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(54) Title: ANTI-PROLIFERATIVE AGENTS

(57) Abstract: The present invention relates to the compositions, methods, and applications of a novel approach to selective inhibition of several cellular or molecular targets with a single small molecule. More specifically, the present invention relates to multi-functional small molecules capable of inhibiting a different cellular or molecular pathway involved in aberrant cell proliferation, differentiation or survival.

# ANTI-PROLIFERATIVE AGENTS

## RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/974,655, filed on September 24, 2007. The entire teachings of the above application are incorporated herein by reference.

## BACKGROUND OF THE INVENTION

Elucidation of the complex and multifactorial nature of various diseases that involve multiple pathogenic pathways and numerous molecular components suggests that multi-targeted therapies may be advantageous over mono-therapies. Recent combination therapies with two or more agents for many such diseases in the areas of oncology, infectious disease, cardiovascular disease and other complex pathologies demonstrate that this combinatorial approach may provide advantages with respect to overcoming drug resistance, reduced toxicity and, in some circumstances, a synergistic therapeutic effect compared to the individual components.

Certain cancers have been effectively treated with such a combinatorial approach; however, treatment regimes using a cocktail of cytotoxic drugs often are limited by dose limiting toxicities and drug-drug interactions. More recent advances with molecularly targeted drugs have provided new approaches to combination treatment for cancer, allowing multiple targeted agents to be used simultaneously, or combining these new therapies with standard chemotherapeutics or radiation to improve outcome without reaching dose limiting toxicities. However, the ability to use such combinations currently is limited to drugs that show compatible pharmacologic and pharmacodynamic properties. In addition, the regulatory requirements to demonstrate safety and efficacy of combination therapies can be more costly and lengthy than corresponding single agent trials. Once approved, combination strategies may also be associated with increased costs to patients, as well as decreased patient compliance owing to the more intricate dosing paradigms required.

In the field of protein and polypeptide-based therapeutics it has become commonplace to prepare conjugates or fusion proteins that contain most or all of the amino acid sequences of two different proteins/polypeptides and that retain the

individual binding activities of the separate proteins/polypeptides. This approach is made possible by independent folding of the component protein domains and the large size of the conjugates that permits the components to bind their cellular targets in an essentially independent manner. Such an approach is not, however, generally feasible in the case of small molecule therapeutics, where even minor structural modifications can lead to major changes in target binding and/or the pharmacokinetic/ pharmacodynamic properties of the resulting molecule.

Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed histone deacetylases (HDACs). HDAC's are divided into four distinct classes (*J Mol Biol*, **2004**, 338:1, 17-31). In mammalians class I HDAC's (HDAC1-3, and HDAC8) are related to yeast RPD3 HDAC, class 2 (HDAC4-7, HDAC9 and HDAC10) related to yeast HDA1, class 4 (HDAC11), and class 3 (a distinct class encompassing the sirtuins which are related to yeast Sir2).

Csordas, *Biochem. J.*, **1990**, 286: 23-38 teaches that histones are subject to post-translational acetylation of the ε-amino groups of N-terminal lysine residues, a reaction that is catalyzed by histone acetyl transferase (HAT1). Acetylation neutralizes the positive charge of the lysine side chain, and is thought to impact chromatin structure. Indeed, access of transcription factors to chromatin templates is enhanced by histone hyperacetylation, and enrichment in underacetylated histone H4 has been found in transcriptionally silent regions of the genome (Taunton *et al.*, *Science*, **1996**, 272:408-411). In the case of tumor suppressor genes, transcriptional silencing due to histone modification can lead to oncogenic transformation and cancer.

Several classes of HDAC inhibitors currently are being evaluated by clinical investigators. The first FDA approved HDAC inhibitor is Suberoylanilide hydroxamic acid (SAHA, Zolinza®) for the treatment of cutaneous T-cell lymphoma (CTCL). Other HDAC inhibitors include hydroxamic acids, cyclic peptides, benzamides, and short-chain fatty acids. Hydroxamic acid derivatives PXD101 and LAQ824, are currently in the clinical development. In the benzamide class of HDAC inhibitors, MS-275, MGCD0103 and CI-994 have reached clinical trials. Mourne *et al.* (Abstract #4725, AACR 2005), demonstrate that thiophenyl modification of benzamides significantly enhance HDAC inhibitory activity against HDAC1. PCT publication numbers WO 2006061638, WO 2006005955, and WO

2006005941 recently disclosed HDAC inhibitors containing amide and ketone moieties.

Use of HDAC inhibitors in combination with a wide range of molecularly targeted therapies as well as standard chemotherapeutics and radiation has been shown to produce synergistic effects. Co-treatment with SAHA significantly increased EGFR2 antibody trastuzumab-induced apoptosis of BT-474 and SKBR-3 cells and induced synergistic cytotoxic effects against the breast cancer cells (Bali, *Clin. Cancer Res.*, **2005**, 11, 3392). HDAC inhibitors, such as SAHA, have demonstrated synergistic antiproliferative and apoptotic effects when used in combination with gefitinib in head and neck cancer cell lines, including lines that are resistant to gefitinib monotherapy (Bruzzese *et al.*, *Proc. AACR*, 2004). Pretreating gefitinib resistant cell lines with the HDAC inhibitor, MS-275, led to a growth-inhibitory and apoptotic effect of gefitinib similar to that seen in gefitinib-sensitive NSCLC cell lines, including those harboring EGFR mutations (Witta S.E., *et al.*, *Cancer Res*, **2006**, 66:2, 944-50). The HDAC inhibitor PXD101 has been shown to act synergistically to inhibit proliferation with the EGFR1 inhibitor Tarceva (erlotinib) (WO2006082428A2).

Similarly, inhibition of HDAC activity has also been shown to synergize with inhibition of angiogenesis (Kim, MS, *et al.*, *Nat Med*, **2001**, 7:4, 437-43; Deroanne, CF, *et al.*, *Oncogene*, **2002**, 21:3, 427-36). Indeed, the anti-tumor activity of the HDAC inhibitor FK228 observed in PC3 xenografts is dependent upon the repression of angiogenic factors such as VEGF and bFGF (Sasakawa *et al.*, *Biochem. Pharmacol.*, **2003**, 66, 897). The HDAC inhibitor NVP-LAQ824 has been shown to inhibit angiogenesis and have a greater anti-tumor effect when used in combination with the vascular endothelial growth factor receptor tyrosine kinase inhibitor PTK787/ZK222584 (Qian et al., *Cancer Res.*, **2004**, 64, 66260). The increase in anti-tumor activity was associated with a down regulation of the pro-angiogenic factors angiopoietin-2, Tie-2, and survivin in endothelial cells and with down regulation of hypoxia-inducible factor 1- and VEGF expression in tumor cells. Similarly the HDAC inhibitor, LBH589, has been shown to target endothelial cells leading to a reduction in an angiogenic response (Qian et al., *Clin Cancer Res*, **2006**, 12:2, 634-42).

Histone deacetylase inhibitors have been shown to promote Gleevec (imatinib mesylate)-mediated apoptosis in both Gleevec-sensitive and -resistant (Bcr/Abl+)

human myeloid leukemia cells Yu *et al.*, *Cancer Res*, **2003**, 63:9, 2118-26; Nimmanapalli *et al.*, *Cancer Res* 63:16, **2003**, 5126-35. Similarly, strong synergy between NVP-LAQ824 and imatinib mesylate was demonstrated against the BCR/ABL-expressing myeloid leukemia cell line, K562. These compounds were minimally toxic when used alone but, in combination, resulted in a marked increase in mitochondrial damage (e.g., cytochrome c, Smac/DIABLO, and apoptosis-inducing factor release), caspase activation, and apoptosis. (Weisberg *et al.*, *Leukemia*. **2004**, 18, 1951).

In addition, HDAC inhibitors have been shown to synergistically block cell proliferation when used in combinations with standard chemotherapeutics including 5-FU, Topotecan, Gemcitabine, Cisplatin, Doxorubicin, Docetaxle, Tomoxifen, 5-Azacytidine, Alimta, and Irinotecan (WO2006082428A2). A combination of the HDAC inhibitor, MS-275, and the nucleoside analogue fludarabine sharply increased mitochondrial injury, caspase activation, and apoptosis in leukemia cells (Maggio, SC., *et. al.*, *Cancer Res*, **2004**, 64:7, 2590-600). Addition of the HDAC inhibitor SAHA and topoisomerase II inhibitors (e.g., epirubicin, doxorubicin, m-AMSA, VM-26, and teniposide) have also shown synergistic effects in terms of increased cell death (Marchion, DC., *J Cell Biochem*, **2004**, 92:2, 223-37). Similarly HDAC inhibitors have shown synergy when combined with radiation therapy (Paoluzzi, L, *Cancer Biol Ther*, **2004**, 3:7, 612-3; Entin-Meer, M., *Mol Cancer Ther*, **2005**, 4:12, 1952-61; Cerna, D, *Curr Top Dev Biol*, **2006**, 73, 173-204) further illustrating the potential synergy between HDAC's and other cancer therapeutics.

Furthermore, HDAC inhibitors have also been shown to synergize with mitogen-activated protein kinase/ERK kinase (MEK), Cyclin-dependent kinase (CDK), proteasome, HSP90, and TRAIL inhibitors (*Mol Pharmacol.* **2006**, 69(1), 288-98; *Biochem Biophys Res Commun.* **2006**, 27, 339(4), 1171-7; *Mol Pharmacol.* **2005** 67(4):1166-76; *Blood*, **2005**, 105(4), 1768-76; *Cancer Res.* **2006**, 66(7), 3773-81; *Acta Haematol.* **2006**, 115(1-2), 78-90; *Clin Cancer Res.* **2004**, 10(11), 3839-52; *Oncogene* **2005** 24(29), 4609-23; *Mol Cancer Ther.* **2003**, 2(12), 1273-84; *Biochem Pharmacol.* **2003**, 66(8), 1537-45; and *Mol Cancer Ther.* **2005**, 4(11), 1772-85).

Current therapeutic regimens of the types described above attempt to address the problem of drug resistance by the administration of multiple agents. However, the combined toxicity of multiple agents due to off-target side effects as well as drug-drug interactions often limit the effectiveness of this approach. Moreover, it

often is difficult to combine compounds having differing pharmacokinetics into a single dosage form, and the consequent requirement of taking multiple medications at different time intervals leads to problems with patient compliance that can undermine the efficacy of the drug combinations. In addition, the health care costs of combination therapies may be greater than for single molecule therapies. Moreover, it may be more difficult to obtain regulatory approval of a combination therapy since the burden for demonstrating activity/safety of a combination of two agents may be greater than for a single agent. (Dancey J & Chen H, *Nat. Rev. Drug Dis.*, **2006**, 5:649). The development of novel agents that target multiple therapeutic targets selected not by virtue of cross reactivity, but through rational design will help improve patient outcome while avoiding these limitations. Thus, enormous efforts are still directed to the development of selective anti-cancer drugs as well as to new and more efficacious combinations of known anti-cancer drugs.

## SUMMARY OF THE INVENTION

The present invention relates to the compositions, methods, and applications of a novel approach to selective inhibition of several cellular targets with a single small molecule. More specifically, the present invention relates to multi-functional small molecules wherein one pharmacophore is functionally capable of binding zinc ions and/or inhibits zinc-dependent enzymes (e.g.,histone deacetylases (HDAC) and matrix metalloproteinases (MMPs)) and is covalently bound to a second pharmacophore with one or more functionalities capable of inhibiting a different cellular or molecule pathway or biological function involved in aberrant proliferation, differentiation or survival of cells. Such aberrant proliferation, differentiation or survival of cells may be observed in disorders such as cancer, precancerous growths or lesions, hyperplasias, and dysplasias.

In a preferred embodiment, the zinc-binding pharmacophore inhibits a HDAC and is linked to a second pharmacophore that induces apoptosis, inhibits angiogenesis, and/or inhibits aberrant proliferation.

In one embodiment, the second pharmacophore is selected from, but not limited to, chemical compounds that are functionally capable of inhibiting the activity of tyrosine kinase, serine/threonine kinases, DNA methyl transferases (DNMT), proteasomes, and heat-shock proteins (HSPs), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR),

fibroblast growth factor receptor (FGFR), mitogen-activated protein kinase (MAPK/MEK), cyclin-dependent kinase (CDK), and the phosphatidylinositol 4,5-bisphosphate-AKT-mammalian target of the rapamycin pathway [P13K-AKT (RAF, mTOR)], matrix metalloproteinase, farnesyl transferase, and apoptosis.

In a most preferred embodiment, the second pharmacophore is selected from, but not limited to, chemical compounds that are functionally capable of inhibiting the activity of DNMT, EGFR, ErbB2, ErbB3, ErbB4, HER-2, VEGFR-1, VEGFR-2, VEGFR-3Flt-3, c-kit, Abl, JAK, PDGFR-α, PDGFR-β, IGF-IR, c-Met, FGFR1, FGFR3, FGFR4, c-Ret, Src, Lyn, Yes, PKC, CDK, Erk, Merk, PI3K-Akt, mTOR, Raf, CHK, Aurora, HSP90, TRAILR, caspases, IAPs, Bcl-2, Survivin, MDM2, MDM4.

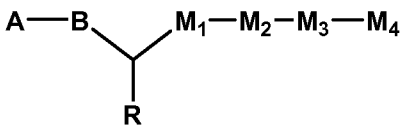
Another aspect of the invention makes available the treatment, prevention or recurrence of cancer with one or more compounds of the invention.

In one embodiment, one or more compounds of the invention maybe combined with another therapy that includes, but is not limited to, anti-neoplastic agents, immunotherapeutic agents, antibodies, adjunctive agents, device, radiation therapies, chemoprotective agents, vaccines, and/or demethylating agents.

## DETAILED DESCRIPTION OF THE INVENTION

This invention provides a novel class of agents capable of inhibiting multiple biological activities. The agents of the present invention are designed with two or more activities or functionalities, where the compound comprises a first pharmacophore that binds zinc ions and/or inhibits zinc-dependent enzymes such as HDAC and MMPs, and a second pharmacophore, which is covalently bound to the zinc-binding moiety, and which inhibits one or more different signaling pathways or biological functions. In one embodiment, the first pharmacophore binds to $Zn^{+2}$ and inhibits HDAC. In particular embodiments, the compounds have activities that address aberrant proliferation, differentiation and/or survival of cells. Advantageously, these new agents are tumor selective and anti-neoplastic.

The general structure of these novel multi-functional agents is shown below in formula (I):




(I)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein

A is a pharmacophore of an agent that inhibits aberrant cell proliferation; preferably A is an anti-cancer agent;

B is a linker;

R is selected from the group consisting of hydrogen, $N(R_2)COR_4$, $N(R_2)CON(R_3)R_4$, $N(R_2)COOR_4$, $N(R_2)S(O)_nR_3$, $N(R_2)S(O)_nN(R_3)R_4$; where $R_2$ and $R_3$ are independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; n is 1 or 2; preferably R comprises a moiety that interacts with an HDAC enzyme and/or zinc;

$M_1$ is absent or selected from substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

$M_2$ is absent, O, S, SO, $SO_2$, $N(R_2)$ or CO;

$M_3$ is absent, O, S, SO, $SO_2$, $N(R_2)$, CO, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, cycloalkyl, heterocyclic, aryl, or heteroaryl;

$M_4$ is hydrogen, $NR_5R_6$, $CF_3$, $OR_4$, halogen, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl; where $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl or substituted cycloalkyl; preferably, $-M_1$-$M_2$-$M_3$-$M_4$ comprises a moiety that will interacts with an HDAC enzyme and/or zinc;

provided that –R and $-M_1$-$M_2$-$M_3$-$M_4$ cannot be both hydrogen.

In one embodiment of the invention, the pharmacophores for the compounds of the invention may be chosen from large numbers of anti-cancer agents available in commercial use or in clinical or pre-clinical evaluation. These agents may affect one or more protein kinases, a number of which have been demonstrated to be proto-

oncogenes. These kinases may themselves become oncogenic by over-expression or mutation. Thus, by inhibiting the protein kinase activity of these proteins the disease process may be disrupted.

In one embodiment, the second pharmacophore inhibits the enzyme DNA methyltransferase (DNMT). Aberrant DNA methylation patterns are closely associated with epigenetic mutations or epimutations, which can have the same consequences as genetic mutations. For example, many tumors show hypermethylation and concomitant silencing of tumor suppressor genes. Several developmental disorders are also associated with aberrant DNA methylation. Thus, changes in DNA methylation play an important role in developmental and proliferative diseases, particularly in tumorigenesis. Inhibition of DNA methylation, particularly by inhibition of DNMTs, more particularly DNMT1, is considered a promising strategy for treatment of proliferative diseases. Azacitidine is approved for the treatment of patients in both low- and high-risk subtypes of myelodysplastic syndrome (MDS), and decitabine is currently under review by the FDA (Christine 2006; Lewis *et al*, 2005). It is widely accepted that histone modification and DNA methylation are intricately interrelated, working together to determine the status of gene expression and to decide cell fate (Yoo & Jones, *Nat. Rev. Drug Dis*, 2006, 5, 37-50). Cameron *et al*., disclose synergy of demethylation and histone deacetylase inhibition in the re-expression of genes silenced in cancer (*Nat. Genet.* 1999, 21,103-107). HDAC inhibitor TSA acts synergistically with the DNMT inhibitor 5-aza-2'-deoxycytidine to reactivate DNA methylation-silenced genes (REF). HDAC inhibitors decrease DNA methyltransferase-3B messenger RNA stability and down-regulate de novo DNA methyltransferase activity in human endometrial cells (Xiong *et al*., *Cancer Res*., 2005, 65, 2684). Combination of the DNMT inhibitor (5-aza-dC) and HDAC inhibitor (trichostatin A) induced a 300-400 fold increase in ER mRNA expression (30-40 fold for 5-aza-dC & 5 fold for TSA individually) in human ER-negative breast cancer cell lines (Yang *et al*. *Cancer Res.,* 2001, 61,7025).

In one embodiment, the second pharmacophore inhibits MAP/ERK kinase (MEK). MEK inhibitors suppress a large number of human tumor cells and markedly enhance the efficacy of HDAC inhibitors to induce apoptotic cell death (Ozaki *et al*., *BBRC*, 2006, 339,1171). HDAC inhibitor VPA inhibits angiogenesis and increases extracellular ERK phosphorylation. PD98059, a MEK inhibitor

prevented the VPA-induced ERK phosphorylation. The combination of VPA with PD98059 synergistically inhibited angiogenesis *in vitro* and *in vivo* (Michaelis *et al.*, *Cell Death Differ.* 2006, 13,446). Coadministration of HDAC inhibitor SAHA and MEK inhibitor PD184352 (or U0126) resulted in a synergistic increase in mitochondrial damage, caspase activation, and apoptosis in K562 and LAMA 84 cells (Yu *et al.*, *Leukemia* 2005, 19).

In one embodiment, the second pharmacophore inhibits Cyclin-dependent kinases (CDK). A variety of genetic and epigenetic events cause universal overactivity of the cell cycle cdks in human cancer, and their inhibition can lead to both cell cycle arrest and apoptosis (Shapiro, *J Clin Oncol.,* 2006, 24, 1770). Combined treatment of human leukemia cells with HDAC inhibitor LAQ824 and CDK inhibitor roscovitine disrupts maturation and synergistically induces apoptosis, lending further support for an anti-leukemic strategy combining novel histone deacetylase and cyclin-dependent kinase inhibitors (Rosato *et al.*, *Mol. Cancer Ther.*, 2005, 4,1772). Coadministration of Cyclin-dependent kinase inhibitor flavopiridol with HDAC inhibitor suberoylanilide hydroxamide and butyrate synergistically potentiated mitochondrial damage, caspase activation, poly(ADP-ribose) polymerase degradation, and cell death in both wild type and Bcl-2- or Bcl-x(L)-overexpressing cells (U937 and HL-60) and induced a pronounced loss of clonogenicity. A strategy combining CDK and HDAC inhibitors may be effective against drug-resistant leukemia cells overexpressing Bcl-2 or Bcl-x(L). (Dasmahapatra *et al.*, Mol. Pharmacol. 2006, 69, 288).

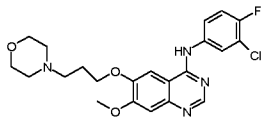
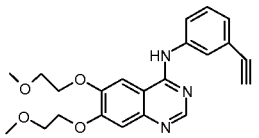
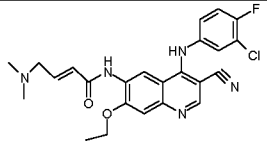
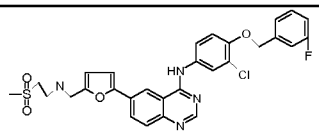
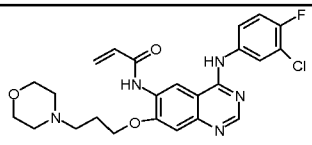
In one embodiment, the second pharmacophore inhibits the proteosome. Inhibition of the proteasome results in disruption of protein homeostasis within the cell that can lead to apoptosis, a phenomenon preferentially observed in malignant cells. Bortezomib (Velcade®), a first-in-class proteasome inhibitor approved as an antineoplastic agent, sensitized multiple myeloma cells to HDAC inhibitor (butyrate and suberoylanilide)-induced mitochondrial dysfunction, caspase 9, 8 and 3 activation; and polypolymerase degradation (Pei *et al.*, *Clin. Cancer Res.*, 2004,10, 3839). HDAC inhibitor (depsipeptide)-induced apoptosis and mitochondrial translocation of Bax were markedly enhanced by the proteasome inhibitor bortezomib in myeloid leukemic cell lines HL-60 and K562 (Sutheesophon *et al.*, *Acta Haematol.*, 2006, 115, 78).

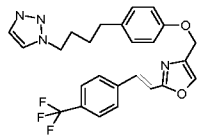
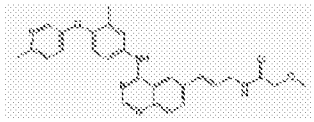
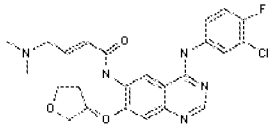
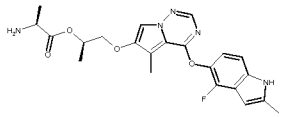
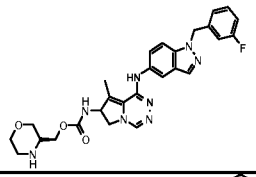
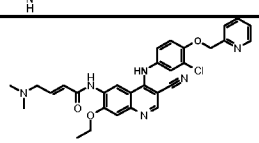
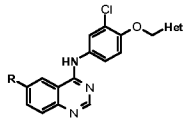
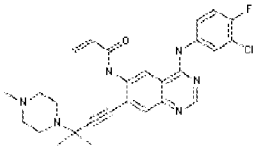
In one embodiment, the second pharmacophore promotes apoptosis of cancerous cells. Apoptosis targets that are currently being explored for cancer drug discovery include, the tumor-necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptors, the Bcl-2 family of anti-apoptotic proteins, inhibitor of apoptosis (IAP) proteins and MDM2. The HDAC inhibitor, Suberic bishydroxamate (SBHA), sensitizes melanoma to TRAIL-induced apoptosis (Zhang *et al.*, *Biochem. Pharmacol.*, 2003, 66,1537). Coadministration of TNF-related apoptosis-inducing ligand (TRAIL) with HDAC inhibitors synergistically induces apoptosis, and leads to dramatic increase in mitochondrial injury and activation of caspase cascade in human myeloid leukemia cells. (Rosato *et al.*, Mol. Pharmacol., 2003, 2,1273). HDAC inhibitors enhance the apoptosis-induced potential of TRAIL in leukemia cells through multiple mechanisms (Shankar *et al.*, Int. J. Mol. Med., 2005, 16,1125).

In one embodiment, A is a pharmacophore selected from anti-cancer compound such as, but not limited to:

1. Tyrosine Kinases

1-1 ErbB family (EGFR, ErbB2, ErbB3, ErbB4)

| Compound | Structures | Known Targets |
|---|---|---|
| Gefitinib/Iressa® |  | EGFR |
| Erlotinib/Tarceva® |  | EGFR |
| EKB-569 |  | EGFR, HER-2 |
| Lapitinib/Tykerb /GW-572016 |  | EGFR, HER-2 |
| Canertinib/CI-1033 |  | EGFR, HER-2, ErbB3, HrbB4 |

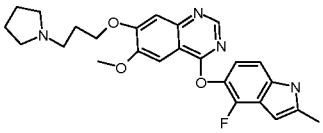
| | | |
|---|---|---|
| Mubritinib /TAK165 |  | HER-2 |
| CP-724714 |  | ErbB2 |
| BIBW-2992 |  | EGFR, HER-2 |
| BMS-582664 |  | VEGFR-2 |
| BMS-599626 |  | EGFR,HER-2, |
| HKI-272 |  | HER-2, EGFR |
| ARRY-334543 |  | EGFR, HER-2 |
| AV-412 |  | ErbB2, EGFR |

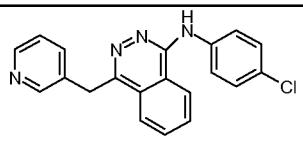
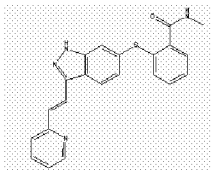
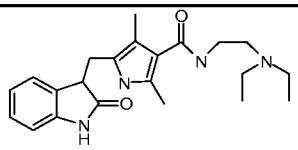
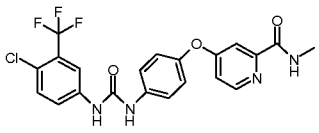
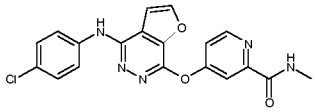
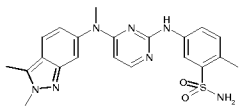
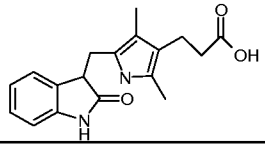
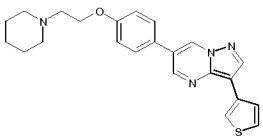
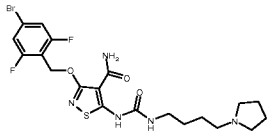
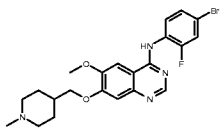
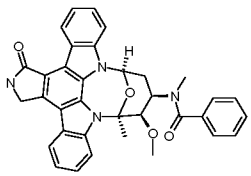
1-2 Split kinase family

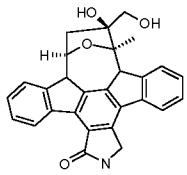
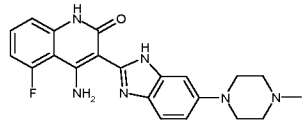
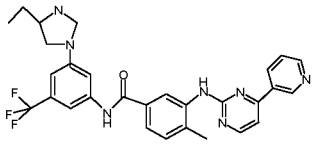
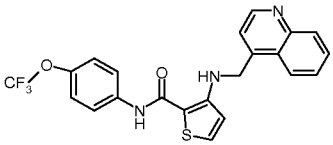
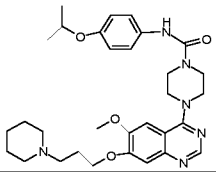
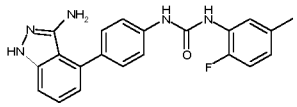
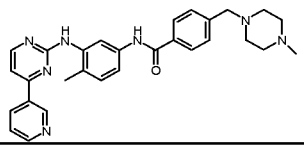
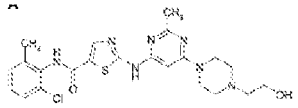
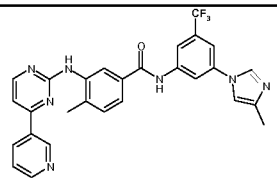
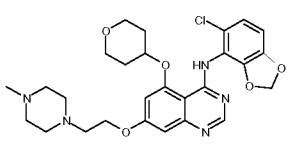
VEGFR family -VEGFR-1, VEGFR-2, Flt-3, c-Kit, Abl, JAK

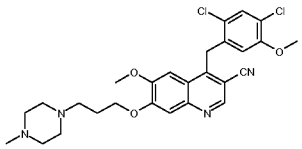
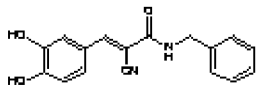
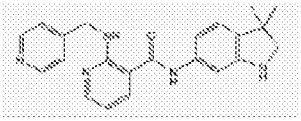
PDGFR family-PDGFR-a, PDGFR-b, IGF-IR, c-Met

FGFR family - FGFR1, FGFR3, FGFR4, c-Ret

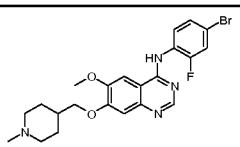
| Compound | Structures | Known Targets |
|---|---|---|
| Cediranib/AZD-2171 |  | VEGF1, VEGF2, VEGF3, Flt-1, c-Kit |

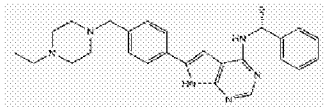
| | | |
|---|---|---|
| Vatalanib/PTK787 /ZK222584 |  | VEGFR1,2 &3, PDGFR, c-Kit |
| Axitinib/AG-013736 |  | VEGFR-1, PDGFR, VDGF-2 |
| Sunitinib/Sutent /SU11248 |  | VEGFR-2, PDGFR, FLT3, c-Kit |
| Sorafenib/Nexavar/BAY 43-9006 |  | Raf, VEGFR, PDGFR, FLT3, c-Kit, |
| BAY--57-9352 |  | VEGFR-2 & 3, PDGFR, c-kit |
| Pazopanib/GW-786034 |  | VEGF1, VEGF2, VEGF3, PDGFR, c-Kit |
| SU6668 |  | VEGFR-2, PDGFR, FLT3, c-Kit |
| L-21649 |  | VEGFR-2, Flt-3 |
| CP-547632 |  | VEGFR-2 |
| Vandetanib/AZD-6474 |  | VEGFR-2 |
| Midostaurin/PKC412 |  | FLT3, kit, PDGFR |

| | | |
|---|---|---|
| Lestaurtinib/CEP-701 |  | FLT3 |
| CHIR-258/TKI-258 |  | FLT3, VEGFR, c-Kit |
| AMN107 |  | Acr-Abl, Kit, PDGFR |
| OSI-930 |  | c-Kit, VEGFR |
| Tandutinib/MLN-518 /CT53518 |  | FLT3, PDGFR, c-Kit |
| ABT-869 |  | Flt-3, KDR, VEGFR-3 |
| Imatinib/Gleevec /STI-571 |  | Bcr-Abl, PDGFR, c-Kit |
| Dasatinib /BMS-354825 |  | Bcr-Abl, Src, Fyn |
| Nilotinib/AMN-107 |  | Bcr-Abl, cKit, PDGFR |
| AZD-0530 |  | Src, Bcr-Abl |

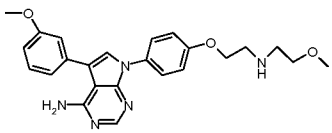
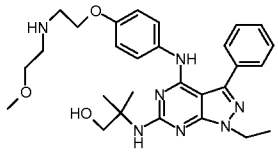
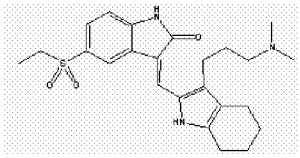
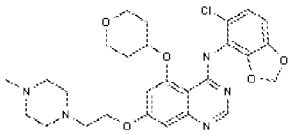
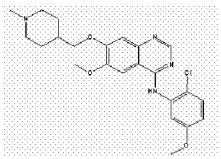
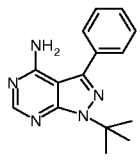
| | | |
|---|---|---|
| Bosutinib/SKI-606 |  | Src, Bcr-Abl |
| AG490 |  | Jak |
| AMG706 |  | VEGF, PDGF, Kit |
| BIBF-7055 | | VEGF-2, PDGF, Kit |
| XL999 | | FGFR, VEGFR,PDGFR, Flt3 |
| XL880 | | c-Met, VEGFR2 |
| XL647 | | EGFR, HER2, VEGFR |
| XL184 | | VEGFR2 and Met |
| XL820 | | KIT, VEGFR and PDGFR |

1-3 Combined ErbB kinase and Split kinase family (EGFR and VEGFR)

| Compound | Structures | Known Targets |
|---|---|---|
| Vandetanib/ZD6474 |  | VEGFR, EGFR |

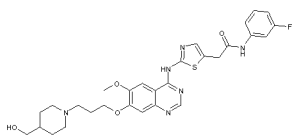
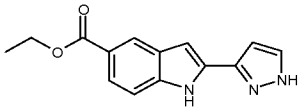
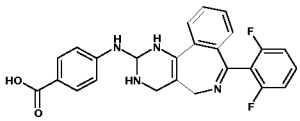
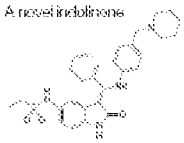
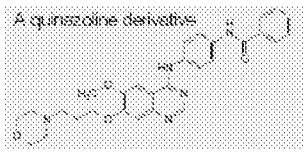
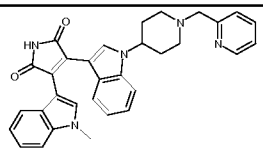
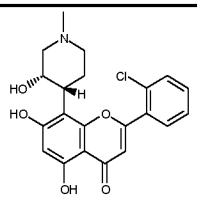
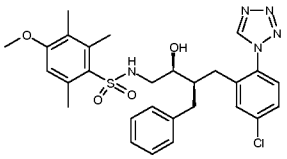
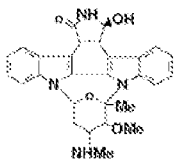
| | | |
|---|---|---|
| AEE788 |  | EGFR, HerB2, VEGFR |

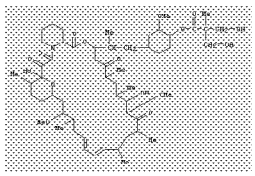
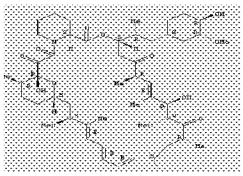
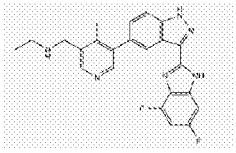
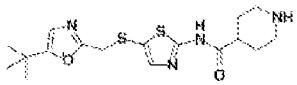
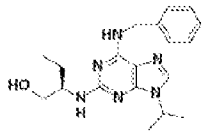
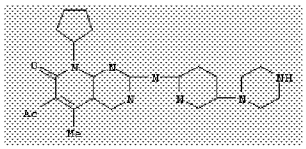
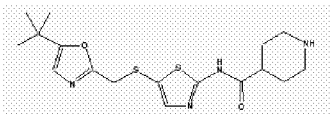
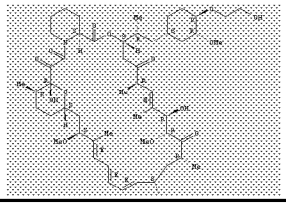
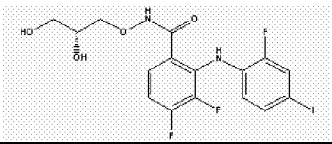
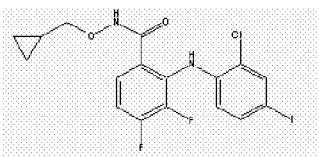
1-4 Src Family Kinases: Src, Lyn, Yes

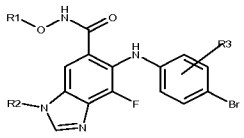
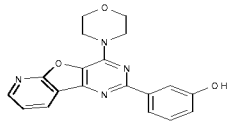
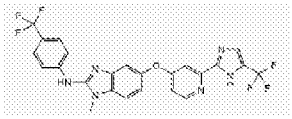
| Compound | Structures | Known Targets |
|---|---|---|
| CGP76030 |  | Src, Yes, Fgr, lyn,abl |
| NVP-AAAK980 |  | Src |
| SU-6656 |  | Src |
| AZD-0530 |  | Src |
| AZM-475271 |  | Src |
| PP-1 |  | Src, Abl |

2. Serine/threonine kinases: PKC, CDK, Erk, Mek, PI3K-Akt, mTOR, Raf, CHK, Aurora

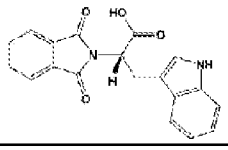
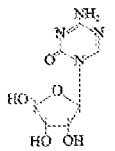
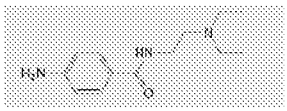
| Compound | Structures | Known Targets |
|---|---|---|

| | | |
|---|---|---|
| VX-680/MK0457 |  | Aurora |
| AZD-1152 |  | Aurora |
| PHA-739358 |  | Aurora |
| MLN-8054 |  | Aurora |
| Hesperedin |  | Aurora |
| AM447439 |  | Aurora |
| Enzastaurin/LY-317615 |  | PKC, AKT |
| Alvocidib/HMR-1275 |  | CDK |
| AT-7519 |  | CDK |
| UCN-01 |  | PKC, CDK |

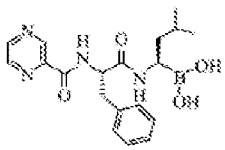
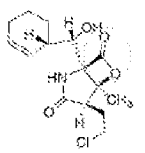
| | | |
|---|---|---|
| CCI-779 |  | mTOR |
| Rapamycin/sirolimus |  | mTOR |
| AG-024322 |  | CDK |
| BMS 387032 |  | CDK |
| R-Roscovitine /CYC202/Seliciclib |  | CDK |
| PD-0332991 |  | CDK |
| SNS-032 |  | CDK |
| RAD001/Everolimus |  | mTOR |
| PD-0325901 |  | MEK 1&2 |
| CI-1040/PD 184352 |  | MEK |

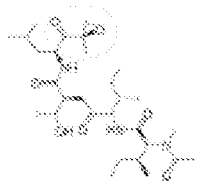
| | | |
|---|---|---|
| AZD6244/ARRY-142886 |  | MEK 1&2 |
| PI-103 |  | PI-3 |
| CHIR-265 |  | B-Raf, VEGFR2 |

3. DNA methyl transferase (DNMT)

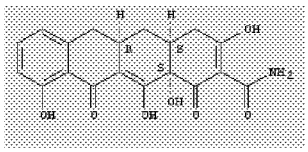
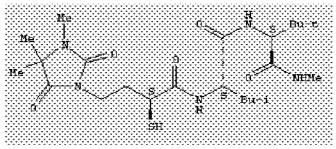
| Compound | Structures | Known Targets |
|---|---|---|
| RG108 |  | DNMT |
| Azacitidine |  | DNMT |
| Procainamide |  | DNMT |

4. Proteasome

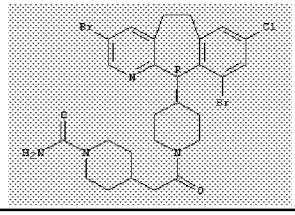
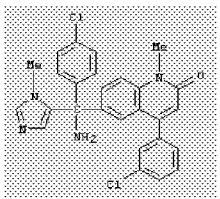
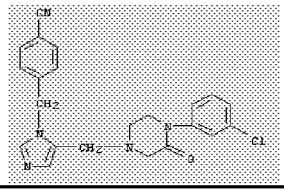
| Compound | Structures | Known Targets |
|---|---|---|
| Bortezomib/Velcade |  | Proteasome |
| salinosporamide A /NBI-0052 |  | Proteasome |

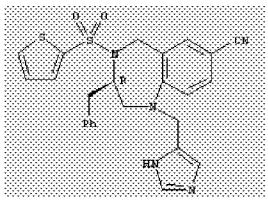
| | | |
|---|---|---|
| PR-171 |  | Proteasome |

5. Matrix metalloproteinase

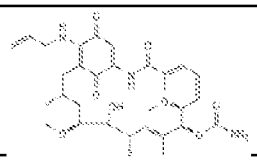
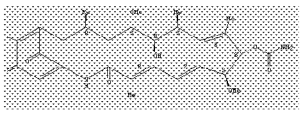
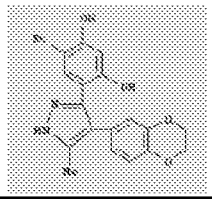
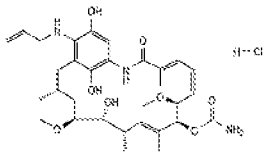
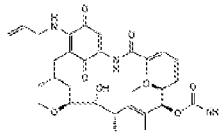
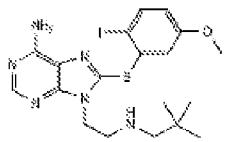
| Compound | Structures | Known Targets |
|---|---|---|
| COL-3 |  | matrix metalloproteinase inhibitor |
| BMS-275291 |  | matrix metalloproteinase inhibitor |

6. Farnesyl Transferase

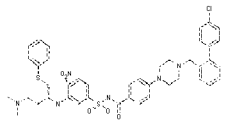
| Compound | Structures | Known Targets |
|---|---|---|
| SCH66336 |  | Farnesyl Transferase |
| R115777 |  | Farnesyl Transferase |
| L778123 |  | Farnesyl Transferase |

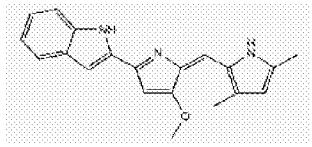
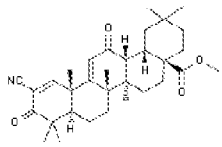
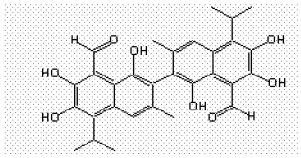
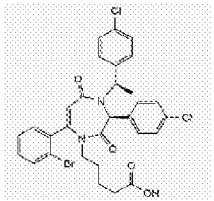
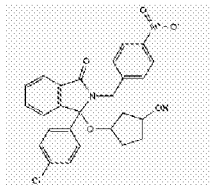
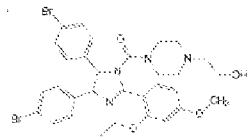
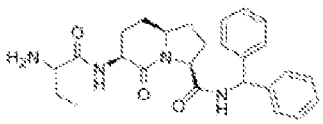
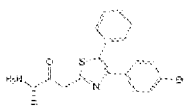
| | | |
|---|---|---|
| BMS-214662 |  | Farnesyl Transferase |

7. Heat-shock proteins (HSPs), especially HSP90

| Compound | Structures | Known Targets |
|---|---|---|
| 17AAG/KOS-953 |  | HSP90 |
| DMAG/KOS-1022 /Geldeanamycin |  | HSP90 |
| CCT018159 |  | HSP90 |
| IPI-504 |  | HSP90 |
| CNF-1010 |  | HSP90 |
| CNF-2024 |  | HSP90 |

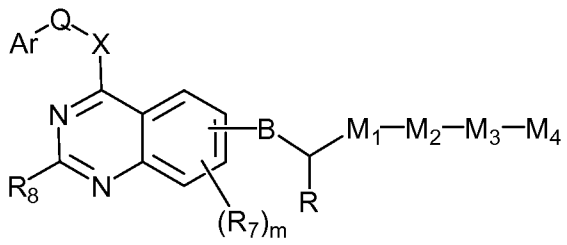
8. Apotosis agents: TRAILR, caspases, IAPs, Bcl-2,Survivin, MDM2, MDM4,

| Compound | Structures | Known Targets |
|---|---|---|
| ABT-737 |  | Bcl |

| | | |
|---|---|---|
| Obatoclax |  | Bcl |
| TP-115C |  | Bcl |
| AT-101 |  | Bcl |
| IPI-191 | | Bcl |
| JNJ-2729199 |  | MDM2 |
| NU-8001 |  | MDM2 |
| Nutlin 2 |  | MDM2 |
| Smac-mimetic |  | XIAP |
| Smac-mimetic |  | XIAP |

In one preferred embodiment, A is a pharmacophore selected from anti-cancer compound that is characterized by having at least one nitrogen containing heterocycle or heteroaryl ring.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (II) or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(II)

wherein Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Q is absent or substituted or unsubstituted alkyl;

X is O, S, NH, or alkylamino;

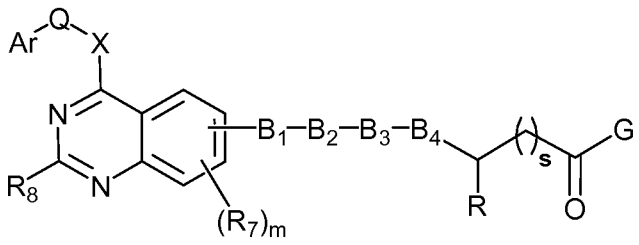
m is 0, 1, 2 or 3;

each of $R_7$ is independently selected from hydrogen, hydroxy, amino, halogen, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio, substituted alkylthio, alkylsulfonyl, substituted alkylsulfonyl, $CF_3$, CN, $N_3$, $NO_2$, sulfonyl, acyl, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$R_8$ is hydrogen, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In a preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (III) or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(III)

wherein

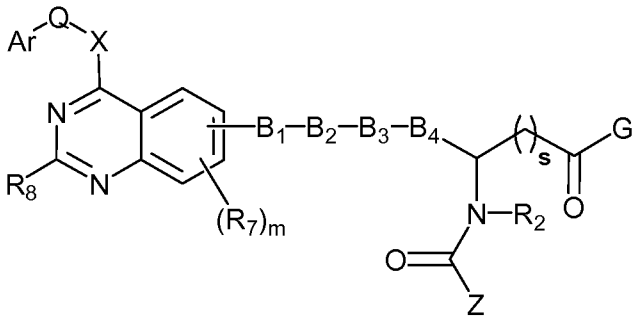
s is 2-10; preferably 3-7;

G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably, $B_4$ is imidazole or amide; and

Ar, Q, X, m, R, $R_4$, $R_5$, $R_6$, $R_7$, and $R_8$ are as previously defined.

In another preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (IV) or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



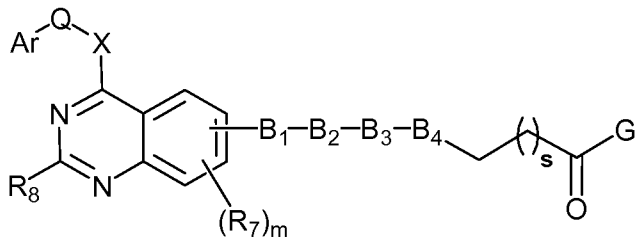
(IV)

wherein

Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

Ar, Q, X, $B_1$, $B_2$, $B_3$, $B_4$, s, m, G, $R_2$, $R_7$, and $R_8$ are as previously defined.

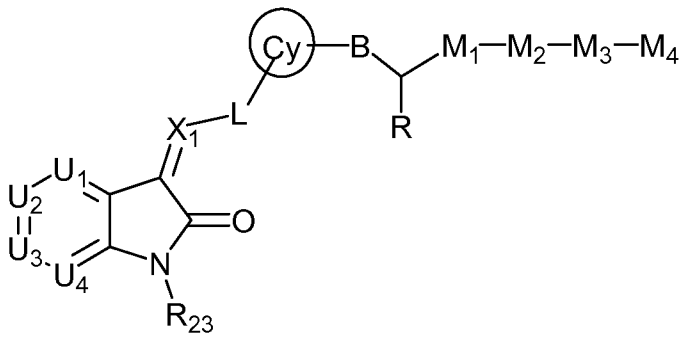
In an alternative preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (V) or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(V)

wherein Ar, Q, X, $B_1$, $B_2$, $B_3$, $B_4$, m, s, G, $R_7$, and $R_8$ are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (VI) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(VI)

wherein $X_1$ is N, $CR_2$; where $R_2$ is as previously defined;

L is absent or NH;

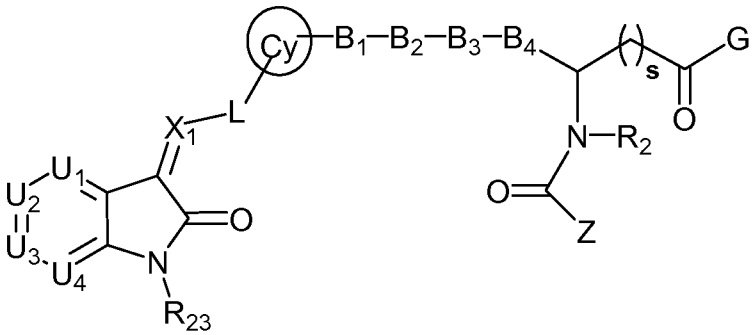
Cy is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

$U_1$-$U_4$ are independently N or $CR_{21}$, where $R_{21}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

$R_{23}$ is hydrogen or aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In a preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (VII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(VII)

wherein

s is 2-10; preferably 3-7;

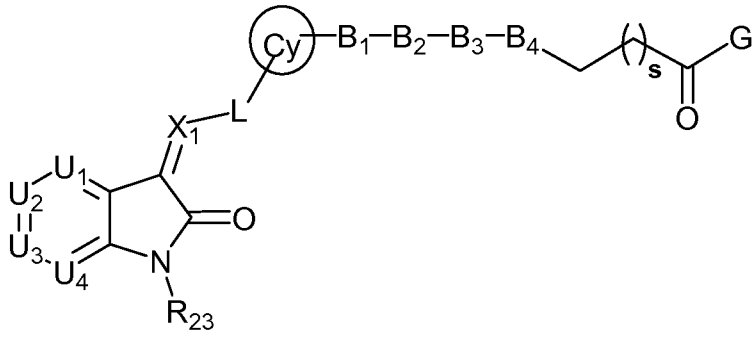
G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably $B_4$ is imidazole or amide; and

Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N;

and $X_1$, L, $U_1$-$U_4$, Cy, $R_{23}$ and $R_2$ are as previously defined.

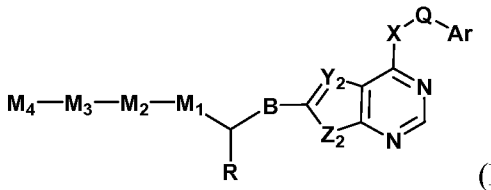
In an alternative preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (VIII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



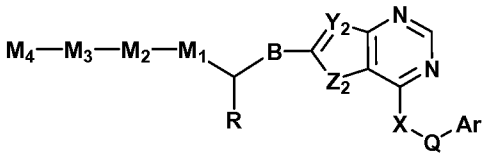
(VIII)

wherein $X_1$, L, $U_1$-$U_4$, Cy, $R_{23}$, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (IX) or (X) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(IX) or



(X)

wherein $Z_2$ is O, S, NH or alkylamino

$Y_2$ is N or $CR_{20}$; where $R_{20}$ is selected from hydrogen, halogen, aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

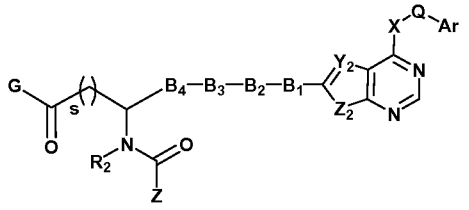
X is O, S, NH, or alkylamino;

Q is absent or substituted or unsubstituted alkyl;

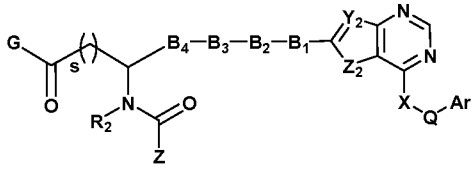
Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In a preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XI) or (XII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XI) or



(XII)

wherein

s is 2-10; preferably 3-7;

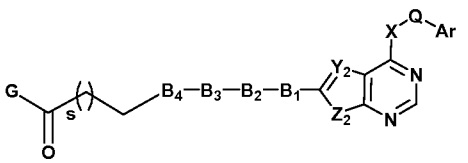
G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably $B_4$ is imidazole or amide;

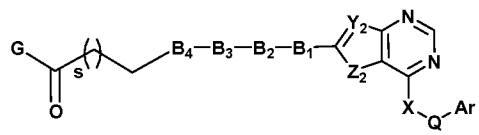
Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

$Z_2$, $Y_2$, X, Q, Ar and $R_2$, are as previously defined.

In an alternative preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XIII) or (XIV) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XIII) or

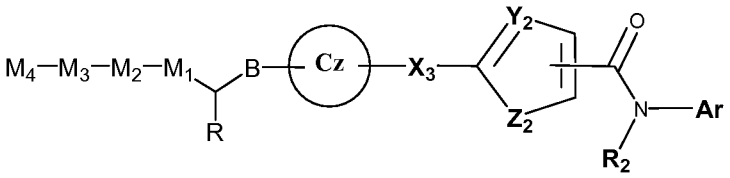


(XIV)

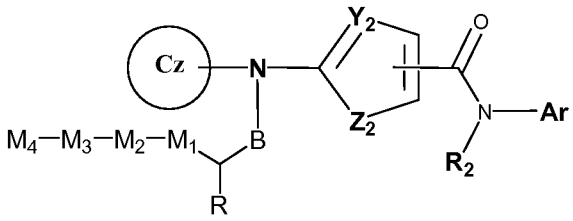
wherein $Z_2$, $Y_2$, X, Q, Ar, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XV) or (XVI) as illustrated below, or its

geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XV)



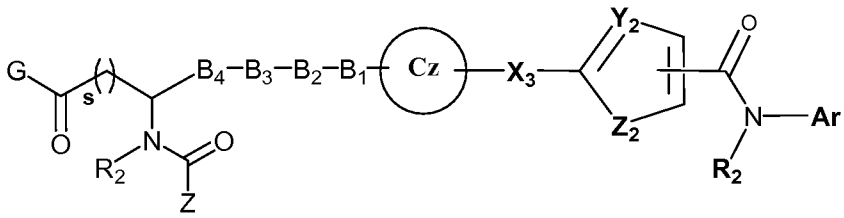
(XVI)

wherein Cz is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, and heterocylic;

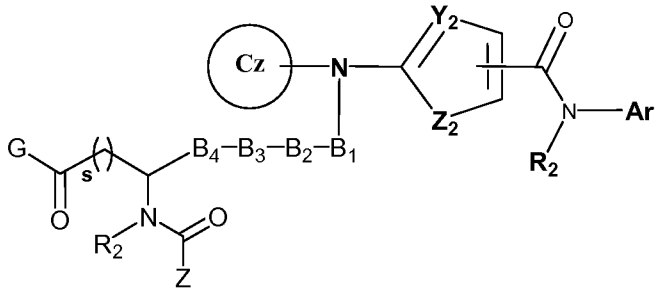
$X_3$ is NH, alkylamino, O or S;

B, R, $Y_2$, $Z_2$, Ar, $R_2$, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In one preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XVII) or (XVIII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XVII)



(XVIII)

wherein

s is 2-10; preferably 3-7;

G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or –

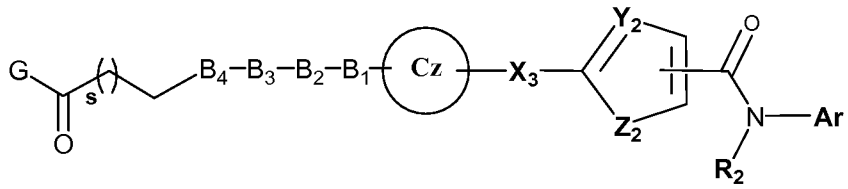
$C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably $B_4$ is imidazole or amide;

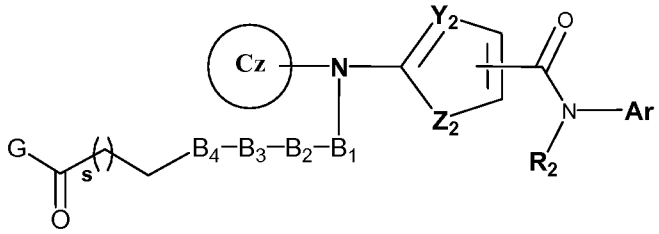
Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

Cz, $X_3$, $Y_2$, $Z_2$, Ar and $R_2$ are as previously defined.

In an alternative preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XIX) or (XX) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



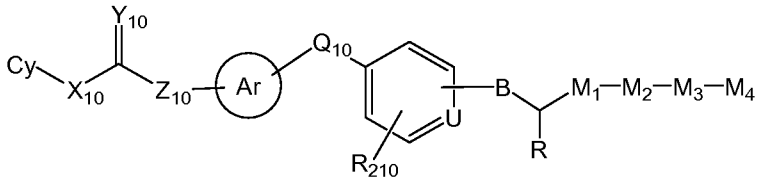
(XIX)



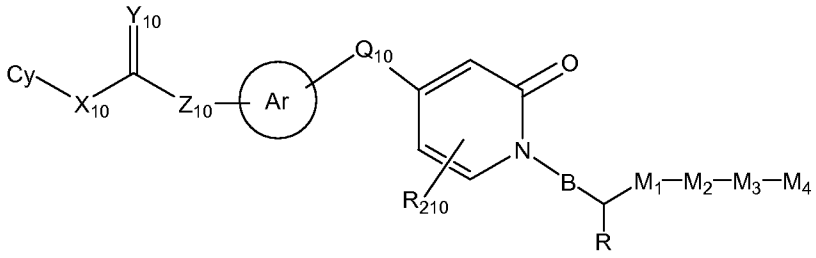
(XX)

wherein Cz, $X_3$, $Y_2$, $Z_2$, Ar, $R_2$, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXI) or (XXII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XXI)



(XXII)

wherein U is N, CH or C;

Ar is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocylic or substituted heterocyclic;

$Q_{10}$ is O, S, SO, $SO_2$, NH, substituted or unsubstituted alkylamino, or substituted or unsubstituted $C_1$-$C_3$ alkyl;

$Y_{10}$ is O, S or NH;

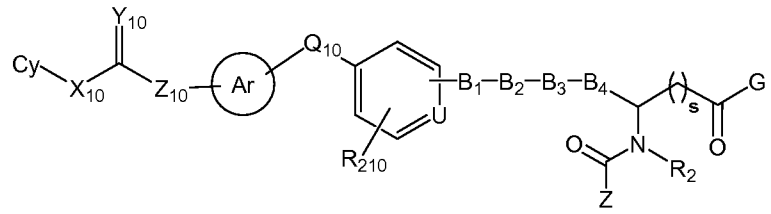
$X_{10}$ and $Z_{10}$ are independently NH, substituted or unsubstituted alkylamino, or substituted or unsubstituted $C_1$-$C_3$ alkyl;

Cy is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

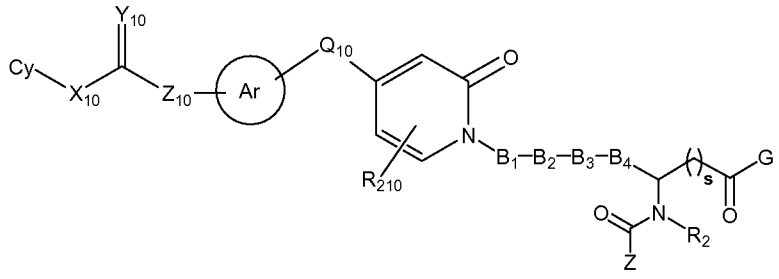
$R_{210}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfonyl, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aliphatic, and substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In a preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXIII) or (XXIV) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XXIII)



(XXIV)

wherein

s is 2-10; preferably 3-7;

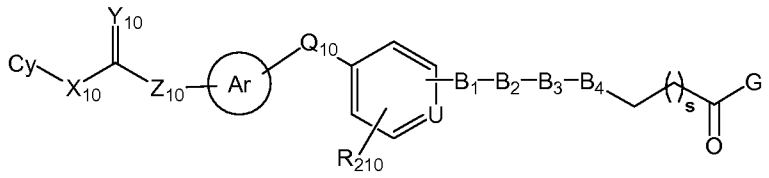
G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably $B_4$ is imidazole or amide;

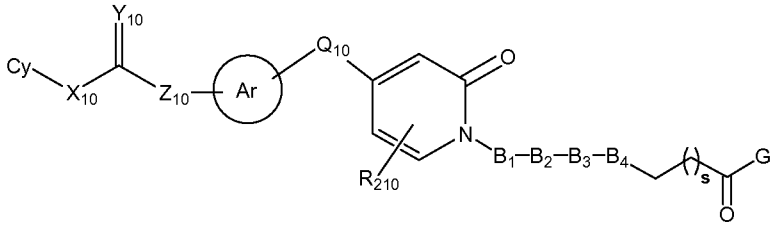
Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

U, Ar, $Q_{10}$, $Y_{10}$, $X_{10}$, $Z_{10}$, Cy, $R_{210}$, and $R_2$ are as previously defined.

In an alternative preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXV) or (XXVI) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



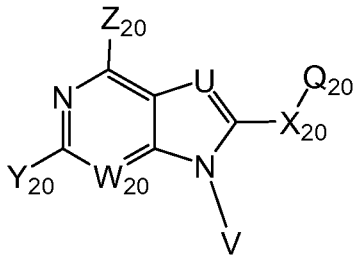
(XXV)



(XXVI)

wherein U, Ar, $Q_{10}$, $Y_{10}$, $X_{10}$, $Z_{10}$, Cy, $R_{210}$, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXVII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XXVII)

wherein U is N or CH;

$W_{20}$ is N or CH;

$X_{20}$ is absent, O, S, S(O), $S(O)_2$, $N(R_2)$, $CF_2$ or $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, in which one or more methylene can be interrupted or terminated by O, S, SO, $SO_2$, $N(R_2)$;

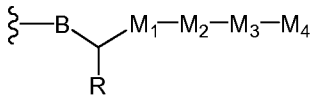
$Y_{20}$ is independently hydrogen, halogen, $NO_2$, CN, or lower alkyl;

$Z_{20}$ is amino, alkylamino, or dialkylamino;

$Q_{20}$ is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, or heterocycloalkyl;

V is hydrogen, straight- or branched-, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, which one or more methylenes can be interrupted or terminated by O, S, S(O), $SO_2$, $N(R_{18})$, C(O), substituted or unsubstituted aryl, substituted or

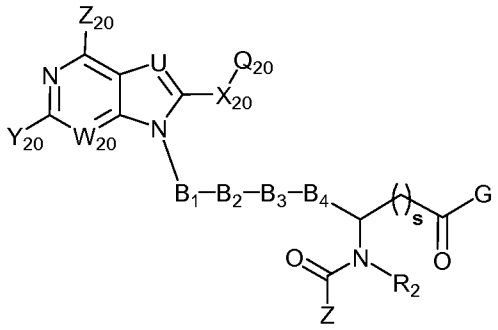
unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; substituted or unsubstituted cycloalkyl;



and wherein $Q_{20}$ and/or V is further substituted by ;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In one preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXVIII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XXVIII)

wherein

s is 2-10; preferably 3-7;

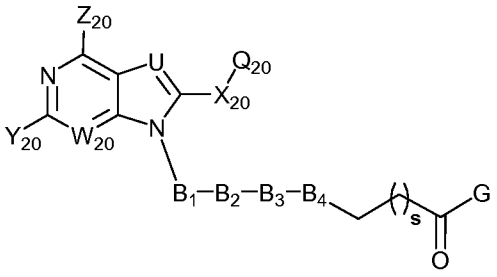
G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably $B_4$ is imidazole or amide;

Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

U, $W_{20}$, $X_{20}$, $Y_{20}$, $Z_{20}$, $Q_{20}$ and $R_2$ are as previously defined.

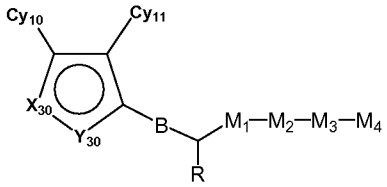
In one preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXVIIIa) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



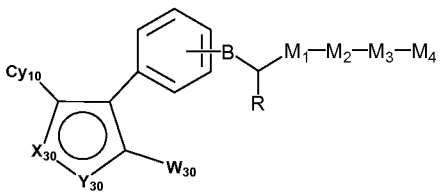
(XXVIIIa)

wherein U, $W_{20}$, $X_{20}$, $Y_{20}$, $Z_{20}$, $Q_{20}$, $R_2$, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXIX) or (XXX) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XXIX)



(XXX)

wherein $Cy_{10}$ and $Cy_{11}$ are each independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

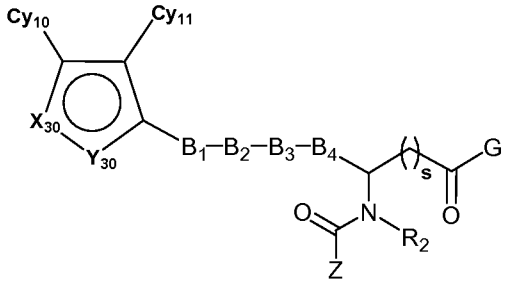
$Y_{30}$ is N, $NR_{18}$ or $CR_{18}$, where $R_{18}$ is hydrogen, acyl, aliphatic or substituted aliphatic;

$X_{30}$ is $CR_{18}$, $NR_{18}$, N, O or S;

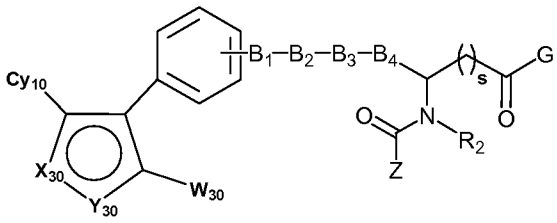
$W_{30}$ is hydrogen, acyl, aliphatic or substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In one preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXXI) or (XXXII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XXXI)



(XXXII)

wherein

s is 2-10; preferably 3-7;

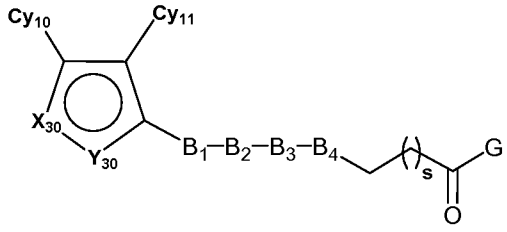
G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably $B_4$ is imidazole or amide;

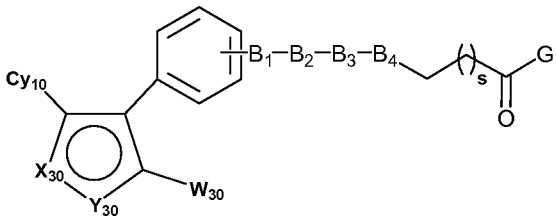
Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

$Cy_{10}$, $Cy_{11}$, $Y_{30}$, $X_{30}$, $W_{30}$ and $R_2$ are as previously defined.

In an alternative preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXXIII) or (XXXIV) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



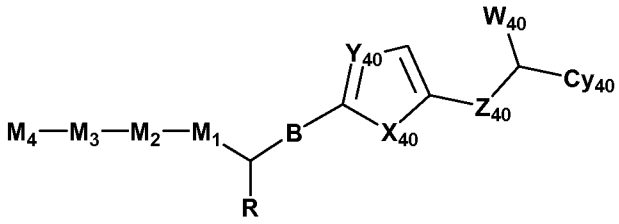
(XXXIII)



(XXXIV)

wherein $Cy_{10}$, $Cy_{11}$, $Y_{30}$, $X_{30}$, $W_{30}$, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXXV) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XXXV)

wherein $Cy_{40}$ is each independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

$W_{40}$ is each independently selected from hydrogen, halogen, acyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

$Z_{40}$ is O, S, S(O), $SO_2$, $SO_2NH$, $NR_{18}$, C(O) or $C(O)NH_2$;

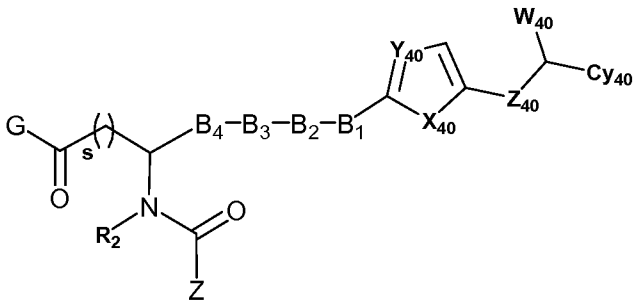
$Y_{40}$ is N or $CR_{18}$, where $R_{18}$ is hydrogen, acyl, aliphatic or substituted aliphatic;

$X_{40}$ is $CR_{18}$, $NR_{18}$, O or S;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In one preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXXVI) as illustrated below, or

its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XXXVI)

wherein

s is 2-10; preferably 3-7;

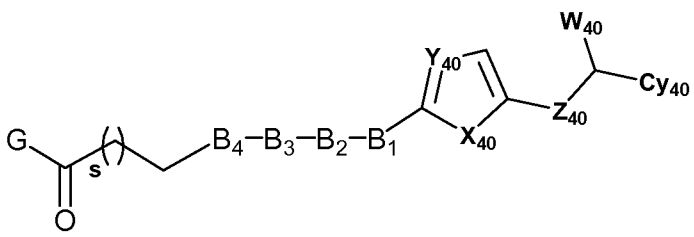
G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably $B_4$ is imidazole or amide;

Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

$Cy_{40}$, $W_{40}$, $Z_{40}$, $X_{40}$, $Y_{40}$ and $R_2$ is as previously defined.

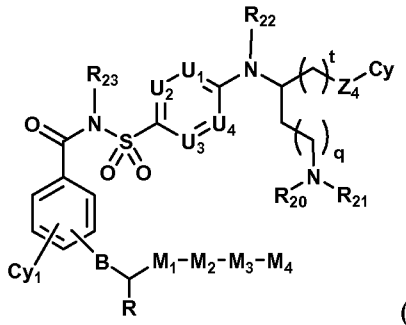
In an alternative preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXXVII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



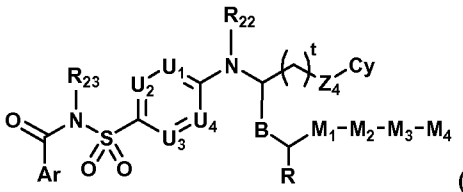
(XXXVII)

wherein $Cy_{40}$, $W_{40}$, $Z_{40}$, $X_{40}$, $Y_{40}$, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XXXVIII) or (XXXIX) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XXXVIII) or



(XXXIX)

wherein Cy and $Cy_1$ are each independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

$Z_4$ is O, S, $CR_{18}$, or $NR_{18}$;

$R_{20}$ and $R_{21}$ are each independently selected from hydrogen, acyl, aliphatic and substituted aliphatic; alternatively, $R_{20}$ and $R_{21}$ can be taken together with the atom they are attached to form a heterocyclic or substituted heterocyclic;

t is 1, 2 or 3;

q is 1, 2, 3 or 4;

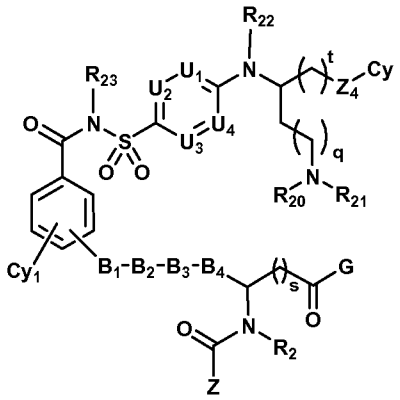
$R_{22}$ and $R_{23}$ are each independently selected from hydrogen, acyl, aliphatic and substituted aliphatic;

$U_1$-$U_4$ are independently N or $CR_{21}$, where $R_{21}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or

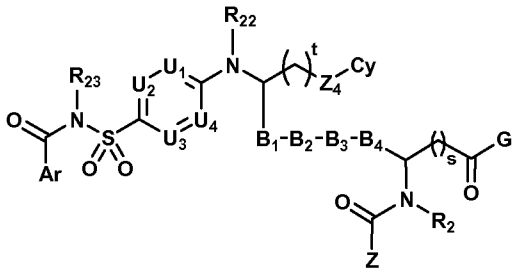
unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In one preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XL) or (XLI) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XL) or



(XLI)

wherein

s is 2-10; preferably 3-7;

G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

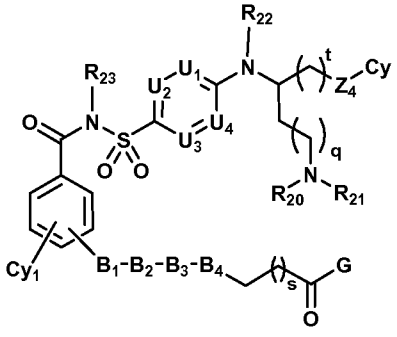
$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably $B_4$ is imidazole or amide;

Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted

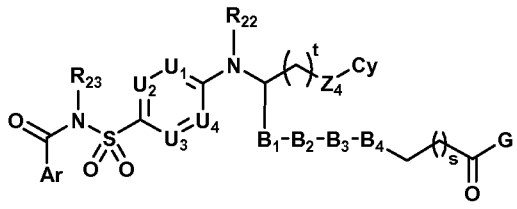
heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

Ar, $R_{23}$, Cy, $Cy_1$, $Z_4$, $U_1$-$U_4$, $R_{22}$, t, q and $R_2$ are as previously defined.

In an alternative preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XLII) or (XLIII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



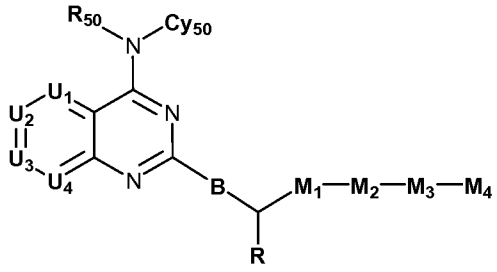
(XLII) or



(XLIII)

wherein Ar, $R_{23}$, Cy, $Cy_1$, $Z_4$, $U_1$-$U_4$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{23}$, t, q, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XLIV) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XLIV)

wherein

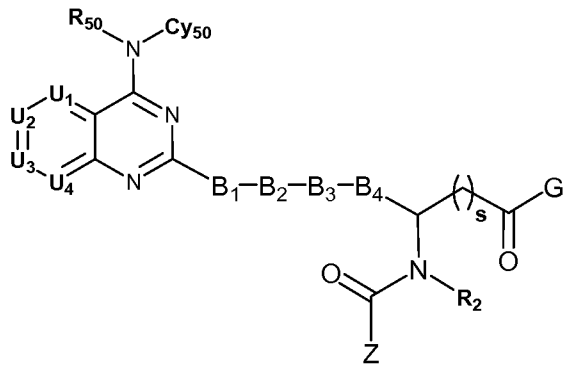
$Cy_{50}$ is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloakyl and substituted cycloalkyl;

$R_{50}$ is lower alkyl;

$U_1$-$U_4$ are independently N or $CR_{21}$, where $R_{21}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In one preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XLV) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XLV)

wherein

s is 2-10; preferably 3-7;

G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

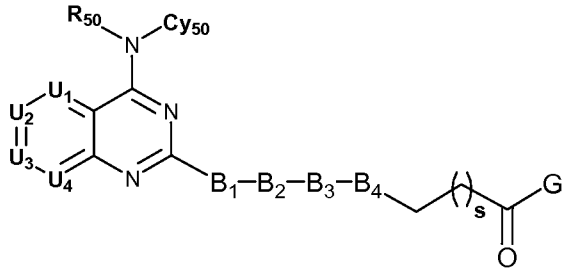
$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably $B_4$ is imidazole or amide;

Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting

of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

$Cy_{50}$, $R_{50}$, $U_1$-$U_4$ and $R_2$ is as previously defined.

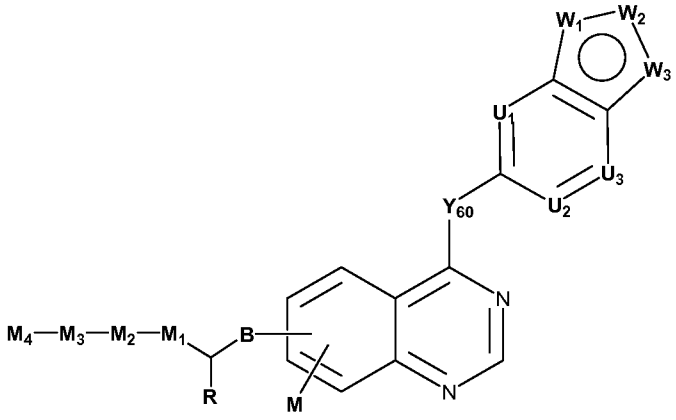
In an alternative preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XLVI) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(XLVI)

wherein $Cy_{50}$, $R_{50}$, $U_1$-$U_4$, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XLVII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



( XLVII)

wherein

$W_1$, $W_2$ and $W_3$ are independently selected from the group consisting of $CR_{21}$, $NR_{18}$, N, O or S, where $R_{18}$ is hydrogen, acyl, aliphatic or substituted aliphatic; $R_{21}$ is independently selected from the group consisting of hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted

or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

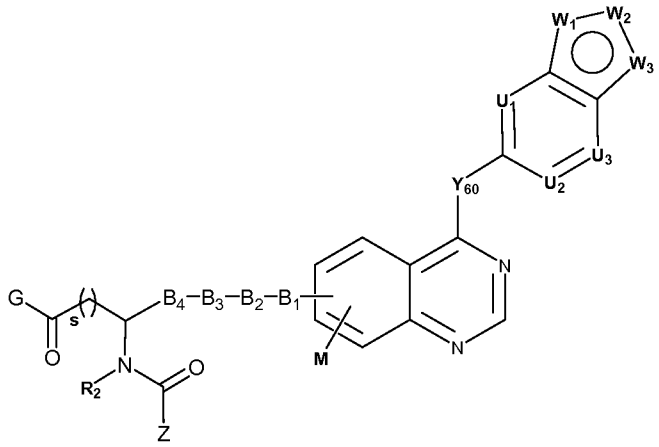
$U_1$-$U_3$ are independently N or $CR_{21}$, where $R_{21}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

$Y_{60}$ is $NR_{18}$, O, S, SO, $SO_2$, aliphatic, and substituted aliphatic;

M is independently selected from hydrogen, hydroxy, amino, halogen, $CF_3$, CN, $N_3$, $NO_2$, sulfonyl, acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclylalkyl, alkylheterocyclylalkenyl, alkylhererocyclylalkynyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, or alkynylheterocyclylalkynyl, which one or more methylenes can be interrupted or terminated by O, S, S(O), $SO_2$, $N(R_{18})$, C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where $R_{18}$ hydrogen, acyl, aliphatic or substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In one preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XLVIII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



( XLVIII)

wherein

s is 2-10; preferably 3-7;

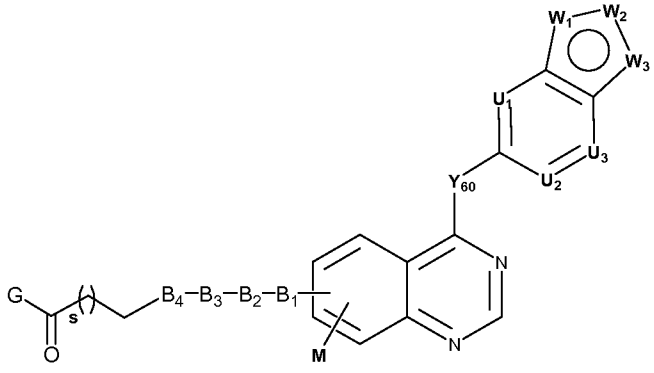
G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; ; preferably $B_4$ is imidazole or amide;

Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

$W_1$-$W_3$, $U_1$-$U_3$, $Y_{60}$, M and $R_2$ is as previously defined.

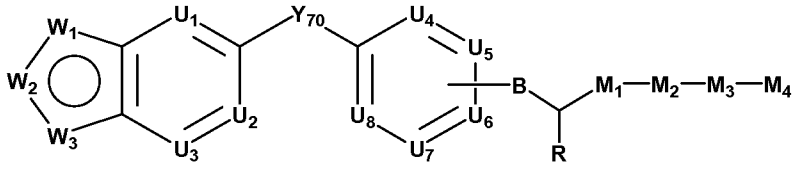
In an alternative preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (XLIX) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



( XLIX)

wherein $W_1$-$W_3$, $U_1$-$U_3$, $Y_{60}$, M, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (L) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(L)

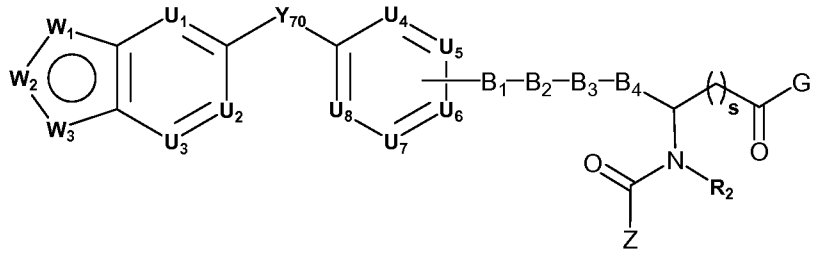
wherein $W_1$, $W_2$ and $W_3$ are independently selected from the group consisting of $CR_{21}$, $NR_{18}$, N, O or S, where $R_{18}$ is hydrogen, acyl, aliphatic or substituted aliphatic; $R_{21}$ is independently selected from the group consisting of hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

$U_1$-$U_8$ are independently N or $CR_{21}$, where $R_{21}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

$Y_{70}$ is $NR_{18}$, O, S, SO, $SO_2$, aliphatic, and substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In one preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (LI) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(LI)

wherein

s is 2-10; preferably 3-7;

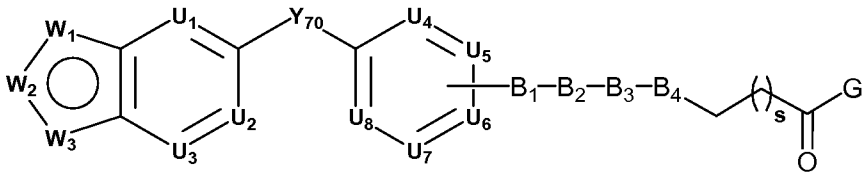
G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably $B_4$ is imidazole or amide;

Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

$W_1$-$W_3$, $U_1$-$U_8$, $Y_{70}$ and $R_2$ are as previously defined.

In an alternative preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (LII) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

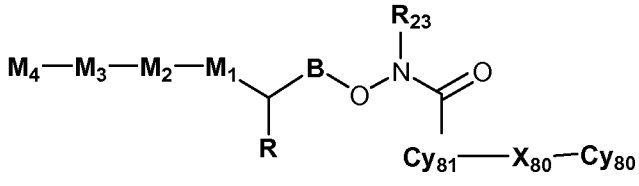


(LII)

wherein $W_1$-$W_3$, $U_1$-$U_8$, $Y_{70}$, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

In one embodiment, the multi-functional compounds of the present invention are compounds represented by formula (LIII) as illustrated below, or its geometric

isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(LIII)

wherein

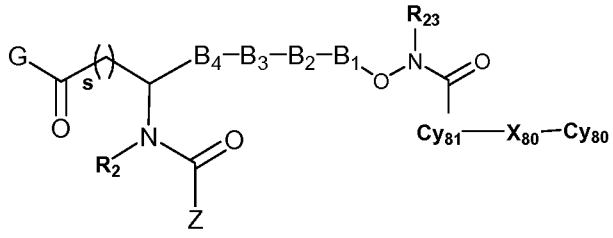
$Cy_{80}$ and $Cy_{81}$ are each independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

$X_{80}$ is $NR_{18}$, O, S, SO, $SO_2$, CO alkyl or substituted alkyl;

$R_{23}$ is hydrogen, aliphatic, substituted aliphatic or acyl;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

In one preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (LIV) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(LIV)

wherein

s is 2-10; preferably 3-7;

G is selected from hydrogen, $NR_5R_6$, halogen, $OR_4$, $CF_3$, C(O)H, $COR_4$, $CONH_2$, $CONHR_4$, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

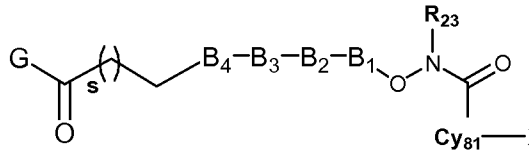
$B_1$, $B_2$, $B_3$ and $B_4$ are each independently absent or selected from O, S, SO, $SO_2$, $N(R_2)$, CO, substituted or unsubstituted $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl or $C_2$-$C_6$ alkynyl, substituted or unsubstituted cycloalkyl, heterocyclic, heteroaryl or aryl; preferably $B_4$ is imidazole or amide;

Z is $R_4$, $N(R_3)R_4$, and $OR_4$; where $R_3$ is independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting

of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; and

$Cy_{80}$, $Cy_{81}$, $X_{80}$, $R_{23}$ and $R_2$ are as previously defined.

In one preferred embodiment, the multi-functional compounds of the present invention are compounds represented by formula (LV) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

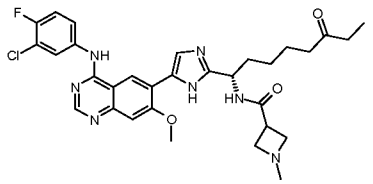
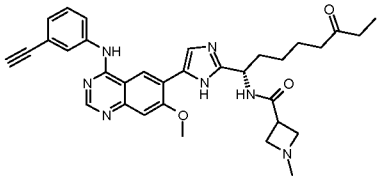
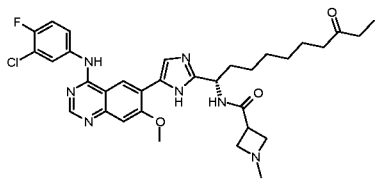


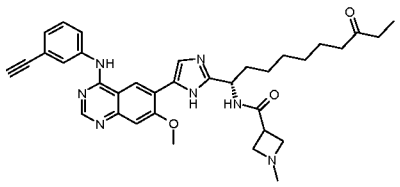
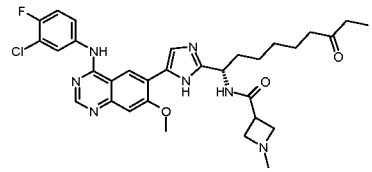
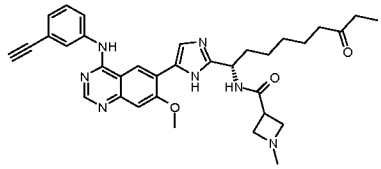
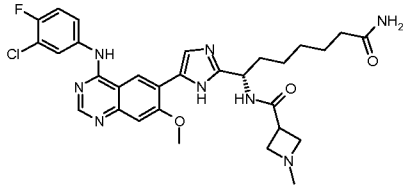
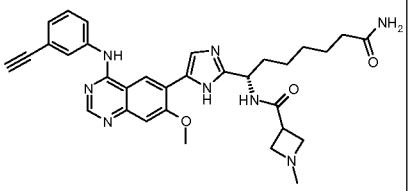
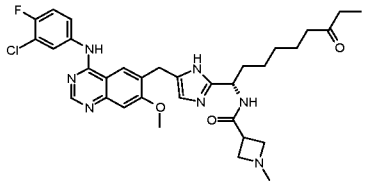
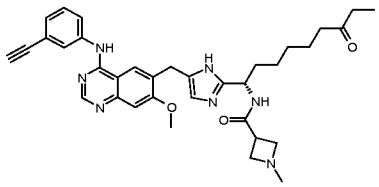
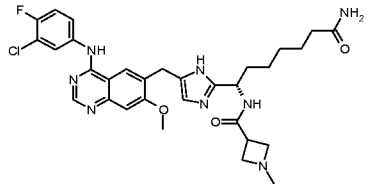
(LV)

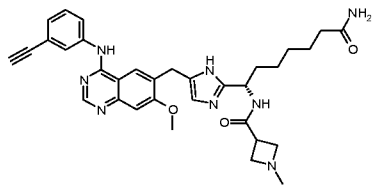
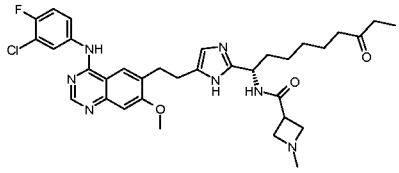
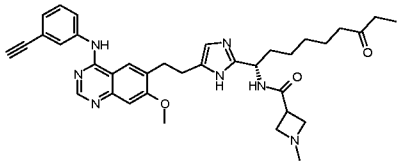
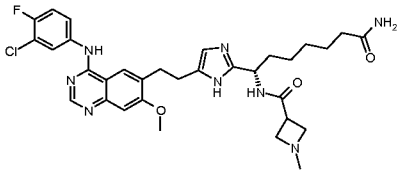
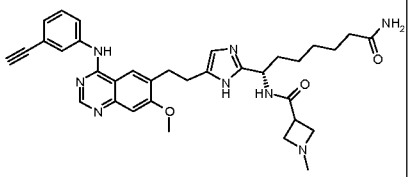
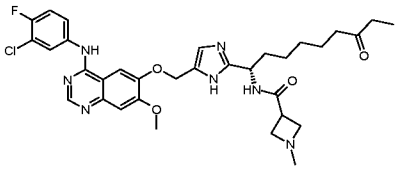
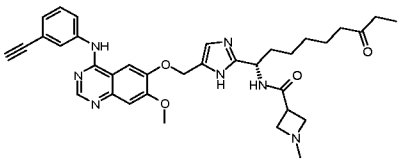
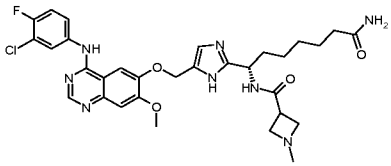
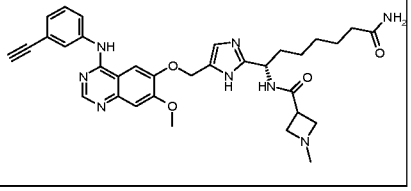
wherein $Cy_{80}$, $Cy_{81}$, $X_{80}$, $R_{23}$, $B_1$, $B_2$, $B_3$, $B_4$, G and s are as previously defined.

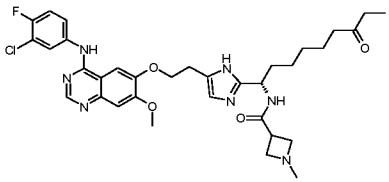
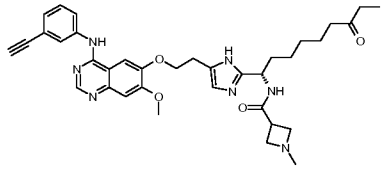
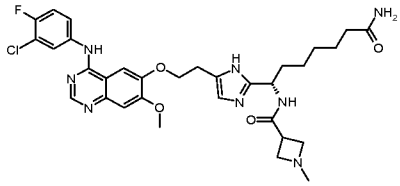
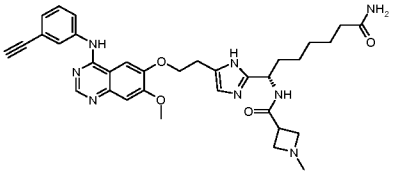
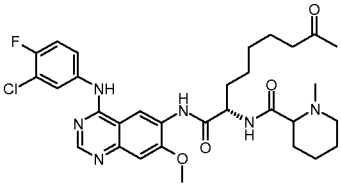
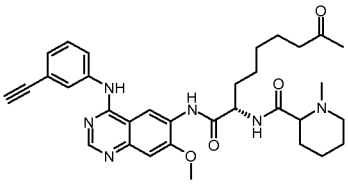
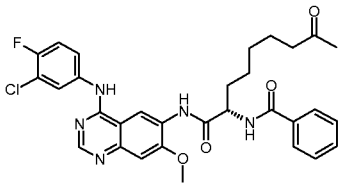
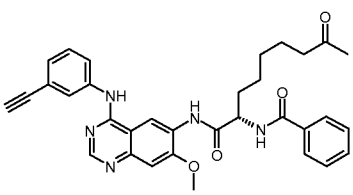
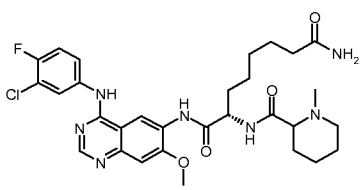
Representative compounds according to the invention are those selected from the Table A below or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

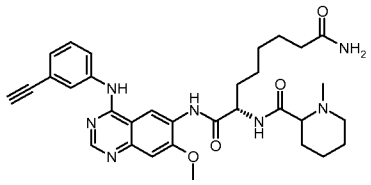
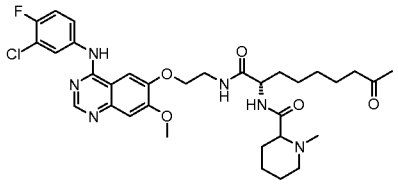
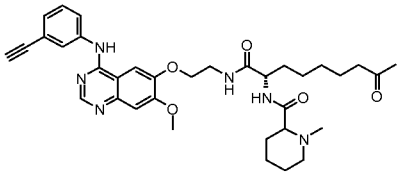
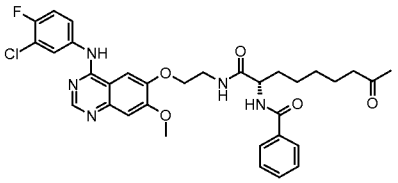
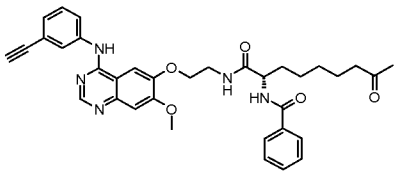
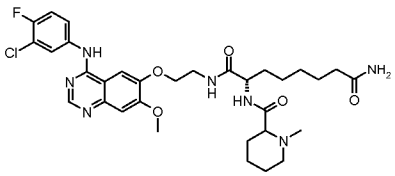
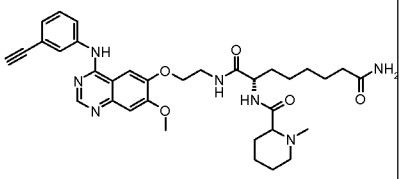
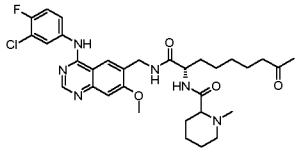
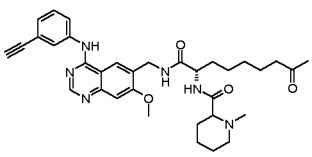
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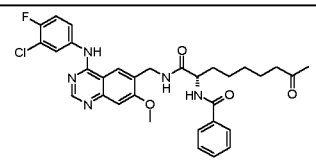
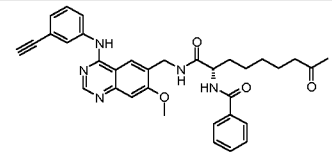
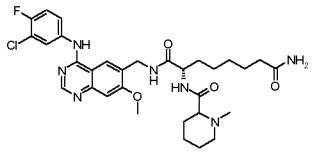
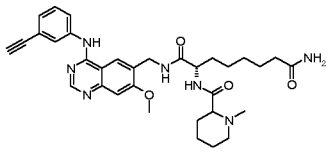
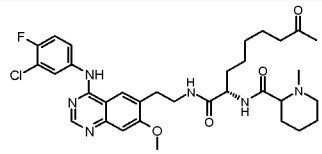
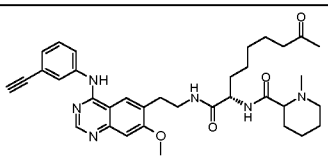
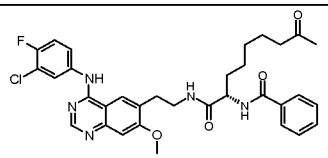
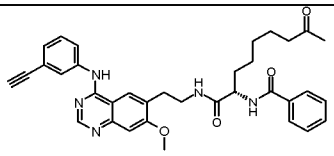
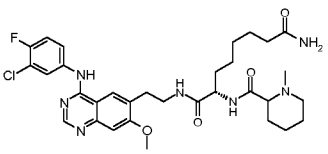
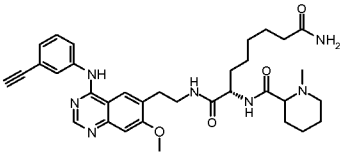
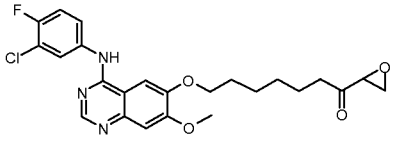
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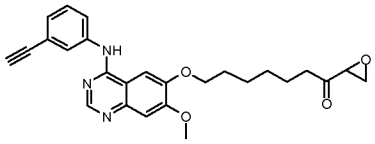
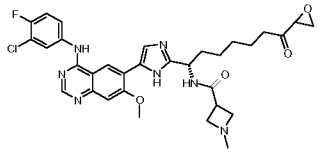
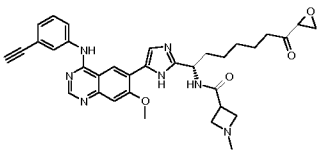
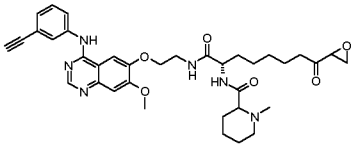
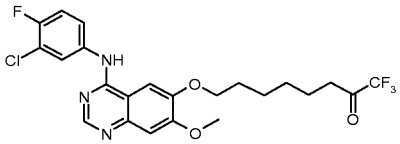
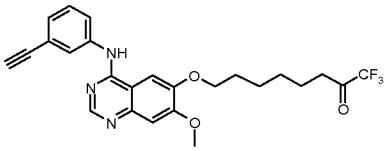
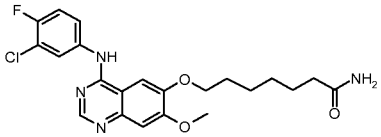
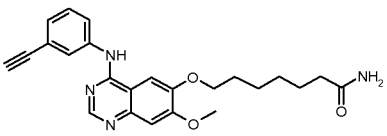
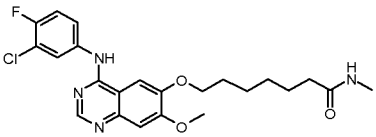
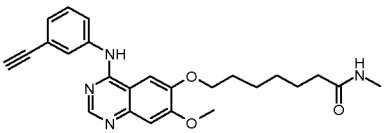
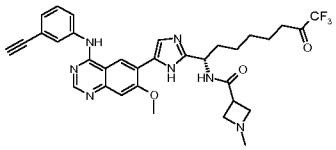
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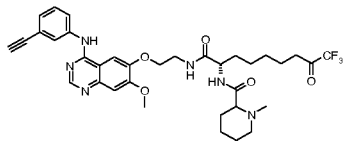
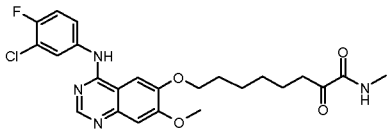
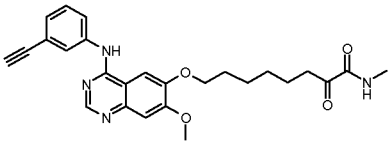
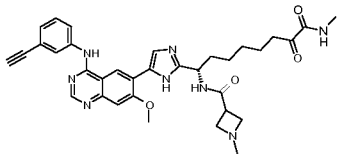
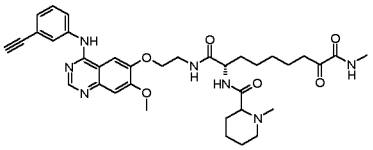
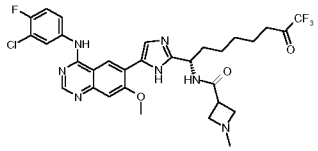
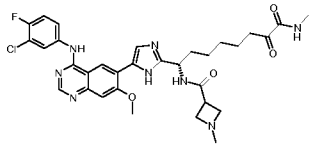
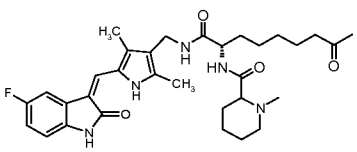
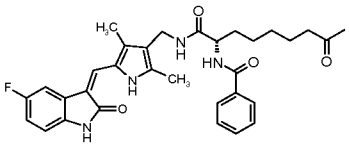
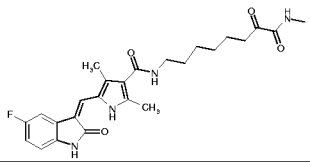
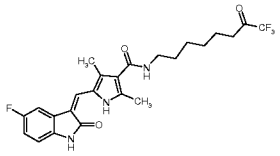
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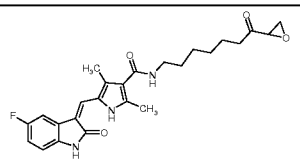
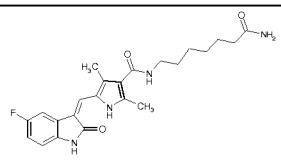
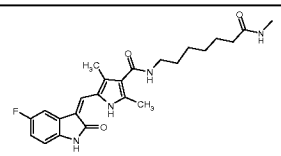
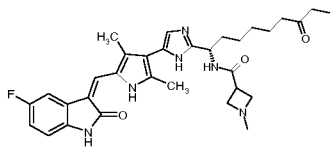
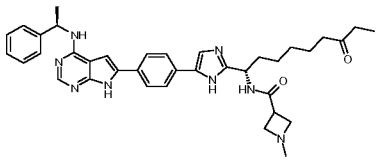
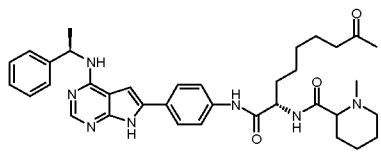
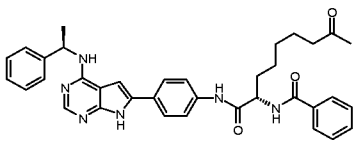
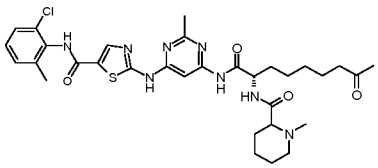
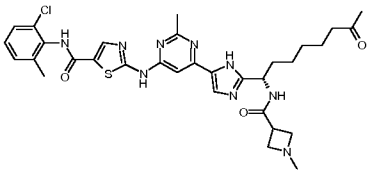
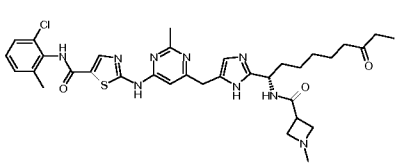
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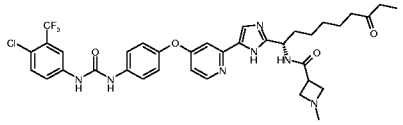
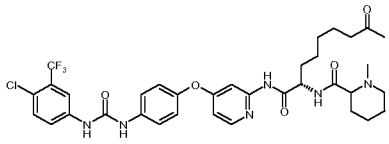
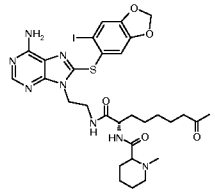
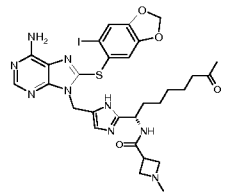
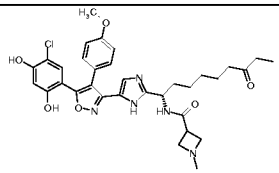
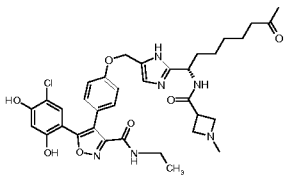
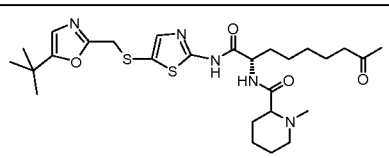
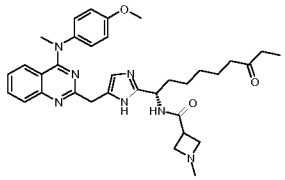
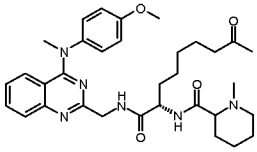
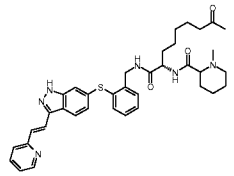
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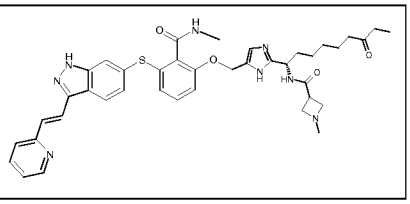
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The invention further provides methods for the prevention or treatment of diseases or conditions involving aberrant proliferation, differentiation or survival of cells. In one embodiment, the invention further provides for the use of one or more compounds of the invention in the manufacture of a medicament for halting or decreasing diseases involving aberrant proliferation, differentiation, or survival of cells. In preferred embodiments, the disease is cancer. In one embodiment, the invention relates to a method of treating cancer in a subject in need of treatment comprising administering to said subject a therapeutically effective amount of a compound of the invention.

The term "cancer" refers to any cancer caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, lymphomas and the like. For example, cancers include, but are not limited to, mesothelioma, leukemias and lymphomas such as cutaneous T-cell lymphomas (CTCL), noncutaneous peripheral T-cell lymphomas, lymphomas associated with human T-cell lymphotrophic virus (HTLV) such as adult T-cell leukemia/lymphoma (ATLL), B-cell lymphoma, acute nonlymphocytic leukemias, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, lymphomas, and multiple myeloma, non-Hodgkin lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), Hodgkin's lymphoma, Burkitt lymphoma, adult T-cell leukemia lymphoma, acute-myeloid leukemia (AML), chronic myeloid leukemia (CML), or hepatocellular carcinoma. Further examples include myelodisplastic syndrome, childhood solid tumors such as brain tumors, neuroblastoma, retinoblastoma, Wilms' tumor, bone tumors, and soft-tissue sarcomas, common solid tumors of adults such as head and neck cancers (e.g., oral, laryngeal, nasopharyngeal and esophageal), genitourinary cancers (e.g., prostate, bladder, renal, uterine, ovarian, testicular), lung cancer (e.g., small-cell and non small cell), breast cancer, pancreatic cancer, melanoma and other skin cancers, stomach cancer, brain tumors, tumors related to Gorlin's syndrome (e.g., medulloblastoma, meningioma, etc.), and liver cancer. Additional exemplary forms

of cancer which may be treated by the subject compounds include, but are not limited to, cancer of skeletal or smooth muscle, stomach cancer, cancer of the small intestine, rectum carcinoma, cancer of the salivary gland, endometrial cancer, adrenal cancer, anal cancer, rectal cancer, parathyroid cancer, and pituitary cancer.

Additional cancers that the compounds described herein may be useful in preventing, treating and studying are, for example, colon carcinoma, familiary adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, or melanoma. Further, cancers include, but are not limited to, labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tongue carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, thyroid cancer (medullary and papillary thyroid carcinoma), renal carcinoma, kidney parenchyma carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, testis carcinoma, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, gall bladder carcinoma, bronchial carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroidea melanoma, seminoma, rhabdomyosarcoma, craniopharyngeoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma, and plasmocytoma. In one aspect of the invention, the present invention provides for the use of one or more compounds of the invention in the manufacture of a medicament for the treatment of cancer.

In one embodiment, the present invention includes the use of one or more compounds of the invention in the manufacture of a medicament that prevents further aberrant proliferation, differentiation, or survival of cells. For example, compounds of the invention may be useful in preventing tumors from increasing in size or from reaching a metastatic state. The subject compounds may be administered to halt the progression or advancement of cancer or to induce tumor apoptosis or to inhibit tumor angiogenesis. In addition, the instant invention includes use of the subject compounds to prevent a recurrence of cancer.

This invention further embraces the treatment or prevention of cell proliferative disorders such as hyperplasias, dysplasias and pre-cancerous lesions. Dysplasia is the earliest form of pre-cancerous lesion recognizable in a biopsy by a pathologist. The subject compounds may be administered for the purpose of preventing said hyperplasias, dysplasias or pre-cancerous lesions from continuing to

expand or from becoming cancerous. Examples of pre-cancerous lesions may occur in skin, esophageal tissue, breast and cervical intra-epithelial tissue.

"Combination therapy" includes the administration of the subject compounds in further combination with other biologically active ingredients (such as, but not limited to, a second and different antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). For instance, the compounds of the invention can be used in combination with other pharmaceutically active compounds, preferably compounds that are able to enhance the effect of the compounds of the invention. The compounds of the invention can be administered simultaneously (as a single preparation or separate preparation) or sequentially to the other drug therapy. In general, a combination therapy envisions administration of two or more drugs during a single cycle or course of therapy.

In one aspect of the invention, the subject compounds may be administered in combination with one or more separate agents that modulate protein kinases involved in various disease states. Examples of such kinases may include, but are not limited to: serine/threonine specific kinases, receptor tyrosine specific kinases and non-receptor tyrosine specific kinases. Serine/threonine kinases include mitogen activated protein kinases (MAPK), meiosis specific kinase (MEK), RAF and aurora kinase. Examples of receptor kinase families include epidermal growth factor receptor (EGFR) (e.g. HER2/neu, HER3, HER4, ErbB, ErbB2, ErbB3, ErbB4, Xmrk, DER, Let23); fibroblast growth factor (FGF) receptor (e.g. FGF-R1,GFF-R2/BEK/CEK3, FGF-R3/CEK2, FGF-R4/TKF, KGF-R); hepatocyte growth/scatter factor receptor (HGFR) (*e.g*, MET, RON, SEA, SEX); insulin receptor (e.g. IGFI-R); Eph (e.g. CEK5, CEK8, EBK, ECK, EEK, EHK-1, EHK-2, ELK, EPH, ERK, HEK, MDK2, MDK5, SEK); Axl (e.g. Mer/Nyk, Rse); RET; and platelet-derived growth factor receptor (PDGFR) (e.g. PDGFα-R, PDGβ-R, CSF1-R/FMS, SCF-R/C-KIT, VEGF-R/FLT, NEK/FLK1, FLT3/FLK2/STK-1). Non-receptor tyrosine kinase families include, but are not limited to, BCR-ABL (e.g. $p43^{abl}$, ARG); BTK (e.g. ITK/EMT, TEC); CSK, FAK, FPS, JAK, SRC, BMX, FER, CDK and SYK.

In another aspect of the invention, the subject compounds may be administered in combination with one or more separate agents that modulate non-kinase biological targets or processes. Such targets include histone deacetylases

(HDAC), DNA methyltransferase (DNMT), heat shock proteins (e.g. HSP90), and proteosomes.

In a preferred embodiment, subject compounds may be combined with antineoplastic agents (e.g. small molecules, monoclonal antibodies, antisense RNA, and fusion proteins) that inhibit one or more biological targets such as Zolinza, Tarceva, Iressa, Tykerb, Gleevec, Sutent, Sprycel, Nexavar, Sorafinib, CNF2024, RG108, BMS387032, Affinitak, Avastin, Herceptin, Erbitux, AG24322, PD325901, ZD6474, PD184322, Obatodax, ABT737 and AEE788. Such combinations may enhance therapeutic efficacy over efficacy achieved by any of the agents alone and may prevent or delay the appearance of resistant mutational variants.

In certain preferred embodiments, the compounds of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents encompass a wide range of therapeutic treatments in the field of oncology. These agents are administered at various stages of the disease for the purposes of shrinking tumors, destroying remaining cancer cells left over after surgery, inducing remission, maintaining remission and/or alleviating symptoms relating to the cancer or its treatment. Examples of such agents include, but are not limited to, alkylating agents such as mustard gas derivatives (Mechlorethamine, cylophosphamide, chlorambucil, melphalan, ifosfamide), ethylenimines (thiotepa, hexamethylmelanine), Alkylsulfonates (Busulfan), Hydrazines and Triazines (Altretamine, Procarbazine, Dacarbazine and Temozolomide), Nitrosoureas (Carmustine, Lomustine and Streptozocin), Ifosfamide and metal salts (Carboplatin, Cisplatin, and Oxaliplatin); plant alkaloids such as Podophyllotoxins (Etoposide and Tenisopide), Taxanes (Paclitaxel and Docetaxel), Vinca alkaloids (Vincristine, Vinblastine, Vindesine and Vinorelbine), and Camptothecan analogs (Irinotecan and Topotecan); anti-tumor antibiotics such as Chromomycins (Dactinomycin and Plicamycin), Anthracyclines (Doxorubicin, Daunorubicin, Epirubicin, Mitoxantrone, Valrubicin and Idarubicin), and miscellaneous antibiotics such as Mitomycin, Actinomycin and Bleomycin; anti-metabolites such as folic acid antagonists (Methotrexate, Pemetrexed, Raltitrexed, Aminopterin), pyrimidine antagonists (5-Fluorouracil, Floxuridine, Cytarabine, Capecitabine, and Gemcitabine), purine antagonists (6-Mercaptopurine and 6-Thioguanine) and adenosine deaminase inhibitors (Cladribine, Fludarabine, Mercaptopurine, Clofarabine, Thioguanine, Nelarabine and Pentostatin); topoisomerase inhibitors such as topoisomerase I

inhibitors (Ironotecan, topotecan) and topoisomerase II inhibitors (Amsacrine, etoposide, etoposide phosphate, teniposide); monoclonal antibodies (Alemtuzumab, Gemtuzumab ozogamicin, Rituximab, Trastuzumab, Ibritumomab Tioxetan, Cetuximab, Panitumumab, Tositumomab, Bevacizumab); and miscellaneous anti-neoplastics such as ribonucleotide reductase inhibitors (Hydroxyurea); adrenocortical steroid inhibitor (Mitotane); enzymes (Asparaginase and Pegaspargase); anti-microtubule agents (Estramustine); and retinoids (Bexarotene, Isotretinoin, Tretinoin (ATRA)).

In certain preferred embodiments, the compounds of the invention are administered in combination with a chemoprotective agent. Chemoprotective agents act to protect the body or minimize the side effects of chemotherapy. Examples of such agents include, but are not limited to, amfostine, mesna, and dexrazoxane.

In one aspect of the invention, the subject compounds are administered in combination with radiation therapy. Radiation is commonly delivered internally (implantation of radioactive material near cancer site) or externally from a machine that employs photon (x-ray or gamma-ray) or particle radiation. Where the combination therapy further comprises radiation treatment, the radiation treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and radiation treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the radiation treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

It will be appreciated that compounds of the invention can be used in combination with an immunotherapeutic agent. One form of immunotherapy is the generation of an active systemic tumor-specific immune response of host origin by administering a vaccine composition at a site distant from the tumor. Various types of vaccines have been proposed, including isolated tumor-antigen vaccines and anti-idiotype vaccines. Another approach is to use tumor cells from the subject to be treated, or a derivative of such cells (reviewed by Schirrmacher *et al.* (1995) J. Cancer Res. Clin. Oncol. 121:487). In U.S. Pat. No. 5,484,596, Hanna Jr. *et al.* claims a method for treating a resectable carcinoma to prevent recurrence or metastases, comprising surgically removing the tumor, dispersing the cells with collagenase, irradiating the cells, and vaccinating the patient with at least three consecutive doses of about $10^7$ cells.

It will be appreciated that the compounds of the invention may advantageously be used in conjunction with one or more adjunctive therapeutic agents. Examples of suitable agents for adjunctive therapy include a $5HT_1$ agonist, such as a triptan (e.g. sumatriptan or naratriptan); an adenosine A1 agonist; an EP ligand; an NMDA modulator, such as a glycine antagonist; a sodium channel blocker (e.g. lamotrigine); a substance P antagonist (e.g. an $NK_1$ antagonist); a cannabinoid; acetaminophen or phenacetin; a 5-lipoxygenase inhibitor; a leukotriene receptor antagonist; a DMARD (e.g. methotrexate); gabapentin and related compounds; a tricyclic antidepressant (e.g. amitryptilline); a neurone stabilising antiepileptic drug; a mono-aminergic uptake inhibitor (e.g. venlafaxine); a matrix metalloproteinase inhibitor; a nitric oxide synthase (NOS) inhibitor, such as an iNOS or an nNOS inhibitor; an inhibitor of the release, or action, of tumour necrosis factor .alpha.; an antibody therapy, such as a monoclonal antibody therapy; an antiviral agent, such as a nucleoside inhibitor (e.g. lamivudine) or an immune system modulator (e.g. interferon); an opioid analgesic; a local anaesthetic; a stimulant, including caffeine; an $H_2$-antagonist (e.g. ranitidine); a proton pump inhibitor (e.g. omeprazole); an antacid (e.g. aluminium or magnesium hydroxide; an antiflatulent (e.g. simethicone); a decongestant (e.g. phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine); an antitussive (e.g. codeine, hydrocodone, carmiphen, carbetapentane, or dextramethorphan); a diuretic; or a sedating or non-sedating antihistamine.

Matrix metalloproteinases (MMPs) are a family of zinc-dependent neutral endopeptidases collectively capable of degrading essentially all matrix components. Over 20 MMP modulating agents are in pharmaceutical develop, almost half of which are indicated for cancer. The University of Toronto researchers have reported that HDACs regulate MMP expression and activity in 3T3 cells. In particular, inhibition of HDAC by trichostatin A (TSA), which has been shown to prevent tumorigenesis and metastasis, decreases mRNA as well as zymographic activity of gelatinase A (MMP2; Type IV collagenase), a matrix metalloproteinase, which is itself, implicated in tumorigenesis and metastasis (Ailenberg M., Silverman M., *Biochem Biophys Res Commun.* 2002 , 298:110-115). Another recent article that discusses the relationship of HDAC and MMPs can be found in Young D.A., et al., *Arthritis Research & Therapy*, 2005, 7: 503. Furthermore, the commonality

between HDAC and MMPs inhibitors is their zinc-binding functionality. Therefore, in one aspect of the invention, compounds of the invention can be used as MMP inhibitors and may be of use in the treatment of disorders relating to or associated with dysregulation of MMP. The overexpression and activation of MMPs are known to induce tissue destruction and are also associated with a number of specific diseases including rheumatoid arthritis, periodontal disease, cancer and atherosclerosis.

The compounds may also be used in the treatment of a disorder involving, relating to or, associated with dysregulation of histone deacetylase (HDAC). There are a number of disorders that have been implicated by or known to be mediated at least in part by HDAC activity, where HDAC activity is known to play a role in triggering disease onset, or whose symptoms are known or have been shown to be alleviated by HDAC inhibitors. Disorders of this type that would be expected to be amenable to treatment with the compounds of the invention include the following but not limited to: Anti-proliferative disorders (e.g. cancers); Neurodegenerative diseases including Huntington's disease, Polyglutamine disease, Parkinson's disease, Alzheimer's disease, Seizures, Striatonigral degeneration, Progressive supranuclear palsy, Torsion dystonia, Spasmodic torticollis and dyskinesis, Familial tremor, Gilles de la Tourette syndrome, Diffuse Lewy body disease, Progressive supranuclear palsy, Pick's disease, intracerebral hemorrhage, Primary lateral sclerosis, Spinal muscular atrophy, Amyotrophic lateral sclerosis, Hypertrophic interstitial polyneuropathy, Retinitis pigmentosa, Hereditary optic atrophy, Hereditary spastic paraplegia, Progressive ataxia and Shy-Drager syndrome; Metabolic diseases including Type 2 diabetes; Degenerative diseases of the Eye including Glaucoma, Age-related macular degeneration, Rubeotic glaucoma; Inflammatory diseases and/or Immune system disorders including Rheumatoid Arthritis (RA), Osteoarthritis, Juvenile chronic arthritis, Graft versus Host disease, Psoriasis, Asthma, Spondyloarthropathy, Crohn's Disease, inflammatory bowel disease Colitis Ulcerosa, Alcoholic hepatitis, Diabetes, Sjoegrens's syndrome, Multiple Sclerosis, Ankylosing spondylitis, Membranous glomerulopathy, Discogenic pain, Systemic Lupus Erythematosus; Disease involving angiogenesis including cancer, psoriasis, rheumatoid arthritis; Psychological disorders including bipolar disease, schizophrenia, mania, depression and dementia; Cardiovascular Diseases including heart failure, restenosis and arteriosclerosis; Fibrotic diseases

including liver fibrosis, cystic fibrosis and angiofibroma; Infectious diseases including Fungal infections, such as Candida Albicans, Bacterial infections, Viral infections, such as Herpes Simplex, Protozoal infections, such as Malaria, Leishmania infection, Trypanosoma brucei infection, Toxoplasmosis and coccidlosis and Haematopoietic disorders including thalassemia, anemia and sickle cell anemia.

In one embodiment, compounds of the invention can be used to induce or inhibit apoptosis, a physiological cell death process critical for normal development and homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. Compounds of the invention, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in apoptosis including cancer (particularly, but not limited to, follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostate and ovary, and precancerous lesions such as familial adenomatous polyposis), viral infections (including, but not limited to, herpes virus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), autoimmune diseases (including, but not limited to, systemic lupus, erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases, and autoimmune diabetes mellitus), neurodegenerative disorders (including, but not limited to, Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), AIDS, myelodysplastic syndromes, aplastic anemia, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol induced liver diseases, hematological diseases (including, but not limited to, chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including, but not limited to, osteoporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases, and cancer pain.

In one aspect, the invention provides the use of compounds of the invention for the treatment and/or prevention of immune response or immune-mediated responses and diseases, such as the prevention or treatment of rejection following transplantation of synthetic or organic grafting materials, cells, organs or tissue to replace all or part of the function of tissues, such as heart, kidney, liver, bone marrow, skin, cornea, vessels, lung, pancreas, intestine, limb, muscle, nerve tissue, duodenum, small-bowel, pancreatic-islet-cell, including xeno-transplants, etc.; to

treat or prevent graft-versus-host disease, autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes uveitis, juvenile-onset or recent-onset diabetes mellitus, uveitis, Graves disease, psoriasis, atopic dermatitis, Crohn's disease, ulcerative colitis, vasculitis, auto-antibody mediated diseases, aplastic anemia, Evan's syndrome, autoimmune hemolytic anemia, and the like; and further to treat infectious diseases causing aberrant immune response and/or activation, such as traumatic or pathogen induced immune disregulation, including for example, that which are caused by hepatitis B and C infections, HIV, staphylococcus aureus infection, viral encephalitis, sepsis, parasitic diseases wherein damage is induced by an inflammatory response (e.g., leprosy); and to prevent or treat circulatory diseases, such as arteriosclerosis, atherosclerosis, vasculitis, polyarteritis nodosa and myocarditis. In addition, the present invention may be used to prevent/suppress an immune response associated with a gene therapy treatment, such as the introduction of foreign genes into autologous cells and expression of the encoded product. Thus in one embodiment, the invention relates to a method of treating an immune response disease or disorder or an immune-mediated response or disorder in a subject in need of treatment comprising administering to said subject a therapeutically effective amount of a compound of the invention.

In one aspect, the invention provides the use of compounds of the invention in the treatment of a variety of neurodegenerative diseases, a non-exhaustive list of which includes: I. Disorders characterized by progressive dementia in the absence of other prominent neurologic signs, such as Alzheimer's disease; Senile dementia of the Alzheimer type; and Pick's disease (lobar atrophy); II. Syndromes combining progressive dementia with other prominent neurologic abnormalities such as A) syndromes appearing mainly in adults (e.g., Huntington's disease, Multiple system atrophy combining dementia with ataxia and/or manifestations of Parkinson's disease, Progressive supranuclear palsy (Steel-Richardson-Olszewski), diffuse Lewy body disease, and corticodentatonigral degeneration); and B) syndromes appearing mainly in children or young adults (e.g., Hallervorden-Spatz disease and progressive familial myoclonic epilepsy); III. Syndromes of gradually developing abnormalities of posture and movement such as paralysis agitans (Parkinson's disease), striatonigral degeneration, progressive supranuclear palsy, torsion dystonia (torsion spasm; dystonia musculorum deformans), spasmodic torticollis and other dyskinesis,

familial tremor, and Gilles de la Tourette syndrome; IV. Syndromes of progressive ataxia such as cerebellar degenerations (e.g., cerebellar cortical degeneration and olivopontocerebellar atrophy (OPCA)); and spinocerebellar degeneration (Friedreich's atazia and related disorders); V. Syndrome of central autonomic nervous system failure (Shy-Drager syndrome); VI. Syndromes of muscular weakness and wasting without sensory changes (motorneuron disease such as amyotrophic lateral sclerosis, spinal muscular atrophy (e.g., infantile spinal muscular atrophy (Werdnig-Hoffman), juvenile spinal muscular atrophy (Wohlfart-Kugelberg-Welander) and other forms of familial spinal muscular atrophy), primary lateral sclerosis, and hereditary spastic paraplegia; VII. Syndromes combining muscular weakness and wasting with sensory changes (progressive neural muscular atrophy; chronic familial polyneuropathies) such as peroneal muscular atrophy (Charcot-Marie-Tooth), hypertrophic interstitial polyneuropathy (Dejerine-Sottas), and miscellaneous forms of chronic progressive neuropathy; VIII Syndromes of progressive visual loss such as pigmentary degeneration of the retina (retinitis pigmentosa), and hereditary optic atrophy (Leber's disease). Furthermore, compounds of the invention can be implicated in chromatin remodeling.

The invention encompasses pharmaceutical compositions comprising pharmaceutically acceptable salts of the compounds of the invention as described above. The invention also encompasses pharmaceutical compositions comprising hydrates of the compounds of the invention. The term "hydrate" includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate and the like. The invention further encompasses pharmaceutical compositions comprising any solid or liquid physical form of the compound of the invention. For example, the compounds can be in a crystalline form, in amorphous form, and have any particle size. The particles may be micronized, or may be agglomerated, particulate granules, powders, oils, oily suspensions or any other form of solid or liquid physical form.

The compounds of the invention, and derivatives, fragments, analogs, homologs, pharmaceutically acceptable salts or hydrate thereof can be incorporated into pharmaceutical compositions suitable for administration, together with a pharmaceutically acceptable carrier or excipient. Such compositions typically comprise a therapeutically effective amount of any of the compounds above, and a pharmaceutically acceptable carrier. Preferably, the effective amount when treating

cancer is an amount effective to selectively induce terminal differentiation of suitable neoplastic cells and less than an amount which causes toxicity in a patient.

Compounds of the invention may be administered by any suitable means, including, without limitation, parenteral, intravenous, intramuscular, subcutaneous, implantation, oral, sublingual, buccal, nasal, pulmonary, transdermal, topical, vaginal, rectal, and transmucosal administrations or the like. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. Pharmaceutical preparations include a solid, semisolid or liquid preparation (tablet, pellet, troche, capsule, suppository, cream, ointment, aerosol, powder, liquid, emulsion, suspension, syrup, injection etc.) containing a compound of the invention as an active ingredient, which is suitable for selected mode of administration. In one embodiment, the pharmaceutical compositions are administered orally, and are thus formulated in a form suitable for oral administration, i.e., as a solid or a liquid preparation. Suitable solid oral formulations include tablets, capsules, pills, granules, pellets, sachets and effervescent, powders, and the like. Suitable liquid oral formulations include solutions, suspensions, dispersions, emulsions, oils and the like. In one embodiment of the present invention, the composition is formulated in a capsule. In accordance with this embodiment, the compositions of the present invention comprise in addition to the active compound and the inert carrier or diluent, a hard gelatin capsule.

Any inert excipient that is commonly used as a carrier or diluent may be used in the formulations of the present invention, such as for example, a gum, a starch, a sugar, a cellulosic material, an acrylate, or mixtures thereof. A preferred diluent is microcrystalline cellulose. The compositions may further comprise a disintegrating agent (e.g., croscarmellose sodium) and a lubricant (e.g., magnesium stearate), and may additionally comprise one or more additives selected from a binder, a buffer, a protease inhibitor, a surfactant, a solubilizing agent, a plasticizer, an emulsifier, a stabilizing agent, a viscosity increasing agent, a sweetener, a film forming agent, or any combination thereof. Furthermore, the compositions of the present invention may be in the form of controlled release or immediate release formulations.

For liquid formulations, pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, emulsions or oils. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable

organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Examples of oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, mineral oil, olive oil, sunflower oil, and fish-liver oil. Solutions or suspensions can also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

In addition, the compositions may further comprise binders (e.g., acacia, cornstarch, gelatin, carbomer, ethyl cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, povidone), disintegrating agents (e.g., cornstarch, potato starch, alginic acid, silicon dioxide, croscarmellose sodium, crospovidone, guar gum, sodium starch glycolate, Primogel), buffers (e.g., tris-HCI., acetate, phosphate) of various pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), protease inhibitors, surfactants (e.g., sodium lauryl sulfate), permeation enhancers, solubilizing agents (e.g., glycerol, polyethylene glycerol), a glidant (e.g., colloidal silicon dioxide), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite, butylated hydroxyanisole), stabilizers (e.g., hydroxypropyl cellulose, hydroxypropylmethyl cellulose), viscosity increasing agents (e.g., carbomer, colloidal silicon dioxide, ethyl cellulose, guar gum), sweeteners (e.g., sucrose, aspartame, citric acid), flavoring agents (e.g., peppermint, methyl salicylate, or orange flavoring), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), lubricants (e.g., stearic acid, magnesium stearate, polyethylene glycol, sodium lauryl sulfate), flow-aids (e.g., colloidal silicon dioxide), plasticizers (e.g., diethyl phthalate, triethyl citrate), emulsifiers (e.g., carbomer, hydroxypropyl cellulose, sodium lauryl sulfate), polymer coatings (e.g., poloxamers or poloxamines), coating and film forming agents (e.g., ethyl cellulose, acrylates, polymethacrylates) and/or adjuvants.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat No. 4,522,811.

It is especially advantageous to formulate oral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

Daily administration may be repeated continuously for a period of several days to several years. Oral treatment may continue for between one week and the life of the patient. Preferably the administration may take place for five consecutive days after which time the patient can be evaluated to determine if further administration is required. The administration can be continuous or intermittent, e.g., treatment for a number of consecutive days followed by a rest period. The compounds of the present invention may be administered intravenously on the first day of treatment, with oral administration on the second day and all consecutive days thereafter.

The preparation of pharmaceutical compositions that contain an active component is well understood in the art, for example, by mixing, granulating, or tablet-forming processes. The active therapeutic ingredient is often mixed with excipients that are pharmaceutically acceptable and compatible with the active ingredient. For oral administration, the active agents are mixed with additives customary for this purpose, such as vehicles, stabilizers, or inert diluents, and converted by customary methods into suitable forms for administration, such as tablets, coated tablets, hard or soft gelatin capsules, aqueous, alcoholic or oily solutions and the like as detailed above.

The amount of the compound administered to the patient is less than an amount that would cause toxicity in the patient. In certain embodiments, the amount of the compound that is administered to the patient is less than the amount that causes a concentration of the compound in the patient's plasma to equal or exceed the toxic level of the compound. Preferably, the concentration of the compound in the patient's plasma is maintained at about 10 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 25 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 50 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 100 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 500 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 1000 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 2500 nM. In one embodiment, the concentration of the compound in the patient's plasma is maintained at about 5000 nM. The optimal amount of the compound that should be administered to the patient in the practice of the present invention will depend on the particular compound used and the type of cancer being treated.

DEFINITIONS

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

An “aliphatic group” or “aliphatic” is non-aromatic moiety that may be saturated (e.g. single bond) or contain one or more units of unsaturation, (e.g., double and/or triple bonds). An aliphatic group may be straight chained, branched or cyclic, contain carbon, hydrogen or, optionally, one or more heteroatoms and may be substituted or unsubstituted. An aliphatic group preferably contains between about 1 and about 24 atoms, more preferably between about 4 to about 24 atoms, more preferably between about 4-12 atoms, more typically between about 4 and about 8 atoms.

The term "acyl" refers to hydrogen, alkyl, partially saturated or fully saturated cycloalkyl, partially saturated or fully saturated heterocycle, aryl, and heteroaryl substituted carbonyl groups. For example, acyl includes groups such as ($C_1$-$C_6$)alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, valeryl, caproyl, t-butylacetyl, etc.), ($C_3$-$C_6$)cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), heterocyclic carbonyl (e.g., pyrrolidinylcarbonyl, pyrrolid-2-one-5-carbonyl, piperidinylcarbonyl, piperazinylcarbonyl, tetrahydrofuranylcarbonyl, etc.), aroyl (e.g., benzoyl) and heteroaroyl (e.g., thiophenyl-2-carbonyl, thiophenyl-3-carbonyl, furanyl-2-carbonyl, furanyl-3-carbonyl, 1H-pyrroyl-2-carbonyl, 1H-pyrroyl-3-carbonyl, benzo[b]thiophenyl-2-carbonyl, etc.). In addition, the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be any one of the groups described in the respective definitions. When indicated as being "optionally substituted", the acyl group may be unsubstituted or optionally substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted" or the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be substituted as described above in the preferred and more preferred list of substituents, respectively.

For simplicity, chemical moieties are defined and referred to throughout can be univalent chemical moieties (e.g., alkyl, aryl, etc.) or multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, an "alkyl" moiety can be referred to a monovalent radical (e.g. $CH_3$-$CH_2$-), or in other instances, a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (e.g., -$CH_2$-$CH_2$-), which is equivalent to the term "alkylene." Similarly, in circumstances in which

divalent moieties are required and are stated as being “alkoxy”, “alkylamino”, “aryloxy”, “alkylthio”, "aryl", “heteroaryl”, “heterocyclic”, “alkyl” “alkenyl”, “alkynyl”, “aliphatic”, or “cycloalkyl”, those skilled in the art will understand that the terms alkoxy”, “alkylamino”, “aryloxy”, “alkylthio”, "aryl", “heteroaryl”, “heterocyclic”, “alkyl”, “alkenyl”, “alkynyl”, “aliphatic”, or “cycloalkyl” refer to the corresponding divalent moiety.

The term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about eight carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about ten carbon atoms and more preferably about two to about eight carbon atoms. Examples of alkenyl radicals include ethenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl", and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" embraces linear or branched radicals having at least one carbon-carbon triple bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms and more preferably about two to about eight carbon atoms. Examples of alkynyl radicals include propargyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butynyl and 1-pentynyl.

The term "cycloalkyl" embraces saturated carbocyclic radicals having three to about twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. Cycloalkenyl radicals that are partially unsaturated carbocyclic radicals that contain two double bonds (that may or may not be conjugated) can be called "cycloalkyldienyl". More preferred cycloalkenyl

radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl and cyclohexenyl.

The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to about ten carbon atoms and more preferably having one to about eight carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl.

The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes (C=O).

The term "carbanoyl", whether used alone or with other terms, such as "arylcarbanoylyalkyl", denotes C(O)NH.

The terms "heterocyclyl", "heterocycle" "heterocyclic" or "heterocyclo" embrace saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, which can also be called "heterocyclyl", "heterocycloalkenyl" and "heteroaryl" correspondingly, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Heterocyclyl radicals may include a pentavalent nitrogen, such as in tetrazolium and pyridinium radicals. The term "heterocycle" also embraces radicals where

heterocyclyl radicals are fused with aryl or cycloalkyl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like.

The term "heteroaryl" embraces unsaturated heterocyclyl radicals. Examples of heteroaryl radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g. benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like.

The term "heterocycloalkyl" embraces heterocyclo-substituted alkyl radicals. More preferred heterocycloalkyl radicals are "lower heterocycloalkyl" radicals having one to six carbon atoms in the heterocycloalkyl radicals.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. Preferred alkylthio radicals have alkyl radicals of one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkylthio radicals have alkyl radicals are "lower alkylthio" radicals having one to about ten carbon atoms. Most preferred are alkylthio radicals having lower alkyl radicals of one to about eight carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio.

The terms "aralkyl" or "arylalkyl" embrace aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl.

The term "aryloxy" embraces aryl radicals attached through an oxygen atom to other radicals.

The terms "aralkoxy" or "arylalkoxy" embrace aralkyl radicals attached through an oxygen atom to other radicals.

The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. Preferred aminoalkyl radicals have alkyl radicals having about one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred aminoalkyl radicals are "lower aminoalkyl" that have alkyl radicals having one to about ten carbon atoms. Most preferred are aminoalkyl radicals having lower alkyl radicals having one to eight carbon atoms. Examples of such radicals include aminomethyl, aminoethyl, and the like.

The term "alkylamino" denotes amino groups which are substituted with one or two alkyl radicals. Preferred alkylamino radicals have alkyl radicals having about one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkylamino radicals are "lower alkylamino" that have alkyl radicals having one to about ten carbon atoms. Most preferred are alkylamino radicals having lower alkyl radicals having one to about eight carbon atoms. Suitable lower alkylamino may be monosubstituted N-alkylamino or disubstituted N,N-alkylamino, such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

The term "linker" means an organic moiety that connects two parts of a compound. Linkers typically comprise a direct bond or an atom such as oxygen or sulfur, a unit such as $NR_{18}$, C(O), C(O)NH, SO, $SO_2$, $SO_2NH$ or a chain of atoms, such as substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl,

alkynylheteroarylalkynyl, alkylheterocyclylalkyl, alkylheterocyclylalkenyl, alkylhererocyclylalkynyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, alkynylheterocyclylalkynyl, alkylaryl, alkenylaryl, alkynylaryl, alkylheteroaryl, alkenylheteroaryl, alkynylhereroaryl, which one or more methylenes can be interrupted or terminated by O, S, S(O), $SO_2$, $N(R_{18})$, C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where $R_{18}$ is hydrogen, acyl, aliphatic or substituted aliphatic. In one embodiment, the linker B is between 1-24 atoms, preferably 2-24 atoms, preferably 2-18 atoms, more preferably 2-12 atoms, and most preferably about 2-8 atoms.

The term "substituted" refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, thiol, alkylthio, arylthio, alkylthioalkyl, arylthioalkyl, alkylsulfonyl, alkylsulfonylalkyl, arylsulfonylalkyl, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, trifluoromethyl, cyano, nitro, alkylamino, arylamino, alkylaminoalkyl, arylaminoalkyl, aminoalkylamino, hydroxy, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, acyl, aralkoxycarbonyl, carboxylic acid, sulfonic acid, sulfonyl, phosphonic acid, aryl, heteroaryl, heterocyclic, and aliphatic. It is understood that the substituent may be further substituted.

The terms "halogen" or "halo" as used herein, refers to an atom selected from fluorine, chlorine, bromine and iodine.

As used herein, the term "aberrant proliferation" refers to abnormal cell growth.

The phrase "adjunctive therapy" encompasses treatment of a subject with agents that reduce or avoid side effects associated with the combination therapy of the present invention, including, but not limited to, those agents, for example, that reduce the toxic effect of anticancer drugs, e.g., bone resorption inhibitors, cardioprotective agents; prevent or reduce the incidence of nausea and vomiting associated with chemotherapy, radiotherapy or operation; or reduce the incidence of infection associated with the administration of myelosuppressive anticancer drugs.

The term "angiogenesis," as used herein, refers to the formation of blood vessels. Specifically, angiogenesis is a multi-step process in which endothelial cells focally degrade and invade through their own basement membrane, migrate through interstitial stroma toward an angiogenic stimulus, proliferate proximal to the migrating tip, organize into blood vessels, and reattach to newly synthesized basement membrane (see Folkman *et al.*, Adv. Cancer Res., Vol. 43, pp. 175-203 (1985)). Anti-angiogenic agents interfere with this process. Examples of agents that interfere with several of these steps include thrombospondin-1, angiostatin, endostatin, interferon alpha and compounds such as matrix metalloproteinase (MMP) inhibitors that block the actions of enzymes that clear and create paths for newly forming blood vessels to follow; compounds, such as .alpha.v.beta.3 inhibitors, that interfere with molecules that blood vessel cells use to bridge between a parent blood vessel and a tumor; agents, such as specific COX-2 inhibitors, that prevent the growth of cells that form new blood vessels; and protein-based compounds that simultaneously interfere with several of these targets.

The term "apoptosis" as used herein refers to programmed cell death as signaled by the nuclei in normally functioning human and animal cells when age or state of cell health and condition dictates. An "apoptosis inducing agent" triggers the process of programmed cell death.

The term "cancer" as used herein denotes a class of diseases or disorders characterized by uncontrolled division of cells and the ability of these cells to invade other tissues, either by direct growth into adjacent tissue through invasion or by implantation into distant sites by metastasis.

The term "compound" is defined herein to include pharmaceutically acceptable salts, solvates, hydrates, polymorphs, enantiomers, diastereoisomers, racemates and the like of the compounds having a formula as set forth herein.

The term "devices" refers to any appliance, usually mechanical or electrical, designed to perform a particular function.

As used herein, the term "dysplasia" refers to abnormal cell growth, and typically refers to the earliest form of pre-cancerous lesion recognizable in a biopsy by a pathologist.

The term "hyperplasia," as used herein, refers to excessive cell division or growth.

The phrase an "immunotherapeutic agent" refers to agents used to transfer the immunity of an immune donor, e.g., another person or an animal, to a host by inoculation. The term embraces the use of serum or gamma globulin containing performed antibodies produced by another individual or an animal; nonspecific systemic stimulation; adjuvants; active specific immunotherapy; and adoptive immunotherapy. Adoptive immunotherapy refers to the treatment of a disease by therapy or agents that include host inoculation of sensitized lymphocytes, transfer factor, immune RNA, or antibodies in serum or gamma globulin.

The term "inhibition," in the context of neoplasia, tumor growth or tumor cell growth, may be assessed by delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, among others. In the extreme, complete inhibition, is referred to herein as prevention or chemoprevention.

The term “metastasis,” as used herein, refers to the migration of cancer cells from the original tumor site through the blood and lymph vessels to produce cancers in other tissues. Metastasis also is the term used for a secondary cancer growing at a distant site.

The term “neoplasm,” as used herein, refers to an abnormal mass of tissue that results from excessive cell division. Neoplasms may be benign (not cancerous), or malignant (cancerous) and may also be called a tumor. The term “neoplasia” is the pathological process that results in tumor formation.

As used herein, the term “pre-cancerous” refers to a condition that is not malignant, but is likely to become malignant if left untreated.

The term “proliferation” refers to cells undergoing mitosis.

The phrase a "radio therapeutic agent" refers to the use of electromagnetic or particulate radiation in the treatment of neoplasia.

The term “recurrence” as used herein refers to the return of cancer after a period of remission. This may be due to incomplete removal of cells from the initial cancer and may occur locally (the same site of initial cancer), regionally (in vicinity of initial cancer, possibly in the lymph nodes or tissue), and/or distally as a result of metastasis.

The term "treatment" refers to any process, action, application, therapy, or the like, wherein a mammal, including a human being, is subject to medical aid with the object of improving the mammal's condition, directly or indirectly.

The term "vaccine" includes agents that induce the patient's immune system to mount an immune response against the tumor by attacking cells that express tumor associated antigens (Teas).

As used herein, the term "effective amount of the subject compounds," with respect to the subject method of treatment, refers to an amount of the subject compound which, when delivered as part of desired dose regimen, brings about, e.g. a change in the rate of cell proliferation and/or state of differentiation and/or rate of survival of a cell to clinically acceptable standards. This amount may further relieve to some extent one or more of the symptoms of a neoplasia disorder, including, but is not limited to: 1) reduction in the number of cancer cells; 2) reduction in tumor size; 3) inhibition (i.e., slowing to some extent, preferably stopping) of cancer cell infiltration into peripheral organs; 4) inhibition (i.e., slowing to some extent, preferably stopping) of tumor metastasis; 5) inhibition, to some extent, of tumor growth; 6) relieving or reducing to some extent one or more of the symptoms associated with the disorder; and/or 7) relieving or reducing the side effects associated with the administration of anticancer agents.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical *Sciences*, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid or inorganic acid. Examples of pharmaceutically acceptable nontoxic acid addition salts include, but are not limited to, salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid lactobionic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable

salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

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

The term “pharmaceutically acceptable prodrugs” as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. "Prodrug", as used herein means a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to a compound of the invention. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krogsgaard-Larsen,

et al., (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development, Chapter 5, 113-191 (1991); Bundgaard, *et al.*, Journal of Drug Deliver Reviews, 8:1-38(1992); Bundgaard, J. of Pharmaceutical Sciences, 77:285 et seq. (1988); Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

As used herein, "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration, such as sterile pyrogen-free water. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

As used herein, the term "pre-cancerous" refers to a condition that is not malignant, but is likely to become malignant if left untreated.

The term "subject" as used herein refers to an animal. Preferably the animal is a mammal. More preferably the mammal is a human. A subject also refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, fish, birds and the like.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and may include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan,

further methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- , or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, et al., Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds, other unsaturation, or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers and/or cis- and trans- isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond or carbon-heteroatom double bond depicted arbitrarily herein as *trans* may be *cis, trans*, or a mixture of the two in any proportion.

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers or excipients.

As used herein, the term "pharmaceutically acceptable carrier or excipient" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; cyclodextrins such as alpha- (α), beta- (B) and gamma- (γ) cyclodextrins; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

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

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the

ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract,

optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

For pulmonary delivery, a therapeutic composition of the invention is formulated and administered to the patient in solid or liquid particulate form by direct administration e.g., inhalation into the respiratory system. Solid or liquid particulate forms of the active compound prepared for practicing the present invention include particles of respirable size: that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Delivery of aerosolized therapeutics, particularly aerosolized antibiotics, is known in the art (see, for example U.S. Pat. No. 5,767,068 to VanDevanter *et al.*, U.S. Pat. No. 5,508,269 to Smith *et al.,* and WO 98/43650 by Montgomery, all of which are incorporated herein by reference). A discussion of

pulmonary delivery of antibiotics is also found in U.S. Pat. No. 6,014,969, incorporated herein by reference.

By a "therapeutically effective amount" of a compound of the invention is meant an amount of the compound which confers a therapeutic effect on the treated subject, at a reasonable benefit/risk ratio applicable to any medical treatment. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). An effective amount of the compound described above may range from about 0.1 mg/Kg to about 500 mg/Kg, preferably from about 1 to about 50 mg/Kg. Effective doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or contemporaneously with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other animal in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

The compounds of the formulae described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.1 to about 500 mg/kg of body weight, alternatively

dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with pharmaceutically excipients or carriers to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations may contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

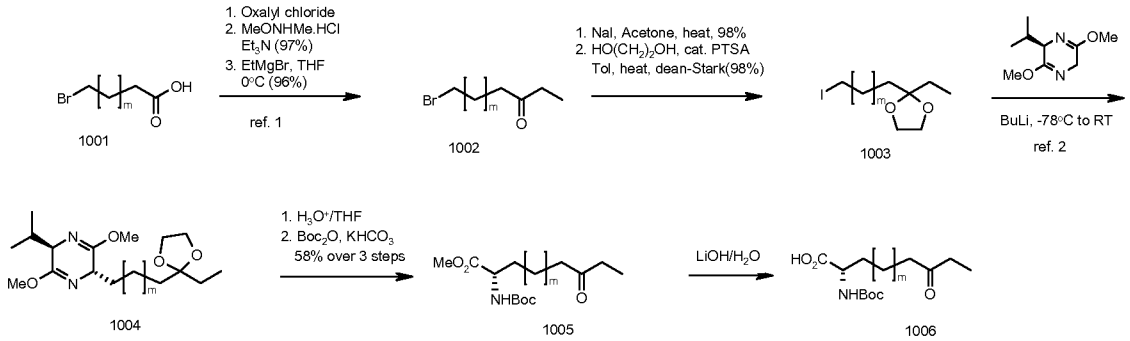
SYNTHETIC METHODS AND EXAMPLES

The compounds of the inventions may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes for making certain intermediates include, for example, those illustrated in PCT publication numbers WO 2006061638, WO 2006005955, WO 2006005941 and US Application number 11/852,458 which are herein incorporated by reference. Necessary starting materials may be obtained by standard procedures of organic

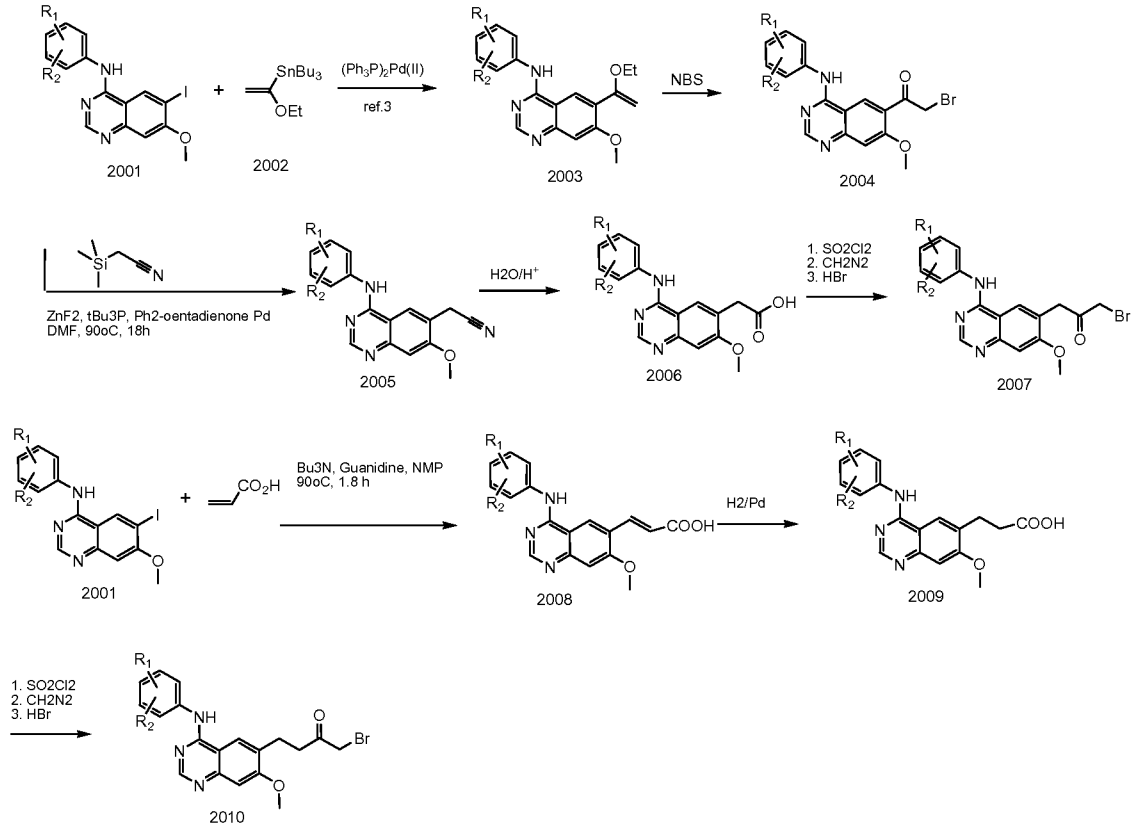
chemistry. The preparation of such starting materials is described in US Application number 11/852,458. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of a chemist.

The compounds and processes of the present invention will be better understood in connection with the following representative synthetic schemes and examples, which are intended as an illustration only and not limiting of the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

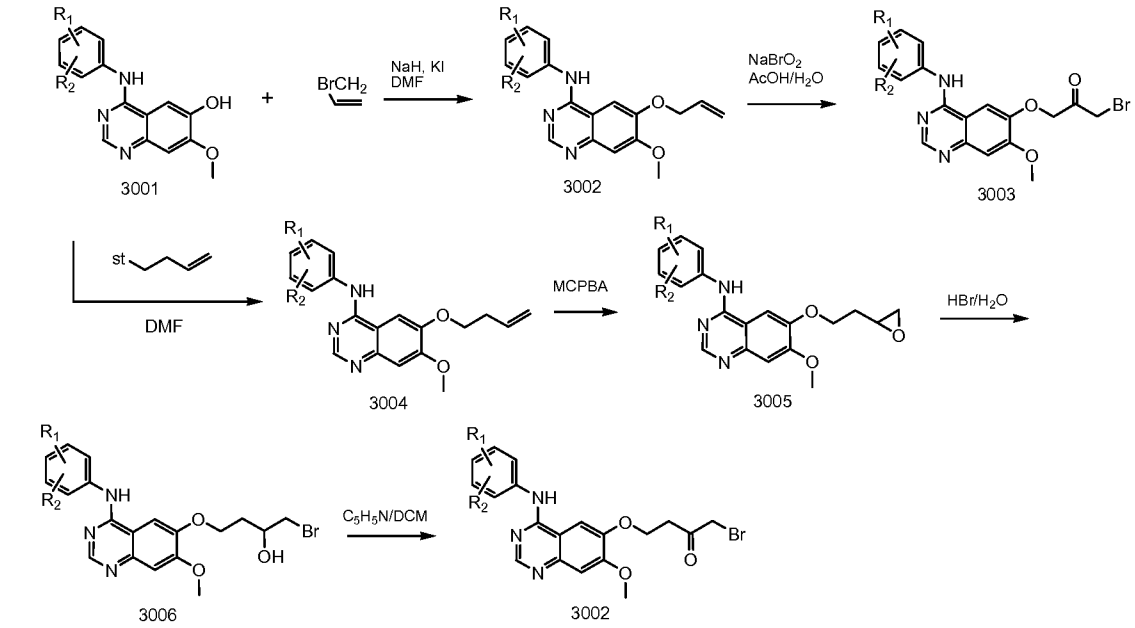
Scheme 1



Scheme 2

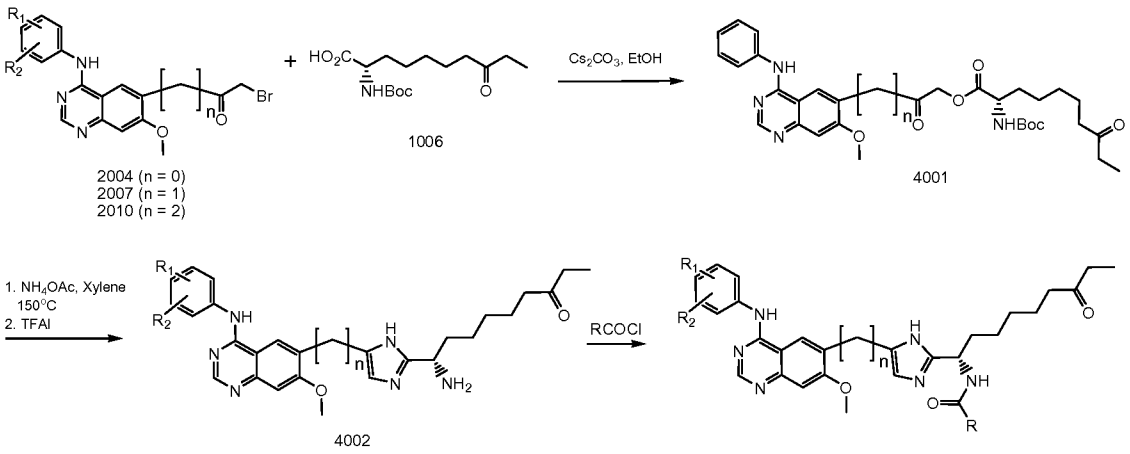



Scheme 3

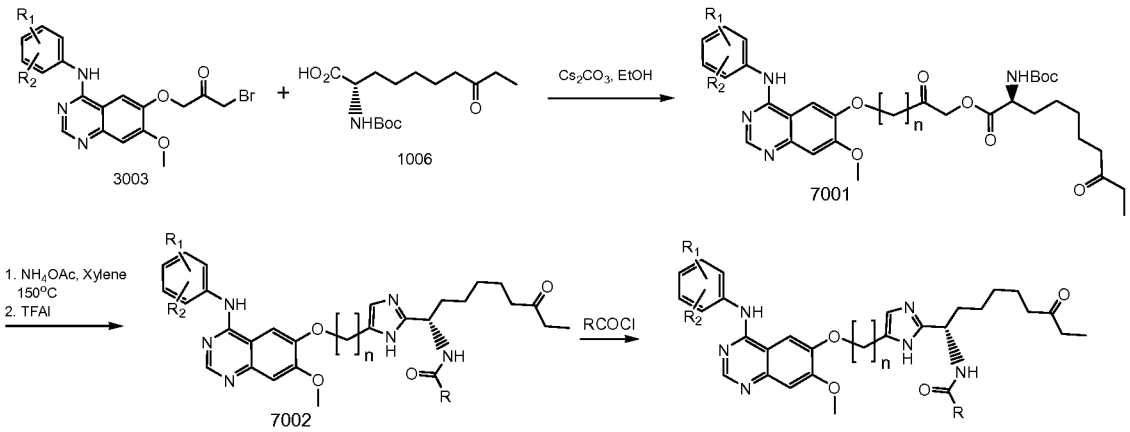



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Scheme 4

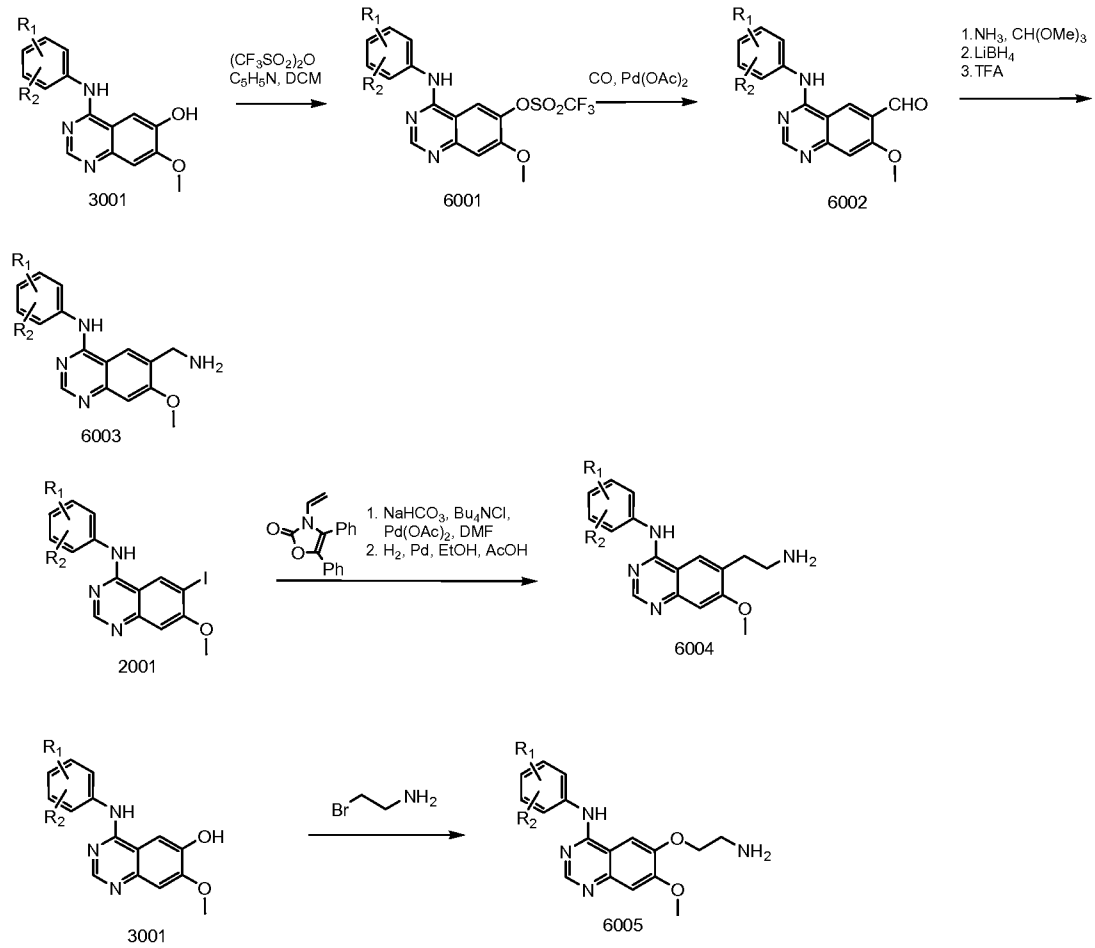



Scheme 5

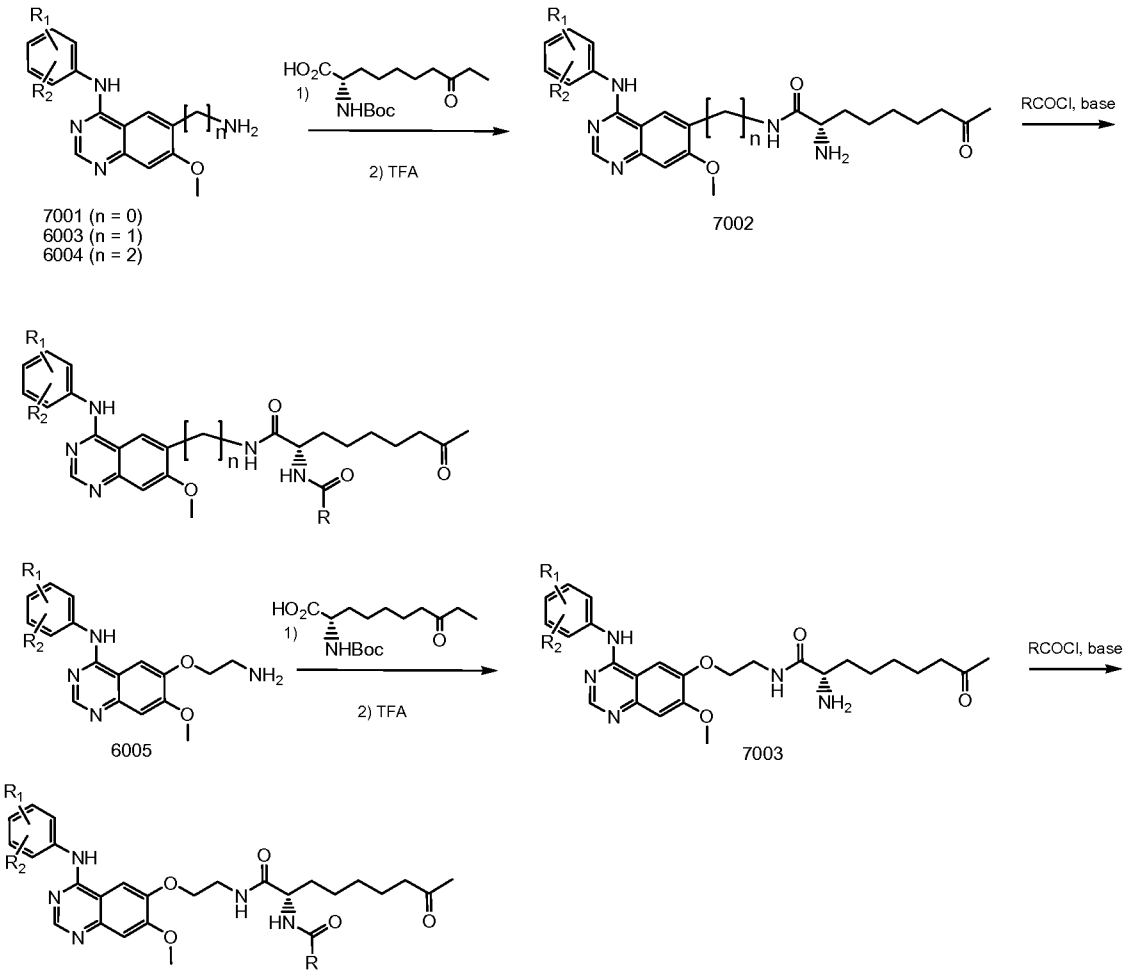



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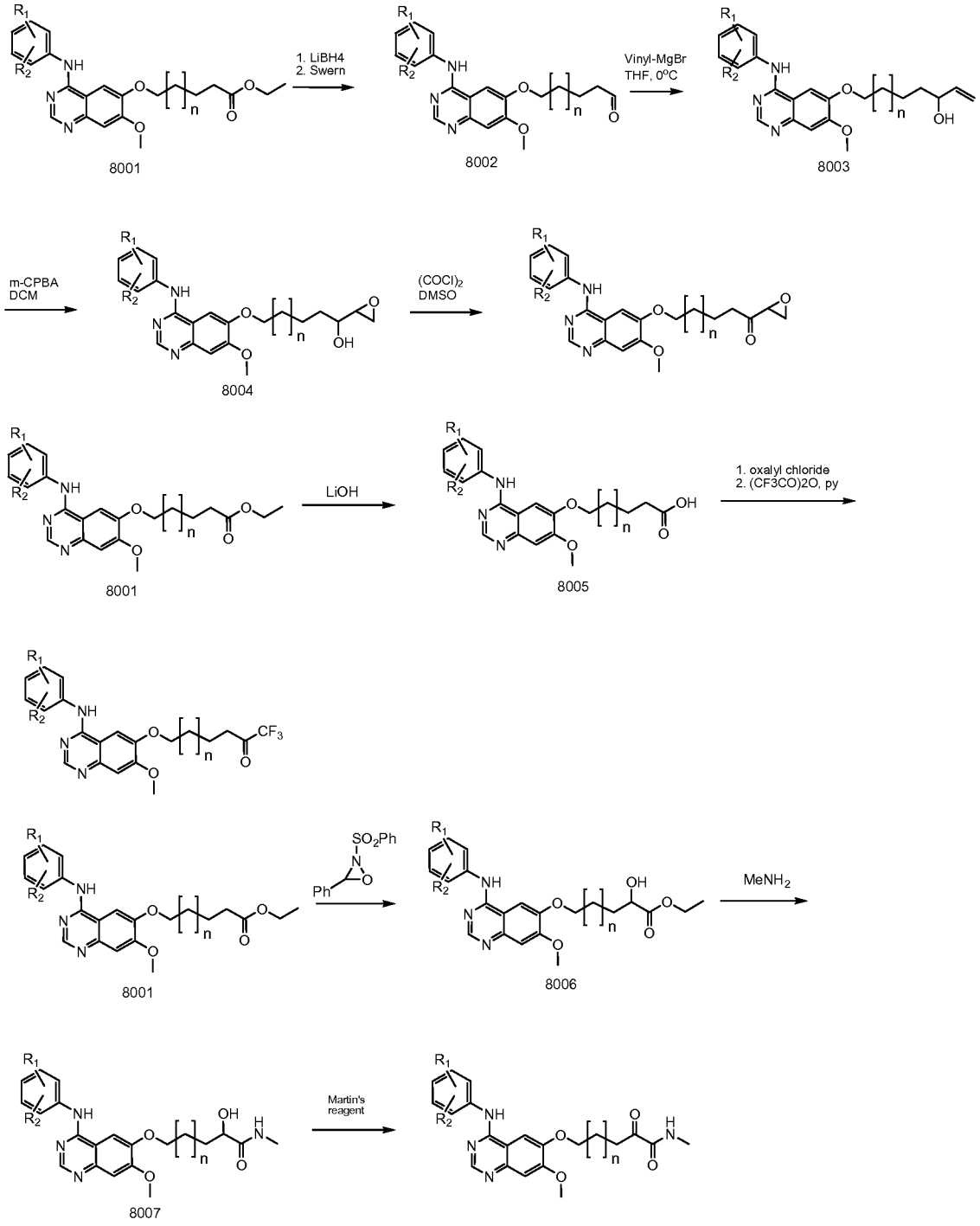
Scheme 6


(CF3SO2)2O
C5H5N, DCM
CO, Pd(OAc)2
1.NH3, CH(OMe)3
2.LiBH4
3.TFA
3001
6001
6002
6003
2001
1. NaHCO3, Bu4NCl,
Pd(OAc)2, DMF
2. H2, Pd, EtOH, AcOH
6004
3001
6005

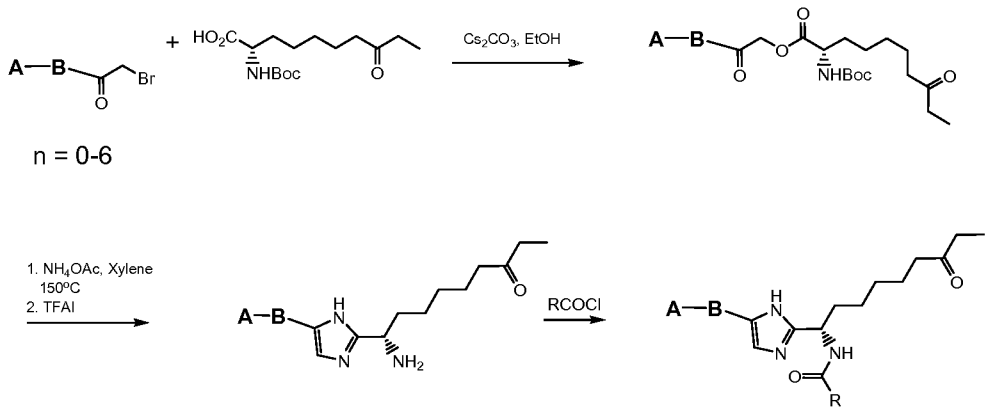
Scheme 7



Scheme 8


1. LiBH4
2. Swern
Vinyl-MgBr
THF, 0°C
m-CPBA
DCM
(COCl)2
DMSO
LiOH
1. oxalyl chloride
2. (CF3CO)2O, py
MeNH2
Martin's
reagent
8001
8002
8003
8004
8005
8006
8007

Scheme 9




**Biological Assays:**

Anti-proliferation activities of the compounds can be assessed, for example, using one or more of the procedures set out below:

(a) An *in vitro* assay which determines the ability of a test compound to inhibit EGFR kinase.

The ability of compounds to inhibit receptor kinase (EGFR) activity is assayed using HTScan™ EGF Receptor Kinase Assay Kits (Cell Signaling Technologies, Danvers, MA). EGFR tyrosine kinase is obtained as GST-kinase fusion protein which is produced using a baculovirus expression system with a construct expressing human EGFR (His672-Ala1210) (GenBank Accession No. NM_005228) with an amino-terminal GST tag. The protein is purified by one-step affinity chromatography using glutathione-agarose. An anti-phosphotyrosine monoclonal antibody, P-Tyr-100, is used to detect phosphorylation of biotinylated substrate peptides (EGFR, Biotin-PTP1B (Tyr66). Enzymatic activity is tested in 60 mM HEPES, 5 mM $MgCl_2$ 5 mM $MnCl_2$ 200 μM ATP, 1.25 mM DTT, 3 μM $Na_3VO_4$, 1.5 mM peptide, and 50 ng EGF Recpetor Kinase. Bound antibody is detected using the DELFIA system (PerkinElmer, Wellesley, MA) consisting of DELFIA® Europium-labeled Anti-mouse IgG (PerkinElmer, #AD0124), DELFIA® Enhancement Solution (PerkinElmer, #1244-105), and a DELFIA® Streptavidin coated, 96-well Plate (PerkinElmer, AAAND-0005). Fluorescence is measured on a WALLAC Victor 2 plate reader and reported as relative fluorescence units (RFU). Data are plotted using GraphPad Prism (v4.0a) and IC50's calculated using a sigmoidal dose response curve fitting algorithm.

Test compounds are dissolved in dimethylsulphoxide (DMSO) to give a 20 mM working stock concentration. Each assay is setup as follows: Added 100 µl of 10 mM ATP to 1.25 ml 6 mM substrate peptide. Diluted the mixture with $dH_20$ to 2.5 ml to make 2X ATP/substrate cocktail ([ATP]=400 mM, [substrate] =3 mM). Immediately transfer enzyme from –80°C to ice. Allowed enzyme to thaw on ice. Microcentrifuged briefly at 4°C to bring liquid to the bottom of the vial. Returned immediately to ice. Added 10 µl of DTT (1.25 mM) to 2.5 ml of 4X HTScanTM Tyrosine Kinase Buffer (240 mM HEPES pH 7.5, 20 mM $MgCl_2$, 20 mM MnCl, 12 mM $NaVO_3$) to make DTT/Kinase buffer. Transfer 1.25 ml of DTT/Kinase buffer to enzyme tube to make 4X reaction cocktail ([enzyme] = 4 ng/µL in 4X reaction cocktail). Incubated 12.5 µl of the 4X reaction cocktail with 12.5 µl/well of prediluted compound of interest (usually around 10 µM) for 5 minutes at room temperature. Added 25 µl of 2X ATP/substrate cocktail to 25 µl/well preincubated reaction cocktail/compound. Incubated reaction plate at room temperature for 30 minutes. Added 50 µl/well Stop Buffer (50 mM EDTA, pH 8) to stop the reaction. Transferred 25 µl of each reaction and 75 µl $dH_2O$/well to a 96-well streptavidin-coated plate and incubated at room temperature for 60 minutes. Ished three times with 200 µl/well PBS/T (PBS, 0.05% Tween-20). Diluted primary antibody, Phospho-Tyrosine mAb (P-Tyr-100), 1:1000 in PBS/T with 1% bovine serum albumin (BSA). Added 100 µl/well primary antibody. Incubated at room temperature for 60 minutes. Ished three times with 200 µl/well PBS/T. Diluted Europium labeled anti-mouse IgG 1:500 in PBS/T with 1% BSA. Added 100 µl/well diluted antibody. Incubated at room temperature for 30 minutes. Ished five times with 200 µl/well PBS/T. Added 100 µl/well DELFIA® Enhancement Solution. Incubated at room temperature for 5 minutes. Detected 615 nm fluorescence emission with appropriate Time-Resolved Plate Reader.

(b) An *in vitro* assay which determines the ability of a test compound to inhibit the EGF-stimulated EGFR phosphorylation.

Allowed A431 cell growth in a T75 flask using standard tissue culture procedures until cells reach near confluency (~$1.5x10^7$) cells; D-MEM, 10% FBS). Under sterile conditions dispensed 100 µl of the cell suspension per well in 96-well microplates (x cells plated per well). Incubated cells and monitor cell density until confluency is achieved with well-to-well consistency; approximately three days.

Removed complete media from plate wells by aspiration or manual displacement. Replaced media with 50 µl of pre-warmed serum free media per well and incubated 4 to 16 hours. Made two fold serial dilutions of inhibitor using pre-warmed D-MEM so that the final concentration of inhibitor range from 10 µM to 90 pM. Removed media from A431 cell plate. Added 100 µl of serial diluted inhibitor into cells and incubate 1 to 2 hours. Removed inhibitor from plate wells by aspiration or manual displacement. Added either serum free media for resting cells (mock) or serum free media with 100 ng/ml EGF. Used 100 µl of resting/activation media per well. Allowed incubation at 37 °C for 7.5 minutes. Removed activation or stimulation media manually or by aspiration. Immediately fixed cells with 4% formaldehyde in 1X PBS. Allowed incubation on bench top for 20 minutes at RT with no shaking. Ished five times with 1X PBS containing 0.1% Triton X-100 for 5 minutes per Ish. Removed Fixing Solution. Using a multi-channel pipettor, added 200 µl of Triton Ishing Solution (1X PBS + 0.1% Triton X-100). Allowed ish to shake on a rotator for 5 minutes at room temperature. Repeated ishing steps 4 more times after removing ish manually. Using a multi-channel pipettor, blocked cells/wells by adding 100 µl of LI-COR Odyssey Blocking Buffer to each well. Allowed blocking for 90 minutes at RT with moderate shaking on a rotator. Added the two primary antibodies into a tube containing Odyssey Blocking Buffer. Mixed the primary antibody solution well before addition to wells (Phospho-EGFR Tyr1045, (Rabbit; 1:100 dilution; Cell Signaling Technology, 2237; Total EGFR, Mouse; 1:500 dilution; Biosource International, AHR5062). Removed blocking buffer from the blocking step and added 40 µl of the desired primary antibody or antibodies in Odyssey Blocking Buffer to cover the bottom of each well. Added 100 µl of Odyssey Blocking Buffer only to control wells. Incubated with primary antibody overnight with gentle shaking at RT. Ished the plate five times with 1x PBS + 0.1% Tween-20 for 5 minutes at RT with gentle shaking, using a generous amount of buffer. Using a multi-channel pipettor added 200 µl of Tween Ishing Solution. Allowed ish to shake on a rotator for 5 minutes at RT. Repeated ishing steps 4 more times. Diluted the fluorescently labeled secondary antibody in Odyssey Blocking Buffer (Goat anti-mouse IRDyeTM 680 (1:200 dilution; LI-COR Cat.# 926-32220) Goat anti-rabbit IRDyeTM 800CW (1:800 dilution; LI-COR Cat.# 926-32211). Mixed the antibody solutions well and added 40 µl of the secondary

antibody solution to each well. Incubated for 60 minutes with gentle shaking at RT. Protected plate from light during incubation. Ished the plate five times with 1x PBS + 0.1% Tween-20 for 5 minutes at RT with gentle shaking, using a generous amount of buffer. Using a multi-channel pipettor added 200 µl of Tween Ishing Solution. Allowed ish to shake on a rotator for 5 minutes at RT. Repeated ishing steps 4 more times. After final ish, removed ish solution completely from wells. Turned the plate upside down and tap or blot gently on paper towels to remove traces of ish buffer. Scanned the plate with detection in both the 700 and 800 channels using the Odyssey Infrared Imaging System (700 nm detection for IRDyeTM 680 antibody and 800 nm detection for IRDyeTM 800CW antibody). Determined the ratio of total to phosphorylated protein (700/800) using Odyssey software and plot the results in Graphpad Prism (V4.0a). Data are plotted using GraphPad Prism (v4.0a) and IC50's calculated using a sigmoidal dose response curve fitting algorithm.

(c) An *in vitro* assay which determines the ability of a test compound to inhibit a receptor tyrosine kinase.

The ability of compounds to inhibit receptor kinase (EGFR, HER2/ErbB2, and VEGFR2) activity is assayed using HTScan™ Receptor Kinase Assay Kits (Cell Signaling Technologies, Danvers, MA). EGFR tyrosine kinase is obtained in partially purified form from GST-kinase fusion protein which is produced using a baculovirus expression system from a construct expressing human EGFR (His672-Ala1210) (GenBank Accession No. NM_005228) with an amino-terminal GST tag. HER2/ErbB2 tyrosine kinase is produced using a baculovirus expression system from a construct containing a human HER2/ErbB2 c-DNA (GenBank Accession No. NM_004448) fragment (Lys676-Val1255) amino-terminally fused to a GST tag. VEGFR2 tyrosine kinase is produced using a baculovirus expression system from a construct containing a human VEGFR2 cDNA kinase domain (Asp805-Val1356) (GenBank accession No. AF035121) fragment amino-terminally fused to a GST-HIS6-Thrombin cleavage site. The proteins are purified by one-step affinity chromatography using glutathione-agarose. An anti-phosphotyrosine monoclonal antibody, P-Tyr-100, is used to detect phosphorylation of biotinylated substrate peptides (EGFR, Biotin-PTP1B (Tyr66); HER2/ErbB2, Biotinylated FLT3 (Tyr589); VEGFR2, Biotin-Gastrin Precursor (Tyr87).). Enzymatic activity is tested in 60 mM HEPES, 5 mM $MgCl_2$ 5 mM $MnCl_2$ 200 µM ATP, 1.25 mM DTT, 3 µM

$Na_3VO_4$, 1.5 mM peptide, and 50 ng EGF Recpetor Kinase. Bound antibody is detected using the DELFIA system (PerkinElmer, Wellesley, MA) consisting of DELFIA® Europium-labeled Anti-mouse IgG (PerkinElmer, #AD0124), DELFIA® Enhancement Solution (PerkinElmer, #1244-105), and a DELFIA® Streptavidin coated, 96-well Plate (PerkinElmer, AAAND-0005). Fluorescence is measured on a WALLAC Victor 2 plate reader and reported as relative fluorescence units (RFU). Data are plotted using GraphPad Prism (v4.0a) and IC50's calculated using a sigmoidal dose response curve fitting algorithm.

Test compounds are dissolved in dimethylsulphoxide (DMSO) to give a 20 mM working stock concentration. Each assay is setup as follows: Added 100 µl of 10 mM ATP to 1.25 ml 6 mM substrate peptide. Diluted the mixture with $dH_20$ to 2.5 ml to make 2X ATP/substrate cocktail ([ATP]=400 mM, [substrate] =3 mM). Immediately transfer enzyme from –80°C to ice. Allowed enzyme to thaw on ice. Microcentrifuged briefly at 4°C to bring liquid to the bottom of the vial. Returned immediately to ice. Added 10 µl of DTT (1.25 mM) to 2.5 ml of 4X HTScanTM Tyrosine Kinase Buffer (240 mM HEPES pH 7.5, 20 mM $MgCl_2$, 20 mM MnCl, 12 mM $NaVO_3$) to make DTT/Kinase buffer. Transfer 1.25 ml of DTT/Kinase buffer to enzyme tube to make 4X reaction cocktail ([enzyme] = 4 ng/µL in 4X reaction cocktail). Incubated 12.5 µl of the 4X reaction cocktail with 12.5 µl/well of prediluted compound of interest (usually around 10 µM) for 5 minutes at room temperature. Added 25 µl of 2X ATP/substrate cocktail to 25 µl/well preincubated reaction cocktail/compound. Incubated reaction plate at room temperature for 30 minutes. Added 50 µl/well Stop Buffer (50 mM EDTA, pH 8) to stop the reaction. Transferred 25 µl of each reaction and 75 µl $dH_2O$/well to a 96-well streptavidin-coated plate and incubated at room temperature for 60 minutes. Ished three times with 200 µl/well PBS/T (PBS, 0.05% Tween-20). Diluted primary antibody, Phospho-Tyrosine mAb (P-Tyr-100), 1:1000 in PBS/T with 1% bovine serum albumin (BSA). Added 100 µl/well primary antibody. Incubated at room temperature for 60 minutes. Ished three times with 200 µl/well PBS/T. Diluted Europium labeled anti-mouse IgG 1:500 in PBS/T with 1% BSA. Added 100 µl/well diluted antibody. Incubated at room temperature for 30 minutes. Ished five times with 200 µl/well PBS/T. Added 100 µl/well DELFIA® Enhancement Solution.

Incubated at room temperature for 5 minutes. Detected 615 nm fluorescence emission with appropriate Time-Resolved Plate Reader.

(d) An *in vitro* assay which determined the ability of a test compound to inhibit DNMT activity.

DNMT inhibitors are screened using methylation specific PCR (MSP). Test compounds are dissolved in dimethylsulphoxide (DMSO) to give a 20 mM working stock concentration. HT-29 colon adenocarcinoma cells are plated in 6 well plates and treated for 72 hours with test compound or 2.5 μM 5-Aza-2'-deoxycytidine, replacing the media daily. DNA is harvested from cells after 72 hours using a non-organic DNA extraction kit (S4520, Chemicon International, Temecula, CA). Bisulfite chemical modification is achieved using the CpCenome DNA Modification Kit (S7820, Chemicon International, Temecula, CA). In a screwcap 1.5-2.0 mL microcentrifuge tube are added 7.0 μL 3M NaOH to 1.0 μg DNA in 100 μL of water (10 ng/μL) and mixed. The DNA is incubated for 10 minutes at 50°C. 550 μL of freshly prepared DNA Modification Reagent I is added and vortexed. The mixture is incubated at 50°C for 4-16 hours in a heat block or water bath protected from light. DNA is resuspended in DNA Modification III by vortexing vigorously. The suspension is drawn into and out of a 1 ml plastic pipette tip 10x to disperse any remaining clumps. 5 μL of well-suspended DNA Modification Reagent III is added to the DNA solutions in the tubes. 750 μL of DNA Modification Reagent II is added and mixed briefly. The mixture is incubated at room temperature for 5-10 minutes. The tubes are spun for 10 seconds at 5,000 X g to pellet the DNA Reagent III. Supernatant is discarded. 1.0 mL of 70% EtOH is added, vortexed, centrifuged for 10 seconds at 5,000 X g and the supernatant is discarded. This step is performed for a total of 3 times. After removing the supernatant from the third ish, the tube is centrifuged at high speed for 2 minutes, and the remaining supernatant is removed. 50 μL of the 20 mM NaOH/90% EtOH solution is added to the appropriate samples. The tube is vortexed briefly to resuspend the pellet, and incubated at room temperature for 5 minutes. The tubes are spun for 10 seconds at 5,000 X g to move all contents to the tip of the tube. 1.0 mL of 90% EtOH is added and vortexed to ish the pellet. The tubes are spun again and the supernatant removed. This step is repeated one additional time. After the supernatant from the second ish is removed, the sample is centrifuged at high speed for 3 minutes. The remaining supernatant is

removed and the tube allowed to dry for 10-20 minutes at room temperature. The sample is incubated for 15 minutes at 50-60°C to elute the DNA, centrifuged at high speed for 2-3 minutes and transferred to a new tube. MSP is carried out using the CpG WIZ p16 Amplification Kit (S7800, Chemicon International, Temecula, CA) which enables detection of methylated vs unmethylated promoter regions within the p16 gene. Ratio's of methylated vs unmethylated DNA are determined from gel densitometric analysis of ethidium bromide stained gels of the PCR products.

(e) An *in vitro* assay which determines the ability of a test compound to inhibit a kinase.

The Raf kinase assay is performed by following the protocol of Raf kinase assay kit (B-Raf, Upstate, catalog# 17-359; C-Raf, Upstate, catalog# 17-360) with modifications. Briefly, assay buffer, ATP, substrate and Raf kinase are mixed in a 96 well assay plate. The final kinase assay mixture contained 20 mM MOPS, pH7.2, 25 mM β-glycerol phosphate, 5 mM EGTA, 1 mM sodium orthovanadate, 1 mM DTT, 250 μM ATP and 37.5 mM magnesium chloride, 0.1 μg/well of Raf kinase, and 1 μg/well of MEK-1 substrate protein. Assay samples are incubated for 30 min at room temperature. The kinase reaction is stopped by adding EDTA, pH8 to a final concentration of 25 mM. A 10 μl of the reaction sample is spotted onto nitrocellulose filter and dot blot is performed by adding 1 μg/ml of anti-phospho-MEK-1 antibody in the blocking solution (Licor Bioscience, catalogue # 927-40000). The nitrocellulose filter is subsequently incubated with secondary IRDye 800CW goat anti-rabbit antibody (Licor Bioscience, catalogue # 926-32211) before reading the signal on an Odyssey imager (Licor Bioscience).

The ability of compounds to inhibit VEGFR2 kinase activity is assayed using HTScan™ VEGFR2 Kinase Assay Kits (Cell Signaling Technologies, Danvers, MA). VEGFR2 tyrosine kinase is produced using a baculovirus expression system from a construct containing a human VEGFR2 cDNA kinase domain (Asp805-Val1356) (GenBank accession No. AF035121) fragment amino-terminally fused to a GST-HIS6-Thrombin cleavage site. The protein is purified by one-step affinity chromatography using glutathione-agarose. An anti-phosphotyrosine monoclonal antibody, P-Tyr-100, is used to detect phosphorylation of biotinylated substrate peptides (VEGFR2, Biotin-Gastrin Precursor (Tyr87)). Enzymatic activity is tested in 60 mM HEPES, 5 mM MgCl2 5 mM MnCl2 200 μM ATP, 1.25 mM DTT, 3 μM

Na3VO4, 1.5 mM peptide, and 50 ng EGF Receptor Kinase. Bound antibody is detected using the DELFIA system (PerkinElmer, Wellesley, MA) consisting of DELFIA® Europium-labeled Anti-mouse IgG (PerkinElmer, #AD0124), DELFIA® Enhancement Solution (PerkinElmer, #1244-105), and a DELFIA® Streptavidin coated, 96-well Plate (PerkinElmer, AAAND-0005). Fluorescence is measured on a WALLAC Victor 2 plate reader and reported as relative fluorescence units (RFU). Data are plotted using GraphPad Prism (v4.0a) and IC50's calculated using a sigmoidal dose response curve fitting algorithm.

Test compounds are dissolved in dimethylsulphoxide (DMSO) to give a 20 mM working stock concentration. Each assay is setup as follows: Added 100 µl of 10 mM ATP to 1.25 ml 6 mM substrate peptide. Diluted the mixture with $dH_20$ to 2.5 ml to make 2X ATP/substrate cocktail ([ATP]=400 mM, [substrate] =3 mM). Immediately transfer enzyme from –80°C to ice. Allowed enzyme to thaw on ice. Microcentrifuged briefly at 4°C to bring liquid to the bottom of the vial. Returned immediately to ice. Added 10 µl of DTT (1.25 mM) to 2.5 ml of 4X HTScanTM Tyrosine Kinase Buffer (240 mM HEPES pH 7.5, 20 mM $MgCl_2$, 20 mM MnCl, 12 mM $NaVO_3$) to make DTT/Kinase buffer. Transfer 1.25 ml of DTT/Kinase buffer to enzyme tube to make 4X reaction cocktail ([enzyme] = 4 ng/µL in 4X reaction cocktail). Incubated 12.5 µl of the 4X reaction cocktail with 12.5 µl/well of prediluted compound of interest (usually around 10 µM) for 5 minutes at room temperature. Added 25 µl of 2X ATP/substrate cocktail to 25 µl/well preincubated reaction cocktail/compound. Incubated reaction plate at room temperature for 30 minutes. Added 50 µl/well Stop Buffer (50 mM EDTA, pH 8) to stop the reaction. Transferred 25 µl of each reaction and 75 µl $dH_2O$/well to a 96-well streptavidin-coated plate and incubated at room temperature for 60 minutes. Ished three times with 200 µl/well PBS/T (PBS, 0.05% Tween-20). Diluted primary antibody, Phospho-Tyrosine mAb (P-Tyr-100), 1:1000 in PBS/T with 1% bovine serum albumin (BSA). Added 100 µl/well primary antibody. Incubated at room temperature for 60 minutes. Ished three times with 200 µl/well PBS/T. Diluted Europium labeled anti-mouse IgG 1:500 in PBS/T with 1% BSA. Added 100 µl/well diluted antibody. Incubated at room temperature for 30 minutes. Ished five times with 200 µl/well PBS/T. Added 100 µl/well DELFIA® Enhancement Solution.

Incubated at room temperature for 5 minutes. Detected 615 nm fluorescence emission with appropriate Time-Resolved Plate Reader.

(f) An *in vitro* assay which determines the ability of a test compound to inhibit Hsp90 chaperone activity.

The Hsp90 chaperone assay is performed to measure the ability of HSP90 protein to refold the heat-denatured luciferase protein. HSP90 is first incubated with different concentrations of test compounds in denaturation buffer (25 mM Tris, pH7.5, 8 mM MgSO4, 0.01% bovine gamma globulin and 10% glycerol) at room temperature for 30 min. Luciferase protein is added to denaturation mix and incubated at 50 °C for 8 min. The final concentration of HSP90 and luciferase in denaturation mixture are 0.375 μM and 0.125 μM respectively. A 5 μl sample of the denatured mix is diluted into 25 μl of renaturation buffer (25 mM Tris, pH7.5, 8 mM MgSO4, 0.01% bovine gamma globulin and 10% glycerol, 0.5 mM ATP, 2 mM DTT, 5 mM KCl, 0.3 μM HSP70 and 0.15 μM HSP40). The renaturation reaction is incubated at room temperature for 150 min, followed by dilution of 10μl of the renatured sample into 90 μl of luciferin reagent (Luclite, PerkinElmer Life Science). The mixture is incubated at dark for 5 min before reading the luminescence signal on a TopCount plate reader (PerkinElmer Life Science).

(g) HSP90 Competition Binding (Fluorescence Polarization) Assay.

A fluorescein isothiocyanate (FITC) labeled GM is purchase from InvivoGen (ant-fgl-1). The interaction between HSP90 and labeled GM forms the basis for the fluorescence polarization assay. A free and fast-tumbling FITC labeled GM emits random light with respect to the plane of polarization plane of excited light, resulting in a lower polarization degree (mP) value. When GM is bound to HSP90, the complex tumble slower and the emitted light is polarized, resulting in a higher mP value. This competition binding assay is performed in 96-well plate and with each assay contained 10 and 50nM of labeled GM and purified HSP90 protein (Assay Design, SPP-776F) respectively. The assay buffer contained 20mM HEPES (pH 7.3), 50mM KCl, 1mM DTT, 50mM $MgCl_2$, 20mM $Na_2MoO_4$, 0.01% NP40 with 0.1mg/ml bovine gamma-globulin. Compounds are diluted in DMSO and added to the final assay before labeled GM with concentration range from 20uM to 2nM. mP value is determined by BioTek Synergy II with background subtraction after 24 hours of incubation at 4°C.

(h) An *in vitro* assay which determines the ability of a test compound to inhibit CDK activity.

**MATERIALS:**

**CDK2/cyclinE (Accession number for CDK2; EMBL M68520, for cyclinE1; GenBank NM_001238):** *C*-terminal 6His-tagged, recombinant full-length CDK2 in complex with *N*-terminal GST-tagged, recombinant full-length cyclinE1. Both are expressed by baculovirus in Sf21 cells. Purified using Ni2+/NTA agarose. Combined purity 76% by SDS-PAGE and Coomassie blue staining. CDK2 MW = 34kDa, cyclinE1 MW = 74kDa. Specific Activity of 1336U/mg, where one unit of CDK2/cylinE1 activity is defined as 1nmol phosphate incorporated into 0.1mg/ml histone H1 per minute at 30°C with a final ATP concentration of 100μM. Enzyme at 0.1 mg/ml in 50mM Tris/HCl pH 7.5, 150mM NaCl, 0.03% Brij-35, 0.1mM EGTA, 0.2mM PMSF, 1mM benzamidine, 0.1% 2-mercaptoethanol, 270mM sucrose.

**CDK6/cyclinD3 (Accession number for CDK6; GenBank X66365, for cyclin D3; EMBL M90814):** N-terminal, 6His-tagged full-length human cdk6 complexed with N-terminal GST-tagged full-length human cyclin D3, expressed in Sf21 cells. Purified using glutathione-agarose, activated with CAK, and repurified on Ni2+/NTA-agarose. Purity 68%. MW = 38kDa (cdk6) and 59kDa (cyclin D3). Specific Activity of 39U/mg, where one unit of cdk6/cyclinD3 activity is defined as 1nmol phosphate incorporated into 0.1mg/ml histone H1 per minute at 30°C with a final ATP concentration of 100μM. Enzyme at 0.1 mg/ml in 50mM Tris-HCl, pH 7.5, 270mM sucrose, 150mM NaCl, 1mM benzamidine, 0.2mM PMSF, 0.1% 2-mercaptoethanol, 0.1mM EGTA, 0.03% Brij 35.

**Histon H1 (Substrate for CDK2 & 6):** Sigma cat# H4524, isolated as a lysine rich fraction from calf thymus, 93% purity, Mw=21.5kDa, stock at 20 mg/ml=930 μM in DW.

**Reaction Buffer:** 20 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 1 mM EGTA, 0.02% Brij 35, 0.02 mg/ml BSA, 0.1 mM $Na_3VO_4$, 2 mM DTT.

**[γ-$^{33}$P]-ATP:** Perkin Elmer cat# NEG602H1MC (EasyTides), 10 mCi/ml = 10 μCi/μl, 100 μl in vial, specific activity=3000 Ci/mmol, 3.3-5 μM in 50 mM Tricine (pH 7.6), amber gold dye.

**ASSAY CONDITIONS:**

**CDK2/cyclinE:** 0.5 nM CDK2/cyclinE and 5 μM Histon H1 are in the reaction buffer plus 1 μM ATP and 1% DMSO final. Incubate for 2 hours at room temperature.

Conversion rate of ATP: 4.5%

**CDK6/cyclinD3:** 50 nM CDK6/cyclinD3 and 5 μM Histon H1 are in the reaction buffer plus 1 μM ATP and 1% DMSO final. Incubate for 2 hours at room temperature.

Conversion rate of ATP: 13%

(i) Bcl-2 and Bcl-xL Competition Binding (Fluorescence Polarization) Assay

*Background:*

Bcl-2 and Bcl-xL proteins are antiapoptotic proteins whose biological function can be inhibited by proapototic proteins such as Bak, Bad and Bax through protein interaction. The interaction between antiapoptotic and proapototic proteins are mediated primarily by Bcl-2 homology (BH) 3 domain of Bak, Bad, Bax that bind to the hydrophobic groove of Bcl-2 and Bcl-xL. The demonstration of BH3 peptide alone induce apoptosis encourage the possibility of design or identify a chemical compound that mimics the function of BH3 peptide by blocking Bcl-2 or Bcl-xLs' interaction with their downstream binding partners. These chemical compounds are expected to bind to the hydrophobic groove of Bcl-xL or Bcl-2 proteins with high affinity. A labeled BH3 peptide can be used for competition binding and to monitor the interaction between compounds and Bcl-2 and Bcl-xL proteins.

*Rational and Method:*

A 26-mer fluorescein labeled BH3 peptide (NLWAAQRYGRELRRMSDKFVD) is purchase from CalBiochem (197216). The interaction between Bcl-xL or Bcl-2 and peptide forms the basis for the fluorescence polarization assay. A free and fast-tumbling fluoresein labeled BH3 peptide emits random light with respect to the plane of polarization plane of excited light, resulting in a lower polarization degree (mP) value. When the peptide is bound to Bcl-xl or Bcl-2, the complex tumble slower and the emitted light is polarized, resulting in a higher mP value. This binding assay is performed in 96-well plate and with each assay contained 1 and 100nM of labeled peptide and purified Bcl-xL (R&D System,

894-BX-050) or Bcl-2 protein (R&D System, 827-BC-050) respectively. The assay buffer contained 120mM sodium phosphate (pH 7.55), 0.01% BSA and 0.1% sodium azide. Compounds are diluted in DMSO and added to the final assay with concentration range from 20uM to 2nM. mP value is determined by BioTek Synergy II with background subtraction after 3 hours of incubation at room temperature.

(j) MEK Enzyme Assay

The activity of the compounds of the present invention may be determined by the following procedure. N-terminal 6 His-tagged MEK-1 (2-393) is expressed in E. coli and protein is purified by conventional methods (Ahn et al., *Science* 1994, 265, 966-970) and activated by Raf-1. The activity of MEK1 is assessed by measuring the incorporation of $\gamma$-$^{33}$P-phosphate from $\gamma$-$^{33}$P-ATP onto N-terminal His tagged, kinase mutated (K52R) ERK2, which is expressed in E. coli and is purified by conventional methods. The assay is carried out in 96-well polypropylene plate. The incubation mixture (100 μL) comprises of 20 mM Hepes, pH 7.4, 10 mM MgCl.sub.2, 1mM EGTA, 0.02% Brij, 0.02mg/ml BSA, 100 .mu.M Na-orthovanadate, 2mM DTT, 0.5 nM MEK1, and 1 μM ERK2. Inhibitors are suspended in DMSO, and all reactions, including controls are performed at a final concentration of 1% DMSO. Reactions are carried in the presence of 1 μM ATP (with 0.5 μCi $\gamma$-$^{33}$P-ATP/well) and incubated at ambient temperature for 120 minutes. Equal volume of 25% TCA is added to stop the reaction and precipitate the proteins. Precipitated proteins are trapped onto glass fiber B filterplates, and excess labeled ATP ished off using a Tomtec MACH III harvestor. Plates are allowed to air-dry prior to adding 30 μL/well of Packard Microscint 20, and plates are counted using a Perkin Elmer TopCount. In this assay, compounds of the invention exhibited an IC50 of less than 50 micromolar.

(k) Cellular ERK 1/2 Phosphorylation Assay

The MEK 1/2 inhibition properties of the compounds of the invention may be determined by the following in vitro cellular assay. Inhibition of basal ERK1/2 phosphorylation is determined by incubating cells with compound for 1 hour and quantifying the pERK signal on fixed cells and normalizing to total ERK signal. Materials and Methods: Malme-3M cells are obtained from ATCC and grown in RPMI-1640 supplemented with 10% fetal bovine serum. Cells are plated in 96-well plates at 15,000 cells/well and allowed to attach for 1-2 hours. Diluted compounds

are then added at a final concentration of 1% DMSO. After 1 hour, cells are ished with PBS and fixed in 3.7% para-formaldehyde in PBS for 15 minutes. This is followed by ishing in PBS/0.1% Triton X-100. Cells are blocked in Odyssey blocking buffer (LI-COR Biosciences) for at least 1 hour. Antibodies to phosphorylated ERK 1/2 (Cell Signaling #9106, monoclonal) and total ERK 12 (Santa Cruz Biotechnology #sc-94, polyclonal) are added to the cells and incubated for at least 1 hour. After ishing with PBS/0.1% TritonX-100, the cells are incubated with fluorescently-labeled secondary antibodies (goat anti-rabbit IgG-IRDye800, Rockland and goat anti-mouse IgG-Alexa Fluor 680, Molecular Probes) for an additional hour. Cells are then ished and analyzed for fluorescence at both wavelengths using the Odyssey Infrared Imaging System (LI-COR Biosciences). Phosphorylated ERK signal is normalized to total ERK signal.

(l) An *in vitro* assay which determines the ability of a test compound to inhibit HDAC enzymatic activity.

HDAC inhibitors are screened using an HDAC fluorimetric assay kit (AK-500, Biomol, Plymouth Meeting, PA). Test compounds are dissolved in dimethylsulphoxide (DMSO) to give a 20 mM working stock concentration. Fluorescence is measured on a WALLAC Victor 2 plate reader and reported as relative fluorescence units (RFU). Data are plotted using GraphPad Prism (v4.0a) and IC50's calculated using a sigmoidal dose response curve fitting algorithm. Each assay is setup as follows: Defrosted all kit components and kept on ice until use. Diluted HeLa nuclear extract 1:29 in Assay Buffer (50 mM Tris/Cl, pH 8.0, 137 mM NaCl, 2.7 mM KCl, 1 mM MgCl2). Prepared dilutions of Trichostatin A (TSA, positive control) and tested compounds in assay buffer (5x of final concentration). Diluted Fluor de LysTM Substrate in assay buffer to 100 uM (50 fold = 2x final). Diluted Fluor de LysTM developer concentrate 20-fold (e.g. 50 µl plus 950 µl Assay Buffer) in cold assay buffer. Second, diluted the 0.2 mM Trichostatin A 100-fold in the 1x Developer (e.g. 10 µl in 1 ml; final Trichostatin A concentration in the 1x Developer = 2 µM; final concentration after addition to HDAC/Substrate reaction = 1 µM). Added Assay buffer, diluted trichostatin A or test inhibitor to appropriate wells of the microtiter plate. Added diluted HeLa extract or other HDAC sample to all wells except for negative controls. Allowed diluted Fluor de LysTM Substrate and the samples in the microtiter plate to

equilibrate to assay temperature (e.g. 25 or 37°C. Initiated HDAC reactions by adding diluted substrate (25 μl) to each well and mixing thoroughly. Allowed HDAC reactions to proceed for 1 hour and then stopped them by addition of Fluor de LysTM Developer (50 μl). Incubated plate at room temperature (25°C) for 10-15 min. Read samples in a microtiter-plate reading fluorimeter capable of excitation at a wavelength in the range 350- 380 nm and detection of emitted light in the range 440-460 nm.

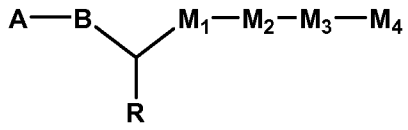
The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound represented by formula (I),



(I)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein

A is a pharmacophore of an agent that inhibits aberrant cell proliferation; preferably A is an anti-cancer agent;

B is a linker;

R is selected from the group consisting of hydrogen, $N(R_2)COR_4$, $N(R_2)CON(R_3)R_4$, $N(R_2)COOR_4$, $N(R_2)S(O)_nR_3$, $N(R_2)S(O)_nN(R_3)R_4$; where $R_2$ and $R_3$ are independently selected from hydrogen, aliphatic or substituted aliphatic; $R_4$ is selected from the group consisting of: aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cyloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, and substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl each containing 0, 1, 2, or 3 heteroatoms selected from O, S or N; n is 1 or 2;

$M_1$ is absent or selected from substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

$M_2$ is absent, O, S, SO, $SO_2$, $N(R_2)$ or CO;

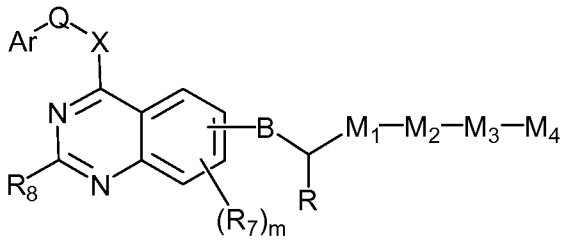
$M_3$ is absent, O, S, SO, $SO_2$, $N(R_2)$, CO, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, cycloalkyl, heterocyclic, aryl, or heteroaryl;

$M_4$ is hydrogen, $NR_5R_6$, $CF_3$, $OR_4$, halogen, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl; where $R_5$ and $R_6$ are independently selected from the group consisting of hydrogen, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl or substituted cycloalkyl;

provided that –R and $-M_1$-$M_2$-$M_3$-$M_4$ cannot be both hydrogen.

2. A compound of Claim 1, wherein the anticancer agent is selected from inhibitors of EGFR, ErbB2, ErbB3, ErbB4, HER-2, VEGFR-1, VEGFR-2, VEGFR-3Flt-3, c-kit, Abl, JAK, PDGFR-a, PDGFR-b, IGF-IR, c-Met, FGFR1, FGFR3, FGFR4, c-Ret, Src, Lyn, Yes, PKC, CDK, Erk, Merk, PI3K-Akt, mTOR, Raf, CHK, Aurora, HSP90, TRAILR, caspases, IAPs, Bcl-2, Survivin, MDM2, MDM4.

3. A compound according to Claim 1 represented by formula (II):




(II)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Q is absent or substituted or unsubstituted alkyl;

X is O, S, NH, or alkylamino;

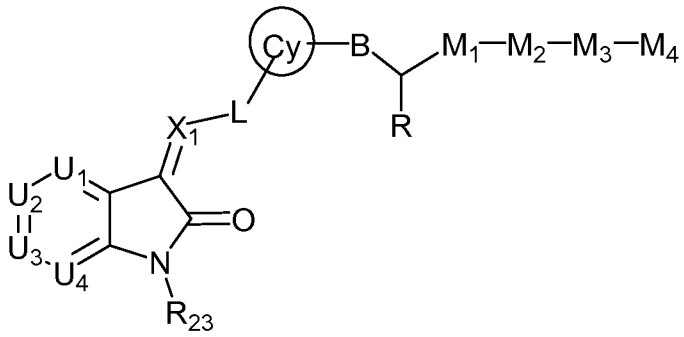
m is 0, 1, 2 or 3;

each of $R_7$ is independently selected from hydrogen, hydroxy, amino, halogen, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio, substituted alkylthio, alkylsulfonyl, substituted alkylsulfonyl, $CF_3$, CN, $N_3$, $NO_2$, sulfonyl, acyl, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl or substituted heteroaryl;

$R_8$ is hydrogen, substituted or unsubstituted $-C_1$-$C_6$ alkyl, $-C_2$-$C_6$ alkenyl, or $-C_2$-$C_6$ alkynyl;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

4. A compound according to Claim 1 represented by formula (VI):



(VI)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

$X_1$ is N, $CR_2$; where $R_2$ is as previously defined;

L is absent or NH;

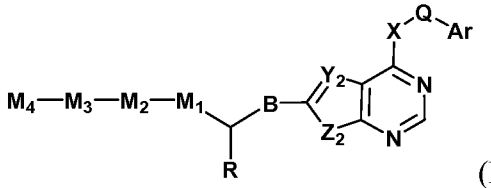
Cy is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

$U_1$-$U_4$ are independently N or $CR_{21}$, where $R_{21}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

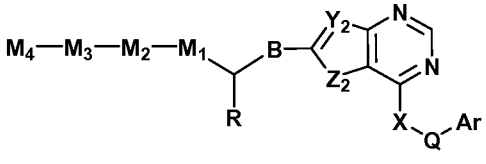
$R_{23}$ is hydrogen or aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

5. A compound according to Claim 1 represented by formula (IX) or (X):



(IX) or



(X)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

$Z_2$ is O, S, NH or alkylamino;

$Y_2$ is N or $CR_{20}$; where $R_{20}$ is selected from hydrogen, halogen, aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl;

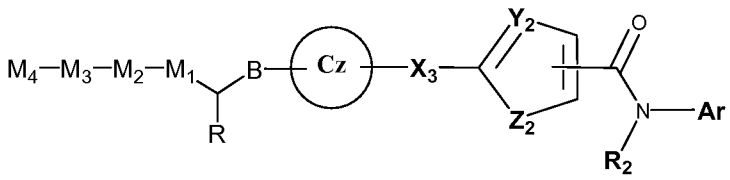
X is O, S, NH, or alkylamino;

Q is absent or substituted or unsubstituted alkyl;

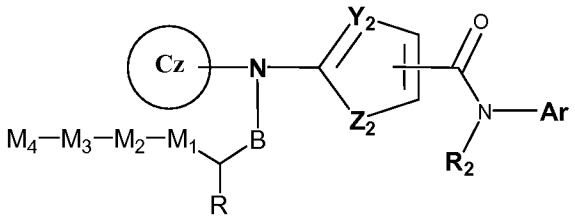
Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

6. A compound according to Claim 1 represented by formula (XV) or (XVI):




(XV)




(XVI)

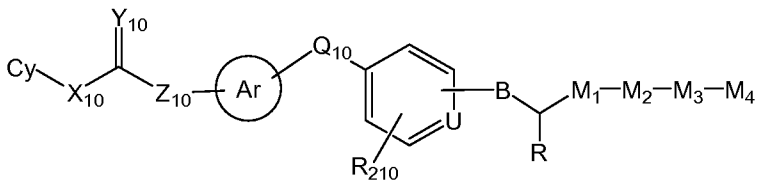
or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

Cz is selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, and heterocylic;

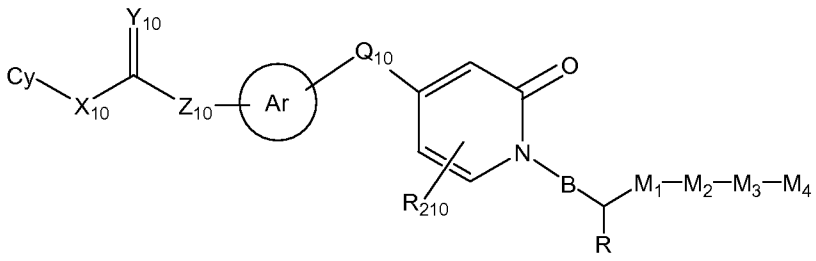
$X_3$ is NH, alkylamino O or S;

B, R, $Y_2$, $Z_2$, Ar, $R_2$, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

7. A compound according to Claim 1 represented by formula (XXI) or (XXII):




(XXI)




(XXII)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

U is N, CH or C;

Ar is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocylic or substituted heterocyclic;

$Q_{10}$ is O, S, SO, $SO_2$, NH, substituted or unsubstituted alkylamino, or substituted or unsubstituted $C_1$-$C_3$ alkyl;

$Y_{10}$ is O, S or NH;

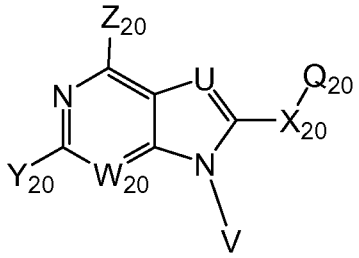
$X_{10}$ and $Z_{10}$ are independently NH, substituted or unsubstituted alkylamino, or substituted or unsubstituted $C_1$-$C_3$ alkyl;

Cy is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, or heterocycloalkyl;

$R_{210}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfonyl, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aliphatic, and substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

8. A compound according to Claim 1 represented by formula (XXVII):




(XXVII)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

U is N or CH;

$W_{20}$ is N or CH;

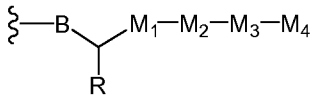
$X_{20}$ is absent, O, S, S(O), $S(O)_2$, $N(R_{18})$, $CF_2$ or $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, in which one or more methylene can be interrupted or terminated by O, S, SO, $SO_2$, $N(R_{18})$., $R_{18}$ is hydrogen, acyl, aliphatic or substituted aliphatic;

$Y_{20}$ is independently hydrogen, halogen, $NO_2$, CN, or lower alkyl;

$Z_{20}$ is amino, alkylamino, or dialkylamino;

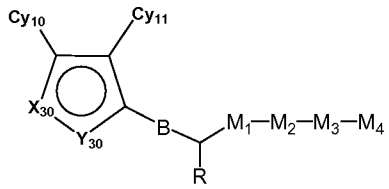
$Q_{20}$ is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, or heterocycloalkyl;

V is hydrogen, straight- or branched-, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, which one or more methylenes can be interrupted or terminated by O, S, S(O), $SO_2$, $N(R_{18})$, C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; substituted or unsubstituted cycloalkyl;

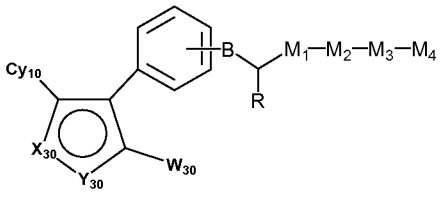
and wherein $Q_{20}$ and/or V is further substituted by ;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

9. A compound according to Claim 1 represented by formula (XXIX) or (XXX):



(XXIX)



(XXX)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

$Cy_{10}$ and $Cy_{11}$ are each independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

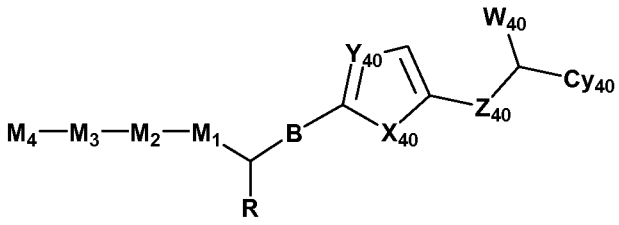
$Y_{30}$ is N, $NR_{18}$ or $CR_{18}$, where $R_{18}$ is hydrogen, acyl, aliphatic or substituted aliphatic;

$X_{30}$ is $CR_{18}$, $NR_{18}$, N, O or S;

$W_{30}$ is hydrogen, acyl, aliphatic or substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

10. A compound according to Claim 1 represented by formula (XXXV):



(XXXV)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

$Cy_{40}$ is each independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

$W_{40}$ is each independently selected from hydrogen, halogen, acyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

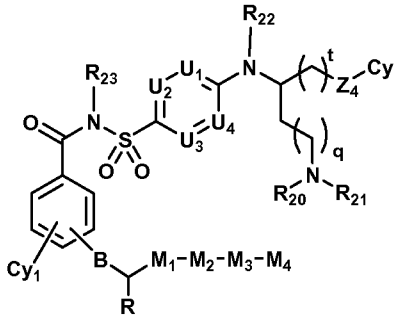
$Z_{40}$ is O, S, S(O), $SO_2$, $SO_2NH$, $NR_{18}$, C(O) or $C(O)NH_2$;

$Y_{40}$ is N or $CR_{18}$, where $R_{18}$ is hydrogen, acyl, aliphatic or substituted aliphatic;

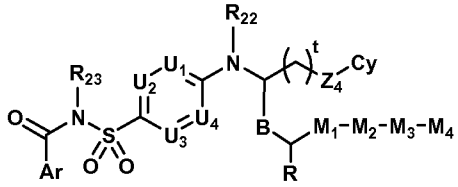
$X_{40}$ is $CR_{18}$, $NR_{18}$, O or S;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

11. A compound according to Claim 1 represented by formula (XXXVIII) or (XXXIX):



(XXXVIII) or



(XXXIX)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

Cy and $Cy_1$ are each independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

$Z_4$ is O, S, $CR_{18}$, or $NR_{18}$; where $R_{18}$ is hydrogen, acyl, aliphatic or substituted aliphatic;

$R_{20}$ and $R_{21}$ are each independently selected from hydrogen, acyl, aliphatic and substituted aliphatic; alternatively, $R_{20}$ and $R_{21}$ can be taken together with the atom they are attached to form a heterocyclic or substituted heterocyclic;

t is 1, 2 or 3;

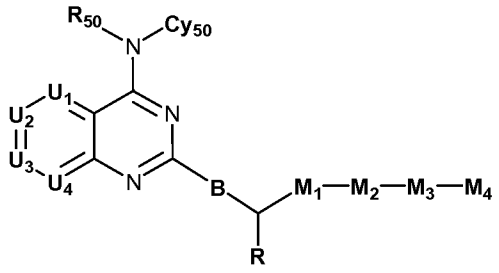
q is 1, 2, 3 or 4;

$R_{22}$ and $R_{23}$ are each independently selected from hydrogen, acyl, aliphatic and substituted aliphatic;

$U_1$-$U_4$ are independently N or $CR_{21}$, where $R_{21}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

12. A compound according to Claim 1 represented by formula (XLIV):




(XLIV)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

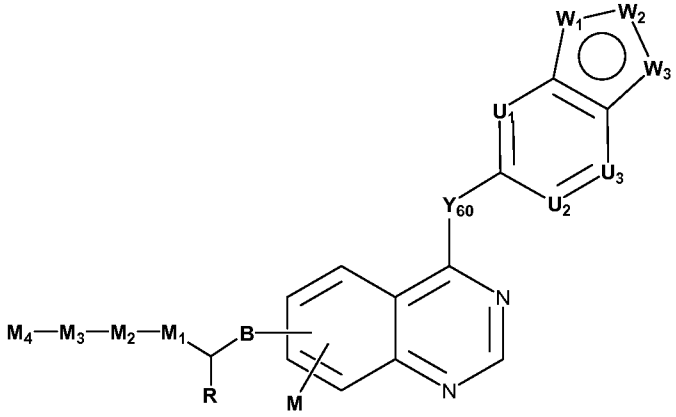
$Cy_{50}$ is selected from the group consisting of aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloakyl and substituted cycloalkyl;

$R_{50}$ is lower alkyl;

$U_1$-$U_4$ are independently N or $CR_{21}$, where $R_{21}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

13. A compound according to Claim 1 represented by formula (XLVII):




( XLVII)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

$W_1$, $W_2$ and $W_3$ are independently selected from the group consisting of $CR_{21}$, $NR_{18}$, N, O or S, where $R_{18}$ is hydrogen, acyl, aliphatic or substituted aliphatic; $R_{21}$ is independently selected from the group consisting of hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

$U_1$-$U_3$ are independently N or $CR_{21}$, where $R_{21}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

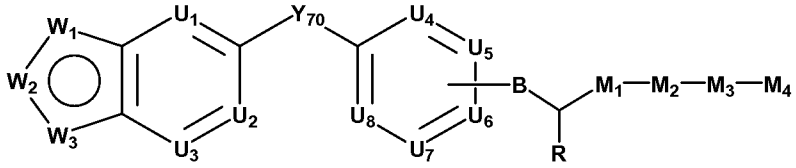
$Y_{60}$ is $NR_{18}$, O, S, SO, $SO_2$, aliphatic, and substituted aliphatic;

M is independently selected from hydrogen, hydroxy, amino, halogen, $CF_3$, CN, $N_3$, $NO_2$, sulfonyl, acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, arylalkyl,

arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, alkylarylalkyl, alkylarylalkenyl, alkylarylalkynyl, alkenylarylalkyl, alkenylarylalkenyl, alkenylarylalkynyl, alkynylarylalkyl, alkynylarylalkenyl, alkynylarylalkynyl, alkylheteroarylalkyl, alkylheteroarylalkenyl, alkylheteroarylalkynyl, alkenylheteroarylalkyl, alkenylheteroarylalkenyl, alkenylheteroarylalkynyl, alkynylheteroarylalkyl, alkynylheteroarylalkenyl, alkynylheteroarylalkynyl, alkylheterocyclylalkyl, alkylheterocyclylalkenyl, alkylhererocyclylalkynyl, alkenylheterocyclylalkyl, alkenylheterocyclylalkenyl, alkenylheterocyclylalkynyl, alkynylheterocyclylalkyl, alkynylheterocyclylalkenyl, or alkynylheterocyclylalkynyl, which one or more methylenes can be interrupted or terminated by O, S, S(O), $SO_2$, $N(R_{18})$, C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where $R_{18}$ hydrogen, acyl, aliphatic or substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

14. A compound according to Claim 1 represented by formula (L):




(L)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

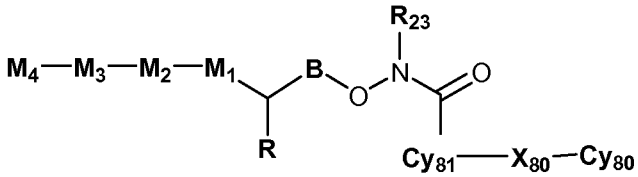
$W_1$, $W_2$ and $W_3$ are independently selected from the group consisting of $CR_{21}$, $NR_{18}$, N, O or S, where $R_{18}$ is hydrogen, acyl, aliphatic or substituted aliphatic; $R_{21}$ is independently selected from the group consisting of hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

$U_1$-$U_8$ are independently N or $CR_{21}$, where $R_{21}$ is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, $CF_3$, CN, $NO_2$, $N_3$, sulfonyl, acyl, aliphatic, and substituted aliphatic;

$Y_{70}$ is $NR_{18}$, O, S, SO, $SO_2$, aliphatic, and substituted aliphatic;

B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined in claim 1.

15. A compound according to Claim 1 represented by formula (LIII):




(LIII)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof wherein

$Cy_{80}$ and $Cy_{81}$ are each independently selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkyl and substituted cycloalkyl;

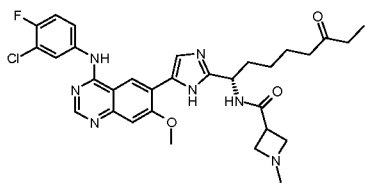
$X_{80}$ is $NR_{18}$, O, S, SO, $SO_2$, CO alkyl or substituted alkyl;

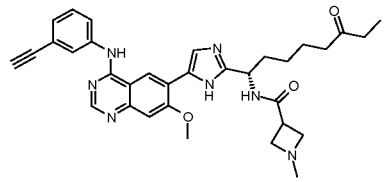
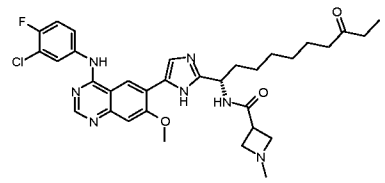
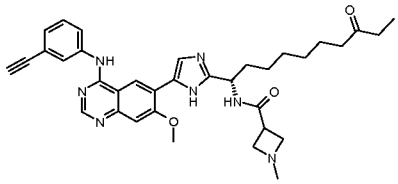
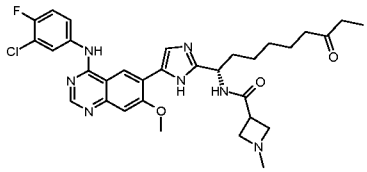
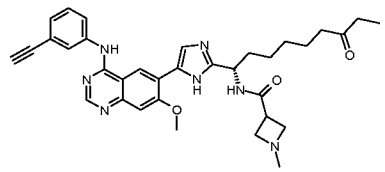
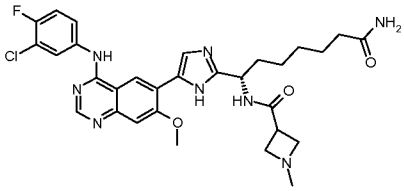
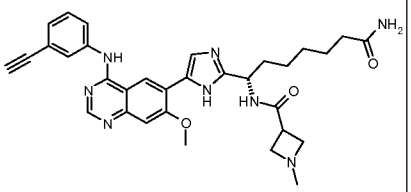
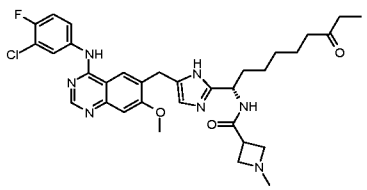
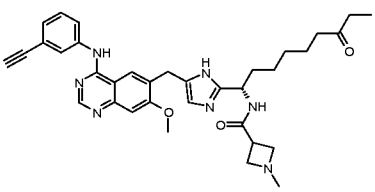
$R_{23}$ is hydrogen, aliphatic, substituted aliphatic or acyl;

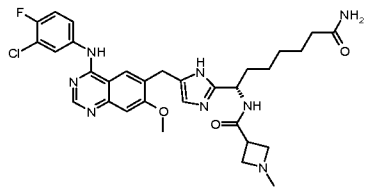
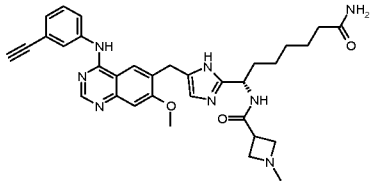
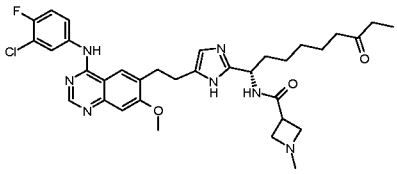
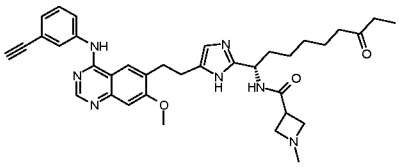
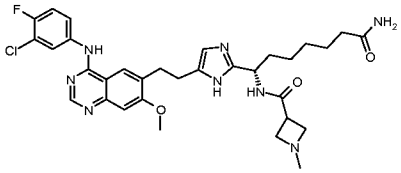
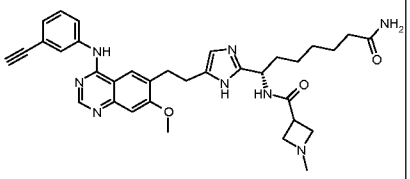
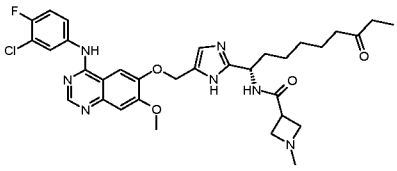
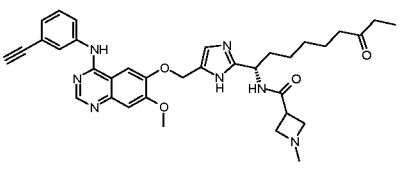
B, R, $M_1$, $M_2$, $M_3$ and $M_4$ are as previously defined.

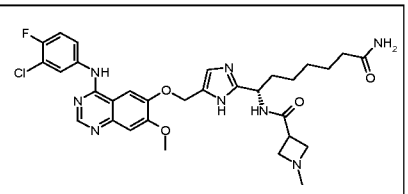
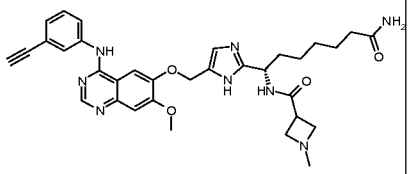
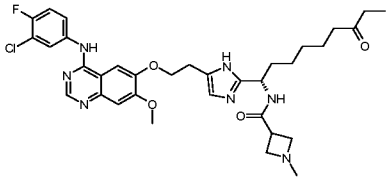
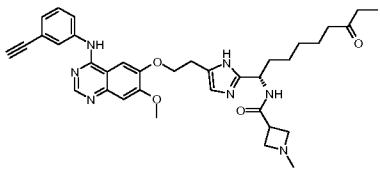
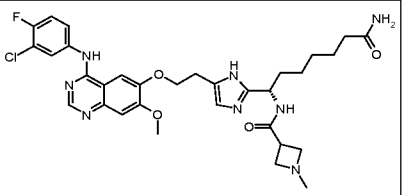
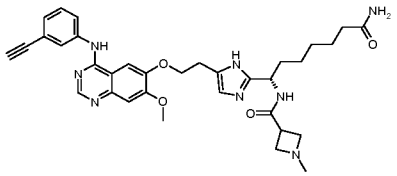
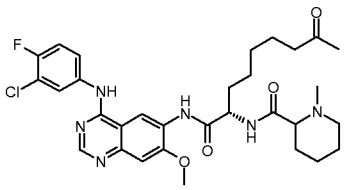
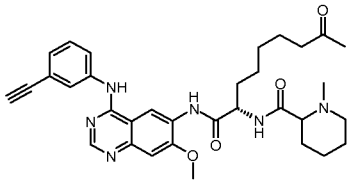
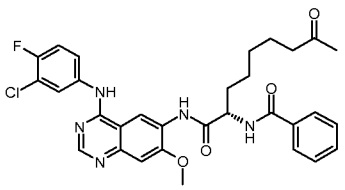
16. A compound according to Claim 1 selected from the compounds delineated in Table A or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

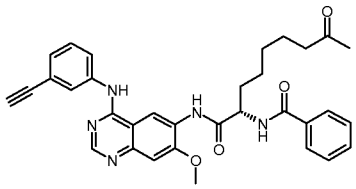
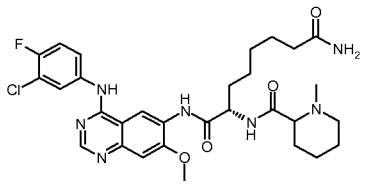
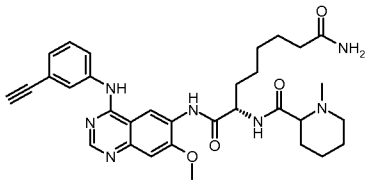
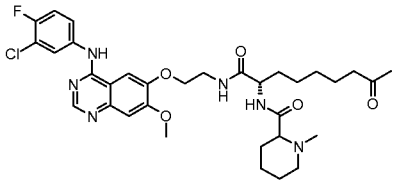
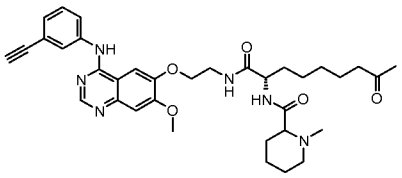
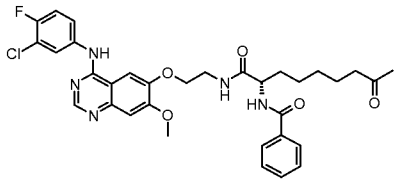
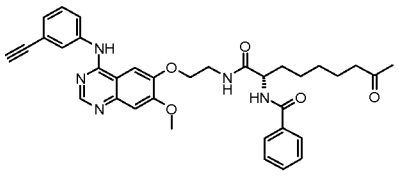
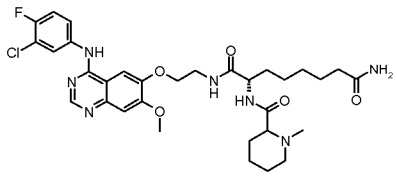
TABLE A

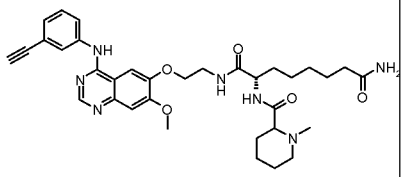
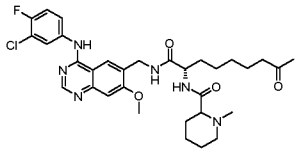
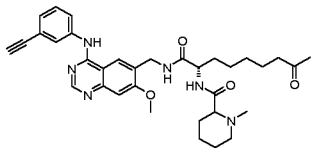
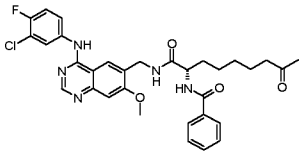
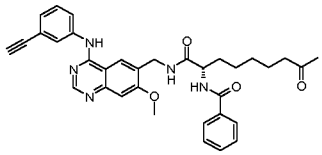
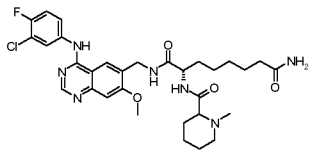
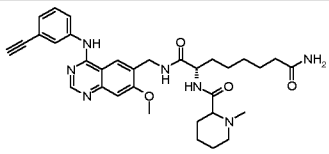
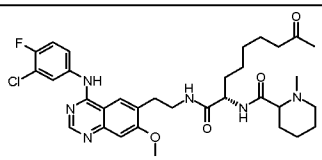
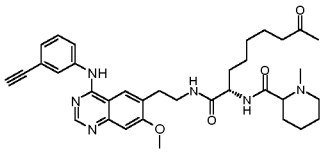
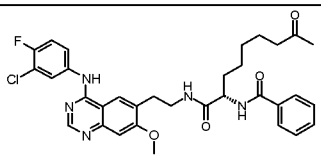
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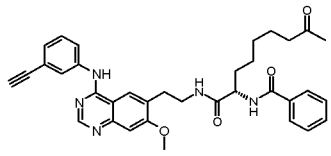
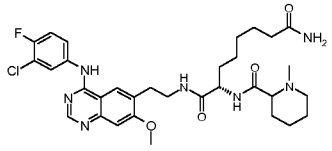
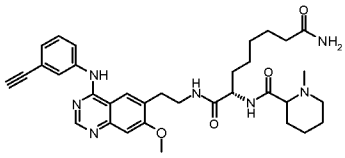
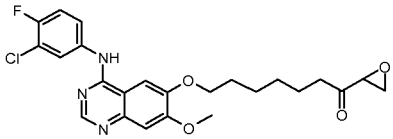
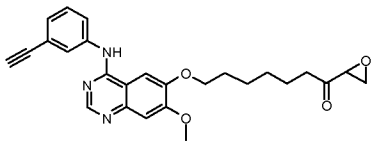
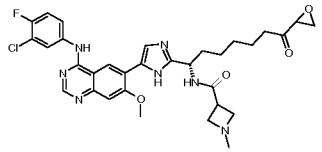
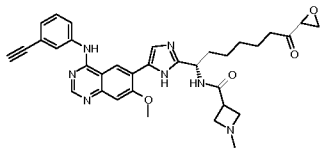
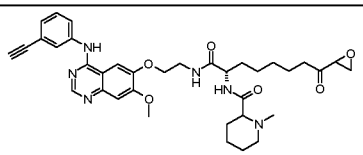
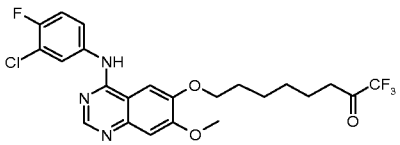
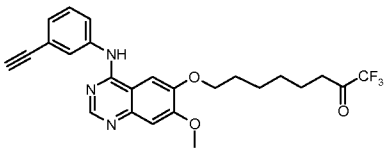
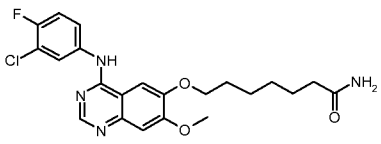
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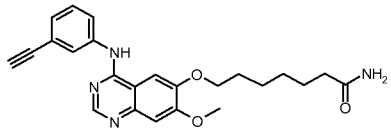
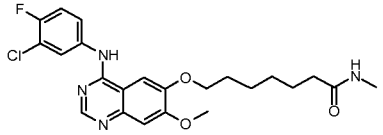
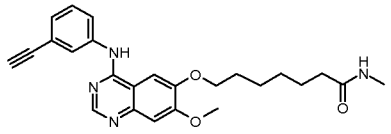
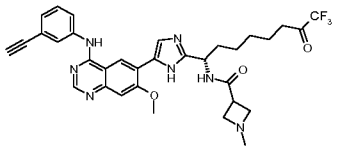
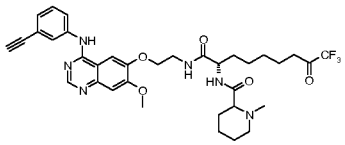
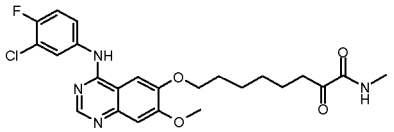
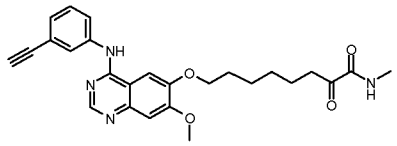
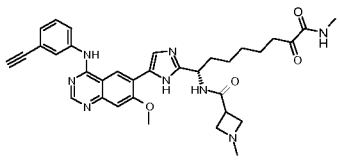
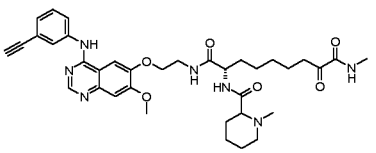
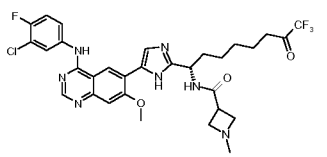
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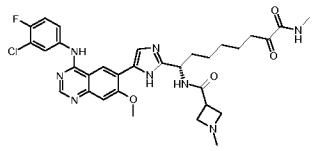
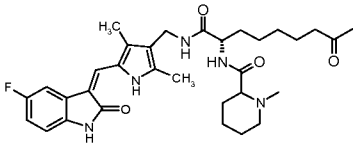
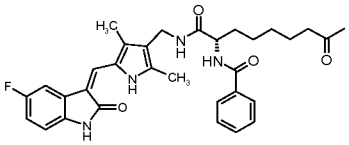
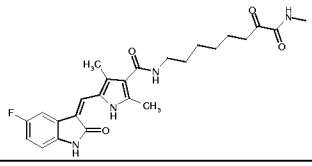
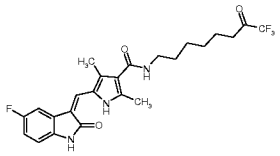
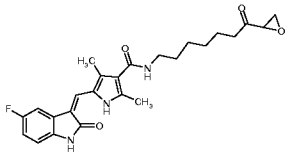
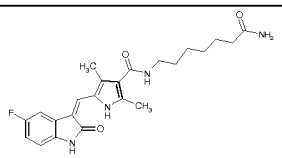
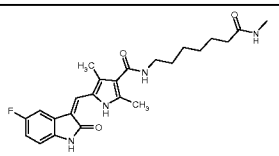
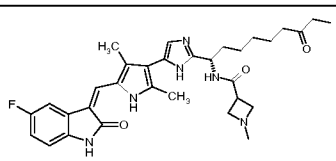
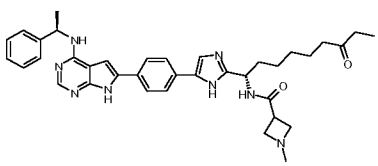
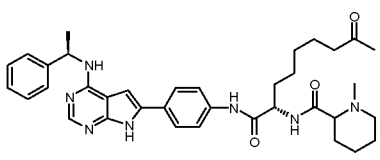
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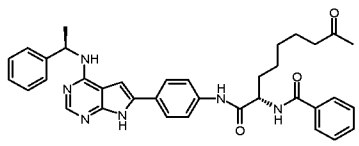
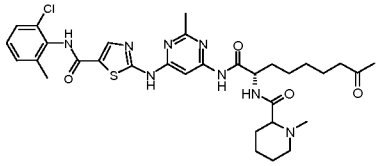
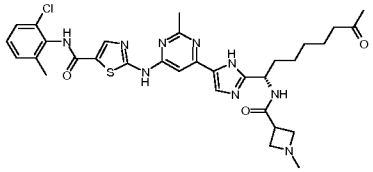
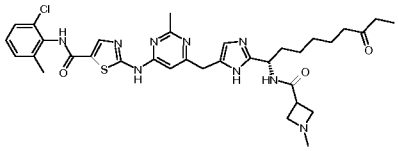
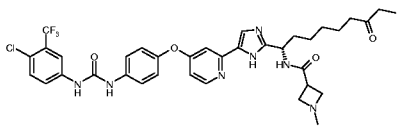
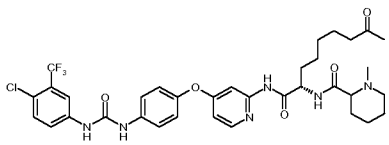
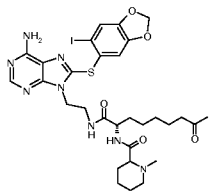
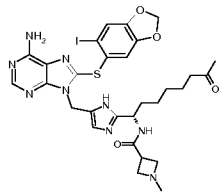
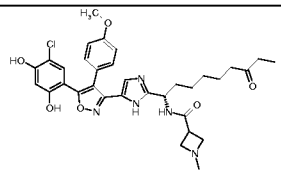
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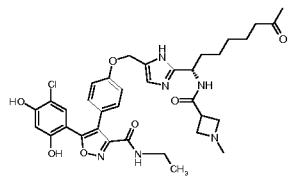
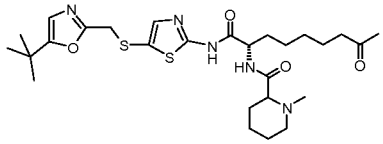
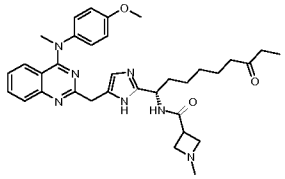
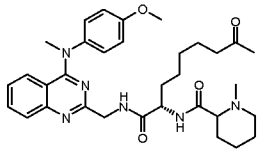
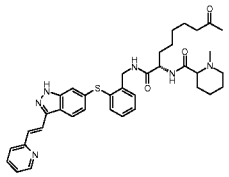
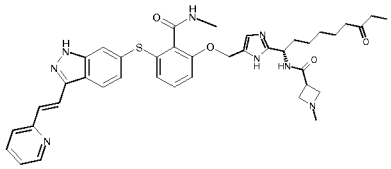
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17. A pharmaceutical composition comprising as an active ingredient a compound of Claim 1 or 4 and a pharmaceutical acceptable carrier.

18. A method of treating a cell proliferative disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of Claim 17.

19. A method of treating and/or preventing immune response or immune-mediated responses and diseases in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of Claim 17.

20. A method of treating neurodegenerative diseases in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of Claim 17.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/77456

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/08 (2008.04)
USPC - 514/472
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- A01N 43/08 (2008.04)
IPC (8): 514/472

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- A01N 43/08 (2008.04) (see keywords below)
IPC (8): 514/472 ; 549/475 (see keywords Below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST: DB=PGPB,USPT,USOC,EPAB,JPAB: Google: scholar/patents: antiproliferative agents quinazoline hdac

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2007/0032513 A1 (HENNEQUIN et al) 08 February 2007 (08.02.2007) para [0006]; [0022]; [0023]; [0031]; [0032]; [0034];[0036]; [0037]; [0041]; [0042]; [0052]; [0065]; [0641]; [0647] | 1-20 |
| Y | US 6,683,192 B2 (BAXTER et al) 27 January 2004 (27.01.2004) Col 6, ln 20-63; Col 7, ln 15-29 | 1-20 |
| Y | US 7,250,514 B1 (XIAO) 31 July 2007 (31.07.2007) Col 15, ln 13-66 | 4, 5, 8 |
| Y | WO 2006/061638 A2 (ATTENNI et al) 15 June 2006 (15.06.2006) pg 1, ln 1-5; pg 1, ln 30-31; pg 2, ln 1-12; pg 11, ln 1-29; pg 19, ln 27-30; pg 20, ln 1-5; pg 62, ln 4-29; pg 58, ln 36-38; pg 60, ln 6-14 | 6, 9, 10, 19, 20 |
| Y | US 2007/0004806 A1 (KALVINSH et al) 04 January 2007 (04.01.2007) para [0063]; [0087]-[0094]; [0109]; [0210]-[0228] | 11, 15 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 23 November 2008 (23.11.2008) | 04 DEC 2008 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (April 2007)