TETRAHYDROINDOLONE AND TETRAHYDROINDAZOLONE DERIVATIVES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of Provisional Application No. 60/656,230, filed February 25, 2005, Provisional Application No. 60/705,715, filed August 4, 2005, and Provisional Application No. 60/727,965, filed October 18, 2005.

BACKGROUND OF THE INVENTION

Field of the invention

The invention relates to benzene, pyridine, and pyridazine derivatives and more specifically to such compounds that are useful in the treatment and/or prevention of diseases and/or conditions related to cell proliferation, such as cancer, inflammation and inflammation-associated disorders, and conditions associated with angiogenesis. Compounds of the invention are also useful in the treatment and/or prevention of infectious diseasaes, in particular, fungal infections.

Description of the Related Art

Cancer is characterized by abnormal cellular proliferation. Cancer cells exhibit a number of properties that make them dangerous to the host, typically including an ability to invade other tissues and to induce capillary ingrowth, which assures that the proliferating cancer cells have an adequate supply of blood. A hallmark of cancerous cells is their abnormal response to control mechanisms that regulate cell division in normal cells and continue to divide until they ultimately kill the host.

Angiogenesis is a highly regulated process under normal conditions, however many diseases are driven by persistent unregulated angiogenesis. Unregulated angiogenesis may either

cause a particular disease directly or exacerbate an existing pathological condition. For example, ocular neovascularization has not only been implicated as the most common cause of blindness, but also is believed the dominant cause of many eye diseases. Further, in certain existing conditions, for example arthritis, newly formed capillary blood vessels invade the joints and destroy cartilage, or in the case of diabetes, new capillaries formed in the retina invade the vitreous, bleed, and cause blindness. Growth and metastasis of solid tumors are also dependent on angiogenesis (Folkman, J., Cancer Research, 46, 467-473 (1986), Folkman, J., Journal of the National Cancer Institute, 82, 4-6 (1989). It has been shown, for example, that tumors which enlarge to greater than 2 mm must obtain their own blood supply and do so by inducing the growth of new capillary blood vessels. Once these new blood vessels become embedded in the tumor, they provide a means for tumor cells to enter the circulation and metastasize to distant sites such as liver, lung or bone (Weidner, N., et al., The New England Journal of Medicine, 324(1), 1-8 (1991). Under conditions of unregulated angiogenesis, therapeutic methods designed to control, repress, and/or inhibit angiogenesis could lead to the abrogation or mitigation of these conditions and diseases.

Inflammation is related to a variety of disorders such as pain, headaches, fever, arthritis, asthma, bronchitis, menstrual cramps, tendonitis, bursitis, psoriasis, eczema, burns, dermatitis, inflammatory bowel syndrome, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, vascular diseases, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, hypersensitivity, conjunctivitis, gingivitis, post-injury swelling, myocardial ischemia, and the like.

Heat-shock protein 90 (HSP-90) is a cellular chaperone protein required for the activation of several eukaryotic protein kinases, including the cyclin-dependent kinase CDK4. Geldanamycin, an inhibitor of the protein-refolding activity of HSP-90, has been shown to have antiproliferative and antitumor activities.

HSP-90 is a molecular chaperone that guides the normal folding, intracellular disposition and proteolytic turnover of many key regulators of cell growth and survival. Its function is subverted during oncogenesis to make malignant transformation possible and to facilitate rapid somatic evolution, and to allow mutant proteins to retain or even gain function. Inhibition of HSP-90 will slow those process thus has potential therapeutic use (Whitesell L, Lindquist, SL, Nature Rev. Cancer, 2005, 10, 761-72).

Ansamycin antibiotics, e.g., herbimycin A (HA), geldanamycin (GM), and 17-allylaminogeldanamycin (17-AAG) are thought to exert their anticancerous effects by tight binding of the N-terminus pocket of HSP-90, thereby destabilizing substrates that normally interact with HSP-90 (Stebbins, C. et al. Cell 1997, 89, 239-250). This pocket is highly conserved and has weak homology to the ATP-binding siteof DNA gyrase (Stebbins, C. et al., supra ; Grenert, J. P. et al.J. Biol. Chem. 1997,272,23843-50).

In vitro and in vivo studies have demonstrated that occupancy of this N-terminal pocket by ansamycins and other HSP-90 inhibitors alters HSP-90 function and inhibits protein folding. At high concentrations, ansamycins and other HSP-90 inhibitors have been shown to prevent binding of protein substrates to HSP-90 (Scheibel, T. H. et al.Proc. Natl. Acad. Sci. USA 1999, 96, 1297-302; Schulte, T. W. et al.J. Biol. Chem. 1995,270,24585-8 ; Whitesell, L. , et al. Proc. Natl.Acad. Sci. USA 1994, 91, 8324-8328). Ansamycins have also been demonstrated to inhibit the ATP-dependent release of

chaperone-associated protein substrates (Schneider, C. L. et al. Proc.Natl. Acad. Sci., USA 1996, 93, 14536-41; Sepp-Lorenzinoet al. J. Biol Chem. 1995,270,16580-16587). In either event, the substrates are degraded by a ubiquitin- dependent process in the proteasome (Schneider, C. L., supra ;Sepp-Lorenzino, L. , et al. J. Biol.Claim. 1995,270, 16580-16587; Whitesell, L. et al. Proc. Natl.Acad. Sci. USA 1994, 91, 8324-8328). HSP-90 substrate destabilization occurs in tumor and non-transformed cells alike and has been shown to be especially effective on a subset of signaling regulators, e.g., Raf (Schulte, T. W. et al., Biochem. Biophys. Res. Commun. 1997, 239, 655-9 Schulte, T. W., et al., J. Biol. Chem. 1995,270, 24585-8), nuclear steroid receptors(Segnitz, B.; U. Gehring J. Biol. Chem. 1997, 272, 18694-18701 ; Smith, D. F. et al. Mol. Cell Biol. 1995,15, 6804-12), v-Src (Whitesell, L. , et al. Proc. Natl.Acad. Sci. USA 1994, 91, 8324-8328) and certain transmembrane tyrosine kinases (Sepp-Lorenzino,L. et al. J. Biol.Chez. 1995,270, 16580-16587) such as EGF receptor (EGFR) and HER2/Neu(Hartmann, F. , et al. Int. J. Cancer 1997,70, 221-9; Miller, P. et al.CancerRes. 1994,54, 2724-2730; Mimnaugh, E. G. , et al.J.Biol. Clzem. 1996,271, 22796-801 ; Schnur, R. et al. J. Med.Chenu. 1995, 38,3806-3812), CDK4, and mutant p53. Erlichman et al. Proc. AACR 2001, 42, abstract 4474. The ansamycin-induced loss of these proteins leads to the selective disruption of certain regulatory pathways and results in growth arrest at specific phases of the cell cycle (Muise-Heimericks, R. C. et al. J. Biol. Chez. 1998, 273, 29864-72), and apoptosis, and/or differentiation of cells so treated (Vasilevskaya, A. et al. CancerRes., 1999,59, 3935-40). Inhibitors of HSP-90 thus hold great promise for the treatment and/or prevention of many types of cancers and proliferative disorders, and also hold promise as traditional antibiotics.

Inhibition of HSP-90 is also known to result in up regulation of the expression of the chaperone HSP70. HSP70 up regulation is considered to be of therapeutic benefit for treatment of a wide range of neurodegenerative diseases including, but not limited to: Alzheimer's disease; Parkinson's disease; Dementia with Lewy bodies; Amyotropic lateral scleriosis (ALS); Polyglutamine disease; Huntington's disease; Spinal and bulbar muscular atrophy (SBMA); and Spinocerebellar ataxias (SCA1-3,7). Therefore, the compounds described in the invention are of potential therapeutic use for treatment of such neurodegenerative diseases (Muchowski, P.J., Wacker J.L., Nat. Rev. Neurosci. 2005, 6, 11-22. ; Shen H.Y., *et al.* J. Biol. Chem. 2005, 280, 39962-9).

Inhibition of HSP-90 also has anti-fungal activity, both as a stand alone therapy and in combination with standard anti-fungal therapies such as the azole class of drugs. Therefore, the compounds described in the invention are of potential therapeutic use for treatment of fungal infections including, but not limited to, life threatening systemic fungal infections (Cowen, L.E., Lindquist, S., Science 2005, 309, 2185-9).

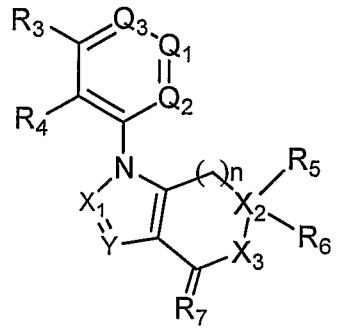
Inhibition of HSP-90 also has antimalarial activity; thus, inhibitors of this protein are useful as antimalarial drugs.

Therefore, there is a continuing need in the art for new methods of treating cancer, inflammation and inflammation-associated disorders, and conditions or diseases related to uncontrolled angiogenesis.

SUMMARY OF THE INVENTION

In a broad aspect, the invention encompasses the compounds of formula I shown below, pharmaceutical compositions containing those compounds and methods employing such compounds or compositions in the treatment of diseases and/or conditions related to cell proliferation, such as cancer, inflammation, arthritis, angiogenesis, or the like.

The invention provides compounds of formula I,



I

or a pharmaceutically acceptable salt thereof, wherein

R_3 and R_4 are independently

(a) H,

(b) halo, or

(c) a C_1-C_{15} alkyl group where up to six of the carbon atoms in said alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other, wherein

R_{22} is

(i) heteroaryl,

(ii) aryl,

(iii) saturated or unsaturated C_3-C_{10} cycloalkyl, or

(iv) saturated or unsaturated C_2-C_{10} heterocycloalkyl, wherein

each aryl, heteroaryl, saturated or unsaturated cycloalkyl, or saturated or unsaturated heterocycloalkyl, independently, is optionally substituted with at least one group, which independently is hydroxy, halo, amino, cyano, carboxy, carboxamido, nitro, oxo, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO-aryl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, (C_1-C_6)alkoxy, or mono- or di-(C_1-C_{10})alkylamino; and

each R_{22} is optionally fused to a C_6-C_{10} aryl group, C_5-C_8 saturated cyclic group, or a C_5-C_{10} heterocycloalkyl group;

wherein each (c) is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}, wherein

Z is OR_0 or -N(R_{30})$_2$, wherein

each R_{30} is independently -H or C_1-C_6 alkyl, or N(R_{30})$_2$ represents pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, 1,3- or 1,4-diazepanyl, or morpholinyl, each of which is optionally substituted with hydroxy, amino, aminoalkyl, C_1-C_6 alkyl, mono- or di(C_1-C_6)alkylamino, C_1-C_6 alkoxy, or halogen;

R_O is -H, -C_1-C_{10} alkyl, -C_2-C_{10} alkenyl, -C_2-C_{10} alkynyl, aryl, heteroaryl, or -C_1-C_6 acyl;

R_{23} is

(1) heteroaryl,

(2) aryl,

(3) saturated or unsaturated C_5-C_{10} cycloalkyl, or

(4) saturated or unsaturated C_5-C_{10} heterocycloalkyl, and

the R_{23} groups are optionally substituted at least one group which is independently hydroxy, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO-aryl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, (C_1-C_6)alkoxy, or mono- or di-(C_1-C_{10})alkylamino;

or R_3 and R_4 together with the atoms to which they are attached form a 5-12 membered mono-, bi-, or tricyclic ring system fused to the ring containing Q_1 and Q_2, where the 5-12 membered ring is partially unsaturated or aromatic and optionally contains one or two of oxygen, $S(O)_m$ where m is 0, 1, or 2, nitrogen, or NR_{33} where R_{33} is hydrogen or C_1-C_6 alkyl;

R_7 is O, S, NH, N-OH, N-NH_2, N-NHR_{22}, N-NH-(C_1-C_6 alkyl), N-O-(C_0-C_6)alkyl-R_{22}, or N-(C_1-C_6 alkoxy optionally substituted with carboxy);

Y is N or CR_C, wherein

each R_C independently is hydrogen, halogen, cyano, nitro, -C(O)$R_{C'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl, heterocycloalkyl, aryl, or heteroaryl, wherein

each alkyl, aryl, cycloalkyl, heterocycloalkyl, and heteroaryl group is optionally substituted with from 1-4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, mono- or di-(C_1-C_6) alkylamino, cyano, nitro, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, carboxamide, heterocycloalkyl, aryl, or heteroaryl, wherein

the aryl and heteroaryl groups are optionally substituted with from 1-4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, mono- or di-(C_1-C_6) alkylamino, halo(C_1-C_6)alkyl, or carboxamide;

$R_{C'}$ is $-C_1$-C_6 alkyl, $-OR_{C''}$, or $-N(R_{CN})_2$, wherein

$R_{C''}$ is -H, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R_{CN} is independently -H, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, C_1-C_6 acyl, aryl, or heteroaryl, wherein

each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl group is optionally substituted with from 1-4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, mono- or di-(C_1-C_6) alkylamino, nitro, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, or carboxamide;

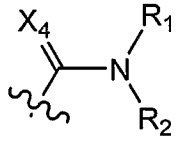
X_1 is N or CR_C;

Q_1, Q_2, and Q_3 are independently N or CR_Q, wherein one and only one of Q_1, Q_2, and Q_3 is C-R_{21}, and wherein

each R_Q is independently hydrogen, halogen, $-N(R_{CN})_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, aryl, or heteroaryl, or R_{21}, wherein

each alkyl, cycloalkyl, aryl, and heteroaryl group is optionally substituted with from 1-4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, mono- or di-(C_1-C_6) alkylamino, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, or carboxamide;

R_{21} is cyano, -C(O)OH, -C(O)-O(C_1-C_6alkyl), or a group of the formula



wherein

R_1 and R_2 are independently H, hydroxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, heteroaryl, aryl, C_3-C_8 cycloalkyl, heterocycloalkyl, wherein

each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl group is optionally substituted with from 1-4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, mono- or di-(C_1-C_6) alkylamino, nitro, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, or carboxamide;

or R_1 and R_2 together with the nitrogen to which they are both attached, form a heterocycloalkyl which optionally contains one or more additional heteroatoms which are, independently, O, N, S, or $N(R_{CN})$;

and

X_4 is O, S, NH, NOH, N-NH_2, N-NHaryl, N-NH-(C_1-C_6 alkyl), or N-(C_1-C_6 alkoxy);

X_2 and X_3 are independently C, O, N, or $S(O)_p$ wherein

p is 0, 1, or 2; and

n is 0, 1, 2, 3, or 4;

provided that when

(i) X_2 is C, then

R_5 and R_6 are independently H, C_1-C_6 alkyl, or aryl, wherein the aryl is optionally substituted with from 1-4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, mono- or di-(C_1-C_6) alkylamino, nitro, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, or carboxamide,

or wherein any two adjacent substituted aryl positions, together with the carbon atoms to which they are attached, form an unsaturated cycloalkyl or heterocycloalkyl; or

R_5 and R_6 together with the carbon to which they are attached form a 3-8 membered ring;

(ii) X_2 is N, then

R_6 is absent and R_5 is H or C_1-C_6 alkyl;

(iii) X_3 is C, then

it is substituted with two groups that are independently H or C_1-C_6 alkyl, or mono- or di-(C_1-C_6)alkylamino(C_1-C_6)alkyl; and

(iv) X_2 is O or $S(O)_p$, then R_6 and R_5 are absent.

The invention also includes intermediates that are useful in making the compounds of the invention.

The invention also provides pharmaceutical compositions comprising a compound or pharmaceutically acceptable salt of Formula I and at least one pharmaceutically acceptable carrier, solvent, adjuvant or diluent.

The invention further provides methods of treating disease such as cancer, inflammation, arthritis, angiogenesis, and infection in a patient in need of such treatment, comprising administering to the patient a compound or pharmaceutically acceptable salt of Formula I, or a

pharmaceutical composition comprising a compound or salt of Formula I.

The invention also provides the use of a compound or salt according to Formula I for the manufacture of a medicament for use in treating cancer, inflammation, arthritis, angiogenesis, or infection.

The invention also provides methods of preparing the compounds of the invention and the intermediates used in those methods.

The invention also provides methods of treating a disease or condition related to cell proliferation comprising administering a therapeutically effective amount of a compound or salt of Formula I to a patient in need of such treatment.

The invention also provides methods of treating a disease or condition related to cell proliferation comprising administering a therapeutically effective amount of a compound or salt of Formula I to a patient in need of such treatment, where the disease of condition is cancer, inflammation, or arthritis.

The invention further provides methods of treating a subject suffering from a disease or disorder of proteins that are either client proteins for HSP-90 or indirectly affect its client proteins, comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound or salt of Formula I.

The invention further provides methods of treating a subject suffering from a disease or disorder of proteins that are either client proteins for HSP-90 or indirectly affect its client proteins, comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound or salt of Formula I, wherein the HSP-90 mediated disorder is selected from the group of inflammatory diseases, infections, autoimmune disorders, stroke, ischemia, cardiac disorders, neurological disorders, fibrogenetic disorders,

proliferative disorders, tumors, leukemias, neoplasms, cancers, carcinomas, metabolic diseases and malignant disease.

The invention further provides methods of treating a subject suffering from a fibrogenetic disorder of proteins that are either client proteins for HSP-90 or indirectly affect its client proteins, comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound or salt of Formula I, wherein the fibrogenetic disorder is selected from the group of scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis and pulmonary fibrosis.

The invention provides methods of protecting a subject from infection caused by an organism selected from *Plasmodium* species, preferably *Plasmodium falciparum*. These methods comprising administering a compound or salt of Formula I, preferably in an effective amount, to a subject at risk of infection due to exposure to such organism.

The invention additionally provides methods of reducing the level of infection in a subject where the infection is caused by an organism selected from *Plasmodium* species, again preferably *Plasmodium falciparum*. These methods comprise administering to an infected subject an effective amount of a compound or salt of Formula I.

The invention further provides methods for treating a patient infected with a metazoan parasite. These methods involve administering an amount of a compound of the invention effective to kill the parasite.

The invention further provides methods for treating a patient infected with a metazoan parasite wherein the parasite is *Plasmodium falciparum*. These methods involve administering an amount of a compound or salt of the invention effective to kill the parasite.

The invention further provides a compound or pharmaceutical composition thereof in a kit with instructions for using he compound or composition.

The invention further provides compounds that may be administered alone or in combination with other drugs or therapies known to be effective to treat the disease to enhance overall effectiveness of therapy.

The invention further provides methods for treating a fungal infection in a patient in need of such treatment, comprising administering an effective amount of a compound or salt of Formula I and an optional anti-fungal agent or drug.

DETAILED DESCRIPTION OF THE INVENTION

In Formula I, R_3 and R_4 are, as noted above, independently (a) hydrogen, (b) halo, or (c) an alkyl group having from 1-15 carbon atoms. All, but no more than about six, of the carbon atoms in the alkyl group may be replaced independently by the various groups listed above in connection with Formula I.

Thus, when the alkyl group is methyl, i.e., a one carbon atom alkyl group, replacement of that carbon atom with, for example, nitrogen or sulfur, the resulting group will not be an alkyl group but instead will be an amino or thio group, respectively. Similarly, when the carbon atom being replaced terminates the alkyl group, the terminal group will become another moiety such as pyrimidinyl, amino, phenyl, or hydroxy.

Replacement of a carbon atom with a group such as, for example, oxygen, nitrogen, or sulfur will require appropriate adjustment of the number of hydrogens or other atoms required to satisfy the replacing atom's valency. Thus, when the replacement is N or O, the number of groups attached to the atom being replaced will be reduced by one or two to satisfy the valency of the nitrogen or oxygen respectively. Similar considerations will be readily apparent to those skilled in the art with respect to replacement by ethenyl and ethynyl.

Thus, replacement as permitted herein results in the term "C_1-C_{15} alkyl" as defined in connection with Formula I encompassing groups such as, but not limited to:

amino, hydroxy, phenyl, benzyl, propylaminoethoxy, butoxyethylamino, pyrid-2-ylpropyl, diethylaminomethyl, pentylsulfonyl, methylsulfonamidoethyl, 3-[4-(butylpyrimidin-2-yl)ethyl]phenyl, butoxy, dimethylamino, 4-(2-(benzylamino)ethyl)pyridyl, but-2-enylamino, 4-(1-(methylamino)pent-3-en-2-ylthio)phenyl, 2-(N-methyl-hexanamido)ethoxy)methyl, and 4-(((3-methoxy-4-(4-methyl-1H-imidazol-2-yl)but-1-enyl)(methyl)amino)-methyl)phenyl.

Preferred compounds of Formula I include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH-$aryl, $-SO_2-$aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2-$aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1-C_{10}$ alkyl-Z, or R_{23}.

Even more preferred compounds of Formula I include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH-$aryl, $-SO_2-$aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2-$aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1-C_{10}$ alkyl-Z, or R_{23}.

Additional preferred compounds of Formula I include those where R_3 and R_4 are independently hydrogen, halo, or $-N(H)R_{z1}$, wherein R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1$-C_{10} alkyl-Z, or R_{23}.

Most preferred compounds of Formula I include those where R_3 and R_4 are independently hydrogen, halo, or $-N(H)R_{z1}$, wherein R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, C_1-C_6 alkoxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1$-C_{10} alkyl-Z, or R_{23}.

Additional preferred compounds of Formula I include those where R_3 and R_4 are independently hydrogen, halo, or $-OR_{z1}$, wherein R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O

atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Most preferred compounds of Formula I include those where R_3 and R_4 are independently hydrogen, halo, or -OR_{Z1}, wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, C_1-C_6 alkoxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Preferred compounds of Formula I include those where X_1 is carbon optionally substituted with C_1-C_6 alkyl, more preferably C_1-C_3 alkyl. Other preferred compounds of Formula I are those where X_1 is carbon optionally substituted with C_1-C_6 alkyl and Y is CR_C wherein R_C is -H, C_1-C_6 alkyl, C_1-C_3 haloalkyl, C_3-C_7 cycloalkyl, or C_3-C_7 cycloalkyl(C_1-C_6)alkyl. More preferably, in compounds of Formula I, X_1 is carbon optionally substituted with C_1-C_2 alkyl and Y is CR_C wherein R_C is -H, C_1-C_4 alkyl, C_1-C_3 haloalkyl, cyclopropyl, or cyclopropyl(C_1-C_2)alkyl.

Still more preferred compounds of Formula I are those where X_1 is CH. Other more preferred compounds of Formula I are those where X_1 is CH and Y is CR_C wherein R_C is -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_5 cycloalkyl, or C_3-C_5 cycloalkyl(C_1-

C_2)alkyl. Even more preferred compounds of Formula I are those where X_1 is CH and Y is CR_C wherein R_C is -H, methyl, ethyl, trifluoromethyl, cyclopropyl, or cyclopropylmethyl. Particularly preferred compounds of Formula I are those where X_1 is CH and Y is CR_C wherein R_C is methyl, ethyl, or cyclopropyl. Other particularly preferred compounds of Formula I are those where X_1 is CH and Y is CR_C wherein R_C is trifluoromethyl. Other particularly preferred compounds of Formula I are those where X_1 is CH and Y is CR_C wherein R_C is methyl. Other particularly preferred compounds of Formula I are those where X_1 is CH and Y is CR_C wherein R_C is ethyl. Other particularly preferred compounds of Formula I are those where X_1 is CH and Y is CR_C wherein R_C is cyclopropyl.

Still other preferred compounds of formula I are those where X_1 is CH, Y is CR_C wherein R_C is -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_7 cycloalkyl, and R_3 is amino or C_1-C_3 alkylamino substituted on the amino or the alkyl with an optionally substituted aryl, optionally substituted heterocycloalkyl, or optionally substituted cycloalkyl group. Preferred substituents on these cyclic groups are hydroxy, C_1-C_3 alkoxy, oxo, halo, C_1-C_3 alkyl, amino, mono- or di-C_1-C_3alkylamino, and nitro. More preferably the optional substituents on these cyclic groups are hydroxy, C_1-C_3alkoxy, and oxo. These cyclic groups are optionally substituted with from 1-4, preferably 1-3 of these substituents.

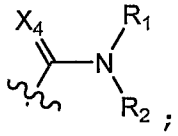
Still more preferred compounds of Formula I are those where X_1 is N. Other more preferred compounds of Formula I are those where X_1 is N and Y is CR_C wherein R_C is -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_3-C_5 cycloalkyl, or C_3-C_5 cycloalkyl(C_1-C_2)alkyl. Even more preferred compounds of Formula I are those where X_1 is N and Y is CR_C wherein R_C is -H, methyl, ethyl, trifluoromethyl, cyclopropyl, or cyclopropylmethyl. Particularly preferred compounds of Formula I are those where X_1 is N and Y is CR_C wherein R_C is methyl, ethyl, or

cyclopropyl. Other particularly preferred compounds of Formula I are those where X_1 is N and Y is CR_C wherein R_C is trifluoromethyl. Other particularly preferred compounds of Formula I are those where X_1 is N and Y is CR_C wherein R_C is methyl. Other particularly preferred compounds of Formula I are those where X_1 is N and Y is CR_C wherein R_C is ethyl. Other particularly preferred compounds of Formula I are those where X_1 is N and Y is CR_C wherein R_C is cyclopropyl.

Still other preferred compounds of formula I are those where X_1 is N, Y is CR_C wherein R_C is -H, C_1-C_3 alkyl, C_1-C_3 haloalkyl, or C_3-C_7 cycloalkyl and R_3 is amino or C_1-C_3 alkylamino substituted on the amino or the alkyl with an optionally substituted aryl, optionally substituted heterocycloalkyl, or optionally substituted cycloalkyl group. Preferred substituents on these cyclic groups are hydroxy, C_1-C_3alkoxy, oxo, halo, C_1-C_3alkyl, amino, mono- or di-C_1-C_3alkylamino, and nitro. More preferably the optional substituents on these cyclic groups are hydroxy, C_1-C_3alkoxy, and oxo. These cyclic groups are optionally substituted with from 1-4, preferably 1-3 of these substituents.

Other preferred compounds of Formula I are those where Q_3 is CR_{21}, wherein

R_{21} is a group of the formula,



;

R_7 is O; and

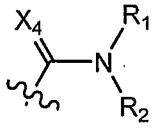
Y is CR_C, wherein R_C is hydrogen, C_1-C_3 alkyl, C_3-C_5 cycloalkyl, trifluoromethyl, or C_3-C_5 cycloalkyl(C_1-C_2)alkyl. Such compounds are compounds of Formula II herein.

Other preferred compounds of Formula II are those where, R_3 and R_4 are, as noted above, independently (a) hydrogen, (b) halo, or (c) an alkyl group having from 1-15 carbon atoms. All, but no more than about six, of the carbon atoms in the

alkyl group may be replaced independently by the various groups listed above in connection with Formula I.

Other preferred compounds of Formula I are those where Q_3 is CR_{21}, wherein

R_{21} is a group of the formula,

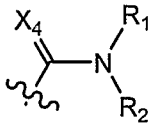

; and

X_3 is C substituted with R_{9a} and R_{9b}, wherein R_{9a} and R_{9b} are independently H or C_1-C_6 alkyl.

Such compounds are hereinafter compounds of Formula III.

Other preferred compounds of Formula I are those where Q_3 is CR_{21}, wherein

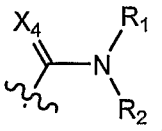
R_{21} is a group of the formula,


; and

Q_1 and Q_2 are independently C substituted with R_{10a} and R_{10b} respectively, wherein R_{10a} and R_{10b} are independently H or C_1-C_6 alkyl. Such compounds are hereinafter compounds of Formula IV.

Other preferred compounds of Formula I are those where Q_3 is CR_{21}, wherein

R_{21} is a group of the formula,


; and

X_1 is C substituted with R_{11} where R_{11} hydrogen, halogen, cyano, nitro, $-C(O)R_{C'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl, heterocycloalkyl, aryl, or heteroaryl, wherein

$R_{C'}$ is $-C_1$-C_6 alkyl, $-OR_{C''}$, or $-N(R_{CN})_2$, wherein

$R_{C''}$ is -H, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

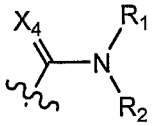
each R_{CN} is independently -H, -C_1-C_{10} alkyl, -C_1-C_{10} -haloalkyl, -C_3-C_7 cycloalkyl, -heterocycloalkyl, -C_1-C_6 acyl, -aryl, or -heteroaryl. Such compounds are hereinafter compounds of Formula V.

Preferred compounds of Formula V are those where R_{11} is hydrogen, halogen, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl, aryl, or heteroaryl.

More preferred compounds of Formula V are those where R_{11} is H or C_1-C_6 alkyl.

Other preferred compounds of Formula I are those where Q_3 is CR_{21}, wherein

R_{21} is a group of the formula,

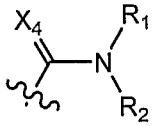


; and

X_1 is N. Such compounds are hereinafter compounds of Formula Va.

Other preferred compounds of Formula I are those where Q_3 is CR_{21}, wherein

R_{21} is a group of the formula,



; and

X_2 is C substituted with R_5 and R_6, wherein R_5 and R_6 are independently H or C_1-C_4 alkyl. Such compounds are hereinafter compounds of Formula VI.

Preferred compounds of any of Formulas I-VI include compounds where R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{Z1}, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl,

ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

More preferred compounds of the invention are those of Formulas I-VI where R_3 and R_4 are independently hydrogen, halo, or -N(H)R_{z1}, wherein R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

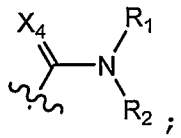
More preferred compounds of the invention are those of Formulas I-VI where R_4 is H, C_1-C_4 alkyl or halogen.

Preferred compounds of Formulas II-VI include those where X_1 is carbon optionally substituted with C_1-C_3 alkyl (preferably methyl) and Y is CR_C wherein R_C is C_1-C_2 alkyl, trifluoromethyl, cyclopropyl, or cyclopropyl(C_1-C_2)alkyl. More preferably in

compounds of Formulas II-VI, X_1 is CH and Y is CR_C wherein R_C is C_1-C_2 alkyl (preferably methyl).

More preferred compounds of the invention are those of Formula I wherein Q_3 is CR_{21}, wherein

R_{21} is a group of the formula,



X_2 is C substituted with two groups that are independently H or C_1-C_4 alkyl;

X_1 is C substituted with H or C_1-C_6 alkyl;

Q_1 and Q_2 are independently C substituted with H or C_1-C_6 alkyl;

R_7 is O;

Y is CR_C, wherein

R_C is -H, methyl, ethyl, trifluoromethyl, or cyclopropyl;

R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1$-C_{10} alkyl-Z, or R_{23}; and

n is 1 or 2.

More preferred compounds of the invention are those of Formula I wherein

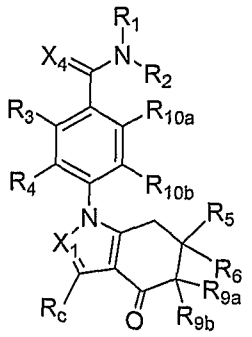
R_1 and R_2 are independently H or C_1-C_4 alkyl;

Q_1 and Q_2 are both CH;

X_2 is C substituted with two independently selected C_1-C_4 alkyl groups; and

n is 1.

Other preferred compounds of the invention include those having the formula VII,



VII

wherein X_1 and R_C are as defined in Formula I;

R_5 and R_6 are independently H or C_1-C_4 alkyl;

R_{11} is H or C_1-C_6 alkyl;

R_{10a} and R_{10b} are independently H or C_1-C_6 alkyl;

R_{9a} and R_{9b} are independently H or C_1-C_6 alkyl;

R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10}

alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

n is 1 or 2.

Preferred compounds of Formula VII include those where

R_1 and R_2 are independently H or C_1-C_4 alkyl;

R_{10a} and R_{10b} are both H; and

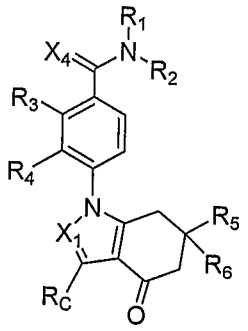
R_5 and R_6 are independently C_1-C_4 alkyl.

Other preferred compounds of Formula VII include those where

X_1 is N.

Other preferred compounds of Formula VII include those where X_1 is CR_c, wherein R_c is hydrogen, methyl, ethyl, cyclopropyl, cyclopropylmethyl, fluoromethyl, difluoromethyl, or trifluoromethyl. In a preferred embodiment of this aspect, the R_c group derived from X_1 is hydrogen, methyl, or trifluoromethyl, and the R_c group derived from Y carries the definition given in connection with Formula I.

Other preferred compounds of Formula I include those of formula VIII,



VIII

wherein R_c is H, C_1-C_6 alkyl, trifluoromethyl, or cyclopropyl; and

R_1-R_6, X_1, and X_4 carry the same definitions as for Formula I.

Preferred compounds of Formula VIII include those where X_1 is N.

Preferred compounds of Formula VIII include those where X_1 is CR_c, wherein R_c is hydrogen, methyl, ethyl, cyclopropyl,

cyclopropylmethyl, fluoromethyl, difluoromethyl, or trifluoromethyl. In a preferred embodiment of this aspect, the R_c group derived from X_1 is hydrogen, methyl, or trifluoromethyl, and the R_c group derived from Y carries the definition given in connection with Formula I.

Preferred compounds of Formula VIII include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH-$aryl, $-SO_2-$aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2-$aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1-C_{10}$ alkyl-Z, or R_{23}.

Preferred compounds of Formula VIII include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido,

oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is O.

Preferred compounds of Formula VIII include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is N-OH.

Other preferred compounds of Formula VIII include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10}

alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Other preferred compounds of Formula VIII include those where R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{Z1}, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is O.

Other preferred compounds of Formula VIII include those where R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{Z1}, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido,

oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is N-OH.

Still other preferred compounds of Formula VIII are those wherein R_3 and R_4 are independently hydrogen, halo, or -N(H)R_{Z1}, wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Still other preferred compounds of Formula VIII are those wherein R_3 and R_4 are independently hydrogen, halo, or -N(H)R_{Z1}, wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -

SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is O.

Still other preferred compounds of Formula VIII are those where R_3 and R_4 are independently hydrogen, halo, or -N(H)R_{Z1}, wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

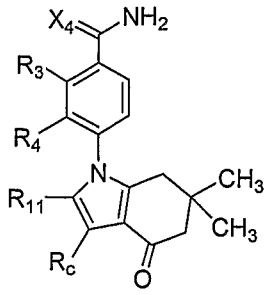
X_4 is N-OH.

Yet other preferred compounds of Formula VIII are those where R_3, R_4 and the carbons to which they are attached form a 6-membered ring.

Yet other preferred compounds of Formula VIII are those where R_3, R_4 and the carbons to which they are attached form a 6-membered ring; and X_4 is O.

Yet other preferred compounds of Formula VIII are those where R_3, R_4 and the carbons to which they are attached form a 6-membered ring; and X_4 is N-OH.

Other preferred compounds of Formula I are those of Formula IX:



IX

where R_{11} is hydrogen or methyl, preferably hydrogen;

R_C is H, C_1-C_2 alkyl, trifluoromethyl, or cyclopropyl; and

R_3, R_4, and X_4 carry the same definitions as for Formula I. Preferred compounds of Formula IX include those where R_C is C_1-C_2 alkyl, trifluoromethyl, or cyclopropyl.

Preferred compounds of Formula IX include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1$-C_{10} alkyl-Z, or R_{23}.

Preferred compounds of Formula IX include those where R_C is methyl, ethyl, trifluoromethyl, or cyclopropyl; R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in

the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is O.

Preferred compounds of Formula IX include those where R_C is methyl, ethyl, trifluoromethyl, or cyclopropyl; R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{z1}, wherein Z_1 is -O-, -NH-, -S(O)$_p$-, or -S(O)$_2$NH-, wherein p is 0, 1 or 2; and R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is N-OH.

Still other preferred compounds of Formula IX include those where R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{z1}, wherein Z_1 is -O- or -NH-; and R_{z1} is a C_1-C_{14} alkyl group

where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Still other preferred compounds of Formula IX include those where R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{z1}, wherein Z_1 is -O- or -NH-; and R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is O.

Still other preferred compounds of Formula IX include those where R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{z1}, wherein Z_1 is -O- or -NH-; and R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are

optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is N-OH.

Yet other preferred compounds of Formula IX include those where R_3 and R_4 are independently hydrogen, halo, or -N(H)R_{Z1}, wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Yet other preferred compounds of Formula IX include those where R_3 and R_4 are independently hydrogen, halo, or -N(H)R_{Z1}, wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety

selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is O.

Yet other preferred compounds of Formula IX include those where R_3 and R_4 are independently hydrogen, halo, or -N(H)R_{z1}, wherein R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is N-OH.

Still other preferred compounds of Formula IX include those where R_3, R_4 and the carbons to which they are attached form a 6-membered ring.

Still other preferred compounds of Formula IX include those where R_3, R_4 and the carbons to which they are attached form a 6-membered ring; and X_4 is O.

Still other preferred compounds of Formula IX include those where R_3, R_4 and the carbons to which they are attached form a 6-membered ring; and X_4 is N-OH.

Preferred compounds of Formulas I-IX include compounds where X_4 is O.

Still other preferred compounds of Formulas I-IX are those where X_4 is N-OH.

Other preferred compounds of Formula I are those where R_{21} is cyano, R_7 is O, and Y is CR_C, wherein R_C is H, methyl, ethyl, trifluoromethyl, or cyclopropyl.

Other preferred compounds of Formula I are those where, R_{21} is cyano; R_7 is O; and Y is CR_C, wherein R_C is H, methyl, trifluoromethyl, or cyclopropyl.

Yet other preferred compounds of Formula I are those where R_{21} is cyano, and X_3 is C substituted with two groups that are independently H or C_1-C_6 alkyl.

More preferred compounds of Formula I are those where R_{21} is cyano, and Q_1 and Q_2 are independently C substituted with H or C_1-C_6 alkyl.

Yet other preferred compounds of Formula I are those where R_{21} is cyano, and X_1 is C substituted with H or C_1-C_6 alkyl.

Still other preferred compounds of Formula I are those where R_{21} is cyano, and X_2 is C substituted with two groups that are independently H or C_1-C_4 alkyl.

In other preferred compounds of Formula I, R_{21} is cyano, and R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{Z1}, wherein Z_1 is -O-, -NH-, -$S(O)_p$-, or -$S(O)_2NH$-, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety

selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

In still other preferred compounds of Formula I, R_{21} is cyano, and R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{Z1}, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

In still other preferred compounds of Formula I, R_{21} is cyano, and R_3 and R_4 are independently hydrogen, halo, or -N(H)R_{Z1}, wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O

atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Other more preferred compounds of Formula I are those where R_{21} is cyano, and R_4 is H, C_1-C_4 alkyl or halogen.

Particularly preferred compounds of Formula I include those where

R_{21} is cyano, and

X_2 is C substituted with two groups that are independently H or C_1-C_4 alkyl;

X_1 is C substituted with H or C_1-C_6 alkyl;

Q_1 and Q_2 are independently C substituted with H or C_1-C_6 alkyl;

X_3 is C substituted with two groups that are independently H or C_1-C_6 alkyl;

R_7 is O;

Y is CR_C wherein R_C is H or CH_3; and

R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{Z1}, wherein Z_1 is -O-, -NH-, -S(O)$_p$-, or -S(O)$_2$NH-, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido,

oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

n is 1 or 2.

Such compounds are referred to herein as compounds of Formula X.

Preferred compounds of Formula X include those where

R_1 and R_2 are independently H or C_1-C_4 alkyl;

Q_1 and Q_2 are both CH;

X_2 is C substituted with two independently selected C_1-C_4 alkyl groups; and

n is 1.

Particularly preferred compounds of Formula I include those where R_{21} is cyano. Such compounds are referred to hereinafter as compounds of Formula XI.

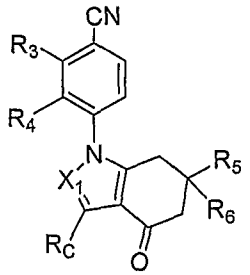
Preferred compounds of Formula XI are those where R_3 and R_4 are independently halogen or hydrogen.

Preferred compounds of Formula XI are those where R_3 is halogen.

Preferred compounds of Formula XI are those where R_3 is hydrogen and R_4 is halogen.

Preferred compounds of Formula XI are those where R_4 is halogen.

Other preferred compounds of Formula I include those of Formula XII:



XII

R_3 and R_4 are independently halogen or hydrogen, provided that at least one of R_3 and R_4 is halogen, and X_1, R_C, R_5 and R_6 are as defined for Formula I.

Preferred compounds of Formula XII include those where X_1 is N.

Preferred compounds of Formula XII include those where X_1 is CR_C, wherein R_C is hydrogen, methyl, ethyl, cyclopropyl, cyclopropylmethyl, fluoromethyl, difluoromethyl, or trifluoromethyl.

Preferred compounds of Formula XII are those where R_3 is halogen.

Other preferred compounds of Formula XII are those where R_4 is halogen.

Still other preferred compounds of Formula XII are those where R_3 is fluoro and R_4 is hydrogen or fluoro.

Particularly preferred compounds of Formula XII are those where R_4 is fluoro and R_3 is hydrogen, bromo, or fluoro.

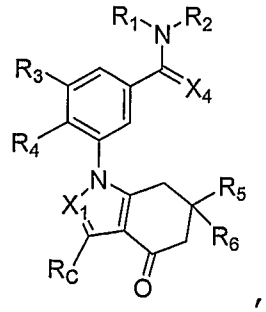
Other particularly preferred compounds of Formula XII are those where R_4 is hydrogen.

Still other preferred compounds of Formula XII are those where R_3 is hydrogen.

Particularly preferred compounds of Formula XII include those where R_3 and R_4 are fluoro.

Preferred compounds of Formula XII are those where R_3 and R_4 are bromo and fluoro respectively.

Yet other preferred compounds of Formula I include those of Formula XIII,



XIII

wherein R_1-R_6, X_4, X_1, and R_C are as defined in Formula I.

Preferred compounds of Formula XIII include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1$-C_{10} alkyl-Z, or R_{23}.

Other preferred compounds of Formula XIII are those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1$-C_{10} alkyl-Z, or R_{23}.

Other preferred compounds of Formula XIII are those where R_3 and R_4 are independently hydrogen, halo, or $-N(H)R_{z1}$, wherein R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1$-C_{10} alkyl-Z, or R_{23}.

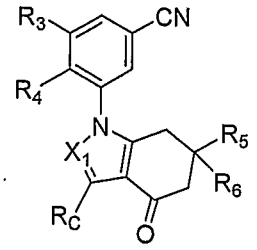
In still other preferred compounds of Formula XIII R_3, R_4 and the carbons to which they are attached form a 6-membered ring.

In more preferred aspects, the previously described preferred embodiments of Formula XIII include compounds wherein X_1 is N or CR_C, wherein R_C is hydrogen, methyl, ethyl, cyclopropyl, cyclopropylmethyl, fluoromethyl, difluoromethyl, or trifluoromethyl.

In more preferred aspects, the previously described preferred embodiments of Formula XIII include compounds wherein X_1 is N.

In more preferred aspects, the previously described preferred embodiments of Formula XIII include compounds wherein X_1 is CR_C, wherein R_C is hydrogen, methyl, ethyl, cyclopropyl, cyclopropylmethyl, fluoromethyl, difluoromethyl, or trifluoromethyl.

Other preferred compounds of Formula I include those of Formula XIV,



XIV

wherein R_C is -H, $-CH_3$, $-CF_3$, or cyclopropyl; and

R_3 and R_4 are independently halogen or hydrogen, provided that at least one of R_3 and R_4 is halogen, and R_5 and R_6 are as defined for Formula I.

Yet other preferred compounds of Formula II through XIV are those where R_{21} is cyano; R_7 is O; and Y is CH or $C(CH_3)$.

Yet other preferred compounds of Formula II through XIV are those where R_{21} is cyano; and R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH-$aryl, $-SO_2-$aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2-$aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1-C_{10}$ alkyl-Z, or R_{23}.

Yet other preferred compounds of Formula II through XIV are those where R_{21} is cyano; and R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22},

carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Yet other preferred compounds of Formula II through XIV are those where R_{21} is cyano; and R_3 and R_4 are independently hydrogen, halo, or -N(H)R_{Z1}, wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

In another aspect, the invention encompasses compounds of Formula I, wherein Y is CR_C, wherein R_C is -H, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, or C_3-C_7 cycloalkyl.

In another aspect, the invention encompasses compounds of Formula I, wherein Y is CH.

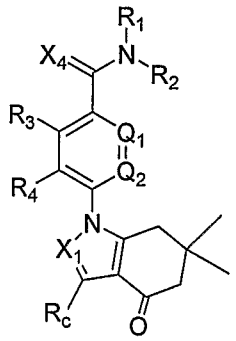
In another aspect, the invention encompasses compounds of Formula I, wherein Y is CR_C, wherein R_C is C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, or C_3-C_7 cycloalkyl.

In another aspect, the invention encompasses compounds of Formula I, wherein Y is CR_C, wherein R_C is methyl, ethyl, trifluoromethyl, or cyclopropyl.

In another aspect, the invention encompasses compounds of Formula I, wherein Y is CR_C, wherein R_C is methyl.

In another aspect, the invention encompasses compounds of Formula I, wherein Y is CR_C, wherein R_C is cyclopropyl.

Yet other preferred compounds of Formula I include those of Formula XV,



XV

wherein X_1-X_4, Q_1, Q_2, R_C, and R_1-R_4 are as defined in Formula I.

Preferred compounds of formula XV are those where Q_1 and Q_2 are each independently hydrogen or C_1-C_6 alkyl.

Other preferred compounds of formula XV are those where R_c is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6 haloalkyl, C_3-C_7cycloalkyl(C_1-C_6)alkyl, or heterocycloalkyl.

More preferred compounds of Formula XV include those where R_c is C_3-C_7cycloalkyl, C_1-C_6 haloalkyl, heterocycloalkyl, or C_3-C_7cycloalkyl(C_1-C_6)alkyl.

Particularly preferred compounds of Formula XV include those where R_c is C_1-C_3alkyl, C_3-C_5cycloalkyl, C_3-C_5cycloalkyl(C_1-C_3)alkyl, or C_1-C_2 haloalkyl.

Additional preferred compounds of Formula XV include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH-$aryl, $-SO_2-$aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2-$aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1-C_{10}$ alkyl-Z, or R_{23}.

Other preferred compounds of Formula XV include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH-$aryl, $-SO_2-$aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2-$aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1-C_{10}$ alkyl-Z, or R_{23}.

Still other preferred compounds of Formula XV are those wherein R_3 and R_4 are independently hydrogen, halo, or $-N(H)R_{Z1}$, wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

More preferred compounds of Formula XV are those wherein R_3 and R_4 are independently hydrogen, $-N(H)-R_{22}-R_{Z2}$, wherein

R_{Z2} is a C_1-C_{13} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z2} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Such compounds are referred to herein as compounds of Formula XVa.

Preferred compounds of Formula XVa are those where X_1 is N.

Preferred compounds of Formula XVa are those where R_{22} is heteroaryl, aryl, saturated C_3-C_{10} cycloalkyl, or saturated C_2-C_{10} heterocycloalkyl.

More preferred compounds of Formula XVa are those where R_{22} is heteroaryl, aryl, saturated C_3-C_{10} cycloalkyl, or saturated C_2-C_{10} heterocycloalkyl; and X_1 is N.

Particularly preferred compounds of Formula XVa are those where R_{22} is saturated C_3-C_7 cycloalkyl, or saturated C_2-C_6 heterocycloalkyl.

Particularly preferred compounds of Formula XVa are those where R_{22} is saturated C_3-C_7 cycloalkyl, or saturated C_2-C_6 heterocycloalkyl and X_1 is N.

Preferred compounds of Formula XV are those where X_1 is N. Such compounds are referred to herein as compounds of Formula XVI.

Preferred compounds of Formula XVI include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10}

alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Preferred compounds of Formula XVI include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and X_4 is O.

Preferred compounds of Formula XVI include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O-, -NH-, $-S(O)_p-$, or $-S(O)_2NH-$, wherein p is 0, 1 or 2; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1-C_6)$alkyl, $-SO_2-(C_1-C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1-C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10}

alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and X_4 is N-OH.

Other preferred compounds of Formula XVI include those where R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{Z1}, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Other preferred compounds of Formula XVI include those where R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{Z1}, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and X_4 is O.

Other preferred compounds of Formula XVI include those where R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein Z_1 is -O- or -NH-; and R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and X_4 is N-OH.

Still other preferred compounds of Formula XVI are those wherein R_3 and R_4 are independently hydrogen, halo, or $-N(H)R_{Z1}$, wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

Still other preferred compounds of Formula XVI are those wherein R_3 and R_4 are independently hydrogen, halo, or $-N(H)R_{Z1}$,

wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is O.

Still other preferred compounds of Formula XVI are those where R_3 and R_4 are independently hydrogen, halo, or -N(H)R_{Z1}, wherein R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

X_4 is N-OH.

Yet other preferred compounds of Formula XVI are those where R_3, R_4 and the carbons to which they are attached form a 6-membered ring.

Yet other preferred compounds of Formula XVI are those where R_3, R_4 and the carbons to which they are attached form a 6-membered ring; and X_4 is O.

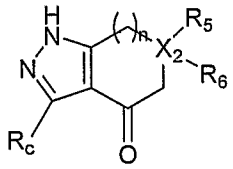
Yet other preferred compounds of Formula XVI are those where R_3, R_4 and the carbons to which they are attached form a 6-membered ring; and X_4 is N-OH.

Yet other preferred compounds of Formula XVI are those where R_3 and R_4 are both -H.

Yet other preferred compounds of Formula XVI are those where R_3 and R_4 are both -H; and X_4 is O.

Yet other preferred compounds of Formula XVIII are those where R_3 and R_4 are both -H; and X_4 is N-OH.

In another aspect, the invention provides compounds of Formula XXII



XXII.

Preferred compounds of Formula XXII include those where R_c is C_1-C_6alkyl, C_3-C_7cycloalkyl, C_1-C_6 haloalkyl, C_3-C_7cycloalkyl(C_1-C_6)alkyl, or heterocycloalkyl.

More preferred compounds of Formula XXII include those where R_c is C_3-C_7cycloalkyl, C_1-C_6 haloalkyl, heterocycloalkyl, or C_3-C_7cycloalkyl(C_1-C_6)alkyl, and X_2 is carbon and R_5 and R_6 are C_1-C_6alkyl.

Particularly preferred compounds of Formula XXII include those where R_c is C_1-C_3alkyl, C_3-C_5cycloalkyl, C_3-C_5cycloalkyl(C_1-C_3)alkyl, or C_1-C_2 haloalkyl.

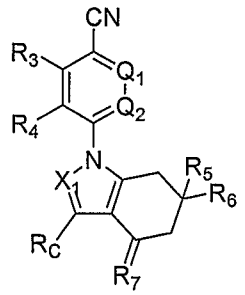
Other particularly preferred compounds of Formula XXII include those where R_c is methyl, ethyl, cyclopropyl,

cyclopropylmethyl, perfluoropropyl, 2,2,2-trifluoroethyl, fluoromethyl, difluoromethyl, perfluoroethyl, or trifluoromethyl.

In a preferred aspect, the invention provides compounds formula I, wherein Q_3 is C-R_{21}.

In a more preferred aspect, the invention provides compounds formula I, wherein Q_3 is C-R_{21}, wherein R_{21} is cyano.

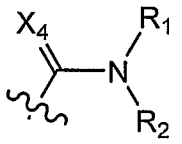
In more preferred aspect, the invention provides compounds Formula XXIV,



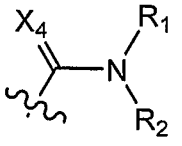
XXIV.

In another preferred aspect, the invention provides compounds formula I, wherein X_1 is N.

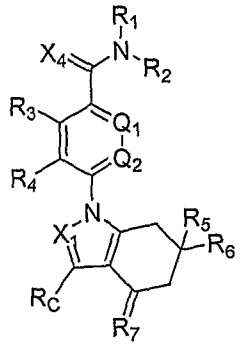
In a more preferred aspect, the invention provides compounds
formula I, wherein Q_3 is C-R_{21}, wherein R_{21} is -C(O)OH, -C(O)-O(C_1-C_6 alkyl), or a group of the formula,



In a another more preferred aspect, the invention provides compounds formula I, wherein Q_3 is C-R_{21}, wherein R_{21} is a group of the formula,



In a preferred aspect, the invention provides compounds formula XXV,



XXV.

In a preferred aspect, the invention provides compounds formula XXV, wherein X_1 is N.

In a preferred aspect, the invention provides compounds formula XXV, wherein X_1 is N; and

R_3 and R_4 are independently hydrogen, halo, or $-Z_1R_{Z1}$, wherein

Z_1 is -O- or -NH-;

R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

In a preferred aspect, the invention provides compounds formula XXV, wherein X_1 is N; and

R_4 is H; and

R_3 hydrogen, halo, or $-Z_1R_{z1}$, wherein

Z_1 is -O- or -NH-;

R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

In a preferred aspect, the invention provides compounds formula XXV, wherein X_1 is N; and

R_4 is H; and

R_3 is -N(H)R_{z1}, wherein

R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo,

amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

In a preferred aspect, the invention provides compounds formula XXV, wherein X_1 is N;

R_4 is H;

R_3 is -N(H)R_{z1}, wherein

R_{z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

R_C is methyl, ethyl, cyclopropyl, cyclopropylmethyl, fluoromethyl, difluoromethyl, or trifluoromethyl.

In a preferred aspect, the invention provides compounds formula XXV, wherein X_1 is N; and

R_3 is H; and

R_4 is hydrogen, halo, or -Z_1R_{z1}, wherein

Z_1 is -O- or -NH-;

R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

In a preferred aspect, the invention provides compounds formula XXV, wherein X_1 is N;

R_3 is H;

R_4 is hydrogen, halo, or -Z_1R_{Z1}, wherein

Z_1 is -O- or -NH-;

R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -

SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23};

and

R_C is methyl, ethyl, cyclopropyl, cyclopropylmethyl, fluoromethyl, difluoromethyl, or trifluoromethyl.

In a preferred aspect, the invention provides compounds formula XXV, wherein

X_1 is CR_{11}, wherein

R_{11} is hydrogen, halogen, cyano, nitro, -C(O)$R_{C'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl, heterocycloalkyl, aryl, or heteroaryl, wherein

$R_{C'}$ is -C_1-C_6 alkyl, -O$R_{C''}$, or -N(R_{CN})$_2$, wherein

$R_{C''}$ is -H, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R_{CN} is independently -H, -C_1-C_{10} alkyl, -C_1-C_{10} -haloalkyl, -C_3-C_7 cycloalkyl, -heterocycloalkyl, -C_1-C_6 acyl, -aryl, or -heteroaryl.

In a more preferred aspect, the invention provides compounds formula XXV, wherein

X_1 is CR_{11}, wherein

R_{11} is hydrogen, halogen, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl, aryl, or heteroaryl.

In a preferred aspect, the invention provides compounds formula XXV, wherein

X_1 is CR_{11}, wherein

R_{11} is hydrogen, halogen, cyano, nitro, -C(O)$R_{C'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-

C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl, heterocycloalkyl, aryl, or heteroaryl, wherein

$R_{C'}$ is -C_1-C_6 alkyl, -$OR_{C''}$, or -$N(R_{CN})_2$, wherein

$R_{C''}$ is -H, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R_{CN} is independently -H, -C_1-C_{10} alkyl, -C_1-C_{10} -haloalkyl, -C_3-C_7 cycloalkyl, -heterocycloalkyl, -C_1-C_6 acyl, -aryl, or -heteroaryl; and

R_3 and R_4 are independently hydrogen, halo, or -Z_1R_{Z1}, wherein

Z_1 is -O- or -NH-;

R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

In a preferred aspect, the invention provides compounds formula XXV, wherein

X_1 is CR_{11}, wherein

R_{11} is hydrogen, halogen, cyano, nitro, $-C(O)R_{C'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl, heterocycloalkyl, aryl, or heteroaryl, wherein

$R_{C'}$ is $-C_1$-C_6 alkyl, $-OR_{C''}$, or $-N(R_{CN})_2$, wherein

$R_{C''}$ is -H, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R_{CN} is independently -H, $-C_1$-C_{10} alkyl, $-C_1$-C_{10} -haloalkyl, $-C_3$-C_7 cycloalkyl, -heterocycloalkyl, $-C_1$-C_6 acyl, -aryl, or -heteroaryl;

R_4 is H; and

R_3 hydrogen, halo, or $-Z_1R_{Z1}$, wherein

Z_1 is -O- or -NH-;

R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1$-$C_6)$alkyl, $-SO_2-(C_1$-$C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1$-$C_6)$alkyl, $-SO_2$NH-aryl, $-SO_2$-aryl, $-SO-(C_1$-$C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-$(C_1$-$C_{10})$alkylamino, $-OC_1$-C_{10} alkyl-Z, or R_{23}.

In a preferred aspect, the invention provides compounds formula XXV, wherein

X_1 is CR_{11}, wherein

R_{11} is hydrogen, halogen, cyano, nitro, $-C(O)R_{C'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl, heterocycloalkyl, aryl, or heteroaryl, wherein

$R_{C'}$ is $-C_1$-C_6 alkyl, $-OR_{C''}$, or $-N(R_{CN})_2$, wherein

$R_{C''}$ is -H, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R_{CN} is independently -H, $-C_1$-C_{10} alkyl, $-C_1$-C_{10} -haloalkyl, $-C_3$-C_7 cycloalkyl, -heterocycloalkyl, $-C_1$-C_6 acyl, -aryl, or -heteroaryl;

R_4 is H; and

R_3 is $-N(H)R_{Z1}$, wherein

R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1$-$C_6)$alkyl, $-SO_2-(C_1$-$C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1$-$C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1$-$C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-$(C_1$-$C_{10})$alkylamino, $-OC_1$-C_{10} alkyl-Z, or R_{23}.

In a preferred aspect, the invention provides compounds formula XXV, wherein

X_1 is CR_{11}, wherein

R_{11} is hydrogen, halogen, cyano, nitro, $-C(O)R_{C'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl, heterocycloalkyl, aryl, or heteroaryl, wherein

$R_{C'}$ is $-C_1$-C_6 alkyl, $-OR_{C''}$, or $-N(R_{CN})_2$, wherein

$R_{C''}$ is -H, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R_{CN} is independently -H, $-C_1$-C_{10} alkyl, $-C_1$-C_{10} -haloalkyl, $-C_3$-C_7 cycloalkyl, -heterocycloalkyl, $-C_1$-C_6 acyl, -aryl, or -heteroaryl;

R_4 is H;

R_3 is $-N(H)R_{Z1}$, wherein

R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1$-$C_6)$alkyl, $-SO_2-(C_1$-$C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1$-$C_6)$alkyl, $-SO_2NH$-aryl, $-SO_2$-aryl, $-SO-(C_1$-$C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-$(C_1$-$C_{10})$alkylamino, $-OC_1$-C_{10} alkyl-Z, or R_{23}; and

R_C is hydrogen, methyl, ethyl, cyclopropyl, cyclopropylmethyl, fluoromethyl, difluoromethyl, or trifluoromethyl.

In a preferred aspect, the invention provides compounds formula XXV, wherein

X_1 is CR_{11}, wherein

R_{11} is hydrogen, halogen, cyano, nitro, $-C(O)R_{C'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl, heterocycloalkyl, aryl, or heteroaryl, wherein

$R_{C'}$ is $-C_1$-C_6 alkyl, $-OR_{C''}$, or $-N(R_{CN})_2$, wherein

$R_{C''}$ is $-H$, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R_{CN} is independently $-H$, $-C_1$-C_{10} alkyl, $-C_1$-C_{10} -haloalkyl, $-C_3$-C_7 cycloalkyl, -heterocycloalkyl, $-C_1$-C_6 acyl, -aryl, or -heteroaryl;

R_3 is H; and

R_4 is hydrogen, halo, or $-Z_1R_{Z1}$, wherein

Z_1 is -O- or -NH-;

R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, $-S-(C_1$-$C_6)$alkyl, $-SO_2-(C_1$-$C_6)$alkyl, $-SO_2NH_2$, $-SO_2NH-(C_1$-$C_6)$alkyl, -

SO_2NH-aryl, $-SO_2$-aryl, $-SO-(C_1-C_6)$alkyl, $-SO_2$-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, $-OC_1-C_{10}$ alkyl-Z, or R_{23}.

In a preferred aspect, the invention provides compounds formula XXV, wherein

X_1 is CR_{11}, wherein

R_{11} is hydrogen, halogen, cyano, nitro, $-C(O)R_{C'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl, heterocycloalkyl, aryl, or heteroaryl, wherein

$R_{C'}$ is $-C_1-C_6$ alkyl, $-OR_{C''}$, or $-N(R_{CN})_2$, wherein

$R_{C''}$ is $-H$, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R_{CN} is independently $-H$, $-C_1-C_{10}$ alkyl, $-C_1-C_{10}$ $-$haloalkyl, $-C_3-C_7$ cycloalkyl, $-$heterocycloalkyl, $-C_1-C_6$ acyl, $-$aryl, or $-$heteroaryl;

R_3 is H;

R_4 is hydrogen, halo, or $-Z_1R_{Z1}$, wherein

Z_1 is $-O-$ or $-NH-$;

R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, $-SH$, $-S-(C_1-C_6)$alkyl, $-$

SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}; and

R_c is hydrogen, methyl, ethyl, cyclopropyl, cyclopropylmethyl, fluoromethyl, difluoromethyl, or trifluoromethyl.

In another aspect, the invention encompasses a method of treating cancer comprising administering to a patient in need thereof, a pharmaceutically acceptable amount of a compound or salt of Formula I or a pharmaceutical composition comprising a compound or salt of Formula I.

In another aspect, the invention encompasses the use of a therapeutically effective amount of a compound or salt of Formula I for the preparation of a medicament for the treatment of cancer, inflammation, or arthritis in a patient in need of such treatment.

In another aspect, the invention encompasses a package comprising a compound or salt of Formula I in a container with instructions on how to use the compound.

In another aspect, the invention encompasses the use of a therapeutically effective amount of a compound or salt according of Formula I for the preparation of a medicament for the treatment of a disease or condition related to cell proliferation in a patient in need of such treatment.

In another aspect, the invention encompasses the use of a therapeutically effective amount of a compound or salt according of Formula I for the preparation of a medicament for the treatment of a disease or condition related to cell proliferation in a patient in need of such treatment, wherein the disease or condition is cancer, inflammation, or arthritis.

In another aspect, the invention encompasses the use of therapeutically effective amount of a compound or salt of Formula I for the preparation of a medicament for the treatment of a disease or disorder related to the activity of heat shock protein 90, in a subject in need of such.

In another aspect, the invention encompasses the use of therapeutically effective amount of a compound or salt of Formula I, alone or in combination with another therapeutic agent, for the preparation of a medicament for the treatment of a disease or disorder related to the activity of heat shock protein 90 and/or its client protiens, in a subject in need of such, wherein the HSP-90 mediated disorder is selected from the group of inflammatory diseases, infections, autoimmune disorders, stroke, ischemia, cardiac disorders, neurological disorders, fibrogenetic disorders, proliferative disorders, tumors, leukemias, neoplasms, cancers, carcinomas, metabolic diseases and malignant disease.

In a preferred aspect, the invention encompasses methods for the treatment of cancer in a subject in need of such treatment comprising administration of therapeutically effective amount of a compound or salt of Formula I, in combination with at least one other therapeutic agent..

In a more preferred aspect, the invention encompasses methods for treating cancer in a subject in need of such treatment, the methods comprising administration of therapeutically effective amount of a compound or salt of Formula I, in combination with at least one other anti-cancer agent..

In another preferred aspect, the invention encompasses methods for treating cancer, the methods comprising administration, to a subject in need of such treatment, of a therapeutically effective amount of a compound or salt of Formula I, in combination with radiation therapy.

In another aspect, the invention encompasses the use of therapeutically effective amount of a compound or salt of Formula I for the preparation of a medicament for the treatment of a fibrogenetic disorder related to the activity of heat shock protein 90, in a subject in need of such, wherein the fibrogenetic disorder is selected from the group of scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis and pulmonary fibrosis.

In another aspect, the invention encompasses the use of a therapeutically effective amount of a compound or salt of Formula I for the preparation of a medicament for protecting a subject from infection caused by an organism selected from *Plasmodium* species.

In a preferred aspect, the invention encompasses the use of a therapeutically effective amount of a compound or salt of Formula I for the preparation of a medicament for protecting a subject from infection caused by *Plasmodium falciparum*.

In another aspect, the invention encompasses the use of a therapeutically effective amount of a compound or salt of Formula I for the preparation of a medicament for reducing the level of infection caused by an organism selected from *Plasmodium* species in a subject in need of such treatment.

In a preferred aspect, the invention encompasses the use of a therapeutically effective amount of a compound or salt of Formula I for the preparation of a medicament for reducing the level of infection caused by *Plasmodium falciparum* in a subject in need of such treatment

In another aspect, the invention encompasses the use of a therapeutically effective amount of a compound or salt of Formula I for the preparation of a medicament for treating a patient infected with a metazoan parasite.

In a preferred aspect, the invention encompasses the use of a therapeutically effective amount of a compound or salt of

Formula I for the preparation of a medicament for treating a patient infected by a metazoan parasite which is *Plasmodium falciparum*.

In another aspect, the invention encompasses the use of a therapeutically effective amount of a compound or salt of Formula I in combination with one or more known anti-fungal drugs for the preparation of a medicament for treating a patient infected with a fungal infection.

Definitions

The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached to the parent molecular moiety through an oxygen bridge. Examples of alkoxy groups include, for example, methoxy, ethoxy, propoxy and isopropoxy.

As used herein, the term "alkyl" includes those alkyl groups of a designated number of carbon atoms. Alkyl groups may be straight, or branched. Examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, iso-, sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, and the like.

The term "alkenyl" as used herein, means a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

The term "alkenoxy" refers to an alkenyl group attached to the parent group through an oxygen atom.

The term "alkynyl" as used herein, means a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not

limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butynyl, 2-pentynyl, and 1-butynyl.

The term "aryl" refers to an aromatic hydrocarbon ring system containing at least one aromatic ring. The aromatic ring may optionally be fused or otherwise attached to other aromatic hydrocarbon rings or non-aromatic hydrocarbon rings. Examples of aryl groups include, for example, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalene and biphenyl. Preferred examples of aryl groups include phenyl, naphthyl, and anthracenyl. More preferred aryl groups are phenyl and naphthyl. Most preferred is phenyl. The aryl groups of the invention may be substituted with various groups as provided herein. Thus, any carbon atom present within an aryl ring system and available for substitution may be further bonded to a variety of ring substituents, such as, for example, halogen, hydroxy, nitro, cyano, amino, C_1-C_8alkyl, C_1-C_8alkoxy, mono- and di(C_1-C_8alkyl)amino, C_3-C_{10}cycloalkyl, (C_3-C_{10}cycloalkyl)alkyl, (C_3-C_{10}cycloalkyl)alkoxy, C_2-C_9heterocycloalkyl, C_1-C_8alkenyl, C_1-C_8alkynyl, halo(C_1-C_8)alkyl, halo(C_1-C_8)alkoxy, oxo, amino(C_1-C_8)alkyl, mono- and di(C_1-C_8alkyl)amino(C_1-C_8)alkyl, C_1-C_8acyl, C_1-C_8acyloxy, C_1-C_8sulfonyl, C_1-C_8thio, C_1-C_8sulfonamido, C_1-C_8aminosulfonyl .

The term "carboxy" as used herein, means a $-CO_2H$ group.

The term "cycloalkyl" refers to a C_3-C_8 cyclic hydrocarbon. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. More preferred are C_3-C_6 cycloalkyl groups. The cycloalkyl groups of the invention may be substituted with various groups as provided herein. Thus, any carbon atom present within a cycloalkyl ring system and available for substitution may be further bonded to a variety of ring substituents, such as, for example, halogen, hydroxy, nitro, cyano, amino, C_1-C_8alkyl, C_1-C_8alkoxy, mono- and di(C_1-C_8alkyl)amino, C_3-C_{10}cycloalkyl, (C_3-C_{10}cycloalkyl)alkyl, (C_3-

C_{10}cycloalkyl)alkoxy, C_2-C_9heterocycloalkyl, C_1-C_8alkenyl, C_1-C_8alkynyl, halo(C_1-C_8)alkyl, halo(C_1-C_8)alkoxy, oxo, amino(C_1-C_8)alkyl and mono- and di(C_1-C_8alkyl)amino(C_1-C_8)alkyl.

The terms "halogen" or "halo" indicate fluorine, chlorine, bromine, and iodine.

The term "haloalkoxy" refers to an alkoxy group substituted with one or more halogen atoms, where each halogen is independently F, Cl, Br or I. Preferred halogens are F and Cl. Preferred haloalkoxy groups contain 1-6 carbons, more preferably 1-4 carbons, and still more preferably 1-2 carbons. "Haloalkoxy" includes perhaloalkoxy groups, such as OCF_3 or OCF_2CF_3. A preferred haloalkoxy group is trifluoromethoxy.

The term "haloalkyl" refers to an alkyl group substituted with one or more halogen atoms, where each halogen is independently F, Cl, Br or I. Preferred halogens are F and Cl. Preferred haloalkyl groups contain 1-6 carbons, more preferably 1-4 carbons, and still more preferably 1-2 carbons. "Haloalkyl" includes perhaloalkyl groups, such as CF_3 or CF_2CF_3. A preferred haloalkyl group is trifluoromethyl.

The term "heterocycloalkyl" refers to a ring or ring system containing at least one heteroatom selected from nitrogen, oxygen, and sulfur, wherein said heteroatom is in a non-aromatic ring. The heterocycloalkyl ring is optionally fused to or otherwise attached to other heterocycloalkyl rings and/or non-aromatic hydrocarbon rings and/or phenyl rings. Preferred heterocycloalkyl groups have from 3 to 7 members. More preferred heterocycloalkyl groups have 5 or 6 members. Examples of heterocycloalkyl groups include, for example, 1,2,3,4-tetrahydroisoquinolinyl, piperazinyl, morpholinyl, piperidinyl, tetrahydrofuranyl, pyrrolidinyl, pyridinonyl, and pyrazolidinyl. Preferred heterocycloalkyl groups include piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, pyridinonyl, dihydropyrrolidinyl, and pyrrolidinonyl. The heterocycloalkyl groups of the invention may be substituted

with various groups as provided herein. Thus, any atom present within a heterocycloalkyl ring and available for substitution may be further bonded to a variety of ring substituents, such as, for example, halogen, hydroxy, nitro, cyano, amino, C_1-C_8alkyl, C_1-C_8alkoxy, mono- and di(C_1-C_8alkyl)amino, C_3-C_{10}cycloalkyl, (C_3-C_{10}cycloalkyl)alkyl, (C_3-C_{10}cycloalkyl)alkoxy, C_2-C_9heterocycloalkyl, C_1-C_8alkenyl, C_1-C_8alkynyl, halo(C_1-C_8)alkyl, halo(C_1-C_8)alkoxy, oxo, amino(C_1-C_8)alkyl and mono- and di(C_1-C_8alkyl)amino(C_1-C_8)alkyl.

The term "heteroaryl" refers to an aromatic ring system containing at least one heteroatom selected from nitrogen, oxygen, and sulfur. The heteroaryl ring may be fused or otherwise attached to one or more heteroaryl rings, aromatic or non-aromatic hydrocarbon rings or heterocycloalkyl rings. Examples of heteroaryl groups include, for example, pyridine, furan, thienyl, 5,6,7,8-tetrahydroisoquinoline and pyrimidines. The heteroaryl groups of the invention may be substituted with various groups as provided herein. Thus, any carbon atom present within an heteroaryl ring system and available for substitution may be further bonded to a variety of ring substituents, such as, for example, halogen, hydroxy, nitro, cyano, amino, C_1-C_8alkyl, C_1-C_8alkoxy, mono- and di(C_1-C_8alkyl)amino, C_3-C_{10}cycloalkyl, (C_3-C_{10}cycloalkyl)alkyl, (C_3-C_{10}cycloalkyl)alkoxy, C_2-C_9heterocycloalkyl, C_1-C_8alkenyl, C_1-C_8alkynyl, halo(C_1-C_8)alkyl, halo(C_1-C_8)alkoxy, oxo, amino(C_1-C_8)alkyl and mono- and di(C_1-C_8alkyl)amino(C_1-C_8)alkyl.

Preferred examples of heteroaryl groups include thienyl, benzothienyl, pyridyl, quinolyl, pyrazolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, dibenzofuranyl, thiazolyl, benzothiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, pyrrolyl, indolyl, pyrazolyl, and benzopyrazolyl.

The compounds of this invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in

different stereoisomeric forms. These compounds can be, for example, racemates, chiral non-racemic or diastereomers. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent; chromatography, using, for example a chiral HPLC column; or derivatizing the racemic mixture with a resolving reagent to generate diastereomers, separating the diastereomers via chromatography, and removing the resolving agent to generate the original compound in enantiomerically enriched form. Any of the above procedures can be repeated to increase the enantiomeric purity of a compound.

When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless otherwise specified, it is intended that the compounds include the cis, trans, Z- and E- configurations. Likewise, all tautomeric forms are also intended to be included.

Pharmaceutical Compositions

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or

diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques. In some cases such coatings may be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules, wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Formulations for oral use may also be presented as lozenges.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the

active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-

or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

For disorders of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical gel, spray, ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base.

Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related

analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane. The transdermal patch may include the compound in a suitable solvent system with an adhesive system, such as an acrylic emulsion, and a polyester patch. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should

preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w. For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared

from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient. The daily dose can be administered in one to four doses per day. In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It may be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a

premix for addition to the feed or drinking water. Preferred non-human animals include domesticated animals.

The compounds of the present invention may be administed alone or in combination with at least one additional therapeutic agent or therapy, e.g., radiation therapy, to a patient in need of such treatment. The additional therapeutic agent or therapy may be administed at the same time, separately, or sequentially with respect to the administration of a compound of the invention. Such additional therapeutic agents included, but are not limited to, anti-cancer agents, anti-inflammatory agents, and the like.

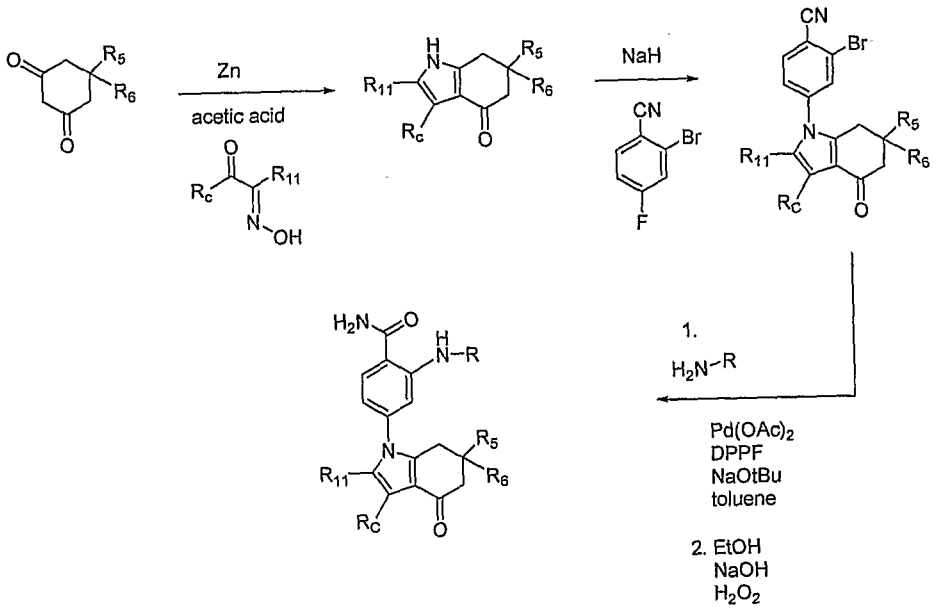
The compounds of the present invention may be prepared by use of known chemical reactions and procedures. Representative methods for synthesizing compounds of the invention are presented below. It is understood that the nature of the substituents required for the desired target compound often determines the preferred method of synthesis. All variable groups of these methods are as described in the generic description if they are not specifically defined below.

Methods of Preparation

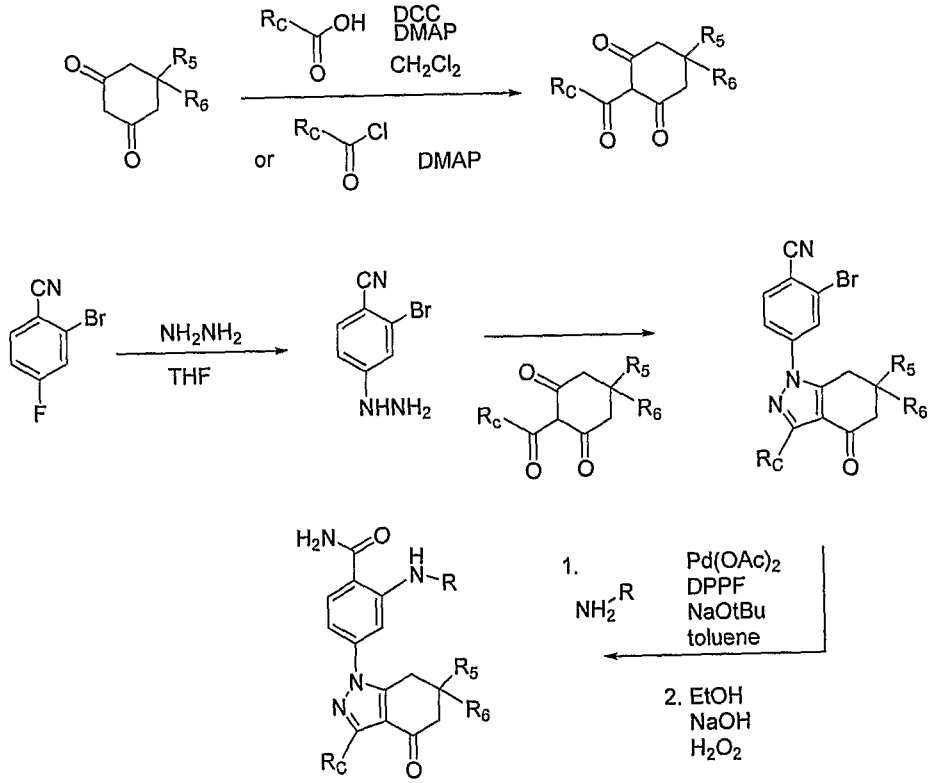
General procedure

Representative synthetic procedures for the preparation of compounds of the invention are outlined below in following schemes. Unless otherwise indicated, X_1, X_2, X_3, n, R_5, R_6, R_7, R_c, R_{11}, and Y carry the definitions given in connection with Formula I. The definition of R is as set forth above in connection with Formula XVII.

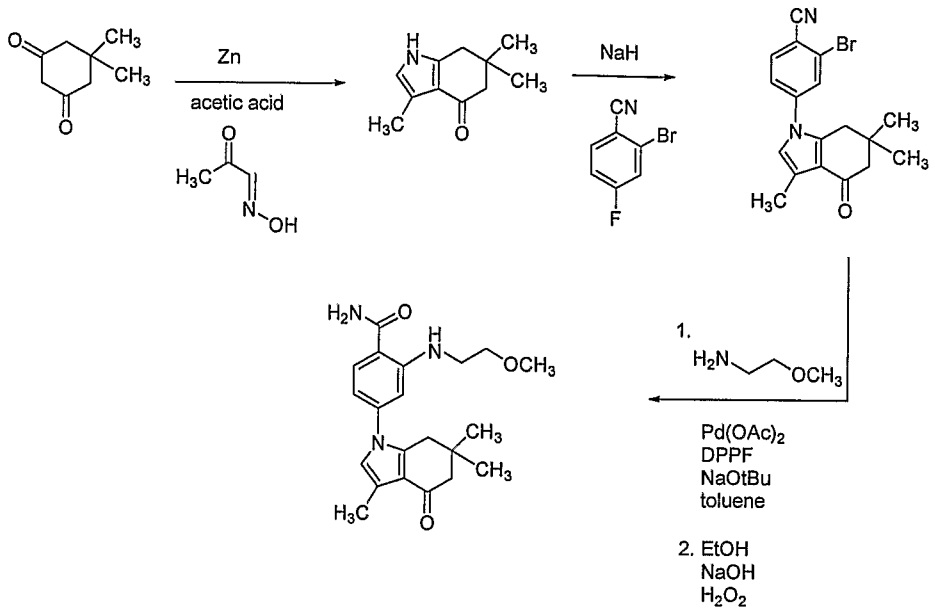
Scheme 1



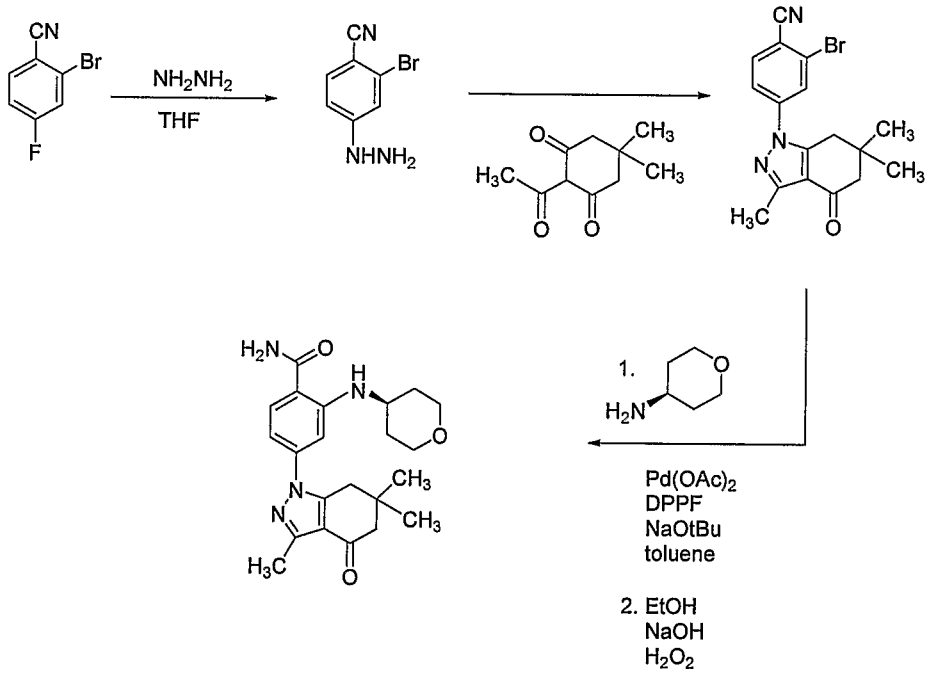
Scheme 2



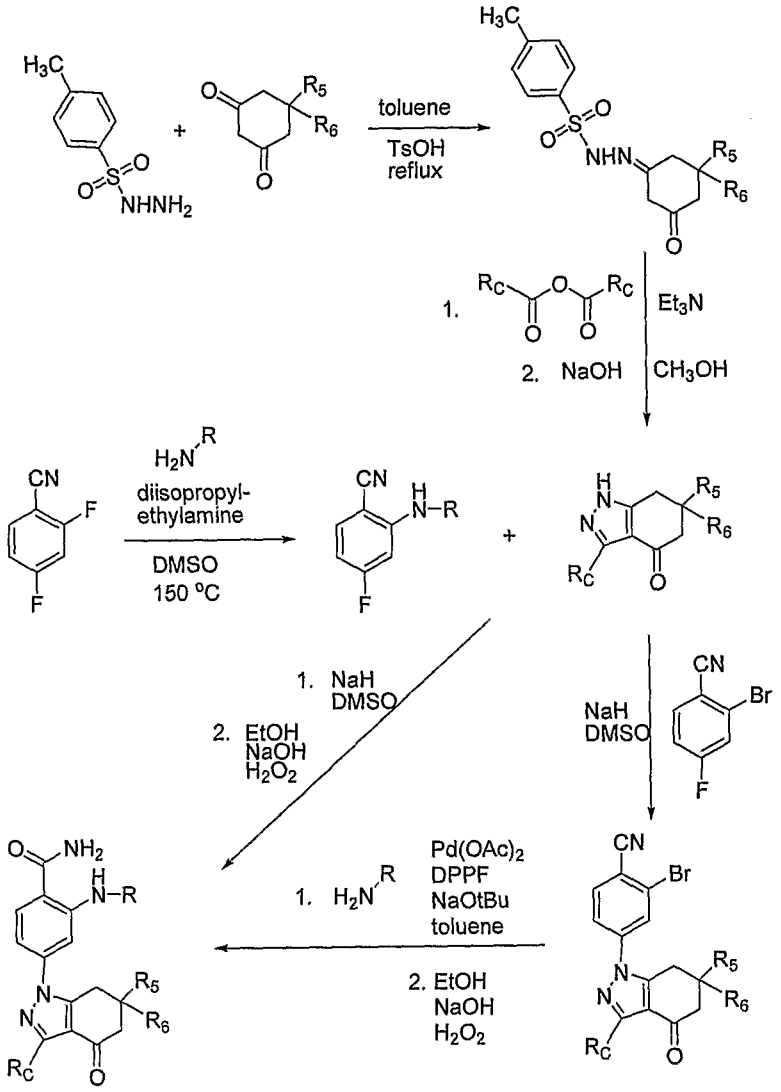
Scheme 3



Scheme 4

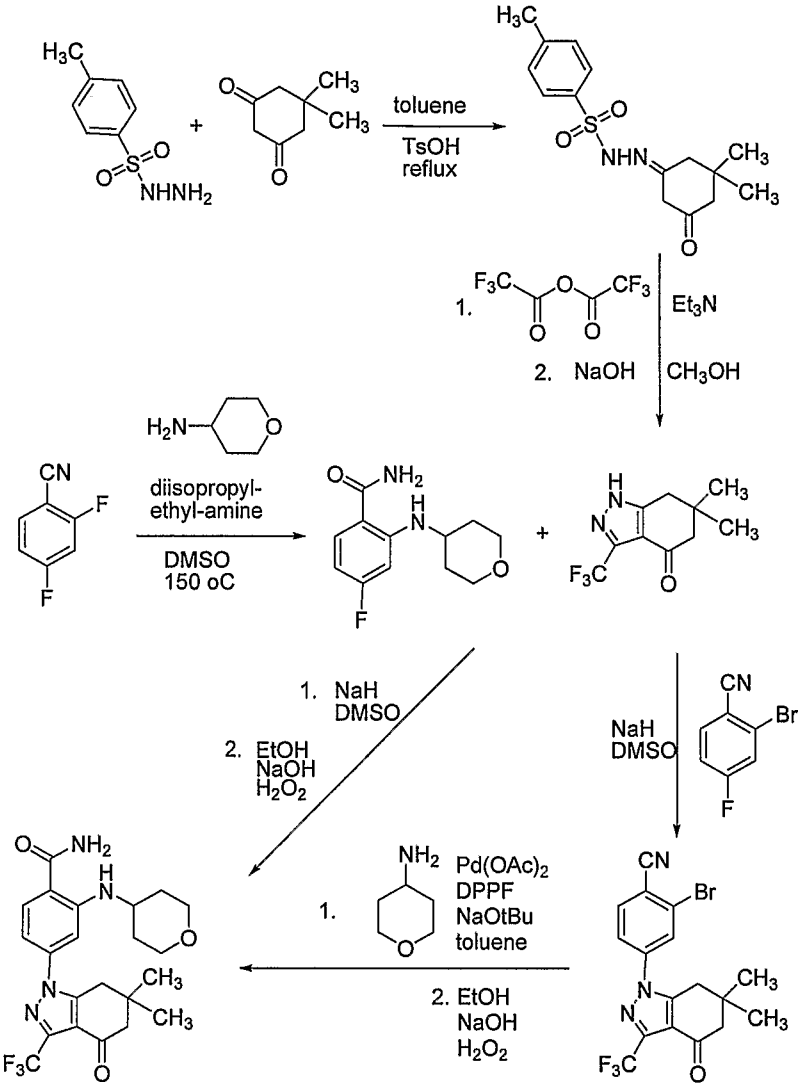


Scheme 5


toluene
TsOH
reflux
1. Et3N
2. NaOH CH3OH
diisopropyl-
ethylamine
DMSO
150 °C
1. NaH
DMSO
2. EtOH
NaOH
H2O2
NaH
DMSO
Pd(OAc)2
DPPF
NaOtBu
toluene
1. H2N R
2. EtOH
NaOH
H2O2

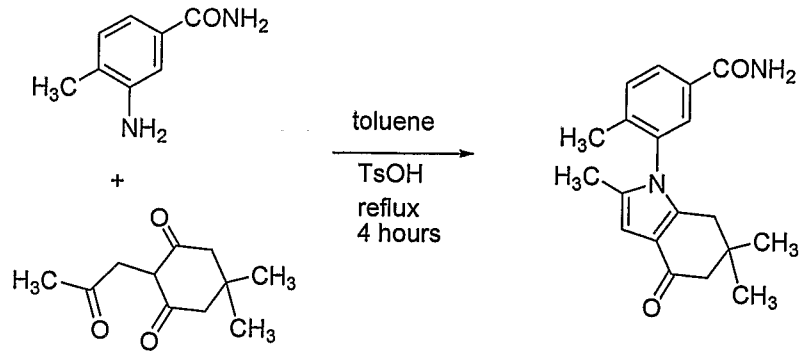
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Scheme 6

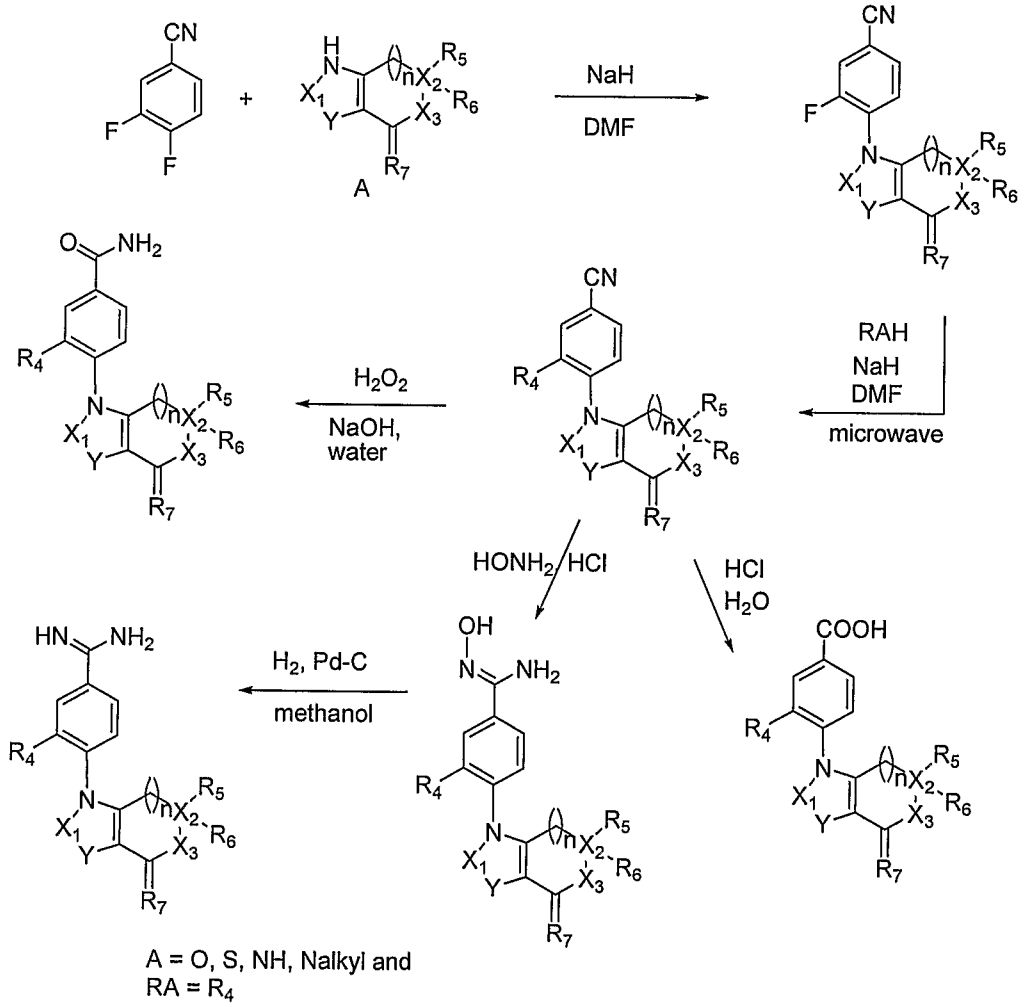

toluene
TsOH
reflux
1.
Et3N
2. NaOH
CH3OH
diisopropyl-
ethyl-amine
DMSO
150 oC
1. NaH
DMSO
2. EtOH
NaOH
H2O2
NaH
DMSO
Pd(OAc)2
DPPF
NaOtBu
toluene
2. EtOH
NaOH
H2O2

5

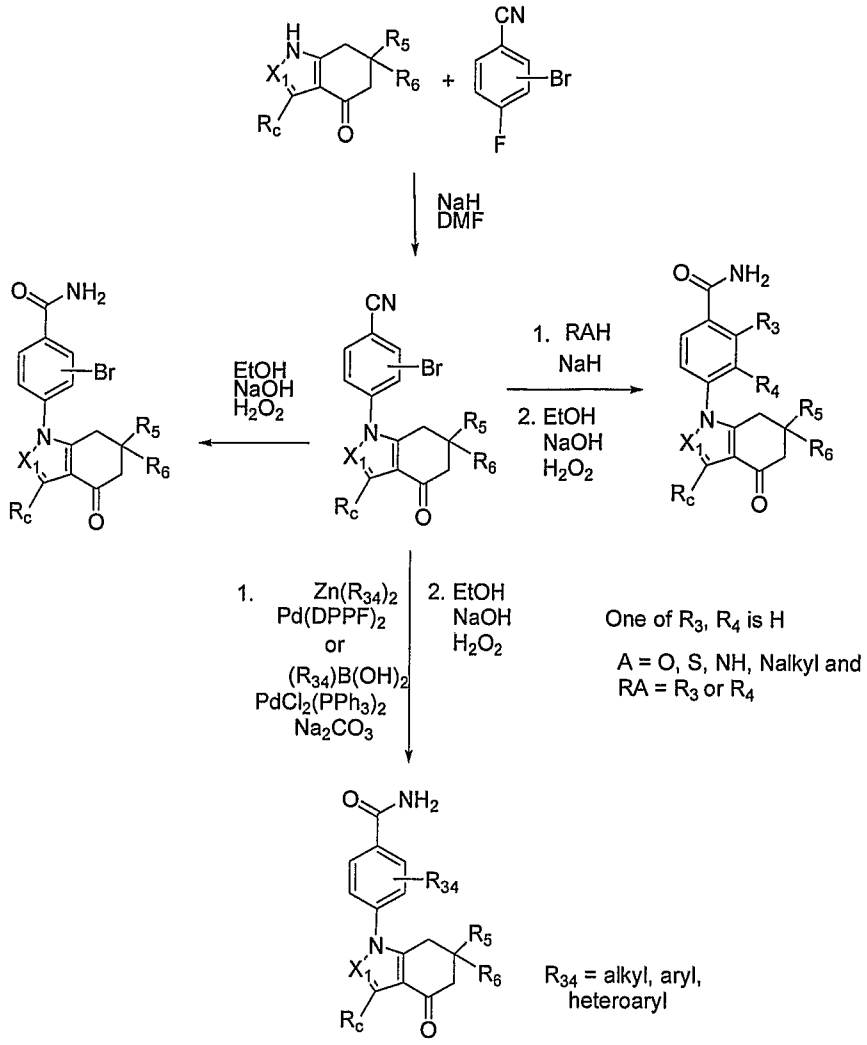
Scheme 7



Scheme 8



Scheme 9



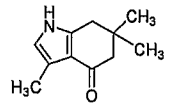
Those having skill in the art will recognize that the starting materials and reaction conditions may be varied, the sequence of the reactions altered, and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples. In some cases, protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general, the need for such protecting groups as well as the conditions necessary to attach and remove such groups will be apparent to those skilled in the art of organic synthesis.

The disclosures of all articles and references mentioned in this application, including patents, are incorporated herein by reference in their entirety.

EXAMPLES

The preparation of the compounds of the invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them. In all cases, unless otherwise specified, the column chromatography is performed using a silica gel solid phase.

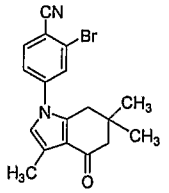
Example 1



3,6,6-Trimethyl-1,5,6,7-tetrahydro-indol-4-one (Compound 1)

To a solution of *anti*-pyruvic aldehyde-1-oxime (10 g, 1 eq) and 5,5-dimethyl-1,3-cyclohexanedione (16.1 g, 1 eq) in HOAc-H_2O (7:3, 200 mL) was added zinc powder (14.95 g, 2 eq) slowly with cooling by a water bath at room temperature. The mixture then was refluxed overnight, concentrated to dryness, partitioned between brine (300 mL) and dichloromethane (300 mL). The pH was adjusted to *ca.* 6 with saturated aqueous $NaHCO_3$, then the mixture was extracted with dichloromethane (3x200 mL). The organic layers were combined, dried over Na_2SO_4, filtered, concentrated. The crude product was purified by flash chromatography eluting with 5% ethyl acetate in dichloromethane. The combined organic fractions were concentrated, triturated in ether-hexane (2:1) for 1 hour, then filtered, washed with hexane to give the pure title compound (9 g, 45% yield) as a solid. LCMS m/z: (M+H) = 178.1.

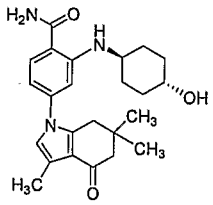
Example 2



2-Bromo-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile (Compound 2)

The title compound of Example 1 (9.8 g, 55.3 mmol) and 2-bromo-4-fluorobenzonitrile (13.27 g, 66.4 mmol) were dissolved in anhydrous dimethylformamide (DMF, 300 mL). To this was added sodium hydride (95%, 2.79 g, 111 mmol) and the reaction was stirred at 55 °C for 1 hour. The reaction mixture was cooled to room temperature and water was added. A tan solid precipitated which was filtered, washed with water and ether and then dried *in vacuo* (16.5 g, 84%). LCMS m/z: (M+H) = 358.1.

Example 3

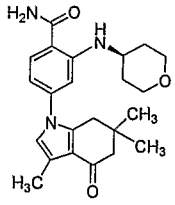


2-(trans-4-Hydroxy-cyclohexylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (Compound 3)

A "Personal Chemistry" microwave vial was charged with the title compound of Example 2 [2-Bromo-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile (1.072 g, 3.0 mmol)], *trans*-4-aminocyclohexanol (1.382 g, 12.0 mmol), palladium (II) acetate (33.7 mg, 5 mol %), 1,1'-bis(diphenylphosphino)ferrocene (DPPF) (166.3 mg, 10 mol %), and sodium *tert*-butoxide (576.7 mg, 6.0 mmol). To this was

added toluene (20 mL) and the reaction was heated with microwave irradiation to 115°C for 15 min. After allowing the reaction vessel to cool, a suspension formed and was filtered and the filtrate evaporated. The residue was purified by flash chromatography. The intermediate product was hydrolyzed by dissolution in 25% dimethylsulfoxide/ethanol, adding 0.5 mL of 1 N sodium hydroxide and 0.5 mL of 30% aqueous hydrogen peroxide, followed by stirring at room temperature for 4 hours. After judging the reaction to be complete by TLC, the DMSO/ethanol mixture was diluted with water and extracted with ethyl acetate (3x). The combined organics were washed with brine (2x), dried over Na_2SO_4, and evaporated. The compound was purified by column chromatography eluting with EtOAc-MeOH to yield 575 mg (47% yield) of the title compound as a white powder. LCMS m/z: (M+H) = 410.3

Example 4

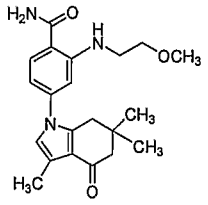


2-(Tetrahydro-pyran-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (Compound 4)

A "Personal Chemistry" microwave vial was charged with the title compound of Example 2 (2.858 g, 8.0 mmol), 4-aminotetrahydropyran (3.236 g, 32.0 mmol), palladium (II) acetate (89.8 mg, 5 mol %), 1,1'-bis(diphenylphosphino)ferrocene (443.6 mg, 10 mol %), and sodium *tert*-butoxide (1.538 g, 16.0 mmol). The reagents were suspended in toluene (40 mL) and were heated with microwave radiation to a temperature of 115°C for fifteen minutes. After allowing the reaction vessel to cool, the suspension was

filtered and the filtrate concentrated. After purifying the crude intermediate nitrile by flash chromatography, the nitrile was dissolved in 25% dimethylsulfoxide/ethanol, and 2 mL of 1 N sodium hydroxide and 2 mL of 30% aqueous hydrogen peroxide were added, followed by stirring at room temperature for 16 hours. The DMSO/ethanol mixture was then diluted with water and extracted with ethyl acetate (3x). The combined organics were washed with brine (2x), dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (EtOAc/MeOH) to yield 1.132 g (36%) of the title compound as an off-white powder. LCMS m/z: (M+H) = 396.7.

Example 5

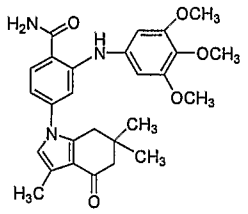


2-(2-Methoxy-ethylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (Compound 5)

A "Personal Chemistry" microwave vial was charged with the title compound of Example 2 (107.1 mg, 0.3 mmol), 2-methoxyethylamine (91.3 mg, 1.2 mmol), palladium (II) acetate (3.4 mg, 5 mol %), 1,1'-bis(diphenylphosphino)ferrocene (16.6 mg, 10 mol %), and sodium *tert*-butoxide (57.7 mg, 0.6 mmol). The reagents were suspended in toluene (2 mL) and were heated with microwave radiation to a temperature of 115°C for fifteen minutes. After allowing the reaction vessel to cool, the suspension was filtered and the filtrate evaporated. After purifying the crude intermediate nitrile by flash chromatography, hydrolysis was performed by dissolving the residue in 25% dimethylsulfoxide/ethanol, adding 5 drops of 1 N sodium hydroxide and 5 drops of 30% aqueous hydrogen peroxide, followed by stirring at room temperature for 3

hours. The DMSO/ethanol mixture was then diluted with water and extracted with CH_2Cl_2 (3x). The combined organics were washed with brine (2x), dried over Na_2SO_4, and concentrated. The compound was purified by column chromatography (hexane/EtOAc) to yield the title compound (94.4 mg, 85% yield) of an off-white powder. LCMS m/z: (M+H) 370.2.

Example 6

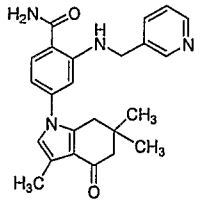


2-(3,4,5-Trimethoxy-phenylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (Compound 6)

A "Personal Chemistry" microwave vial was charged with the title compound of Example 2 (107.1 mg, 0.3 mmol), 3,4,5-trimethoxyaniline (219.9 mg, 1.2 mmol), palladium (II) acetate (3.4 mg, 5 mol %), 1,1'-bis(diphenylphosphino)ferrocene (16.6 mg, 10 mol %), and sodium *tert*-butoxide (57.7 mg, 0.6 mmol). The reagents were suspended in toluene (2 mL) and were heated with microwave radiation to a temperature of 115°C for fifteen minutes. After allowing the reaction vessel to cool, the suspension was filtered and the filtrate evaporated. The residue was purified by flash chromatography, and hydrolysis was performed by dissolving the product in 25% dimethylsulfoxide/ethanol, adding 5 drops of 1 N sodium hydroxide and 5 drops of 30% aqueous hydrogen peroxide, followed by stirring at room temperature for 3 hours. The DMSO/ethanol mixture was then diluted with water and extracted into EtOAc (3x). The combined organics were washed with brine (2x), dried over Na_2SO_4, and concentrated. The compound was purified by column chromatography (hexane/EtOAc) to yield 28.4

mg (20%) of the title compound as a yellow powder. LCMS m/z: (M+H) 478.3

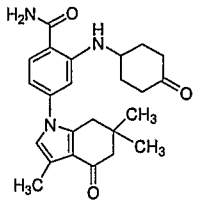
Example 7



2-[(Pyridin-3-ylmethyl)-amino]-4-(3,6,6-trimethyl-4-ox-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (Compound 7)

A "Personal Chemistry" microwave vial was charged with the title compound of Example 2 (107.1 mg, 0.3 mmol), 3-(aminomethyl)pyridine (129.8 mg, 1.2 mmol), palladium (II) acetate (3.4 mg, 5 mol %), 1,1'-bis(diphenylphosphino)ferrocene (16.6 mg, 10 mol %), and sodium *tert*-butoxide (57.7 mg, 0.6 mmol). The reagents were suspended in toluene (2 mL) and were heated with microwave radiation to a temperature of 125°C for fifteen minutes. The crude intermediate nitrile was purified by flash chromatography (hexane/EtOAc) chromatography. Hydrolysis was performed by dissolving the residue in 25% dimethyl sulfoxide/ethanol, adding 4 drops of 1 N sodium hydroxide and 4 drops of 30% aqueous hydrogen peroxide, and stirring at room temperature for 15 minutes. The DMSO/ethanol mixture was then diluted with water and extracted into EtOAc (3x). The combined organics were washed with brine (2x), dried over Na_2SO_4, and concentrated. The compound was purified by column chromatography (hexane/EtOAc) to yield 50 mg (41%) of the title compound as a yellow powder. LCMS m/z: (M+H) 403.

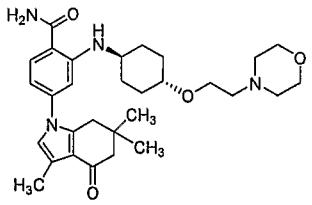
Example 8



2-(4-oxo-cyclohexylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (Compound 8)

The title compound of Example 3 [2-(4-Hydroxy-cyclohexylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide] (150 mg, 0.366 mmol) and Dess-Martin periodinane (0.366 mmol) were dissolved in anhydrous CH_2Cl_2 and stirred at room temperature for one hour. The reaction mixture was concentrated and the title compound was isolated as a white solid (36.2 mg, 24% yield) after purification by column chromatography eluting with EtOAc-MeOH. LCMS m/z: (M+H) = 408.3.

Example 9

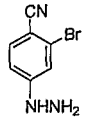


2-[trans-4-(2-Morpholin-4-yl-ethoxy)-cyclohexylamino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (Compound 9)

A microwave reaction vial was charged with the title compound of Example 3 [2-(trans-4-Hydroxy-cyclohexylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide] (100 mg, 0.244 mmol), 4-(2-chloroethyl)morpholine hydrochloride (45.4 mg, 0.244 mmol), sodium hydride (17.3 mg, 0.732 mmol), and a catalytic amount of potassium iodide. After suspending in DMF, the reaction mixture was heated to

180°C in the "Personal Chemistry" microwave for eight minutes. The solution was then diluted with water and extracted into EtOAc (2x). The organic layers were extracted with 2N HCl (2x). The aqueous extracts basified with aqueous sodium hydroxide, and were extracted with EtOAc (3x). The combined organics were dried over Na_2SO_4, concentrated, and purified by column chromatography (EtOAc/MeOH) to yield the title compounds as a white solid. LCMS m/z: (M+H) 523.9.

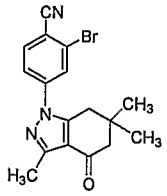
Example 10



3-bromo-4-cyanophenylhydrazine (Compound 10)

In a clean, dry 250-mL round-bottom flask, 2-bromo-4-fluorobenzonitrile (25.34 g) was dissolved in tetrahydrofuran (50 mL) under N_2. To this was slowly added anhydrous hydrazine (50 mL). The solution color changed from yellow to red-orange. The reaction was allowed to stir at room temperature for 16 hours. A yellow-white crystalline solid precipitated from the solution. The mixture was then diluted with THF (50 mL) to dissolve the solids. The organic layer was then washed with saturated sodium bicarbonate solution until the pH of the organic layer was approximately 8.5. The organic layer was isolated and the solvent was removed under reduced pressure to give a white solid. This was place in a fritted glass funnel and washed with 1.5 L of water, followed by of diethyl ether (ca. 200 mL). The ether wash was then combined with the white solid and dried under reduced pressure. The title compound was isolated as a fluffy, white or off-white solid (23.43 g, 87.2% yield). LCMS m/z: calculated = 212.05; observed = 252.98 (M+H+ acetonitrile).

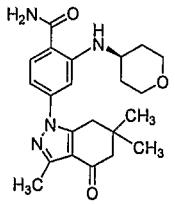
Example 11



2-Bromo-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (Compound 11)

In a clean, dry 20 mL microwave reaction vial, the title compound of Example 10 (2.49 g) was combined with 2-acetyl-5,5-dimethyl-1,3-cyclohexanedione (2.14 g). The contents of the vial were dissolved in ethanol-acetic acid (12 mL, 3:1). The vial was sealed and agitated on a vortex. The vial was then placed in the microwave reactor and heated to 150 °C for 15 min. The vial was then cooled then placed in the refrigerator for 1 hour. The cooled solution was then diluted with water (8 mL) and poured onto a fritted glass funnel. The orange solid was washed with H_2O (100 mL) followed by ethanol (25 mL). The solid was then dried under reduced pressure. The title compound was obtained as of a light-orange crystalline solid (3.7463 g, 88.85% yield). LCMS m/z M+H = 358.1.

Example 12

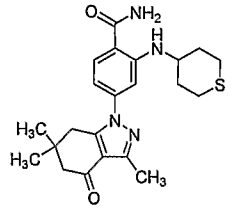


2-(Tetrahydro-pyran-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide (Compound 12)

The title compound of Example 11 (100 mg, 0.28 mmol), $Pd(OAc)_2$ (3.2 mg, 5 mol%), DPPF (15.5 mg, 10 mol%) and NaO^tBu (54 mg, 0.56 mmol) were added to a 2 mL microwave vial. Toluene (0.5

mL) and 4-aminotetrahydropyran (56 µL, 0.56 mmol) were added and the vial was evacuated and back-filled with N_2. The reaction mixture was heated at 120 °C for 15 min (microwave). The reaction mixture was filtered and the solids washed with methylene chloride. The product was purified using flash chromatography eluting with hexanes and ethyl acetate. Product was recovered as an off-white solid (88 mg, 83%), LCMS m/z: (M+H) = 379.3. Ethanol (0.8 mL), DMSO (0.2 mL), NaOH (5 N, 93 µL, 2 mol eq) and H_2O_2 (0.1 mL, 30% solution in H_2O) were added to the pyrazole (88 mg, 0.23 mmol) in a 2 mL microwave vial. The reaction mixture was heated at 100 °C for 10 min. Product was recovered by washing with H_2O and ethyl acetate. Solvent was removed *in vacuo* to yield the title compound as a yellow solid (88 mg, 100%), LCMS m/z: (M+H) = 397.3.

Example 13



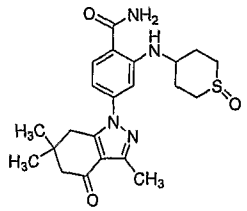
2-(Tetrahydrothiopyran-4-ylamino)-4-(3,6,6-trimethyl-4-oxo4,5,6,7-tetrahydroindazol-1-yl)benzamide (Compound 13)

Tetrahydro-thiopyran-4-one (10.0 g, 86.0 mmol) and NH_4OAc (60 g, 10 mole eq) were dissolved in 200 mL of MeOH/H_2O (1:1). To this was added $NaCNBH_3$ (10.8 g, 172.0 mmol) and the reaction mixture was allowed to stir at room temperature overnight. Methanol was removed under vacuum and the product was extracted from the aqueous layer with ethyl acetate (3x100 mL) and washed with brine. The organic layer was washed with 10% aqueous HCl (150 mL) that was then basified with 10% NaOH solution (to pH 11). The basic solution was then washed with ethyl acetate and dried over $MgSO_4$, to give 4-

aminotetrahydrothiopyran which was used without further purification, LCMS m/z: $(M+H)^+$ = 118.2. Compound 11 (1.4 g, 3.9 mmol), $Pd(OAc)_2$ (44.7 mg, 5 mol%), DPPF (229 mg, 10 mol%) and NaO^tBu (790 mg, 7.8 mmol) were added to a 20 mL microwave vial. Toluene (12 mL) and 4-aminotetrahydrothiopyran (550 mg, 1.2 mol eq) were added and the vial was evacuated and back-filled with N_2. The reaction mixture was heated at 130°C for 20 min (microwave). The reaction mixture was filtered and the solids washed with CH_2Cl_2. The product was purified using flash chromatography eluting with Hexanes and Ethyl acetate. The product, 2-(tetrahydro-thiopyran-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile, was recovered as a off-white solid (350 mg), LCMS m/z $(M+H)^+$ = 395.3.

The preceeding product (830 mg, 2.1 mmol) was dissolved in ethanol (12 mL) and DMSO (3 mL) to which NaOH (5 N, 841 µL, 2 mol eq) was added. The reaction mixture was heated at 70°C overnight. The reaction mixture was washed with H_2O and EtOAc. The product was purified by flash chromatography eluting with Hexanes and Ethyl acetate. The title compound was obtained as an off-white solid (490 mg), LCMS m/z $(M+H)^+$ = 413.2

Example 14

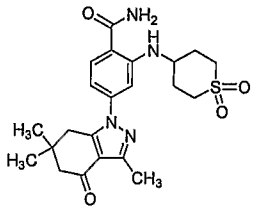


2-(1-Oxo-hexahydro-1-Tetrahydrothiopyran-4-ylamino)-4-(3,6,6-trimethyl-4-oxo4,5,6,7-tetrahydroindazol-1-yl)benzamide (Compound 14)

2-(Tetrahydrothiopyran-4-ylamino)-4-(3,6,6-trimethyl-4-oxo4,5,6,7-tetrahydroindazol-1-yl)benzamide was dissolved in

ethanol to which H_2O_2 (a few drops of 30% solution in H_2O) was added. The reaction mixture was allowed to stir at rt for 30 min. Product was isolated via extraction with EtOAc and H_2O. The title compound was obtained as an off-white solid (20 mg), LCMS m/z $(M+H)^+$ = 429.2

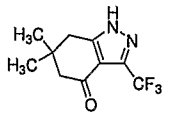
Example 15



2-(1,1-Dioxo-hexahydro-1-Tetrahydrothiopyran-4-ylamino)-4-(3,6,6-trimethyl-4-oxo4,5,6,7-tetrahydroindazol-1-yl)benzamide (Compound 15)

2-(Tetrahydrothiopyran-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazol-1-yl)benzamide (25 mg, 0.063 mmol) was dissolved in a mixture of ethanol (1 mL) and DMSO (0.25 mL) to which NaOH (5 N, 25 µL, 2 mol eq) and H_2O_2 (excess, 30% solution in H_2O) was added. The reaction mixture was heated at 70°C overnight. The reaction mixture was washed with H_2O and EtOAc. The product was purified using flash chromatography eluting with dichloromethane and methanol. The title compound was obtained as an off-white solid (20 mg), LCMS m/z $(M+H)^+$ = 445.2

Example 16



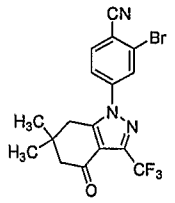
6,6-Dimethyl-3-trifluoromethyl-1,5,6,7-tetrahydro-indazol-4-one (Compound 16)

A mixture of 5,5-dimethyl-1,3-cyclohexandione (7.0 g, 49.9 mmol, 1.0 equiv), *p*-toluenesulfonylhydrazide (9.3 g, 49.9 mmol, 1.0 eq.), and *p*-toluenesulfonic acid (100 mg, 0.53 mmol, 0.01 eq.) in 300 mL of toluene was heated at reflux. After 30 minutes the reaction mixture was cooled, and 50 mL of toluene was added to the reaction mixture. The reaction was returned to heating at reflux. After 1 hour the reaction mixture was cooled to ambient temperature. The solids were collected by filtration, washed three times with ether, and dried under vacuum to afford 3,3-dimethyl-5-(*p*-tolylsulfonylhydrazono)-cyclohexanone (14.26 g, 93%) as a light yellow solid: LC/MS (*m/z*) $[M+H]^+$ = 309.1.

To a solution/suspension of 3,3-dimethyl-5-(*p*-tolylsulfonylhydrazono)-cyclohexanone (4.0g, 12.97 mmol, 1.0 eq.) in 72 ml of tetrahydrofuran and 24 mL of triethylamine was added trifluoroacetic anhydride (1.8 mL, 12.97 mmol, 1.0 eq.). The dark red reaction mixture was heated at 55 °C. After 15 min the reaction mixture was homogeneous. After 2 h the reaction mixture was cooled to ambient temperature. Methanol (16 mL) and a 1:1 solution of water-1 M aqueous sodium hydroxide (16 mL) were added. After stirring for 3 h, the reaction mixture was diluted with 50 mL of saturated aqueous ammonium chloride and extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was filtered through a plug of silica gel, eluting with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was treated with ether. The solids were collected by filtration and washed with ether. The filtrate was concentrated in vacuo, and the resulting residue was treated with ether. The solids were collected by filtration, washed with ether, and combined with the initial solids to provide 6,6-dimethyl-3-trifluoromethyl-1,5,6,7-

tetrahydro-indazol-4-one (1.24 g, 41%) as a reddish orange solid: LC/MS (*m/z*): $[M+H]^+$ 233.1.

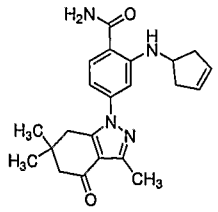
Example 17



2-bromo-4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (Compound 17)

Sodium hydride (168 mg, 7.02 mmol, 1.0 eq.) was added to a solution of 6,6-dimethyl-3-trifluoromethyl-1,5,6,7-tetrahydro-indazol-4-one (1.63 g, 7.02 mmol, 1.0 eq.) in 35 mL of anhydrous dimethyl sulfoxide. After 15 min 2-bromo-4-fluorobenzonitrile (2.25 g, 11.23 mmol, 1.6 eq.) was added as a solid. The reaction mixture was heated at 45 °C. After 23 h the reaction mixture was cooled to ambient temperature and quenched with 10 mL of saturated aqueous ammonium chloride. The mixture was diluted with water and extracted with ethyl acetate (4x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on a Biotage (SiO_2, hexanes-ethyl acetate) to afford 2-bromo-4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (1.83 g, 63%) as an off-white powder, LC/MS: (M+H) = 412.0.

Example 18

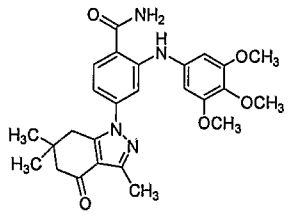


2-(Cyclopent-3-enylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)benzamide (Compound 18)

1-(2-Bromo-4-cyanophen-4-yl)-3,6,6-trimethyltetrahydroindazal-4-one (2.0 g, 5.6 mmol), $Pd(OAc)_2$ (64 mg, 5 mol%), DPPF (328 mg, 10 mol%) and NaO^tBu (1.13 mg, 11.2 mmol) were added to a 20 mL microwave vial. Toluene (15 mL) and 1-amino-3-cyclopentene (11.2 mmol) were added and the vial was evacuated and back-filled with N_2. The reaction mixture was heated at 120°C for 15 minutes. The reaction mixture was filtered and the solids washed with CH_2Cl_2. The product was purified using flash chromatography eluting with hexanes and ethyl acetate. Product was obtained as an off-white solid (1.35 g), LCMS m/z $(M+H)^+$ = 361.2.

The preceeding product (2.71g, 7.5 mmol) was dissolved in ethanol (20 mL) and DMSO (5 mL), and NaOH (5 N, 2.51 mL, 2 mol eq) and H_2O_2 (3.0 mL, 30% solution in H_2O) were added. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with H_2O and extracted with EtOAc. The product was purified using flash chromatography eluting with hexanes and ethyl acetate. The title compound was obtained as an off-white solid (490 mg), LCMS m/z: $(M+H)^+$ = 379.2

Example 19

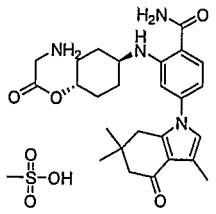


4-(6,6-Dimethyl-4-oxo-3-methyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(3,4,5-trimethoxyanilino)-benzamide (Compound 19)

Sodium *tert*-butoxide (269 mg, 2.80 mmol, 2.0 equiv) was added to a stirred solution/suspension of 2-bromo-4-(6,6-dimethyl-4-oxo-3-methyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (500 mg, 1.40 mmol, 1.0 eq.), 3,4,5-trimethoxyaniline (513 mg, 2.80 mmol, 2.0 eq.), palladium (II) acetate (16 mg, 0.07 mmol, 0.05 eq.), and 1,1'-bis(diphenylphosphino)ferrocene (78 mg, 0.14 mmol, 0.10 eq.) in 3.75 mL of toluene. The reaction vial was capped, and the reaction mixture was heated 20 minutes at 120°C under microwave irradiation. The individual reaction mixtures were diluted with ethyl acetate, combined, and partitioned with water. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on a Biotage System (SiO_2, hexanes-ethyl acetate) to afford 4-(6,6-dimethyl-4-oxo-3-methyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(3,4,5-trimethoxyanilino)-benzonitrile (1.59 g, 82 %) as a tan solid: LC/MS (*m/z*): $[M+H]^+$ 461.9.

To a mixture of 4-(6,6-dimethyl-4-oxo-3-methyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(3,4,5-trimethoxyanilino)-benzonitrile (1.56 g, 3.39 mmol, 1.0 eq.) in 17 mL of a mixture of 4:1 ethanol-dimethyl sulfoxide was added 2 mL of 1 M aqueous sodium hydroxide and 2 mL of 30% hydrogen peroxide. After 3 hours the reaction mixture was diluted with water and extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo to afford the title compound, 4-(6,6-dimethyl-4-oxo-3-methyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(3,4,5-trimethoxyanilino)-benzamide, (1.61 g, 99%) as a tan solid: LC/MS (*m/z*): $[M+H]^+$ 479.3.

Example 20



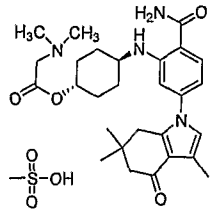
Amino-acetic acid trans-4-[2-carbamoyl-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-phenylamino]-cyclohexyl ester; methanesulfonic acid salt (Compound 20)

2-(trans-4-Hydroxy-cyclohexylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (750.0 mg, 1.832 mmol), *N*-(*tert*-butoxycarbonyl)glycine (641.8 mg, 3.664 mmol, 2.0 eq.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (702.4 mg, 3.664 mmol, 2.0 eq.) and a catalytic amount of 4-dimethylaminopyridine were dissolved in 20 mL of CH_2Cl_2 and stirred at room temperature for sixteen hours. The solvent was removed *in vacuo*, and the residue purified by column chromatography (eluting with EtOAc), yielding 780.5 mg (75.2% yield) of a Boc protected pale yellow foam.

The preceeding product was dissolved in 15 mL of CH_2Cl_2 and cooled to 0°C in an ice bath. 15 mL of trifluoroacetic acid was then added and the reaction mixture stirred at 0°C for 5 minutes and 30 minutes at room temperature. The trifluoroacetic acid and CH_2Cl_2 were removed *in vacuo*, and the residue dissolved in water. The aqueous solution was basified by addition of saturated aqueous sodium bicarbonate. The aqueous suspension was extracted with EtOAc (3x), and the combined organics washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo* yielded 569.7 mg (66.6% yield through coupling and deprotection) of an off-white foam, which by LC/MS showed pure product (m/z: (M+H)= 467.3). This free base was then converted to the mesylate salt by dissolution in CH_2Cl_2, and adding one equivalent dropwise of methanesulfonic acid, followed by stirring at room temperature for 1 hour.

Removal of the solvent *in vacuo* yielded 680.7 mg of the title compound as an off-white powder.

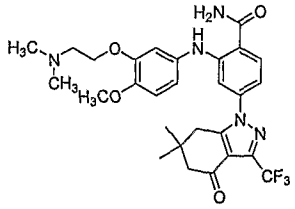
Example 21



Dimethylamino-acetic acid trans-4-[2-carbamoyl-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-phenylamino]-cyclohexyl ester; methanesulfonic acid salt (Compound 21)

The procedure of **Example 20** was used, substituting dimethylamino-acetic acid for *N*-(*tert*-butoxycarbonyl)glycine to give the title compound. LCMS m/z: (M+H) = 495.2.

Example 22



2-[3-(2-Dimethylamino-ethoxy)-4-methoxy-phenylamino]-4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide (Compound 22)

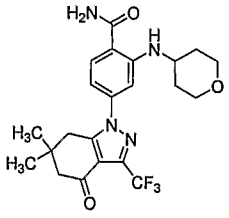
To a solution of 2-methoxy-5-nitro-phenol (10 g), (2-chloro-ethyl)-dimethyl-amine hydrochloride (9.37 g) in dimethylformamide (150mL) was added NaH (2.98 g) slowly under N_2 and at room temperature. The mixture was then stirred at 140 °C heating with an oil bath for 5 hours. The reaction was concentrated to dryness, dissolved in 2 M HCl (200 mL) and washed with ethyl acetate (2x100 mL). The aqueous layer was basified with K_2CO_3, extracted with dichloromethane (3x200 mL)

and ethyl acetate (2x100 mL), dried over Na_2SO_4, filtered, concentrated to give [2-(2-Methoxy-5-nitro-phenoxy)-ethyl]-dimethylamine (9.17 g, 65% yield). LCMS (m/z) M+H: 241.1.

The preceding product (10.53 g) and 10% Pd/C (1 g) were mixed with EtOH (200 mL) and hydrogenated at 50 psi overnight. The reaction mixture was filtered through a Celite plug, and the filter cake was washed with MeOH. The filtrate was concentrated to dryness to give 3-(2-dimethylamino-ethoxy)-4-methoxy-phenylamine (9.05 g, 98% yield). LCMS (m/z) M+H: 211.2.

2-bromo-4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (500 mg, 1 eq), 3-(2-dimethylamino-ethoxy)-4-methoxy-phenylamine (306 mg, 1.2 eq), $Pd(OAc)_2$ (14 mg), DPPF (66 mg), and NaO*t*Bu (214 mg, 2 eq) were mixed in toluene (5 mL) and microwaved at 140°C for 25 minutes. Then 10 mL of EtOH(4)/H_2O(1) were added, followed by NaOH (700 mg, 2 eq) and H_2O_2 (1 mL). The mixture was microwaved at 100°C for 15 min, then concentrated to dryness, and purified by flash chromatography, eluting with 20% EtOH in dichloromethane to give the title compound (480 mg, 71% two-step yield). LCMS (m/z): M+H = 560.3.

Example 23



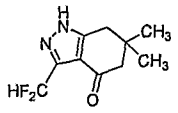
4-(6,6-Dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide (Compound 23)

4-Aminotetrahydropyran (245 mg, 2.42 mmol, 2.0 eq) and sodium *tert*-butoxide (233 mg, 2.42 mmol, 2.0 eq) were added to a

stirred solution/suspension of 2-bromo-4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (500 mg, 1.21 mmol, 1.0 eq), palladium (II) acetate (14 mg, 0.06 mmol, 0.05 eq), and DPPF (67 mg, 0.12 mmol, 0.10 eq) in 3.75 mL of toluene. The reaction vial was capped, and the reaction mixture was heated 20 minutes at 120°C under microwave irradiation. The reaction mixture was diluted with water and ethyl acetate and combined. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on a Biotage system (SiO_2, hexanes-ethyl acetate) to afford 4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzonitrile (772 mg, 49 %) as a tan solid: LC/MS (*m/z*): $[M+H]^+$ 433.7. Further elution with ethyl acetate afforded 4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide (713 mg, 44%) as a yellow solid: LC/MS (*m/z*): $[M+H]^+$ 451.2.

To a solution/suspension of 4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzonitrile (772 mg, 1.79 mmol, 1.0 eq) in 10 mL of 4:1 ethanol-dimethyl sulfoxide was added 1 mL of 1 M aqueous sodium hydroxide and 1 mL of 30% hydrogen peroxide. After 30 minutes the reaction mixture was diluted with water and extracted with ethyl acetate (4x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo to afford the title compound, 4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide (788 mg, 98%) as a tan solid: LC/MS (*m/z*): $[M+H]^+$ 451.2.

Example 24

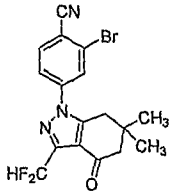


3-Difluoromethyl-6,6-dimethyl-1,5,6,7-tetrahydro-indazol-4-one (Compound 24)

A mixture of 5,5-Dimethyl-cyclohexane-1,3-dione (10 g), *p*-toluenesulfonylhydrazide (13.3 g) *p*-toluesulfonic acid (140 mg) in toluene (450 mL) was refluxed for 0.5 h. Then 100 mL of toluene was added and the mixture was refluxed for another 1 h. The mixture was cooled to room temperature, filtered, the solids were washed by ether (3x200 mL), and dried completely to give the hydrazone as a solid (20.4 g, 92.7%). LCMS M+H: 309.1 (MW: 308). It was used in the next step without further purification.

The preceeding product (8.86 g) was dissolved in a mixture of tetrahydrofuran (100 mL) and triethylamine (30 mL), placed under N_2, and difluoroacetic anhydride (5 g) was added slowly while swirling, then the mixture was heated to 55°C overnight. The mixture was cooled to room temperature, and MeOH (35.5 mL) was added, followed by 35.5 mL of a 1:1 mixture of H_2O and 1 N NaOH. This mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (120 mL), extracted with ethyl aetate (4x150 mL), dried over Na_2SO_4, filtered, concentrated, purified by column chromatography eluting with a 1:1 mixture of ethyl acetate and hexanes to give 3-difluoromethyl-6,6-dimethyl-1,5,6,7-tetrahydro-indazol-4-one (3.12 g, 50.6%). LCMS (M+H): 215.1 (MW: 214).

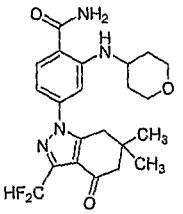
Example 25



2-Bromo-4-(3-difluoromethyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (Compound 25)

NaH (350 mg) was added to a solution of 3-difluoromethyl-6,6-dimethyl-1,5,6,7-tetrahydro-indazol-4-one (3.12 g) in DMSO (75 mL) at room temperature. After 20 minutes of stirring, 2-bromo-4-fluorobenzonitrile (4.67 g) was added and stirred at 45 °C overnight. The reaction was diluted with saturated aqueous NH_4Cl (100 mL), H_2O (100 mL). The mixture was extracted with ethyl acetate (4x150 mL), dried over Na_2SO_4, filtered, concentrated, purified by column chromatography eluting with a 1:2 mixture of ethyl acetate/hexanes. The concentrate of desired fractions was made into a slurry in ether, stirred for 2 h, filtered, washed by hexane to give pure solid 2-bromo-4-(6,6-dimethyl-4-oxo-3-difluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (2.82 g, 49.2%). LCMS m/z: (M+H) = 395.65, (MW: 394).

Example 26



4-(6,6-Dimethyl-4-oxo-3-difluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide (Compound 26)

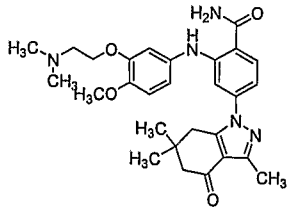
The following reaction was conducted at the 300 mg scale and in duplicate at the 500 mg scale: 4-Aminotetrahydropyran (154

mg, 1.52 mmol, 2.0 eq.) and sodium *tert*-butoxide (146 mg, 1.52 mmol, 2.0 eq.) were added to a stirred solution/suspension of 2-bromo-4-(6,6-dimethyl-4-oxo-3-difluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (300 mg, 0.76 mmol, 1.0 eq.), palladium (II) acetate (8.5 mg, 0.04 mmol, 0.05 eq.), and 1,1'-bis(diphenylphosphino)ferrocene (42 mg, 0.08 mmol, 0.1 eq.) in toluene (2.25 mL). The reaction vial was capped, and the reaction mixture was heated for 20 min at 120°C under microwave irradiation. The reaction mixture was diluted with water and ethyl acetate and combined. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified on a Biotage system (SiO_2, hexanes-ethyl acetate) to afford 4-(6,6-dimethyl-4-oxo-3-difluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzonitrile (897 mg, 65 % yield) as a tan solid: LC/MS (*m/z*): $[M+H]^+$ 415.2. Further elution with ethyl acetate afforded the title compound, 4-(6,6-dimethyl-4-oxo-3-difluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide, (131 mg, 9%) as a yellow solid: LC/MS (*m/z*): $[M+H]^+$ 433.3.

To a solution/suspension of 4-(6,6-dimethyl-4-oxo-3-difluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzonitrile (897 mg, 2.16 mmol, 1.0 eq) in 10.8 mL of 4:1 mixture of ethanol-dimethyl sulfoxide was added 1 mL of 1 M aqueous sodium hydroxide and 1 mL of 30% hydrogen peroxide. After 30 minues the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford the title compound, 4-(6,6-dimethyl-4-oxo-3-difluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-pyran-4-

ylamino)-benzamide, (869 mg, 93%) as a tan solid: LC/MS (*m/z*): $[M+H]^+$ 433.3.

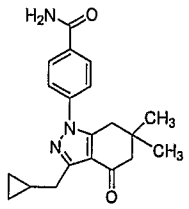
Example 27



2-[3-(2-Dimethylamino-ethoxy)-4-methoxy-phenylamino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide (Compound 27)

2-Bromo-4-(6,6-dimethyl-4-oxo-3-methyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (100 mg, 0.28 mmol), $Pd(OAc)_2$ (3.1 mg, 5 mol%), DPPF (15.5 mg, 10 mol%) and NaO^tBu (52 mg, 0.56 mmol) were added to a microwave vial. Toluene (0.5 mL) and 3-(2-dimethylamino-ethoxy)-4-methoxy-phenylamine (118 mg, 2 mol eq) were added and the vial was evacuated and back-filled with N_2. The reaction mixture was heated at 130°C for 30 min (microwave). The reaction mixture was filtered and the solids washed with CH_2Cl_2. The product nitrile was purified using flash chromatography eluting with CH_2Cl_2 and methanol. This nitrile (32 mg, 0.66 mmol) was dissolved in ethanol (0.8 mL) and DMSO (0.2 mL) to which NaOH (5 N, 26 µL, 2 eq) and H_2O_2 (excess, 30% solution in H_2O) was added. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was washed with H_2O and extracted with EtOAc. The product was purified using flash chromatography eluting with CH_2Cl_2 and methanol. The title compound was obtained as a yellow solid (10 mg, 30%); LC/MS (m/z): M+H = 506.5.

Example 28



4-(3-Cyclopropylmethyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide (Compound 28)

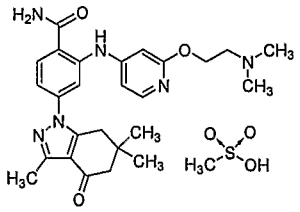
5,5-Dimethyl-1,3-cyclohexanedione (1.051 g, 7.5 mmol, 1.5 eq), cyclopropylacetic acid (500.6 mg, 5.0 mmol), and 4-dimethylaminopyridine (916.3 mg, 7.5 mmol, 1.5 eq) were dissolved in 10 mL of CH_2Cl_2, cooled to 0°C in an ice bath. A solution of *N,N'*-dicyclohexylcarbodiimide (1.238 g, 16.0 mmol, 1.2 eq) in 5 mL of CH_2Cl_2 was added dropwise over two minutes to the cyclohexanedione solution. The reaction mixture was then stirred at 0°C for 10 minutes and at room temperature for 16 hours. The reaction mixture was then filtered and the filtrate purified by column chromatography (hexane to 30% EtOAc/hexane) to yield 1.022 g (92% yield) 2-(2-Cyclopropyl-acetyl)-5,5-dimethyl-cyclohexane-1,3-dione as a pale yellow oil.

2-(2-Cyclopropyl-acetyl)-5,5-dimethyl-cyclohexane-1,3-dione (111.1 mg, 0.5 mmol) and 4-cyanophenylhydrazine hydrochloride (84.8 mg, 0.5 mmol, 1.0 eq) were suspended in 4 mL of 3:1 EtOH:AcOH and microwaved at 100°C for 10 minutes. The solvent was removed *in vacuo* and the resultant residue purified by column chromatography to yield 81.8 mg (51% yield) of 4-(3-Cyclopropylmethyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile as an off-white powder.

After dissolving the nitrile in 10 mL of 4:1 EtOH-DMSO, approximately 0.1 mL of 1 N NaOH (aq.) and 0.1 mL of 30% H_2O_2 (aq.) were added and the solution stirred for 1.5 hours. The reaction mixture was poured into brine, extracted with EtOAc (x3), and the combined organics washed with brine (x2). The

organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford 73.2 mg (43% yield) of 4-(3-Cyclopropylmethyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide as an off-white solid. LCMS (m/z): M+H = 339.4.

Example 29



2-[2-(2-Dimethylamino-ethoxy)-pyridin-4-ylamino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide, methansulfonic acid salt (Compound 29)

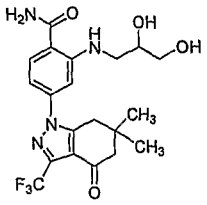
2-Chloro-4-nitropyridine (5.3 g, 33.43 mmol) and N,N-dimethylethanolamine (8 mL) were sealed in a pressure tube and stirred at 110°C for 24 hours. The reaction mixture was then concentrated and dried under reduced pressure to remove excess N,N-dimethylethanolamine. The resulting yellow residue diluted with 1 N HCl, and a yellow solid, which was identified as 2-chloro-4-nitropyridine, was collected by filtration. The acidic aqueous solution was washed with EtOAc (x 2), made basic by the addition of 3 N NaOH, and extracted into EtOAc (x 4). The combined organics were dried over Na_2SO_4 and the solvent removed *in vacuo*, yielding 3.55 g (50.3% yield) of N,N-dimethyl-N'-(4-nitro-pyridin-2-yl)-ethane-1,2-diamine as an orange solid.

This product (3.55 g, 16.807 mmol) was dissolved in 60 mL ethanol. About five drops of conc. HCl was added, followed by addition of a spatula tip of Pd/C (10% wt). The reaction vessel was purged with N_2 filled with H_2 and evacuated three times, and filled with H_2 to a pressure of 60 psi. After shaking at room temperature for three hours, complete reduction of the nitro group was verified by LC/MS. The

reaction mixture was filtered through Celite and the solvent removed *in vacuo*. The residue was then dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$, water, and brine, and dried over Na_2SO_4. After removing the solvent *in vacuo*, 2.95 g (48.7% yield over two steps) of 2-(2-dimethylamino-ethoxy)-pyridin-4-ylamine as a waxy red solid was obtained.

2-Bromo-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (358.2 mg, 1.0 mmol), 2-(2-dimethylamino-ethoxy)-pyridin-4-ylamine (362.5 mg, 2.0mmol, 2.0 eq.), palladium (II) acetate (11.2 mg, 5 mol%), 1,1'-bis(diphenylphosphino)ferrocene (55.4 mg, 10 mol%), and sodium *tert*-butixide (192.2 mg, 2.0 mmol, 2.0 eq.) were suspended in 4 mL of toluene. The reaction mixture was microwaved at 120°C for 20 minutes. After cooling the reaction mixture, the solvent was removed *in vacuo*, and the residue diluted with water. The aqueous suspension was extracted with EtOAc x 3 and the combined organics washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The intermediate nitrile and the desired amide were collected and combined after purifying by column chromatography (EtOAc/MeOH), and were dissolved in 20 mL of 4:1 EtOH/DMSO. Five drops of 1 N NaOH and five drops of 30% H_2O_2 were added, and the reaction mixture stirred at room temperature for 2 hours. The solution was diluted with water, extracted into EtOAc (x3), and the combined organics washed with brine (x2), dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by column chromatography (EtOAc/MeOH), yielding 347.3 mg (72.9% yield) of a pink foam. This was dissolved in CH_2Cl_2 and treated with of one equivalent of methanesulfonic acid, stirring at room temperature for 1 hour. The mixture was evaporated under reduced pressure to yield the title compound. LCMS m/z (M+H) = 477.3.

Example 30



2-(2,3-Dihydroxy-propylamino)-4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide (Compound 30)

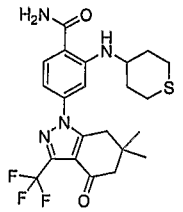
A mixture of 2,4-Difluoro-benzonitrile (1.39 g, 10 mmol), 3-amino-propane-1,2-diol (0.911 g, 10 mmol), and ethyl-diisopropyl-amine (1.74 mL) in DMSO (10 mL) was microwaved at 200 °C for 7 min. Then the reaction mixture was poured into a saturated NH_4Cl aq. solution (100 mL), extracted with EtOAc (3x100 mL), dried over Na_2SO_4, filtered, concentrated. The crude mixture was purified by flash silica gel chromatography (EtOAc-Hexane 1:1) to give 2-(2,3-Dihydroxy-propylamino)-4-fluoro-benzonitrile (0.87 g, 41.4% yield). LCMS (m/z): M+H = 211.

To a mixture of 6,6-Dimethyl-3-trifluoromethyl-1,5,6,7-tetrahydro-indazol-4-one (0.961 g, 4.14 mmol, 1 eq) and NaH (99 mg, 4.14 mmol, 1 eq) in dimethyl acetamide (20 mL) was added slowly 2-(2,3-Dihydroxy-propylamino)-4-fluoro-benzonitrile (0.87 g, 4.14 mmol, 1 eq). Then the reaction mixture was stirred at 150 °C overnight, cooled, poured into saturated NH_4Cl aq. solution (100 mL), extracted by EtOAc (3x150 mL), dried over Na_2SO_4, filtered, concentrated. The crude product was purified by flash silica gel chromatography, eluted by EtOAc to give 2-(2,3-Dihydroxy-propylamino)-4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (1.7g, 97% yield). LCMS (m/z): M+H = 423.

2-(2,3-Dihydroxy-propylamino)-4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (1.7 g, 4 mmol, 1 eq), NaOH (806 mg, 20 mmol, 5 eq), and H_2O_2

(3 mL) were dissolved in EtOH-water (4:1) (40 mL). The mixture was microwaved at 120 °C for 15 min, then concentrated to dryness, and purified by flash chromatography, eluted by 10% MeOH in EtOAc to give pure 2-(2,3-Dihydroxy-propylamino)-4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-y
l)-benzamide (0.52 g, 29% yield). LCMS (m/z): M+H = 441.

Example 31



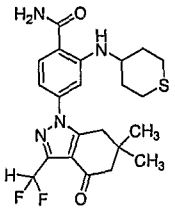
4-(6,6-Dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-thiopyran-4-ylamino)-benzamide (Compound 31)

1-(2-Bromo-4-cyanophen-4-yl)-3-trifluoromethyl-6,6-dimethyltetrahydroindazal-4-one (313 mg, 0.76 mmol), $Pd(OAc)_2$ (8.7 mg, 5 mol%), DPPF (44.5 mg, 10 mol%) and NaO^tBu (153 mg, 1.52 mmol) were added to a microwave vial. Toluene (1 mL) and 4-aminotetrahydrothiopyran (116 mg, 1.3 mol eq) were added and the vial was evacuated and back-filled with N_2. The reaction mixture was heated at 130°C for 20 min (microwave). The reaction mixture was filtered and the solids washed with CH_2Cl_2. The product was purified using flash chromatography eluting with hexanes and EtOAc. Product was recovered as a off-white solid (23 mg, 7%), LCMS $(M+H)^+$ = 449.4

This pyrazole (23 mg, 0.05 mmol) was dissolved in ethanol (0.8 mL) and DMSO (0.2 mL) to which NaOH (5 N, 21 µL, 2 mol eq) was added and the reaction mixture was heated at 70 °C for 12 hours. The reaction mixture was washed with water and EtOAc. The product was purified using flash chromatography

eluting with hexanes and EtOAc. The title compound was obtained as an off-white solid (16 mg, 67%); LC/MS (m/z): M+H = 467.2.

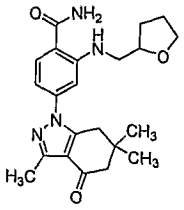
Example 32



4-(3-Difluoromethyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-thiopyran-4-ylamino)-benzamide (Compound 32)

2-Bromo-4-(3-difluoromethyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide (300 mg, 0.76 mmol), $Pd(OAc)_2$ (8.7 mg, 5 mol%), DPPF (44.5 mg, 10 mol%) and NaO^tBu (153 mg, 1.52 mmol) were added to a microwave vial. Toluene (1 mL) and 4-aminotetrahydrothiopyran (116 mg, 1.3 mol eq) were added and the vial was evacuated and back-filled with N_2. The reaction mixture was heated at 120 °C for 15 min (microwave). The reaction mixture was filtered and the solids washed with CH_2Cl_2. The product was purified using flash chromatography eluting with hexanes and EtOAc. Product was recovered as an off-white solid (70 mg, 21%).
The preceding product pyrazole (70 mg, 0.16 mmol) was dissolved in ethanol (0.8 mL) and DMSO (0.2 mL) to which NaOH (5 N, 65 mL, 2 eq) was added and the reaction mixture was heated at 70°C for 12 hours. The reaction mixture was washed with H_2O and EtOAc. The product was purified using flash chromatography eluting with hexanes and EtOAc. The title compound was obtained as an off-white solid (40 mg, 56% yield), LC/MS (m/z): M+H = 449.2.

Example 33

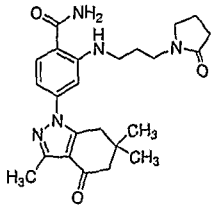


2-[(Tetrahydro-furan-2-ylmethyl)-amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide (Compound 33)

2-Bromo-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (1.0 mmol, 358 mg), palladium acetate (0.13 mmol, 30 mg), 1,1'-bis(diphenylphosphino)ferrocene (0.1 mmol, 56 mg), sodium *t*-butoxide (2 mmol, 192 mg), toluene (2 mL), and 2-(aminomethyl)tetrahydrofuran (3 mmol, 0.31 mL) were combined in a microwave tube, stirred briefly, and heated in a Personal Chemistry microwave set at high absorbance to 110 °C for 900 seconds. After cooling, the reaction mixture was taken up in ethyl acetate (200 mL) and washed with water (50 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated. The residue was subjected to chromatography, affording the desired nitrile intermediate as a tan solid (305 mg, 81% yield).

DMSO (6 drops) and ethanol (4 mL) were added to the above nitrile (0.79 mmol, 300 mg). The flask was lowered into a 50 °C oil bath and KOH (5.8 mmol, 325 mg) was added, followed by 30% hydrogen peroxide (*ca.* 10 mmol, 1mL). After 45 minutes, the reaction was taken up in ethyl acetate (100 mL) and washed with water (50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. Chromatography of the residue afforded the title compound as a white solid (313 mg, 100% yield). LCMS (m/z): M+H = 397.3.

Example 34

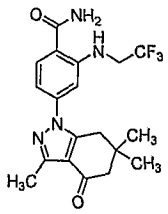


2-[3-(2-Oxo-pyrrolidin-1-yl)-propylamino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide (Compound 34)

2-Bromo-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (1.0 mmol, 358 mg), palladium acetate (0.13 mmol, 30 mg), 1,1'bis(diphenylphosphino)ferrocene (0.1 mmol, 56 mg), sodium *t*-butoxide (2 mmol, 192 mg), toluene (2 mL), and N-(3-aminopropyl)-2-pyrrolidinone (2 mmol, 0.28 mL) were combined in a 2-5 mL microwave tube, stirred briefly, and heated in a Personal Chemistry microwave set at high absorbance to 110 °C for 900 seconds. After cooling, the reaction mixture was taken up in ethyl acetate (200 mL) and washed with water (25 mL). The aqueous layer was extracted with additional ethyl acetate (200 mL), and the combined organic phase was dried over magnesium sulfate, filtered, and concentrated. The residue was subjected to chromatography, affording the desired nitrile as a tan solid (258 mg, 61%).

DMSO (0.1 mL) and ethanol (4 mL) were added to the above nitrile (0.60 mmol, 250 mg). The flask was lowered into a 50 °C oil bath and KOH (4.5 mmol, 255 mg) was added, followed by 30% hydrogen peroxide (ca 10 mmol, 1 mL). After 30 minutes, the reaction was taken up in ethyl acetate (100 mL) and washed with water (50 mL). The aqueous layer was extracted with additional ethyl acetate (100 mL). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated. Chromatography of the residue afforded the title benzamide as a white solid (187 mg, 71%). LCMS (m/z): M+H = 438.2.

Example 35



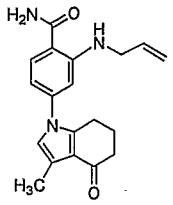
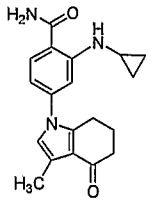
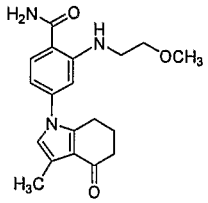
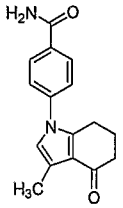
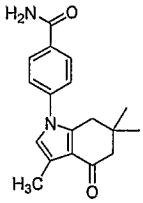
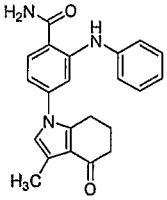
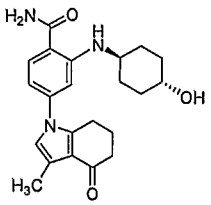
2-(2,2,2-Trifluoro-ethylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide (Compound 35)

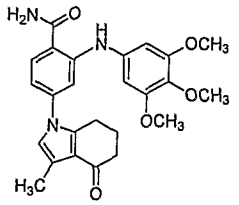
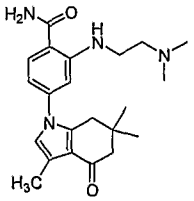
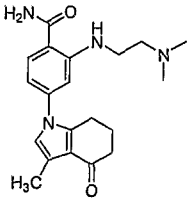
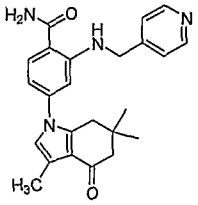
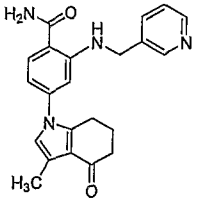
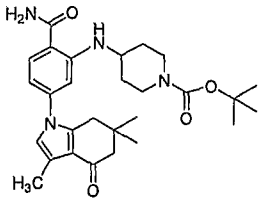
2-Bromo-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (2.0 mmol, 714 mg), palladium acetate (0.13 mmol, 60 mg), 1,1'-bis(diphenylphosphino)ferrocene (0.2 mmol, 112 mg), sodium *t*-butoxide (4 mmol, 384 mg), toluene (4 mL), and 2,2,2-trifluoroethylamine (8 mmol, 0.63 mL) were combined in a 2-5 mL microwave tube, stirred briefly, and heated in a Personal Chemistry microwave set at high absorbance to 110 °C for 900 seconds. After cooling, the reaction mixture was taken up in ethyl acetate (200 mL) and washed with water (25 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated. The residue was subjected to chromatography, affording a mixture of the anticipated 2-(2,2,2-trifluoro-ethylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (346 mg, 50%) as a tan solid, and the desired ultimate product, 2-(2,2,2-trifluoro-ethylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide, as a tan solid (77 mg, 10%). LCMS (m/z): M+H = 395.1.

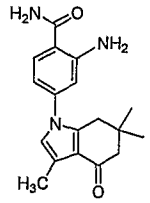
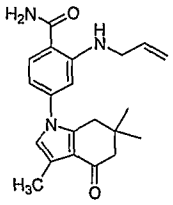
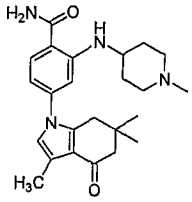
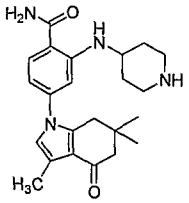
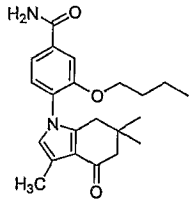
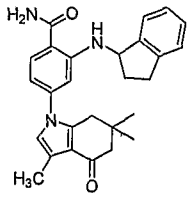
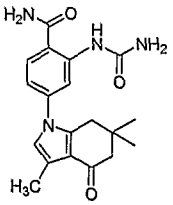
Example 36

The following compounds are prepared essentially according to the procedures set forth in Schemes 1-4 above and described in the above examples.

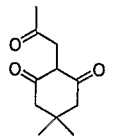
Compound No.	Structure	Name

36		2-(allylamino)-4-(3-methyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 324.1
37		2-(cyclopropylamino)-4-(3-methyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 324.1
38		2-(2-methoxyethylamino)-4-(3-methyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 342.1
39		4-(3-methyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 269.1
40		4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 297.1
41		4-(3-methyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)-2-(phenylamino)benzamide; M+H = 360.1
42		2-(trans-4-hydroxycyclohexylamino)-4-(3-methyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 382.2

43		4-(3-methyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)-2-(3,4,5-trimethoxyphenylamino)benzamide; M+H = 450.2
44		2-(2-(dimethylamino)ethylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 383.2
45		2-(2-(dimethylamino)ethylamino)-4-(3-methyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 355.2
46		2-(pyridin-4-ylmethylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 403.2
47		4-(3-methyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)-2-(pyridin-3-ylmethylamino)benzamide; M+H = 375.1
48		tert-butyl 4-(2-carbamoyl-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)phenylamino)piperidine-1-carboxylate; M+H = 495.2

49		2-amino-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 312.1
50		2-(allylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 352.2
51		2-(1-methylpiperidin-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 409.2
52		2-(piperidin-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 395.2
53		3-butoxy-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 369.2
54		2-(2,3-dihydro-1H-inden-1-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 428.2
55		1-(2-carbamoyl-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)phenyl)urea M+H = 355.1

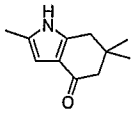
Example 37



5,5-dimethyl-2-(2-oxopropyl)cyclohexane-1,3-dione (Compound 56)

An oven dried flask was charged with sodium hydride (3.61 g, 142.7 mmol) to which 200 mL of anhydrous DMF was added. The flask was cooled in an ice bath before adding 5,5-dimethyl-1,3-cyclohexanedione (20.0 g, 142.7 mmol) and chloroacetone (11.36 mL, 142.7 mmol) in 100 mL DMF in a controlled manner. The reaction was allowed to warm to RT and stirred for 3 h. Saturated NH_4Cl was added and the mixture was washed several times with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, the solvent removed *in vacuo* (below 40 °C). LCMS m/z M+H = 197.1.

Example 38

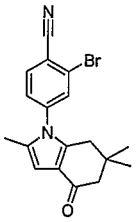


2,6,6-trimethyl-6,7-dihydro-1H-indol-4(5H)-one (Compound 57)

The crude tri-ketone from Example 37 was dissolved in 300 mL of acetic acid to which ammonium acetate (55 g, 0.714 mmol) was added. The reaction mixture was heated at 65 °C until all starting material had disappeared (2-3 h), cooled to RT, added to H_2O, and washed with EtOAc. The organic layer was washed with saturated $NaHCO_3$ (x3), brine (x1) and dried over $MgSO_4$. Solvent was removed *in vacuo* and the oily residue was passed through a plug of silica. The appropriate fractions were collected and solvent was removed. The resulting solid was

washed with EtOAc and hexanes (if too much hexanes is added the material crashing back out of solution after the addition of EtOAc will be gummy. To remedy this simply add a little EtOAc). The solid was filtered and washed with hexanes. More solid can be recovered by removing the solvent and repeating this procedure. LCMS m/z M+H = 178.1. Approximately 5 g of a tan solid was collected and identified as 2,6,6-trimethyltetrahydroindol-4-one.

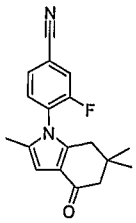
Example 39



2-bromo-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzonitrile (Compound 58)

Pyrrole (2,6,6-trimethyltetrahydroindol-4-one) (1.5 g, 8.5 mmol) and 2-bromo-4-fluorobenzonitrile (1.69 g, 8.5 mmol) were dissolved in anhydrous DMF (50 mL). To this NaH (95%, 408 mg, 17.0 mmol) was added and stirred at 50 °C for 1 h. The reaction mixture was cooled to RT and H_2O was added. Product crashed out of solution and was filtered and dried under vacuo (2.4 g, 79%). (100% clean by LCMS, product M+H = 357).

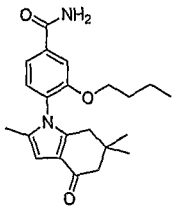
Example 40



3-fluoro-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzonitrile (Compound 59)

Pyrrole (2,6,6-trimethyltetrahydroindol-4-one) (1.0 g, 5.6 mmol) and 3,4-difluorobenzonitrile (785 mg, 5.6 mmol) were dissolved in anhydrous DMF (20 mL). To this NaH (95%, 270 mg, 11.2 mmol) was added and stirred at 50 °C for 30 min. The reaction mixture was cooled to RT and washed with H_2O and EtOAc. The organic layer was dried over $MgSO_4$. Column chromatography on silica eluting with EtOAc-hexanes (1:1) gave the product as a yellow solid (100% clean by LCMS, product M+H = 397.1).

Example 41

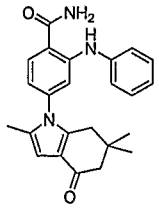


3-butoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide (Compound 60)

3-Fluoro-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile (148 mg, 0.5 mmol) and 1-butanol (185.3 mg, 2.5 mmol) were dissolved in anhydrous DMF (1.5 mL). To this solution was added NaH (24.0 mg, 1 mmol). After purging the reaction vessel (Personal Chemistry Microwave Vial) with nitrogen, the reaction vessel was sealed and heated to 100 °C for 300 seconds in an Emyrs Optimizer Microwave. After cooling, the reaction mixture was diluted with H_2O and extracted into EtOAc (x2). The combined organics were washed with brine (x2), dried over Na_2SO_4, and concentrated to dryness. The yellow residue (3-Butoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile) was then dissolved in EtOH (3 mL) and treated with 1 mL of 1 N NaOH (aq) and a catalytic amount of H_2O_2. Quantitative conversion of the nitrile to the amide occurred after heating this solution at 65°C for 3 hours. Column chromatography on silica

eluting with EtOAc gave the product as a white solid (119.9 mg, 65%). (100% clean by LC/MS, product M+H = 369.2).

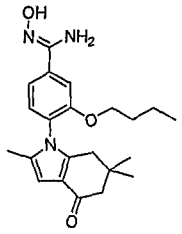
Example 42



2-(phenylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide (Compound 61)

2-Bromo-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile (107.2 mg, 0.3 mmol), aniline (111.8 mg, 1.2 mmol), $Pd(OAc)_2$ (10.1 mmol, 5 mol%), DPPF (16.6 mg, 10 mol%), and NaO*t*Bu (57.7 mg, 0.6 mmol) were placed in a Personal Chemistry Microwave Vial. The reagents were suspended in 2.5 mL of anhydrous toluene and the vessel purged with nitrogen. The reaction vessel was sealed and heated to 110 °C for 480 seconds. Upon cooling, the reaction mixture was filtered through SiO_2 (eluted with 2:1 EtOAc/hexanes) and the eluent concentrated *in vacuo*. The residue was then dissolved in 2 mL EtOH and treated with 0.6 mL of 1 N NaOH and a catalytic amount of H_2O_2. After stirring this solution at 50 °C for 2 hours, the mixture of nitrile and amide was purified by column chromatography (silica, EtOAc/hexanes). The product 2-(phenylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide was isolated as a yellow powder (55.6 mg, 47%). (100% clean by LC/MS, product M+H = 388.1). The corresponding nitrile was also isolated (46.9 mg, 42%). (100% clean by LC/MS).

Example 43

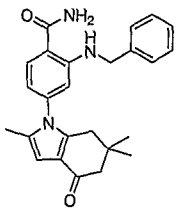
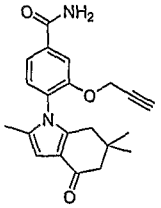


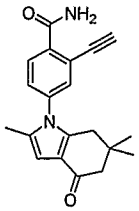
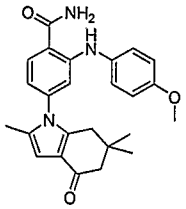
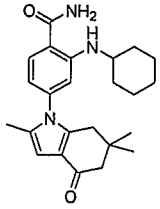
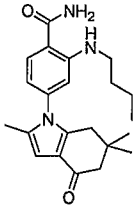
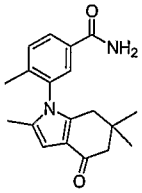
(Z)-3-butoxy-N'-hydroxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzimidamide (Compound 62)

Treatment of 3-Butoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile with hydroxylamine hydrochloride affords the title compound, LCMS m/z M+H = 384.2.

Example 44

The following compounds are prepared essentially according to the procedures forth in Scheme 7-9 and described in the preceding examples.

Compound No.	Structure	Name
63		2-Benzylamino-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide; M+H = 402.2
64		3-Prop-2-ynyloxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide; M+H = 351.1

65		2-Ethynyl-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide; M+H = 321.1
66		2-(4-Methoxy-phenylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide; M+H = 418.2
67		2-Cyclohexylamino-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide; M+H = 394.1
68		2-(butylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindol-1-yl)benzamide; M+H = 368.2
69		4-Methyl-3-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indol-1-yl)-benzamide M+H = 311.1

Example 45

The following compounds are prepared essentially according to the procedures forth in Scheme 1-9 and described in the preceding examples.

Compound No.	M+H	Name
70	379.1	3-(3-thienyl)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide

71	311.1	2-methyl-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
72	412.1	2-[(3-ethynylphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
73	422.1	2-[(4-chlorophenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
74	360.1	2-anilino-4-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
75	389.1	3-anilino-5-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)pyridine-2-carboxamide
76	478.2	2-[(3,4,5-trimethoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
77	374.1	2-pyridin-4-yl-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
78	412.2	N-[2-(aminocarbonyl)-5-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]-L-valine
79	382.2	2-morpholin-4-yl-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
80	363.1	2-(1H-imidazol-1-yl)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
81	513.2	4-(3-chloro-2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)-2-[(3,4,5-trimethoxyphenyl)amino]benzamide
82	404.1	2-[(4-hydroxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
83	406.2	2-[(1-ethyl-1H-pyrazol-5-yl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
84	393.1	2-[(5-methylisoxazol-3-yl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
85	403.1	2-{[4-(aminocarbonyl)phenyl]amino}-4-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
86	436.1	4-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)-2-[(3,4,5-trimethoxyphenyl)amino]benzamide

87	419.2	2-[(6-methoxypyridin-3-yl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
88	310.1	2-(allylamino)-4-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
89	283.1	4-(2,3-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
90	361	3-bromo-4-(2,3-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
91	338.1	2-(allylamino)-4-(2,3-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
92	356.1	4-(2,3-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)-2-[(2-methoxyethyl)amino]benzamide
93	519.2	2-({3-[3-(dimethylamino)propoxy]-4-methoxyphenyl}amino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
94	397.2	2-(morpholin-4-ylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
95	371.2	2-[(2-methoxyethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
96	425.2	2-[(2-morpholin-4-ylethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
97	389.1	2-(pyridin-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
98	354.1	2-(acetylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
99	395.2	2-(4-methylpiperazin-1-yl)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
100	367.2	2-[(cyclopropylmethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
101	384.1	2-[(methoxyacetyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
102	326.1	2-ethyl-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
103	386.1	2-(butylthio)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide

104	505.2	2-({3-[2-(dimethylamino)ethoxy]-4-methoxyphenyl}amino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
105	406.1	2-(pyridin-4-ylthio)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
106	417.2	2-{[(1R)-1-phenylethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
107	533.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(3,4,5-trimethoxyphenyl)amino]benzamide
108	476.2	2-({2-[2-(dimethylamino)ethoxy]pyridin-4-yl}amino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
109	480.2	2-{[1-(N,N-dimethylglycyl)piperidin-4-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
110	359.1	4-(6,6-dimethyl-4-oxo-3-phenyl-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
111	455.2	2-[(2-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]amino}ethyl)amino]-2-oxoethyl acetate
112	413.2	2-{[2-(glycoloylamino)ethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide
113	419.1	2-{[2-(methylsulfonyl)ethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
114	419.2	2-[(4-methoxyphenyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
115	406.1	2-[(6-oxo-1,6-dihydropyridin-3-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
116	415.2	2-(cyclopent-3-en-1-ylamino)-4-[3-(difluoromethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide
117	367.2	2-(cyclobutylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
118	455.2	2-[trans-4-(2-Hydroxy-ethoxy)-cyclohexylamino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide

119	411.2	2-(trans-4-Hydroxy-cyclohexylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide
120	415.2	2-(2-Methoxy-1-methoxymethyl-ethylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide;
121	415.2	2-{[3-hydroxy-1-(2-hydroxyethyl)propyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
122	469.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-{[2-methoxy-1-(methoxymethyl)ethyl]amino}benzamide
123	451.1	2-{[3-(methylsulfinyl)phenyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
124	528.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-{[1-(methylsulfonyl)piperidin-4-yl]amino}benzamide
125	465.2	4-(6,6-Dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(trans-4-hydroxy-cyclohexylamino)-benzamide
126	509.2	4-(6,6-Dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-[trans-4-(2-hydroxy-ethoxy)-cyclohexylamino]-benzamide
127	537.3	2-{[1-(3-morpholin-4-ylpropanoyl)piperidin-4-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
128	508.2	2-[trans-4-(2-Amino-ethoxy)-cyclohexylamino]-4-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide
129	453.2	2-[(1-glycylpiperidin-4-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
130	454.2	2-[trans-4-(2-Amino-ethoxy)-cyclohexylamino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide
131	446.1	2-{[1-(methylsulfonyl)azetidin-3-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
132	433.1	2-{[3-(methylsulfonyl)propyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide

133	488.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-({2-[(methylsulfonyl)amino]ethyl}amino)benzamide
134	338.1	4-(3-but-3-en-1-yl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
135	460.1	2-{[(3S)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide
136	502.1	2-({2-[(dimethylamino)sulfonyl]ethyl}amino)-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide
137	327.1	4-[3-(2-Amino-ethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-indazol-1-yl]-benzamide

Example 46

The following compounds have been prepared essentially according to the procedures set forth in Schemes 1-9 above and described in the above examples.

Compound No.	M + H	Name
138	285.1	4-(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzoic acid;
139	284.1	4-(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
140	297.1	4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
141	313.1	4-[(4Z)-4-(methoxyimino)-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
142	299.1	4-[(4Z)-4-(hydroxyimino)-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
143	311.1	4-methyl-3-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
144	297.1	3-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
145	332.1	2-chloro-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzoic acid;

146	327.1	4-[(4Z)-4-(ethoxyimino)-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
147	375.1	4-[(4Z)-6,6-dimethyl-4-(phenoxyimino)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
148	355.2	4-[(4Z)-4-(isobutoxyimino)-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
149	339.1	4-{(4Z)-4-[(allyloxy)imino]-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-1-yl}benzamide;
150	383.2	4-{(4Z)-6,6-dimethyl-4-[(tetrahydro-2H-pyran-2-yloxy)imino]-4,5,6,7-tetrahydro-1H-indazol-1-yl}benzamide;
151	389.1	4-{(4Z)-4-[(benzyloxy)imino]-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-1-yl}benzamide;
152	312.1	4-[(4E)-4-(hydroxyimino)-2,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indol-1-yl]benzamide;
153	326.1	4-[(4E)-4-(methoxyimino)-2,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indol-1-yl]benzamide;
154	352.1	4-{(4E)-4-[(allyloxy)imino]-2,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indol-1-yl}benzamide;
155	368.2	4-[(4E)-4-(isobutoxyimino)-2,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indol-1-yl]benzamide;
156	402.2	4-{(4E)-4-[(benzyloxy)imino]-2,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indol-1-yl}benzamide;
157	340.1	3-[(4Z)-4-(methoxyimino)-2,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indol-1-yl]-4-methylbenzamide;
158	326.1	3-[(4Z)-4-(hydroxyimino)-2,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indol-1-yl]-4-methylbenzamide;
159	377.1	4-[6-(1,3-benzodioxol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzoic acid;
160	376.1	4-[6-(1,3-benzodioxol-5-yl)-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;

161	391.1	4-[(4Z)-6-(1,3-benzodioxol-5-yl)-4-(hydroxyimino)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
162	365.1	2-(trifluoromethyl)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
163	327.1	2-methoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
164	369.2	2-butoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
165	368.2	2-(butylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
166	385.2	3-(2-ethoxyethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
167	371.1	3-(2-methoxyethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
168	341.1	2-ethoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
169	357.1	2-(2-hydroxyethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
170	370.2	2-[(2-methoxyethyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
171	385.2	2-(2-ethoxyethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
172	255.1	4-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
173	384.2	3-[2-(dimethylamino)ethoxy]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
174	397.2	3-(tetrahydrofuran-3-ylmethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
175	407.1	3-(4-fluorophenoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

176	383.2	2-{[2-(dimethylamino)ethyl]amino}-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
177	388.1	2-anilino-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
178	315.1	3-fluoro-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
179	359.1	4-(6,6-dimethyl-4-oxo-2-phenyl-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
180	331.1	2-chloro-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
181	402.2	2-(benzylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
182	375	2-bromo-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
183	357.1	3-(2-hydroxyethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
184	312.1	2-amino-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
185	385.1	3-(tert-butylthio)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
186	405.1	3-(phenylthio)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
187	385.1	3-(butylthio)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
188	340.1	2-(dimethylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
189	327.1	3-methoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
190	341.1	3-ethoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
191	355.1	3-propoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

192	403.1	3-(benzyloxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
193	426.2	3-(2-morpholin-4-ylethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
194	404.1	3-(pyridin-2-ylmethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
195	404.1	3-(pyridin-4-ylmethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
196	399.2	3-(2-isopropoxyethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
197	410.2	3-(2-pyrrolidin-2-ylethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
198	411.2	3-(tetrahydro-2H-pyran-2-ylmethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
199	397.2	3-(tetrahydro-2H-pyran-4-yloxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
200	368.2	3-(butylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
201	331.1	3-chloro-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
202	393.1	3-(1H-imidazol-4-ylmethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
203	418.2	2-[(4-methoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
204	370.1	3-butoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzoic acid;

205	388.1	3-anilino-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
206	402.2	3-(benzylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
207	371.1	3-(3-hydroxypropoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
208	385.2	3-(3-hydroxybutoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
209	387.1	3-(2,3-dihydroxypropoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
210	340.1	N-butyl-4-(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
211	383.2	3-(2-methylbutoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
212	383.2	3-(pentyloxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
213	383.2	3-(3-methylbutoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
214	313.1	3-hydroxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
215	360.1	4-(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N-phenylbenzamide;
216	394.2	2-(cyclohexylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
217	395.2	3-(cyclohexyloxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
218	381.2	3-(pent-4-en-1-yloxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
219	432.1	2-(1,3-benzodioxol-5-ylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
220	396.2	2-(hexylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

221	341.1	3-butoxy-4-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
222	385.2	3-(4-hydroxybutoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
223	397.2	3-[(3-methyloxetan-3-yl)methoxy]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
224	384.2	3-(4-aminobutoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
225	383.1	3-(tetrahydrofuran-3-yloxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
226	397.2	3-(tetrahydrofuran-2-ylmethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
227	381.2	3-[(1-ethylprop-2-en-1-yl)oxy]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
228	362	2-bromo-4-(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
229	409.1	3-(2-thienylmethoxy)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
230	283.1	4-(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
231	390.1	2-[(methylsulfonyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
232	354.1	2-(acetylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
233	355.1	2-[(aminocarbonyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
234	416.1	2-(benzoylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

235	382.2	2-(butyrylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
236	342.1	3-ethoxy-5-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)pyridine-2-carboxamide;
237	389.1	2-(pyridin-3-ylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
238	390.1	2-(pyridin-2-ylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzoic acid;
239	432.2	2-[(3-ethoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
240	418.2	2-[(3-methoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
241	356.1	3-butoxy-4-(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
242	371.2	3-butoxy-4-(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N'-hydroxybenzenecarboximidamide;
243	326.1	N'-hydroxy-3-methyl-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzenecarboximidamide;
244	311.1	3-methyl-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
245	346.1	2-chloro-N-hydroxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzenecarboximidamide;
246	348.1	2,3-difluoro-N-hydroxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzenecarboximidamide;
247	355.1	8-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)-2,3-dihydro-1,4-benzodioxine-5-carboxamide;

248	367.2	2-pentyl-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
249	367.2	3-pentyl-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
250	460.2	2-[(4-butoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
251	403.2	2-anilino-N'-hydroxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzenecarboximidamide;
252	472.1	2-{[4-(trifluoromethoxy)phenyl]amino}-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
253	440.1	2-[(2-chloro-4-fluorophenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
254	436.1	2-[(2-chloro-4-methylphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
255	452.1	2-[(2-chloro-4-methoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
256	448.2	2-[(3,4-dimethoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
257	436.2	2-[(3-fluoro-4-methoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
258	448.2	2-[(3,5-dimethoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
259	448.2	2-[(2,5-dimethoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

260	432.2	2-[(4-ethoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
261	406.1	2-[(4-fluorophenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
262	389.1	2-phenoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
263	405.1	2-(phenylthio)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
264	352.1	2-(cyclopropylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
265	350.1	2-(prop-2-yn-1-ylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
266	371.1	3-(propylthio)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
267	386.1	N-hydroxy-3-(propylthio)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzenecarboximidamide;
268	460.2	N-[2-(aminocarbonyl)-5-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]-L-phenylalanine;
269	371.2	3-butoxy-4-[(4Z)-4-(hydroxyimino)-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
270	469.3	2-(diethylamino)ethyl 3-butoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzoate;
271	546.1	2-[(2-chloro-3,4,5-trimethoxyphenyl)amino]-4-(3-chloro-2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
272	464.2	4-(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)-2-[(3,4,5-trimethoxyphenyl)amino]benzamide;

273	450.2	4-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)-2-[(3,4,5-trimethoxyphenyl)amino]benzamide;
274	442.1	2-[(3,4,5-trifluorophenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
275	410.2	2-[(trans-4-hydroxycyclohexyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
276	408.2	2-[(4-oxocyclohexyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
277	402.2	2-[(4-methylphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
278	428.2	2-(2,3-dihydro-1H-inden-4-ylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
279	430.2	2-[(2-propylphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
280	430.2	2-[(2-isopropylphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
281	351.1	2-(3-hydroxyprop-1-yn-1-yl)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
282	512.1	2-[(2-chloro-3,4,5-trimethoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
283	331.1	4-(4-oxo-2-phenyl-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
284	442.1	2-[(2,4,5-trifluorophenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

285	492.2	2-[(3,4,5-trimethoxybenzyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
286	406.1	2-[(2-fluorophenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
287	406.2	2-[(3-fluorophenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
288	420.2	2-[(4-fluoro-3-methylphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
289	434.2	2-[(3-hydroxy-4-methoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
290	436.2	2-[(2-fluoro-4-methoxyphenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
291	396.2	2-(tetrahydro-2H-pyran-4-ylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
292	424.1	2-[(2,4-difluorophenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
293	424.1	2-[(3,4-difluorophenyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
294	445.2	2-anilino-4-{5-[(dimethylamino)methyl]-2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl}benzamide;
295	346.1	4-[(4E)-4-(hydroxyimino)-2-phenyl-4,5,6,7-tetrahydro-1H-indol-1-yl]benzamide;
296	494.2	2-{[4-(benzyloxy)phenyl]amino}-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

297	396.2	2-[(tetrahydrofuran-2-ylmethyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
298	398.2	2-[(1,3-dioxolan-2-ylmethyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
299	384.2	2-[(2-methoxy-1-methylethyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
300	400.2	2-{[2-(2-hydroxyethoxy)ethyl]amino}-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
301	356.1	2-[(4-hydroxybutyl)amino]-4-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
302	411.2	4-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)-2-[(3-morpholin-4-ylpropyl)amino]benzamide;
303	403.2	2-[(pyridin-2-ylmethyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
304	503.2	2-{[2-(diethylamino)-4-ethoxyphenyl]amino}-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
305	454.1	2-{[4-(difluoromethoxy)phenyl]amino}-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
306	462.2	2-[(3,4-dimethoxybenzyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
307	370.2	2-[(3-hydroxypropyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
308	352.1	2-(allylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

309	493.2	4-[(4E)-4-(hydroxyimino)-2,6,6-trimethyl-4,5,6,7-tetrahydro-1H-indol-1-yl]-2-[(3,4,5-trimethoxyphenyl)amino]benzamide;
310	384.2	2-[(3-methoxypropyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
311	389.1	2-(pyridin-4-ylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
312	420.2	2-{[3-(1H-imidazol-1-yl)propyl]amino}-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
313	406.2	2-{[2-(1H-imidazol-1-yl)ethyl]amino}-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
314	379.1	2-(isoxazol-3-ylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
315	403.2	2-[(pyridin-3-ylmethyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
316	340.1	4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phthalamide;
317	348	3-bromo-N'-hydroxy-4-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzenecarboximidamide;
318	342.1	4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phthalic acid;
319	467.3	2-[(10-aminodecyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
320	324.1	2-(allylamino)-4-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
321	386.1	2-(2,3-dihydro-1H-inden-1-ylamino)-4-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
322	338.1	2-(cyclopropylamino)-4-(2,3-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

323	342.1	2-[(2-methoxyethyl)amino]-4-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
324	324.1	3-[(cyclopropylmethyl)amino]-4-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
325	492.2	2-{[3-(3-hydroxypropoxy)-4-methoxyphenyl]amino}-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
326	324.1	2-(allylamino)-4-(3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
327	324.1	2-(cyclopropylamino)-4-(3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
328	342.1	2-[(2-methoxyethyl)amino]-4-(3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
329	269.1	4-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
330	297.1	4-(3-ethyl-2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
331	269.1	4-(3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
332	487.2	2-[(2-{2-[2-(2-aminoethoxy)ethoxy]ethoxy}ethyl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
333	382.2	2-[(trans-4-hydroxycyclohexyl)amino]-4-(2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
334	297.1	4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
335	360.1	2-anilino-4-(3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
336	382.2	2-[(trans-4-hydroxycyclohexyl)amino]-4-(3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

337	396.2	4-(2,3-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)-2-[(trans-4-hydroxycyclohexyl)amino]benzamide;
338	374.1	2-anilino-4-(2,3-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
339	450.2	4-(3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)-2-[(3,4,5-trimethoxyphenyl)amino]benzamide;
340	383.2	2-{[2-(dimethylamino)ethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
341	355.2	2-{[2-(dimethylamino)ethyl]amino}-4-(3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
342	395.2	2-(piperidin-4-ylamino)-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
343	298.1	4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
344	333	2-bromo-5-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
345	410.2	2-[(trans-4-hydroxycyclohexyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
346	409.2	2-[(1-methylpiperidin-4-yl)amino]-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
347	453.2	(4-{[2-(aminocarbonyl)-5-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]amino}piperidin-1-yl)acetic acid;
348	370.2	2-[(2-methoxyethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

349	403.2	2-[(pyridin-4-ylmethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
350	396.2	2-(tetrahydro-2H-pyran-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
351	478.2	2-[(3,4,5-trimethoxyphenyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
352	340.1	4-(3-isobutyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
353	312.1	2-amino-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
354	352.1	2-(allylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
355	409.2	2-[(1-methylpiperidin-4-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
356	395.2	2-(piperidin-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
357	369.2	3-butoxy-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
358	428.2	2-(2,3-dihydro-1H-inden-1-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
359	408.2	2-[(4-oxocyclohexyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
360	355.1	2-[(aminocarbonyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
361	397.2	2-(tetrahydro-2H-pyran-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;

362	376	2-bromo-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
363	440.2	2-[(3-morpholin-4-ylpropyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
364	397.2	2-[(tetrahydrofuran-2-ylmethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
365	523.3	2-{[trans-4-(2-morpholin-4-ylethoxy)cyclohexyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
366	435.2	2-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
367	312.1	4-(3-ethyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
368	394.2	2-(cyclohexylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
369	410.2	2-[(1-methylpiperidin-4-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
370	353.1	2-(cyclopropylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
371	352.1	2-(cyclopropylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
372	366.2	2-[(cyclopropylmethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
373	448.2	2-[(3,4-dimethoxyphenyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;

374	449.2	2-[(3,4-dimethoxyphenyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
375	479.2	2-[(3,4,5-trimethoxyphenyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
376	519.2	2-({3-[3-(dimethylamino)propoxy]-4-methoxyphenyl}amino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
377	411.2	2-[(trans-4-hydroxycyclohexyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
378	409.2	2-[(4-oxocyclohexyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
379	412.1	2-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]amino}-2-oxoethyl acetate;
380	385.2	2-[(3-methoxypropyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
381	421.2	2-{[3-(1H-imidazol-1-yl)propyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
382	467.2	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]amino}cyclohexyl glycinate;
383	355.2	2-[(2-aminoethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
384	452.2	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]amino}cyclohexyl acetate;

385	383.2	4-(3-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)-2-[(tetrahydrofuran-2-ylmethyl)amino]benzamide;
386	413.2	2-[(1,4-dioxan-2-ylmethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
387	393.1	2-[(2-furylmethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
388	392.1	2-[(2-furylmethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
389	425.2	2-[(2-piperazin-1-ylethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
390	424.2	2-[(2-piperazin-1-ylethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
391	506.2	2-({3-[2-(dimethylamino)ethoxy]-4-methoxyphenyl}amino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
392	352.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
393	353.1	2-(allylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
394	468.2	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl]amino}cyclohexyl glycinate;
395	411.2	2-[(cis-4-hydroxycyclohexyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
396	324	4-[4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;

397	398.2	4-(3-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)-N'-hydroxy-2-[(tetrahydrofuran-2-ylmethyl)amino]benzenecarboximidamide;
398	424.2	2-{[2-(1-methylpyrrolidin-2-yl)ethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
399	423.2	2-{[2-(1-methylpyrrolidin-2-yl)ethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
400	384.2	2-{[2-(dimethylamino)ethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
401	495.2	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]amino}cyclohexyl N,N-dimethylglycinate;
402	332.1	3-chloro-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
403	299.1	4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzoic acid;
404	390.1	2-(pyridin-3-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
405	407.1	2-(pyridin-4-ylthio)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
406	452.2	2-[(1-glycylpiperidin-4-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
407	314.1	N-hydroxy-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
408	356.1	N-(2-methoxyethyl)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;

409	416.2	2-{[(1R)-1-phenylethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
410	423.2	2-[(1-ethylpiperidin-3-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
411	416.2	2-{[(1S)-1-phenylethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
412	417.2	2-{[(1S)-1-phenylethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
413	424.2	2-[(trans-4-methoxycyclohexyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
414	438.2	2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
415	574.2	2-({3-[3-(dimethylamino)propoxy]-4-methoxyphenyl}amino)-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
416	447.1	2-(2,1,3-benzothiadiazol-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
417	423.1	2-[(3-chlorophenyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
418	419.2	2-[(3-methoxyphenyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
419	477.2	2-({2-[2-(dimethylamino)ethoxy]pyridin-4-yl}amino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;

420	465.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(trans-4-hydroxycyclohexyl)amino]benzamide;
421	451.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-(tetrahydro-2H-pyran-4-ylamino)benzamide;
422	445.2	2-{[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
423	445.2	2-{[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
424	433.1	3-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl]amino}benzoic acid;
425	496.2	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl]amino}cyclohexyl N,N-dimethylglycinate;
426	430.1	2-[(1-oxidotetrahydro-2H-thiopyran-4-yl)oxy]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
427	446.1	2-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)oxy]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
428	382.2	4-(3-methyl-4-oxo-5,6,7,8-tetrahydrocyclohepta[b]pyrrol-1(4H)-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide;
429	387.1	2-{[2-(methylthio)ethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;

430	560.2	2-({3-[2-(dimethylamino)ethoxy]-4-methoxyphenyl}amino)-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
431	531.2	2-({2-[2-(dimethylamino)ethoxy]pyridin-4-yl}amino)-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
432	511.2	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl]amino}cyclohexyl (acetyloxy)acetate;
433	413.1	2-(tetrahydro-2H-thiopyran-4-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
434	429.1	2-[(1-oxidotetrahydro-2H-thiopyran-4-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
435	445.2	2-[(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
436	432.2	2-{[3-(aminocarbonyl)phenyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
437	379.2	2-(cyclopent-3-en-1-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
438	395.1	2-[(2,2,2-trifluoroethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
439	413.2	2-{[(3R,4S)-3,4-dihydroxycyclopentyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;

440	420.2	2-[(6-methoxypyridin-3-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
441	420.2	2-[(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
442	483.2	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl]amino}cyclohexyl methoxyacetate;
443	491.2	2-({1-[3-(dimethylamino)propyl]-6-oxo-1,6-dihydropyridin-3-yl}amino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
444	424.2	2-{[2-(2-oxopyrrolidin-1-yl)ethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
445	473.1	2-{[3-(trifluoromethoxy)phenyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
446	433.2	4-[3-(difluoromethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-(tetrahydro-2H-pyran-4-ylamino)benzamide;
447	447.2	4-[3-(difluoromethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(trans-4-hydroxycyclohexyl)amino]benzamide;
448	467.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-(tetrahydro-2H-thiopyran-4-ylamino)benzamide;
449	449.1	4-[3-(difluoromethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-(tetrahydro-2H-thiopyran-4-ylamino)benzamide;
450	385.2	2-[(2-methoxy-1-methylethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;

451	460.2	N-(2-aminophenyl)-3-butoxy-4-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
452	410.2	2-{[(3S)-6-oxopiperidin-3-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
453	482.2	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl]amino}cyclohexyl L-alaninate;
454	482.2	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl]amino}cyclohexyl D-alaninate;
455	481.2	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]amino}cyclohexyl L-alaninate;
456	481.2	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]amino}cyclohexyl D-alaninate;
457	427.1	1-[4-(aminocarbonyl)-3-(tetrahydro-2H-pyran-4-ylamino)phenyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid;
458	475.1	5-bromo-2-[(tetrahydrofuran-2-ylmethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
459	411.2	2-[(3-hydroxycyclohexyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
460	439.2	4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl]amino}cyclohexanecarboxylic acid;
461	522.2	Trans-4-({2-(aminocarbonyl)-5-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]phenyl}amino)cyclohexyl glycinate;

462	509.3	Trans-4-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)phenyl]amino}cyclohexyl L-valinate;
463	429.2	2-[(2,6-dihydroxytetrahydro-2H-pyran-4-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
464	433.1	2-(cyclopent-3-en-1-ylamino)-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
465	445.2	4-[3-(difluoromethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(4-oxocyclohexyl)amino]benzamide;
466	463.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(4-oxocyclohexyl)amino]benzamide;
467	483.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(1-oxidotetrahydro-2H-thiopyran-4-yl)amino]benzamide;
468	465.1	4-[3-(difluoromethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(1-oxidotetrahydro-2H-thiopyran-4-yl)amino]benzamide;
469	393.2	2-(cyclohex-3-en-1-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
470	427.2	2-{[(3S,4R)-3,4-dihydroxycyclohexyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
471	473.1	2-{[4-(trifluoromethoxy)phenyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;

472	504.2	trans-4-({2-(aminocarbonyl)-5-[3-(difluoromethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]phenyl}amino)cyclohexyl glycinate;
473	467.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(3-ethynylphenyl)amino]benzamide;
474	383.2	4-(6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide;
475	492.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}benzamide;
476	365.1	4-(trifluoromethyl)-3-(2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
477	465.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(cis-4-hydroxycyclohexyl)amino]benzamide;
478	435.1	2-{[3-(methylthio)phenyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
479	366.1	4-(trifluoromethyl)-3-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
480	338.1	3-(3-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)-4-(trifluoromethyl)benzamide;
481	465.2	2-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-4-[(trans-4-hydroxycyclohexyl)amino]benzamide;
482	450.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-(piperidin-4-ylamino)benzamide;
483	492.2	2-[(1-acetylpiperidin-4-yl)amino]-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;

484	540.2	2-[(1-benzylpiperidin-4-yl)amino]-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
485	521.2	4-({2-(aminocarbonyl)-5-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]phenyl}amino)-N,N-dimethylpiperidine-1-carboxamide;
486	445	2-bromo-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-N'-hydroxybenzenecarboximidamide;
487	526.2	2-[(1-benzylpyrrolidin-3-yl)amino]-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
488	526.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(1-phenylpiperidin-4-yl)amino]benzamide;
489	524.2	({[(4E)-1-[4-(aminocarbonyl)-3-(tetrahydro-2H-pyran-4-ylamino)phenyl]-6,6-dimethyl-3-(trifluoromethyl)-1,5,6,7-tetrahydro-4H-indazol-4-ylidene]amino}oxy)acetic acid;
490	471.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-{[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino}benzamide;
491	437.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(3R)-tetrahydrofuran-3-ylamino]benzamide;
492	536.2	trans-4-({2-(aminocarbonyl)-5-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]phenyl}amino)cyclohexyl L-alaninate; methanesulfonate

493	564.2	trans-4-({2-(aminocarbonyl)-5-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]phenyl}amino)cyclohexyl L-valinate methanesulfonate;
494	505.2	2-[allyl(trans-4-hydroxycyclohexyl)amino]-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
495	536.2	2-Amino-propionic acid trans-4-[2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-phenylamino]-cyclohexyl ester;
496	513.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-(4-pyridin-2-ylpiperazin-1-yl)benzamide;
497	539.2	2-[(2,3-dihydroxypropyl)(trans-4-hydroxycyclohexyl)amino]-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
498	507.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(trans-4-hydroxycyclohexyl)(2-oxoethyl)amino]benzamide;
499	441.1	2-[(2,3-dihydroxypropyl)amino]-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
500	442.1	2-[(2,3-dihydroxypropyl)amino]-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzoic acid;
501	597.2	2-(acetoxymethyl)-2-(2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenylamino)propane-1,3-diyl diacetate;

502	555.2	2-({2-(aminocarbonyl)-5-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]phenyl}amino)-2-(hydroxymethyl)propane-1,3-diyl diacetate;
503	513.1	2-({2-(aminocarbonyl)-5-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]phenyl}amino)-3-hydroxy-2-(hydroxymethyl)propyl acetate;
504	509.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(trans-4-hydroxycyclohexyl)(2-hydroxyethyl)amino]benzamide;
505	555.1	2-({4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl}amino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
506	550.3	2-({1-[3-(4-methylpiperazin-1-yl)propanoyl]piperidin-4-yl}amino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
507	501.2	2-[(1-isonicotinoylpiperidin-4-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
508	501.2	2-{[1-(pyridin-3-ylcarbonyl)piperidin-4-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
509	422.2	2-(1-azabicyclo[2.2.2]oct-3-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
510	460.1	2-{[(3R)-1-(methylsulfonyl)pyrrolidin-3-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;

511	467.2	2-[(1-beta-alanylpiperidin-4-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
512	493.2	2-[(1-prolylpiperidin-4-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
513	424.2	2-{[(3R)-1-acetylpyrrolidin-3-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
514	453.2	(3R)-3-{[2-(aminocarbonyl)-5-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl]amino}-N,N-dimethylpyrrolidine-1-carboxamide;
515	523.2	[[2-Carbamoyl-5-(6,6-dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-phenyl]-(trans-4-hydroxy-cyclohexyl)-amino]-acetic acid;
516	419.2	2-{[4-(hydroxymethyl)phenyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
517	451.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-{[(1R,3S)-3-hydroxycyclopentyl]amino}benzamide;
518	451.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-{[(1R,3R)-3-hydroxycyclopentyl]amino}benzamide;
519	397.2	2-{[(2R)-tetrahydrofuran-2-ylmethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
520	505.2	2-{[trans-4-(allyloxy)cyclohexyl]amino}-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;

521	397.2	2-{[(2S)-tetrahydrofuran-2-ylmethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
522	473.2	2-[(1-isonicotinoylazetidin-3-yl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
523	473.2	2-{[1-(pyridin-3-ylcarbonyl)azetidin-3-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
524	509.2	2-{[1-(3-morpholin-4-ylpropanoyl)azetidin-3-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
525	522.3	2-({1-[3-(4-methylpiperazin-1-yl)propanoyl]azetidin-3-yl}amino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
526	401.1	2-{[3-(methylthio)propyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
527	437.1	2-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-4-[(3R)-tetrahydrofuran-3-ylamino]benzamide;
528	385.2	2-{[(1S)-2-methoxy-1-methylethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
529	396.2	2-(tetrahydro-2H-pyran-2-ylamino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
530	655.3	2-[[trans-4-(allyloxy)cyclohexyl](3,5-dimethoxybenzyl)amino]-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;

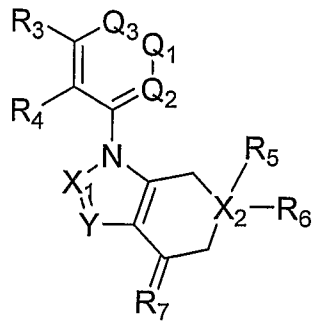
531	689.3	2-[[trans-4-(2,3-dihydroxypropoxy)cyclohexyl](3,5-dimethoxybenzyl)amino]-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
532	404.1	4-{3-[(benzyloxy)methyl]-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl}benzamide;
533	448.2	2-({2-[(dimethylamino)sulfonyl]ethyl}amino)-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
534	382.2	2-[(3S)-pyrrolidin-3-ylamino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide hydrochloride;
535	424.2	2-{[(3S)-1-acetylpyrrolidin-3-yl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
536	507.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-{[trans-4-(2-oxoethoxy)cyclohexyl]amino}benzamide;
537	539.2	2-{[4-(2,3-dihydroxypropoxy)cyclohexyl]amino}-4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
538	516.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-({2-[(isopropylsulfonyl)amino]ethyl}amino)benzamide;
539	509.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-{[trans-4-(2-hydroxyethoxy)cyclohexyl]amino}benzamide;
540	523.2	{[trans-4-({2-(aminocarbonyl)-5-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]phenyl}amino)cyclohexyl]oxy}acetic acid;

541	550.1	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-({2-[(phenylsulfonyl)amino]ethyl}amino)benzamide;
542	490.2	2-{[2-(morpholin-4-ylsulfonyl)ethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
543	327.1	4-[3-(2-aminoethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
544	451.1	2-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-4-{methyl[(3R)-tetrahydrofuran-3-yl]amino}benzamide;
545	439.1	2-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-4-[(2-methoxy-1-methylethyl)amino]benzamide;
546	430	4-bromo-2-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
547	425.2	4-(3-ethyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)-2-[(trans-4-hydroxycyclohexyl)amino]benzamide;
548	522.2	4-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(trans-4-{[(2E)-2-(hydroxyimino)ethyl]oxy}cyclohexyl)amino]benzamide;
549	453.2	2-[(trans-4-hydroxycyclohexyl)amino]-4-(3-isobutyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
550	437.2	4-(3-cyclopropyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)-2-[(trans-4-hydroxycyclohexyl)amino]benzamide;

551	426.2	4-[3-(aminomethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(trans-4-hydroxycyclohexyl)amino]benzamide methanesulfonate (salt);
552	452.2	2-[(1-methyl-2-oxo-2-piperidin-1-ylethyl)amino]-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
553	440.2	4-[3-(2-aminoethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(trans-4-hydroxycyclohexyl)amino]benzamide;
554	439.2	2-[(trans-4-hydroxycyclohexyl)amino]-4-(3-isopropyl-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;
555	437.1	2-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]-4-(tetrahydrofuran-3-ylamino)benzamide;
556	451.2	4-[3-(cyclopropylmethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]-2-[(trans-4-hydroxycyclohexyl)amino]benzamide;
557	424.2	2-[(trans-4-hydroxycyclohexyl)amino]-4-(2,3,6,6-tetramethyl-4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)benzamide;
558	338.1	4-[3-(cyclopropylmethyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl]benzamide;
559	398.2	2-{[2-(dimethylamino)-2-oxoethyl]amino}-4-(3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)benzamide;

Example 47

Additional compounds of the invention are represented by Formula XXIII and have substituents R_3, R_4, R_5, R_6, R_7, Q_1, Q_2, Q_3, Y, X_1, and X_2 as listed in the tables below. These compounds are prepared essentially according to the procedures set forth in Schemes 1-9 above and described in the above examples.



XXIII

Table A1. Substructures and codes for R_3, R_4

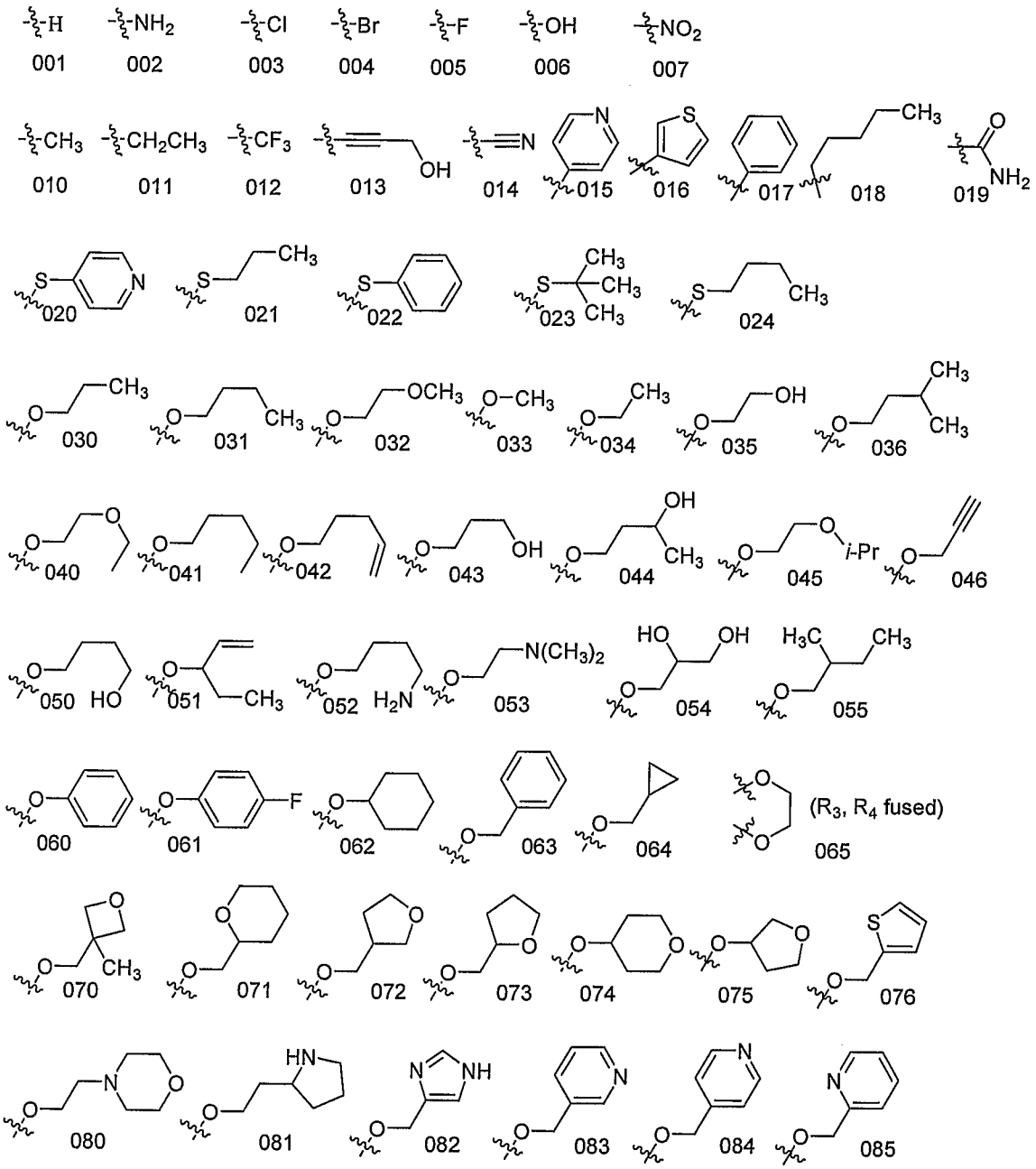


Table A2. Substructures and codes for R_3, R_4

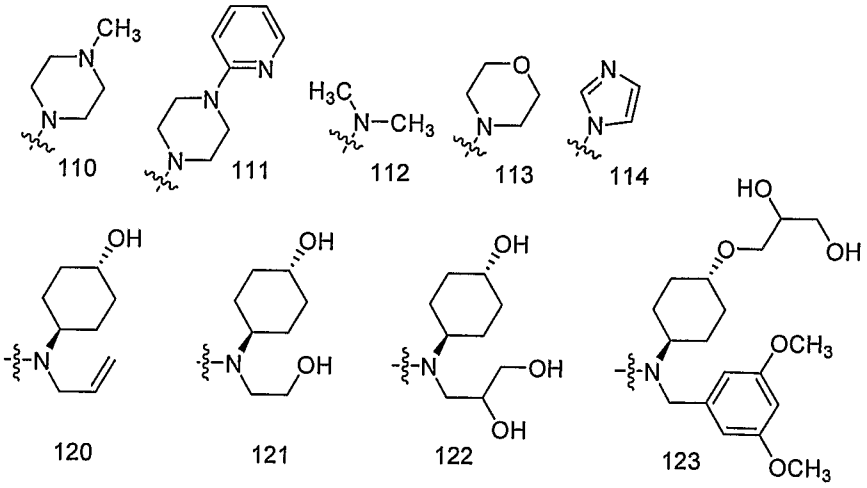


Table A3. Substructures and codes for R_3, R_4

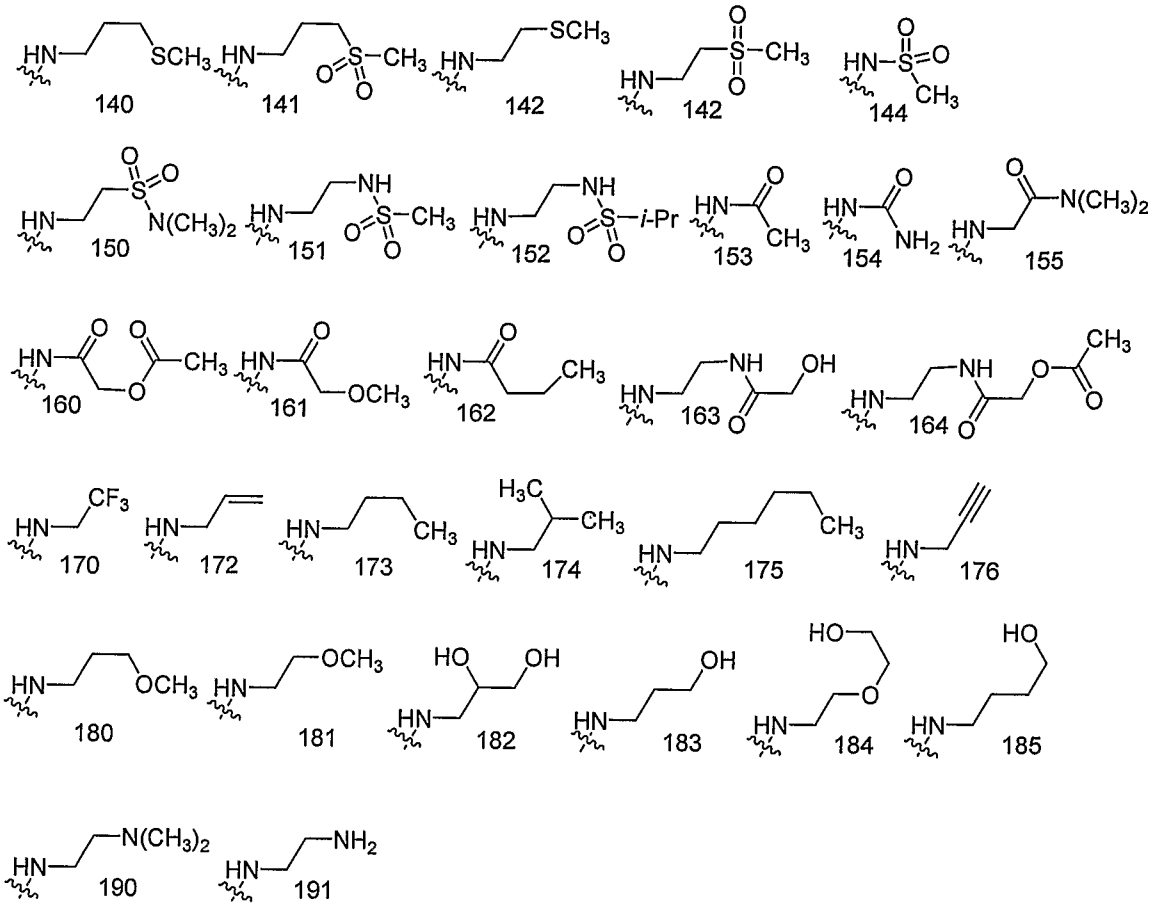


Table A4. Substructures and codes for R_3, R_4

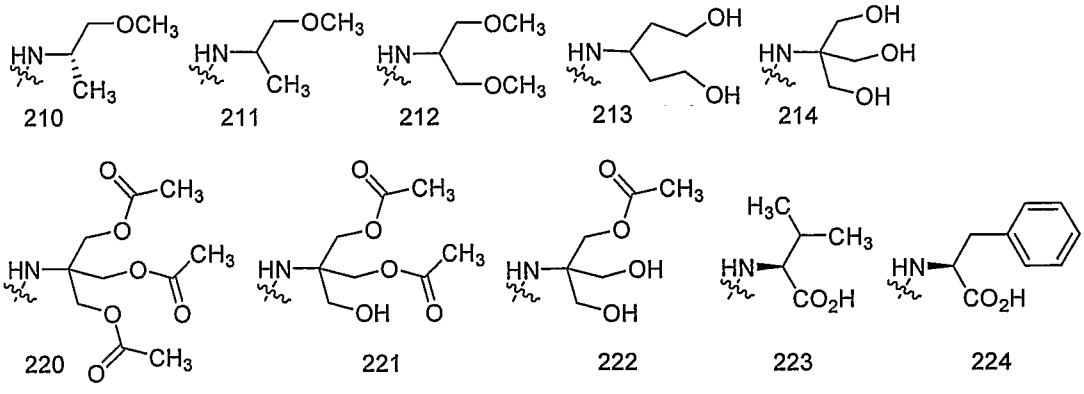


Table A5. Substructures and codes for R_3, R_4

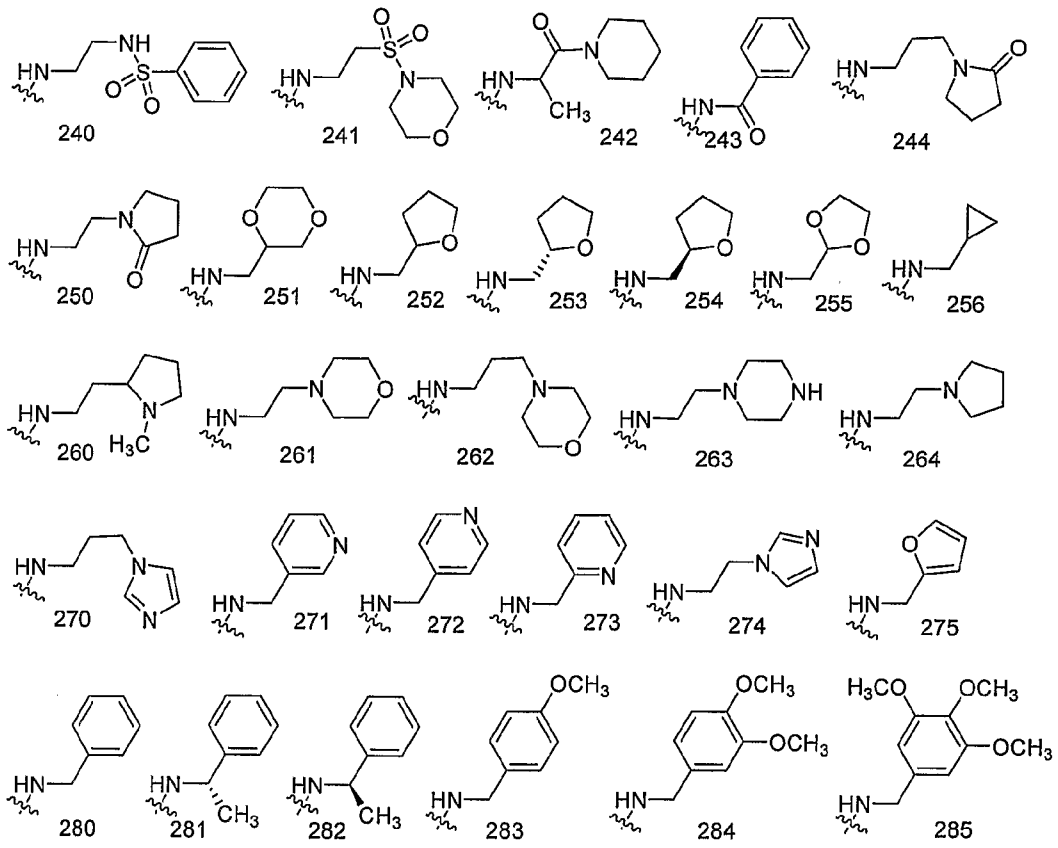


Table A6. Substructures and codes for R_3, R_4

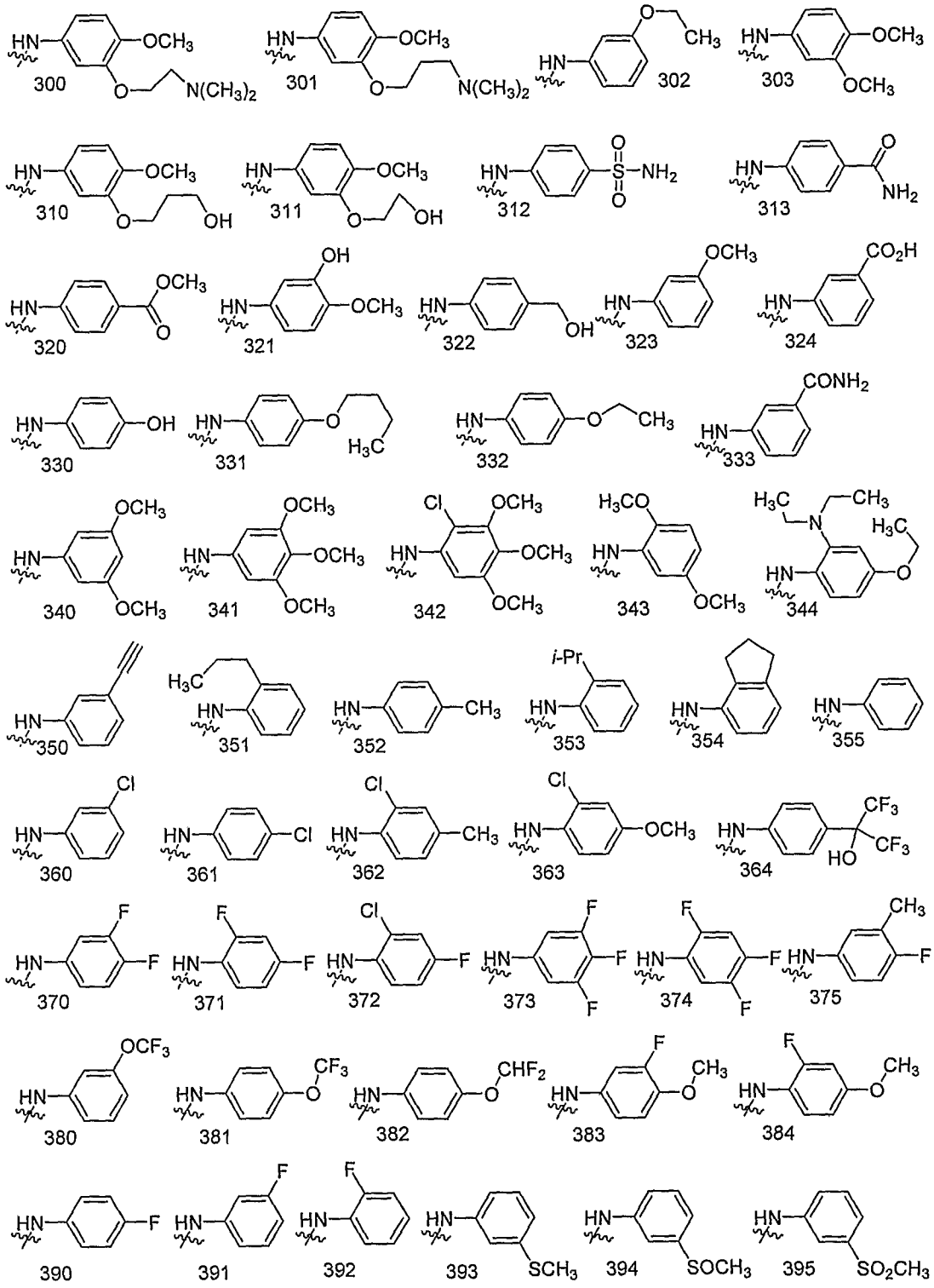


Table A7. Substructures and codes for R_3, R_4

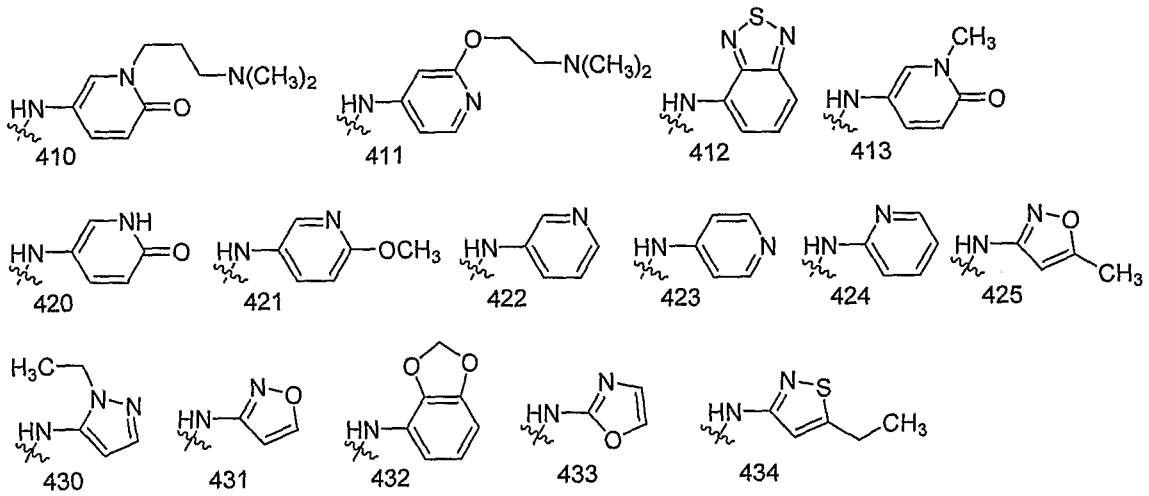


Table A8. Substructures and codes for R_3, R_4

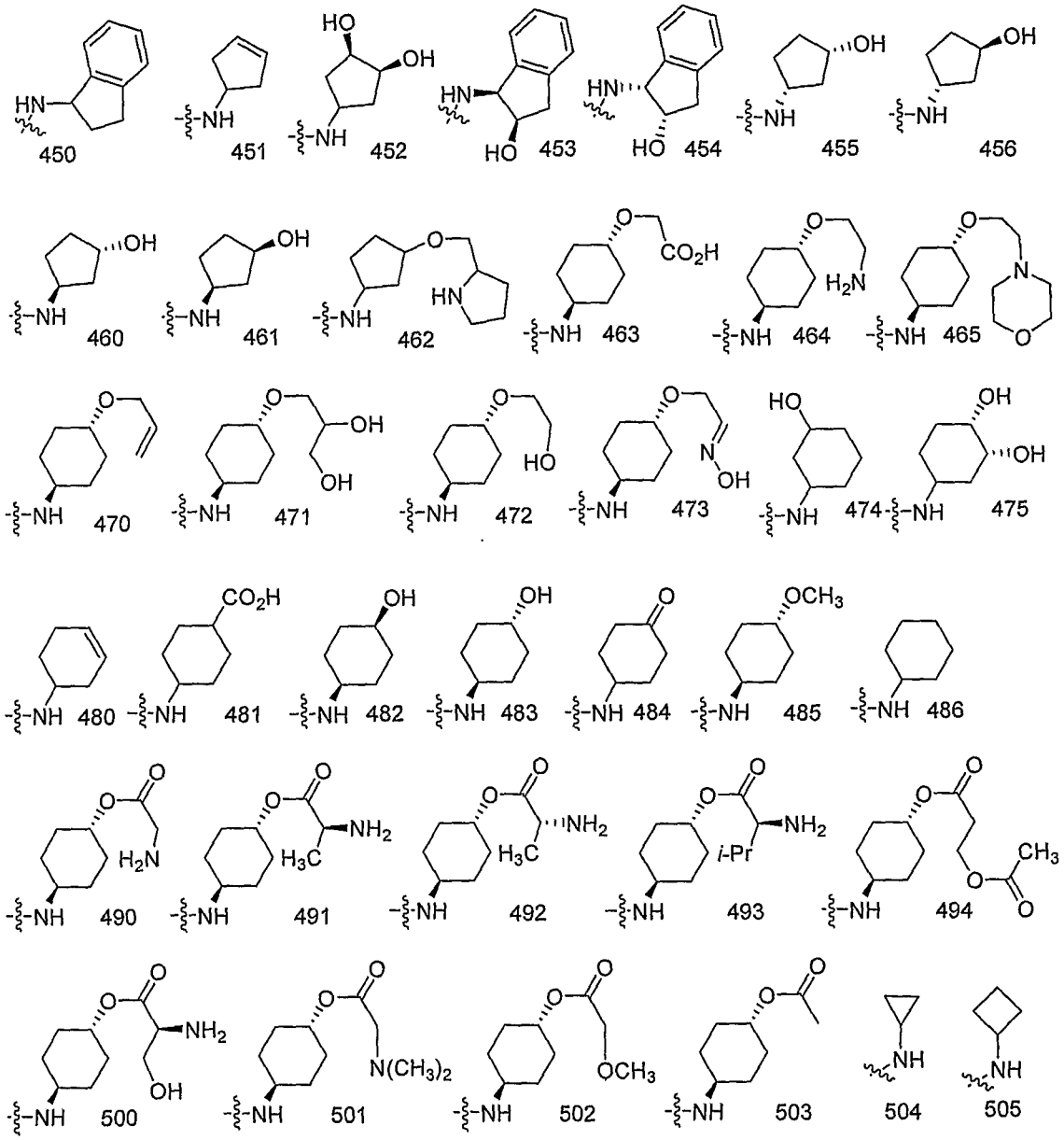


Table A9. Substructures and codes for R_3, R_4

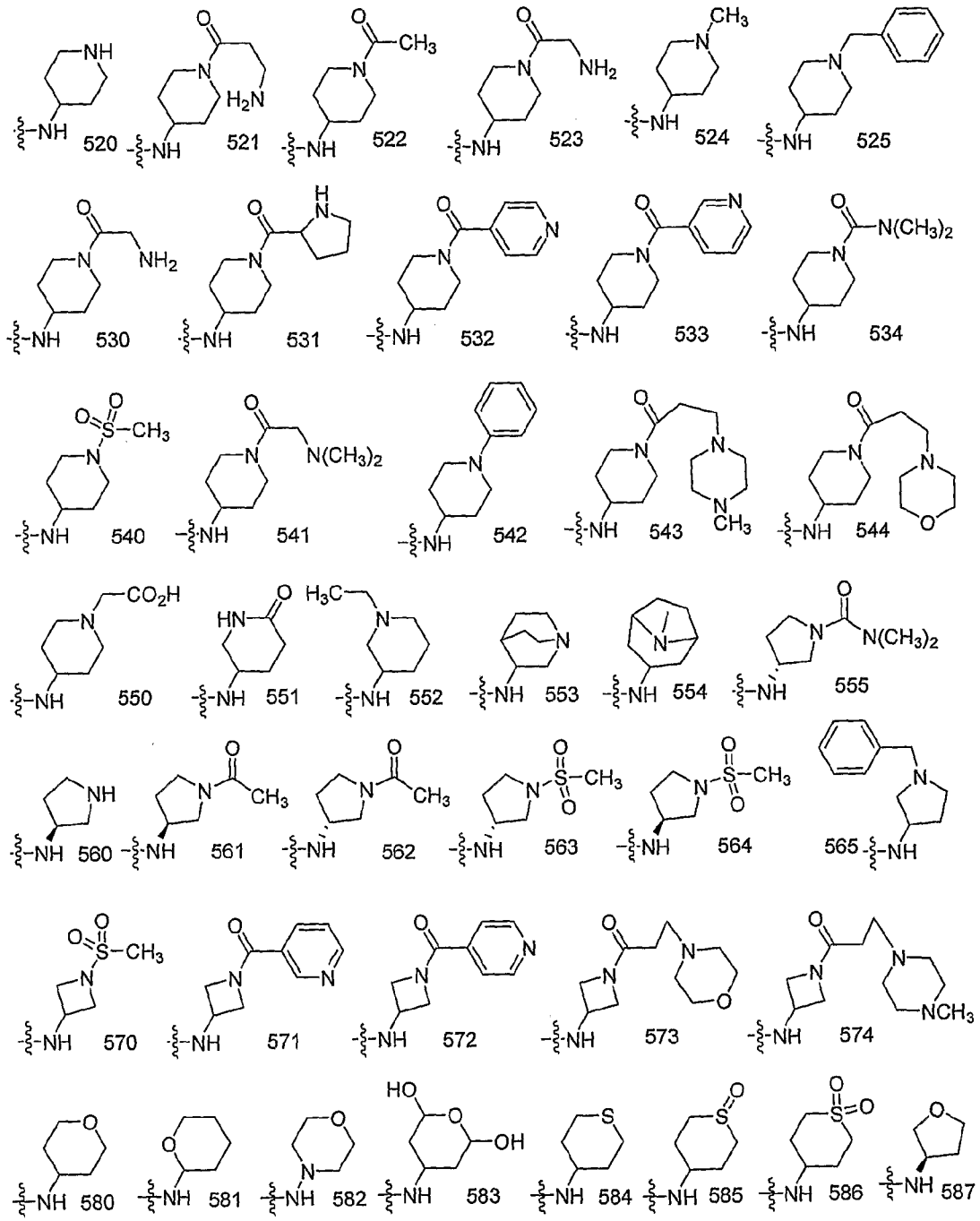


Table B. Substructures and codes for Q_2, Q_1, Q_3

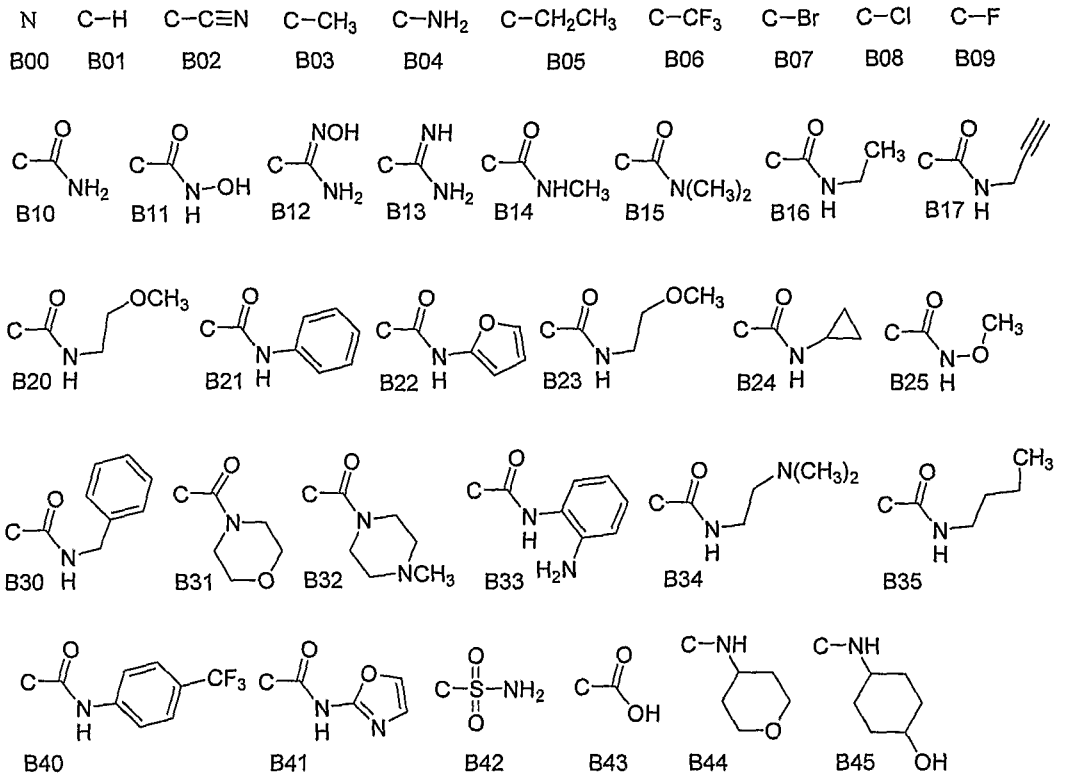


Table C. Substructures and codes for X_1, Y

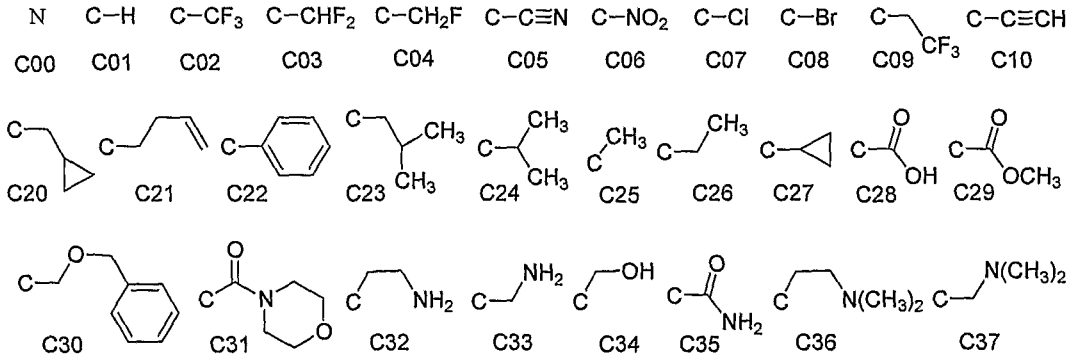


Table D. Substructures and codes for R_7

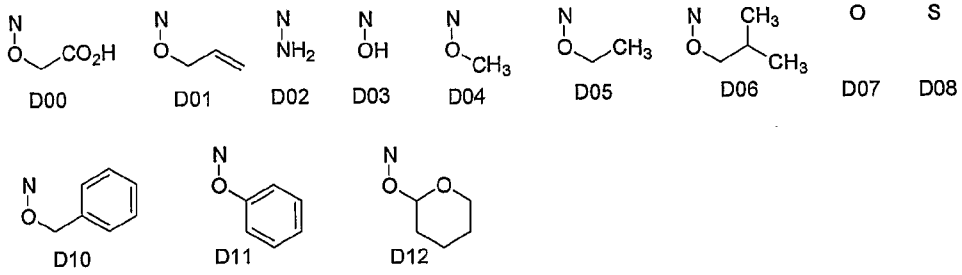
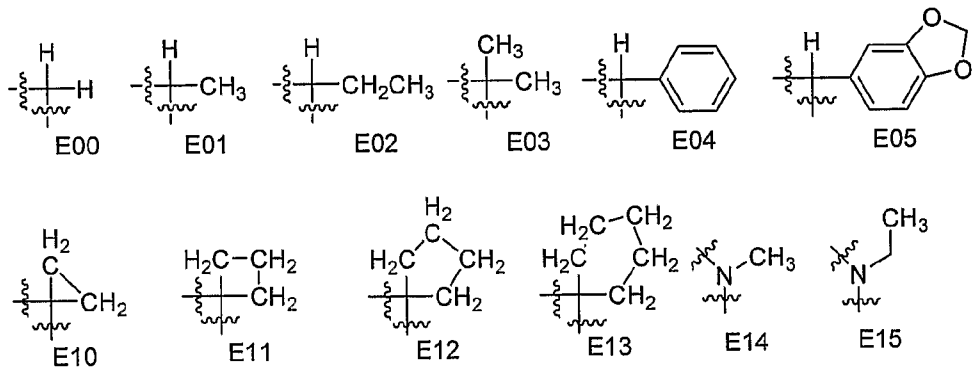


Table E. Substructures and codes for $X_2(R_5,R_6)$



Biological Evaluation

Example 48

Cell Proliferation Assays

A panel of cancer cell lines was obtained from the DCTP Tumor Repository, National Cancer Institute (Frederick, MD) or ATCC (Rockville, MD). Cell cultures were maintained in Hyclone RPMI 1640 medium (Logan, UT) supplemented with 10% fetal bovine serum and 20 mM HEPES buffer, final pH 7.2, at 37 °C with a 5% CO_2 atmosphere. Cultures were maintained at sub-confluent densities. Human umbilical vein endothelial cells

(HUVEC) were purchased from Clonetics, a division of Cambrex (Walkersville, MD). Cultures were established from cryopreserved stocks using Clonetics EGM-2 medium supplemented with 20 mM HEPES, final pH 7.2, at 37 °C with a 5% CO_2 atmosphere.

For proliferation assays, cells were seeded with the appropriate medium into 96 well plates at 1,000-2,500 cells per well, depending on the cell line, and were incubated overnight. The following day, test compound, DMSO solution (negative control), or Actinomycin D (positive control) was added to the appropriate wells as 10x concentrated stocks prepared in phosphate buffered saline. The cell plates were then incubated for an additional 2-5 days, depending on the cell line, to allow proliferation to occur. To measure cell density, 50 µL of WST-1 solution (Roche Applied Science, IN) diluted 1:5 in phosphate buffered saline was added to each well, and the cells incubated for an additional 1-5 hrs., again depending on the cell line. Optical density was determined for each well at 450 nM using a Tecan GeniosPro plate reader (RTP, NC). The percentage of cell growth was determined by comparing the cell growth in the presence of test compounds to the cells treated with DMSO vehicle (control, 100% growth) and cells treated with Actinomycin D (10 µM, 0% growth).

Immediately after the WST-1 determination, the medium was removed from the PC-3, NCI-H460 and HUVEC cell lines, and the plates stored at -80°C. Using these assay plates, relative amounts of DNA in each well were determined using the Cyquant DNA assay kit from R&D Systems (Eugene, OR) following the manufacturer's directions. Results for each compound treatment were compared to DMSO vehicle control (100%) and 10 µM Actinomycin D treated cells (0%).

Several exemplary compounds useful in the methods of the invention are listed below. The range of their inhibitory

activity against PC-3 cell proliferation is demonstrated, where +++ stands for an IC_{50} value that is less than 0.5 μM, ++ between 0.5 and 5 μM, + between 5 and 50 μM.

Compound 70	+		Compound 103	++
Compound 72	++		Compound 27	+++
Compound 74	+		Compound 104	+++
Compound 76	++		Compound 105	+
Compound 77	+		Compound 106	++
Compound 81	+++		Compound 108	+++
Compound 82	++		Compound 110	+
Compound 84	++		Compound 112	+
Compound 93	++		Compound 113	+++
Compound 94	+		Compound 114	+++
Compound 5	++		Compound 31	+++
Compound 53	+		Compound 116	+++
Compound 55	++		Compound 117	+++
Compound 97	+++		Compound 121	++
Compound 98	+++		Compound 123	++
Compound 99	+		Compound 124	+++
Compound 100	+++		Compound 127	+++
Compound 19	+++		Compound 129	++
Compound 101	++		Compound 133	+
Compound 102	+		Compound 136	++

Example 49

Determination of Affinity for HSP-90

(Heat Shock Protein 90)

Affinity of test compounds for HSP-90 was determined as follows: Protein mixtures obtained from a variety of organ tissues (for example: spleen, liver and lung) were reversibly bound to a purine affinity column to capture purine-binding proteins, especially HSP-90. The purine affinity column was washed several times, and then eluted with 20μM, 100 μM, and 500 μM of test compound. Compounds of Formula I elute HP-90

in a dose-dependent manner vs. a control elution using dimethylsulfoxide. The elution profile of Formula I compounds was determined by 1-dimensional SDS polyacrylamide gel electrophoresis. Gels were stained with a fluorescent stain such as sypro ruby (a highly sensitive fluorescent protein stain that can readily detect less than 1 fmol of total protein, i.e., less than 0.04ng for a 40kDa protein) or silver nitrate. The gels were imaged using a standard flat bed gel imager and the amount of protein estimated by densitometry. The percent of HSP-90 protein eluted from the column at each concentration was determined and IC_{50} values were calculated from these estimates. The identity of a band containing HSP-90 was determined by protein sequencing using mass spectroscopy.

Compounds of the invention are inhibitors of HSP-90 (heat shock protein 90). Several exemplary compounds useful in the methods of the invention are listed below. The range of their relative binding affinity to HSP-90 is demonstrated, where +++ stands for very high, ++ for high and + for moderate.

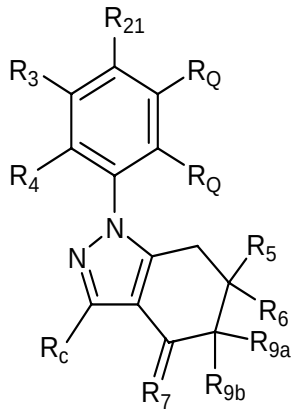
Compound 30	++		Compound 55	++
Compound 70	+		Compound 96	+++
Compound 73	+		Compound 98	+++
Compound 75	+++		Compound 99	++
Compound 76	+++		Compound 102	++
Compound 77	++		Compound 103	++
Compound 78	+		Compound 105	++
Compound 79	+		Compound 34	++
Compound 80	+		Compound 107	++
Compound 83	+++		Compound 109	++
Compound 86	++		Compound 111	+++
Compound 87	++		Compound 115	+++
Compound 88	++		Compound 32	+++
Compound 91	++		Compound 117	+++
Compound 92	++		Compound 121	+++
Compound 94	++		Compound 131	++

Compound 50	+++		Compound 132	+++
Compound 53	++		Compound 133	++
Compound 95	+++		Compound 134	++
Compound 54	+		Compound 135	+++

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the invention and that modifications may be made therein without departing from the spirit or scope of the invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

What is claimed is:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

R_4 is H;

R_3 is

(a) halo, or

(b) a C_1-C_{15} alkyl group where up to six of the carbon atoms in said alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other, wherein

R_{22} is

(i) heteroaryl,

(ii) aryl,

(iii) saturated or unsaturated C_3-C_{10} cycloalkyl, or

(iv) saturated or unsaturated C_2-C_{10} heterocycloalkyl, wherein

each aryl, heteroaryl, saturated or unsaturated cycloalkyl, or saturated or unsaturated heterocycloalkyl, independently, is optionally substituted with at least one group, which independently is hydroxy,

halo, amino, cyano, carboxy, carboxamido, nitro, oxo, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO-aryl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, (C_1-C_6)alkoxy, or mono- or di-(C_1-C_{10})alkylamino; and

each R_{22} is optionally fused to a C_6-C_{10} aryl group, C_5-C_8 saturated cyclic group, or a C_5-C_{10} heterocycloalkyl group;

wherein each (~~c~~ b) is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}, wherein

Z is OR_0 or -$N(R_{30})_2$, wherein

each R_{30} is independently –H or C_1-C_6 alkyl, or $N(R_{30})_2$ represents pyrrolidinyl, piperidinyl, piperazinyl, azepanyl, 1,3- or 1,4-diazepanyl, or morpholinyl, each of which is optionally substituted with hydroxy, amino, aminoalkyl, C_1-C_6 alkyl, mono- or di(C_1-C_6)alkylamino, C_1-C_6 alkoxy, or halogen;

R_0 is –H, -C_1-C_{10} alkyl, -C_2-C_{10} alkenyl, -C_2-C_{10} alkynyl, aryl, heteroaryl, or -C_1-C_6 acyl;

R_{23} is

(1) heteroaryl,

(2) aryl,

(3) saturated or unsaturated C_5-C_{10} cycloalkyl, or

(4) saturated or unsaturated C_5-C_{10} heterocycloalkyl, and

the R_{23} groups are optionally substituted with at least one group which independently is hydroxy, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO-aryl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, (C_1-C_6)alkoxy, or mono- or di-(C_1-C_{10})alkylamino;

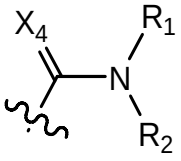
R_7 is O, N-OH, N-O-(C_0-C_6)alkyl-R_{122} where R_{122} is C_1-C_6 alkyl or phenyl, or N-(C_1-C_6 alkenoxy);

R_C is hydrogen, halogen, cyano, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} haloalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl(C_1-C_{10})alkyl

each R_Q is independently hydrogen, halogen, -$N(R_{CN})_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, or C_3-C_7 cycloalkyl, ~~aryl, or~~

each R_{CN} is –H, -C_1-C_{10} alkyl, -C_1-C_{10} -haloalkyl, or -C_3-C_7 cycloalkyl,

R_{21} is a group of the formula



wherein

R_1 and R_2 are independently H, hydroxy, or C_1-C_6 alkyl

X_4 is O or NOH;

R_5 and R_6 are independently H, C_1-C_6 alkyl, or aryl, wherein the aryl is optionally substituted with from 1-4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, mono- or di-(C_1-C_6) alkylamino, nitro, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, or carboxamide,

wherein any two adjacent substituted aryl positions, together with the carbon atoms to which they are attached, form an unsaturated cycloalkyl or heterocycloalkyl; or

R_5 and R_6 together with the carbon to which they are attached form a 3-8 membered ring; and

R_{9a} and R_{9b} are independently H, C_1-C_6 alkyl, or mono- or di-(C_1-C_6)alkylamino(C_1-C_6)alkyl

2. A compound according to claim 1, wherein

R_3 is halo, or $-Z_1R_{Z1}$, wherein

Z_1 is -O- or -NH-, $-S(O)_p$-, or $-S(O)_2NH$-, wherein p is 0, 1 or 2; and

R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -

SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

3. A compound or salt according to claim 2, wherein

R_7 is O; and

R_c is H, -CH_3, ethyl, cyclopropyl, or –CF_3.

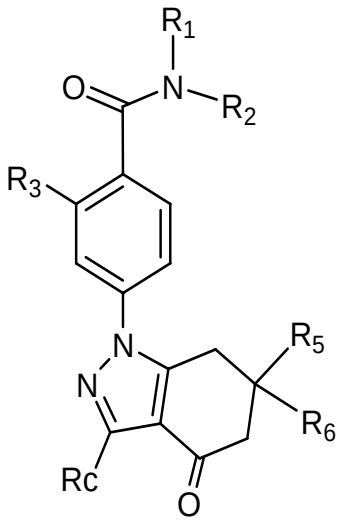
4. A compound according to claim 1, wherein

R_5 and R_6 are independently H or C_1-C_6 alkyl.

5. A compound according to claim 1, wherein

each R_Q is independently H or C_1-C_6 alkyl.

6. A compound or salt according to claim 1, of the formula,



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7. A compound or salt according to claim 6, wherein

R_3 is halo, or –Z_1R_{Z1}, wherein

Z_1 is -O- or -NH-, -$S(O)_p$-, or –$S(O)_2NH$-, wherein p is 0, 1 or 2; and

R_{Z1} is a C_1-C_{14} alkyl group where up to five of the carbon atoms in the alkyl group are optionally

replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

8. A compound or salt according to claim 6, wherein R_3 is halo, or Z_1R_{Z1}, wherein

Z_1 is –O- or –NH-; and R_{Z1} is a C1-C4 alkyl group where up to five of the carbon atoms in the alkyl group are optionally replaced independently by R_{22}, carbonyl, ethenyl, ethynyl or a moiety selected from N, O, S, SO_2, or SO, with the proviso that two O atoms, two S atoms, or an O and S atom are not immediately adjacent each other,

wherein R_{Z1} is optionally substituted at any available position with C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, hydroxy, carboxy, carboxamido, oxo, halo, amino, cyano, nitro, -SH, -S-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -SO_2NH_2, -SO_2NH-(C_1-C_6)alkyl, -SO_2NH-aryl, -SO_2-aryl, -SO-(C_1-C_6)alkyl, -SO_2-aryl, C_1-C_6 alkoxy, C_2-C_{10} alkenyloxy, C_2-

C_{10} alkynyloxy, mono- or di-(C_1-C_{10})alkylamino, -OC_1-C_{10} alkyl-Z, or R_{23}.

9. A compound of the name 4-(6,6-Dimethyl-4-oxo-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(trans-4-hydroxy-cyclohexylamino)-benzamide, or a pharmaceutically acceptable salt thereof.

10. A compound of the name trans-4-({2-(aminocarbonyl)-5-[6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]phenyl}amino)cyclohexyl glycinate, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising the compound or salt of claim 1, and a pharmaceutically acceptable carrier.

12. The use of the compound or salt of claim 1, in the preparation of a medicament for the treatment of cancer.