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(56) Related Art
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(54) Title: PYRAZOLE KINASE MODULATORS AND METHODS OF USE

(57) Abstract: The present invention provides compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Compounds of the invention inhibit, regulate and/or modulate kinases. Methods of using the compounds and pharmaceutical compositions thereof to treat kinase-dependent diseases and conditions are also an aspect of the invention.

WO 2006/033943 A3

Pyrazole Kinase Modulators and Methods of Use

REFERENCE TO RELATED APPLICATIONS

[0000] This application claims priority to U.S. provisional patent application US 60/610,689 filed 9/17/2004. The contents of the prior applications are hereby incorporated in their entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to compounds for modulating protein kinase enzymatic activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. Even more specifically, the invention relates to compounds that inhibit, regulate and/or modulate kinases, particularly Kit and flt-3. Kinase receptor signal transduction pathways related to the changes in cellular activities as mentioned above are modulated using compounds of the invention. Methods of using the compounds to treat kinase-dependent diseases and conditions are also an aspect of the invention.

Summary of Related Art

[0002] Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms.

[0003] Protein kinases are enzymes that catalyze the phosphorylation of proteins, in particular, hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell differentiation and proliferation; i.e., virtually all aspects of cell life in one-way or another depend on protein kinase activity. Furthermore, abnormal protein kinase activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer).

[0004] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular.

[0005] Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR (HER1), HER2, HER3, and HER4. Ligands of this subfamily of receptors identified so far include epithelial growth factor, TGF-alpha, amphiregulin, HB-EGF, betacellulin and heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-alpha and beta receptors, CSFIR, c-kit and FLK-II. Then there is the FLK family, which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., *DN&P* 7(6): 334-339, 1994, which is hereby incorporated by reference.

[0006] The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen, *Oncogene*, 8:2025-2031 (1993), which is hereby incorporated by reference.

[0007] Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases. These include, but are not limited to: immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, both receptor and non-receptor protein kinases are attractive targets for small molecule drug discovery.

[0008] One attractive goal for therapeutic use of kinase modulation relates to oncological indications. For example, modulation of protein kinase activity for the treatment of cancer has been demonstrated successfully with the FDA approval of Gleevec® (imatinib mesylate, produced by Novartis Pharmaceutical Corporation of East Hanover, NJ) for the treatment of Chronic Myeloid Leukemia (CML) and gastrointestinal stroma cancers (GIST). Gleevec is a c-Kit and Abl kinase inhibitor.

[0009] Modulation (particularly inhibition) of cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc Technol 2001 6, 1005-1024), is an alluring goal for development of small-molecule drugs. Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization, including ischemic coronary artery disease, diabetic retinopathy, psoriasis and rheumatoid arthritis. As well, cell antiproliferative agents are desirable to slow or stop the growth of tumors.

[0010] One particularly attractive target for small-molecule modulation is c-Kit. The proto-oncogene *c-Kit* was first identified as the oncogenic component of the acutely transforming Hardy-Zuckerman 4-feline sarcoma virus (Besmer et al Nature 1986 320:415-421). c-Kit (also called stem cell factor receptor or steel factor receptor) is a type 3 receptor tyrosine kinase (RTK) belonging to the platelet-derived growth factor receptor subfamily. c-Kit binds the ligand stem cell factor (SCF), and triggers its multiple signal transduction pathways including Src family kinases, phosphatidyl-inositol 3 kinase, the Ras-Raf-Map kinase cascade, and phospholipase C (Broudy et al Blood 1999 94: 1979-1986; Lennartsson et al Oncogene 1999 18: 5546-5553 ; Timokhina et al EMBO J 1998 17:6250-6262; Chian et al Blood 2001 98(5)1365-1373; Blume-Jensen et al Curr Biol 1998 8:779-782; Kissel et al EMBO J 2000 19:1312-1326; Lennartsson et al. Oncogene 1999 18: 5546-5553; Sue et al Blood, 199892:1242-1149; Lev. et al EMBO J 1991 10:647-654). c-Kit is required for normal hematopoiesis, melanogenesis, and gametogenesis. c-Kit is expressed in mast cells, immature myeloid cells, melanocytes, epithelial breast cells and the interstitial cells of Cajal (ICC). In mast cells, it is required not only for the differentiation, maturation, chemotaxis, and haptotaxis but also for the promotion of survival and proliferation.

[0011] Mutations in c-Kit have been implicated in human disease. Mutations in the juxtamembrane domain are found in many human gastrointestinal stromal tumors, and

mutations in the kinase domain are found in mastocytosis, germ cell tumors, acute myeloid leukemia (AML), NK lymphoma, and other hematologic disorders (Hirota et al *Science* 1998 279:577-580; Singer et al *J Clin Oncol* 2002 20:3898-3905; Longley et al *Proc Natl Acad Sci USA* 1999; 1609-1614; Tian et al *Am J Pathol* 1999 154: 1643-1647; Beghini et al *Blood* 2000 95:726-727; Hongyo et al *Cancer Res* 2000 60:2345-2347). These mutations result in ligand-independent tyrosine kinase activity, autophosphorylation of c-Kit, uncontrolled cell proliferation, and stimulation of downstream signaling pathways. Overexpression of c-Kit and c-Kit ligand have also been described in other tumors including small-cell lung cancer, neuroblastomas, gynecological tumors, and colon carcinoma, which might result in autocrine or paracrine c-Kit activation.

[0012] The overexpression of c-Kit has also been implicated in the development of neoplasia associated with neurofibromatosis type 1 (NF1). Mutations in the tumor suppressor gene *NF1* lead to a deficiency in neurofibromin, a GTPase-activating protein for Ras. This deficiency results in abnormal proliferation of Schwann cells in the peripheral nervous system, and predisposes affected individuals to peripheral nerve sheath tumors (neurofibromas), astrocytomas (optic pathway gliomas), learning disabilities, seizures, strokes, macrocephaly, vascular abnormalities, and juvenile myelomonocytic leukemia (Lynch & Gutmann *Neurol Clin* 2002 20:841-865). Genetic experiments in mice demonstrate that haploinsufficiency at *NF1* partially rescues some of the phenotypes associated with mutations in the gene for c-Kit, indicating that these genes function along a common developmental pathway (Ingram, et al. *J. Exp Med* 2000 191:181-187). Also, c-Kit is expressed in schwannoma cells from NF1 patients, but not in normal schwann cells (Ryan et al. *J Neurosci Res* 1994 37:415-432). These data indicate that elevated c-Kit expression and sensitivity to stem cell factor may play important roles in the development of proliferative disorders associated with NF-1. Therefore, c-Kit inhibitors may be effective chemotherapeutic agents for treating patients with NF-1.

[0013] GISTs are the most common mesenchymal tumors of the gastrointestinal tract, and they are generally resistant to chemotherapy and radiation therapy. However, recent results with the c-Kit/BCR-Abl inhibitor ST1571 indicate that targeting c-Kit may be an effective therapeutic strategy for this disease (Eisenberg & Mehren *Expert Opin Pharmacother* 2003 4:869-874). Malignant mast cell disease often suggests an extremely poor prognosis, and no reliable effective chemotherapeutic agents have been identified (Marone et al *Leuk Res* 2001

25:583-594). Systemic mast cell disorders have been treated with interferon-alpha, although the effectiveness of this therapy has been variable (Lehmann & Lammle Ann Hematol 1999 78:483-484; Butterfield Br J Dermatol 1998 138: 489-495). Therefore, activated c-Kit might serve as a therapeutic target in GISTs and mast cell disease, as well as other disorders associated with activated c-Kit.

[0014] Flt-3 is normally expressed on hematopoietic progenitor cells and a subset of mature myeloid and lymphoid cells, where it modulates cell survival and proliferation. Flt-3 is constitutively activated via mutation, either in the juxtamembrane region or in the activation loop of the kinase domain, in a large proportion of patients with AML (Reilly Leuk Lymphoma 2003 44: 1-7). Also, mutations in flt-3 are significantly correlated with poor prognosis in AML patients (Sawyers Cancer Cell 2002 1: 413-415).

[0015] Accordingly, the identification of small-molecule compounds that specifically inhibit, regulate, and/or modulate the signal transduction of kinases, particularly c-Kit and flt-3, is desirable as a means to treat or prevent disease states associated with abnormal cell proliferation, and is an object of this invention.

SUMMARY OF THE INVENTION

[0016] In one aspect, the present invention provides compounds for modulating c-Kit and flt-3 kinase activity and methods of treating diseases mediated by c-Kit and flt-3 activity utilizing the compounds and pharmaceutical compositions described herein. Diseases mediated by c-Kit and flt-3 activity include, but are not limited to, diseases characterized in part by migration, invasion, proliferation and other biological activities associated with invasive cell growth.

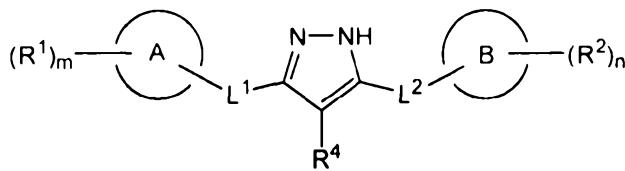
[0017] In another aspect, the invention provides methods of screening for modulators of c-Kit and flt-3 activity. The methods comprise combining a composition of the invention, c-Kit or flt-3, and at least one candidate agent and determining the effect of the candidate agent on the c-Kit or flt-3 activity.

[0018] In yet another aspect, the invention also provides pharmaceutical c-Kits comprising one or more containers filled with one or more of the ingredients of pharmaceutical compounds and/or compositions of the present invention, including, one or more c-Kit or flt-3 enzyme activity modulators as described herein. Such c-Kits can also include, for example,

other compounds and/or compositions (e.g., diluents, permeation enhancers, lubricants, and the like), a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which instructions can also reflect approval by the agency of manufacture, use or sale for human administration.

[0019] In still yet another aspect, the invention also provides a diagnostic agent comprising a compound of the invention and, optionally, pharmaceutically acceptable adjuvants and excipients.

[0019A] In a further aspect, the invention provides a compound according to formula I,



I

or a pharmaceutically acceptable salt, or hydrate thereof, wherein,

each of R¹ and R² is independently halo C₁-C₈alkyl, halo C₁-C₈alkoxy, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -SO₂N(R³)R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -NCO₂R³, -N(R³)C(O)₂R³, -C(=O)R³, optionally substituted C₆-C₁₄aryl, optionally substituted C₆-C₁₄aryl C₁-C₆alkyl, optionally substituted cyclo(C₃-C₁₃)alkyl, optionally substituted cyclo(C₃-C₁₃)alkyl C₁-C₆alkyl, optionally substituted 3-15 membered heteroaryl, optionally substituted 3-15 membered heteroaryl C₁-C₆alkyl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 3-15 membered heterocyclyl C₁-C₆alkyl;

each of m and n is independently one to five;

each of A and B is independently a five- to ten-membered aryl or heteroaryl;

R^3 is -H, optionally substituted C_1 - C_6 alkyl, optionally substituted C_6 - C_{14} aryl, optionally substituted C_6 - C_{14} aryl C_1 - C_6 alkyl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 3-15 membered heterocyclyl C_1 - C_6 alkyl;

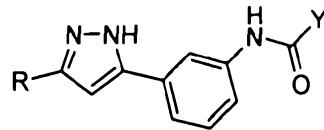
two of R^3 , together with the nitrogen to which they are attached, can combine to form an optionally substituted heterocyclyl containing between one and three additional heteroatoms;

R^4 is selected from -H and optionally substituted C_1 - C_6 alkyl;

each R^5 is independently -H, -CN, -NO₂, -OR³, -S(O)₀₋₂R³, -CO₂R³, optionally substituted C_1 - C_6 alkyl, optionally substituted C_2 - C_6 alkenyl, or optionally substituted C_2 - C_6 alkynyl; and

each of L^1 and L^2 is independently selected from absent and -C(R³)=C(R³)-;

provided the compound is not according to formula i,



i

wherein R is optionally substituted phenyl; and Y is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyl, N,N-dialkylamino, or N- C_1 - C_6 alkyl-N- C_1 - C_6 alkoxyamino; wherein the optionally substituted alkoxy, alkyl, alkenyl, alkynyl, aryl, aryl C_1 - C_6 alkyl, cycloalkyl, cycloalkyl C_1 - C_6 alkyl, heteroaryl, heteroaryl C_1 - C_6 alkyl, heterocyclyl and heterocyclyl C_1 - C_6 alkyl are, when substituted, independently substituted with one or more substituents independently selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_8 alkoxy, halo, halo C_1 - C_6 alkyl, halo C_1 - C_8 alkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -SO₂N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -NCO₂R³, -N(R³)C(O)R³, -C(=O)R³, C_6 - C_{14} aryl, C_6 - C_{14} aryl C_1 - C_6 alkyl, cyclo(C₃-C₁₃)alkyl, cyclo(C₃-C₁₃)alkyl C_1 - C_6 alkyl, 3-15 membered heterocyclyl, 3-15 membered heterocyclyl C_1 - C_6 alkyl, 3-15 membered heteroaryl, and 3-15 membered heteroaryl C_1 - C_6 alkyl.

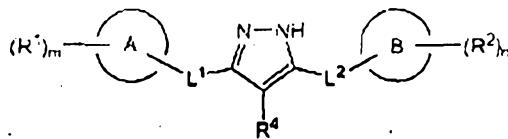
[0020] These and other features and advantages of the present invention will be described in more detail below with reference to the associated drawings.

DETAILED DESCRIPTION OF THE INVENTION

[0021] The compositions of the invention are used to treat diseases associated with abnormal and or unregulated cellular activities. Disease states which can be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), immunological disorders such as rheumatoid arthritis, graft-host diseases, multiple sclerosis, psoriasis; cardiovascular diseases such as atherosclerosis, myocardioinfarction, ischemia, stroke and restenosis; other inflammatory and degenerative diseases such as interbowel diseases, osteoarthritis, macular degeneration, diabetic retinopathy.

[0022] It is appreciated that in some cases the cells may not be in a hyper- or hypoproliferative and/or migratory state (abnormal state) and still require treatment. For example, during wound healing, the cells may be proliferating "normally", but proliferation and migration enhancement may be desired. Alternatively, reduction in "normal" cell proliferation and/or migration rate may be desired.

[0023] The present invention comprises a compound for modulating kinase activity, particularly c-Kit and/or flt-3, according to Formula I,



I

[0024] or a pharmaceutically acceptable salt, hydrate, or prodrug thereof, wherein,

[0025] each of R¹ and R² is independently selected from -H, halogen, haloalkyl, haloalkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -SO₂N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -NCO₂R³, -N(R³)C(O)₂R³, -C(=O)R³, optionally substituted alkoxy, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocycl, or optionally substituted lower heterocyclalkyl;

[0026] each of m and n is independently one to five;

[0027] each of A and B is independently selected from a five- to ten-membered aryl or heteroaryl;

[0028] R³ is selected from -H, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocycl, or optionally substituted lower heterocyclalkyl;

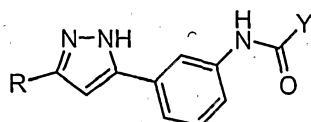
[0029] two of R³, together with the nitrogen to which they are attached, can combine to form an optionally substituted heterocycl containing between one and three additional heteroatoms;

[0030] R⁴ is selected from -H, halogen or optionally substituted lower alkyl;

[0031] each R⁵ is independently selected from -H, -CN, -NO₂, -OR³, -S(O)₀₋₂R³, -CO₂R³, optionally substituted lower alkyl, optionally substituted lower alkenyl, and optionally substituted lower alkynyl; and

[0032] each of L¹ and L² is independently selected from absent or -C(R³)=C(R³)-;

[0033] provided the compound is not either N'-[3-[5-(3-chlorophenyl)-1H-pyrazol-3-yl]phenyl]-N,N-dimethyl-urea (registry number 143704-64-7) or N'-[3-[5-(2-chlorophenyl)-1H-pyrazol-3-yl]phenyl]-N,N-dimethyl-urea (registry number 143704-63-6), and provided the compound is not according to formula i,



i

[0034] wherein R is lower alkyl or optionally substituted phenyl; and Y is lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, N,N-dialkylamino, and N-lower alkyl-N-lower alkoxyamino.

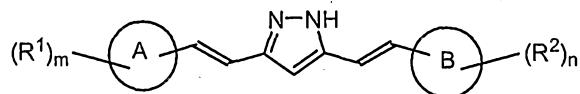
[0035] In one example, the compound according to [0023], wherein substituents such as alkoxy, alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycl or heterocyclalkyl is optionally substituted with one or more substituents independently selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, haloalkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -SO₂N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -NCO₂R³, -N(R³)C(O)₂R³, -C(=O)R³, optionally substituted aryl, optionally substituted arylakyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycl, optionally substituted heterocyclalkyl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl.

[0036] In one example, the compound is according to paragraph [0023], wherein R⁴ is -H.

[0037] In another example, the compound is according to paragraph [0036], wherein L¹ and L² are both -C(R³)=C(R³)-.

[0038] In another example, the compound is according to paragraph [0037], wherein L¹ and L² are both E- -C(R³)=C(R³)-.

[0039] In another example, the compound is according to paragraph [0038], of formula II,



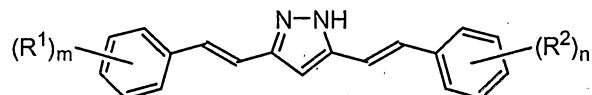
II

[0040] wherein each of R¹ and R² is independently selected from -H, halogen, haloalkyl, haloalkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -SO₂N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³,

$-C(=NR^5)R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)C(O)_2R^3$, $-NCO_2R^3$, $-C(=O)R^3$, optionally substituted alkoxy, optionally substituted lower alkyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycl or optionally substituted aryl;

[0041] each of A and B is a radical independently selected from the group consisting of phenyl, benzothiophenyl, pyridyl, pyrazinyl, benzofuranyl, benzpyrazolyl, benzoxazolyl, naphthyl, benzimidazolyl, indolyl, and biphenyl.

[0042] In another example, the compound is according to paragraph [0039], of formula IIa,



IIa

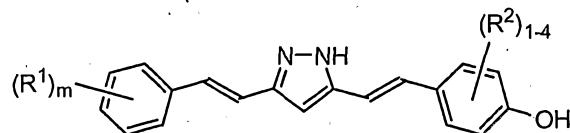
wherein each of R^1 and R^2 is independently selected from -H, halogen, haloalkyl, haloalkoxy, $-CN$, $-NO_2$, $-OR^3$, $-N(R^3)R^3$, $-S(O)_{0-2}R^3$, $-N(R^3)C(=O)N(R^3)R^3$, $-N(R^3)C(=O)C(=O)N(R^3)R^3$, $-SO_2N(R^3)R^3$, $-CO_2R^3$, $-C(=O)N(R^3)R^3$, $-C(=NR^5)N(R^3)R^3$, $-C(=NR^5)R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)C(O)_2R^3$, $-NCO_2R^3$, $-C(=O)R^3$, optionally substituted aryl, optionally substituted alkoxy, optionally substituted lower alkyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocycl or optionally substituted aryl.

[0043] In another example, the compound is according to paragraph [0042], wherein each of R^1 and R^2 is independently selected from -H, halogen, haloalkyl, haloalkoxy, $-CN$, $-NO_2$, $-OR^3$, $-N(R^3)R^3$, $-C(=O)R^3$, or optionally substituted lower alkyl.

[0044] In another example, the compound is according to paragraph [0043], wherein R^1 is selected from -H, halogen, haloalkyl, haloalkoxy, $-CN$, $-NO_2$, and optionally substituted lower alkyl; and R^2 is selected from -H, $-OR^3$, $-N(R^3)R^3$, or optionally substituted lower alkyl.

[0045] In another example, the compound is according to paragraph [0044], wherein R^1 is selected from -H, halogen, haloalkyl or haloalkoxy; and R^2 is selected from -H, $-OR^3$, $-N(R^3)R^3$, or optionally substituted lower alkyl.

[0046] In another example, the compound is according to paragraph [0045], of formula III,



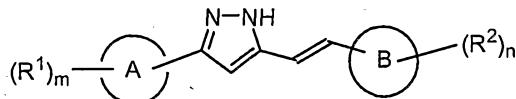
III

wherein R^1 is selected from -H, halogen, haloalkyl or haloalkoxy; and R^2 is selected from -H, -OR³, -N(R³)R³, or optionally substituted lower alkyl.

[0047] In another example, the compound is according to paragraph [0036], wherein L¹ is absent and L² is -C(R³)=C(R³)-.

[0048] In another example, the compound is according to paragraph [0047], wherein L¹ is absent and L² is -C(H)=C(H)-.

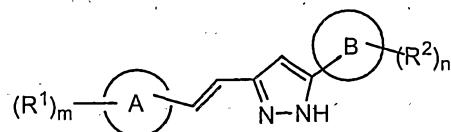
[0049] In another example, the compound is according to paragraph [0048], of formula IV,



IV

wherein each of R¹ and R² is independently selected from -H, halogen, haloalkyl, haloalkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -SO₂N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -N(R³)C(O)₂R³, -NCO₂R³, -C(=O)R³, optionally substituted alkoxy, optionally substituted heterocyclyl, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted cycloalkyl; and each A and B is a radical independently selected from phenyl, benzothiophenyl, pyridyl, pyrazinyl, benzofuranyl, naphthyl, benzimidazolyl, indolyl, or biphenyl.

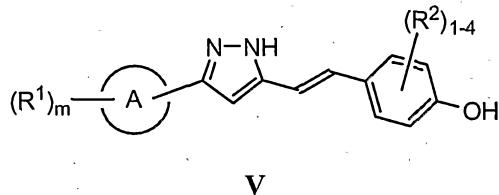
[0050] In another example, the compound is according to paragraph [0049], of formula IVa,



IVa

wherein each of R^1 and R^2 is independently selected from -H, halogen, haloalkyl, haloalkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -SO₂N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -N(R³)C(O)₂R³, -NCO₂R³, -C(=O)R³, optionally substituted alkoxy, optionally substituted heterocycl, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted cycloalkyl; and each A and B is a radical independently selected from the group consisting of phenyl, benzothiophenyl, pyridyl, pyrazinyl, benzofuranyl, benzpyrazolyl, benzoxazolyl, naphthyl, benzimidazolyl, indolyl, and biphenyl.

[0051] In another example, the compound is according to paragraph [0050], of formula V,



wherein each of R^1 and R^2 is independently selected from -H, halogen, haloalkyl, haloalkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -CO₂R³, -C(=O)N(R³)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -N(R³)C(O)₂R³, -NCO₂R³, -C(=O)R³, optionally substituted alkoxy, optionally substituted heterocycl, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted cycloalkyl; and A is a radical selected from phenyl, benzothiophenyl, pyridyl, benzofuranyl, benzimidazolyl, or indolyl.

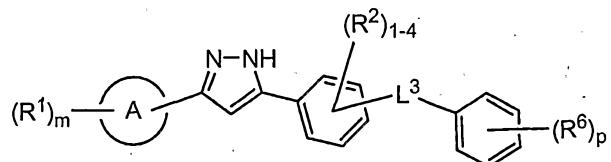
[0052] In another example, the compound is according to paragraph [0051], wherein A is either phenyl or 2-benzimidazolyl.

[0053] In another example, the compound is according to paragraph [0052], wherein A is substituted with at least one of -N(R³)R³, an optionally substituted heteroalicycyl, or a lower alkyl substituted with at least one of -N(R³)R³.

[0054] In another example, the compound is according to paragraph [0036], wherein L¹ and L² are both absent.

[0055] In another example, the compound is according to paragraph [0054], wherein A is a six- or nine-membered aryl or heteroaryl and B is a six-membered aryl or heteroaryl.

[0056] In another example, the compound is according to paragraph [0055], of formula VI,



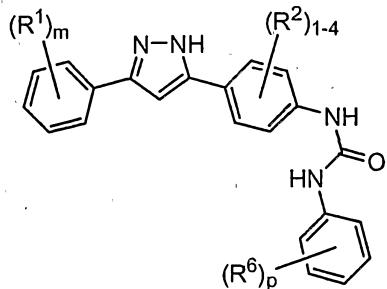
VI

wherein each of R¹, R² and R⁶ is independently selected from -H, halogen, haloalkyl, haloalkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -N(R³)C(=S)N(R³)R³, -SO₂N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -N(R³)C(O)₂R³, -NCO₂R³, -C(=O)R³, optionally substituted alkoxy, optionally substituted heterocycl, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted cycloalkyl; p is one to five; A is a radical selected from phenyl, benzothiophenyl, pyridyl, pyrazinyl, benzofuranyl, benzimidazolyl, or indolyl; L³ is selected from absent, -(CH₂)₀₋₁N(R³)C(=O)N(R³)-, -N(R³)C(=O)N(R³)(CH₂)₀₋₁-, -(CH₂)₀₋₁N(R³)C(=O)-, -N(R³)C(=O)(CH₂)₀₋₁-, -(CH₂)₀₋₁SO₂N(R³)-, -SO₂N(R³)(CH₂)₀₋₁-, -C(=NR⁵)N(R³)-, -C(=NR⁵)-, -(CH₂)₀₋₁N(R³)CO₂-, -N(R³)CO₂(CH₂)₀₋₁-, -C(=O)-, -CO₂-, -(CH₂)₀₋₁N(R³)C(=NR⁵)N(R³)-, or -(CH₂)₀₋₁N(R³)-.

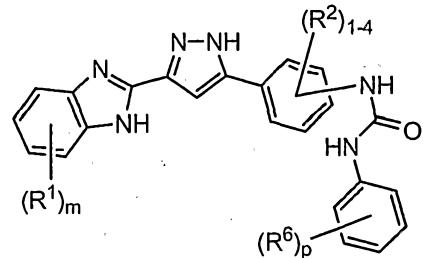
[0057] In another example, the compound is according to paragraph [0056], wherein when A is phenyl, L³ is -N(R³)C(=O)N(R³)-.

[0058] In another example, the compound is according to paragraph [0057], wherein A is either phenyl or benzimidazolyl.

[0059] In another example, the compound is according to paragraph [0058], of either formula VIIa or VIIb,



VIIa

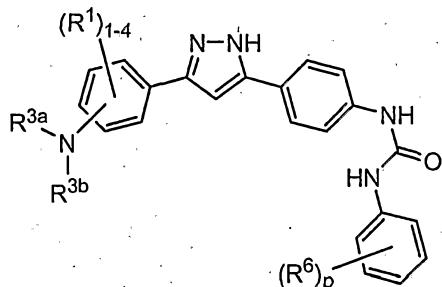


VIIb

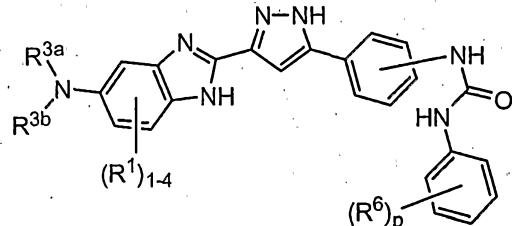
wherein R¹ is selected from -H, halogen, haloalkyl, haloalkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -CO₂R³, -C(=O)N(R³)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -NCO₂R³, -C(=O)R³, optionally substituted alkoxy, optionally substituted heterocycl, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted cycloalkyl; m is one to five; R² is selected from -H, halogen, haloalkyl, -CN, -NO₂, -OR³, -N(R³)R³, or optionally substituted lower alkyl; R⁶ is selected from -H, halogen, haloalkyl, -CN, -NO₂, -OR³, -S(O)₀₋₂R³, -N(R³)C(=O)C(=O)N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -NCO₂R³, -C(=O)R³, optionally substituted alkoxy, optionally substituted heterocycl, or optionally substituted lower alkyl; p is one to five.

[0060] In another example, the compound is according to paragraph [0059] wherein the phenyl urea in VIIb is either *meta*- or *para*- to the pyrazole moiety.

[0061] In another example, the compound is according to paragraph [0060], of either formula VIIc or VIId,



VIIc



VIId

wherein R¹ is selected from -H, halogen, haloalkyl, haloalkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -CO₂R³, -C(=O)N(R³)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -NCO₂R³, -C(=O)R³,

optionally substituted alkoxy, optionally substituted heterocyclyl, or optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, or optionally substituted cycloalkyl; R^{3a} and R^{3b} are each independently selected from -H or optionally substituted lower alkyl; optionally R^{3a} and R^{3b}, together with the nitrogen to which they are attached, combine to form an optionally substituted heteroalicycyl containing between one and two additional heteroatoms; R⁶ is selected from -H, halogen, haloalkyl, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)C(=O)N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -NCO₂R³, -C(=O)R³, optionally substituted alkoxy, optionally substituted heterocyclyl, or optionally substituted lower alkyl; p is one to five;

[0062] In another example, the compound is according to paragraph [0061], wherein for formula VIIc, -N(R^{3a})R^{3b} is either *meta*- or *para*- to the pyrazole moiety; and the phenyl urea in VIId is either *meta*- or *para*- to the pyrazole moiety.

[0063] In another example, the compound is according to paragraph [0023], selected from Table 1.

Table 1

Entry	Name	Structure
1	4-((E)-2-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}ethenyl)phenol	
2	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
3	N-(3-ethylphenyl)-N'-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
4	N-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(3-(trifluoromethyl)phenyl)urea	

Table 1

Entry	Name	Structure
5	N-(3-acetylphenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
6	N-(3,4-dichlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
7	N-(3-bromophenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
8	N-[4-fluoro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
9	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(4-(phenyloxy)phenyl)urea	
10	N-(3-chlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
11	N-[3,5-bis(methoxy)phenyl]-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	

Table 1

Entry	Name	Structure
12	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-{4-[(trifluoromethyl)oxy]phenyl}urea	
13	N-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-[4-(trifluoromethyl)phenyl]urea	
14	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
15	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea	
16	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	
17	N-(3,4-dimethylphenyl)-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	
18	N-(4-chlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	

Table 1

Entry	Name	Structure
19	N-(3,5-difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
20	N-[3-(methoxy)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
21	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[4-(4-ethylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	
22	N-(3-fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
23	N-(4-fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
24	N-(3-cyanophenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
25	N-(3,4-difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	

Table 1

Entry	Name	Structure
26	N-[3,4-bis(methoxy)phenyl]-N'-{4-[3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl]urea	
27	N-[5-chloro-2-(methoxy)phenyl]-N'-{4-[5-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl]urea	
28	N-(4-[5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]phenyl)-N'-[4-(phenyloxy)phenyl]urea	
29	N-(2,4-difluorophenyl)-N'-{4-[3-[6-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl]urea	
30	N-{4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea	
31	N-{4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea	
32	N-(2,4-difluorophenyl)-N'-{4-[3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl]urea	

Table 1

Entry	Name	Structure
33	N-{4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-phenylurea	
34	N-[3,5-bis(trifluoromethyl)phenyl]-N'-(4-[3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl]phenyl)urea	
35	N-(2-fluorophenyl)-N'-(4-[3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl]phenyl)urea	
36	4-((E)-2-{5-[(E)-2-phenylethenyl]-1H-pyrazol-3-yl}ethenyl)phenol	
37	2-(methoxy)-4-((E)-2-{5-[(E)-2-phenylethenyl]-1H-pyrazol-3-yl}ethenyl)phenol	
38	N-(5-fluoro-2-methylphenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
39	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-phenylurea	

Table 1

Entry	Name	Structure
40	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[3-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	
41	N-(2,4-difluorophenyl)-N'-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	
42	N-(2,3-dihydro-1,4-benzodioxin-6-yl)-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	
43	N-[2,4-bis(methyloxy)phenyl]-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	
44	4-((E)-2-{3-[(E)-2-(4-fluorophenyl)ethenyl]-1H-pyrazol-5-yl}ethenyl)-2-(methyloxy)phenol	
45	4-((E)-2-[3-(1-benzofuran-2-yl)-1H-pyrazol-5-yl]ethenyl)phenol	
46	N-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)-N'-(2-phenylethyl)ethanediamide	

Table 1

Entry	Name	Structure
47	4-{(E)-2-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]ethenyl}phenol	
48	4-((E)-2-{3-[(E)-2-(4-chlorophenyl)ethenyl]-1H-pyrazol-5-yl} ethenyl)-2-(methyloxy)phenol	
49	4-{(E)-2-[3-(1-benzothien-2-yl)-1H-pyrazol-5-yl]ethenyl}phenol	
50	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-(3-phenyl-1H-pyrazol-5-yl)phenyl)urea	
51	4-((E)-2-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl} ethenyl)phenol	
52	1,1-dimethylethyl {4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl} carbamate	
53	N-(5-fluoro-2-methylphenyl)-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	
54	4-[(E)-2-(3-phenyl-1H-pyrazol-5-yl)ethenyl]phenol	

Table 1

Entry	Name	Structure
55	2-(methyloxy)-4-[(E)-2-(5-phenyl-1H-pyrazol-3-yl)ethenyl]phenol	
56	4-[(E)-2-(5-naphthalen-2-yl-1H-pyrazol-3-yl)ethenyl]phenol	
57	4-[(E)-2-[5-(2-fluorophenyl)-1H-pyrazol-3-yl]ethenyl]phenol	
58	4-[(E)-2-{3-[3-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}ethenyl]phenol	
59	4-[(E)-2-{3-[(E)-2-(2,4-difluorophenyl)ethenyl]-1H-pyrazol-5-yl}ethenyl]-2-(methyloxy)phenol	
60	4-[(E)-2-[5-(4-fluorophenyl)-1H-pyrazol-3-yl]ethenyl]phenol	
61	4-[(E)-2-[3-(4-chlorophenyl)-1H-pyrazol-5-yl]ethenyl]phenol	
62	4-[(E)-2-(5-pyridin-2-yl-1H-pyrazol-3-yl)ethenyl]phenol	
63	4-[(E)-2-[3-(5-chloro-1-benzofuran-2-yl)-1H-pyrazol-5-yl]ethenyl]phenol	

Table 1

Entry	Name	Structure
64	N-(1,1-dimethylethyl)-N'-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
65	4-[(E)-2-(3-pyridin-4-yl-1H-pyrazol-5-yl)ethenyl]phenol	
66	4-[(E)-2-[3-(3-chlorophenyl)-1H-pyrazol-5-yl]ethenyl]phenol	
67	4-[(E)-2-{5-[2-(methyloxy)phenyl]-1H-pyrazol-3-yl}ethenyl]phenol	
68	4-[(E)-2-[3-(2-chlorophenyl)-1H-pyrazol-5-yl]ethenyl]phenol	
69	4-[(E)-2-(3-pyridin-3-yl-1H-pyrazol-5-yl)ethenyl]phenol	
70	4-[(E)-2-{5-[3-(methyloxy)phenyl]-1H-pyrazol-3-yl}ethenyl]phenol	
71	1,1-dimethylethyl (4-{3-[(E)-2-phenylethenyl]-1H-pyrazol-5-yl}phenyl)carbamate	

Table 1

Entry	Name	Structure
72	4-{(E)-2-[3-(3,4-dichlorophenyl)-1H-pyrazol-5-yl]ethenyl}phénol	
73	2-{5-[(E)-2-phenylethenyl]-1H-pyrazol-3-yl}-1-benzofuran-6-ol	
74	4-{(E)-2-[5-(3-fluorophenyl)-1H-pyrazol-3-yl]ethenyl}phenol	
75	2-(5-phenyl-1H-pyrazol-3-yl)-1H-benzimidazole	
76	N-phenyl-N'-[4-(3-phenyl-1H-pyrazol-5-yl)phenyl]urea	
77	4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]aniline	
78	4-[(E)-2-(5-biphenyl-3-yl)-1H-pyrazol-3-yl]ethenylphenol	
79	4-((E)-2-{5-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-3-yl}ethenyl)phenol	

[0064] Another aspect of the invention is a pharmaceutical composition comprising the compound according to any one of paragraphs [0023]-[0063] and a pharmaceutically acceptable carrier.

[0065] Another aspect of the invention is a metabolite of the compound or the pharmaceutical composition according to any one of paragraphs [0023]-[0064].

[0066] Another aspect of the invention is a method of modulating the *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of a composition comprising at least one of the compound according to any of paragraphs [0023]-[0063] and the pharmaceutical composition according to paragraph [0064].

[0067] Another aspect of the invention is the method according to paragraph [0066], wherein the kinase is selected from c-Kit and flt-3.

[0068] Another aspect of the invention is the method according to paragraph [0067], wherein modulating the *in vivo* activity of said kinase comprises inhibition of said kinase.

[0069] Another aspect of the invention is a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of a composition comprising at least one of the compound according to any of paragraphs [0023]-[0063] and the pharmaceutical composition according to paragraph [0064].

[0070] Another aspect of the invention is a method of screening for modulator of a kinase, the method comprising combining either a composition comprising at least one of the compound according to any of paragraphs [0023]-[0063] and the pharmaceutical composition according to paragraph [0064], and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase.

[0071] Another aspect of the invention is a method of inhibiting proliferative activity in a cell or a plurality of cells, the method comprising administering an effective amount of at least one of the compound according to any of paragraphs [0023]-[0063] and the pharmaceutical composition according to paragraph [0064] to said cell or plurality of cells.

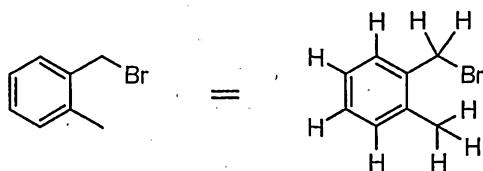
Definitions

[0072] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

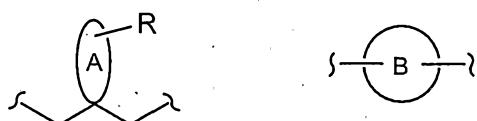
[0073] The symbol “-” means a single bond, “=” means a double bond, “≡” means a triple bond. The symbol “~” refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached; that is, the geometry, *E*- or *Z*-, of the double bond is ambiguous. When a double bond is depicted in textual format, for example -C(H)=C(H)-, then this is meant to construe both *E*- and *Z*- geometries. When a group is depicted removed from its parent formula, the “~” symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

[0074] Chemical formulae use descriptors such as “R¹” accompanied by a list of formulae or verbage describing the scope of what is meant by the descriptor. A subsequent descriptor such as “R^{1a}” is used to describe some subset of the scope of R¹, and “R^{1b}” is used to describe another subset of the scope of R¹, and so on. In such subsequent cases, all other formulae containing simply “R¹” are meant to include the entire scope of the descriptor.

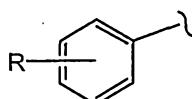
[0075] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, -CH₂CH₂- . It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.



[0076] In this application, some ring structures are depicted generically and will be described textually. For example, in the schematic below, if in the structure on the left, ring A is used to describe a "spirocyclyl," then if ring A is cyclopropyl, there are at most four hydrogens on ring A (when "R" can also be -H). In another example, as depicted on the right side of the schematic below, if ring B is used to describe a "phenylene" then there can be at most four hydrogens on ring B (assuming depicted cleaved bonds are not C-H bonds).

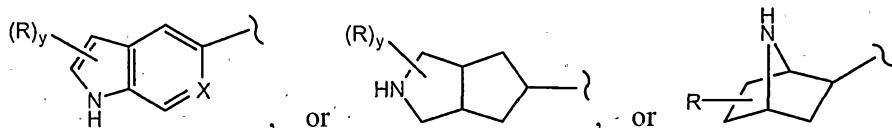


[0077] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



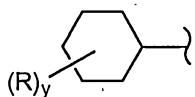
then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[0078] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:

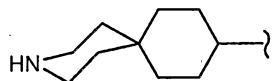


then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "X" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0079] When a group “R” is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, “y” can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two “R’s” may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an “annular” carbon). In another example, two R’s on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a “spirocyclyl” group) structure with the depicted ring as for example in the formula:



[0080] “Alkyl” is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof, inclusively. For example, “C₈ alkyl” may refer to an *n*-octyl, *iso*-octyl, cyclohexylethyl, and the like. Lower alkyl refers to alkyl groups of from one to six carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, isobutyl, pentyl, hexyl and the like. Higher alkyl refers to alkyl groups containing more than eight carbon atoms. Exemplary alkyl groups are those of C₂₀ or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from three to thirteen carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like. In this application, alkyl refers to alkanyl, alkenyl, and alkynyl residues (and combinations thereof); it is intended to include cyclohexylmethyl, vinyl, allyl, isoprenyl, and the like. Thus, when an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of *carbons* are intended to be encompassed; thus, for example, either “butyl” or “C₄alkyl” is meant to include *n*-butyl, *sec*-butyl, isobutyl, *t*-butyl, isobutetyl and but-2-yne radicals; and for example, “propyl” or “C₃alkyl” each include *n*-propyl, propenyl, and isopropyl. Otherwise, if alkenyl and/or alkynyl descriptors *are used* in a particular definition of a group, for example “C₄alkyl” along “C₄alkenyl,” then C₄alkenyl geometric isomers are not meant to be included in “C₄alkyl,” but

other 4-carbon isomers are, for example C_4 alkynyl. For example, a more general description, intending to encompass the invention as a whole may describe a particular group as “ C_{1-8} alkyl” while a preferred species may describe the same group as including, “ C_{1-8} alkyl,” “ C_{1-6} alkenyl” and “ C_{1-5} alkynyl.”

[0081] “Alkylene” refers to straight or branched chain divalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to ten carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene and the like. Alkylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, fully saturated. Examples of alkylene include ethylene (- CH_2CH_2 -), propylene (- $CH_2CH_2CH_2$ -), dimethylpropylene (- $CH_2C(CH_3)_2CH_2$ -), and cyclohexylpropylene (- $CH_2CH_2CH(C_6H_{13})$).

[0082] “Alkylidene” refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to ten carbon atoms, for example, ethylidene, propylidene, *n*-butylidene, and the like. Alkylidene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, double bond unsaturation. The unsaturation present includes at least one double bond.

[0083] “Alkylidyne” refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms having from two to ten carbon atoms, for example, propylid-2-ynyl, *n*-butylid-1-ynyl, and the like. Alkylidyne is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, triple bond unsaturation. The unsaturation present includes at least one triple bond.

[0084] Any of the above radicals, “alkylene,” “alkylidene” and “alkylidyne,” when optionally substituted, may contain alkyl substitution which itself contains unsaturation. For example, 2-(2-phenylethynyl-but-3-enyl)-naphthalene (IUPAC name) contains an *n*-butylid-3-ynyl radical with a vinyl substituent at the 2-position of said radical.

[0085] “Alkoxy” or “alkoxyl” refers to the group -O-alkyl, for example including from one to eight carbon atoms of a straight, branched, cyclic configuration, unsaturated chains, and combinations thereof attached to the parent structure through an oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropoxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to six carbons.

[0086] “Substituted alkoxy” refers to the group -O-(substituted alkyl), the substitution on the alkyl group generally containing more than only carbon (as defined by alkoxy). One exemplary substituted alkoxy group is “polyalkoxy” or -O-optionally substituted alkylene-optionally substituted alkoxy, and includes groups such as -OCH₂CH₂OCH₃, and glycol ethers such as polyethyleneglycol and -O(CH₂CH₂O)_xCH₃, where x is an integer of between about two and about twenty, in another example, between about two and about ten, and in a further example between about two and about five. Another exemplary substituted alkoxy group is hydroxyalkoxy or -OCH₂(CH₂)_yOH, where y is for example an integer of between about one and about ten, in another example y is an integer of between about one and about four.

[0087] “Acyl” refers to groups of from one to ten carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, *t*-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to six carbons.

[0088] “ α -Amino Acids” refer to naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available α -amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, ornithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, ortho-tyrosine, meta-tyrosine, para-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. A “side chain of an α -amino acid” refers to the radical found on the α -carbon of an α -amino acid as defined above, for example, hydrogen (for glycine), methyl (for alanine), benzyl (for phenylalanine), and the like.

[0089] “Amino” refers to the group -NH₂. “Substituted amino,” refers to the group -N(H)R or -N(R)R where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted

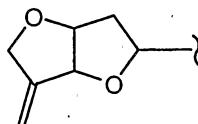
heterocyclyl, acyl, carboxy, alkoxy carbonyl, sulfanyl, sulfinyl and sulfonyl, for example, diethylamino, methylsulfonylamino, and furanyl-oxy-sulfonamino.

[0090] “Aryl” refers to aromatic six- to fourteen-membered carbocyclic ring, for example, benzene, naphthalene, indane, tetralin, fluorene and the like, univalent radicals. As univalent radicals, the aforementioned ring examples are named, phenyl, naphthyl, indanyl, tetralinyl, and fluorenyl.

[0091] “Arylene” generically refers to any aryl that has at least two non-hydrogen groups attached thereto. For a more specific example, “phenylene” refers to a divalent phenyl ring radical. A phenylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto. The terms “ortho-arylene,” “meta-arylene” or “para-arylene” refer to geometrical isomers of a particular arylene wherein, two groups attached to an aryl as depicted in a formula are situated in an ortho, meta or para geometrical relationship about the aryl, respectively.

[0092] “Arylalkyl” refers to a residue in which an aryl moiety is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. Both the aryl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of an arylalkyl group may be optionally substituted. “Lower arylalkyl” refers to an arylalkyl where the “alkyl” portion of the group has one to six carbons; this can also be referred to as aryl C₁₋₆alkyl.

[0093] “Exo-alkenyl” refers to a double bond that emanates from an annular carbon, and is not within the ring system, for example the double bond depicted in the formula below.



[0094] In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (i.e. saturated ring structures) can contain two substitution groups.

[0095] “Fused-polycyclic” or “fused ring system” refers to a polycyclic ring system that contains bridged or fused rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems are not necessarily all aromatic ring systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the invention may themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic.

[0096] “Halogen” or “halo” refers to fluorine, chlorine, bromine or iodine. “Haloalkyl” and “haloaryl” refer generically to alkyl and aryl radicals that are substituted with one or more halogens, respectively. Thus, “dihaloaryl,” “dihaloalkyl,” “trihaloaryl” etc. refer to aryl and alkyl substituted with a plurality of halogens, but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[0097] “Heteroarylene” generically refers to any heteroaryl that has at least two groups attached thereto. For a more specific example, “pyridylene” refers to a divalent pyridyl ring radical. A pyridylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto. For the purposes of this application, the term “ortho-heteroarylene” refers to a geometrical isomer of a particular heteroarylene wherein two groups attached to a heteroaryl as depicted in a formula are situated on contiguous atoms of the heteroaryl.

[0098] “Heteroatom” refers to O, S, N, or P.

[0099] “Heterocyclyl” refers to a stable three- to fifteen-membered ring radical that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems as well as spirocyclic systems; and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized to various oxidation states. In a specific example, the group $-S(O)_{0-2}-$, refers to $-S-$ (sulfide), $-S(O)-$ (sulfoxide), and $-SO_2-$ (sulfone). For convenience, nitrogens, particularly but not exclusively, those defined as annular aromatic nitrogens, are meant to include their corresponding *N*-oxide form, although

not explicitly defined as such in a particular example. Thus, for a compound of the invention having, for example, a pyridyl ring; the corresponding pyridyl-*N*-oxide is meant to be included as another compound of the invention. In addition, annular nitrogen atoms may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of heterocyclyl radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzpyrazolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothieliyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, and oxadiazolyl.

[0100] “Heteroalicyclic” refers specifically to a non-aromatic heterocyclyl radical. A heteroalicyclic may contain unsaturation, but is not aromatic.

[0101] “Heteroaryl” refers specifically to an aromatic heterocyclyl radical.

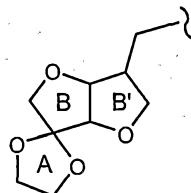
[0102] “Heterocyclalkyl” refers to a residue in which a heterocyclyl is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include (4-methylpiperazin-1-yl) methyl, (morpholin-4-yl) methyl, (pyridine-4-yl) methyl, 2-(oxazolin-2-yl) ethyl, 4-(4-methylpiperazin-1-yl)-2-butenyl, and the like. Both the heterocyclyl and the corresponding alkylene, alkylidene, or alkylidyne radical portion of a heterocyclalkyl group may be optionally substituted. “Lower heterocyclalkyl” refers to a heterocyclalkyl where the “alkyl” portion of the group has one to six carbons. “Heteroalicyclylalkyl” refers specifically to a heterocyclalkyl where the heterocyclyl portion of the group is non-aromatic; and “heteroarylalkyl” refers specifically to a heterocyclalkyl where the heterocyclyl portion of the group is aromatic. Such terms may be

described in more than one way, for example, "lower heterocyclylalkyl" and "heterocyclyl C₁₋₆alkyl" are equivalent terms.

[0103] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that, with respect to any molecule described as containing one or more optional substituents, that only sterically practical and/or synthetically feasible compounds are meant to be included. "Optionally substituted" refers to all subsequent modifiers in a term, for example in the term "optionally substituted aryl C₁₋₈alkyl," optional substitution may occur on both the "C₁₋₈alkyl" portion and the "aryl" portion of the molecule; and for example, optionally substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*. A list of exemplary optional substitutions is included below in the definition of "substituted."

[0104] "Saturated bridged ring system" refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-aza-bicyclo[2.2.1]heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class "saturated bridged ring system."

[0105] "Spirocyclyl" or "spirocyclic ring" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B'), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto. A spirocyclyl can be carbocyclic or heteroalicyclic.



[0106] "Substituted" alkyl, aryl, and heterocyclyl, refer respectively to alkyl, aryl, and heterocyclyl, wherein one or more (for example up to about five, in another example, up to

about three) hydrogen atoms are replaced by a substituent independently selected from: optionally substituted alkyl (for example, fluoromethyl, hydroxypropyl, nitromethyl, aminoethyl and the like.), optionally substituted aryl (for example, 4-hydroxyphenyl, 2,3-difluorophenyl, and the like), optionally substituted arylalkyl (for example, 1-phenyl-ethyl, *para*-methoxyphenylethyl and the like), optionally substituted heterocyclalkyl (for example, 1-pyridin-3-yl-ethyl, N-ethylmorpholino and the like), optionally substituted heterocyclyl (for example, 5-chloro-pyridin-3-yl, 1-methyl-piperidin-4-yl and the like), optionally substituted alkoxy (for example methoxyethoxy, hydroxypropoxy, methylenedioxy and the like), optionally substituted amino (for example, methylamino, diethylamino, trifluoroacetylarnino and the like), optionally substituted amidino, optionally substituted aryloxy (for example, phenoxy, *para*-chlorophenoxy, *meta*-aminophenoxy, *para*-phenoxyphenoxy and the like), optionally substituted arylalkyloxy (for example, benzyloxy, 3-chlorobenzylxy, *meta*-phenoxybenzyloxy and the like), carboxy (-CO₂H), optionally substituted carboalkoxy (that is, acyloxy or -OC(=O)R), optionally substituted carboxamido, optionally substituted benzyloxycarbonylarnino (CBZ-amino), cyano, optionally substituted acyl, halogen, hydroxy, nitro, optionally substituted alkylsulfanyl, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, thiol, oxo, carbamyl, optionally substituted acylarnino, optionally substituted hydrazino, optionally substituted hydroxylarnino, and optionally substituted sulfonamido.

[0107] “Sulfanyl” refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), and -S-(optionally substituted heterocyclyl).

[0108] “Sulfinyl” refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-optionally substituted aryl), and -S(O)-(optionally substituted heterocyclyl).

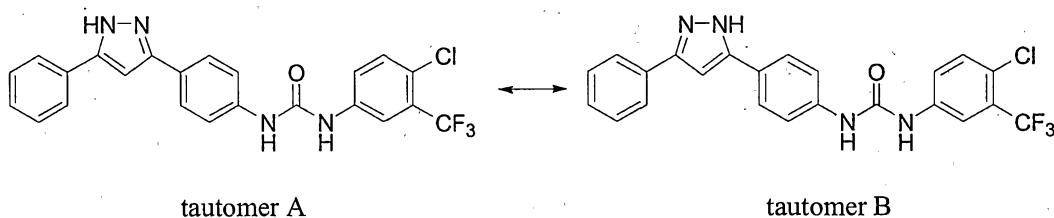
[0109] “Sulfonyl” refers to the groups: -S(O₂)-H, -S(O₂)-(optionally substituted alkyl), -S(O₂)-optionally substituted aryl), -S(O₂)-(optionally substituted heterocyclyl), -S(O₂)-(optionally substituted alkoxy), -S(O₂)-optionally substituted aryloxy), and -S(O₂)-(optionally substituted heterocyclxyloxy).

[0110] “Yield” for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0111] Some of the compounds of the invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocycl systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, i.e., amino, imino, hydroxy or oxo, respectively.

[0112] Compounds of the invention are named according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS).

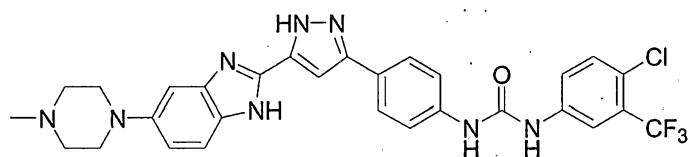
[0113] Tautomers. As known to one of ordinary skill in the art, compounds can exist in tautomeric forms. Of particular relevance to this invention is the possibility of tautomeric forms of pyrazoles, benzimidazoles, and 1,3-diketones, for example. An exemplary depiction of pyrazole tautomerism is shown below.



[0114] In this application, a compound may be drawn in a particular tautomeric form for illustrative purposes, however such illustrations are meant to include all tautomeric forms. Note, the tautomeric form in which a compound is drawn also determines, for example, the IUPAC name of the compound. As depicted above, tautomers A and B have different IUPAC names (other naming schemes may also generate distinct names for particular tautomers). Under the IUPAC system, tautomer A is *N*-[4'-chloro-3-(trifluoromethyl)phenyl]-*N'*-[4-(5-phenyl-1*H*-pyrazol-3-yl)phenyl]urea, and tautomer B is *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N*'-[4-(3-phenyl-1*H*-pyrazol-5-yl)phenyl]urea. One of ordinary skill in the art would understand that these names (and tautomeric representations) are meant to describe the same compound.

[0115] The tautomer/name issue is seemingly more complex when various parts of a molecule each have possible tautomers. For example the compound depicted below (a compound of the invention) has four different tautomeric forms each with a corresponding unique IUPAC name. The compound, depending on how its pyrazole and benzimidazole

moiety tautomers are drawn, can be named as *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{5-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-3-yl}phenyl)urea, *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{5-[4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-3-yl}phenyl)urea, *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea or *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea. Thus in this description, particular tautomeric illustrations and names are used for convenience purposes. Such illustrations and names are meant to include all tautomeric forms of the particular molecule indicated



[0116] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

[0117] The compounds of the invention and their pharmaceutically acceptable salts may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

[0118] It is assumed that when considering generic descriptions of compounds of the invention for the purpose of constructing a compound, such construction results in the creation of a stable structure. That is, one of ordinary skill in the art would recognize that there can theoretically be some constructs which would not normally be considered as stable compounds (that is, sterically practical and/or synthetically feasible, *supra*).

[0100] When a particular group with its bonding structure is denoted as being bonded to two partners; that is, a divalent radical, for example, -OCH₂- , then it is understood that either of the two partners may be bound to the particular group at one end, and the other partner is necessarily bound to the other end of the particular group, unless stated explicitly otherwise. Stated another way, divalent radicals are not to be construed as limited to the depicted

orientation, for example “-OCH₂-” is meant to mean not only “-OCH₂-” as drawn, but also “-CH₂O-.”

[0101] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[0102] “Patient” for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In a preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[0103] “Kinase-dependent diseases or conditions” refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion. Diseases associated with kinase activities include tumor growth, the pathologic neovascularization that supports solid tumor growth, and associated with other diseases where excessive local vascularization is

involved such as ocular diseases (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

[0104] While not wishing to be bound to theory, phosphatases can also play a role in “kinase-dependent diseases or conditions” as cognates of kinases; that is, kinases phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore compounds of the invention, while modulating kinase activity as described herein, may also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, may be synergistic (or not) to activity of compounds of the invention toward a related or otherwise interdependent kinase or kinase family. In any case, as stated previously, the compounds of the invention are useful for treating diseases characterized in part by abnormal levels of cell proliferation (i.e. tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[0105] “Therapeutically effective amount” is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a “therapeutically effective amount” will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

[0106] “Cancer” refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [neuroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma,

adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendrogloma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, SertoliLeydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma [embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0107] "Pharmaceutically acceptable acid addition salt" refers to those salts that retain the biological effectiveness of the free bases and that are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, as well as organic acids such as acetic

acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0108] "Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Exemplary salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977;66:1-19 which is incorporated herein by reference.)

[0109] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) wherein the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V.

Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0110] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[0111] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0112] In addition, it is intended that the present invention cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry or by biological methods, such as bacterial digestion, metabolism, enzymatic conversion, and the like.

[0113] "Treating" or "treatment" as used herein covers the treatment of a disease-state in a human, which disease-state is characterized by abnormal cellular proliferation, and invasion and includes at least one of: (i) preventing the disease-state from occurring in a human, in particular, when such human is predisposed to the disease-state but has not yet been diagnosed as having it; (ii) inhibiting the disease-state, i.e., arresting its development; and (iii) relieving the disease-state, i.e., causing regression of the disease-state. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health,

sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

[0114] One of ordinary skill in the art would understand that certain crystallized, protein-ligand complexes, in particular c-Kit and flt-3-ligand complexes, and their corresponding x-ray structure coordinates can be used to reveal new structural information useful for understanding the biological activity of kinases as described herein. As well, the key structural features of the aforementioned proteins, particularly, the shape of the ligand binding site, are useful in methods for designing or identifying selective modulators of kinases and in solving the structures of other proteins with similar features. Such protein-ligand complexes, having compounds of the invention as their ligand component, are an aspect of the invention.

[0115] As well, one of ordinary skill in the art would appreciate that such suitable x-ray quality crystals can be used as part of a method of identifying a candidate agent capable of binding to and modulating the activity of kinases. Such methods may be characterized by the following aspects: a) introducing into a suitable computer program, information defining a ligand binding domain of a kinase in a conformation (e.g. as defined by x-ray structure coordinates obtained from suitable x-ray quality crystals as described above) wherein the computer program creates a model of the three dimensional structures of the ligand binding domain, b) introducing a model of the three dimensional structure of a candidate agent in the computer program, c) superimposing the model of the candidate agent on the model of the ligand binding domain, and d) assessing whether the candidate agent model fits spatially into the ligand binding domain. Aspects a-d are not necessarily carried out in the aforementioned order. Such methods may further entail: performing rational drug design with the model of the three-dimensional structure, and selecting a potential candidate agent in conjunction with computer modeling.

[0116] Additionally, one of ordinary skill in the art would appreciate that such methods may further entail: employing a candidate agent, so-determined to fit spatially into the ligand binding domain, in a biological activity assay for kinase modulation, and determining whether said candidate agent modulates kinase activity in the assay. Such methods may also include administering the candidate agent, determined to modulate kinase activity, to a

mammal suffering from a condition treatable by kinase modulation, such as those described above.

[0117] Also, one of ordinary skill in the art would appreciate that compounds of the invention can be used in a method of evaluating the ability of a test agent to associate with a molecule or molecular complex comprising a ligand-binding domain of a kinase. Such a method may be characterized by the following aspects: a) creating a computer model of a kinase binding pocket using structure coordinates obtained from suitable x-ray quality crystals of the kinase, b) employing computational algorithms to perform a fitting operation between the test agent and the computer model of the binding pocket, and c) analyzing the results of the fitting operation to quantify the association between the test agent and the computer model of the binding pocket.

General Administration

[0118] Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[0119] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc. Compositions of the invention may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It

may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0120] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylaltd hydroxytoluene, etc.

[0121] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0122] One preferable route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[0123] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and

bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0124] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0125] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0126] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0127] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0128] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[0129] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[0130] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[0131] The compounds of the invention, or their pharmaceutically acceptable salts, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

Utility of compounds of the invention as screening agents

[0132] To employ the compounds of the invention in a method of screening for candidate agents that bind to, for example c-Kit or flt-3 receptor kinase, the protein is bound to a support, and a compound of the invention is added to the assay. Alternatively, the compound of the invention is bound to the support and the protein is added. Classes of candidate agents among which novel binding agents may be sought include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for candidate agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled *in vitro* protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

[0133] The determination of the binding of the candidate agent to, for example, c-Kit or flt-3 protein may be done in a number of ways. In one example, the candidate agent (the compound of the invention) is labeled, for example, with a fluorescent or radioactive moiety and binding determined directly. For example, thus may be done by attaching all or a portion of the c-Kit or flt-3 protein to a solid support, adding a labeled agent (for example a compound of the invention in which at least one atom has been replaced by a detectable isotope), washing off excess reagent, and determining whether the amount of the label is that present on the solid support. Various blocking and washing steps may be utilized as is known in the art.

[0134] By "labeled" herein is meant that the compound is either directly or indirectly labeled with a label which provides a detectable signal, for example, radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, and the like. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin, and the like. For the specific binding members, the complementary member would normally be labeled with a molecule which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

[0135] In some embodiments, only one of the components is labeled. For example, c-Kit or flt-3 protein may be labeled at tyrosine positions using ^{125}I , or with fluorophores. Alternatively, more than one component may be labeled with different labels; using ^{125}I for the proteins, for example, and a fluorophor for the candidate agents.

[0136] The compounds of the invention may also be used as competitors to screen for additional drug candidates. "candidate bioactive agent" or "drug candidate" or grammatical equivalents as used herein describe any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for bioactivity. They may be capable of directly or indirectly altering the cellular proliferation phenotype or the expression of a cellular proliferation sequence, including both nucleic acid sequences and protein sequences. In other cases, alteration of cellular proliferation protein binding and/or activity is screened. In the case where protein binding or activity is screened, some embodiments exclude molecules already known to bind to that particular protein. Exemplary embodiments of assays described herein include candidate agents, which do not bind the target protein in its endogenous native state, termed herein as "exogenous" agents. In one example, exogenous agents further exclude antibodies to c-Kit or flt-3.

[0137] Candidate agents can encompass numerous chemical classes, though typically they are organic molecules having a molecular weight of more than about 100 and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl, hydroxyl, ether, or carboxyl group, for example at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclyl structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs, or combinations thereof.

[0138] Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced.

Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification to produce structural analogs.

[0139] In one example, the binding of the candidate agent is determined through the use of competitive binding assays. In this example, the competitor is a binding moiety known to bind to c-Kit or flt-3, such as an antibody, peptide, binding partner, ligand, etc. Under certain circumstances, there may be competitive binding as between the candidate agent and the binding moiety, with the binding moiety displacing the candidate agent.

[0140] In some embodiments, the candidate agent is labeled. Either the candidate agent, or the competitor, or both, is added first to c-Kit or flt-3 protein for a time sufficient to allow binding, if present. Incubations may be performed at any temperature that facilitates optimal activity, typically between 4°C and 40°C.

[0141] Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

[0142] In one example, the competitor is added first, followed by the candidate agent. Displacement of the competitor is an indication the candidate agent is binding to c-Kit or flt-3 and thus is capable of binding to, and potentially modulating, the activity of the c-Kit or flt-3. In this embodiment, either component can be labeled. Thus, for example, if the competitor is labeled, the presence of label in the wash solution indicates displacement by the agent. Alternatively, if the candidate agent is labeled, the presence of the label on the support indicates displacement.

[0143] In an alternative embodiment, the candidate agent is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate the candidate agent is bound to c-Kit or flt-3 with a higher affinity. Thus, if the candidate agent is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate the candidate agent is capable of binding to c-Kit or flt-3.

[0144] It may be of value to identify the binding site of c-Kit or flt-3. This can be done in a variety of ways. In one embodiment, once c-Kit or flt-3 has been identified as binding to the candidate agent, the c-Kit or flt-3 is fragmented or modified and the assays repeated to identify the necessary components for binding.

[0145] Modulation is tested by screening for candidate agents capable of modulating the activity of c-Kit or flt-3 comprising the steps of combining a candidate agent with c-Kit or flt-3, as above, and determining an alteration in the biological activity of the c-Kit or flt-3. Thus, in this embodiment, the candidate agent should both bind to (although this may not be necessary), and alter its biological or biochemical activity as defined herein. The methods include both *in vitro* screening methods and *in vivo* screening of cells for alterations in cell viability, morphology, and the like.

[0146] Alternatively, differential screening may be used to identify drug candidates that bind to native c-Kit or flt-3, but cannot bind to modified c-Kit or flt-3.

[0147] Positive controls and negative controls can be used in the assays. For example, all control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of samples is for a time sufficient for the binding of the agent to the protein. Following incubation, samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent determined. For example, where a radiolabel is employed, the samples can be counted in a scintillation counter to determine the amount of bound compound.

[0148] A variety of other reagents can be included in the screening assays. These include reagents like salts, neutral proteins, e.g., albumin, detergents, etc which may be used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may be used. The mixture of components can be added in any order that provides for the requisite binding.

Abbreviations and their Definitions

[0149] The following abbreviations and terms have the indicated meanings throughout:

Abbreviation	Meaning
Ac	acetyl

Abbreviation	Meaning
ACN	acetonitrile
ATP	adenosine triphosphate
BNB	4-bromomethyl-3-nitrobenzoic acid
Boc	t-butyloxycarbonyl
br	broad
Bu	butyl
°C	degrees Celsius
c-	cyclo
CBZ	CarboBenZoxy = benzyloxycarbonyl
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DBU	Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane = methylene chloride = CH ₂ Cl ₂
DCE	dichloroethylene
DEAD	diethyl azodicarboxylate
DIC	diisopropylcarbodiimide
DIEA	N,N-diisopropylethyl amine
DMAP	4-N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DVB	1,4-divinylbenzene
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
EI	Electron Impact ionization
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
g	gram(s)
GC	gas chromatography
h or hr	hour(s)
HATU	O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazane
HOAc	acetic acid
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography
L	liter(s)
M	molar or molarity
m	multiplet
Me	methyl

Abbreviation	Meaning
mesyl	methanesulfonyl
mg	milligram(s)
MHz	megahertz (frequency)
Min	minute(s)
mL	milliliter(s)
mM	millimolar
mmol	millimole(s)
mol	mole(s)
MS	mass spectral analysis
MTBE	methyl t-butyl ether
N	normal or normality
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
nM	nanomolar
NMO	N-methylmorpholine oxide
NMR	nuclear magnetic resonance spectroscopy
PEG	polyethylene glycol
pEY	poly-glutamine, tyrosine
Ph	phenyl
PhOH	phenol
PfP	pentafluorophenol
PfPy	pentafluoropyridine
PPTS	Pyridinium p-toluenesulfonate
Py	pyridine
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	quartet
RT	Room temperature
Sat'd	saturated
s	singlet
s-	secondary
t-	tertiary
t or tr	triplet
TBDMS	t-butyldimethylsilyl
TES	triethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMOF	trimethyl orthoformate
TMS	trimethylsilyl

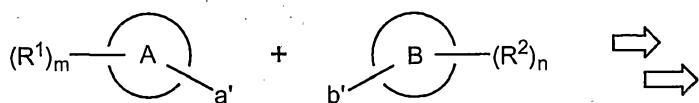
Abbreviation	Meaning
tosyl	p-toluenesulfonyl
Trt	triphenylmethyl
μL	microliter(s)
μM	Micromole(s) or micromolar

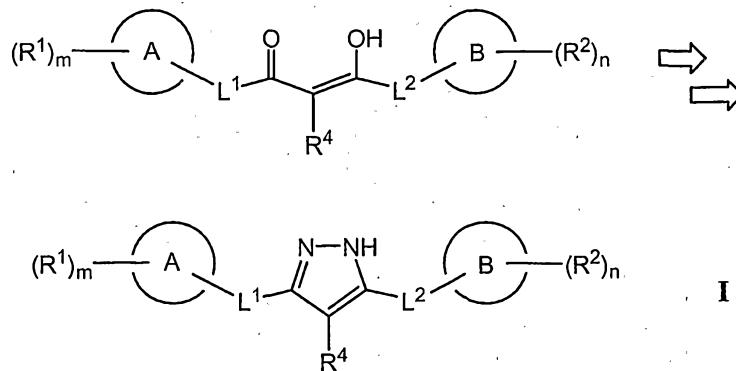
Compound Synthesis

[0150] Schemes 1 - 2 depict general synthetic routes for compounds of the invention and are not intended to be limiting. Specific examples are described subsequently to this general synthetic description. With the descriptions of the general routes and the specific examples thereafter, one of ordinary skill in the art would be able to make compounds of the invention as described.

[0151] Scheme 1 shows that in general, compounds of formula I can be made, for example, via a convergent route. For example, ring A and ring B can be linked via functionality a' and b', respectively. Functionality a' and b' are used to construct a linking group between ring A and ring B. Typically, but not necessarily, such a linking group contains functionality according to formula I (e.g. L¹, L² and R⁴) along with a 1,3-diketo moiety. Such 1,3-diketones are converted to the corresponding pyrazines, typically using hydrazine, according to formula I. Although Scheme 1 depicts functionality (e.g. L¹, L², R¹, R² and R⁴) according to formula I as being introduced at particular stages of synthesis, one of ordinary skill in the art would understand that such functionality can be introduced or manipulated at any of various stages of the synthetic procedure used to make particular compounds depending on the nature of the functionality and the chemistry needed to introduce or otherwise protect the functionality.

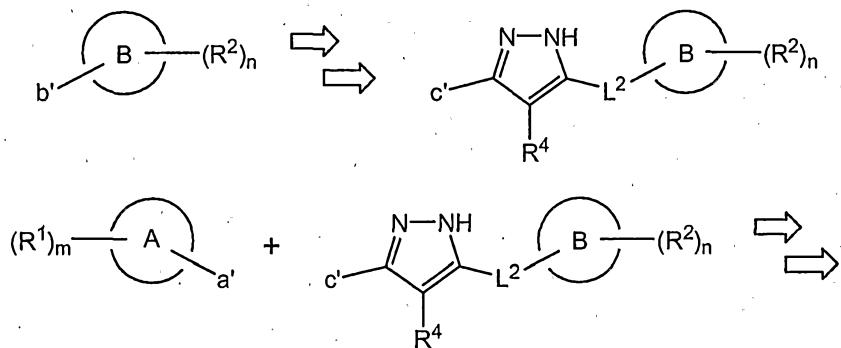
Scheme 1

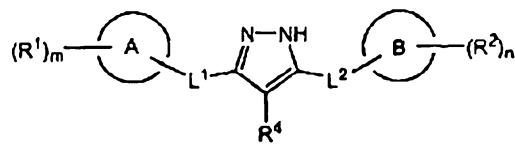




[0152] Scheme 2 shows another example using terminology consistent with Scheme 1. In this case a linear approach is used wherein the pyrazole ring and linker L^2 are appended onto ring B via functionality b' . Generally, but not necessarily, a radical containing a 1,3-diketo moiety is appended to ring B using b' . Then, the pyrazole ring is introduced as described in relation to Scheme 1. Once the pyrazole is made, then functionality c' is used to couple ring A and thereby form linking group L^1 and produce compounds according to formula I. The order of the steps described above can be varied, that is, ring A and the pyrazole can be linked first, followed by appending ring B to the pyrazole to make compounds of formula I. Again, although Scheme 2 depicts functionality (e.g. L^1 , L^2 , R^1 , R^2 and R^4) according to formula I as being introduced at particular stages of synthesis, one of ordinary skill in the art would understand that such functionality can be introduced or manipulated at any of various stages of the synthetic procedure.

Scheme 2





[0153] One of ordinary skill in the art would recognize that the descriptions associated with Schemes 1-2 are generalizations; provided below are exemplary chemistries used to make compounds in accordance with Schemes 1-2 and formula I. One of ordinary skill in the art would also appreciate that there are other combinations of steps and chemistries that can be used to make compounds of the invention.

[0153A] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

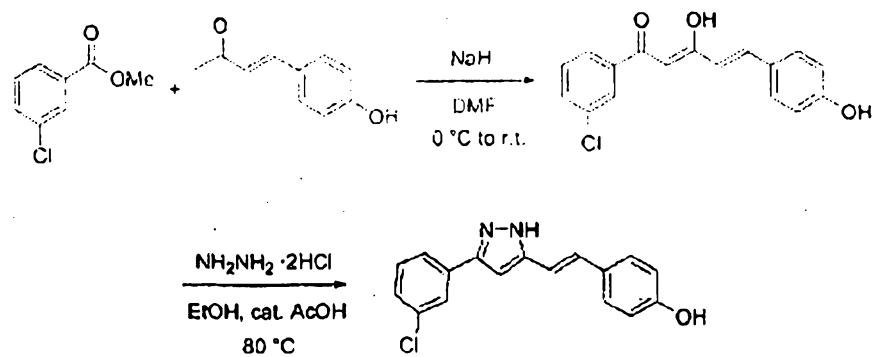
[0153B] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Examples

[0154] The following examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best mode contemplated for carrying out various aspects of the invention. It is understood that these examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. All references cited herein are incorporated by reference in their entirety.

Example 1

4-{{(EV2-r3-f3-chlorophenyl)H-üyrazol-5-vnethenyl}phenol



[0155] (2Z,4E)-1-(3-Chlorophenyl)-3-hydroxy-5-(4-hydroxyphenyl)penta-2,4-dien-1-one: NaH (60% dispersion, 0.477 g, 11.9 mmol) was added to a solution of methyl 3-chlorobenzoate (0.677 g, 3.97 mmol) and 4-hydroxybenzylideneacetone (0.644 g, 3.97 mmol) in anhydrous DMF (20 mL) at 0 °C. The reaction was allowed to warm to room temperature overnight and quenched with saturated aqueous NH₄Cl and neutralized with 1M HCl. The reaction was diluted with ethyl acetate (80 mL) and the organic layer washed successively with saturated aqueous NaHCO₃ and brine. The organic phase was separated and dried over Na₂SO₄, filtered, and concentrated in vacuo to provide the condensation product as a yellow oil (0.717 g, 60 % yield).

[0156] 4-{(E)-2-[3-(3-Chlorophenyl)-1*H*-pyrazol-5-yl]ethenyl}phenol: Hydrazine dihydrochloride (0.263 g, 2.50 mmol) was added to a sealed tube charged with (2Z,4E)-1-(3-chlorophenyl)-3-hydroxy-5-(4-hydroxyphenyl)penta-2,4-dien-1-one (0.717 g, 2.39 mmol) in absolute ethanol (8 mL) and a catalytic amount of acetic acid. The reaction tube was sealed and heated to 80 °C. After 12 hours the reaction was cooled to room temperature and concentrated in vacuo. The residue was dissolved in a small amount of methanol and precipitated with water, and the solid was collected by vacuum filtration to provide the title compound in (288 mg, 41 % yield) as a yellow solid: ¹H NMR (400 MHz, CD₃OD): δ 7.79 (bs, 1H), 7.68 (bd, *J* = 7.6 Hz, 1H), 7.37 (m, 3H), 7.29 (bd, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 16.4 Hz, 1H), 6.86 (d, *J* = 16.4 Hz, 1H), 6.81 (bs, 1H), 6.77 (m, 2H); MS (EI) for C₁₇H₁₃ClN₂O: 297.1 (MH⁺).

[0157] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0158] 4-[(E)-2-(3-Phenyl-1*H*-pyrazol-5-yl)ethenyl]phenol: ¹H NMR (400 MHz, CD₃OD): δ 7.76 (bs, 2H), 7.37 (m, 4H), 7.31 (bs, 1H), 7.12 (d, *J* = 16.4 Hz, 1H), 6.87 (bs, *J* = 16.8 Hz, 1H), 6.77 (m, 3H); MS (EI) for C₁₇H₁₄N₂O: 263.1 (MH⁺).

[0159] 4-{(E)-2-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]ethenyl}phenol: ¹H NMR (400 MHz, CD₃OD): δ 7.74 (bs, 2H), 7.38 (m, 4H), 7.11 (d, *J* = 16.8 Hz, 1H), 6.87 (bd, *J* = 16.4 Hz, 1H), 6.76 (m, 3H); MS (EI) for C₁₇H₁₃ClN₂O: 297.1 (MH⁺).

[0160] 4-{(E)-2-[3-(2-Chlorophenyl)-1H-pyrazol-5-yl]ethenyl}phenol: ^1H NMR (400 MHz, CD_3OD): δ 7.68 (bs, 1H), 7.49 (bs, 1H), 7.39 (m, 2H), 7.35 (m, 2H), 7.12 (d, $J = 16.4$ Hz, 1H), 6.90 (bd, $J = 16.4$ Hz, 1H), 6.82 (bs, 1H), 6.78 (m, 2H); MS (EI) for $\text{C}_{17}\text{H}_{13}\text{ClN}_2\text{O}$: 297.1 (MH^+).

[0161] 4-{(E)-2-[3-(1-Benzothien-2-yl)-1H-pyrazol-5-yl]ethenyl}phenol: ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.62 (bs, 1H), 7.92 (d, $J = 7.6$ Hz, 1H), 7.81 (d, $J = 7.6$ Hz, 1H), 7.70 (s, 1H), 7.39-7.30 (m, 4H), 7.13 (d, $J = 16.4$ Hz, 1H), 6.89 (s, 1H), 6.88 (d, $J = 16.4$ Hz, 1H), 6.78 (m, 2H); MS (EI) for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{OS}$: 319.1 (MH^+).

[0162] 4-{(E)-2-[3-(3,4-Dichlorophenyl)-1H-pyrazol-5-yl]ethenyl}phenol: ^1H NMR (400 MHz, CD_3OD): δ 7.95 (d, $J = 2.0$ Hz, 1H), 7.69 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.37 (m, 2H), 7.12 (d, $J = 16.4$ Hz, 1H), 6.87 (d, $J = 16.4$ Hz, 1H), 6.84 (s, 1H), 6.76 (m, 2H); MS (EI) for $\text{C}_{17}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}$: 331.01 (M $^+$).

[0163] 4-{(E)-2-[3-(5-Chloro-1-benzofuran-2-yl)-1H-pyrazol-5-yl]ethenyl}phenol: ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.63 (bs, 1H), 7.72 (d, $J = 2.4$ Hz, 1H), 7.64 (d, $J = 8.4$ Hz, 1H), 7.37 (m, 2H), 7.31 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.17 (d, $J = 16.4$ Hz, 1H), 7.16 (s, 1H), 6.91 (s, 1H), 6.89 (d, $J = 16.4$ Hz, 1H), 6.77 (m, 2H); MS (EI) for $\text{C}_{19}\text{H}_{13}\text{ClN}_2\text{O}_2$: 337.1 (MH^+).

[0164] 4-{(E)-2-[3-(1-Benzofuran-2-yl)-1H-pyrazol-5-yl]ethenyl}phenol: ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.63 (bs, 1H), 7.64 (d, $J = 7.6$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 1H), 7.37 (m, 2H), 7.27 (m, 2H), 7.17 (s, 1H), 7.16 (d, $J = 16.4$ Hz, 1H), 6.89 (s, 1H), 6.89 (d, $J = 16.4$ Hz, 1H), 6.77 (m, 2H); MS (EI) for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_2$: 303.1 (MH^+).

[0165] 4-{(E)-2-[5-(2-Fluorophenyl)-1H-pyrazol-3-yl]ethenyl}phenol: ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 7.81 (m, 2H), 7.36 (d, 2H), 7.24 (m, 2H), 7.08 (d, 1H), 6.88 (d, 1H), 6.86 (s, 1H), 6.75 (d, 2H); MS (EI) for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{OF}$: 281.1 (MH^+).

[0166] 4-{(E)-2-[5-(3-fluorophenyl)-1H-pyrazol-3-yl]ethenyl}phenol: ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 7.63 (d, 1H), 7.58 (d, 1H), 7.44 (m, 1H), 7.36 (d, 2H), 7.13 (m, 1H), 7.09 (d, 1H), 6.94 (s, 1H), 6.85 (d, 1H), 6.78 (d, 2H); MS (EI) for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{OF}$: 281.1 (MH^+).

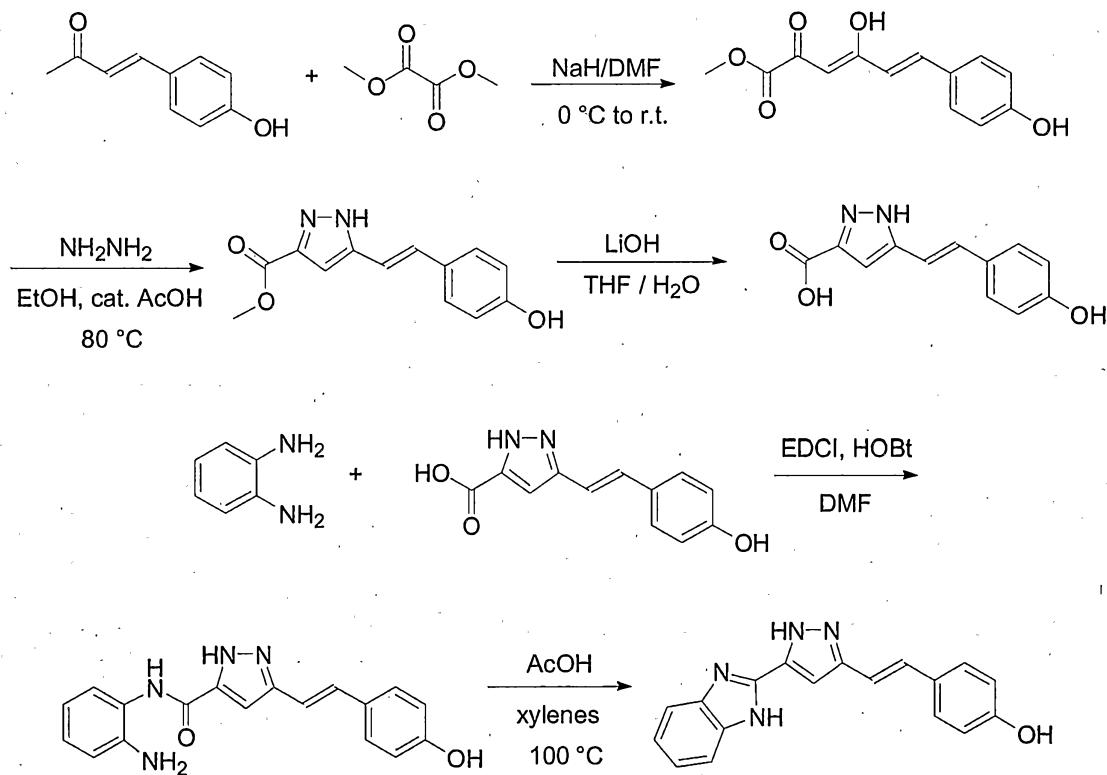
[0167] 4-{(E)-2-[5-(4-fluorophenyl)-1H-pyrazol-3-yl]ethenyl}phenol: ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 7.80 (t, 2H), 7.36 (d, 2H), 7.23 (t, 2H), 7.07 (d, 1H), 6.88 (d, 1H), 6.85 (s, 1H), 6.74 (d, 2H); MS (EI) for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{OF}$: 281.1 (MH^+).

[0168] 4-((E)-2-{5-[2-(methyloxy)phenyl]-1H-pyrazol-3-yl}ethenyl)phenol: ^1H NMR (400 MHz, DMSO-d₆): δ 7.77 (dd, 1H), 7.38 (d, 2H), 7.31 (dt, 1H), 7.11 (d, 1H), 7.00 (dt, 1H), 6.91 (d, 1H), 6.90 (s, 1H), 3.90 (s, 3H); MS (EI) for C₁₈H₁₆N₂O₂: 293.1 (MH⁺).

[0169] 4-((E)-2-{5-[3-(methyloxy)phenyl]-1H-pyrazol-3-yl}ethenyl)phenol: ^1H NMR (400 MHz, DMSO-d₆): δ 7.35 (m, 5H), 7.08 (d, 1H), 6.88 (m, 3H), 6.76 (d, 2H), 3.80 (s, 3H); MS (EI) for C₁₈H₁₆N₂O₂: 293.1 (MH⁺).

Example 2

4-((E)-2-[3-(1H-Benzimidazol-2-yl)-1H-pyrazol-5-yl]ethenyl)phenol



[0170] Methyl (2Z,4E)-3-hydroxy-5-(4-hydroxyphenyl)penta-2,4-dienoate: NaH (60% dispersion, 0.183 g, 7.6 mmol) was added to a solution of dimethyl oxylate (0.375 g, 3.2 mmol) and 4-hydroxybenzylideneacetone (0.515 g, 3.2 mmol) in anhydrous DMF (10 mL) at 0 °C. The reaction was allowed to warm to room temperature overnight and quenched with

saturated aqueous NH_4Cl and neutralized with 1M HCl. The reaction was diluted with ethyl acetate (80 mL) and the organic layer washed successively with saturated aqueous NaHCO_3 and brine. The organic phase was separated and dried over Na_2SO_4 , filtered, and concentrated in vacuo to provide the condensation product as a yellow oil (0.391 g, 50 % yield).

[0171] *1H-Pyrazole-3-carboxylic acid, 5-[(E)-2-(4-hydroxyphenyl)ethenyl]-, methyl ester:* Hydrazine (0.079 g, 1.6 mmol) was added to a sealed tube charged with methyl (2*Z*,4*E*)-3-hydroxy-5-(4-hydroxyphenyl)penta-2,4-dienoate (0.391 g, 1.6 mmol) in absolute ethanol (8 mL) and a catalytic amount of acetic acid. The reaction tube was sealed and heated to 80 °C. After 12 hours the reaction was cooled to room temperature and concentrated in vacuo. The residue was dissolved in a small amount of methanol and precipitated with water and the solid was collected by vacuum filtration to provide the title compound (240 mg, 41 % yield): ^1H NMR (400 MHz, CD_3OD): δ 13.15 (bs, 1H), 7.37 (d, J = 8.59 Hz, 1H), 7.18 (d, J = 16.6 Hz, 1H), 6.87 (s, 1H), 6.85 (d, J = 16.6 Hz, 1H), 6.78 (d, J = 8.59 Hz, 1H), 3.80 (s, 3H).

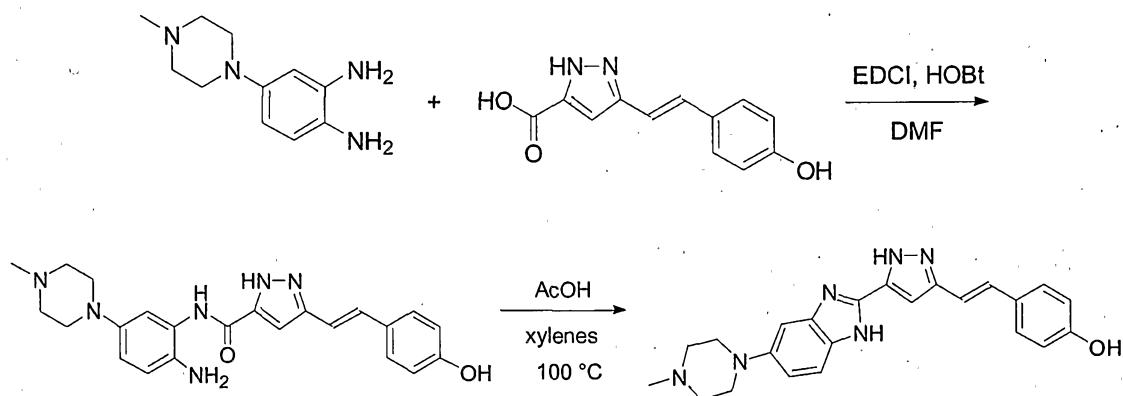
[0172] *5-[(E)-2-(4-Hydroxyphenyl)ethenyl]-1H-pyrazole-3-carboxylic acid:* Lithium hydroxide hydrate (0.522 g, 12.44 mmol) was added to the solution of 1*H*-pyrazole-3-carboxylic acid, 5-[(E)-2-(4-hydroxyphenyl)ethenyl]-, methyl ester (1.52 g, 6.22 mmol) in THF (50 mL) and H_2O (12.5 mL). The reaction mixture was stirred overnight at room temperature. THF was removed on a rotary evaporator. The residue was neutralized with 3N HCl, and the solid was collected by vacuum filtration to provide the title compound in (1.2 g, 84 % yield).

[0173] *N-(2-Aminophenyl)-3-[(E)-2-(4-hydroxyphenyl)ethenyl]-1H-pyrazole-5-carboxamide:* 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI, 0.377 g, 1.97 mmol) was added to a solution of 1,2-diaminobenzene (0.141 g, 1.31 mmol), 5-[2[(4-hydroxyphenyl)-vinyl]-2*H*-pyrazol-3-carboxylic acid (0.301 g, 1.31 mmol) and HOEt (0.266 g, 1.97 mmol) in anhydrous DMF (7 mL). The reaction was stirred under nitrogen at room temperature. After twelve hours the reaction was concentrated in vacuo and precipitated from methanol with a small amount of water. The solid was collected by vacuum filtration and further purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the corresponding amide (44 mg, 10 % yield).

[0174] 4-((E)-2-[3-(1*H*-Benzimidazol-2-yl)-1*H*-pyrazol-5-yl]ethenyl)phenol: Glacial acetic acid (1.0 mL) was added to a sealed tube charged with a solution of *N*-(2-aminophenyl)-3-[(*E*)-2-(4-hydroxyphenyl)ethenyl]-1*H*-pyrazole-5-carboxamide (0.044 g, 1.36 mmol) in xylenes (1.0 mL) and heated to 100 °C. After twelve hours the reaction was cooled to room temperature and concentrated in vacuo. The residue was purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the title benzimidazole (10 mg, 25 % yield) as a white solid: ¹H NMR (400 MHz, CD₃OD): δ 7.59 (bs, 2H), 7.41 (m, 2H), 7.25 (m, 2H), 7.16 (d, *J* = 16.4 Hz, 1H), 7.03 (s, 1H), 6.92 (d, *J* = 16.4 Hz, 1H), 6.79 (m, 2H); MS (EI) for C₁₈H₁₄N₄O: 303.1 (MH⁺).

Example 3

4-((E)-2-[3-[6-(4-Methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl]ethenyl)phenol



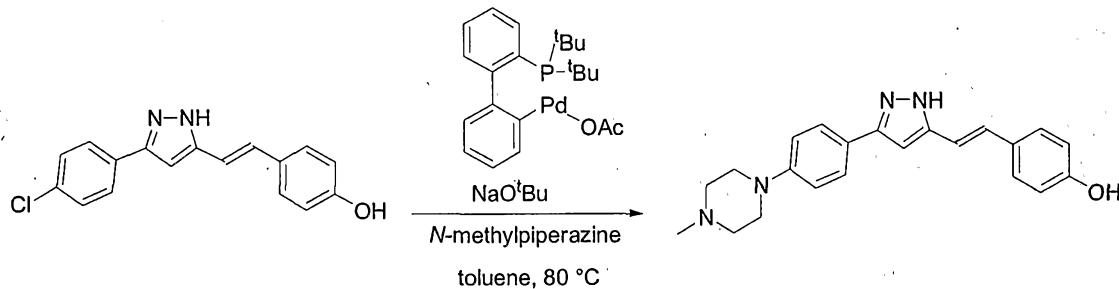
[0175] *N*-[2-Amino-5-(4-methylpiperazin-1-yl)phenyl]-3-[(*E*)-2-(4-hydroxyphenyl)ethenyl]-1*H*-pyrazole-5-carboxamide: EDCI (0.078 g, 0.41 mmol) was added to a solution of 5-(4-methyl-piperazin-1-yl)-1,2-aminobenzene (0.085 g, 0.41 mmol), 5-[2[(4-hydroxyphenyl)-vinyl]-2*H*-pyrazol-3-carboxylic acid (0.047 g, 0.21 mmol) and DMAP (0.050 g, 0.41 mmol) in anhydrous DMF (2 mL) at room temperature. After twelve hours the reaction was concentrated in vacuo affording crude product.

[0176] 4-((*E*)-2-[5-(4-Methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-3-yl)ethenyl)phenol: The 0.21 mmol of crude *N*-[2-amino-5-(4-methylpiperazin-1-yl)phenyl]-3-[(*E*)-2-(4-hydroxyphenyl)ethenyl]-1*H*-pyrazole-5-carboxamide in a solution of

AcOH:xylenes (1:1, 2 mL) was heated to 100 °C in a sealed tube. After twelve hours the reaction was cooled to room temperature and concentrated in vacuo. The residue was purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the title benzimidazole (12 mg, 14 % yield) as a dark purple solid: ¹H NMR (400 MHz, CD₃OD): δ 7.89 (s, 1H), 7.65 (bs, 1H), 7.36 (m, 2H), 7.23 (bs, 1H), 7.14 (bd, J = 16.4 Hz, 2H), 6.86 (bd, J = 15.2 Hz, 1H), 6.75 (m, 2H), 3.92 (bd, J = 11.6 Hz, 2H), 3.65 (bd, J = 11.2 Hz, 2H), 3.39-3.21 (m, 3H), 2.99 (s, 3H), 2.90 (bt, J = 12.4 Hz, 1H); MS (EI) for C₂₃H₂₄N₆O: 401.2 (MH⁺).

Example 4

4-((E)-2-{3-[4-(4-Methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}ethenyl)phenol



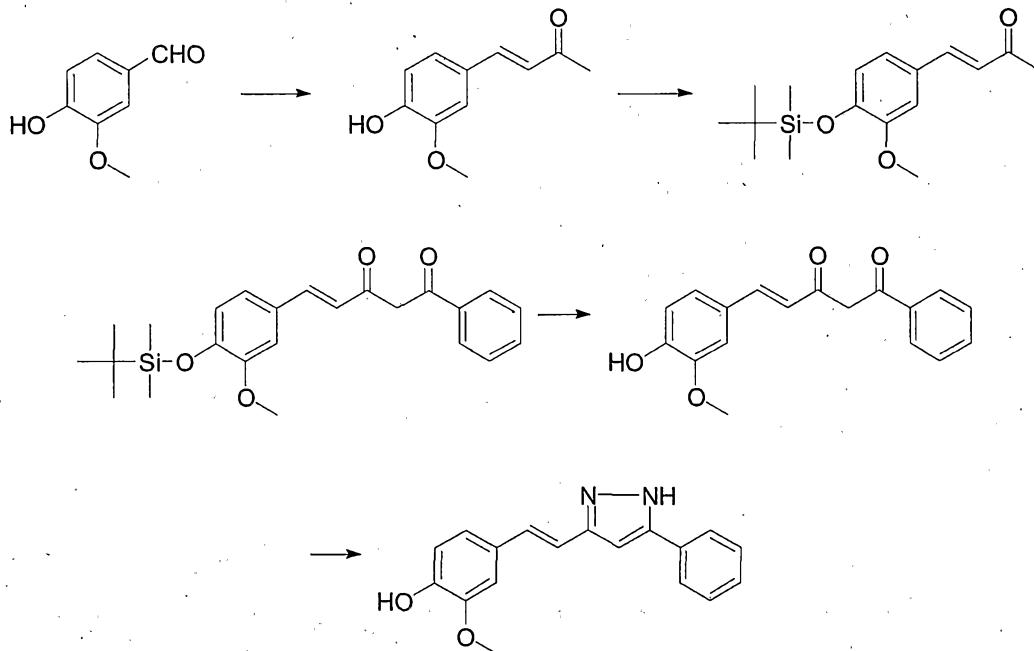
[0177] 4-((E)-2-{3-[4-(4-Methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}ethenyl)phenol: N-Methylpiperazine (50 μ L, 0.49 mmol) was added to a suspension of 4-((E)-2-[3-(4-chlorophenyl)-1H-pyrazol-5-yl]ethenyl)phenol (0.097 g, 0.33 mmol), NaOtBu (0.110 g, 1.14 mmol) and acetato(2'-di-tert-butylphosphino-1,1'-biphenyl-2-yl)palladium (0.015 g, 33 μ mol, 10 mol %) in anhydrous toluene (1.5 mL) and heated to 80 °C. After 24 hours, the reaction was cooled to room temperature, diluted with methanol and filtered through a celite pad. The filtrate was concentrated in vacuo and the residue purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the title compound (10 mg, 9 % yield) as an off-white solid: ¹H NMR (400 MHz, CD₃OD): δ 7.71 (m, 2H), 7.40 (m, 2H), 7.20 (d, J = 16.4 Hz, 1H), 7.10 (m, 2H), 6.87 (d, J = 16.4 Hz, 1H), 6.84 (s, 1H), 6.79 (m, 2H), 3.95 (bd, J = 14.4 Hz, 2H), 3.63 (bd, J = 11.2 Hz, 2H), 2.28 (m, 2H), 3.10 (bt, J = 13.2 Hz, 2H), 2.99 (s, 3H); MS (EI) for C₂₂H₂₄N₄O: 361.2 (MH⁺).

[0178] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compound of the invention was prepared:

[0179] 4-((E)-2-{3-[3-(4-Methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}ethenyl)phenol: ^1H NMR (400 MHz, CD_3OD): δ 7.50-7.45 (m, 4H), 7.36 (bd, $J = 8.4$ Hz, 1H), 7.34 (s, 1H), 7.21 (dd, $J = 8.0, 2.4$ Hz, 1H), 6.89 (d, $J = 16.4$ Hz, 1H), 6.82 (m, 2H), 3.99 (bd, $J = 14.0$ Hz, 2H), 3.65 (bd, $J = 12.0$ Hz, 2H), 3.31 (m, 2H), 3.20 (dt, $J = 13.6, 1.6$ Hz, 2H), 2.99 (s, 3H); MS (EI) for $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}$: 361.2 (MH^+).

Example 5

2-(Methyloxy)-4-[(E)-2-(5-phenyl-1H-pyrazol-3-yl)ethenyl]phenol



[0180] 4-(4-Hydroxy-3-methoxy-phenyl)but-3-ene-2-one: To a solution of acetone (15.30 g, 263.76 mmol) in a mixture of ethanol (35 mL) and water (15 mL) were added sodium hydroxide (2.90 g, 72.54 mmol) and 4-hydroxy-3-methoxybenzaldehyde (5.01 g, 32.97 mmol). The reaction mixture was stirred at room temperature for 15 h. The reaction was cooled to 0° C and quenched with 2.0 N hydrochloric acid until the solution became slightly acidic. The solution was extracted with ethyl acetate (4x 100 mL). The combined organic layers were washed with water (50 mL) and saturated aqueous sodium chloride (50 mL).

The organic layer was dried over magnesium sulfate, filtered, and concentrated at reduced pressure to afford 4-(4-hydroxy-3-methoxy-phenyl)but-3-ene-2-one (5.52 g, 87% yield) as a yellow solid: MS (EI) for $C_{11}H_{12}O_3$: 193 (MH^+).

[0181] 4-{4-[(*tert*-Butyl-dimethyl-silanyloxy)-methyl]-3-methoxy-phenyl}-but-3-ene-2-one: To a solution of 4-(4-Hydroxy-3-methoxy-phenyl)but-3-ene-2-one (4.402 g, 22.93 mmol) in N,N-dimethylformamide (28.5 mL) were added imidazole (1.71 g, 25.22 mmol) and *tert*-butyldimethylsilyl chloride (3.8 g, 25.22 mmol). The reaction was allowed to stir for 4h, then diluted with ethyl acetate (300 mL) and washed with water (50 mL), saturated aqueous sodium bicarbonate (40 mL), and saturated aqueous sodium chloride (50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated at reduced pressure to give crude product. Column purification on silica (8:2 hexanes/ethyl acetate) afforded 4-{4-[(*tert*-butyl-dimethyl-silanyloxy)-methyl]-3-methoxy-phenyl}-but-3-ene-2-one (5.24 g, 73% yield) as a solid: 1H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, 2H), 6.92 (m, 2H), 6.78 (d, 1H), 6.53 (d, 2H), 3.78 (s, 3H), 2.28 (s, 3H), 0.92 (s, 9H), 0.16 (s, 6H).

[0182] 5-(Hydroxy-3-methoxy-phenyl)-1-phenyl-pent-4-ene-1,3-dione: To a slurry solution of sodium hydride (60%, 0.13 g, 3.28 mmol) in N,N-dimethylformamide were added 4-{4-[(*tert*-butyl-dimethyl-silanyloxy)-methyl]-3-methoxy-phenyl}-but-3-ene-2-one (0.50 g, 1.54 mmol) and methyl benzoate (0.26 g, 1.97 mmol) at 0° C. The reaction was stirred at 0° C for 1 h. The reaction mixture was removed from ice-bath and heated for 1 h at 60° C. The reaction was cooled to room temperature and quenched with aqueous 1.0 N hydrochloric acid (2.0 mL) slowly. Excess tetrabutylammonium fluoride was added to the above solution to deprotect the silyl group. The reaction was diluted with ethyl acetate (200 mL), washed with water (3 x 60 mL) and saturated aqueous sodium chloride (50 mL). The organic layer dried over magnesium sulfate, filtered, and concentrated to give impure crude product. Purification on silica (9:1 to 7:3 hexanes/ethyl acetate) to afford 5-(hydroxy-3-methoxy-phenyl)-1-phenyl-pent-4-ene-1,3-dione (0.14 g, 30% yield) as a solid: MS (EI) for $C_{18}H_{16}O_4$: 297 (MH^+).

[0183] 2-(Methyloxy)-4-[(E)-2-(5-phenyl-1H-pyrazol-3-yl)ethenyl]phenol: To a mixture of 5-(hydroxy-3-methoxy-phenyl)-1-phenyl-pent-4-ene-1,3-dione (0.14 g, 0.48 mmol) and hydrazine monohydrate (0.02 g, 0.48 mmol) were added ethanol (24 mL) and acetic acid (1

drop) in a sealed tube. The reaction was heated at 65-70° C overnight. The solvent was removed under reduced pressure to afford crude product. Purification on triethylamine treated silica (1:1 hexanes/ethyl acetate) afforded a mixture of two products. Reverse phase HPLC purification afforded 2-(methoxy)-4-[(E)-2-(5-phenyl-1H-pyrazol-3-yl)ethenyl]phenol (0.015 g, 10% yield) as trifluoroacetate salt: ¹H NMR (400 MHz, CDCl₃): δ 9.21 (br s, 2H), 7.78 (br s, 2H), 7.42 (m, 3H), 7.20 (br d, 1H), 6.94 (m, 6H), 3.92 (s, 3H); MS (EI) for C₁₈H₁₆N₂O₂: 293 (MH⁺).

[0184] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0185] 2-(methoxy)-4-((E)-2-{5-[(E)-2-phenylethenyl]-1H-pyrazol-3-yl}ethenyl)phenol: ¹H NMR (400 MHz, CDCl₃): δ 7.42 (br d, 2H), 7.30 (m, 3H), 7.15 (m, 2H), 7.02 (m, 3H), 6.85 (m, 3H), 6.68 (br s, 1H), 3.85 (s, 3H); MS (EI) for C₂₀H₁₈N₂O₂: 319 (MH⁺).

[0186] 4-((E)-2-{3-[(E)-2-(4-chlorophenyl)ethenyl]-1H-pyrazol-5-yl}ethenyl)-2-(methoxy)phenol: ¹H NMR (400 MHz, CDCl₃): δ 7.38 (br d, 2H), 7.32 (br d, 2H), 7.20 (m, 3H), 6.90 (m, 6H), 6.62 (br s, 1H), 3.95 (s, 3H); MS (EI) for C₂₀H₁₇N₂O₂Cl: 353, 355 (MH⁺).

[0187] 4-((E)-2-{3-[(E)-2-(4-fluorophenyl)ethenyl]-1H-pyrazol-5-yl}ethenyl)-2-(methoxy)phenol: ¹H NMR (400 MHz, *d*-MeOH): δ 7.46 (m, 2H), 7.08 (m, 5H), 6.90 (m, 2H), 6.75 (d, 1H), 6.68 (br d, 2H), 3.82 (s, 3H); MS (EI) for C₂₀H₁₇N₂O₂F: 337 (MH⁺).

[0188] 4-((E)-2-{3-[(E)-2-(2,4-difluorophenyl)ethenyl]-1H-pyrazol-5-yl}ethenyl)-2-(methoxy)phenol: ¹H NMR (400 MHz, *d*-MeOH): δ 7.42 (m, 1H), 7.25 (d, 1H), 7.15 (m, 3H), 7.02 (m, 3H), 6.90 (d, 1H), 6.78 (br t, 2H), 3.92 (s, 3H); MS (EI) for C₂₀H₁₆N₂O₂F₂: 355 (MH⁺).

[0189] 4-((E)-2-{5-[(E)-2-phenylethenyl]-1H-pyrazol-3-yl}ethenyl)phenol: ¹H NMR (400 MHz, *d*-MeOH): δ 7.64 (br d, 2H), 7.44 (m, 7H), 7.12 (br t, 2H), 6.87 (m, 3H); MS (EI) for C₁₉H₁₆N₂O: 289 (MH⁺).

[0190] 4-[(E)-2-(3-pyridin-3-yl-1H-pyrazol-5-yl)ethenyl]phenol: ¹H NMR (400 MHz, *d*-MeOH): δ 9.20 (br s, 1H), 8.85 (d, 1H), 8.65 (br s, 1H), 8.20 (br s, 1H), 7.42 (d, 2H), 7.20 (d, 1H), 7.04 (s, 1H), 6.85 (d, 1H), 6.80 (d, 2H); MS (EI) for C₁₆H₁₃N₃O: 264 (MH⁺).

[0191] 4-[(E)-2-(3-pyridin-4-yl-1H-pyrazol-5-yl)ethenyl]phenol: ^1H NMR (400 MHz, *d*-MeOH): δ 8.64 (br d, 1H), 8.50 (br t, 1H), 8.34 (br d, 1H), 7.82 (br t, 1H), 7.40 (d, 2H), 7.18 (m, 2H), 6.90 (d, 1H), 6.80 (d, 2H); MS (EI) for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}$: 264 (MH^+).

[0192] 4-[(E)-2-(5-naphthalen-2-yl-1H-pyrazol-3-yl)ethenyl]phenol: ^1H NMR (400 MHz, *d*-MeOH): δ 8.38 br s, 1H), 7.94 (m, 5H), 7.60 (m, 2H), 7.52 (m, 3H), 7.38 (s, 1H), 6.92 (d, 1H), 6.84 (d, 2H); MS (EI) for $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}$: 313 (MH^+).

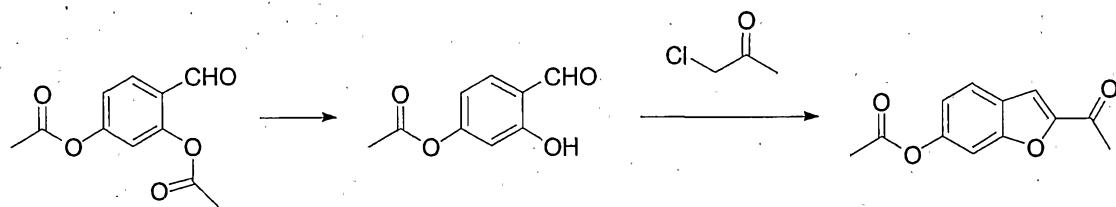
[0193] 4-[(E)-2-(5-pyridin-2-yl-1H-pyrazol-3-yl)ethenyl]phenol: ^1H NMR (400 MHz, *d*-MeOH): δ 8.70 (d, 1H), 8.62 (t, 1H), 8.44 (d, 1H), 7.92 (t, 1H), 7.40 (d, 2H), 7.20 (d, 2H), 6.90 (d, 1H), 6.80 (d, 2H); MS (EI) for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}$: 264 (MH^+).

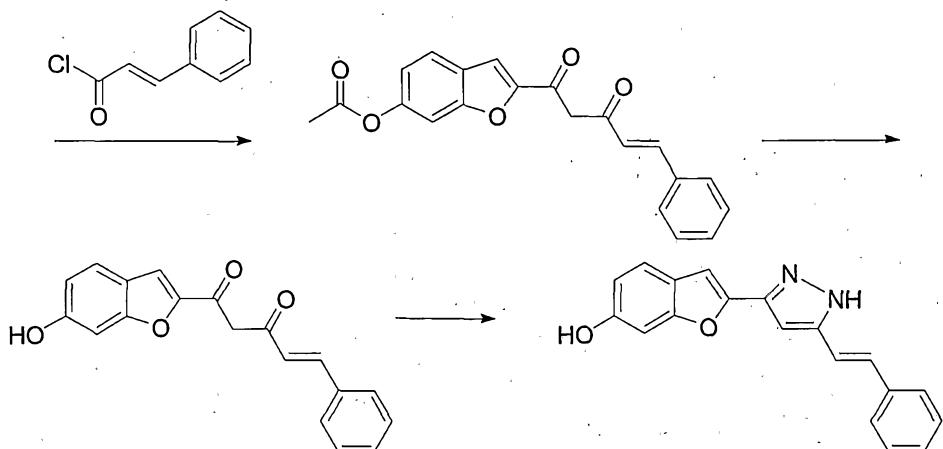
[0194] 4-[(E)-2-(5-biphenyl-3-yl-1H-pyrazol-3-yl)ethenyl]phenol: ^1H NMR (400 MHz, *d*-MeOH): δ 7.42 (m, 1H), 7.25 (d, 1H), 7.15 (m, 3H), 7.02 (m, 3H), 6.90 (d, 1H), 6.78 (br t, 2H), 3.92 (s, 3H); MS (EI) for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2\text{F}_2$: 355 (MH^+).

[0195] 1,1-Dimethylethyl (4-{3-[(E)-2-phenylethenyl]-1H-pyrazol-5-yl}phenyl)carbamate: ^1H NMR (400 MHz, *d*-MeOH): δ 7.66 (br d, 2H), 7.50 (m, 5H), 7.35 (br t, 3H), 7.28 (br d, 1H), 7.20 (d, 1H), 7.08 (d, 1H), 6.82 (s, 1H), 1.50 (s, 9H); MS (EI) for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_2$: 362 (MH^+).

Example 6

2-{5-[(E)-2-phenylethenyl]-1H-pyrazol-3-yl}-1-benzofuran-6-ol





[0196] 4-Formyl-3-hydroxyphenyl acetate: To a solution of 4-formylbenzene-1,3-diyli diacetate (5.56 g, 25.08 mmol) in ethanol (20 mL) was added a solution of sodium hydroxide (1.00 g, 25.08 mmol) in water (12 mL). The reaction was stirred overnight at room temperature. The reaction was carefully neutralized with 2.0 N aqueous solution of hydrochloric acid (12.8 mL) at 0° C and diluted with ethyl acetate (400 mL). The organic layer was washed with water (60 mL) and saturated aqueous sodium chloride (50 mL), dried over magnesium sulfate, filtered, and concentrated to afford the product (2.01 g, 44% yield) as a gray solid: ^1H NMR (400 MHz, *d*-MeOH): δ 9.90 (s, 1H), 7.68 (d, 1H), 6.80 (d, 1H), 6.75 (s, 1H), 4.82 (br s, 1H), 2.20 (s, 3H).

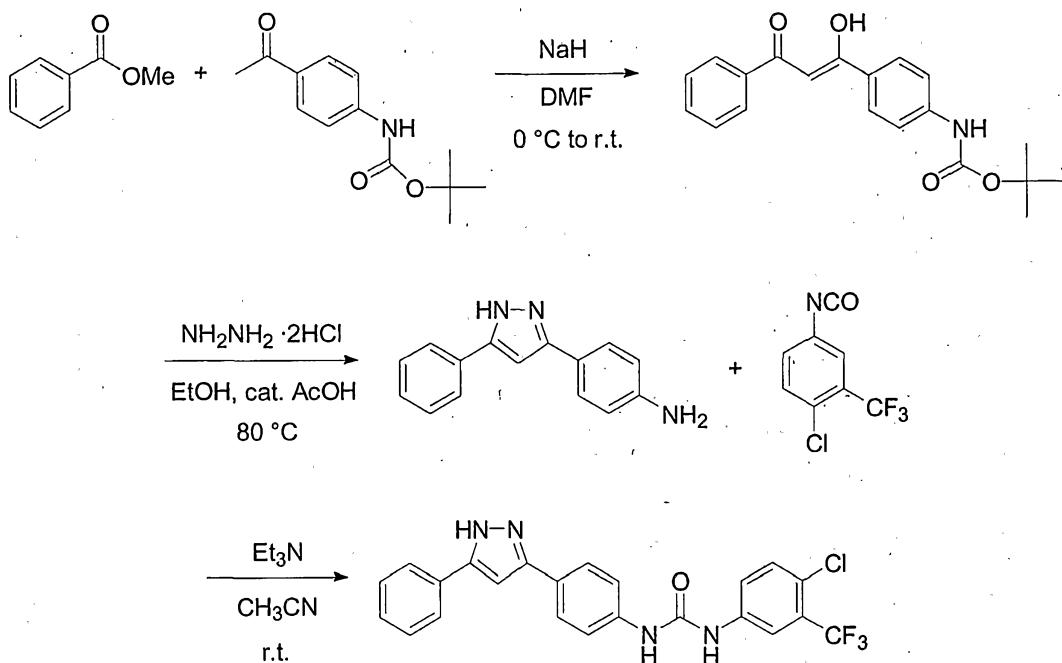
[0197] 2-Acetyl-1-benzofuran-6-yl acetate: To a solution of acetic acid 4-Formyl-3-hydroxyphenyl acetate (1.74 g, 9.67 mmol) in acetonitrile (10 mL) was added solid anhydrous potassium carbonate (1.33 g, 9.67 mmol) and stirred for 30 min at room temperature prior to the slow addition of chloroacetone (0.98 g, 9.67 mmol) *via* a syringe. A reflux condenser was attached and the reaction was heated to reflux overnight, then cooled to room temperature and diluted with ethyl acetate (350 mL). The organic layer was washed with 2.0 N aqueous HCl (100 mL), saturated aqueous sodium chloride (60 mL), dried over magnesium sulfate, filtered, and concentrated to afford crude product. Purification on silica (9:1 to 7:3, hexanes/ethyl acetate) afforded the desired product together with the product without the acetate group. The total weight of the mixture obtained was 0.4421 g. This mixture was taken to the next step without further purification.

[0198] (4E)-1-(6-Hydroxy-1-benzofuran-2-yl)-5-phenylpent-4-ene-1,3-dione: To a solution of the crude 2-acetyl-1-benzofuran-6-yl acetate (0.23 g) in tetrahydrofuran (5 mL) at -78° C was added lithium diisopropylamine (2.0 N solution in THF, 1.63 mL, 3.25 mmol). The mixture was stirred at the same temperature for 20 min prior to the addition of cinnamoyl chloride (0.22 g, 1.3 mmol). The reaction was warmed slowly to room temperature and stirred overnight. The reaction was treated with 1.0 N aqueous hydrochloric acid solution (10 mL) at 0° C and diluted with ethyl acetate (250 mL). The organic layer was washed with 2N aqueous hydrochloric acid (100 mL), saturated aqueous sodium chloride (60 mL), dried over magnesium sulfate, filtered, and concentrated to afford crude product. Purification on silica (gradient 8: 2 to 6:4, hexanes/ethyl acetate) afforded the product (0.12 g, 30% yield) as a yellow solid: MS (EI) for $C_{19}H_{14}O_4$: 307 (MH^+).

[0199] 2-{5-[(E)-2-Phenylethenyl]-1*H*-pyrazol-3-yl}-1-benzofuran-6-ol: To a mixture of (4E)-1-(6-hydroxy-1-benzofuran-2-yl)-5-phenylpent-4-ene-1,3-dione (0.48 mmol) and hydrazine monohydrate (0.02 g, 0.48 mmol) were added ethanol (24 mL) and acetic acid (1 drop) in a sealed tube. The reaction was heated at 65-70° C overnight. The solvent was removed under reduced pressure to afford crude product. The crude product was purified by reverse phase HPLC. The fractions from HPLC were combined, neutralized with 1.0 N aqueous sodium hydroxide solution, and diluted with ethyl acetate (200 mL). The organic layer was washed with saturated aqueous sodium chloride (50 mL), dried over magnesium sulfate, filtered, and concentrated to afford the product (11% yield): 1H NMR (400 MHz, CD_3Cl): δ 7.58 (br d, 2H), 7.35 (m, 4H), 7.25 (t, 2H), 7.10 (br d, 1H), 7.05 (br s, 1H), 6.94 (br d, 1H), 6.88 (br s, 1H), 6.75 (dd, 1H); MS (EI) for $C_{19}H_{14}N_2O_2$: 303 (MH^+).

Example 7

N -[4-chloro-3-(trifluoromethyl)phenyl]- N' -[4-(3-phenyl-1*H*-pyrazol-5-yl)phenyl]urea



[0200] 1,1-Dimethylethyl {4-[(1Z)-1-hydroxy-3-oxo-3-phenylprop-1-en-1-yl]phenyl} carbamate: NaH (60% dispersion, 0.388 g, 16.2 mmol) was added to a solution of methyl benzoate (0.629 g, 4.62 mmol) and 1,1-dimethylethyl (4-acetylphenyl)carbamate (*N*-BOC-4-aminoacetophenone 1.09 g, 4.62 mmol) in anhydrous DMF (20 mL) at 0 °C. The reaction was allowed to warm to room temperature overnight then quenched with saturated aqueous NH₄Cl and neutralized with 1M HCl. The reaction was diluted with ethyl acetate (80 mL) and the organic layer washed successively with saturated aqueous NaHCO₃ and brine. The organic phase was separated and dried over Na₂SO₄, filtered, and concentrated in vacuo to provide the condensation product as a yellow oil (1.31 g, 83 % yield). The product was used in the subsequent step without further purification.

[0201] 4-(5-Phenyl-1*H*-pyrazol-3-yl)aniline: Hydrazine dihydrochloride (0.427 g, 4.00 mmol) was added to a sealed tube charged with the above product (1.31 g, 3.87 mmol) in absolute ethanol (17 mL) and a catalytic amount of acetic acid. The reaction tube was sealed and heated to 85 °C. After 12 hours the reaction was cooled to room temperature and concentrated in vacuo. The residue was dissolved in a small amount of methanol and precipitated with water and the solid was collected by vacuum filtration to provide the desired compound in (974 mg, 75 % yield) as a white solid. The BOC group was removed under the reaction conditions: ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.95 (m, 3H), 7.82 (m,

2H), 7.45 (m, 3H), 7.34 (m, 2H), 7.23 (s, 1H), 2.30 (bs, 2H); MS (EI) for C₁₅H₁₃N₃: 236.1 (MH⁺).

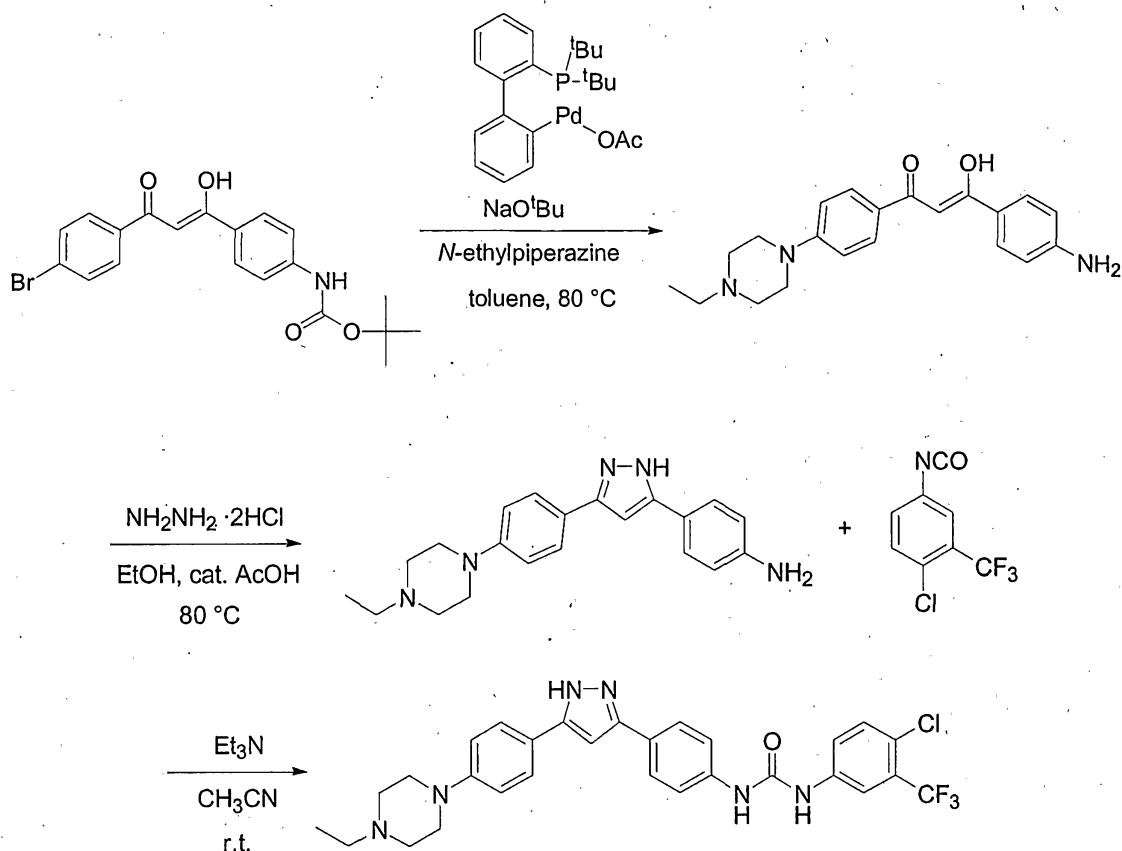
[0202] *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[4-(5-phenyl-1*H*-pyrazol-3-yl)phenyl]urea: Triethylamine (64 mL, 0.45 mmol) was added to a suspension of *N*-[4-(3-phenyl-1*H*-pyrazol-5-yl)aminobenzene (0.102 g, 0.43 mmol) and 4-chloro-3-trifluoromethyl-phenylisocyanate (0.096 g, 0.43 mmol) in anhydrous acetonitrile (2.0 mL) at room temperature. After twelve hours the reaction was concentrated in vacuo and purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the title compound (23 mg, 16 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.24 (s, 1H), 9.01 (s, 1H), 8.11 (d, *J* = 2.0 Hz, 1H), 7.81 (m, 2H), 7.74 (m, 2H), 7.62 (m, 2H), 7.53 (m, 2H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.10 (s, 1H); MS (EI) for C₂₃H₁₆ClF₃N₄O: 457.1 (MH⁺).

[0203] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compound of the invention was prepared:

[0204] *N*-phenyl-*N'*-[4-(3-phenyl-1*H*-pyrazol-5-yl)phenyl]urea: ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.80 (bs, 1H), 8.72 (bs, 1H), 7.81 (d, *J* = 7.2 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.44 (m, 3H), 7.29 (m, 3H), 7.08 (s, 1H), 6.96 (t, *J* = 7.2 Hz, 1H); MS (EI) for C₂₂H₁₈N₄O: 355.1 (MH⁺).

Example 8

N-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-[3-[4-(4-ethylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl]phenyl)urea



[0205] (2Z)-3-(4-Aminophenyl)-1-[4-(4-ethylpiperazin-1-yl)phenyl]-3-hydroxyprop-2-en-1-one: *N*-Ethylpiperazine (334 μ L, 2.62 mmol) was added to a sealed tube charged with {4-[3-(4-bromophenyl)-1-hydroxy-3-oxo-propenyl]-phenyl}-carbamic acid *tert*-butyl ester (0.842 g, 2.01 mmol), NaOtBu (0.483 g, 5.03 mmol) and acetato(2'-di-*t*-butylphosphino-1,1'-biphenyl-2-yl)palladium (0.140 g, 0.30 mmol, 15 mol %) in anhydrous toluene (10 mL). The reaction tube was sealed and heated to 110 °C. After 24 hours, the reaction was cooled to room temperature, diluted with methanol and filtered through a celite pad. The filtrate was concentrated in vacuo and the residue purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide 3-(4-aminophenyl)-3-hydroxy-1-[4-(4-ethylpiperazin-1-yl)-phenyl]-propenone (208 mg, 32% yield) as an off-white solid. Note that the BOC group was removed during the purification: 1 H NMR (400 MHz, CD₃OD): δ 7.97 (m, 2H), 7.85 (m, 2H), 7.10 (m, 2H), 6.84 (s, 1H), 6.78 (m, 2H), 4.11 (bd, J = 12.0 Hz, 2H), 3.69 (bd, J = 10.4 Hz, 2H), 3.32-3.22 (m, 6H), 1.41 (t, J = 5.4 Hz, 3H); MS (EI) for C₂₁H₂₅N₃O₂: 352.1 (MH⁺).

[0206] 4-{3-[4-(4-ethylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl} aniline:

Hydrazine dihydrochloride (0.093 g, 0.89 mmol) was added to a sealed tube charged with the above product (0.208 g, 0.59 mmol) in absolute ethanol (5 mL) and a catalytic amount of acetic acid. The reaction tube was sealed and heated to 85 °C. After 12 hours the reaction was cooled to room temperature and concentrated in vacuo. The residue was dissolved in a small amount of methanol and precipitated with a solution of methylene chloride:hexanes (1:1). The solid was collected by vacuum filtration to provide the corresponding pyrazole product (174 mg, 85 % yield) as a yellow solid: ^1H NMR (400 MHz, CD_3OD): δ 8.01 (m, 2H), 7.77 (m, 2H), 7.51 (m, 2H), 7.24 (s, 1H), 7.16 (m, 2H), 4.03 (bd, J = 12.0 Hz, 2H), 3.70 (bd, J = 10.4 Hz, 2H), 3.32-3.22 (m, 6H), 1.42 (t, J = 5.4 Hz, 3H); MS (EI) for $\text{C}_{21}\text{H}_{25}\text{N}_5$: 348.1 (MH^+).

[0207] *N*-[4-Chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[4-(4-ethylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}phenyl)urea: Triethylamine (35 μL , 0.25 mmol) was added to a suspension of the above pyrazole (0.067 g, 0.19 mmol) and 4-chloro-3-trifluoromethyl-phenylisocyanate (0.055 g, 0.25 mmol) in anhydrous acetonitrile (2.0 mL) at room temperature. After twelve hours the reaction was concentrated in vacuo and purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the title compound (8 mg, 8 % yield) as a white solid: ^1H NMR (400 MHz, CD_3OD): δ 8.02 (bd, J = 2.8 Hz, 1H), 7.78 (m, 4H), 7.64 (bd, J = 2.8 Hz, 1H), 7.61 (m, 2H), 7.51 (d, J = 10.8 Hz, 1H), 7.15 (m, 2H), 7.11 (bs, 1H), 4.03 (bd, J = 12.0 Hz, 2H), 3.71 (bd, J = 10.4 Hz, 2H), 3.31 (m, 4H), 3.13 (m, 2H), 1.42 (t, J = 5.4 Hz, 3H); MS (EI) for $\text{C}_{29}\text{H}_{28}\text{ClF}_3\text{N}_6\text{O}$: 569.2 (MH^+).**[0208] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:****[0209] *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}phenyl)urea:** ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.07 (d, J = 5.6 Hz, 1H), 7.74 (m, 4H), 7.61 (dd, J = 8.4, 2.4 Hz, 1H), 7.54 (m, 3H), 7.07 (m, 3H), 3.92 (bd, J = 13.2 Hz, 2H), 3.52 (bd, J = 12.0 Hz, 2H), 3.17 (dt, J = 11.2, 2.0 Hz, 2H), 3.07 (bt, J = 12.0 Hz, 2H), 2.86 (s, 3H); MS (EI) for $\text{C}_{28}\text{H}_{26}\text{ClF}_3\text{N}_6\text{O}$: 556.2 (MH^+).**[0210] *N*-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}phenyl)-*N'*-(2-phenylethyl)ethanediamide:** ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.85-7.58 (m, 7H), 7.26-

7.13 (m, 6H), 6.92 (m, 4H), 3.81 (bs, 1H), 3.44 (bt, $J = 6.8$ Hz, 2H), 3.17 (m, 5H), 2.82 (t, $J = 7.6$ Hz, 2H), 2.48 (m, 2H), 2.23 (s, 3H); MS (EI) for $C_{30}H_{32}N_6O_2$: 509.3 (MH^+).

[0211] *N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[3-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}phenyl)urea: 1H NMR (400 MHz, CD_3OD): δ 8.10 (d, $J = 2.4$ Hz, 1H), 7.81 (m, 2H), 7.67 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.62 (m, 2H), 7.57 (d, $J = 8.8$ Hz, 1H), 7.53 (bs, 1H), 7.42 (m, 2H), 7.15 (s, 1H), 7.09 (m, 1H), 4.01 (bd, $J = 13.2$ Hz, 2H), 3.65 (bd, $J = 12.0$ Hz, 2H), 3.32 (m, 2H), 3.17 (dt, $J = 13.2, 1.6$ Hz, 2H), 2.99 (s, 3H); MS (EI) for $C_{28}H_{26}ClF_3N_6O$: 555.2 (MH^+).

[0212] *N*-(2,4-difluorophenyl)-*N'*-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}phenyl)urea: 1H NMR (400 MHz, $DMSO-d_6$): δ 8.09 (m, 1H), 7.73 (m, 4H), 7.51 (m, 2H), 7.28 (m, 1H), 7.07 (m, 2H), 7.03 (m, 1H), 7.00 (s, 1H), 3.92 (bd, $J = 12.8$ Hz, 2H), 3.52 (bd, $J = 12.8$ Hz, 2H), 3.17 (dt, $J = 12.4, 2.4$ Hz, 2H), 3.05 (dt, $J = 12.4, 2.4$ Hz, 2H), 2.86 (s, 3H); MS (EI) for $C_{27}H_{26}F_2N_6O$: 489.2 (MH^+).

[0213] *N*-[2,4-bis(methyloxy)phenyl]-*N'*-(4-{5-[4-(4-methylpiperazine-1-yl)phenyl]-1*H*-pyrazol-3-yl}phenyl)urea: 1H NMR (400 MHz, CH_3OH-d_4): δ 8.80 (m, 2H), 7.70 (m, 1H), 7.50 (m, 2H), 6.50 (m, 5H), 3.95 (s, 3H), 3.85 (s, 3H), 3.78 (m, 4H), 2.68 (m, 4H), 2.40 (s, 3H); MS (EI) for $C_{29}H_{32}N_6O_3$: 513.2 (MH^+).

[0214] *N*-[5-chloro-2-(methyloxy)phenyl]-*N'*-(4-{5-[4-(4-methylpiperazine-1-yl)phenyl]-1*H*-pyrazol-3-yl}phenyl)urea: 1H NMR (400 MHz, CH_3OH-d_4): δ 8.25 (s, 1H), 7.70 (dd, 4H), 7.60 (d, 2H), 7.00 (d, 2H), 6.80 (s, 1H), 3.95 (s, 3H), 3.38 (m, 4H), 2.60 (m, 4H), 2.40 (s, 3H); MS (EI) for $C_{28}H_{29}ClN_6O_2$: 517.2 (M)

[0215] *N*-(3,4-dimethylphenyl)-*N'*-(4-{5-[4-(4-methylpiperazine-1-yl)phenyl]-1*H*-pyrazol-3-yl}phenyl)urea: 1H NMR (400 MHz, $DMSO-d_6$): δ 13.0 (s, 1H), 8.78 (s, 1H), 8.60 (s, 1H), 7.60 (m, 7H), 7.30 (m, 5H), 3.20 (m, 4H), 2.50 (m, 4H), 2.10 (m, 9H); MS (EI) for $C_{29}H_{32}N_6O_2$: 481.3 (MH^+).

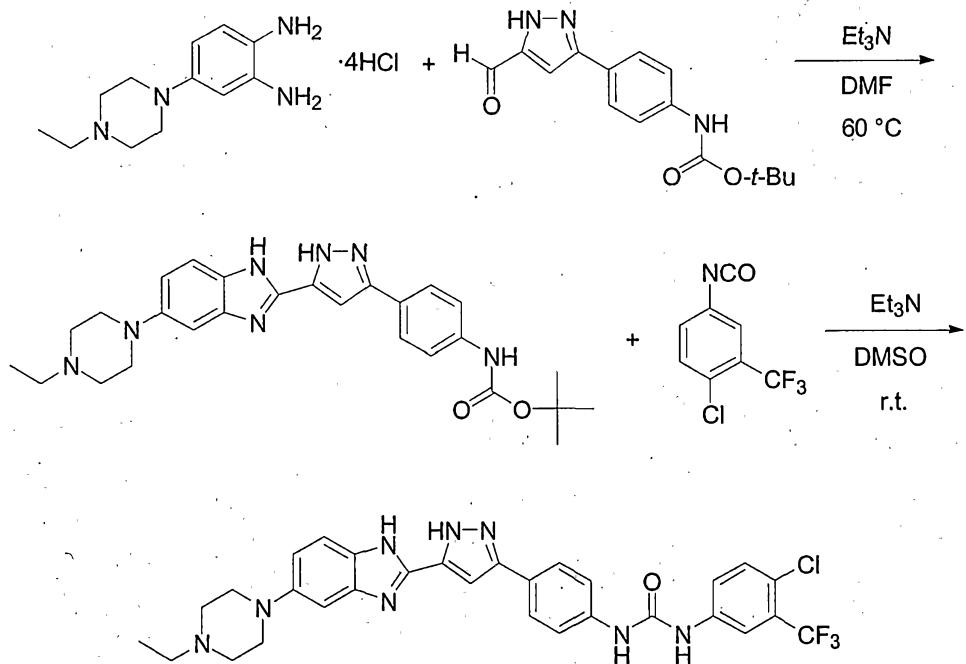
[0216] *N*-(4-{5-[4-(4-methylpiperazine-1-yl)phenyl]-1*H*-pyrazol-3-yl}phenyl)-*N'*-[4-(phenyloxy)phenylurea: 1H NMR (400 MHz, $DMSO-d_6$): δ 8.78 (br, 2H), 7.70 (m, 3H), 7.50 (m, 3H), 7.40 (m, 3H), 7.00 (m, 8H), 3.20 (m, 4H), 2.50 (m, 4H), 2.20 (s, 3H); MS (EI) for $C_{33}H_{32}N_6O_2$: 545.3 (MH^+).

[0217] N-(2,3-dihydro-1,4-benzodioxin-6-yl)-N'-(4-{5-[4-(4-methylpiperazine-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea: ^1H NMR (400 MHz, $\text{CH}_3\text{OH-d4}$): δ 7.70 (m, 4H), 7.50 (d, 2H), 7.10 (m, 3H), 6.90 (s, 1H), 6.80 (m, 2H), 4.20 (m, 4H), 3.90 (m, 2H), 3.60 (m, 2H), 3.30 (m, 2H), 3.10 (m, 2H), 2.90 (s, 3H); MS (EI) for $\text{C}_{29}\text{H}_{30}\text{N}_6\text{O}_3$: 511.3 (MH^+).

[0218] N-(5-fluoro-2-methylphenyl)-N'-(4-{5-[4-(4-methylpiperazine-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea: ^1H NMR (400 MHz, $\text{CH}_3\text{OH-d4}$): δ 7.70 (m, 5H), 7.60 (d, 2H), 7.20 (m, 3H), 6.90 (s, 1H), 6.80 (m, 1H), 4.00 (m, 2H), 3.60 (m, 2H), 3.30 (m, 2H), 3.10 (m, 2H), 2.90 (s, 3H), 2.25 (s, 3H); MS (EI) for $\text{C}_{28}\text{H}_{29}\text{FN}_6\text{O}$: 485.3 (MH^+).

Example 9

$\text{N-}[4\text{-Chloro-3-(trifluoromethyl)phenyl}-\text{N}'-(4\text{-}\{3\text{-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-3-yl}\}\text{phenyl})\text{urea}$



[0219] 4-{5-[5-(4-Ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-3-yl} aniline:

Triethylamine (509 μL , 3.62 mmol) was added to a solution of 4-(4-ethylpiperazin-1-yl)-benzene-1,2-diamine as the tetra-hydrochloride salt in anhydrous DMF (4 mL). After five minutes, a solution of [4-(5-formyl-1H-pyrazol-3-yl)phenyl]carbamic acid *tert*-butyl ester in anhydrous DMF (2 mL) was added to the diamine. The reaction flask was left open to the air

and heated to 65 °C. After twelve hours the reaction was concentrated in vacuo and the residue purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the product (87 mg, 99 % yield) as a light purple solid. Note that the BOC group was removed under the purification conditions: ^1H NMR (400 MHz, CDCl_3): δ 7.90 (m, 2H), 7.71 (d, J = 8.8 Hz, 1H), 7.46 (m, 2H), 7.42 (dd, J = 9.2, 2.0 Hz, 1H), 7.41 (s, 1H), 7.30 (d, J = 2.4 Hz, 1H), 4.01 (bd, J = 12.0 Hz, 2H), 3.74 (bd, J = 10.4 Hz, 2H), 3.35-3.27 (m, 4H), 3.23 (m, 2H), 1.44 (t, J = 7.2 Hz, 3H); MS (EI) for $\text{C}_{22}\text{H}_{25}\text{N}_7$: 388.2 (MH^+).

[0220] *N*-[4-Chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[5-(4-ethylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-3-yl}phenyl)urea: Triethylamine (250 μL , 1.78 mmol) was added to a solution of the above pyrazole (0.087 g, 0.18 mmol) and 4-chloro-3-trifluoromethyl-phenylisocyanate (0.039 g, 0.18 mmol) in anhydrous DMSO (2.0 mL) at room temperature. After twelve hours the reaction was concentrated in vacuo and purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the title compound (46 mg, 43 % yield) as an off-white solid: ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 10.81 (bs, 1H), 9.95 (s, 1H), 9.69 (s, 1H), 8.14 (s, 1H), 7.78 (m, 2H), 7.69 (d, J = 8.8 Hz, 1H), 7.66 (m, 5H), 7.54 (s, 1H), 7.36 (bd, J = 9.2 Hz, 1H), 7.16 (s, 1H), 3.91 (bd, J = 11.2 Hz, 2H), 3.60 (bd, J = 10.8 Hz, 2H), 3.19 (m, 6H), 1.30 (t, J = 7.2 Hz, 3H); MS (EI) for $\text{C}_{30}\text{H}_{28}\text{ClF}_3\text{N}_8\text{O}$: 609.3 (MH^+).

[0221] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0222] *N*-(2,4-difluorophenyl)-*N'*-(4-{3-[6-(4-ethylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-3-yl}phenyl)urea: ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 8.04 (m, 1H), 7.69 (m, 2H), 7.64 (d, J = 9.2 Hz, 1H), 7.54 (m, 2H), 7.34 (s, 1H), 7.31 (dd, J = 9.2, 2.0 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.11 (m, 1H), 6.93 (m, 1H), 3.88 (bd, J = 10.8 Hz, 2H), 3.61 (bd, J = 12.4 Hz, 2H), 3.18 (m, 6H), 1.30 (t, J = 7.2 Hz, 3H); MS (EI) for $\text{C}_{29}\text{H}_{28}\text{F}_2\text{N}_8\text{O}$: 543.3 (MH^+).

[0223] *N*-(3-ethylphenyl)-*N'*-(4-{3-[5-(4-ethylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-3-yl}phenyl)urea: ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 7.77 (m, 2H), 7.71 (d, J = 8.8 Hz, 1H), 7.66 (m, 2H), 7.51 (s, 1H), 7.39 (dd, J = 9.2, 1.6 Hz, 1H), 7.35 (bs, 1H), 7.31 (bd, J = 8.0 Hz, 1H), 7.22 (m, 2H), 6.85 (bd, J = 5.6 Hz, 1H), 3.94 (bd, J = 9.2 Hz, 2H), 3.65 (bd, J

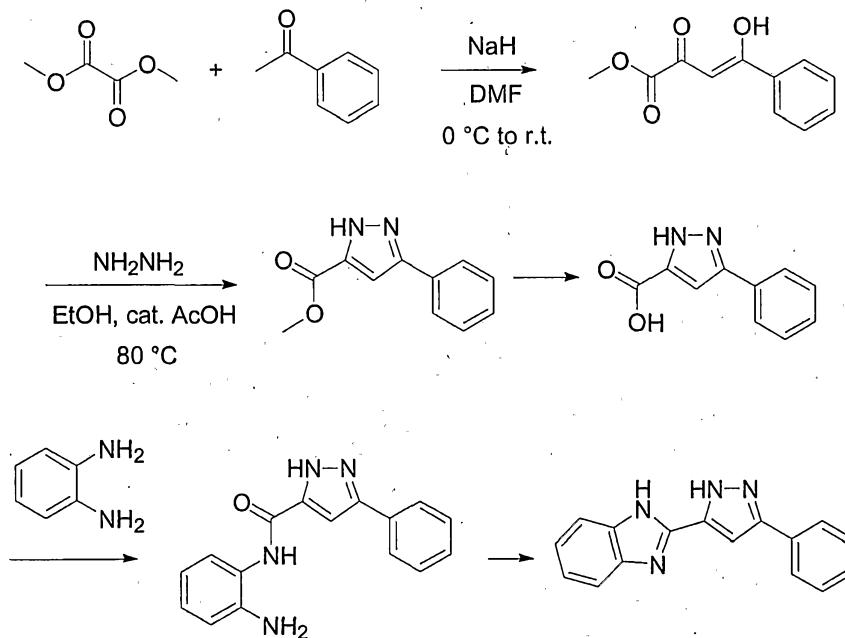
= 8.4 Hz, 2H), 3.22 (m, 4H), 3.14 (m, 2H), 3.10 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.6 Hz, 3H); MS (EI) for $C_{31}H_{34}N_8O$: 535.3 (MH^+).

[0224] *N*-(4-{3-[5-(4-ethylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-3-yl}phenyl)-*N'*-[3-(trifluoromethyl)phenyl]urea: 1H NMR (400 MHz, DMSO-*d*₆): δ 11.0 (bs, 1H), 9.91 (s, 1H), 9.77 (s, 1H), 8.04 (bs, 1H), 7.78 (m, 2H), 7.70 (d, J = 8.8 Hz, 1H), 7.66 (m, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.38 (dd, J = 9.2, 4.0, 1H), 7.32 (bd, J = 7.6 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 3.91 (bd, J = 12.4 Hz, 2H), 3.69 (m, 1H), 3.61 (bd, J = 10.8 Hz, 2H), 3.48 (m, 1H), 3.21 (m, 4H), 1.31 (t, J = 7.2 Hz, 3H); MS (EI) for $C_{30}H_{29}F_3N_8O$: 575.3 (MH^+).

[0225] *N*-(1,1-dimethylethyl)-*N'*-4-{3-[5-(4-ethylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-3-yl}phenyl)urea: 1H NMR (400 MHz, DMSO-*d*₆): δ 7.67 (d, J = 9.2 Hz, 1H), 7.65 (m, 2H), 7.50 (m, 2H), 7.43 (s, 1H), 7.34 (dd, J = 9.2, 2.0 Hz, 1H), 7.16 (d, J = 2.0, 1H), 3.89 (bd, J = 9.2 Hz, 2H), 3.60 (bd, J = 8.8 Hz, 2H), 3.17 (m, 6H), 1.29 (t, J = 7.2 Hz, 3H), 1.27 (s, 9H); MS (EI) for $C_{27}H_{34}N_8O$: 487.3 (MH^+).

Example 10

2-(5-Phenyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazole



[0226] **Methyl (2Z)-3-hydroxy-3-phenylprop-2-enoate:** To a solution of acetophenone (10.0 g, 83.2 mmol) and dimethyl oxalate (11.8 g, 100.0 mmol) in DMF (80 mL) was added sodium hydride (4.0 g, 100 mmol, 60% oil dispersion). This mixture was stirred for 1h at room temperature and reacted for 30 min. at 50 °C. It was cooled on ice bath, quenched with water saturated with sodium chloride and neutralized with 2N hydrochloric acid. The organic layer was separated and dried with sodium sulfate. After flash column chromatography (30% Ethyl acetate / hexane), the product was obtained as a colorless solid (12.0 g, 70.2% yield): MS (EI) for $C_{11}H_{10}O_4$: 207.06 (MH^+).

[0227] **Methyl 3-phenyl-1*H*-pyrazole-5-carboxylate:** To a solution of 2-hydroxy-4-oxo-4-phenyl-but-2-enoic acid methyl ester (12.0 g, 58.2 mmol) in EtOH (30 ml) was added hydrazine monohydrate (2.84 mL, 58.2 mmol) and the mixture was heated at reflux for 5 h. The reaction mixture was cooled to room temperature and filtered in vacuo. The precipitate was washed with EtOH to give the desired product (6.02 g, 51.5% yield): MS (EI) for $C_{11}H_{10}N_2O_2$: 203.08 (MH^+).

[0228] **3-Phenyl-1*H*-pyrazole-5-carboxylic acid:** To a solution of methyl 3-phenyl-1*H*-pyrazole-5-carboxylate (6.02 g, 29.8 mmol) in THF and H_2O (3:1, 140 mL) was added LiOH (3.42 g, 142.8 mmol) and the mixture was stirred overnight at room temperature. It was poured into 2N HCl solution (150 mL) and extracted with ethyl acetate. After extraction, the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to afford product (3.2 g, 57.1 %): MS (EI) for $C_{10}H_8N_2O_2$: 189.26 (MH^+).

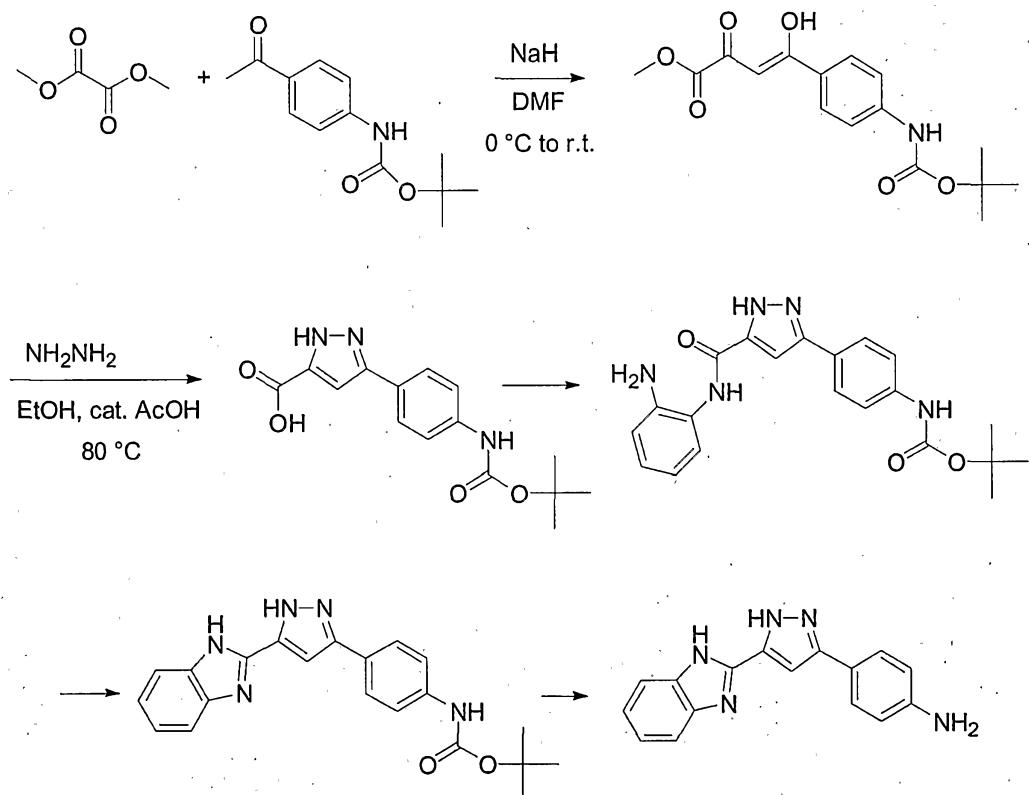
[0229] ***N*-(2-aminophenyl)-3-phenyl-1*H*-pyrazole-5-carboxamide:** EDCI (288 mg, 1.5 mmol) was added to a solution of 1,2-diaminobenzene (0.141 g, 1.31 mmol), 3-phenyl-1*H*-pyrazole-5-carboxylic acid (188 mg, 1.0 mmol) and HOBT (203 mg, 1.5 mmol) in anhydrous DMF (5 mL). The reaction was stirred under nitrogen at room temperature. After twelve hours the reaction was concentrated in vacuo and precipitated from methanol with a small amount of water. The solid was collected by vacuum filtration and further purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the corresponding amide (60 mg, 38 % yield).

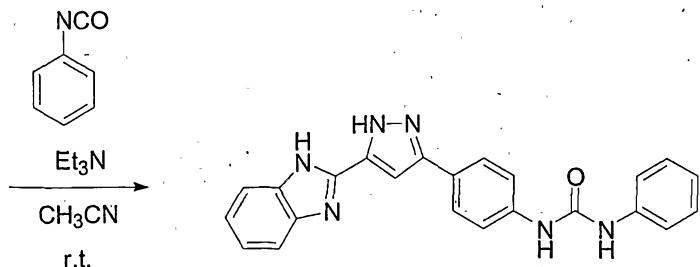
[0230] **2-(3-Phenyl-1*H*-pyrazol-5-yl)-1*H*-benzimidazole:** Glacial acetic acid (1.0 mL) was added to a sealed tube charged with a solution of the amide (60 mg, 0.38 mmol) in xyles

(1.0 mL) and heated to 100 °C. After twelve hours the reaction was cooled to room temperature and concentrated in vacuo. The residue was purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the title benzimidazole (26 mg, 25 % yield) as a white solid: ¹H NMR (400 MHz, DMSO-d₆): δ 13.76 (d, 1H), 12.90 (s, 1H), 7.87 (m, 2H), 7.52 (m, 4H), 7.41 (m, 1H), 6.94 (m, 1H), 7.33 (s, 1H), 7.20 (m, 2H); MS (EI) for C₁₆H₁₂N₄: 261.2 (MH⁺).

Example 11

N-{4-[3-(1H-Benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-phenylurea





[0231] Methyl (2*Z*)-3-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)phenyl]-3-hydroxyprop-2-enoate: NaH (60% dispersion, 2.22 g, 55.5 mmol) was added to a solution of dimethyl oxalate (2.73 g, 23.1 mmol) and 1,1-dimethylethyl (4-acetylphenyl)carbamate (*N*-BOC-4-aminoacetophenone, 5.44 g, 23.1 mmol) in anhydrous DMF (50 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight and quenched with saturated aqueous NH₄Cl and neutralized with 1M HCl. The reaction was diluted with ethyl acetate (80 mL) and the organic layer washed successively with saturated aqueous NaHCO₃ and brine. The organic phase was separated and dried over Na₂SO₄, filtered, concentrated in vacuo and triturated with chloroform to provide the condensation product (3.77 g, 53.1 % yield).

[0232] 3-[4-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)phenyl]-1*H*-pyrazole-5-carboxylic acid: Hydrazine monohydrate (0.696 g, 13.89 mmol) was added to a suspension of the above product (3.27 g, 13.89 mmol) in absolute ethanol (46 mL). The reaction mixture was refluxed for 1 hour. The reaction mixture was cooled to room temperature and filtered to provide the desired product (2.76, 65.5% yield): ¹H NMR (400 MHz, DMSO-d₆): δ 9.44 (s, 1H), 7.68 (d, 2H), 7.48 (d, 2H), 6.88 (s, 1H), 1.48 (s, 9H).

[0233] 1,1-Dimethylethyl [4-(5-{{(2-aminophenyl)amino}carbonyl}-1*H*-pyrazol-3-yl)phenyl]carbamate: EDCI (0.372 g, 1.94 mmol) was added to a solution of 1,2-diaminobenzene (0.28 g, 2.58 mmol), 3-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)phenyl]-1*H*-pyrazole-5-carboxylic acid (0.392 g, 1.29 mmol) and HOEt (0.262 g, 1.94 mmol) in anhydrous DMF (13 mL). The reaction was stirred under nitrogen at room temperature over. After twelve hours the reaction was concentrated in vacuo and precipitated from methanol with a small amount of water. The solid was collected by vacuum filtration and was submitted to the next step.

[0234] 1,1-Dimethylethyl {4-[5-(1*H*-benzimidazol-2-yl)-1*H*-pyrazol-3-yl]phenyl} carbamate: Glacial acetic acid (1.0 mL) was added to a sealed tube charged with the above amide in

xylanes (10.0 mL) and heated to 100 °C. After twelve hours the reaction was cooled to room temperature and concentrated in vacuo. The residue was purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide 40 mg of product (29 % yield over two steps) as a white solid: ^1H NMR (400 MHz, DMSO-d₆): δ 9.62 (s, 1H), 7.74 (m, 4H), 7.61 (m, 2H), 7.45 (s, 2H), 7.35 (s, 1H); MS (EI) for C₂₁H₂₁N₅O₂: 376.2 (MH⁺).

[0235] 4-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl]aniline: To a solution of 1,1-dimethylethyl {4-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl]phenyl} carbamate (130 mg, 0.266 mmol) in methanol (9.0 mL) was added 4M hydrochloric acid in dioxane (3 mL) solution. The reaction mixture was evaporated in vacuo and triturated with ethyl acetate to provide product as the hydrochloride salt (95.2 mg, 88% yield).

[0236] N-{4-[3-(1H-Benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-phenylurea: Triethylamine (35 μ L, 0.25 mmol) was added to a suspension of 4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]aniline (20 mg, 0.064 mmol) and phenyl isocyanate (7.6 mg, 0.064 mmol) in anhydrous acetonitrile (1.0 mL) at room temperature. After twelve hours the reaction was concentrated in vacuo and purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the title compound (9 mg, 36% yield) as a white solid: ^1H NMR (400 MHz, DMSO-d₆): δ 9.08 (s, 1H), 8.92 (s, 1H), 7.78 (m, 4H), 7.63 (m, 2H), 7.48 (m, 4H), 7.40 (s, 1H), 7.30 (m, 2H), 7.00 (m, 1H); MS (EI) for C₂₃H₁₈N₆O: 395.2 (MH⁺).

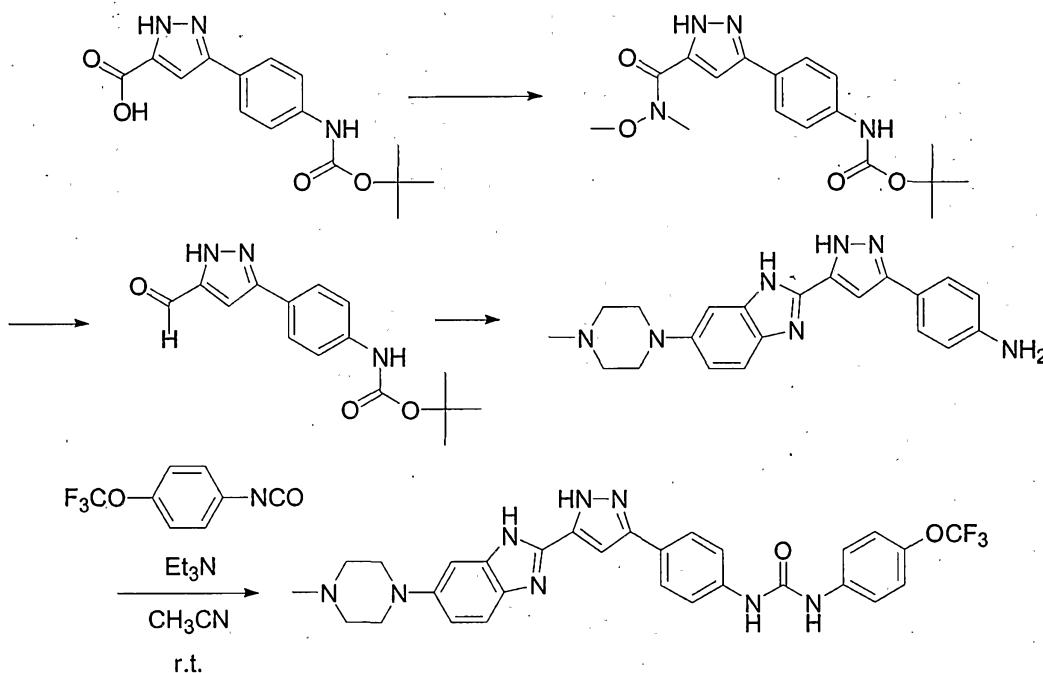
[0237] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0238] N-{4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea: ^1H NMR (400 MHz, DMSO-d₆): δ 9.58 (s, 1H), 9.38 (s, 1H), 8.16 (s, 1H), 7.80 (m, 4H), 7.66 (m, 4H), 7.53 (m, 2H), 7.45 (s, 1H); MS (EI) for C₂₄H₁₆N₆OF₃Cl: 497.1 (MH⁺).

[0239] N-{4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea: ^1H NMR (400 MHz, DMSO-d₆): δ 9.73 (s, 1H), 9.14 (d, 1H), 8.64 (dd, 1H), 7.81 (m, 4H), 7.67 (m, 2H), 7.54 (m, 3H), 7.50 (s, 1H); 7.42 (m, 1H); MS (EI) for C₂₄H₁₆N₆OF₄: 481.1 (MH⁺).

Example 12

N-(4-{3-[5-(4-Methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-{4-[trifluoromethyl]oxy}phenyl}urea



[0240] 1,1-Dimethylethyl [4-(5-{{[methyl(methyloxy)amino]carbonyl}-1H-pyrazol-3-yl}phenyl]carbamate: EDCI (2.56g, 13.35mmol) was added to a solution of *N*, *O*-dimethylhydroxyamine hydrochloride (0.87g, 8.9mmol), 3-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)phenyl]-1*H*-pyrazole-5-carboxylic acid (2.7 g, 8.9 mmol) and HOBr (1.804 g, 13.35 mmol) in anhydrous DMF (30 mL). The reaction was stirred under nitrogen at room temperature. After twelve hours the reaction was concentrated under reduced pressure, diluted with ethyl acetate (200 mL), washed with water. The organic layer was concentrated to afford the crude product (2.46 g, 80% yield).

[0241] 1,1-Dimethylethyl [4-(5-formyl-1*H*-pyrazol-3-yl)phenyl]carbamate: To a suspension of lithium aluminum hydride (0.889 g, 23.44 mmol) in THF (50 mL) was added a solution of 1,1-dimethylethyl [4-(5-{{[methyl(methyloxy)amino]carbonyl}-1*H*-pyrazol-3-yl}phenyl]carbamate (2.46 g, 7.1 mmol) in THF (20 mL) at -78°C. After addition, the reaction mixture was stirred at -78°C for 30 minutes. The reaction mixture was then allowed to warm to room

temperature overnight. The reaction was quenched with 30% sodium hydroxide aqueous solution, and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure to afford the desired product (1.5 g, 74% yield).

[0242] 4-{5-[6-(4-Methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-3-yl} aniline:

Triethylamine (2.32 g, 23 mmol) was added to a solution of 4-(4-methylpiperazin-1-yl)-benzene-1,2-diamine as the tetra-hydrochloride salt in anhydrous DMF (11 mL) after five minutes, a solution of 1,1-dimethylethyl [4-(5-formyl-1*H*-pyrazol-3-yl)phenyl]carbamate in anhydrous DMF (2 mL) was added to the diamine. The reaction flask was left open to the air and heated to 65 °C. After twelve hours the reaction was concentrated in vacuo and the residue purified on reverse phase HPLC using water-acetonitrile gradient (0.1 % TFA) to provide the product (0.60 g, 70% yield). (Note that the BOC group was removed under the purification conditions.)

[0243] N-(4-{3-[5-(4-Methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)-N'-{4-[(trifluoromethyl)oxy]phenyl}urea:

To a solution of 4-{5-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-3-yl} aniline (45 mg, 0.12 mmol) in DMSO (2 mL) were added 1-isocyanato-4-trifluoromethoxybenzene (36.6 mg, 0.18 mmol), triethylamine (36.4 mg, 0.36 mmol) in CH_3CN (1 mL) at room temperature. The reaction mixture was monitored by LC-MS until reaction was complete (1 h). The resulting mixture was concentrated in vacuo and separated by preparative HPLC (0.1 % TFA/ CH_3CN , 0.05 % TFA/water). The corresponding fractions were concentrated and dried. The resulting solid was dissolved in MeOH (1 mL) and was added 4N HCl (0.5 mL). The solution was concentrated and repeated three times to afford product (24 %, 34.7 mg) as light yellow solid as the hydrochloride salt: ^1H NMR (400 MHz, DMSO- d_6): δ 11.07 (s, 1H), 9.68 (d, 2H), 7.79-7.57 (7H, m), 7.38-7.29 (m, 3H), 7.17 (s, 1H), 3.90 (m, 2H), 3.46 (m, 2H), 3.21 (m, 4H), 2.85 (m, 3H) MS (EI) for $\text{C}_{29}\text{H}_{27}\text{F}_3\text{N}_8\text{O}_2$: 577.3 (MH^+).

[0244] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

[0245] N-(4-{3-[5-(4-Methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)-N'-phenylurea: ^1H NMR (400 MHz, DMSO- d_6): δ 10.90 (bs, 1H), 9.51 (s, 1H),

9.29 (s, 1H), 7.77 (d, 2H), 7.70 (d, 1H), 3.91 (m, 2H), 3.69 (m, 2H), 3.19 (m, 4H), 2.86 (s, 3H); MS (EI) for $C_{28}H_{28}N_8O$: 493.2 (MH^+).

[0246] N-[4-Chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: 1H NMR (400 MHz, DMSO- d_6): δ 10.41 (bs, 1H), 9.67 (s, 1H), 9.46 (s, 1H), 8.13 (s, 1H), 7.57 (d, 2H), 7.64 (m, 5H), 7.45 (s, 1H), 7.31 (d, 1H), 7.13 (1H), 3.89 (d, 2H), 3.55 (m, 2H), 3.16 (m, 4H), 2.86 (s, 3H); MS (EI) for $C_{29}H_{26}ClF_3N_8O$: 595.2 (MH^+).

[0247] N-(2,4-Difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: 1H NMR (400 MHz, DMSO- d_6): δ 10.87 (bs, 1H), 9.71 (s, 1H), 8.80 (s, 1H), 8.05 (m, 1H), 7.75 (d, 2H), 7.67 (d, 1H), 7.63 (d, 2H), 7.54 (s, 1H), 7.31 (m, 2H), 7.14 (m, 1H), 7.05 (m, 1H), 3.89 (d, 2H), 3.69 (m, 2H), 3.22 (m, 4H), 2.66 (s, 3H); MS (EI) for $C_{28}H_{26}F_2N_8O$: 529.2 (MH^+).

[0248] N-[3,4-Bis(methyloxy)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: 1H NMR (400 MHz, DMSO- d_6): δ 10.43 (bs, 1H), 9.16 (s, 1H), 8.88 (s, 1H), 7.75 (d, 2H), 7.69 (d, 1H), 7.64 (d, 2H), 7.47 (s, 1H), 7.36 (d, 1H), 7.24 (s, 1H), 7.17 (s, 1H), 6.89 (s, 1H), 3.92 (d, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.56 (d, 2H), 3.22 (d, 2H), 3.17 (d, 2H), 2.87 (d, 3H); MS (EI) for $C_{30}H_{32}N_8O_3$: 553.3 (MH^+).

[0249] N-(4-{3-[5-(4-Methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea: 1H NMR (400 MHz, DMSO- d_6): δ 10.81 (bs, 1H), 9.74 (s, 1H), 9.62 (s, 1H), 8.02 (s, 1H), 7.76 (d, 2H), 7.65 (m, 3H), 7.58 (d, 1H), 7.52 (m, 2H), 7.32 (m, 2H), 7.14 (s, 1H), 3.92 (d, 2H), 3.58 (d, 2H), 3.24 (m, 4H), 2.84 (d, 3H); MS (EI) for $C_{29}H_{27}F_3N_8O$: 561.3 (MH^+).

[0250] N-(4-Chlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: 1H NMR (400 MHz, DMSO- d_6): δ 10.58 (bs, 1H), 9.40 (s, 1H), 9.35 (s, 1H), 7.70 (d, 2H), 7.68 (d, 1H), 7.64 (d, 2H), 7.51 (d, 2H), 7.49 (d, 1H), 7.34 (m, 3H), 7.16 (s, 1H), 3.91 (d, 2H), 3.55 (d, 2H), 3.17 (m, 4H), 2.86 (d, 3H); MS (EI) for $C_{28}H_{27}ClN_8O$: 527.2 (MH^+).

[0251] N-(4-Fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: 1H NMR (400 MHz, DMSO- d_6): δ 10.92 (bs, 1H), 9.50 (s, 1H),

9.36 (s, 1H), 7.76 (d, 2H), 7.69 (d, 1H), 7.64 (d, 2H), 7.55 (s, 1H), 7.49 (dd, 1H), 7.37 (dd, 1H), 7.15 (d, 2H), 7.12 (s, 1H), 3.91 (d, 2H), 3.55 (d, 2H), 3.17 (m, 4H), 2.86 (d, 3H); MS (EI) for $C_{28}H_{27}FN_8O$: 511.3 (MH^+).

[0252] N-(3-Fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: 1H NMR (400 MHz, DMSO- d_6): δ 10.92 (bs, 1H), 9.63 (s, 1H), 9.62 (s, 1H), 7.83 (d, 2H), 7.68 (d, 1H), 7.65 (d, 2H), 7.53 (m, 2H), 7.34 (dd, 2H), 7.17 (s, 1H), 7.13 (d, 1H), 6.80 (m, 1H), 3.90 (d, 2H), 3.69 (m, 2H), 3.23 (m, 4H), 2.84 (s, 3H); MS (EI) for $C_{28}H_{27}FN_8O$: 511.3 (MH^+).

[0253] N-(2-Fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: 1H NMR (400 MHz, DMSO- d_6): δ 11.14 (bs, 1H), 9.91 (s, 1H), 8.90 (s, 1H), 8.15 (t, 1H), 7.79 (d, 2H), 7.68 (m, 3H), 7.61 (s, 1H), 7.37 (d, 1H), 7.25 (dd, 1H), 7.16 (m, 2H), 7.03 (m, 1H), 3.54 (m, 2H), 3.48 (m, 2H), 3.21 (m, 4H), 2.84 (s, 3H); MS (EI) for $C_{28}H_{27}FN_8O$: 511.3 (MH^+).

[0254] N-(3,4-Dichlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: 1H NMR (400 MHz, DMSO- d_6): δ 11.05 (bs, 1H), 9.91 (s, 1H), 9.77 (s, 1H), 7.90 (d, 1H), 7.78 (d, 2H), 7.69 (d, 1H), 7.64 (d, 2H), 7.58 (s, 1H), 7.54 (d, 1H), 7.36 (dt, 2H), 7.16 (s, 1H), 3.90 (d, 2H), 3.53 (m, 2H), 3.20 (m, 4H), 2.84 (d, 3H); MS (EI) for $C_{28}H_{26}Cl_2N_8O$: 561.2 (MH^+).

[0255] N-(4-{3-[5-(4-Methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(4-(phenyloxy)phenyl)urea: 1H NMR (400 MHz, CD₃OD): δ 7.67-7.61 (m, 3H), 7.55-7.52 (m, 2H), 7.45-7.42 (m, 2H), 7.37-7.30 (m, 3H), 7.24 (m, 1H), 7.19 (s, 1H), 7.09-7.05 (m, 1H), 6.97-6.93 (m, 4H), 3.95-3.89 (d, 2H), 3.75-3.71 (m, 1H), 3.68-3.63 (m, 3H), 3.59-3.56 (m, 1H), 3.23-3.15 (m, 2H), 2.97 (s, 3H); MS (EI) for $C_{34}H_{32}N_8O_2$: 585.3 (MH^+).

[0256] N-(3,5-Difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: 1H NMR (400 MHz, CD₃OD): δ (m, 3H), 7.64-7.61 (m, 2H), 7.43-7.40 (m, 1H), 7.31-7.29 (m, 2H), 7.15-7.12 (m, 2H), 6.60-6.54 (m, 1H), 4.01-3.94 (d, 2H), 3.71-3.65 (m, 2H), 3.39-3.32 (m, 1H), 3.25-3.17 (m, 3H), 3.01 (s, 3H); MS (EI) for $C_{28}H_{26}F_2N_8O$: 529.2 (MH^+).

[0257] N-[3,5-Bis(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: ^1H NMR (400 MHz, CD₃OD): δ 8.11 (s, 2H), 7.75-7.64 (m, 5H), 7.56 (m, 5H), 7.43-7.39 (dd, 1H), 7.30 (s, 2H), 4.01-3.94 (d, 2H), 3.75-3.64 (m, 4H), 3.25-3.17 (m, 2H), 3.01 (s, 3H); MS (EI) for C₃₀H₂₆F₆N₈O: 629.2 (MH⁺).

[0258] N-(3-Chlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: ^1H NMR (400 MHz, CD₃OD): δ 7.73-7.66 (m, 4H), 7.63-7.60 (m, 2H), 7.43-7.40 (m, 1H), 7.30-7.25 (m, 4H), 7.04-7.00 (m, 1H), 4.00-3.94 (d, 2H), 3.70-3.65 (m, 2H), 3.39-3.33 (m, 2H), 3.25-3.16 (m, 2H), 3.00 (s, 3H); MS (EI) for C₂₈H₂₇ClN₈O: 527.2 (MH⁺).

[0259] N-[3-(Methyloxy)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: ^1H NMR (400 MHz, CD₃OD): δ 7.65-7.62 (d, 1H), 7.58-7.55 (d, 2H), 7.49-7.45 (d, 2H), 7.35-7.31 (m, 1H), 7.20-7.13 (m, 4H), 6.95 (6.92 (m, 1H), 6.61-6.58 (m, 1H), 3.92-3.87 (d, 2H), 3.79 (s, 3H), 3.68-3.60 (m, 2H), 3.28-3.13 (m, 4H), 2.94 (s, 3H); MS (EI) for C₂₉H₃₀N₈O₂: 523.3 (MH⁺).

[0260] N-(3-Acetylphenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: ^1H NMR (400 MHz, CD₃OD): δ 7.72-7.57 (m, 8H), 7.46-7.38 (m, 2H), 7.29-7.26 (m, 2H), 4.00-3.93 (m, 2H), 3.70-3.64 (m, 4H), 3.25-3.17 (m, 2H), 3.00 (s, 3H), 2.61 (s, 3H); MS (EI) for C₃₀H₃₀N₈O₂: 535.3 (MH⁺).

[0261] N-(3,4-Difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: ^1H NMR (400 MHz, CD₃OD): δ 7.73-7.69 (m, 3H), 7.63-7.58 (m, 3H), 7.43-7.40 (m, 1H), 7.31-7.29 (m, 2H), 7.22-7.15 (m, 1H), 7.10-7.05 (m, 1H), 4.00-3.94 (d, 2H), 3.71-3.56 (m, 3H), 3.40-3.33 (m, 1H), 3.25-3.16 (m, 2H), 3.00 (s, 3H); MS (EI) for C₂₈H₂₆F₂N₈O: 529.2 (MH⁺).

[0262] N-[4-Fluoro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: ^1H NMR (400 MHz, CD₃OD): δ 7.91-7.91 (m, 1H), 7.74-7.62 (m, 6H), 7.44-7.40 (m, 1H), 7.31-7.25 (m, 3H), 4.01-3.94 (d, 2H), 3.71-3.56 (m, 3H), 3.40-3.32 (m, 1H), 3.26-3.16 (m, 2H), 3.01 (s, 3H); MS (EI) for C₂₉H₂₆F₄N₈O: 579.2 (MH⁺).

[0263] N-[3,5-Bis(methyloxy)phenyl]-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: ^1H NMR (400 MHz, *d*-MeOH): δ 7.70 (m, 3H), 7.60 (d, 2H), 7.41 (d, 1H), 7.24 (m, 2H), 6.70 (d, 2H), 6.22 (s, 1H), 3.86 (br d, 2H), 3.78 (s, 6H), 3.62 (br d, 2H), 3.30 (m, 4H), 3.02 (s, 3H); MS (EI) for $\text{C}_{30}\text{H}_{32}\text{N}_8\text{O}_3$: 590 (MH^+).

[0264] N-(3-Bromophenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: ^1H NMR (400 MHz, *d*-MeOH): δ 7.82 (br t, 1H), 7.72 (br d, 3H), 7.62 (br d, 2H), 7.42 (dd, 1H), 7.35 (m, 3H), 7.18 (m, 2H), 3.90 (br d, 2H), 3.78 (s, 6H), 3.63 (br d, 2H), 3.34 (m, 4H), 3.08 (s, 3H); MS (EI) for $\text{C}_{28}\text{H}_{27}\text{BrN}_8\text{O}$: 573 (MH^+).

[0265] N-(3-Cyanophenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: ^1H NMR (400 MHz, *d*-MeOH): δ 8.02 (br s, 1H), 7.61 (m, 6H), 7.51 (t, 1H), 7.34 (m, 4H), 3.90 (br s, 2H), 3.62 (br s, 2H), 3.25 (m, 4H), 3.04 (s, 3H); MS (EI) for $\text{C}_{29}\text{H}_{27}\text{N}_9\text{O}$: 518 (MH^+).

[0266] N-(5-Fluoro-2-methylphenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea: ^1H NMR (400 MHz, *d*-MeOH): δ 7.72 (m, 5H), 7.40 (d, 1H), 7.31 (d, 2H), 7.20 (t, 1H), 6.72 (t, 1H), 3.98 (br d, 2H), 3.68 (br d, 2H), 3.26 (m, 4H), 3.02 (s, 3H); MS (EI) for $\text{C}_{29}\text{H}_{29}\text{FN}_8\text{O}$: 523 (MH^+).

[0267] N-(4-{3-[6-(4-Methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-[4-(trifluoromethyl)phenyl]urea: ^1H NMR (400 MHz, *d*-MeOH): δ 7.71 (m, 3H), 7.64 (m, 3H), 7.62 (m, 3H), 7.42 (br d, 1H), 7.29 (m, 2H), 3.92 (d, 2H), 3.72 (d, 2H), 3.32 (m, 4H), 3.04 (s, 3H); MS (EI) for $\text{C}_{29}\text{H}_{27}\text{FN}_8\text{O}$: 561 (MH^+).

Assays

[0268] Kinase assays were performed by measurement of incorporation of γ - ^{33}P ATP into immobilized myelin basic protein (MBP). High binding white 384 well plates (Greiner) were coated with MBP (Sigma #M-1891) by incubation of 60 μl /well of 20 $\mu\text{g}/\text{ml}$ MBP in Tris-buffered saline (TBS; 50mM Tris pH 8.0, 138mM NaCl, 2.7mM KCl) for 24 hours at 4° C. Plates were washed 3X with 100 μl TBS. Kinase reactions were carried out in a total volume of 34 μl in kinase buffer (5mM Hepes pH 7.6, 15mM NaCl, 0.01% bovine gamma globulin

(Sigma #I-5506), 10mM MgCl₂, 1mM DTT, 0.02% TritonX-100). Compound dilutions were performed in DMSO and added to assay wells to a final DMSO concentration of 1%. Each data point was measured in duplicate, and at least two duplicate assays were performed for each individual compound determination. Enzyme was added to final concentrations of 10nM or 20nM, for example. A mixture of unlabeled ATP and γ -³³P ATP was added to start the reaction (2x10⁶ cpm of γ -³³P ATP per well (3000Ci/mmol) and either 10 μ M or 30 μ M unlabeled ATP, typically. The reactions were carried out for 1 hour at room temperature with shaking. Plates were washed 7x with TBS, followed by the addition of 50 μ l/well scintillation fluid (Wallac). Plates were read using a Wallac Trilux counter. This is only one format of such assays, various other formats are possible, as known to one of ordinary skill in the art.

[0269] The above assay procedure can be used to determine the IC₅₀ for inhibition and/or the inhibition constant, K_i. The IC₅₀ is defined as the concentration of compound required to reduce the enzyme activity by 50% under the conditions of the assay. Exemplary compositions have IC₅₀'s of, for example, less than about 100 μ M, less than about 10 μ M, less than about 1 μ M, and further for example having IC₅₀'s of less than about 100 nM, and still further, for example, less than about 10 nM. The K_i for a compound may be determined from the IC₅₀ based on three assumptions. First, only one compound molecule binds to the enzyme and there is no cooperativity. Second, the concentrations of active enzyme and the compound tested are known (i.e., there are no significant amounts of impurities or inactive forms in the preparations). Third, the enzymatic rate of the enzyme-inhibitor complex is zero. The rate (i.e., compound concentration) data are fitted to equation (1) below; where V is the observed rate, V_{max} is the rate of the free enzyme, I₀ is the inhibitor concentration, E₀ is the enzyme concentration, and K_d is the dissociation constant of the enzyme-inhibitor complex.

$$V = V_{\max} E_0 \left[I - \frac{(E_0 + I_0 + K_d) - \sqrt{(E_0 + I_0 + K_d)^2 - 4E_0 I_0}}{2E_0} \right]$$

Equation (1)

Kinase Specific Assays:

[0270] Kinase activity and compound inhibition are investigated using one or more of the three assay formats described below. The ATP concentrations for each assay are selected to be close to the Michaelis-Menten constant (K_M) for each individual kinase. Dose-response experiments are performed at 10 different inhibitor concentrations in a 384-well plate format. The data are fitted to four-parameter equation (2) below; where Y is the observed signal, X is the inhibitor concentration, Min is the background signal in the absence of enzyme (0% enzyme activity), Max is the signal in the absence of inhibitor (100% enzyme activity), IC_{50} is the inhibitor concentration at 50% enzyme inhibition and H represents the empirical Hill's slope to measure the cooperativity. Typically H is close to unity.

$$Y = Min + (Max - Min) / (1 + (X/IC_{50})^H)$$

Equation (2)

 ^{33}P phosphoryl transfer assay:

[0271] Greiner 384-well white, clear bottom, high binding plates are coated with 2 μ g/well of protein or peptide substrate in a 50 μ L volume overnight at ambient temperature. The coating buffer typically contains 40 μ g/mL substrate, 22.5 mM Na_2CO_3 , 27.5 mM $NaHCO_3$, 150 mM NaCl and 3 mM NaN_3 . The coating solution is aspirated and the plates are washed once with 50 μ L of assay buffer and padded dry. Subsequently compounds and enzymes are mixed with $\gamma^{33}P$ -ATP (3.3 μ Ci/nmol) in a total volume of 20 μ L in suitable assay buffers. The mixture is incubated at ambient temperature for 1.5-2.5 hrs and terminated by aspiration using a Molecular Devices EMBLA 96-head plate washer. The plates are subsequently washed 6-12 times with PBST or TBS buffer. Scintillation fluid (50 μ l/well) is then added,

the plates are sealed and activity assessed by liquid scintillation spectrometry using a Perkin Elmer MicroBeta TriLux.

Luciferase-coupled chemiluminescent assay (LCCA):

[0272] In the LCCA assays, kinase activity is measured as the percent ATP consumed following the kinase reaction using luciferase-luciferin-coupled chemiluminescence. Greiner 384-well white, clear bottom, medium-binding plates are used for LCCA. Briefly, the kinase reaction is initiated by mixing compounds, ATP and kinase in a 20uL volume. The mixture is incubated at ambient temperature for 2-4 hrs. At the end of the kinase reaction, a 20uL luciferase-luciferin mix is added and the chemiluminescent signal is read using a Wallac Victor² reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25mg/mL coenzyme A, 63 uM AMP, 28 ug/mL luciferin and 40,000 units of light/mL luciferase. For the LCCA assays, total ATP consumption has been standardized to 25-45% and the IC₅₀ values correlates well with those determined by radiometric assays.

AlphaScreen

[0273] AlphaScreen technology is a proximity assay which utilizes the increase in fluorescent signal occurring when donor and acceptor beads are close in proximity. Biotinylated poly(Glu,Tyr) 4:1 is used as the kinase substrate, in conjunction with streptavidin-coated donor beads and anti-phosphotyrosine antibody PY100-coated acceptor beads. Upon phosphorylation, the peptide substrate can bind to both donor and acceptor beads giving rise to an increase in fluorescence. Compounds, ATP, biotinylated poly(Glu, Tyr) and kinases are mixed in a volume of 20 uL for 1 hr at ambient temperature using Greiner 384-well white clear bottom medium binding plates. Following incubation a 10 uL solution containing 15-30 mg/mL AlphaScreen beads, 75 mM Hepes, pH 7.4, 300 mM NaCl, 120 mM EDTA, 0.3% BSA and 0.03% Tween-20 is added to each well. After 2-16 hr incubation of the beads, plates are read in a Perkin Elmer AlphaQuest reader. The IC₅₀ values correlates well with those of radiometric assays.

c-Kit Assay

[0274] c-Kit biochemical activity was assessed using AlphaScreen™ (Perkin Elmer) technology, described above. Test compounds, ATP, biotinylated poly(Glu, Tyr) and c-Kit kinase were combined in a volume of 20 μ L in a 384-well white, medium binding microtiter plate (Greiner). Reaction mixtures were incubated for 1 hr at ambient temperature. Reactions were quenched by addition of 10 μ L of 15-30 mg/mL AlphaScreen bead suspension containing 75 mM Hepes, pH 7.4, 300 mM NaCl, 120 mM EDTA, 0.3% BSA and 0.03% Tween-20. After 16 hr incubation at ambient temperature plates were read using an AlphaQuest reader (Perkin Elmer).

flt-3 Assay

[0275] Flt-3 biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 5 μ M ATP, 3 μ M poly-EY and 5 nM Flt-3 (baculovirus expressed human Flt-3 kinase domain R571-S993) in a 20uL assay buffer (20mM Tris-HCL pH7.5, 10mM MgCl₂, 0.01% Triton X-100, 1mM DTT, 2mM MnCl₂). The mixture is incubated at ambient temperature for 3 hours after which 20uL luciferase-luciferin mix is added and the chemiluminescent signal read using a Wallac Victor² reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5ug/mL oxalic acid (pH 7.8), 5 (or 50) mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 μ M AMP, 28 μ g/mL luciferin and 40,000 units of light/mL luciferase.

Structure Activity Relationships

[0276] Table 2 shows structure activity relationship data for exemplary compounds of the invention. Inhibition is indicated as IC₅₀ with the following key: A = IC₅₀ less than 50 nM, B = IC₅₀ greater than 50 nM, but less than 500 nM, C = IC₅₀ greater than 500 nM, but less

than 5000 nM, and D = IC₅₀ equal to, or greater than 5,000 nM. Empty cells indicate lack of data only. Abbreviations for enzymes listed in Table 2 are defined as follows: c-Kit, also called stem cell factor receptor or steel factor receptor; flt-3 refers to fms-like tyrosine kinase-3; EphB4 refers to ephrin receptor tyrosine kinase family member B4; and EGFR refers to epidermal growth factor receptor tyrosine kinase.

Table 2

Entry	Name	c-Kit	flt-3	EphB4	EGFR
1	4-((E)-2-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}ethenyl)phenol	A	A	C	D
2	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
3	N-(3-ethylphenyl)-N'-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	C	D
4	N-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(3-(trifluoromethyl)phenyl)urea	A	A	C	D
5	N-(3-acetylphenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	C	D
6	N-(3,4-dichlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
7	N-(3-bromophenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
8	N-[4-fluoro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
9	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(4-(phenyloxy)phenyl)urea	A	A	D	D

Table 2

Entry	Name	c-Kit	flt-3	EphB4	EGFR
10	N-(3-chlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
11	N-[3,5-bis(methyloxy)phenyl]-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
12	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-[4-[(trifluoromethyl)oxy]phenyl]urea	A	A	D	D
13	N-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-[4-(trifluoromethyl)phenyl]urea	A	A		
14	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
15	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-[3-(trifluoromethyl)phenyl]urea	A	A	C	D
16	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
17	N-(3,4-dimethylphenyl)-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	A	A		
18	N-(4-chlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
19	N-(3,5-difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
20	N-[3-(methyloxy)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
21	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[4-(4-ethylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D

Table 2

Entry	Name	c-Kit	flt-3	EphB4	EGFR
22	N-(3-fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
23	N-(4-fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
24	N-(3-cyanophenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A		
25	N-(3,4-difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
26	N-[3,4-bis(methoxy)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A		
27	N-[5-chloro-2-(methoxy)phenyl]-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	A	A		
28	N-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)-N'-[4-(phenyloxy)phenyl]urea	A	A		
29	N-(2,4-difluorophenyl)-N'-(4-{3-[6-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
30	N-{4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-[4-chloro-3-(trifluoromethyl)phenyl]urea	A	A	D	D
31	N-{4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-[2-fluoro-5-(trifluoromethyl)phenyl]urea	A	A	D	D
32	N-(2,4-difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
33	N-{4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-phenylurea	A	5000	D	D
34	N-[3,5-bis(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	C	D

Table 2

Entry	Name	c-Kit	flt-3	EphB4	EGFR
35	N-(2-fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A	D	D
36	4-((E)-2-{5-[(E)-2-phenylethenyl]-1H-pyrazol-3-yl}ethenyl)phenol	A	A	D	D
37	2-(methoxy)-4-((E)-2-{5-[(E)-2-phenylethenyl]-1H-pyrazol-3-yl}ethenyl)phenol	A	A	C	D
38	N-(5-fluoro-2-methylphenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	A	A		
39	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-phenylurea	B	A	D	D
40	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[3-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	B	A		
41	N-(2,4-difluorophenyl)-N'-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	B	A	D	D
42	N-(2,3-dihydro-1,4-benzodioxin-6-yl)-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	B	A	D	D
43	N-[2,4-bis(methoxy)phenyl]-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	B	A		
44	4-((E)-2-{3-[(E)-2-(4-fluorophenyl)ethenyl]-1H-pyrazol-5-yl}ethenyl)-2-(methoxy)phenol	B	A	D	D
45	4-{(E)-2-[3-(1-benzofuran-2-yl)-1H-pyrazol-5-yl]ethenyl}phenol	B	B	D	D
46	N-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)-N'-(2-phenylethyl)ethanediamide	B	D	C	D
47	4-{(E)-2-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]ethenyl}phenol	B	A	C	D

Table 2

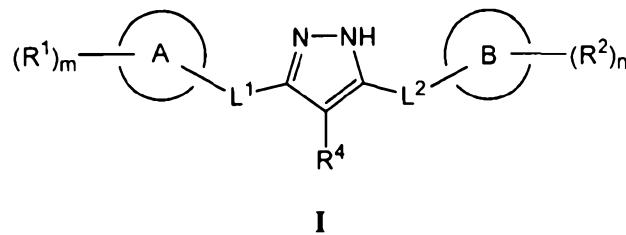
Entry	Name	c-Kit	flt-3	EphB4	EGFR
48	4-((E)-2-{3-[(E)-2-(4-chlorophenyl)ethenyl]-1H-pyrazol-5-yl}ethenyl)-2-(methyloxy)phenol	B	A	D	D
49	4-((E)-2-[3-(1-benzothien-2-yl)-1H-pyrazol-5-yl]ethenyl)phenol	B	B	D	D
50	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-(3-phenyl-1H-pyrazol-5-yl)phenyl)urea	B	B	D	D
51	4-((E)-2-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}ethenyl)phenol	B	A	D	D
52	1,1-dimethylethyl {4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl} carbamate	B	C		
53	N-(5-fluoro-2-methylphenyl)-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	B	B	D	D
54	4-[(E)-2-(3-phenyl-1H-pyrazol-5-yl)ethenyl]phenol	B	A	D	D
55	2-(methyloxy)-4-[(E)-2-(5-phenyl-1H-pyrazol-3-yl)ethenyl]phenol	B	B	D	D
56	4-[(E)-2-(5-naphthalen-2-yl-1H-pyrazol-3-yl)ethenyl]phenol	B	B	D	D
57	4-((E)-2-[5-(2-fluorophenyl)-1H-pyrazol-3-yl]ethenyl)phenol	B	B	D	D
58	4-((E)-2-{3-[3-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}ethenyl)phenol	B	B	D	D
59	4-((E)-2-{3-[(E)-2-(2,4-difluorophenyl)ethenyl]-1H-pyrazol-5-yl}ethenyl)-2-(methyloxy)phenol	B	A	D	D
60	4-[(E)-2-[5-(4-fluorophenyl)-1H-pyrazol-3-yl]ethenyl]phenol	B	A	D	D
61	4-((E)-2-[3-(4-chlorophenyl)-1H-pyrazol-5-yl]ethenyl)phenol	C	B	D	D
62	4-[(E)-2-(5-pyridin-2-yl-1H-pyrazol-3-yl)ethenyl]phenol	C	B		
63	4-((E)-2-[3-(5-chloro-1-benzofuran-2-yl)-1H-pyrazol-5-yl]ethenyl)phenol	C	B		

Table 2

Entry	Name	c-Kit	flt-3	EphB4	EGFR
64	N-(1,1-dimethylethyl)-N'-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	C	C		
65	4-[(E)-2-(3-pyridin-4-yl-1H-pyrazol-5-yl)ethenyl]phenol	C	B		
66	4-{(E)-2-[3-(3-chlorophenyl)-1H-pyrazol-5-yl]ethenyl}phenol	C	C		
67	4-((E)-2-{5-[2-(methyloxy)phenyl]-1H-pyrazol-3-yl}ethenyl)phenol	C	C		
68	4-{(E)-2-[3-(2-chlorophenyl)-1H-pyrazol-5-yl]ethenyl}phenol	C	B		
69	4-[(E)-2-(3-pyridin-3-yl-1H-pyrazol-5-yl)ethenyl]phenol	C	B		
70	4-((E)-2-{5-[3-(methyloxy)phenyl]-1H-pyrazol-3-yl}ethenyl)phenol	C	C		
71	1,1-dimethylethyl (4-{3-[(E)-2-phenylethenyl]-1H-pyrazol-5-yl}phenyl)carbamate	C	C		
72	4-{(E)-2-[3-(3,4-dichlorophenyl)-1H-pyrazol-5-yl]ethenyl}phenol	C	C		
73	2-{5-[(E)-2-phenylethenyl]-1H-pyrazol-3-yl}-1-benzofuran-6-ol	C	A		
74	4-{(E)-2-[5-(3-fluorophenyl)-1H-pyrazol-3-yl]ethenyl}phenol	C	B		
75	2-(5-phenyl-1H-pyrazol-3-yl)-1H-benzimidazole	C	C		
76	N-phenyl-N'-[4-(3-phenyl-1H-pyrazol-5-yl)phenyl]urea	C	C	D	D
77	4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]aniline	C	C		
78	4-[(E)-2-(5-biphenyl-3-yl-1H-pyrazol-3-yl)ethenyl]phenol	C	C		

CLAIMS:

1. A compound according to formula I,



or a pharmaceutically acceptable salt, or hydrate thereof, wherein,

each of R¹ and R² is independently halo C₁-C₈alkoxy, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -SO₂N(R³)R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -NCO₂R³, -N(R³)C(O)₂R³, -C(=O)R³, optionally substituted C₆-C₁₄aryl, optionally substituted C₆-C₁₄aryl C₁-C₆alkyl, optionally substituted cyclo(C₃-C₁₃)alkyl, optionally substituted cyclo(C₃-C₁₃)alkyl C₁-C₆alkyl, optionally substituted 3-15 membered heteroaryl, optionally substituted 3-15 membered heteroaryl C₁-C₆alkyl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 3-15 membered heterocyclyl C₁-C₆alkyl;

each of m and n is independently one to five;

each of A and B is independently a five- to ten-membered aryl or heteroaryl;

R³ is -H, optionally substituted C₁-C₆alkyl, optionally substituted C₆-C₁₄aryl, optionally substituted C₆-C₁₄aryl C₁-C₆alkyl, optionally substituted 3-15 membered heterocyclyl, or optionally substituted 3-15 membered heterocyclyl C₁-C₆alkyl;

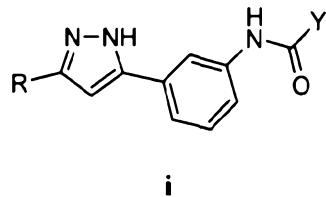
two of R³, together with the nitrogen to which they are attached, can combine to form an optionally substituted heterocyclyl containing between one and three additional heteroatoms;

R⁴ is selected from -H and optionally substituted C₁-C₆alkyl;

each R^5 is independently -H, -CN, -NO₂, -OR³, -S(O)₀₋₂R³, -CO₂R³, optionally substituted C₁-C₆alkyl, optionally substituted C₂-C₆alkenyl, or optionally substituted C₂-C₆alkynyl; and

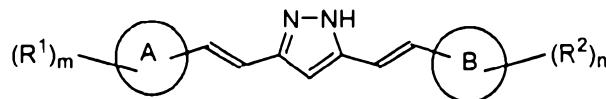
each of L¹ and L² is independently selected from absent and -C(R³)=C(R³)-;

provided the compound is not according to formula **i**,



wherein R is optionally substituted phenyl; and Y is C₁-C₆alkyl, C₂-C₆alkenyl, C₁-C₆alkoxy, C₂-C₆alkenyloxy, N,N-dialkylamino, or N-C₁-C₆alkyl-N-C₁-C₆alkoxyamino; wherein the optionally substituted alkoxy, alkyl, alkenyl, alkynyl, aryl, aryl C₁-C₆alkyl, cycloalkyl, cycloalkyl C₁-C₆alkyl, heteroaryl, heteroaryl C₁-C₆alkyl, heterocyclyl and heterocyclyl C₁-C₆alkyl are, when substituted, independently substituted with one or more substituents independently selected from the group consisting of C₁-C₆alkyl, C₁-C₈alkoxy, halo, halo C₁-C₆alkyl, halo C₁-C₈alkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -SO₂N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -NCO₂R³, -N(R³)C(O)₂R³, -C(=O)R³, C₆-C₁₄aryl, C₆-C₁₄aryl C₁-C₆alkyl, cyclo(C₃-C₁₃)alkyl, cyclo(C₃-C₁₃)alkyl C₁-C₆alkyl, 3-15 membered heterocyclyl, 3-15 membered heterocyclyl C₁-C₆alkyl, 3-15 membered heteroaryl, and 3-15 membered heteroaryl C₁-C₆alkyl.

2. The compound according to claim 1, wherein R⁴ is -H.
3. The compound according to claim 2 wherein L¹ and L² are both -C(R³)=C(R³)-.
4. The compound according to claim 3 wherein L¹ and L² are both E--C(R³)=C(R³)-.
5. The compound according to claim 4 of formula **II**,

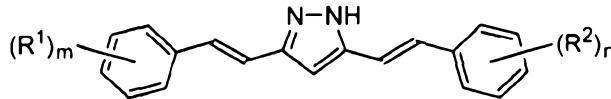


II

wherein each of R^1 and R^2 is independently, halo C_1 - C_8 alkoxy, $-N(R^3)R^3$, $-S(O)_{0-2}R^3$, $-N(R^3)C(=O)N(R^3)R^3$, $-N(R^3)C(=O)C(=O)N(R^3)R^3$, $-SO_2N(R^3)R^3$, $-C(=O)N(R^3)R^3$, $-C(=NR^5)N(R^3)R^3$, $-C(=NR^5)R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)C(O)_2R^3$, $-NCO_2R^3$, $-C(=O)R^3$, optionally substituted 3-15 membered heteroaryl, optionally substituted cyclo(C_3 - C_{13})alkyl, optionally substituted 3-15 membered heterocyclyl or optionally substituted C_6 - C_{14} aryl; and

each of A and B is a radical independently selected from the group consisting of phenyl, benzothiophenyl, pyridyl, pyrazinyl, benzofuranyl, benzpyrazolyl, benzoxazolyl, naphthyl, benzimidazolyl, indolyl, and biphenyl.

6. The compound according to claim 5 of formula IIa,



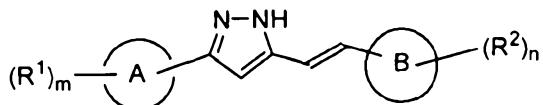
IIa

wherein each of R^1 and R^2 is independently, halo C_1 - C_8 alkoxy, $-N(R^3)R^3$, $-S(O)_{0-2}R^3$, $-N(R^3)C(=O)N(R^3)R^3$, $-N(R^3)C(=O)C(=O)N(R^3)R^3$, $-SO_2N(R^3)R^3$, $-C(=O)N(R^3)R^3$, $-C(=NR^5)N(R^3)R^3$, $-C(=NR^5)R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)C(O)_2R^3$, $-NCO_2R^3$, $-C(=O)R^3$, optionally substituted 3-15 membered heteroaryl, optionally substituted 3-15 membered heterocyclyl, optionally substituted cyclo(C_3 - C_{13})alkyl or optionally substituted C_6 - C_{14} aryl.

7. The compound according to claim 6 wherein each of R^1 and R^2 is independently, halo C_1 - C_8 alkoxy, $-N(R^3)R^3$, or $-C(=O)R^3$.

8. The compound according to claim 7, wherein R^1 is, or halo C_1 - C_8 alkoxy, ; and R^2 is $-N(R^3)R^3$.

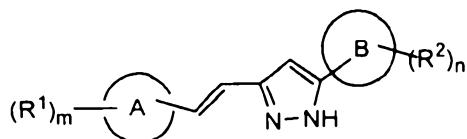
9. The compound according to claim 2, wherein L^1 is absent and L^2 is $-C(R^3)=C(R^3)-$.
10. The compound according to claim 9, wherein L^1 is absent and L^2 is $-C(H)=C(H)-$.
11. The compound according to claim 9, of formula **IV**,

**IV**

wherein each of R^1 and R^2 is independently, haloC₁-C₈alkoxy, $-N(R^3)R^3$, $-S(O)_{0-2}R^3$, $-N(R^3)C(=O)N(R^3)R^3$, $-N(R^3)C(=O)C(=O)N(R^3)R^3$, $-SO_2N(R^3)R^3$, $-C(=O)N(R^3)R^3$, $-C(=NR^5)N(R^3)R^3$, $-C(=NR^5)R^3$, $-N(R^3)SO_2R^3$, $-N(R^3)C(O)R^3$, $-N(R^3)C(O)_2R^3$, $-NCO_2R^3$, $-C(=O)R^3$, optionally substituted 3-15 membered heterocyclyl, optionally substituted C₆-C₁₄aryl, optionally substituted cyclo(C₃-C₁₃)alkyl, or optionally substituted 3-15 membered heteroaryl; and

each A and B is a radical independently selected from the group consisting of phenyl, benzothiophenyl, pyridyl, pyrazinyl, benzofuranyl, benzpyrazolyl, benzoxazolyl, naphthyl, benzimidazolyl, indolyl, and biphenyl.

12. The compound according to claim 2, wherein L^2 is absent and L^1 is $-C(R^3)=C(R^3)-$.
13. The compound according to claim 12, wherein L^2 is absent and L^1 is $-C(H)=C(H)-$.
14. The compound according to claim 13, of formula **Iva**,

**Iva**

wherein each of R^1 and R^2 is independently selected from , haloC₁-C₈alkoxy, $-N(R^3)R^3$, $-S(O)_{0-2}R^3$, $-N(R^3)C(=O)N(R^3)R^3$, $-N(R^3)C(=O)C(=O)N(R^3)R^3$, $-SO_2N(R^3)R^3$,

-C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -N(R³)C(O)₂R³, -NCO₂R³, -C(=O)R³, optionally substituted 3-15 membered heterocyclyl, optionally substituted C₆-C₁₄aryl, optionally substituted 3-15 membered heteroaryl, or optionally substituted cyclo(C₃-C₁₃)alkyl; and

each A and B is a radical independently selected from the group consisting of phenyl, benzothiophenyl, pyridyl, pyrazinyl, benzofuranyl, benzpyrazolyl, benzoxazolyl, naphthyl, benzimidazolyl, indolyl, and biphenyl.

15. The compound according to claim 2, wherein L¹ and L² are both absent.

16. The compound according to claim 15, wherein A is a six- or nine-membered aryl or heteroaryl and B is a six-membered aryl or heteroaryl.

17. The compound according to claim 16 selected from the group consisting of:

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;
N-(3-ethylphenyl)-N'-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;
N-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(3-(trifluoromethyl)phenyl)urea;
N-(3-acetylphenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;
N-(3,4-dichlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;
N-(3-bromophenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;
N-[4-fluoro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;
N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(4-(phenyloxy)phenyl)urea;

N-(3-chlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

N-[3,5-bis(methyloxy)phenyl]-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(4-[(trifluoromethyl)oxy]phenyl)urea;

N-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(4-(trifluoromethyl)phenyl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(3-(trifluoromethyl)phenyl)urea;

N-(4-chlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

N-(3,5-difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

N-[3-(methyloxy)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

N-(3-fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

N-(4-fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

N-(3-cyanophenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

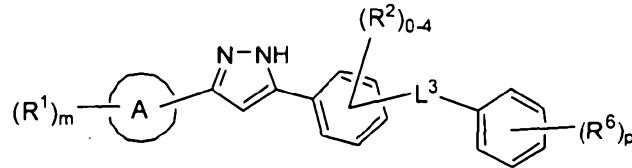
N-(3,4-difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

N-[3,4-bis(methyloxy)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

N-(2,4-difluorophenyl)-N'-(4-{3-[6-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;

N-(2,4-difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;
 N-[3,5-bis(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;
 N-(2-fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;
 N-(5-fluoro-2-methylphenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea;
 N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-phenylurea; and
 N-(1,1-dimethylethyl)-N'-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea.

18. The compound according to claim 16, of formula **VI**,



VI

wherein each of R¹ and R² is independently, halo C₁-C₈alkoxy, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -SO₂N(R³)R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -N(R³)C(O)₂R³, -NCO₂R³, -C(=O)R³, optionally substituted 3-15 membered heterocyclyl, optionally substituted 3-15 membered heteroaryl, optionally substituted C₆-C₁₄aryl, or optionally substituted cyclo(C₃-C₁₃)alkyl;

R⁶ is -H, halogen, halo C₁-C₈alkyl, halo C₁-C₈alkoxy, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -N(R³)C(=O)C(=O)N(R³)R³, -SO₂N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -C(=NR⁵)N(R³)R³, -C(=NR⁵)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -N(R³)C(O)₂R³, -NCO₂R³, -C(=O)R³, optionally substituted C₁-C₈alkoxy, optionally

substituted 3-15 membered heterocyclyl, optionally substituted 3-15 membered heteroaryl, optionally substituted C₆-C₁₄aryl, optionally substituted cyclo(C₃-C₁₃)alkyl, or optionally substituted C₁-C₆alkyl;

p is one to five;

A is a radical selected from phenyl, benzothiophenyl, pyridyl, pyrazinyl, benzofuranyl, benzimidazolyl, and indolyl; and

L³ is absent, -(CH₂)₀₋₁N(R³)C(=O)N(R³)-, -N(R³)C(=S)N(R³)R³, -N(R³)C(=O)N(R³)(CH₂)₀₋₁- , -(CH₂)₀₋₁N(R³)C(=O)-, -N(R³)C(=O)(CH₂)₀₋₁- , -(CH₂)₀₋₁SO₂N(R³)-, -SO₂N(R³)(CH₂)₀₋₁- , -C(=NR⁵)N(R³)-, -C(=NR⁵)-, -(CH₂)₀₋₁N(R³)CO₂- , -N(R³)CO₂(CH₂)₀₋₁- , -C(=O)-, -CO₂- , -(CH₂)₀₋₁N(R³)C(=NR⁵)N(R³)- or -(CH₂)₀₋₁N(R³)-.

19. The compound according to claim 18 selected from the group consisting of :

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-[3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl]phenyl)urea;

N-(3,4-dimethylphenyl)-N'-(4-[5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]phenyl)urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-[3-[4-(4-ethylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl]phenyl)urea;

N-[5-chloro-2-(methyloxy)phenyl]-N'-(4-[5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]phenyl)urea;

N-(4-[5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]phenyl)-N'-[4-(phenyloxy)phenyl]urea;

N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-[3-[3-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl]phenyl)urea;

N-(2,4-difluorophenyl)-N'-(4-[3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl]phenyl)urea;

N-(2,3-dihydro-1,4-benzodioxin-6-yl)-N'-(4-[5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl]phenyl)urea;

N-[2,4-bis(methoxy)phenyl]-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea;

N-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)-N'-(2-phenylethyl)ethanediamide;

4-((E)-2-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}ethenyl)phenol;

N-(5-fluoro-2-methylphenyl)-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea;

4-{{(E)-2-[3-(4-chlorophenyl)-1H-pyrazol-5-yl]ethenyl}phenol;

4-((E)-2-[3-(5-chloro-1-benzofuran-2-yl)-1H-pyrazol-5-yl]ethenyl)phenol;

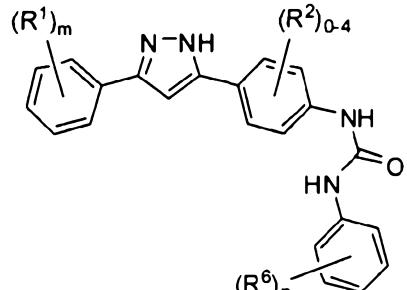
4-[(E)-2-(3-pyridin-4-yl-1H-pyrazol-5-yl)ethenyl]phenol; and

4-<{(E)-2-[3-(3-chlorophenyl)-1H-pyrazol-5-yl]ethenyl}phenol.

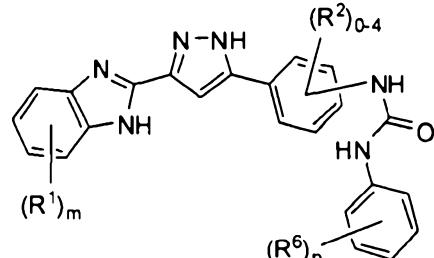
20. The compound according to claim 18 wherein when A is phenyl, then L^3 is $-N(R^3)C(=O)N(R^3)-$.

21. The compound according to claim 20, wherein A is either phenyl or benzimidazolyl.

22. The compound according to claim 21, of either formula VIIa or VIIb,



Villa



VIIb

wherein R¹ is halo C₁-C₈alkoxy, -N(R³)R³, -S(O)₀₋₂R³, -C(=O)N(R³)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -N(R³)C(O)₂R³, -NCO₂R³, -C(=O)R³, optionally substituted 3-15 membered heterocyclyl, optionally substituted 3-15 membered heteroaryl, optionally substituted cyclo(C₃-C₁₃)alkyl, or optionally substituted C₆-C₁₄aryl;

m is one to five;

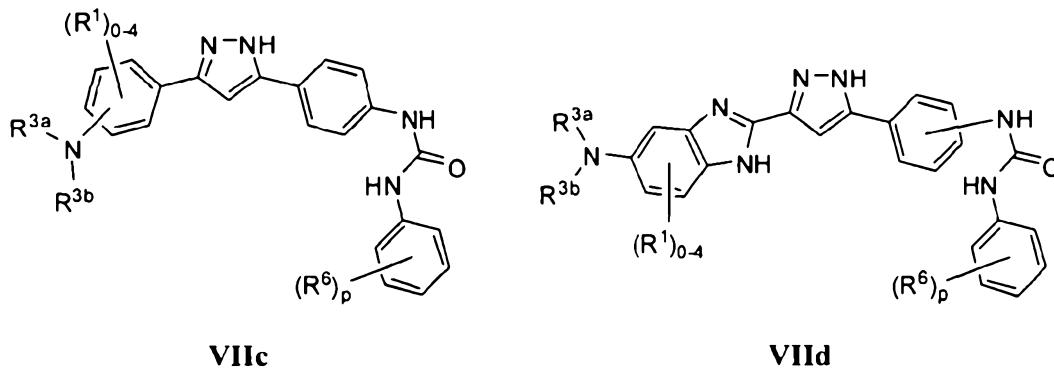
R² is halo C₁-C₈alkoxy, or -N(R³)R³;

R⁶ is -H, halogen, halo C₁-C₈alkyl, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -NCO₂R³, -C(=O)R³, optionally substituted C₁-C₈alkoxy, optionally substituted 3-15 membered heterocycl, or optionally substituted C₁-C₆alkyl; and

p is one to five.

23. The compound according to claim 22 wherein the phenyl urea in **VIIb** is either *meta*- or *para*- to the pyrazole moiety.

24. The compound according to claim 23, of either formula **VIIc** or **VIId**,



wherein R¹ is halo C₁-C₈alkoxy, -N(R³)R³, -S(O)₀₋₂R³, -C(=O)N(R³)R³, -N(R³)SO₂R³, -N(R³)C(O)R³, -N(R³)C(O)R³, -NCO₂R³, -C(=O)R³, or optionally substituted 3-15 membered heterocycl;

R^{3a} and R^{3b} are each independently -H or optionally substituted C₁-C₆alkyl; optionally R^{3a} and R^{3b}, together with the nitrogen to which they are attached, combine to form an optionally substituted heteroalicycyl containing between one and two additional heteroatoms;

R⁶ is -H, halogen, halo C₁-C₈alkyl, -CN, -NO₂, -OR³, -N(R³)R³, -S(O)₀₋₂R³, -N(R³)C(=O)N(R³)R³, -CO₂R³, -C(=O)N(R³)R³, -N(R³)SO₂R³, -N(R³)C(O)R³,

$-\text{NCO}_2\text{R}^3$, $-\text{C}(=\text{O})\text{R}^3$, optionally substituted $\text{C}_1\text{-C}_8\text{alkoxy}$, optionally substituted 3-15 membered heterocycl, or optionally substituted $\text{C}_1\text{-C}_6\text{alkyl}$; and

p is one to five.

25. The compound according to claim 24 wherein for **VIIc**, $-\text{N}(\text{R}^{3a})\text{R}^{3b}$ is either *meta*- or *para*- to the pyrazole moiety; and the phenyl urea in **VIId** is either *meta*- or *para*- to the pyrazole moiety.

26. A compound selected from Table 3:

Table 3

Entry	Name	Structure
1	4-((E)-2-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}ethenyl)phenol	
2	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
3	N-(3-ethylphenyl)-N'-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
4	N-(4-{3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(3-(trifluoromethyl)phenyl)urea	

Table 3

Entry	Name	Structure
5	N-(3-acetylphenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
6	N-(3,4-dichlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
7	N-(3-bromophenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
8	N-[4-fluoro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
9	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(4-(phenyloxy)phenyl)urea	
10	N-(3-chlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	

Table 3

Entry	Name	Structure
11	N-[3,5-bis(methoxy)phenyl]-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
12	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(4-[(trifluoromethyl)oxy]phenyl)urea	
13	N-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(4-(trifluoromethyl)phenyl)urea	
14	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
15	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-(3-(trifluoromethyl)phenyl)urea	
16	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	

Table 3

Entry	Name	Structure
17	N-(3,4-dimethylphenyl)-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	
18	N-(4-chlorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
19	N-(3,5-difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
20	N-[3-(methoxy)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
21	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[4-(4-ethylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	
22	N-(3-fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	

Table 3

Entry	Name	Structure
23	N-(4-fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
24	N-(3-cyanophenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
25	N-(3,4-difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
26	N-[3,4-bis(methoxy)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
27	N-[5-chloro-2-(methoxy)phenyl]-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	
28	N-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)-N'-[4-(phenyloxy)phenyl]urea	

Table 3

Entry	Name	Structure
29	N-(2,4-difluorophenyl)-N'-(4-{3-[6-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
30	N-{4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-(4-chloro-3-(trifluoromethyl)phenyl)urea	
31	N-{4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-(2-fluoro-5-(trifluoromethyl)phenyl)urea	
32	N-(2,4-difluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
33	N-{4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl}-N'-phenylurea	
34	N-[3,5-bis(trifluoromethyl)phenyl]-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	

Table 3

Entry	Name	Structure
35	N-(2-fluorophenyl)-N'-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
36	4-((E)-2-{5-[(E)-2-phenylethenyl]-1H-pyrazol-3-yl}ethenyl)phenol	
37	2-(methoxy)-4-((E)-2-{5-[(E)-2-phenylethenyl]-1H-pyrazol-3-yl}ethenyl)phenol	
38	N-(5-fluoro-2-methylphenyl)-N'-(4-{3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)urea	
39	N-(4-{3-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl}phenyl)-N'-phenylurea	
40	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-{3-[3-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	

Table 3

Entry	Name	Structure
41	N-(2,4-difluorophenyl)-N'-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)urea	
42	N-(2,3-dihydro-1,4-benzodioxin-6-yl)-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	
43	N-[2,4-bis(methoxy)phenyl]-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	
44	4-((E)-2-{3-[(E)-2-(4-fluorophenyl)ethenyl]-1H-pyrazol-5-yl}ethenyl)-2-(methoxy)phenol	
45	4-{(E)-2-[3-(1-benzofuran-2-yl)-1H-pyrazol-5-yl]ethenyl}phenol	
46	N-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}phenyl)-N'-(2-phenylethyl)ethanediamide	
47	4-{(E)-2-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]ethenyl}phenol	

Table 3

Entry	Name	Structure
48	4-((E)-2-{3-[(E)-2-(4-chlorophenyl)ethenyl]-1H-pyrazol-5-yl}ethenyl)-2-(methyloxy)phenol	
49	4-((E)-2-[3-(1-benzothien-2-yl)-1H-pyrazol-5-yl]ethenyl)phenol	
50	N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-(4-(3-phenyl-1H-pyrazol-5-yl)phenyl)urea	
51	4-((E)-2-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}ethenyl)phenol	
52	1,1-dimethylethyl {4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]phenyl} carbamate	
53	N-(5-fluoro-2-methylphenyl)-N'-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-3-yl}phenyl)urea	
54	4-[(E)-2-(3-phenyl-1H-pyrazol-5-yl)ethenyl]phenol	

Table 3

Entry	Name	Structure
55	2-(methyloxy)-4-[(E)-2-(5-phenyl-1H-pyrazol-3-yl)ethenyl]phenol	
56	4-[(E)-2-(5-naphthalen-2-yl-1H-pyrazol-3-yl)ethenyl]phenol	
57	4-[(E)-2-[5-(2-fluorophenyl)-1H-pyrazol-3-yl]ethenyl]phenol	
58	4-((E)-2-{3-[3-(4-methylpiperazin-1-yl)phenyl]-1H-pyrazol-5-yl}ethenyl)phenol	
59	4-((E)-2-{3-[(E)-2-(2,4-difluorophenyl)ethenyl]-1H-pyrazol-5-yl}ethenyl)-2-(methyloxy)phenol	
60	4-[(E)-2-[5-(4-fluorophenyl)-1H-pyrazol-3-yl]ethenyl]phenol	
61	4-[(E)-2-[3-(4-chlorophenyl)-1H-pyrazol-5-yl]ethenyl]phenol	
62	4-[(E)-2-(5-pyridin-2-yl-1H-pyrazol-3-yl)ethenyl]phenol	

Table 3

Entry	Name	Structure
63	4-{(E)-2-[3-(5-chloro-1-benzofuran-2-yl)-1H-pyrazol-5-yl]ethenyl}phenol	
64	N-(1,1-dimethylethyl)-N'-(4-[(3-[5-(4-ethylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-5-yl)phenyl]urea	
65	4-[(E)-2-(3-pyridin-4-yl-1H-pyrazol-5-yl)ethenyl]phenol	
66	4-{(E)-2-[3-(3-chlorophenyl)-1H-pyrazol-5-yl]ethenyl}phenol	
67	4-((E)-2-{5-[2-(methyloxy)phenyl]-1H-pyrazol-3-yl}ethenyl)phenol	
68	4-{(E)-2-[3-(2-chlorophenyl)-1H-pyrazol-5-yl]ethenyl}phenol	
69	4-[(E)-2-(3-pyridin-3-yl-1H-pyrazol-5-yl)ethenyl]phenol	
70	4-((E)-2-{5-[3-(methyloxy)phenyl]-1H-pyrazol-3-yl}ethenyl)phenol	

Table 3

Entry	Name	Structure
71	1,1-dimethylethyl (4-{{(E)-2-phenylethenyl}1H-pyrazol-5-yl}phenyl)carbamate	
72	4-{{(E)-2-[3,4-dichlorophenyl]1H-pyrazol-5-yl}ethenyl}phenol	
73	2-{{(E)-2-phenylethenyl}1H-pyrazol-3-yl}-1-benzofuran-6-ol	
74	4-{{(E)-2-[5-(3-fluorophenyl)1H-pyrazol-3-yl}ethenyl}phenol	
75	2-(5-phenyl-1H-pyrazol-3-yl)-1H-benzimidazole	
76	N-phenyl-N'-[4-(3-phenyl-1H-pyrazol-5-yl)phenyl]urea	
77	4-[3-(1H-benzimidazol-2-yl)-1H-pyrazol-5-yl]aniline	
78	4-[(E)-2-(5-biphenyl-3-yl)-1H-pyrazol-3-yl]ethenyl]phenol	

Table 3

Entry	Name	Structure
79	4-((E)-2-{5-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-pyrazol-3-yl}ethenyl)phenol	

27. A pharmaceutical composition comprising the compound according to any one of claims 1 - 26 and a pharmaceutically acceptable carrier.

28. Use of at least one of the compounds according to any of claims 1 - 26 or a pharmaceutical composition according to claim 27 as a medicament.

29. A compound of claims 1-26 or a pharmaceutical composition of claim 27 for use as a medicament.

30. Use of at least one of the compounds according to any of claims 1 - 26 or a pharmaceutical composition according to claim 27 in the manufacture of a medicament for the treatment of diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities.

31. A compound according to claims 1-26 or a pharmaceutical composition according to claim 27 for use in the treatment of a disease or disorder associated with uncontrolled, abnormal, and/or unwanted cellular activities.

32. A method of screening for a modulator of a kinase, the method comprising combining either a composition comprising at least one of the compounds according to any of claims 1-26 or the pharmaceutical composition according to claim 27, and at least one candidate agent and determining the effect of the candidate agent on the activity of said kinase.

33. An in vitro method of inhibiting proliferative activity in a cell or a plurality of cells, the method comprising administering an effective amount of at least one of the compound according to any of claims 1-26 or the pharmaceutical composition according to claim 27 to said cell or said plurality of cells.