(4-chloro-2,5-dimethoxyphenyl)-6-methoxy-7-(tetrahydro-2*H*-pyran-2-ylmethoxy) quinazolin-4-amine (391 mg, 0.85 mmol) and CAN (345 mg, 21.0 mmol) in $CHCl_3$ (5.6 mL), CH_3CN (11.2 mL) and H_2O (1.4 mL) using the procedure described above for Example 17. The reaction was filtered through a pad of magnesol (eluted with 9:1 CH_2Cl_2 / isopropanol). The solvent was removed by rotary evaporator to give 336 mg (92%) of the title compound as a red solid: mp 215-220 °C; HRMS: calcd for $C_{21}H_{20}ClN_3O_5$ + H+, 430.11643; found (ESI-FTMS, $[M+H]^{1+}$), 430.11652; The purity of the title compound was evaluated on two HPLC systems and found to be 97% (system A, retention time = 8.21 min) and 97 % (system B, retention time = 15.12 min); ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.41 - 1.70 (m, 4 H) 1.75 (d, *J*=11.58 Hz, 1 H) 1.86 - 2.01 (m, 1 H) 3.43 - 3.67 (m, 1 H) 3.76 - 3.93 (m, 1 H) 4.02 - 4.14 (m, 5 H) 4.14 - 4.28 (m, 1 H) 7.02 (s, 1 H) 7.10 (s, 1 H) 7.32 (s, 1 H) 8.29 (s, 1 H) 8.49 (s, 1 H) 8.79 - 8.86 (s, 1 H).

Example 346-348

A solution of 0.67 g (1.5 mmol) of 2-{[6-methoxy-7-(tetrahydropyran-2-ylmethoxy)quinazolin-4-yl]amino}-5-phenoxybenzo-1,4-quinone, 20 ml of the appropriate alcohol and 0.5 ml of triethylamine in 20 ml methylene chloride was stirred for 16 hours. The solvent was evaporated and the residue diluted with ether. The solid was collected and washed with ether giving title compound. The compounds of the invention made by this method are listed in Table 27.

Table 27

Example	Compound Name	MS	HRMS
346	2-methoxy-5-{[6-methoxy-7-(tetrahydro-2H-pyran-2-ylmethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI+) m/z 426.1	HRMS: calcd for $C_{22}H_{23}N_3O_6$ + H+, 426.16596; found (ESI-FTMS, $[M+H]^{1+}$), 426.16578
347	2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-{[6-methoxy-7-(tetrahydro-2H-pyran-2-ylmethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI+) m/z 490.1	HRMS: calcd for $C_{24}H_{25}F_2N_3O_6$ + H+, 490.17842; found (ESI-FTMS, $[M+H]^{1+}$), 490.17771
348	2-methoxy-5-{[6-methoxy-7-(tetrahydro-2H-pyran-2-ylmethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI+) m/z 426.1	HRMS: calcd for $C_{22}H_{23}N_3O_6$ + H+, 426.16596; found (ESI-FTMS, $[M+H]^{1+}$), 426.16578

Example 349

2-chloro-4-hydroxy-3-methoxy-5-nitrobenzaldehyde

To a stirred solution of 2-chloro-3-formyl-6-methoxy-5-nitrophenyl acetate (Helv. Chem. Acta 952 (1989)) (21.33 g, 77.95 mmol) and dimethylsulfate (90 mL, 0.952 mol) in EtOH (192 mL) at 40°C, a 40% KOH (140 mL, 98.2 mol) solution was added drop wise over 45 minutes. The reaction was then stirred at 55°C for 1 hour. The solvent was removed by rotary evaporator and the resulting residue was extracted with ether (2X). The ether solution was dried ($MgSO_4$) and was passed through a column of magnesol. The solvent was removed to give 22.3 g of 2-chloro-3,4-dimethoxy-5-nitro-benzaldehyde as a nearly colorless oil. 2-chloro-3,4-dimethoxy-5-nitro-benzaldehyde (22.33 g, 90.91 mmol), H_2O (1.12 mL) and LiCl (23.12 g, 0.545 mol) in DMF was heated at 110°C for 3 hours. The dark red mixture was cooled and treated with a solution of saturated $NaHCO_3$ (59 mL) and H_2O (800 mL). The aqueous solution was washed with ether (2X), was then made acidic with H_2SO_4 and cooled to 4°C. The resulting solid was collected by vacuum filtration, washed with H_2O and dried in air to give 18.3 g (87%) of the title compound as an off white solid: MS (ESI) m/z 230; 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 4.01 (s, 3 H) 8.54 (s, 1 H) 10.35 (s, 1 H) 11.14 (s, 1 H).

Example 350

2-chloro-3-methoxy-5-nitrobenzene-1,4-diol

To compound 2-chloro-4-hydroxy-3-methoxy-5-nitrobenzaldehyde (17.8 g, 72.47 mmol), 1 N NaOH (72.5 mL, 72.5 mmol), H_2O (158 mL), 30% H_2O_2 (45 mL), and MeOH (158 mL) was added and the mixture was stirred at 50°C for 3.5 hours. The MeOH was removed by rotary evaporator and the solution was then cooled. The resulting solid was collected by vacuum filtration, washed with H_2O, and air dried to yield 7.9 g (50%) of the title compound as an orange solid: MS (ESI) m/z 218; 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 4.01 (s, 3 H) 5.43 (s, 1 H) 7.56 (s, 1 H) 10.37 (d, J=11.33 Hz, 1 H).

Example 351

2-chloro-1,3,4-trimethoxy-5-nitrobenzene

Compound 2-chloro-3-methoxy-5-nitrobenzene-1,4-diol (7.8 g, 35.53 mmol) in DMF (77 mL) was treated with dimethylsulfate (11.2 g, 88.81 mmol) and K_2CO_3 (14.73 g, 106.57 mmol) and was heated to 80°C for 1 hour. The reaction was then poured into H_2O. The resulting solid was collected by vacuum filtration, washed with H_2O, and air dried to give 8.0 g (91%) of the title compound as a gray solid: MS (APCI) m/z 247.1; MS (APCI) m/z 247.1; 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 3.96 (t, J=8.0 Hz, 9 H) 7.17 (s, 1 H).

Example 352

4-chloro-2,3,5-trimethoxy-phenylamine

Compound 2-chloro-1,3,4-trimethoxy-5-nitrobenzene (8.0 g, 32.31 mmol) was dissolved in MeOH (429 mL), was treated with Fe (10.83 g, 193.33 mmol), and AcOH (11.1 mL, 193.83 mmol) and was refluxed with mechanical stirring for 2 hours. The reaction was then treated with NaOH (10 M, 19.38 mL, 193.83 mmol) and filtered. The solid was washed with EtOAc. The filtrate was concentrated and then redissolved in EtOAc, washed with saturated $NaHCO_3$, and dried (MgSO4) and concentrated to give 6.17 g of the title compound as a light tan oil. This material was used without additional purification.

Example 353

N-(4-chloro-2,3,5-trimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy) quinazolin-4-amine

A solution of N'-[2-cyano-4-methoxy-5-(2-methoxyethoxy)phenyl]-N,N-dimethylimidoformamide (7.8 g, 28.13 mmol) and 4-chloro-2, 3, 5-trimethoxy-phenylamine(6.12 g, 28.13 mmol) in AcOH (246 mL) was heated for 3.5 hours. The reaction was cooled to room temperature and diluted with ether. The resulting solid was collected by vacuum filtration to yield 12.03 g of the title compound as a beige powder (95%): MS (ESI) m/z 450.1; 1H NMR (400 MHz, DMSO-D_6) δ ppm 3.34 (s, 3 H) 3.68 (s, 3 H) 3.72 - 3.77 (m, 2 H) 3.81 (s, 3 H) 3.85 (s, 3 H) 3.95 (s, 3 H) 4.23 - 4.30 (m, 2 H) 7.17 (s, 1 H) 7.20 (s, 1 H) 7.83 (s, 1 H) 8.37 (s, 1 H) 9.30 (s, 1 H).

Example 354

2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

Compound N-(4-chloro-2,3,5-trimethoxyphenyl)-6-methoxy-7-(2-methoxyethoxy) quinazolin-4- amine (1.0 g, 2.22 mmol) was boiled to dissolve in CH_3CN (20 mL) and then diluted with H_2O (2 mL). While still hot, the solution was treated with $Ce(NH_4)_2(NO_3)_4$ (2.86 g, 5.22 mmol) in portions over 2 minutes. The reaction was then stirred at room temperature for 1 hour, diluted with H_2O (300 mL) and extracted with $CHCl_3$ (5 X 800 mL). The organic solution was dried (Na_2SO_4) and filtered through a pad of magnesol (eluted with CH_3Cl/ EtOAc). The solvent was removed by rotary evaporator. The resulting solid was dissolved in boiling MeCN (200 mL) and diluted with ether (200 mL). A red solid formed upon cooling and was collected by vacuum filtration (0.59 g, 63%): MS (ESI) m/z 420; 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 3.49 (s, 3 H) 3.82 - 3.95 (m, 2 H) 4.08 (s, 3 H) 4.20 (s, 3 H) 4.26 - 4.40 (m, 2 H) 7.03 (s, 1 H) 7.32 (s, 1 H) 8.20 (s, 1 H) 8.47 (s, 1 H) 8.81 (s, 1 H).

Example 355

2-chloro-3-isopropoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

To a solution of 2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy) quinazolin-4-yl]amino}benzo-1,4-quinone (600 mg, 1.43 mmol) in dichloromethane (86 mL) was added $CsCO_3$ (931.31 mg, 2.86 mmol) and isopropanol (42 mL, 548.5 mmol). The reaction mixture was stirred at room temperature for 2.5 hours and filtered through a short column of silica gel. The solvent was removed in rotary evaporator. The residue was chromatographed on silica gel, eluting with $CHCl_3$/ EtOAc from 1:1. The product fractions were combined and concentrated in rotary evaporator. The residue was stirred in ether. The resulting solid was filtered to yield 0.07 g (10.9%) of the title compound as a red powder: MS (ESI) *m/z* 448; ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.43 (d, *J*=6.30 Hz, 6 H) 3.46 - 3.51 (s, 3 H) 3.85 - 3.91 (m, 2 H) 4.06 - 4.10 (s, 3 H) 4.31 - 4.35 (m, 2 H) 4.88 - 5.03 (m, 1 H) 7.04 (s, 1 H) 7.31 - 7.34 (s, 1 H) 8.21 (s, 1 H) 8.50 (s, 1 H) 8.81 - 8.83 (s, 1 H); Anal. ($C_{21}H_{22}ClN_3O_6$) C, H, N.

Example 356

2-chloro-3-(cyclopropylmethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

To a solution of 2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy) quinazolin-4-yl]amino}benzo-1,4-quinone (650 mg, 1.55 mmol) in dichloromethane (100 mL), $CsCO_3$ (1.01 g, 3.1 mmol) and cyclopropylmethanol (3.35 g, 46.45 mmol) was added. The reaction mixture was stirred at room temperature overnight, and then filtered through a short column of silica gel, eluting with $CHCl_3$/EtOAc = 1:1. The solvent was removed in rotary evaporator. The residue was purified by thin layer chromatography, eluting with EtOAc. The major red band was collected, the silica was extracted with EtOAc / isopropanol. The solvent was removed to yield 0.143 g (20.1%) of the title compound as a red solid: MS (ESI) m/z 460; ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.37 - 0.39 (m, 2 H) 0.63 - 0.69 (m, 2 H) 1.27 - 1.34 (m, 1 H) 3.49 (s, 3 H) 3.87 - 3.91 (m, 2 H) 4.07 (s, 3 H) 4.24 (d, *J*=7.30 Hz, 2 H) 4.31 - 4.36 (m, 2 H) 7.03 (s, 1 H) 7.33 (s, 1 H) 8.21 (s, 1 H) 8.48 (s, 1 H) 8.82 (s, 1 H); Anal. ($C_{22}H_{22}ClN_3O_6$) C, H, N.

Example 357

3-chloro-2-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

A solution of 7.7 g (19 mmol) of 4-[(3-chloro-4-methoxy-2,5-dimethoxyphenyl)amino]-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile in 322 ml of acetonitrile was heated to reflux and to this solution, 65 ml of water was added. The mixture was stirred and when the temperature reached 30°C, 19 g (34.7 mmol) of ceric ammonium nitrate was added over 5 minutes. After 45 minutes, the mixture was diluted with dilute sodium bicarbonate. The solid was collected by filtration and washed with water. This solid was suspended in 300 ml of water and 35 ml of concentrated hydrochloride acid was added. After stirring for 15 minutes, the precipitated solid was collected. The solid was stirred with 700 ml of methylene chloride and saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and the solution was passed onto a column of Magnesol™. The product was eluted from the column using ethyl acetate. The solvent was evaporated from the product fractions to give a solid that was washed with ether, yielding the title compound: MS (ESI) m/z 420.

Example 358

3-chloro-2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

To a solution of 2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (650 mg, 1.55 mmol) in dichloromethane (93 mL), $CsCO_3$ (670.93 mg, 2.06 mmol) and 1,3-difluoro-2-propanol (4.46 g, 46.45 mmol) was added. The reaction mixture was stirred at room temperature overnight and then filtered through a short column of silica gel, eluting with $CHCl_3$/EtOAc = 1:1. The solvent was removed in a rotary evaporator. The residue was stirred with ether. The resulting solid was filtered to yield 0.25 g (33.6%) of the title compound as a red solid: MS (ESI) *m/z* 480.1; HRMS: calcd for $C_{22}H_{23}F_2N_3O_7$ + H+, 480.15768; found (ESI-FTMS, $[M+H]^{1+}$), 480.15833. The purity of the title compound was evaluated on two HPLC systems and found to be 100 % (system C, retention time = 3.89 min) and 89 % (system D, retention time = 12.2 min). MS (ESI) *m/z* 484; HRMS: calcd for $C_{21}H_{20}ClF_2N_3O_6$ + H+, 484.10815; found (ESI-FTMS, $[M+H]^{1+}$), 484.10815;^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 3.45 - 3.50 (s, 3 H) 3.87 - 3.91 (m, 2 H) 4.06 (s, 6 H) 4.28 - 4.39 (m, 2 H) 4.65 - 4.73 (m, 2 H) 4.78 - 4.87 (m, 2 H) 5.07 - 5.22 (m, 1 H) 7.04 (s, 1 H) 7.33 (s, 1 H) 7.91 - 7.94 (s, 1 H) 8.59 (s, 1 H) 8.82 (s, 1 H).

Examples 359-361

2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone was dissolved in methylene chloride and treated with sodium phenoxide (trihydrate, 2.0 equivalents) and the appropriate alcohol in a 10-fold excess. The reaction was then agitated with a vortex shaker overnight. The reactions that were determined to be complete by LC-MS were washed with water and saturated sodium carbonate, dried over sodium sulfate and concentrated. The resulting residues were purified by either HPLC or crystallization from acetonitrile. The compounds of the invention made by this method are listed in Table 28.

Table 28

Example	Compound Name	MS	HRMS
359	3-chloro-2-[(3-fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 514	
360	3-chloro-2-ethoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 434.1	HRMS: calcd for $C_{20}H_{20}ClN_3O_6$ + H+, 434.11134; found (ESI-FTMS, $[M+H]^{1+}$), 434.11093
361	3-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-2-(THF-3-yloxy)benzo-1,4-quinone	MS (ESI) m/z 476	

Examples 362-364

A solution of 1.13 g (2.5 mmol) of 2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone and 1 ml of the appropriate amine in 30 ml of THF was stirred for 3 hours. The solid was collected via filtration and washed with THF and water and dried to yield the title compound. The compounds of the invention made using this method are listed in Table 29.

Table 29

Example	Compound Name	MS	HRMS
362	2-(4-benzylpiperazin-1-yl)-3-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 564.2; MS (ESI) m/z 282.6; MS (ESI) m/z 303.1	HRMS: calcd for $C_{29}H_{30}ClN_5O_5$ + H+, 564.20082; found (ESI-FTMS, $[M+H]^{1+}$), 564.19966
363	3-chloro-2-(3,5-dimethylpiperidin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 501.2	HRMS: calcd for $C_{25}H_{29}ClN_4O_5$ + H+, 501.18992; found (ESI-FTMS, $[M+H]^{1+}$), 501.1892
364	3-chloro-2-(dimethylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 433.1	HRMS: calcd for $C_{20}H_{21}ClN_4O_5$ + H+, 433.12732; found (ESI-FTMS, $[M+H]^{1+}$), 433.1278

Examples 365-366

To a solution of 2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone (800 mg, 1.91 mmol) in dichloromethane (115 mL), $CsCO_3$ (800 mg, 1.91 mmol) and the appropriate alcohol (1.45 mol) were added. The reaction mixture was stirred at room temperature for 2.5 hours and filtered through a short column of silica gel. The solvent was removed in rotary evaporator. The residue was chromatographed on silica gel, eluting with $CHCl_3$/ EtOAc from 7:3 to 5:5. Product fraction was collected and concentrated in rotary evaporator. The residue was stirred in small amount of CH_3CN. The resulting solid was filtered to yield the title compound. The compounds of the invention made by this method are listed in Table 30.

Table 30

Example	Compound Name	MS	HRMS
365	2,3-dimethoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 416.1	
366	2-[2-fluoro-1-(fluoromethyl)ethoxy]-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone	MS (ESI) m/z 480.1	HRMS: calc'd for $C_{22}H_{23}F_2N_3O_7$ + H+, 480.15768; found (ESI-FTMS, $[M+H]^{1+}$), 480.15833

Example 367

(2*E*)-*N*-{4-[(4-chloro-2,5-dimethoxyphenyl)amino]-7-ethoxyquinazolin-6-yl}-4-(dimethylamino) but-2-enamide

Compound *N*-(4-chloro-2,5-dimethoxyphenyl)-7-ethoxyquinazoline-4,6-diamine was prepared by the methods described in United States Patent Nos. 6,251,912 and 6,288,082. The *(E)*-4-(dimethylamino)-2-butenoic acid hydrochloride salt (4.42 g, 26.68 mmol) and oxalyl chloride (4.42 g, 26.68 mmol) in CH_3CN (57 mL) was stirred at 55°C for 20 minutes. A trace of DMF was used after all solid dissolved. About half of the solvent was removed at reduced pressure at 50°C and this solution was cooled. A solution of compound *N*-(4-chloro-2,5-dimethoxyphenyl)-7-ethoxyquinazoline-4,6-diamine (5g, 13.34 mmol) in warm N-methyl pyrolidone (57 mL) was added over 10 minutes. The reaction mixture was stirred at 0°C for 2 hours and diluted with dilute $NaHCO_3$. The resulting solid was collected and dissolved in hot THF, diluted with EtOAc, dried over $MgSO_4$ and filtered. The solid was washed with hot THF-EtOAc. The filtrate was passed through a column of silica gel, eluting with EtOAc, EtOAc/MeOH and 700:300:10 EtOAc/MeOH/Et_3N. The solvent was removed from product fractions. The resulting solid was stirred in ether and collected to yield 5g (77%) of (2*E*)-*N*-{4-[(4-chloro-2,5-dimethoxyphenyl)amino]-7-ethoxyquinazolin-6-yl}-4-(dimethylamino) but-2-enamide as a white solid: MS (ESI) *m/z* 486.1; MS (ESI) *m/z* 264; MS (ESI) *m/z* 243.5; ^{1}H NMR (400 MHz, DMSO-D_6) δ ppm 1.46 (t, *J*=6.92 Hz, 3 H) 2.19 (s, 6 H) 3.08 (d, *J*=4 Hz, 2 H) 3.78 (d, *J*=4 Hz, 6 H) 4.25 - 4.31 (m, 2 H) 6.59 (d, *J*=16 Hz, 1 H) 6.76 - 6.83 (m, 1 H) 7.21 (d, *J*=8 Hz, 2 H) 7.57 (s, 1 H) 8.39 (s, 1 H) 8.90 (s, 1 H) 9.18 (s, 1 H) 9.48 (s, 1 H).

Example 368

(2*E*)-4-(dimethylamino)-*N*-{7-ethoxy-4-[(4-methoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)amino]quinazolin-6-yl}but-2-enamide

Compound (2*E*)-*N*-{4-[(4-chloro-2,5-dimethoxyphenyl)amino]-7-ethoxyquinazolin-6-yl}-4-(dimethylamino) (1.57 g, 3.23 mmol) was dissolved in CH_3CN (80 mL) and water (36 mL) and treated with ceric ammonium nitrate (4.25 g, 7.75 mmol). The reaction mixture was stirred at room temperature for 2.5 hours and then diluted with $CHCl_3$ (700 mL) and saturated Na_2CO_3 (50 mL). The solution was filtered through celite. The solid was washed many times with $CHCl_3$ to give a volume of 1400 mL

organic layer. The solvent was evaporated, washed with water and diluted with MeOH (300 mL). The solution was dried over $MgSO_4$, filtered and treated with Et_3N (50 mL). The solution was refluxed for 2 hours 45 minutes and the solvent was removed. The residue was dissolved in $CHCl_3$, washed with saturated $NaHCO_3$, and dried over $MgSO_4$. The solution was filtered through a short column of magnesol, eluting with $CHCl_3$, and then with 500:500:50 $CHCl_3$-EtOAc-MeOH. The solvent of filtrate was evaporated. The resulting solid was stirred with EtOAc and collected to yield 850 g (58%) of (2*E*)-4-(dimethylamino)-*N*-{7-ethoxy-4-[(4-methoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)amino] quinazolin-6-yl}but-2-enamide as a crystalline orange solid: MS (ESI) m/z 452.2; ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.59 (t, *J*=8 Hz, 3 H) 2.34 (s, 6 H) 3.19 - 3.21 (m, 2 H) 3.91 (s, 3 H) 4.30 - 4.35 (m, 2 H) 5.99(d, *J*=4 Hz, 1 H) 6.25 (d, *J*=16 Hz, 1 H) 7.06 - 7.11 (m, 1 H) 7.30 (s, 1 H) 8.07 (d, *J*=4 Hz, 1 H) 8.14 (s, 1 H) 8.81 (s, 1 H) 8.98 (s, 1 H) 9.30 (s, 1 H).

Examples 369-377

(2*E*)-4-(dimethylamino)-*N*-{7-ethoxy-4-[(4-chloro-3,6-dioxocyclohexa-1,4-dien-1-l)amino]quinazolin-6-yl}but-2-enamide was dissolved in methylene chloride and treated with sodium phenoxide (trihydrate, 2.0 equivalents) and the appropriate alcohol in a 10-fold excess. The reaction was then agitated with a vortex shaker overnight. The reactions that were determined to be complete by LC-MS were washed with water and saturated sodium carbonate, dried over sodium sulfate and concentrated. The resulting residues were purified by either HPLC or crystallization from acetonitrile. The compounds of the invention that were made using this method are listed in Table 31.

Table 31

Example	Compound Name	MS	HRMS
369	(2E)-4-(dimethylamino)-N-[7-ethoxy-4-({4-[(3-fluorobenzyl)oxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)quinazolin-6-yl]but-2-enamide	MS (ESI) m/z 546.2	HRMS: calcd for $C_{29}H_{28}FN_5O_5$ + H+, 546.21472; found (ESI-FTMS, $[M+H]^{1+}$), 546.21347
370	(2E)-4-(dimethylamino)-N-[7-ethoxy-4-({4-[2-fluoro-1-(fluoromethyl)ethoxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)quinazolin-6-yl]but-2-enamide	MS (ESI) m/z 516.2	HRMS: calcd for $C_{25}H_{27}F_2N_5O_5$ + H+, 516.20530; found (ESI-FTMS, $[M+H]^{1+}$), 516.20519
371	(2E)-N-[4-({4-[(3,4-difluorobenzyl)oxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)-7-ethoxyquinazolin-6-yl]-4-(dimethylamino)but-2-enamide	MS (ESI) m/z 564.2	
372	(2E)-N-(4-{[4-(benzyloxy)-3,6-dioxocyclohexa-1,4-dien-1-yl]amino}-7-ethoxyquinazolin-6-yl)-4-(dimethylamino)but-2-enamide	MS (ESI) m/z 528.2	HRMS: calcd for $C_{29}H_{29}N_5O_5$ + H+, 528.22415; found (ESI-FTMS, $[M+H]^{1+}$), 528.22382
		MS (ESI) m/z 285.1	
		MS (ESI) m/z 264.6	
373	(2E)-4-(dimethylamino)-N-(4-{[3,6-dioxo-4-(pyridin-2-ylmethoxy)cyclohexa-1,4-dien-1-yl]amino}-7-ethoxyquinazolin-6-yl)but-2-enamide	MS (ESI) m/z 529.1	HRMS: calcd for $C_{28}H_{28}N_6O_5$ + H+, 529.21940; found (ESI-FTMS, $[M+H]^{1+}$), 529.21897
		MS (ESI) m/z 265	

374	(2E)-N-[4-({4-[(3-chlorobenzyl)oxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)-7-ethoxyquinazolin-6-yl]-4-(dimethylamino)but-2-enamide	MS (ESI) m/z 562	HRMS: calcd for $C_{29}H_{28}ClN_5O_5$ + H+, 562.18517; found (ESI-FTMS, $[M+H]^{1+}$), 562.18608
		MS (ESI) m/z 281.5	
375	(2E)-4-(dimethylamino)-N-(4-{[3,6-dioxo-4-(2-thienylmethoxy)cyclohexa-1,4-dien-1-yl]amino}-7-ethoxyquinazolin-6-yl)but-2-enamide	MS (ESI) m/z 534;	HRMS: calcd for $C_{27}H_{27}N_5O_5S$ + H+, 534.18057; found (ESI-FTMS, $[M+H]^{1+}$), 534.18094
		MS (ESI) m/z 288	
		MS (ESI) m/z 267.5	
376	(2E)-4-(dimethylamino)-N-[7-ethoxy-4-({4-[(3-methoxybenzyl)oxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)quinazolin-6-yl]but-2-enamide	MS (ESI) m/z 558.1	HRMS: calcd for $C_{30}H_{31}N_5O_6$ + H+, 558.23471; found (ESI-FTMS, $[M+H]^{1+}$), 558.23403
377	(2E)-4-(dimethylamino)-N-[7-ethoxy-4-({4-[(2-methylbenzyl)oxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)quinazolin-6-yl]but-2-enamide	MS (ESI) m/z 542.1	HRMS: calcd for $C_{30}H_{31}N_5O_5$ + H+, 542.23980; found (ESI-FTMS, $[M+H]^{1+}$), 542.23995
		MS (ESI) m/z 292	
		MS (ESI) m/z 271.5	

Example 378

2-({7-[3-(diethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-5-methoxybenzo-1,4-quinone

To a solution of 2-({7-[3-(diethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-5-chlorobenzo-1,4-quinone (~1.9 mmol) in dichloromethane (115 mL), $CsCO_3$ (1.91 mmol) and the appropriate alcohol (~1.45 mol) was added. The reaction mixture was stirred at room temperature for 2.5 hours and filtered through a short column of silica gel. The solvent was removed in rotary evaporator. The residue was chromatographed on silica gel, eluting with $CHCl_3$/ EtOAc from 7:3 to 5:5. Product fraction was collected and concentrated in a rotary evaporator. The residue was stirred in small amount of CH_3CN. The resulting solid was filtered to yield 0.2 g (25%) of title compound as a red crystalline solid: MS (ESI+) m/z 441.2; HRMS: calcd for $C_{23}H_{28}N_4O_5$ + H+, 441.21325; found (ESI-FTMS, $[M+H]^{1+}$), 441.21361.

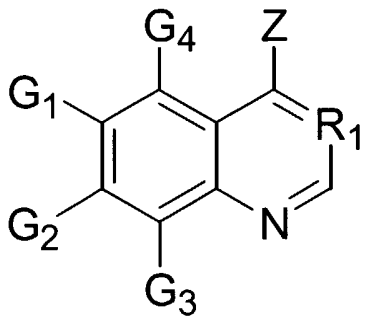
Example 379

2,3,5-tris(ethylthio)-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone

To a degassed stirred solution of acetonitrile:deionized (MilliQ) water (1:1, 1000mL) of the quinone (~0.1 mmol, 40 mg) under N_2, added ethanethiol (10 quiv., ~0.1 mL) was added. The solution was stirred until starting material was consumed shown by TLC or LCMS (1hour-5days). At the end of the reaction, 2.9 g of 0.7 mmol/g loading maleimide resin (Silicycle, Si-maleimide) was added to scavenge the ethanethiol. The suspension was stirred overnight then filtered (medium frit), extracted with 3x150mL EtOAc dried with Na_2SO_3 and concentrated *in vacuo* (30-40° C). The crude residue was purified by RP-HPLC (C18 Phenomenex Luna 150x30mm, 20-80% MeCN:water 0.02% TFA). NaCl was added to the isolated fractions and extracted into DCM, dried with Na_2SO_3 concentrated *in vacuo* (30-40°C) giving 3 mg of title compound: MS (ESI) *m/z* 536.2

WHAT IS CLAIMED IS:

1. A compound of formula 1 having the structure:

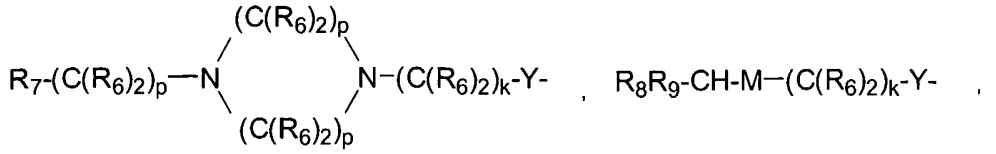


1

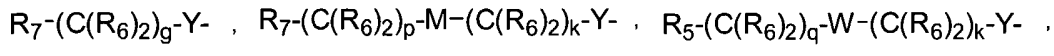
wherein:

R_1 is N, C-CN, C-H, C-F, C-Cl, C-Br, or C-I

G_1, G_2, G_3, and G_4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxymethyl, alkylamido of 2-7 carbon atoms, halomethyl, alkyl-N-alkylamido of 4-10 carbon atoms, alkanoyloxy of 2-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms, alkynoyloxymethyl of 4-9 carbon atoms, alkoxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, phenylacetyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino, R_2NH,

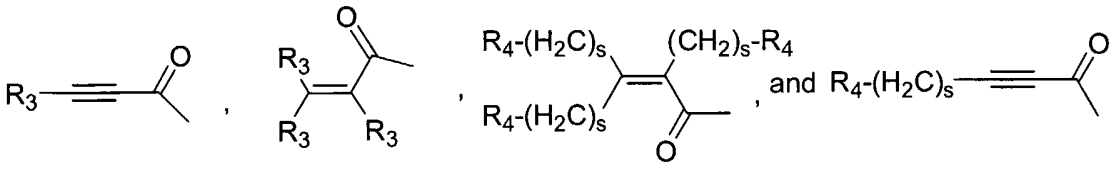


R_8R_9-CH-M—$(C(R_6)_2)_k$-Y- ,

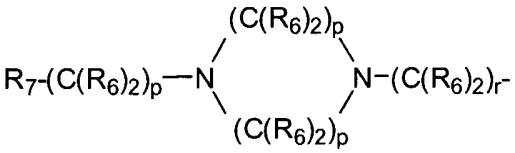


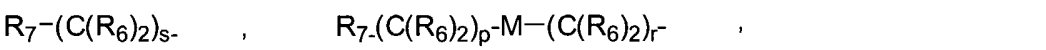
with the proviso that G3 or G4 are not R_2NH;

R_2, is selected from the group consisting of



R_3 is, independently, hydrogen, alkyl of 1-6 carbon atoms, carboxy, carboalkoxy of 1-6 carbon atoms, phenyl, carboalkyl of 2-7 carbon atoms,





R_8R_9-CH-M—$(C(R_6)_2)_r$- , or R_5-$(C(R_6)_2)_q$-W-$(C(R_6)_2)_r$- ;

R_4 is Cl, Br, or I;

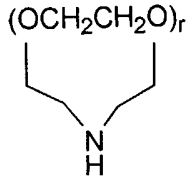
R_6 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 1-6 carbon atoms, carboalkyl of 2-7 carbon atoms, carboxyalkyl 2-7 carbon atoms, phenyl, or phenyl optionally substituted with one or more halogen, alkoxy of 1-6 carbon atoms, trifluoromethyl, amino, alkylamino of 1-3 carbon atoms, dialkylamino of 2-6 carbon atoms, nitro, cyano, azido, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, carboxyl, carboalkoxy of 2-7 carbon atoms, phenoxy,

phenyl, thiophenoxy, benzoyl, benzyl, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, or alkyl of 1-6 carbon atoms; with the proviso that the alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

R_7 is $-NR_6R_6$, $-OR_6$, $-R_4$, $-N(R_6)_3^+$, or $-NR_6(OR_6)$;

M is $>NR_6$, -O-, $>N-(C(R_6)_2)_pNR_6R_6$, or $>N-(C(R_6)_2)_p-OR_6$, or a divalent phenyl radical;

W is $>NR_6$, -O-, a divalent phenyl radical, or is a bond;

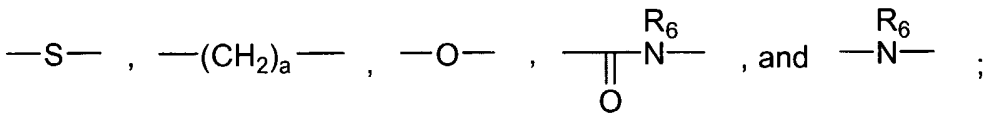
R_5 is a phenyl radical or a heterocyclic radical selected from the group consisting of morpholine, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S,S-dioxide, piperidine, pyrrolidine, aziridine, pyridine, imidazole, 1,2,3-triazole, 1,2,4-triazole, thiazole, thiazolidine , tetrazole, piperazine, furan, thiophene, tetrahydrothiophene, tetrahydrofuran, dioxane, 1,3-dioxolane , tetrahydropyran, and  ;

wherein the phenyl radical or the heterocylic radical may be optionally mono- or di-substituted on carbon with R_6, hydroxy, $-N(R_6)_2$, $-OR_6$ $-(C(R_6)_2)_sOR_6$, or $-(C(R_6)_2)_sN(R_6)_2$ and

wherein the heterocylic radical may be optionally mono-substituted on nitrogen with R_6 and optionally mono or di-substituted on a saturated carbon with divalent radicals -O- or $-O(C(R_6)_2)_sO-$;

R_8 and R_9 are each, independently, $-(C(R_6)_2)_rNR_6R_6$, or $-(C(R_6)_2)_r OR_6$;

Y is a divalent radical selected from the group consisting of



;

a = 0-1;

g = 1-6;

k = 0-4;

p = 2-4;

q= 0-4;

r = 1-4;

s = 1-6;

provided that

when R_6 is alkenyl of 2-7 carbon atoms or alkynyl of 2-7 carbon atoms, such alkenyl or alkynyl moiety is bound to a nitrogen or oxygen atom through a saturated carbon atom;

and provided that

when Y is $-NR_6-$ and R_7 is $-NR_6R_6$, $-N(R_6)_3^+$, or $-NR_6(OR_6)$, then g = 2-6;

when M is -O- and R_7 is $-OR_6$ then p = 1-4;

when Y is $-NR_6-$ then k = 2-4;

when Y is -O- and M or W is -O- then k = 1-4;

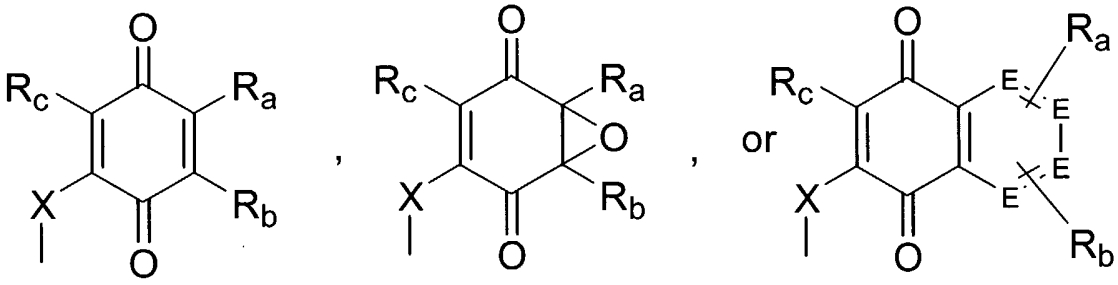
when W is not a bond or a divalent phenyl radical with R_5 bonded through a nitrogen atom then q = 2-4,

when M is a divalent phenyl radical then p = 0-4 and r = 0-4,

when W is a divalent phenyl radical then r = 0-4,

and when W is a bond with R_5 bonded through a nitrogen atom and Y is -O- or $-NR_6-$ then k = 2-4;

Z is a radical selected from the group

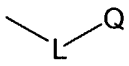


X is a divalent radical selected from the group –NH-, $>NR_{10}$, -O-, and - S-;

R_{10} is an hydrogen, an alkyl group from 1-6 carbon atoms, phenyl or benzyl;

R_a, R_b, R_c are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkenyloxy of 2-6 carbon atoms, alkynyloxy of 2-6 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, haloalkyl of 1-6 carbon atoms, alkanoyloxy of 2-6 carbon atoms, alkenoyloxy of 3-8 carbon atoms, alkynoyloxy of 3-8 carbon atoms, alkylamido of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkenoyloxymethyl of 4-9 carbon atoms,

alkynoyloxymethyl of 4-9 carbon atoms, alkoxyalkyl of 2-14 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, alkylsulphinyl of 1-6 carbon atoms, alkylsulphonyl of 1-6 carbon atoms, alkylsulfonamido of 1-6 carbon atoms, phenylacetyl, alkenylsulfonamido of 2-6 carbon atoms, alkynylsulfonamido of 2-6 carbon atoms, hydroxy, trifluoromethyl, trifluoromethoxy, cyano, nitro, azido, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzyl, benzyloxy, benzylthio, amino, hydroxyamino, alkoxyamino of 1-4 carbon atoms, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, N-alkylcarbamoyl of 2 to 6 carbon atoms, N,N-dialkylcarbamoyl of 2 to 12 carbon atoms, N-alkyl-N-alkenylamino of 4 to 12 carbon atoms, N,N-dialkenylamino of 6-12 carbon atoms, phenylamino, benzylamino,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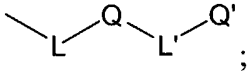

;

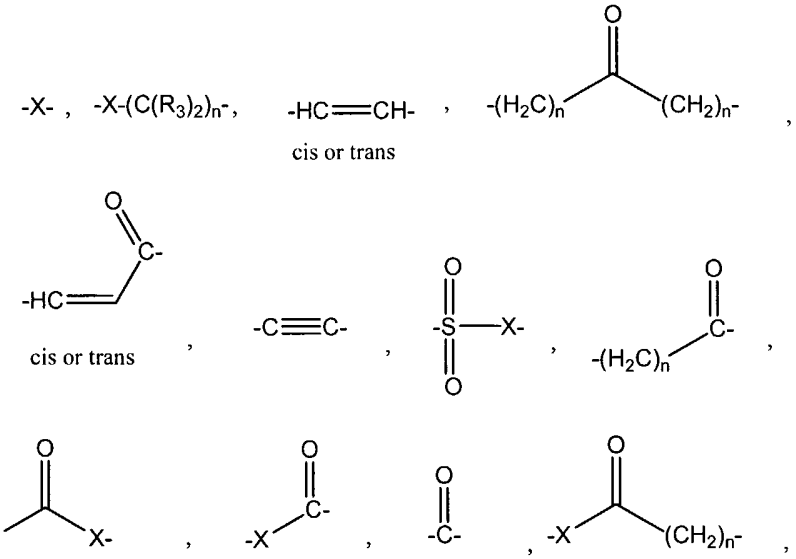
when attached to a double bond at contiguous carbon atoms, R_a and R_b can be taken together as the divalent radicals $-(C(R_{10})_2)_3-$, $-(C(R_{10})_2)_4-$, $-X-(C(R_{10})_2)_3-$, $-X-(C(R_{10})_2)_2-X-$, $-C(R_{10})_2-X-(C(R_{10})_2)_2-$, or $-C(R_{10})_2-X-C(R_{10})_2-$;

Q and Q' are a phenyl mono or divalent radical which may be optionally substituted with 1-5 halogen atoms, or mono- di- or tri-substituted with a substituent selected from the group consisting of hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, hydroxyalkyl of 1-6 carbon atoms, alkylamido of 2-7 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, benzoyl, amino, phenylacetyl, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N-alkylcarbamoyl of 2 to 6 carbon atoms, N,N-dialkylcarbamoyl of 2 to 12 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino, or

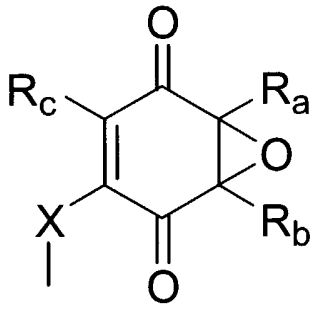
Q and Q' are a mono or divalent radical comprising a 3-8-membered heterocyclic ring where the heterocyclic ring contains 1 to 3 heteroatoms selected from N, O, and S; wherein the heterocyclic ring may be optionally substituted with 1-5 halogen atoms, or mono- or di-substituted with a substituent selected from the group consisting of oxo, thio, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, alkylamido of 2-7 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenyl, thiophenoxy, benzoyl, benzyl, amino, phenylacetyl, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms, alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms, carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-alkylcarbamoyl of 2 to 6 carbon atoms, N,N-dialkylcarbamoyl of 2 to 12 carbon atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10 carbon atoms, mercapto, and benzoylamino, or

Q and Q' are a mono or divalent radical comprising a fused or bridged bicyclic or tricyclic carbocyclic ring system or a fused or bridged bicyclic or tricyclic heterocyclic ring system of 6 to 18 atoms, where the bicyclic or tricyclic heterocyclic ring system contains 1 to 4 heteroatoms selected from N, O, and S; wherein the bicyclic or tricyclic carbocyclic ring system or the bicyclic or tricyclic heterocyclic ring system may be optionally substituted with 1-5 halogen atoms, or mono-, di-, tri-, or tetra-substituted with a substituent selected from the group consisting of oxo, thio, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, azido, alkylamido of 2-7 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, halomethyl, alkoxymethyl of 2-7 carbon atoms, alkanoyloxymethyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, alkylthio of 1-6 carbon atoms, hydroxy, trifluoromethyl, cyano, nitro, carboxy, carboalkoxy of 2-7 carbon atoms, carboalkyl of 2-7 carbon atoms, phenoxy, phenylacetyl, phenyl, thiophenoxy, benzoyl, benzyl, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 2 to 12 carbon atoms, phenylamino, benzylamino, alkanoylamino of 1-6 carbon atoms, alkenoylamino of 3-8 carbon atoms,

159 alkynoylamino of 3-8 carbon atoms, carboxyalkyl of 2-7 carbon atoms,
160 carboalkoxyalkyl of 3-8 carbon atoms, aminoalkyl of 1-5 carbon atoms, N-
161 alkylaminoalkyl of 2-9 carbon atoms, N,N-dialkylaminoalkyl of 3-10 carbon atoms, N-
162 alkylcarbamoyl of 2 to 6 carbon atoms, N,N-dialkylcarbamoyl of 2 to 12 carbon
163 atoms, N-alkylaminoalkoxy of 2-9 carbon atoms, N,N-dialkylaminoalkoxy of 3-10
164 carbon atoms, mercapto, and benzoylamino, or
165 Q and Q' are hydrogen or a mono or divalent radical comprising straight or cyclic
166 alkyl groups of 1 to 10 carbon atoms, both of which can optionally be branched,
167 substituted with 1-6 halogen groups, or contain sites of unsaturation, or be;
168 L and L' are divalent radicals selected from the group



169 -N—O-, -X-(C(R3)2)n-X-; -(C(R3)2)n- -S(O)2-, -S(O)-, or are bonds;
170 n is an integer from 1 to 4;
171 E is CH or N with the proviso that there be no more than 2 ring nitrogen atoms;
172 it is provided that when Z is the moiety



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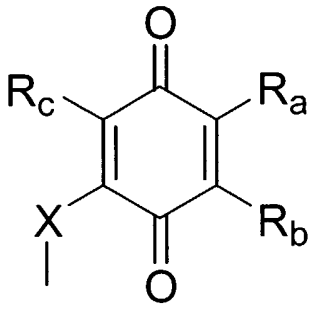
174

175 R_a and R_b are independently hydrogen or are attached to the ring only via carbon
176 atoms;
177 or a pharmaceutically acceptable salt thereof.

1 2. The compound of claim 1, wherein R_1 is N, C-H, C-CN, C-F, C-Cl, C-Br, C-I
2 or a pharmaceutically acceptable salt thereof.

1 3. The compound of claim 2, wherein Z is



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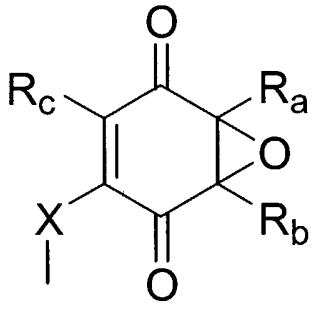
3 or a pharmaceutically acceptable salt thereof.

1 4. The compound of claim 2, wherein Z is



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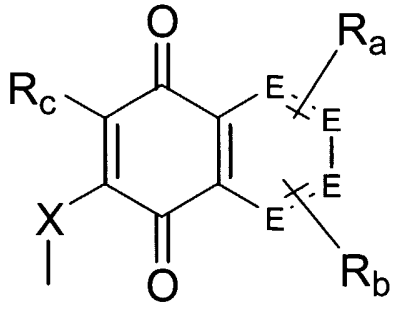
3 or a pharmaceutically acceptable salt thereof.

1 5. The compound of claim 2, wherein Z is



2

or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1, selected from the group consisting of:

(a) 2-chloro-5-[(6,7-dimethoxy-4-quinazolinyl)amino]benzo-1,4-quinone;

(b) 2-[(6,7-dimethoxy-4-quinazolinyl)amino]-5-methylbenzo-1,4-quinone;

(c) 4-[(6,7-dimethoxy-4-quinazolinyl)amino]-1-methyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione;

(d) 2-[(6,7-dimethoxy-4-quinazolinyl)amino]-6-methylbenzo-1,4-quinone;

(e) 2-{[6-methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]amino}-5-methylbenzo-1,4-quinone;

(f) 4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinazolinyl]amino}-1-methyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione;

(g) 2-[(6,7-dimethoxy-4-quinazolinyl)amino]-5-ethylbenzo-1,4-quinone;

(h) 4-[(6,7-dimethoxy-4-quinazolinyl)amino]-1-ethyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione;

(i) 2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-isopropylbenzo-1,4-quinone;

(j) 4-[(6,7-dimethoxyquinazolin-4-yl)amino]-1-isopropyl-7-oxabicyclo[4.1.0]hept-3- ene-2,5-dione;

(k) 2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-morpholin-4-ylbenzo-1,4-quinone;

(l) 2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-(methylamino)benzo-1,4-quinone;

(m) 2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-(dimethylamino)benzo-1,4-quinone;

(n) 2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-piperidin-1-ylbenzo-1,4-quinone;

(o) 2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-[methyl(phenyl)amino]benzo-1,4-quinone;

(p) 2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-phenoxybenzo-1,4-quinone;

(q) 2-(4-chlorophenoxy)-5-[(6,7-dimethoxyquinazolin-4-yl)amino]benzo-1,4-quinone;

(r) 2-[(6,7-dimethoxyquinazolin-4-yl)amino]-5-phenylbenzo-1,4-quinone;

(s) 4-[(6,7-dimethoxyquinazolin-4-yl)amino]-1-phenyl-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione;

(t) 2-anilino-5-[(6,7-dimethoxyquinazolin-4-yl)amino]benzo-1,4-quinone;

(u) 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(v) 6-methoxy-7-(2-methoxyethoxy)-4-[(4-methyl-3,6-dioxocyclohexa-1,4-dien-1-yl)amino]quinoline-3-carbonitrile;

(w) 1-benzyl-4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-7-oxabicyclo[4.1.0]hept-3-ene-2,5-dione;

(x) 2-(dimethylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(y) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-morpholin-4-ylbenzo-1,4-quinone;

(z) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(phenyl)amino]benzo-1,4-quinone;

(aa) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(4-methoxyphenyl)(methyl)amino]benzo-1,4-quinone;

(bb) 2-[cyclohexyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(cc) 2-[benzyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(dd) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3-methylbenzyl)amino]benzo-1,4-quinone;

(ee) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(4-methylphenoxy)benzo-1,4-quinone;

(ff) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(pyridin-3-yloxy)benzo-1,4-quinone;

(gg) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-methylphenoxy)benzo-1,4-quinone;

(hh) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-phenoxybenzo-1,4- quinone

(ii) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-piperidin-1-yl-benzo-1,4-quinone;

(jj) 2-[(4-fluorophenyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4- yl]amino}benzo-1,4-quinone;

(kk) 2-[[4-(dimethylamino)phenyl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ll) 2-[(3-fluorophenyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4- yl]amino}benzo-1,4-quinone;

(mm) 2-[4-(1H-imidazol-1-yl)phenoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4- yl]amino}benzo-1,4-quinone;

(nn) 2-[(3,4-dimethoxyphenyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(oo) 3-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzonitrile;

(pp) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(3-methoxyphenoxy)benzo-1,4-quinone;

(qq) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(4-phenoxyphenoxy)benzo-1,4-quinone;

(rr) 2-(4-fluorophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ss) 4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzonitrile;

(tt) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(4-methoxyphenoxy)benzo-1,4-quinone;

(uu) 2-(3-chlorophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(vv) 2-(3-acetylphenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ww) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(methylthio)phenoxy]benzo-1,4-quinone;

(xx) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(trifluoromethyl)phenoxy]benzo-1,4-quinone;

(yy) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(phenylthio)benzo-1,4- quinone;

(zz) 2-(2-methoxyethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(aaa) 2-(benzyloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4- quinone;

(bbb) 4-[(4-chloro-3,6-dioxocyclohexa-1,4-dien-1-yl)amino]-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile;

(ccc) 4-[(3,6-dioxo-4-phenoxycyclohexa-1,4-dien-1-yl)amino]-6-methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile;

(ddd) 4-({4-[4-(1H-imidazol-1-yl)phenoxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)-6- methoxy-7-(2-methoxyethoxy)quinoline-3-carbonitrile;

(eee) 2-methoxy-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4- quinone;

(fff) 5-methoxy-3-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-2-(phenylthio)benzo-1,4-quinone;

(ggg) 2-(benzylthio)-5-methoxy-3-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(hhh) 2,3-dichloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4- quinone;

(iii) 3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-2-(1,3-thiazol-5-ylthio)benzo-1,4-quinone;

(jjj) ethyl {4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]phenyl}acetate;

(kkk) 4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzenesulfonamide;

(lll) 2-(4-benzoylphenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(mmm) methyl 3-{4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]phenyl}propanoate;

(nnn) 2-(9H-carbazol-2-yloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ooo) methyl 4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzoate;

(ppp) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[3-(trifluoromethyl)phenoxy]benzo-1,4-quinone;

(qqq) 2-(3-fluorophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(rrr) ethyl 5-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]-2-methyl-1H-indole-3-carboxylate;

(sss) 2-(4-bromophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ttt) 2-(2-isoxazol-5-yl-4-methylphenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(uuu) benzyl 4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzoate;

(vvv) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(phenylacetyl)phenoxy]benzo-1,4-quinone;

(www) 2-[3-(ethylamino)phenoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(xxx) 2-[(6-bromo-2-naphthyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(yyy) 2-[2-(benzyloxy)phenoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(zzz) 2-(9H-fluoren-2-yloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(aaaa) 2-[4-(2-aminoethyl)phenoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(bbbb) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-{4-[(2E)-3-phenylprop-2-enoyl]phenoxy}benzo-1,4-quinone;

(cccc) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(1-methyl-1-phenylethyl)phenoxy]benzo-1,4-quinone;

(dddd) 2-chloro-5-methoxy-3-[6-methoxy-7-(2-methoxy-ethoxy)-quinazolin-4-ylamino]benzo-1,4-quinone;

(eeee) 5-methoxy-3-[6-methoxy-7-(2-methoxy-ethoxy)-quinazolin-4-ylamino]-2-(pyridin-2-ylsulfanyl)benzo-1,4-quinone;

(ffff) 2-(2-hydroxy-ethylsulfanyl)-3-[6-methoxy-7-(2-methoxy-ethoxy)-quinazolin-4-ylamino]-[1,4]naphthoquinone;

(gggg) 2-[6-methoxy-7-(2-methoxy-ethoxy)-quinazolin-4-ylamino]-[1,4]naphthoquinone;

(hhhh) 2-chloro-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone;

(iiii) 2-(methoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(jjjj) 2-[ethyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(kkkk) 2-(diisobutylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(llll) 2-(3,5-dimethylpiperidin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(mmmm) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(3-methylpiperidin-1-yl)benzo-1,4-quinone;

(nnnn) 2-[(2,3-dihydroxypropyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(oooo) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-methylaziridin-1-yl)benzo-1,4-quinone;

(pppp) 2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(qqqq) 2-(dipropylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(rrrr) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-pyridin-3-ylpiperidin-1-yl)benzo-1,4-quinone;

(ssss) tert-butyl1-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)-L-prolinate;

(tttt) 2-azocan-1-yl-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(uuuu) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(pentyl)amino]benzo-1,4-quinone;

(vvvv) 2-{4-[4-chloro-3-(trifluoromethyl)phenyl]piperazin-1-yl}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(wwww) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(2S)-2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]benzo-1,4-quinone;

(xxxx) 2-[4-(2-fluoro-4-nitrophenyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(yyyy) 2-[[(3S)-1-benzylpyrrolidin-3-yl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(zzzz) 2-(4-benzylpiperidin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(aaaaa) 2-[4-(2-hydroxyethyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(bbbbb) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(4-pyrazin-2-ylpiperazin-1-yl)benzo-1,4-quinone;

(ccccc) 2-[[2-(1H-indol-3-yl)ethyl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ddddd) ethyl1-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)piperidine-4-carboxylate;

(eeeee) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(2-methoxyphenyl)piperidin-1-yl]benzo-1,4-quinone;

(fffff) 2-(4-benzyl-1,4-diazepan-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ggggg) 2-(1,4'-bipiperidin-1'-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(hhhhh) tert-butylN-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)-N-methylglycinate;

(iiiii) 2-[[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(jjjjj) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]benzo-1,4-quinone;

(kkkkk) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]benzo-1,4-quinone;

(lllll) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(2-phenylethyl)amino]benzo-1,4-quinone;

(mmmmm) 2-[4-(ethylsulfonyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(nnnnn) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-pyrrolidin-1-ylbenzo-1,4-quinone;

(ooooo) 2-(2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl)-5-[6-methoxy-7-(2-methoxy-ethoxy)-quinazolin-4-ylamino]benzo-1,4-quinone;

(ppppp) 2-{4-hydroxy-4-[3-(trifluoromethyl)phenyl]piperidin-1-yl}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(qqqqq) 2-[(1R,4R)-5-(4-chlorophenyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(rrrrr) 1-{4-[6-methoxy-7-(2-methoxyethoxy)-quinazolin-4-ylamino]-3,6-dioxo-cyclohexa-1,4-dienyl}-piperidine-4-carboxylic acid;

(sssss) 1-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)azetidine-3-carboxylic acid;

(ttttt) 2-[[2-(diethylamino)ethyl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(uuuuu) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[2-(trifluoromethyl)pyrrolidin-1-yl]benzo-1,4-quinone;

(vvvvv) N,N-diethyl-1-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)piperidine-3-carboxamide;

(wwwww) ethyl 1-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)piperidine-3-carboxylate;

(xxxxx) 2-(4-benzylpiperazin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(yyyyy) 2-[(1,3-dioxolan-2-ylmethyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(zzzzz) 2-[[2-(dimethylamino)ethyl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(aaaaaa) 2-[(cyclopropylmethyl)(propyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(bbbbbb) 2-[(2-methoxyethyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ccccccc) 2-[6-methoxy-7-(3-methoxy-propyl)-quinazolin-4-ylamino]-5-(3-methylamino-pyrrolidin-1-yl)benzo-1,4-quinone;

(dddddd) 2-[isobutyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(eeeeee) 2-(4-ethylpiperazin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ffffff) 2-[butyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(gggggg) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(1-methylpiperidin-4-yl)amino]benzo-1,4-quinone;

(hhhhhh) 2-[3-(hydroxymethyl)piperidin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(iiiiii) 2-(4-acetylpiperazin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(jjjjjj) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(1-methylpyrrolidin-3-yl)amino]benzo-1,4-quinone;

(kkkkkk) 2-[[3-(dimethylamino)propyl](methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(llllll) 2-(diallylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(mmmmmm) 2-[(2-furylmethyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(nnnnnn) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(4-morpholin-4-ylphenyl)amino]benzo-1,4-quinone;

(oooooo) 2-[allyl(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(pppppp) 2-(2,3-dihydro-1,4-benzodioxin-6-ylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(qqqqqq) 2-[(4-isopropylphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(rrrrrr) 2-[(2-ethylphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ssssss) 2-[(9-ethyl-9H-carbazol-3-yl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(tttttt) 2-[ethyl(3-methylphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(uuuuuu) 2-[(3,5-di-tert-butylphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(vvvvvv) 2-{[4-(4-chlorophenoxy)phenyl]amino}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(wwwwww) ethyl 5-{4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)amino]phenyl}-2-methyl-3-furoate;

(xxxxxx) 2-(4-imidazol-1-yl-phenylamino)-5-[6-methoxy-7-(3-methoxypropyl)-quinazolin-4-ylamino]benzo-1,4-quinone;

(yyyyyy) N-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)-L-valine;

(zzzzzz) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(pentafluorophenoxy)benzo-1,4-quinone;

(aaaaaaa) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(2-methoxypropyl)amino]benzo-1,4-quinone;

(bbbbbbb) 2-[(2-hydroxypropyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ccccccc) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(5-methyl-2-oxo-1,3-oxazolidin-3-yl)benzo-1,4-quinone;

(ddddddd) 3-iodo-2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-methylbenzo-1,4-quinone;

(eeeeeee) 2-Iodo-5-methoxy-3-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(fffffff) 3-[(2-hydroxyethyl)thio]-2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-methylbenzo-1,4-quinone;

(ggggggg) 2-amino-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(hhhhhhh) 2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(iiiiiii) 2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-6- (methylthio)benzo-1,4-quinone;

(jjjjjjj) 5-methoxy-3-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-2-(methylthio)benzo-1,4-quinone;

(kkkkkkk) 2-bromo-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(lllllll) 4-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzamide;

(mmmmmmm)2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(3-methylphenoxy)benzo-1,4-quinone;

(nnnnnnn) 2-[4-(benzyloxy)phenoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ooooooo) N-{3-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]phenyl}acetamide;

(ppppppp) 2-(isoquinolin-5-yloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(qqqqqqq) 2-(2-allylphenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(rrrrrrr) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[3-(trifluoromethyl)phenoxy]benzo-1,4-quinone;

(sssssss) 2-(2-benzoylphenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ttttttt) 2-(2-bromophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(uuuuuuu) 2-(2-chlorophenoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(vvvvvvv) 2-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]benzonitrile;

(wwwwwww) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(quinolin-6-yloxy)benzo-1,4-quinone;

(xxxxxxx) 2-[(1-acetyl-2-naphthyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(yyyyyyy) 2-[(2-acetyl-1-naphthyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(zzzzzzz) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(3-oxobutyl)phenoxy]benzo-1,4-quinone;

(aaaaaaaa) 2-(dibenzo[b,d]furan-2-yloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(bbbbbbbb) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(2-oxo-1,3-benzoxathiol-6-yl)oxy]benzo-1,4-quinone;

(cccccccc) 2-[(4-chloro-1-naphthyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ddddddd) methyl 3-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]-2-naphthoate;

(eeeeeeee) 2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ffffffff) 2-(cyclopropylmethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(gggggggg) 2-(cyclopentyloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(hhhhhhhh) 2-(cyclohexylmethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(iiiiiiii) 3-[(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]propanenitrile;

(jjjjjjjj) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2-phenoxyethoxy)benzo-1,4-quinone;

(kkkkkkkk) 2-[(3-methoxybenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(llllllll) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2,2,2-trifluoroethoxy)benzo-1,4-quinone;

(mmmmmmmm) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(tetrahydrofuran-3-yloxy)benzo-1,4-quinone;

(nnnnnnnn) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(pyridin-3-ylmethoxy)benzo-1,4-quinone;

(oooooooo) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-{2-[methyl(phenyl)amino]ethoxy}benzo-1,4-quinone;

(pppppppp) 2-{[6-methoxy-7-(2-methoxyethoxy)quinolin-4-yl]amino}-5-[4-(1-methyl-1-phenylethyl)phenoxy]benzo-1,4-quinone;

(qqqqqqqq) 2-(dimethylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinolin-4-yl]amino}benzo-1,4-quinone;

(rrrrrrrr) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(yyyyyyyy) 2-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinolin-4 yl]amino}benzo-1,4-quinone;

(zzzzzzzz) 2-(2,5-dimethylpyrrolidin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(aaaaaaaaa) 2-bromo-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(bbbbbbbbb) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(3-methylphenyl)amino]benzo-1,4-quinone;

(ccccccccc) 2-[benzyl(4-methoxyphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ddddddddd) 2-[ethyl(4-methylphenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(eeeeeeeee) 2-[butyl(phenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(fffffffff) 2-[ethyl(phenyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ggggggggg) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[pentyl(phenyl)amino]benzo-1,4-quinone;

(hhhhhhhhh) 2-(5-bromo-2,3-dihydro-1*H*-indol-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(iiiiiiiii) 2-(2,3-dihydro-1*H*-indol-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(jjjjjjjjj) 2-[(4-chlorophenyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(kkkkkkkkk) 2-[1,3-benzodioxol-5-yl(ethyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(lllllllll) 2-[ethyl(1-naphthyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(mmmmmmmmm) 2-[(3-hydroxy-3-phenylpropyl)(methyl)amino]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(nnnnnnnnn) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(2-naphthylmethyl)piperazin-1-yl]benzo-1,4-quinone;

(ooooooooo) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(1-naphthylmethyl)piperazin-1-yl]benzo-1,4-quinone;

(ppppppppp) 2-[4-(2,4-dimethoxybenzyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(qqqqqqqqq) 2-[4-(3-chlorobenzyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(rrrrrrrrr) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[methyl(2-pyridin-2-ylethyl)amino]benzo-1,4-quinone;

(sssssssss) 3-chloro-2-[4-(3-chlorobenzyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ttttttttt) 4-{[4-(4-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)piperazin-1-yl]methyl}benzonitrile;

(uuuuuuuuu) 2-{4-[4-(dimethylamino)benzyl]piperazin-1-yl}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(vvvvvvvvv) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(2-methylbutyl)piperazin-1-yl]benzo-1,4-quinone;

(wwwwwwwww) 2-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(xxxxxxxxx) 2-[4-(3-fluorobenzyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(yyyyyyyyy) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(2-thienylmethyl)piperazin-1-yl]benzo-1,4-quinone;

(zzzzzzzzz) 2-[4-(3,7-dimethyloct-6-en-1-yl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(aaaaaaaaaa) 2-[4-(2-methoxybenzyl)piperidin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(bbbbbbbbbb) 2-[4-(2-furylmethyl)piperazin-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(cccccccccc) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(pyridin-3-ylmethyl)piperazin-1-yl]benzo-1,4-quinone;

(dddddddddd) 2-[4-(2,4-dimethoxybenzyl)-1,4-diazepan-1-yl]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(eeeeeeeeee) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(2-methylbutyl)-1,4-diazepan-1-yl]benzo-1,4-quinone;

(ffffffffff) 5-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-(ethylthio)-2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(gggggggggg) 2-[(2-chlorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(hhhhhhhhhh) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(methylthio)benzo-1,4-quinone;

(iiiiiiiiii) 2-isopropoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(jjjjjjjjjj) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(1-methylbutoxy)benzo-1,4-quinone;

(kkkkkkkkkk) 2-(cycloheptyloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(llllllllll) 2-sec-butoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(mmmmmmmmmm) 2-(1-ethylpropoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(nnnnnnnnnn) 2-[(1,4-dimethylpentyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(oooooooooo) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(1-methylpiperidin-4-yl)oxy]benzo-1,4-quinone;

(pppppppppp) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(1-methylpiperidin-3-yl)oxy]benzo-1,4-quinone;

(qqqqqqqqqq) 2-[(2-fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(rrrrrrrrrr) 2-[(3-fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(sssssssssss) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(tetrahydro-2*H*-pyran-2-ylmethoxy)benzo-1,4-quinone;

(ttttttttttt) 2-[(4-fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(uuuuuuuuuu) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(tetrahydro-2*H*-pyran-4-yloxy)benzo-1,4-quinone;

(vvvvvvvvvv) 2-[2-(dimethylamino)-1-methylethoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(wwwwwwwwww) 2-[(4-methoxybenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(xxxxxxxxxx) 2-(2,3-dihydro-1*H*-inden-2-yloxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(yyyyyyyyyy) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(3-phenoxypropoxy)benzo-1,4-quinone;

(zzzzzzzzzz) 2-ethoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(aaaaaaaaaa) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(tetrahydrofuran-3-ylmethoxy)benzo-1,4-quinone;

(bbbbbbbbbb) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(2,2,2-trifluoro-1-phenylethoxy)benzo-1,4-quinone;

(cccccccccc) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3*R*)-tetrahydrofuran-3-yloxy]benzo-1,4-quinone;

(dddddddddd) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzo-1,4-quinone;

(eeeeeeeeee) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3-methyloxetan-3-yl)methoxy]benzo-1,4-quinone;

(ffffffffff) 2-{[1-(4-chlorophenyl)cyclopropyl]methoxy}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(gggggggggg) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(1-methylpyrrolidin-3-yl)oxy]benzo-1,4-quinone;

(hhhhhhhhhh) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(pentafluorobenzyl)oxy]benzo-1,4-quinone;

(iiiiiiiiii) 2-(2,2-difluoroethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(jjjjjjjjjj) 2-[(2,3,3,4,4,5-hexafluorocyclopentyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(kkkkkkkkkk) 2-(1,3-benzodioxol-5-ylmethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(llllllllll) 2-{[4-(benzyloxy)-3-methoxybenzyl]oxy}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(mmmmmmmmmm) 2-{[4-(benzyloxy)benzyl]oxy}-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(nnnnnnnnnn) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3-phenylprop-2-yn-1-yl)oxy]benzo-1,4-quinone;

(oooooooooo) 2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[(3-phenoxybenzyl)oxy]benzo-1,4-quinone;

(pppppppppp) 2-[(2-hydroxyethyl)amino]-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(qqqqqqqqqq) 2-(2-furylmethoxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(rrrrrrrrrr) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(1-methylprop-2-yn-1-yl)oxy]benzo-1,4-quinone;

(ssssssssss) 2-(allyloxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(tttttttttt) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(prop-2-yn-1-yloxy)benzo-1,4-quinone;

(uuuuuuuuuu) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(1-phenylprop-2-yn-1-yl)oxy]benzo-1,4-quinone;

(vvvvvvvvvv) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(tetrahydrofuran-3-yloxy)benzo-1,4-quinone;

(wwwwwwwwwww) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(2-methylbenzyl)oxy]benzo-1,4-quinone;

(xxxxxxxxxxx) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-{[4-(methylsulfonyl)benzyl]oxy}benzo-1,4-quinone;

(yyyyyyyyyyy) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(pentafluorobenzyl)oxy]benzo-1,4-quinone;

(zzzzzzzzzzz) 2-({4-[(4-fluorobenzyl)oxy]benzyl}oxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(aaaaaaaaaaa) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-{2-[methyl(phenyl)amino]ethoxy}benzo-1,4-quinone;

(bbbbbbbbbbb) 2-(benzyloxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ccccccccccc) 2-[(4-chlorobenzyl)oxy]-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ddddddddddd) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(pyridin-3-ylmethoxy)benzo-1,4-quinone;

(eeeeeeeeeee) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(pyridin-2-ylmethoxy)benzo-1,4-quinone;

(fffffffffff) 3-{[(4-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-3,6-dioxocyclohexa-1,4-dien-1-yl)oxy]methyl}benzonitrile;

(ggggggggggg) 2-[2-chloro-1-(fluoromethyl)ethoxy]-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(hhhhhhhhhhh) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-[(3-phenylprop-2-yn-1-yl)oxy]benzo-1,4-quinone;

(iiiiiiiiiii) 2-[(3-fluorobenzyl)oxy]-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(jjjjjjjjjjj) 2-(2,2-difluoroethoxy)-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(kkkkkkkkkkk) 2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(lllllllllll) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(3-phenoxypropoxy)benzo-1,4-quinone;

(mmmmmmmmmmmm) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-{[(2*E*)-3-phenylprop-2-en-1-yl]oxy}benzo-1,4-quinone;

(nnnnnnnnnnnn) 2-methoxy-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ooooooooooo) 2-(4-benzylpiperazin-1-yl)-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone;

(pppppppppppp) 2-[4-(2-methoxybenzyl)piperidin-1-yl]-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone;

(qqqqqqqqqqq) 2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone;

(rrrrrrrrrrr) 2-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)-5-(2-phenoxyethoxy)benzo-1,4-quinone;

(sssssssssss) 2-(benzyloxy)-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone;

(ttttttttttt) 2-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)-5-{2-[methyl(phenyl)amino]ethoxy}benzo-1,4-quinone;

(uuuuuuuuuuu) 2-ethoxy-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone;

(vvvvvvvvvvv) 2-methoxy-5-({6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-yl}amino)benzo-1,4-quinone;

(wwwwwwwwwww) 2-methoxy-5-{[6-methoxy-7-(3-pyridin-4-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(xxxxxxxxxxx) 2-chloro-5-{[6-methoxy-7-(3-pyridin-4-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(yyyyyyyyyyy) 2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(zzzzzzzzzzz) 2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-5-(pyridin-3-ylmethoxy)benzo-1,4-quinone;

(aaaaaaaaaaa) 2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[2-fluoro-1-(fluoromethyl)ethoxy]benzo-1,4-quinone;

(bbbbbbbbbbbbb) 2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-5-methoxybenzo-1,4-quinone;

(ccccccccccccc) 2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-5-[4-(1*H*-imidazol-1-yl)phenoxy]benzo-1,4-quinone;

(ddddddddddddd) 2-chloro-5-{[6-methoxy-7-(tetrahydro-2*H*-pyran-2-ylmethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(eeeeeeeeeeeee) 2-methoxy-5-{[6-methoxy-7-(tetrahydro-2*H*-pyran-2-ylmethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(fffffffffffff) 2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-{[6-methoxy-7-(tetrahydro-2*H*-pyran-2-ylmethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(ggggggggggggg) 2-chloro-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(hhhhhhhhhhhhh) 2-chloro-3-isopropoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(iiiiiiiiiiiii) 2-chloro-3-(cyclopropylmethoxy)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(jjjjjjjjjjjjj) 3-chloro-2-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(kkkkkkkkkkkkk) 3-chloro-2-[2-fluoro-1-(fluoromethyl)ethoxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(lllllllllllll) 3-chloro-2-[(3-fluorobenzyl)oxy]-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(mmmmmmmmmmmmm) 3-chloro-2-ethoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(nnnnnnnnnnnnn) 3-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}-2-(tetrahydrofuran-3-yloxy)benzo-1,4-quinone;

(ooooooooooooo) 2-({7-[3-(diethylamino)propoxy]-6-methoxyquinazolin-4-yl}amino)-5-methoxybenzo-1,4-quinone;

(ppppppppppppp) 2,3,5-tris(ethylthio)-6-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(qqqqqqqqqqqq) 3-(ethylthio)-5-methoxy-2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone - 3-

(ethylthio)-5-methoxy-2-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzene-1,4-diol (1:1);

(rrrrrrrrrrrrr) 2-ethoxy-5-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(sssssssssssss) 2-{[6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazolin-4-yl]amino}-5-(2-phenoxyethoxy)benzo-1,4-quinone;

(ttttttttttttt) 2-{[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amino}-5-chlorobenzo-1,4-quinone;

(uuuuuuuuuuuuu) 2-(4-benzylpiperazin-1-yl)-3-chloro-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(vvvvvvvvvvvvv) 3-chloro-2-(3,5-dimethylpiperidin-1-yl)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(wwwwwwwwwwwww) 3-chloro-2-(dimethylamino)-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(xxxxxxxxxxxxx) 2,3-dimethoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(yyyyyyyyyyyyy) 2-[2-fluoro-1-(fluoromethyl)ethoxy]-3-methoxy-5-{[6-methoxy-7-(2-methoxyethoxy)quinazolin-4-yl]amino}benzo-1,4-quinone;

(zzzzzzzzzzzzz) (2*E*)-4-(dimethylamino)-*N*-{7-ethoxy-4-[(4-methoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)amino]quinazolin-6-yl}but-2-enamide;

(aaaaaaaaaaaaa) (2*E*)-4-(dimethylamino)-*N*-[7-ethoxy-4-({4-[(3-fluorobenzyl)oxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)quinazolin-6-yl]but-2-enamide;

(bbbbbbbbbbbbb) (2*E*)-4-(dimethylamino)-*N*-[7-ethoxy-4-({4-[2-fluoro-1-(fluoromethyl)ethoxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)quinazolin-6-yl]but-2-enamide ;

(ccccccccccccc) (2*E*)-*N*-[4-({4-[(3,4-difluorobenzyl)oxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)-7-ethoxyquinazolin-6-yl]-4-(dimethylamino)but-2-enamide;

(ddddddddddddd) (2*E*)-*N*-(4-{[4-(benzyloxy)-3,6-dioxocyclohexa-1,4-dien-1-yl]amino}-7-ethoxyquinazolin-6-yl)-4-(dimethylamino)but-2-enamide;

(eeeeeeeeeeeeee) (2*E*)-4-(dimethylamino)-*N*-(4-{[3,6-dioxo-4-(pyridin-2-ylmethoxy)cyclohexa-1,4-dien-1-yl]amino}-7-ethoxyquinazolin-6-yl)but-2-enamide;

(fffffffffffff) (2*E*)-*N*-[4-({4-[(3-chlorobenzyl)oxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)-7-ethoxyquinazolin-6-yl]-4-(dimethylamino)but-2-enamide;

(ggggggggggggg) (2*E*)-4-(dimethylamino)-*N*-(4-{[3,6-dioxo-4-(2-thienylmethoxy)cyclohexa-1,4-dien-1-yl]amino}-7-ethoxyquinazolin-6-yl)but-2-enamide;

(hhhhhhhhhhhhh) (2*E*)-4-(dimethylamino)-*N*-[7-ethoxy-4-({4-[(3-methoxybenzyl)oxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)quinazolin-6-yl]but-2-enamide;

(iiiiiiiiiiiii) (2*E*)-4-(dimethylamino)-*N*-[7-ethoxy-4-({4-[(2-methylbenzyl)oxy]-3,6-dioxocyclohexa-1,4-dien-1-yl}amino)quinazolin-6-yl]but-2-enamide;

and pharmaceutically acceptable salts thereof.

7. A method of treating a disease characterized, in part, by excessive, abnormal, or inappropriate angiogenesis in a mammal in need thereof which comprises administering to said mammal an effective amount of the compound of claim 1.

8. The method of claim 7, wherein the mammal is human.

9. The method of claim 7, wherein the disease is cancer.

10. The method of claim 7, wherein the disease is diabetic retinopathy.

11. The method of claim 7, wherein the disease is macular degeneration.

12. The method of claim 7, wherein the disease is rheumatoid arthritis.

13. The method according to claim 9, wherein the cancer is selected from the group consisting of breast, kidney, bladder, mouth, larynx, esophagus, stomach, prostate, colon, ovary, and lung.

14. A method of inhibiting a tyrosine kinase enzyme consisting of contacting said enzyme with the compound of claim 1, wherein said compound binds irreversibly to said enzyme.

15. The compound of claim 15, wherein the tyrosine kinase enzyme is kinase domain receptor (KDR).

16. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.