(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 September 2008 (25.09.2008)

PCT

(10) International Publication Number
WO 2008/115262 A2

(51) International Patent Classification:
C07D 473/00 (2006.01) *C07D 487/04* (2006.01) *A61K 31/52* (2006.01) *A61P 35/00* (2006.01) *A61K 31/437* (2006.01)

(21) International Application Number: PCT/US2007/077967

(22) International Filing Date: 10 September 2007 (10.09.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/895,915 20 March 2007 (20.03.2007) US

(71) Applicant (*for all designated States except US*): **CURIS, INC.** [US/US]; 45 Moulton Street, Cambridge, MA 02138 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **QIAN, Changgeng** [US/MA]; 163 Old Connecticut Path, Wayland, MA 01778 (US). **CAI, Xiong** [US/MA]; 26 Concord Ave., Belmont, MA 02478 (US). **GOULD, Stephen** [US/CA]; 265 Highland Avenue, San Carlos, CA 94070 (US). **ZHAI, Haixiao** [US/MA]; 283 South Road, Bedford, MA 01730 (US).

(74) Agents: **NAKAJIMA, Suanne, K.** et al.; Elmore Patent Law Group, P.C., 209 Main Street, N. Chelmsford, MA 01863 (US).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

WO 2008/115262 A2

(54) **Title:** HSP90 INHIBITORS CONTAINING A ZINC BINDING MOIETY

(57) **Abstract:** The present invention relates to HSP90 inhibitors and their use in the treatment of cell proliferative diseases such as cancer. The said derivatives may further act as HDAC inhibitors.

HSP90 INHIBITORS CONTAINING A ZINC BINDING MOIETY

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/895,915, filed on March 20, 2007. The entire teaching of the above application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

HSP90s are ubiquitous chaperone proteins that are involved in proper protein folding and stabilization of a wide range of proteins, including key proteins involved in signal transduction, cell cycle control and transcriptional regulation. Researchers have reported that HSP90 chaperone proteins are associated with important signaling proteins, such as steroid hormone receptors and protein kinases, (e.g., Raf-1, EGFR, v-Src family kinases, Cdk4, and ErbB-2), many of which are overexpressed or mutated in various cancers (Buchner J. *TIBS*, **1999**, 24, 136 141; Stepanova, L. *et al. Genes Dev.* **1996**, 10, 1491 502; Dai, K. et al. *J. Biol. Chem.* **1996**, 271, 22030-4). Studies further indicate that certain co-chaperones, e.g., HSP70, p60/Hop/Sti1, Hip, Bag1, HSP40/Hdj2/Hsj1, immunophilins, p23, and p50, may assist HSP90 in its function (Caplan, A. *Trends in Cell Biol.* **1999**, 9, 262 68).

HSP90 has been shown by mutational analysis to be necessary for the survival of normal eukaryotic cells. However, HSP90 is overexpressed in many tumor types indicating that it may play a significant role in the survival of cancer cells and that cancer cells may be more sensitive to inhibition of HSP90 than normal cells. In fact, cancer cells typically have a large number of mutated and overexpressed oncoproteins that are dependent on HSP90 for folding. In addition, because the environment of a tumor is typically hostile due to hypoxia, nutrient deprivation, acidosis, etc., tumor cells may be especially dependent on HSP90 for survival. Moreover, inhibition of HSP90 causes simultaneous inhibition of a number of client oncoproteins, as well as hormone receptors and transcription factors making it an attractive target for an anti-cancer agent.

The two main classes of HSP90 inhibitors that are currently pursued by many companies are based on the natural antibiotic geldanamycin and synthetic purine-scaffold. Several promising geldanamycin related HSP90 inhibitors are currently in clinical trial namely, 17-allylamino 17-demethoxygeldanamycin (17-AAG), 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG) and IPI-504. Furthermore, many of the purine-scaffold

HSP90 inhibitors are showing positive preclinical results. Currently, the frontrunner in the purine-scaffold is CNF-2024, which is currently in phase 1 clinical trial.

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.

The use of HSP90 inhibitors in combination with histone deacetylases (HDAC) has been shown to produce synergistic effects. Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed HDAC's. HDAC's are represented by X genes in humans and 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 acid derivatives, PXD101, LBH589 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.

Recent advances suggest that HSP90 inhibitors in combination with HDAC inhibitors may provide advantageous results in the treatment of cancer. For example, co-treatment with HDAC inhibitor SAHA and HSP90 inhibitor 17-AAG synergistically induces apoptosis in Bcr-Abl^+ cells sensitive and resistant to STI571 (imatinib mesylate) (Rahmani, M., *et al.*, *Mol Pharmacol*, **2005**, 67:1166–1176). In addition, combination of the histone deacetylase inhibitor LBH589 and the HSP90 inhibitor17-AAG was found to be highly active against human CML-BC cells and AML cells with activating mutation of FLT-3 (George, P., *et al.*, *BLOOD*, **2005**, 105(4), 1768-1776).

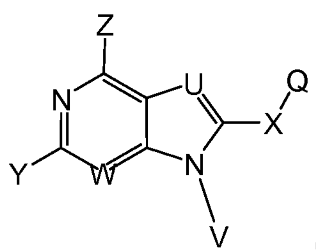
Current therapeutic regimens of the types described above attempt to address the problem of drug resistance by the administration of multiple agents. However, the combined toxicity of multiple agents due to off-target side effects as well as drug-drug interactions often limits the effectiveness of this 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. Furthermore, 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 HSP90 inhibitors containing zinc-binding moiety based derivatives that have enhanced and unexpected properties as inhibitors of HSP90 and their use in the treatment of HSP90 related diseases and disorders such as cancer.

The compounds of the present invention may further act as HDAC or matrix metalloproteinase (MMP) inhibitors by virtue of their ability to bind zinc ions. Surprisingly these compounds are active at multiple therapeutic targets and are effective for treating disease. Moreover, in some cases it has even more surprisingly been found that the compounds have enhanced activity when compared to the activities of combinations of separate molecules individually having the HSP90 and HDAC activities. In other words, the combination of pharmacophores into a single molecule may provide a synergistic effect as compared to the individual pharmacophores. More specifically, it has been found that it is possible to prepare compounds that simultaneously contain a first portion of the molecule that binds zinc ions and thus permits inhibition of HDAC and/or matrix metalloproteinase (MMP) activity and at least a second portion of the molecule that permits binding to a separate and distinct target that inhibits HSP90 and thus provides therapeutic benefit. Preferably, the compounds of the present invention inhibit both HSP90 and HDAC activity.

Accordingly, the present invention provides a compound having the general formula I:



(I)

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

U is N or CH;

W is N or CH;

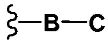
X is absent, O, S, S(O), $S(O)_2$, $N(R_8)$, CF_2 or C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, in which one or more methylene can be interrupted or terminated by O, S, SO, SO_2, $N(R_8)$., R_8 is hydrogen, acyl, aliphatic or substituted aliphatic;

Y is independently hydrogen, halogen, NO_2, CN, or lower alkyl;

Z is amino, alkylamino, or dialkylamino;

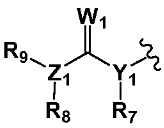
Q is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, or heterocycloalkyl;

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, $N(R_8)$, C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; substituted or unsubstituted cycloalkyl;

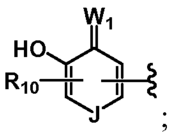
and wherein Q and/or V is further substituted by 

, where

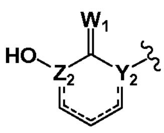
C is selected from:

(a) 

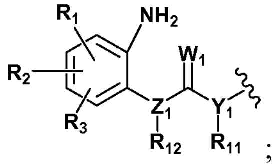
; where W_1 is O or S; Y_1 is absent, N, or CH; Z_1 is N or CH; R_7 and R_9 are independently hydrogen, OR', aliphatic or substituted aliphatic, wherein R' is hydrogen, aliphatic, substituted aliphatic or acyl; provided that if R_7 and R_9 are both present, one of R_7 or R_9 must be OR' and if Y is absent, R_9 must be OR'; and R_8 is hydrogen, acyl, aliphatic or substituted aliphatic;

(b) 

; where W_1 is O or S; J is O, NH or NCH_3; and R_{10} is hydrogen or lower alkyl;

(c) 

; where W_1 is O or S; Y_1 and Z_1 are independently N, C or CH; and

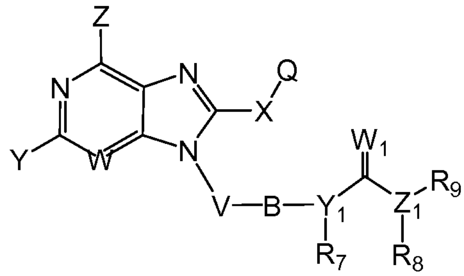
(d)  ; where Z_1, Y_1, and W_1 are as previously defined; R_{11} and R_{12} are independently selected from hydrogen or aliphatic; R_1, R_2 and R_3 are independently selected from hydrogen, hydroxy, amino, halogen, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfonyl, CF_3, CN, NO_2, N_3, sulfonyl, acyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

B is a direct bond or straight- or branched-, 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, $N(R_8)$, C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R_8 is hydrogen, acyl, aliphatic or substituted aliphatic. In one embodiment, the linker B is between 1-24 atoms, preferably 4-24 atoms, preferably 4-18 atoms, more preferably 4-12 atoms, and most preferably about 4-10 atoms.

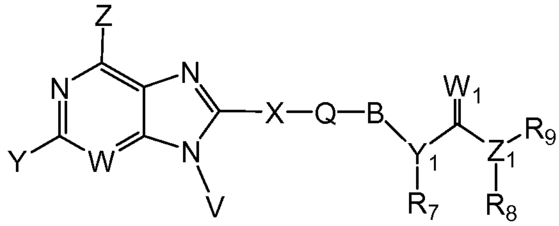
DETAILED DESCRIPTION OF THE INVENTION

In a first embodiment of the compounds of the present invention are compounds represented by formula (I) as illustrated above, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof.

In a second embodiment of the compounds of the present invention are compounds represented by formulae (II) and (III) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



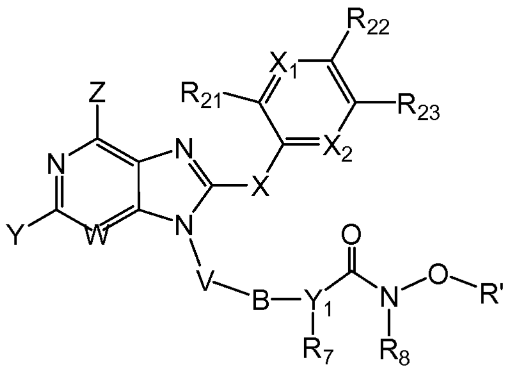
(II) or



(III)

wherein Y, Z, W, X, Q, V, B, Z_1, Y_1, W_1 and R_7-R_9 are as previously defined.

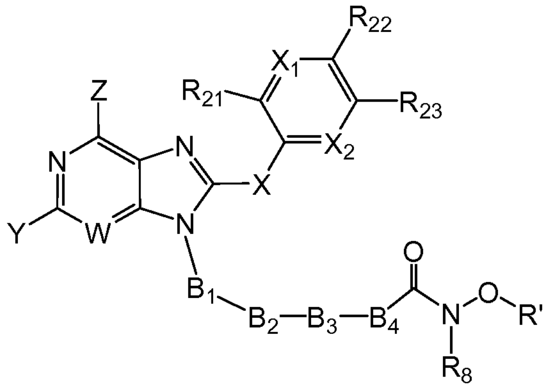
In a third embodiment of the compounds of the present invention are compounds represented by formula (IV) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(IV)

wherein X_1 and X_2 are independently CH or N; R_{21}-R_{23} are 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_{22} and R_{23} can be taken together from the carbon to which they are attached to form a fused saturated or unsaturated 5-8 membered ring optionally substituted with 0-3 heteroatom; and B, X, Y, Z, W, V, Y_1, R', R_7, and R_8 are as previously defined.

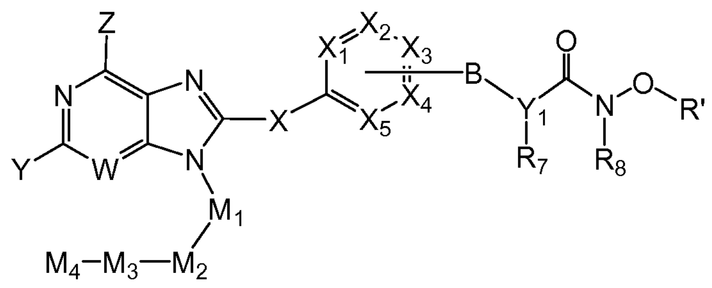
In a fourth embodiment of the compounds of the present invention are compounds represented by formula (V) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(V)

wherein X_1 and X_2 are independently CH or N; R_{21}-R_{23} are 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_{22} and R_{23} can be taken together from the carbon to which they are attached to form a fused saturated or unsaturated 5-8 membered ring optionally substituted with 0-3 heteroatom; B_1 is absent, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl or aryl; B_2 is absent, O, S, SO, SO_2, $N(R_8)$ or CO; B_3 is absent, O, S, SO, SO_2, $N(R_8)$ or CO C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; B_4 is absent , C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; X, Y, Z, W, R' and R_8 are as previously defined.

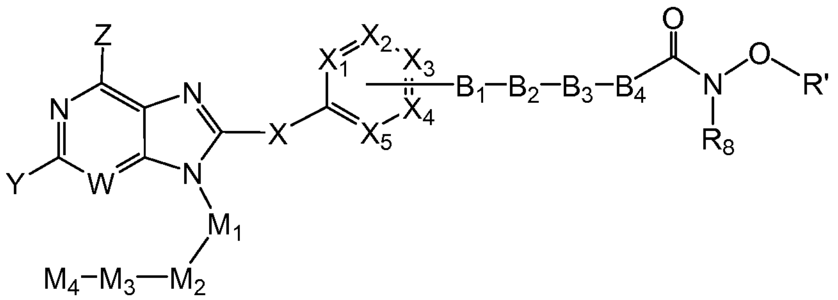
In a fifth embodiment of the compounds of the present invention are compounds represented by formula (VI) as illustrated below, or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:



(VI)

wherein X_1-X_5 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; M_1 is absent, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl; M_2 is absent, O, S, SO, SO_2, $N(R_8)$ or C=O; M_3 is absent, O, S, SO, SO_2, $N(R_8)$, C=O, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocyclic, aryl or heteroaryl; M_4 is absent, O, S, SO, SO_2, $N(R_8)$, C=O, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocyclic, aryl or heteroaryl; B, X, Z, Y, Y_1, R', R_7 and R_8 are as previously defined.

In a sixth embodiment of the 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:

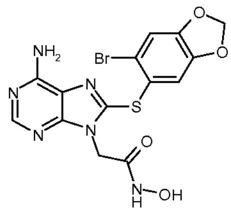
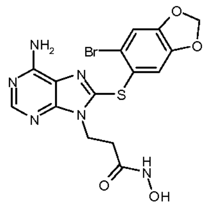
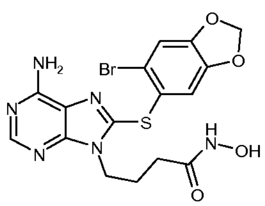
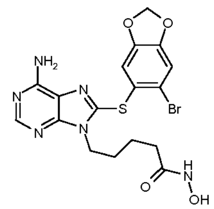
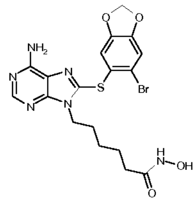
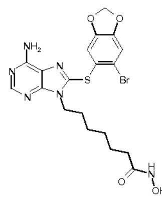
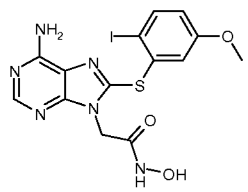


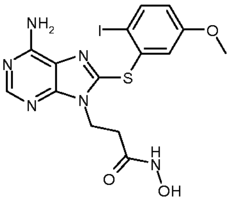
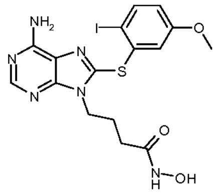
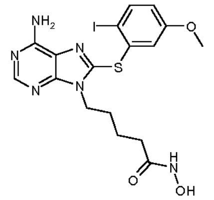
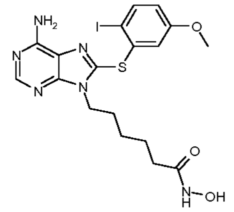
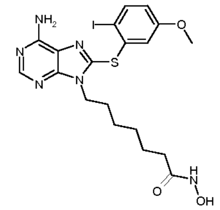
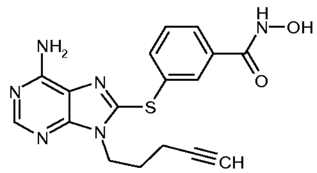
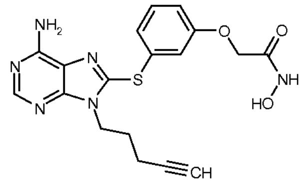
(VII)

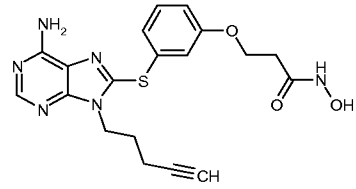
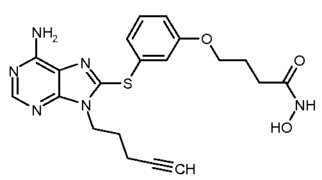
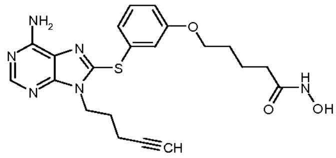
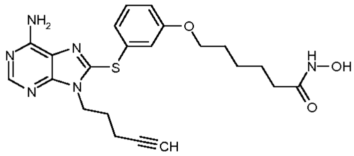
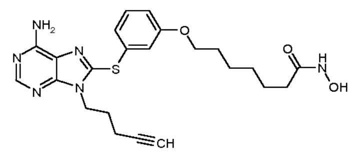
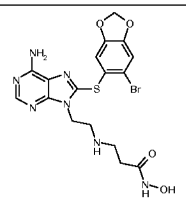
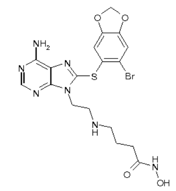
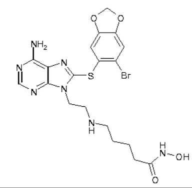
wherein X_1-X_5 are independently N or CR_{21}, where R_{21} is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, CF_3, CN, NO_2, N_3, sulfonyl, acyl, aliphatic, and substituted aliphatic; B_1 is absent, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl or aryl; B_2 is absent, O, S, SO, SO_2, $N(R_8)$ or CO; B_3 is absent, O, S, SO, SO_2, $N(R_8)$ or CO C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; B_4 is absent , C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroary; M_1 is absent, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl; M_2 is absent, O, S, SO, SO_2, $N(R_8)$ or C=O; M_3 is absent, O, S, SO, SO_2, $N(R_8)$, C=O, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocyclic, aryl or heteroaryl; M_4 is absent, O, S, SO, SO_2, $N(R_8)$, C=O, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocyclic, aryl or heteroaryl; X, Z, Y and R_8 are as previously defined.

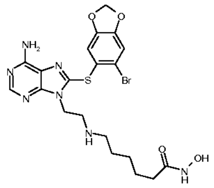
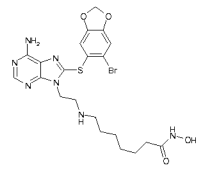
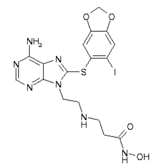
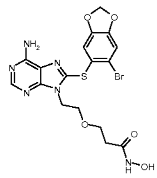
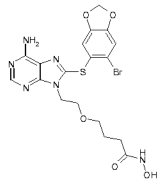
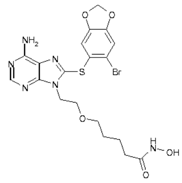
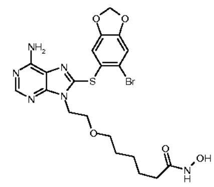
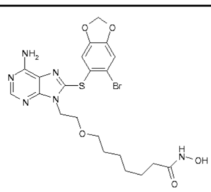
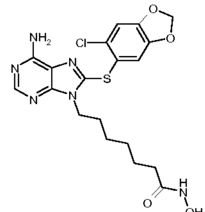
Representative compounds according to the invention are those selected from the Table A below or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

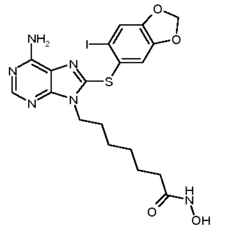
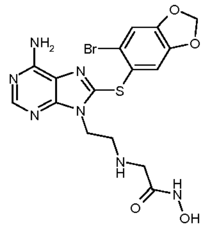
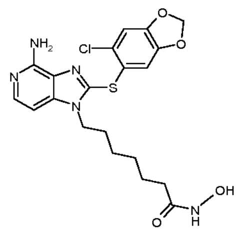
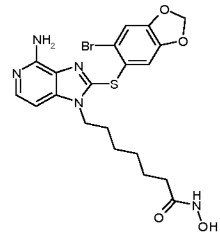
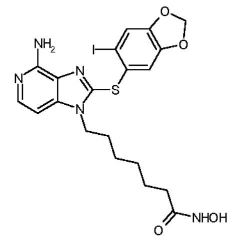
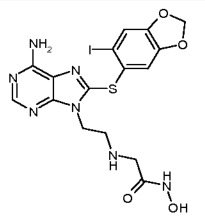
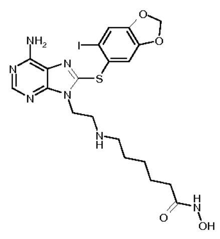
TABLE A

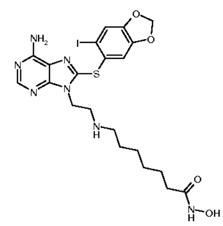
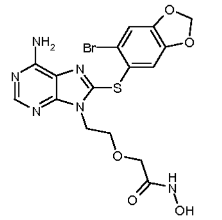
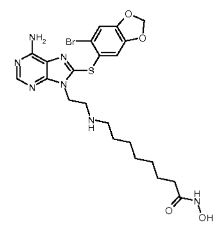
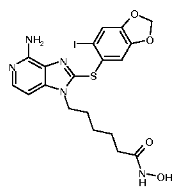
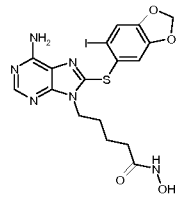
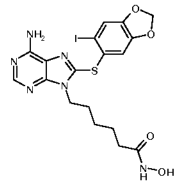
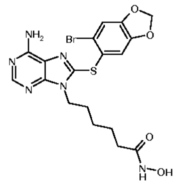
Compound #	Structure
1	
2	
3	
4	
5	
6	
7	

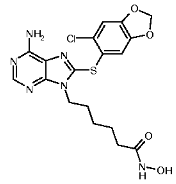
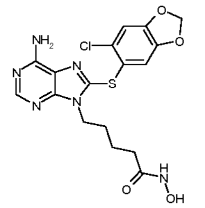
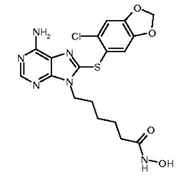
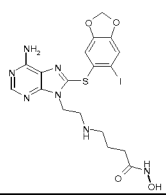
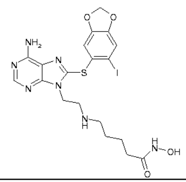
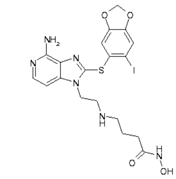
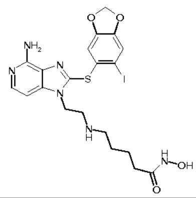
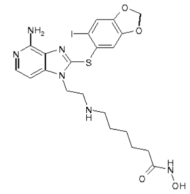
8	
9	
10	
11	
12	
13	
14	

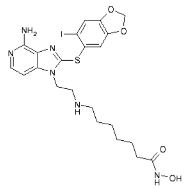
15	
16	
17	
18	
19	
20	
21	
22	

23	
24	
25	
26	
27	
28	
29	
30	
31	

32	
33	
34	
35	
36	
37	
38	

39	
40	
41	
42	
43	
44	
45	

46	
47	
48	
49	
50	
51	
52	
53	

54	

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.

"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.

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. 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_8, 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, $N(R_8)$, C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R_8 is hydrogen, acyl, aliphatic or substituted aliphatic. In one embodiment, the linker B is between 1-24 atoms, preferably 4-24 atoms, preferably 4-18 atoms, more preferably 4-12 atoms, and most preferably about 4-10 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.

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 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 "HSP90 related disease or disorder" refers to a disease or disorder characterized by inappropriate HSP90 activity or over-activity of the HSP90. Inappropriate activity refers to either; (i) HSP90 expression in cells which normally do not express HSP90; (ii) increased HSP90 expression leading to unwanted cell proliferation, differentiation and/or growth; or, (iii) decreased HSP90 expression leading to unwanted reductions in cell proliferation, differentiation and/or growth. Over-activity of HSP90 refers to either amplification of the gene encoding a particular HSP90 or production of a level of HSP90 activity which can correlate with a cell proliferation, differentiation and/or growth disorder (that is, as the level of the HSP90 increases, the severity of one or more of the symptoms of the cellular disorder increases).

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 98/43,650 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.

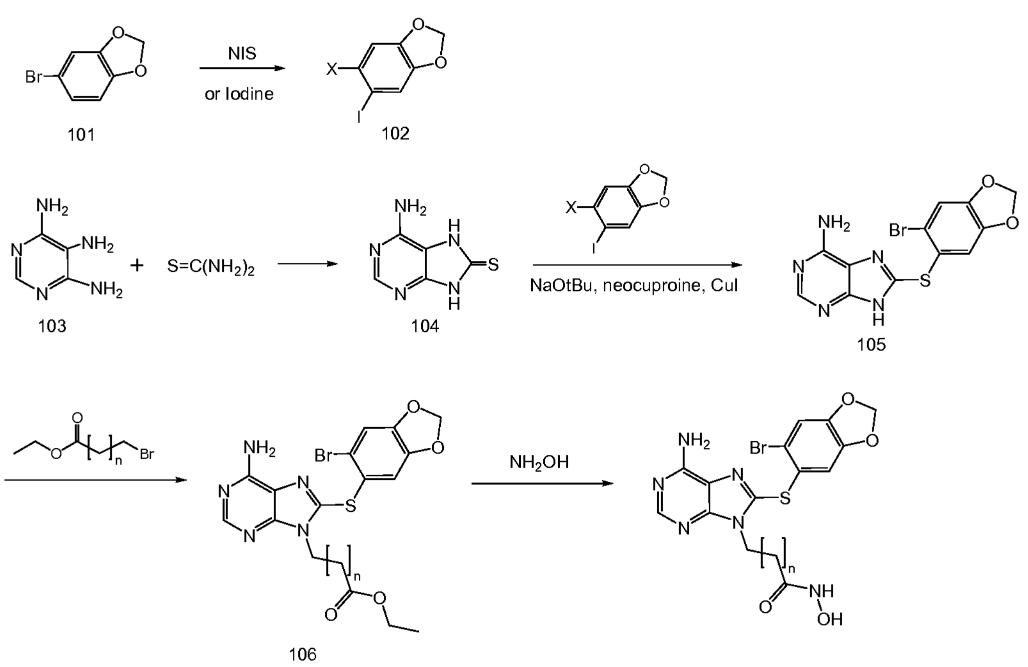
Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved 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

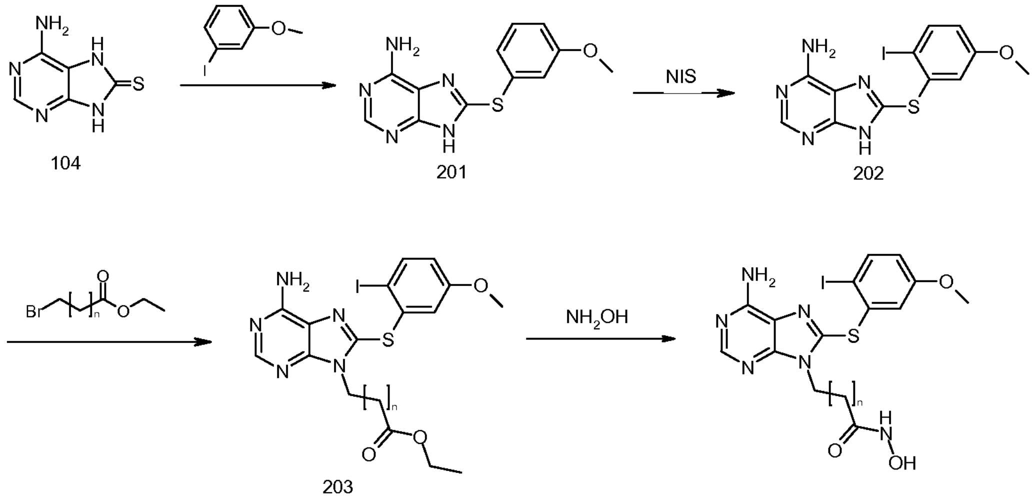
The compounds of formulae I and II, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes for making certain intermediates include, for example, those illustrated in PCT publication numbers WO02/36075, WO03/037860 and WO 06/084030. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. 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 that illustrate the methods by which the compounds of the invention may be prepared, which are intended as an illustration only and not limiting of the scope of the invention.

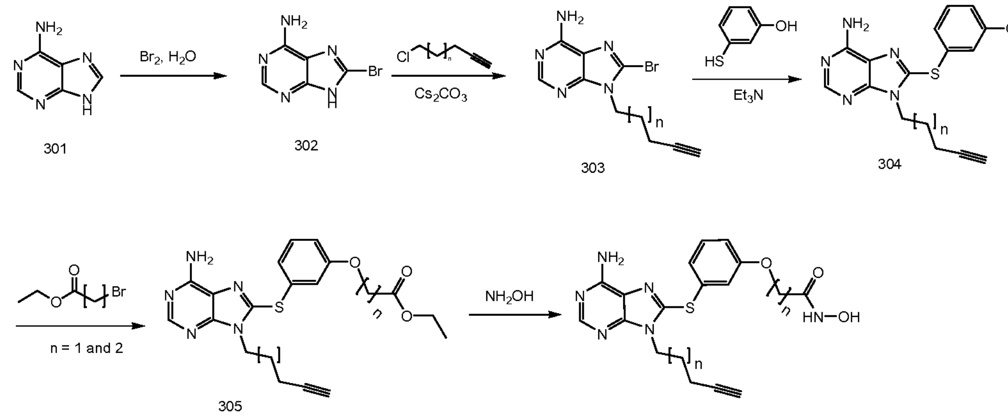
Scheme 1



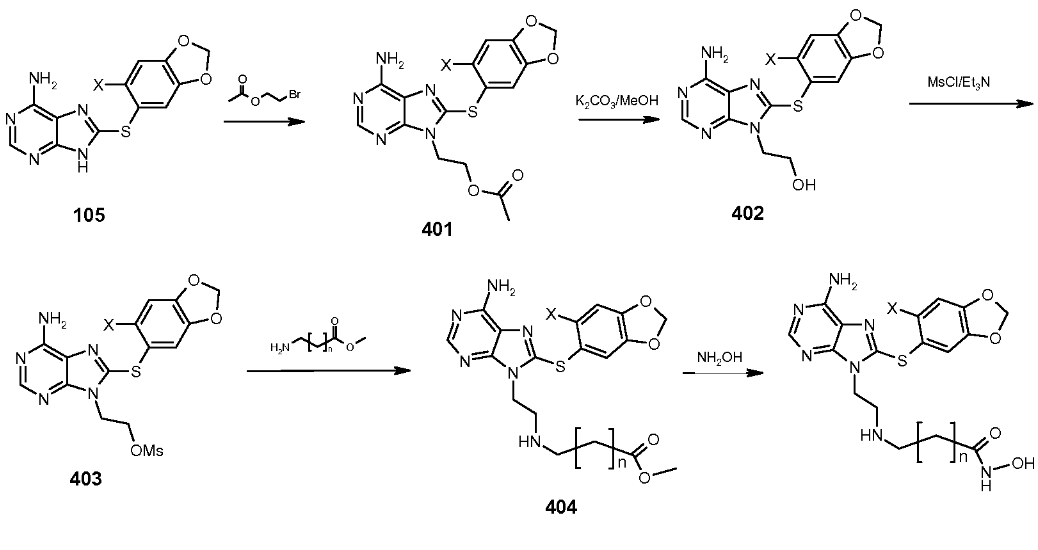
Scheme 2



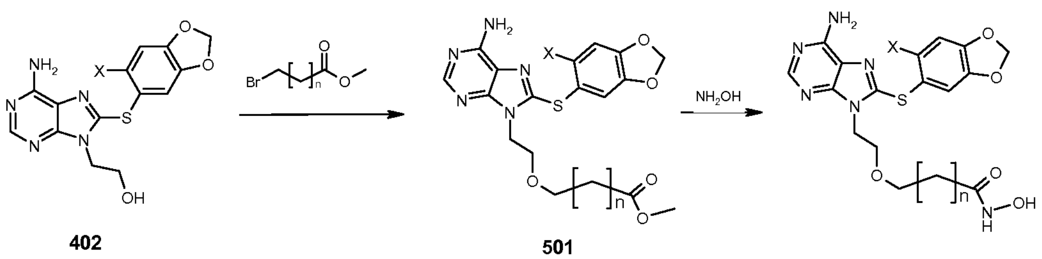
Scheme 3



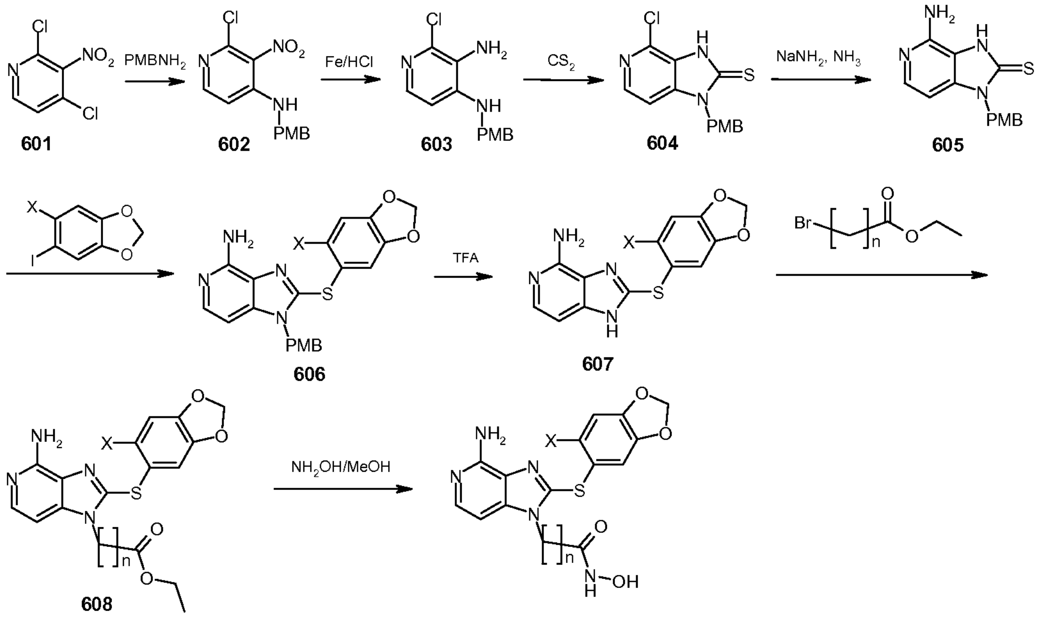
Scheme 4



Scheme 5



Scheme 6



EXAMPLES

The compounds and processes of the present invention will be better understood in connection with the following 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.

EXAMPLE 1: Preparation of 2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)–9*H*-purin-9-yl)-*N*-hydroxyacetamide (Compound 1)

Step 1a. 5-Bromo-6-iodobenzo[*d*][1,3]dioxole (Compound 102)

A solution of compound 101 (10.0 g, 50.0 mmol), anhydrous acetonitrile (150 mL), TFA (11.4 g, 100.0 mmol) and NIS (33.7 g, 150.0 mmol) was stirred at room temperature for 24 h. The solvent was removed under reduce pressure and the crude purified by column chromatography on silica gel (petroleum) to yield compound 102 as a white solid (18.5 g, 91%): ^{1}H NMR (DMSO-d_6) δ 5.99 (s, 2H), 7.10 (s, 1H), 7.26 (s, 1H).

Step 1b. 6-Amino-7*H*-purine-8(9*H*)-thione (Compound 104)

A mixture of 4,5,6-triaminopyfimidine sulfate (50.0 g, 223.0 mmol), NaOH (19.7 g, 493.0 mmol) and water (500 mL) was heated to 80 °C until all the solids dissolved. The solution was cooled to 0~5 °C and the pH was adjusted to 7.0 with 1N HCl, whereupon the free base crystallized as white needles (27.6 g, 99%). A mixture of 4,5,6-triaminopyrimidine 103 (10.0 g, 80.0 mmol), thiourea (18.3 g, 240.0 mmol) in 1,2-dichlorobenzene (60 mL) was stirred for 14 hours at 160 °C. Cooled to room temperature and the mixture solidified. Poured out the clear liquid, the solid was triturate and was diluted with brine. The mixture was stirred for 2 hours at room temperature and filtered to obtain crude product. The crude product was washed with brine and ether, dried to give title compound 104 as a light yellow solid (7.35 g, 54.9%). ^{1}H NMR (DMSO-d_6) δ 6.77 (s, 2H), 8.08 (s, 1H), 12.06 (s, 1H), 13.05 (s, 1H).

Step 1c. 8-(6-Bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (Compound 105)

A mixture of compound 104 (5.0 g, 30.0 mmol), compound 102 (14.7 g, 45.0 mmol), neocuproine hydrate (0.625 g, 3.0 mmol), CuI (0.571 g, 3.0 mmol) and NaO-*t*-Bu (3.5 g, 36.0 mmol) in anhydrous DMF (100 mL) was stirred for 24 hours at 110 °C (oil bath) under nitrogen atmosphere. The solvent was removed under high vacuum and the crude purified by column chromatography on silica gel (CH_2Cl_2/MeOH: 30/1) to provide target compound 105 as a yellow solid (5.3 g, 48.2%): LCMS: 366 $[M]^+$; ^{1}H NMR (DMSO-d_6) δ 6.09 (s, 2H), 7.02 (s, 1H), 7.11 (s, 2H), 7.35 (s, 1H), 8.06 (s, 1H).

Step 1d. Ethyl 2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)acetate (Compound 106-1)

A mixture of compound 105 (1.0 g, 2.73 mmol), Cs_2CO_3 (1.5 g, 4.64 mmol), ethyl 2-bromoacetate (0.685 g, 4.1 mmol) and anhydrous DMF (40 mL) was stirred for 6 hours at room temperature. The solvent was removed under high vacuum and the crude purified by column chromatography on silica gel (CH_2Cl_2/MeOH: 100/1) to provide the title compound 106-1 (0.65 g, 52.6%) as a white solid. LCMS: 452 $[M]^+$.

Step 1e. 2-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)-*N*-hydroxyacetamide (Compound 1)

To a stirred solution of hydroxylamine hydrochloride (4.67 g, 67.0 mmol) in methanol (24 mL) at 0°C was added a solution of potassium hydroxide (5.61 g, 100.0 mmol) in methanol (14 mL). After addition, the mixture was stirred for 30 minutes at 0°C, and was allowed to stand at low temperature. The resulting precipitate was isolated, and the solution was prepared to give free hydroxylamine.

A mixture of compound 106-1 (300 mg, 0.66 mmol) and saturated NH_2OH solution (1.77M, 5 mL) was stirred for 30 minutes at room temperature. The mixture was adjusted to pH 7.0 with AcOH and the solvent was removed. The solid was diluted with water and filtered to provide compound 1 as a white solid (85 mg, 29.2%). m.p. 230 °C (decomp.), LCMS: 439 $[M]^+$; ^1H NMR (DMSO-d_6) δ 4.84 (s, 2H), 6.04 (s, 2H), 7.00 (s, 1H), 7.26 (s, 1H), 8.04 (s, 2H), 8.24 (s, 1H), 9.11 (s, 1H), 10.98 (s, 1H).

EXAMPLE 2: Preparation of 4-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)–9*H*-purin-9-yl)-*N*-hydroxybutanamide (Compound 3)

Step 2a. Ethyl 4-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)butanoate (Compound 106-3)

The title compound 106-3 was prepared as a white solid (280 mg, 21.4%) from compound 105 (1.0 g, 2.73 mmol), Cs_2CO_3 (1.5 g, 4.64 mmol), ethyl 4-bromobutanoate (800 mg, 4.1 mol) using a procedure similar to that described for compound 106-1 (Example 1): LCMS: 480.34 $[M]^+$.

Step 2b. 4-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)-*N*-hydroxybutanamide (Compound 3)

The title compound 3 was prepared as a white solid (207 mg, 76%) from compound 106-3 (280 mg, 0.58 mmol) and NH_2OH solution (1.77M, 5mL) using a procedure similar to that described for compound 1 (Example 1): m.p. 164.7~181.0 °C, LCMS: 468 $[M+1]^+$; ^1H NMR (DMSO-d_6) δ 1.93 (s, 4H), 4.14 (t, 2H, J= 6.3 Hz), 6.07 (s, 2H), 6.84 (s, 1H), 7.34 (s, 1H), 7.35 (s, 2H), 8.12 (s, 1H), 8.70 (s, 1H), 10.35 (s, 1H).

EXAMPLE 3: Preparation of 5-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)–9*H*-purin-9-yl)-*N*-hydroxypentanamide (Compound 4)

Step 3a. Methyl 5-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)pentanoate (Compound 106-4)

The title compound 106-4 was prepared as a pale yellow solid (463 mg, 35.3%) from compound 105 (1.0 g, 2.73 mmol), Cs_2CO_3 (1.5 g, 4.64 mmol), ethyl 5-bromopentanoate (800 mg, 4.1 mol) using a procedure similar to that described for compound 106-1 (Example 1): LCMS: 480 $[M]^+$.

Step 3b. 5-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)-*N*-hydroxypentanamide (Compound 4)

The title compound 4 was prepared as a white solid (130 mg, 28%) from compound 106-4 (463 mg, 0.96 mmol) and NH_2OH solution (1.77M, 5mL) using a procedure similar to that described for compound 1 (Example 1): m.p. 191.8~195.7 °C, LCMS: 481$[M]^+$; ^{1}H NMR (DMSO-d_6) δ 1.43 (q, 2H, J_1= 6.9 Hz, J_2= 14.7 Hz), 1.68 (m, 2H), 1.94 (t, 2H, J= 7.5 Hz), 4.14 (t, 2H, J= 6.9 Hz)), 6.10 (s, 2H), 6.86 (s, 1H), 7.37 (s, 1H), 7.39 (s, 2H), 8.15 (s, 1H), 8.67 (s, 1H), 10.33 (s, 1H).

EXAMPLE 4: Preparation of 6-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)-*N*-hydroxyhexanamide (Compound 5)

Step 4a. Ethyl 6-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)hexanoate (Compound 106-5)

The title compound 106-5 was prepared as a yellow solid (0.35 g, 25.2%) from compound 105 (1.0 g, 2.73 mmol), Cs_2CO_3 (1.5 g, 4.64 mmol), ethyl 6-bromohexanoate (914 mg, 4.1 mol) using a procedure similar to that described for compound 106-1 (Example 1): LCMS: 508 $[M]^+$.

Step 4b. 6-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)-*N*-hydroxyhexanamide (Compound 5)

The title compound 5 was prepared as a pale yellow solid (200 mg, 57.6%) from compound 106-5 (350 mg, 0.7 mmol) and NH_2OH solution (1.77M, 5mL) using a procedure similar to that described for compound 1 (Example 1): m.p. 159.6~169 ℃,LCMS: 496 $[M+1]^+$; ^{1}H NMR (DMSO-d_6) δ 1.18 (q, 2H, J_1= 6.3 Hz, J_2= 14.7 Hz) 1.48 (m, 2H), 1.65 (m, 2H), 1.90 (t, 2H, J= 7.5 Hz), 4.14 (t, 2H, J= 6.9 Hz), 6.11 (s, 2H), 6.86 (s, 1H), 7.39 (s, 1H), 7.41 (s, 2H), 8.17 (s, 1H), 8.68 (s, 1H), 10.33 (s, 1H).

EXAMPLE 5: Preparation of 7-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio) –9*H*-purin-9-yl)-*N*-hydroxyheptanamide (Compound 6)

Step 5a. Ethyl 7-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)heptanoate (Compound 106-6)

The title compound 106-6 was prepared as a yellow solid (542 mg, 43.7%) from compound 105 (1.0 g, 2.73 mmol), Cs_2CO_3 (1.5 g, 4.64 mmol), ethyl 7-bromoheptanoate (972 mg, 4.1 mol) using a procedure similar to that described for compound 106-1 (Example 1): LCMS: 522 $[M]^+$.

Step 5b. 7-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)-*N*-hydroxyheptanamide (Compound 6)

The title compound 6 was prepared as a white solid (130 mg, 24.8%) from compound 106-6 (542 mg, 0.66 mmol) and NH_2OH solution (1.77M, 5mL) using a procedure similar to that described for compound 1 (Example 1): m.p. 193.9~193.9 °C, LCMS: 511 $[M+1]^+$; ^{1}H NMR (DMSO-d^6) δ 1.20 (m, 4H), 1.43 (m, 2H), 1.62 (m, 2H), 1.90 (t, 2H, *J*= 7.5 Hz), 4.13 (t, 2H, *J*= 6.9 Hz), 6.10 (s, 2H), 7.00 (s, 1H), 6.83 (s, 1H), 7.37 (s, 1H), 7.42 (s, 2H), 8.16 (s, 1H), 8.65 (s, 1H), 10.32 (s, 1H).

EXAMPLE 6: Preparation of 6-(6-amino-8-(2-iodo-5-methoxyphenylthio)-9*H*-purin-9-yl)-*N*-hydroxyhexanamide (Compound 11)

Step 6a. 8-(3-Methoxyphenylthio)-9*H*-purin-6-amine (Compound 201)

A mixture of compound 104 (2.0 g, 12 mmol), 1-iodo-3-methoxybenzene (4.21 g, 18 mmol), 1,10-phenanthroline hydrate (0.24 g, 1.2 mmol), CuI (0.23 g, 1.2 mmol) and NaO*t*-Bu (1.38 g, 14.4 mmol) in anhydrous DMF (20 mL) was stirred for 24 h at 110 °C (oil bath) under nitrogen atmosphere. The solvent was removed under high vacuum and the crude purified by column chromatography on silica gel (CH_2Cl_2/MeOH=30/1) to provide target compound 201 as a yellow solid (0.86 g, 26%): LCMS: 274 $[M+1]^+$.

Step 6b. 8-(2-Iodo-5-methoxyphenylthio)-9*H*-purin-6-amine (Compound 202)

A mixture of compound 201 (0.69 mg, 2.52 mmol), NIS (3.4 g, 15.12 mmol), trifluoroacetic acid (1.44 g, 12.6 mmol) and acetonitrile (150 mL) was stirred at room temperature for 4 h. The solvent was removed and the residue was suspended in saturated aqueous $NaHCO_3$ solution, the resulting solid was collected and dried to give compound 202 as a pale yellow solid (810 mg, 80%): LCMS: 400 $[M+1]^+$.

Step 6c. Ethyl 6-(6-amino-8-(2-iodo-5-methoxyphenylthio)-9H-purin-9-yl)hexanoate (Compound 203-11)

A mixture of compound 202 (102 mg, 0.25 mmol), Cs_2CO_3 (98 mg, 0.3 mmol), ethyl 6-bromohexanoate (56 mg, 0.25 mol) and anhydrous DMF (5 mL) was stirred for 2 h at 60 °C. The solvent was removed under high vacuum and the crude purified by column chromatography on silica gel (ethyl acetate/petroleum ether =1/2) to give compound 203-11 as a yellow solid (52 mg, 38%). LCMS: 542 $[M+1]^+$.

Step 6d. 6-(6-Amino-8-(2-iodo-5-methoxyphenylthio)-9*H*-purin-9-yl)-*N*-hydroxyhexanamide (Compound 11)

To a stirred solution of hydroxylamine hydrochloride (4.67 g, 67 mmol) in methanol (24 mL) at 0°C was added a solution of potassium hydroxide (5.61 g, 100 mmol) in methanol (14 mL). After addition, the mixture was stirred for 30 minutes at 0°C, and was allowed to stand at low temperature. The resulting precipitate was isolated, and the solution was prepared to give free hydroxylamine.

A mixture of compound 203-11 (50 mg, 0.09 mmol) and freshly prepared NH_2OH/MeOH (1.77 M, 3 mL, 5.3 mmol) was stirred at room temperature for 15 min. The reaction mixture was neutralized with AcOH, and the solvent was removed to give crude product. The crude product was purified by *pre*-HPLC to give the title compound 11 as a white solid (15 mg, 31%): LCMS: 529 $[M+1]^+$, ^{1}H NMR (DMSO-d_6): δ 1.18 (m, 2H), 1.42 (m, 2H), 1.64 (m, 2H), 1.86 (t, J = 6.9 Hz, 2H), 3.62 (s, 3H), 4.12 (t, J = 7.2 Hz, 2H), 6.49 (d, J = 2.7 Hz, 1H), 6.70 (dd, J_1 = 3.0 Hz, J_2 = 8.4 Hz, 1H), 7.51 (s, 2H), 7.78 (d, J = 8.1 Hz, 1H), 8.19 (s, 1H), 8.65 (s, 1H), 10.29 (s, 1H).

EXAMPLE 7: Preparation of 7-(6-amino-8-(2-iodo-5-methoxyphenylthio)-9*H*-purin-9-yl)-*N*-hydroxyheptanamide (Compound 12)

Step 7a: Ethyl 7-(6-amino-8-(2-iodo-5-methoxyphenylthio)-9*H*-purin-9-yl)heptanoate (Compound 203-12)

The title compound 203-12 was prepared as a yellow solid (72 mg, 22%) from compound 202 (239 mg, 0.6 mmol), Cs_2CO_3 (391 mg, 1.2 mmol), ethyl 7-bromoheptanoate (156 mg, 0.66 mol) and anhydrous DMF (5 mL) using a procedure similar to that described for compound 203-11 (Example 6): LCMS: 556 $[M+1]^+$.

Step 7b. 7-(6-Amino-8-(2-iodo-5-methoxyphenylthio)-9*H*-purin-9-yl)-*N*-hydroxyheptanamide (Compound 12)

The title compound 12 was prepared as a pale white solid (11 mg, 16%) from compound 203-12 (71 mg, 0.13 mmol) and NH_2OH/MeOH (1.77 M, 3 mL, 5.3 mmol) using a procedure similar to that described for compound 11 (Example 6): LCMS: 543 $[M+1]^+$, ^1H NMR (DMSO-d_6): δ 1.16 (m, 4H), 1.37 (m, 2H), 1.61 (m, 2H), 1.87 (t, J = 7.8 Hz, 2H), 3.61 (s, 3H), 4.12 (t, J = 6.9 Hz, 2H), 6.49 (d, J = 3.0 Hz, 1H), 6.70 (dd, J_1 = 2.7 Hz, J_2 = 8.7 Hz, 1H), 7.51 (s, 2H), 7.78 (d, J = 8.7 Hz, 1H), 8.19 (s, 1H), 8.64 (s, 1H), 10.30 (s, 1H).

EXAMPLE 8: Preparation of 2-(3-(6-amino-9-(pent-4-ynyl)-9*H*-purin-8-ylthio) phenoxy)-*N*-hydroxyacetamide (Compound 14)

Step 8a. 8-Bromo-9*H*-purin-6-amine (compound 302)

Bromine (9.36 g , 58.5 mmol) was added to H_2O (25 mL) with stirring, then the compound 301 (1.1 g , 8.1 mmol) was added into the solution. The mixture was stirred at room temperature overnight. The excess bromine was removed and the solvent was evaporated to give compound 302 as a light yellow solid (1.28 g, 74%).. The crude product was used without further purification: LC-MS: 214 $[M+1]^+$.

Step 8b. 8-Bromo-9-(pent-4-ynyl)-9*H*-purin-6-amine (Compound 303-14)

A mixture of compound 302 (1.7 g, 8.1 mmol), 5-chloropent-1-yne (1.7 g, 16.2 mmol), Cs_2CO_3 (5.8 g, 17.8 mmol) and 25 mL of DMF was heated to 85 °C and stirred overnight. Then DMF was removed in vacuo. The residue was purified by column chromatography (dichloromethane : methanol = 40:1) to give compound 303-14 (512 mg, 23%) as a white solid: LC-MS: 280 $[M+1]^+$, ^1H NMR (DMSO-d_6) δ 1.91 (m, 2H) , 2.22 (m, 2H), 2.79 (t, J = 2.4 Hz, 1H), 4.18 (t, J = 7.2 Hz, 2H), 7.36 (s, 2H), 8.11 (s, 1H).

Step 8c. 3-(6-Amino-9-(pent-4-ynyl)-9*H*-purin-8-ylthio)phenol (Compound 304-14)

3-Mercaptophenol (134 mg, 1.1 mmol)and $NH_3 \cdot H_2O$ (60 mg, 3.5 mmol) were dissolved in 2 mL of methanol, the mixture was stirred at 70 °C for 0.5 hour. Then, compound 303-14 (200 mg, 0.7 mmol) in 3 mL of methanol was added into the mixture. The mixture was stirred at 60 °C overnight. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (CH_2Cl_2: MeOH = 40:1) to give compound 304-14 (170 mg, 74%) as a white solid. LC-MS: 326 $[M+1]^+$, ^1H NMR (DMSO-d_6); δ 1.80 (m, 2H) , 2.22 (m, 2H)，2.76 (t, J = 2.4 Hz, 1H), 4.18 (t, J = 7.2 Hz, 2H), 6.59~6.75 (m, 3H), 7.14 (t, J = 7.5 Hz, 1H), 7.44 (b, 2H), 8.15 (s, 1H)，9.66 (s, 1H).

Step 8d. Methyl 2-(3-(6-amino-9-(pent-4-ynyl)-9*H*-purin-8-ylthio)phenoxy) acetate (Compound 305-14)

A mixture of compound 304-14 (120 mg, 0.37 mmol), K_2CO_3 (153 mg, 1.1 mmol) and ethyl 2-bromoacetate (92 mg, 0.55 mmol) was dissolved in 5 mL of DMF. The mixture was heated to 70 °C and stirred for 4 hours. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (CH_2Cl_2: MeOH = 20:1) to give compound 305-14 as a white solid (86 mg, 59%): LC-MS: 398 $[M+1]^+$.

Step 8e. 2-(3-(6-Amino-9-(pent-4-ynyl)-9*H*-purin-8-ylthio)phenoxy)-*N*-hydroxyacetamide (Compound 14)

The title compound 14 was prepared as a white solid (50 mg, 57 %) from compound 305-14 (86 mg, 0.22 mmol) using a procedure similar to that described for compound 11 (Example 6): m.p. 165~166 °C, LC-MS: 399 $[M+1]^+$, ^{1}H NMR (DMSO-d_6): δ 1.84 (m, 2H)，2.15 (m, 2H)，2.78 (t, J = 2.4 Hz, 1H), 4.19 (t, J = 7.2 Hz, 2H), 4.44 (s, 2H), 6.84~6.96 (m, 3H), 7.26 (m, 1H), 7.43 (b, 2H), 8.15 (s, 1H)，8.96 (s, 1H), 10.81 (s, 1H).

EXAMPLE 9: Preparation of 4-(3-(6-amino-9-(pent-4-ynyl)-9*H*-purin-8-ylthio) phenoxy)-*N*-hydroxybutanamide (Compound 16)

Step 9a. Ethyl 4-(3-(6-amino-9-(pent-4-ynyl)-9*H*-purin-8-ylthio)phenoxy)butanoate (Compound 305-16)

The title compound 305-16 was prepared as a white solid (120 mg, 64 %) from compound 304 (135 mg, 0.42 mmol), K_2CO_3 (165 mg, 1.2 mmol) and ethyl 4-bromobutanoate (123 mg, 0.63 mmol) using a procedure similar to that described for compound 305-14 (Example 8): LC-MS: 440 $[M+1]^+$.

Step 9b. 4-(3-(6-Amino-9-(pent-4-ynyl)-9*H*-purin-8-ylthio)phenoxy)-*N*-hydroxybutanamide (Compound 16)

The title compound 16 was prepared as a white solid (50 mg, 48 %) from compound 305-16 (110 mg, 0.25 mmol) using a procedure similar to that described for compound 11 (Example 6): m.p. 159~162 °C, LC-MS: 427 $[M+1]^+$, ^1H NMR (DMSO-d_6): δ 1.83 (m, 4H) , 2.04~2.18 (m, 4H) , 2.77(t, J = 2.4 Hz, 1H), 3.90 (t, J = 6.0 Hz, 2H), 4.20 (t, J = 8.1 Hz, 2H), 6.80~6.90 (m, 3H), 7.24 (m, 1H), 7.42 (b, 2H), 8.14 (s, 1H) , 8.68 (s, 1H), 10.37 (s, 1H).

EXAMPLE 10: Preparation of 6-(3-(6-amino-9-(pent-4-ynyl)-9*H*-purin-8-ylthio)phenoxy)-*N*-hydroxyhexanamide (Compound 18)

Step 10a. Ethyl 6-(3-(6-amino-9-(pent-4-ynyl)-9*H*-purin-8-ylthio)phenoxy)hexanoate (Compound 305-18)

The title compound 305-18 was prepared as a white solid (238 mg, 85.4 %) from compound 304 (194 mg, 0.60 mmol), K_2CO_3 (247 mg, 1.8 mmol) and ethyl 6-bromohexanoate (143 mg, 0.89 mmol) using a procedure similar to that described for compound 305-14 (Example 8): LC-MS: 468 $[M+1]^+$.

Step 10b. 6-(3-(6-Amino-9-(pent-4-ynyl)-9*H*-purin-8-ylthio)phenoxy)-*N*-hydroxyhexanamide (Compound 18)

The title compound 18 was prepared as a white solid (50 mg, 45.8 %) from compound 305-18 (110 mg, 0.24 mmol) using a procedure similar to that described for compound 11 (Example 6):

m.p. 169.1~172.1 °C, LC-MS: 455 $[M+1]^+$, ^1H NMR (DMSO-d_6): δ 1.33 (m, 2H) , 1.49 (m, 2H) , 1.63 (m, 2H) , 1.81 (m, 2H) , 1.95 (t, J = 7.2 Hz, 2H), 2.17 (m, 2H), 2.81(t, J = 2.4 Hz, 1H), 3.89 (t, J = 6.0 Hz, 2H), 4.22 (t, J = 7.5 Hz, 2H), 6.82~6.89 (m, 3H), 7.24 (m, 1H), 7.48 (b, 2H), 8.16 (s, 1H) , 8.69 (s, 1H), 10.35 (s, 1H).

EXAMPLE 11: Preparation of 3-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethylamino)-*N*-hydroxypropanamide (Compound 20)

Step 11a. 2-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethyl acetate (Compound 401-20)

A mixture of compound 105-1 (8.66 g, 23.65 mmol), Cs_2CO_3 (11.53 g, 35.47 mmol), 2-bromoethyl acetate (5.92 g, 35.47 mmol) and anhydrous DMF (150 mL) was stirred for 2 h at 50 °C. The solvent was removed under high vacuum and the crude purified by column chromatography on silica gel (CH_2Cl_2/MeOH=60/1) to provide target compound 401-20 as a pale yellow solid (7.0 g, 65.4%): LCMS: 452 $[M+1]^+$.

Step 11b. 2-(6-Amino-8-(6-bromobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethanol (compound 402-20)

A suspension of compound 401-20 (4.0 g, 8.84 mmol) in MeOH (80 mL) was treated with K_2CO_3 (3.67 g, 26.53 mmol) at 50 °C for 1 h. The reaction was filtered and concentrated to afforded the title compound 402-20 as a pale white solid (1.3 g, 35.7%): LCMS: 410 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 3.72 (t, 2H, *J*= 5.4 Hz), 4.28 (t, 2H, *J*= 5.4 Hz), 5.02 (t, 1H, *J*=5.4 Hz), 6.10 (s, 2H), 6.90 (s, 1H), 7.35 (s, 3H), 8.16 (s, 1H).

Step 11c. 2-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethyl methanesulfonate (Compound 403-20)

The compound 402-20 (0.6 g, 1.46 mmol) was dissolved in hot anhydrous dioxane (35 mL). The solution was cooled to 45 °C and was treated with NEt_3 (0.61 mL, 4.39 mmol) and MsCl (251.2 mg, 2.2 mmol) for 20 min. The mixture was concentrated and purified by column chromatography on silica gel (CH_2Cl_2/MeOH=60/1) to provide compound 403-20 as a pale yellow solid (0.68 g, 95.5%): LCMS: 487 $[M+1]^+$.

Step 11d. Methyl 3-(2-(6-amino-8-(6-bromobenzo[d][1,3]dioxol-5-ylthio)-9H-purin -9-yl)ethylamino)propanoate (Compound 404-20)

Methyl 3-aminopropanoate hydrochloride (494.5 mg, 3.54 mmol) was dissolved in DMF (4.8 mL) and NEt_3 (0.74 mL, 5.31 mmol) was then added to the above solution. The mixture was stirred for 0.5 h at 0 °C and then compound 403-20 (173 mg, 0.35 mmol) was added. The reaction mixture was stirred for 12 h at 80 °C. The DMF was removed under high vacuum and the crude product purified by column chromatography on silica gel (CH_2Cl_2/MeOH=50/1) to provide target compound 404-20 as a viscous yellow solid (121 mg, 69%): LCMS: 495 $[M+1]^+$.

Step 11e. 3-(2-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethylamino)-*N*-hydroxypropanamide (Compound **20**)

The title compound 20 was prepared as a pale white solid (33 mg, 16.5 %) from compound 404-20 (200 mg, 0.40 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 10 mL) using a procedure similar to that described for compound 11 (Example 6): LCMS: 496 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 2.05 (t, 2H, *J*= 6.9 Hz), 2.69 (t, 2H, *J*= 6.9 Hz), 2.83 (t, 2H, J= 6.3 Hz), 4.22 (t, 2H, *J*= 6.3 Hz), 6.10 (s, 2H), 6.88 (s, 1H), 7.36 (s, 1H), 7.37 (s, 2H), 8.16 (s, 1H).

EXAMPLE 12: Preparation of 6-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethylamino)-*N*-hydroxyhexanamide (Compound 23)

Step 12a. Methyl 6-(2-(6-amino-8-(6-bromobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)hexanoate (Compound 404-23)

The title compound 404-23 was prepared as a viscous yellow solid (117 mg, 23.6 %) from compound 403-20 (450 mg, 0.92 mmol), methyl 6-aminohexanoate hydrochloride (1.67 g, 9.21 mmol) and KOH (0.52 g, 9.21 mmol) in MeOH (1.5 mL) using a procedure similar to that described for compound 404-20 (Example 11): LCMS: 537 $[M+1]^+$.

Example 12b. 6-(2-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethylamino)-*N*-hydroxyhexanamide (Compound 23)

The title compound 23 was prepared as a pale white solid (22 mg, 18.8 %) from compound 404-23 (117 mg, 0.22 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 4 mL) using a procedure similar to that described for compound 11 (Example 6): LCMS: 538 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 1.26 (m, 4H), 1.43 (m, 2H), 1.70 (s, 1H), 1.90 (t, 2H, *J*= 7.2 Hz), 2.44 (t, 2H, *J*= 7.2 Hz), 2.81 (t, 2H, *J*= 6.0 Hz), 4.22 (t, 2H, *J*= 6.0 Hz), 6.08 (s, 2H), 6.84 (s, 1H), 7.34 (s, 1H), 7.35 (s, 2H), 8.15 (s, 1H), 8.65 (s, 1H), 10.31 (s, 1H).

EXAMPLE 13: Preparation of 7-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethylamino)-*N*-hydroxyheptanamide (Compound 24)

Step 13a. Ethyl 7-(2-(6-amino-8-(6-bromobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)heptanoate (Compound 404-24)

The title compound 404-24 was prepared as a viscous yellow solid (118 mg, 27 %) from compound 403-20 (373 mg, 0.76 mmol), ethyl 7-aminoheptanoate hydrochloride (1.6 g, 7.6 mmol) and KOH (0.43 g, 7.6 mmol) in MeOH (1.0 mL) using a procedure similar to that described for compound 404-20 (Example 11): LCMS: 565 $[M+1]^+$.

Step 13b. 7-(2-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl) ethylamino)-*N*-hydroxyheptanamide (Compound 24)

The title compound 24 was prepared as a pale white solid (47 mg, 40.5 %) from compound 404-24 (118 mg, 0.21 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 4 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 193~197 °C. LCMS: 552 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 1.17 (m, 6H), 1.44 (m, 2H), 1.91 (t, 2H, *J*= 7.2 Hz), 2.43 (t, 2H, *J*= 7.2 Hz), 2.82 (t, 2H, *J*= 6.0 Hz), 4.22 (t, 2H, *J*= 6.0 Hz), 6.08 (s, 2H), 6.83 (s, 1H), 7.34 (s, 1H), 7.36 (s, 2H), 8.15 (s, 1H), 8.65 (s, 1H), 10.31 (s, 1H).

EXAMPLE 14: Preparation of 6-(2-(6-amino-8-(6-iodobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethylamino)-*N*-hydroxyhexanamide (Compound 38)

Step 14a. 8-(6-Iodobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-6-amine (compound 105-38)

A mixture of compound 104 (0.8 g, 4.78 mmol), 5,6-diiodobenzo[*d*][1,3]dioxole (2.68 g, 7.18 mmol), neocuproine hydrate (0.10 g, 0.48 mmol), CuI (0.091 g, 0.48 mmol) and NaO-*t*-Bu (0.55 g, 5.74 mmol) in anhydrous DMF (40 mL) was stirred for 24 h at 110 °C (oil bath) under nitrogen atmosphere. The solvent was removed under high vacuum and the crude purified by column chromatography on silica gel (CH_2Cl_2/MeOH=30/1) to provide target compound 105-38 as a yellow solid (0.35 mg, 17.6%): LCMS: 414 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 6.09 (s, 2H), 7.01 (s, 1H), 7.22 (s, 2H), 7.51 (s, 1H), 8.08 (s, 1H), 13.20 (s, 1H).

Step 14b. 2-(6-Amino-8-(6-iodobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethyl acetate (Compound 401-38)

A mixture of compound 105-38 (3.89 g, 9.41 mmol), Cs_2CO_3 (3.68 g, 11.3 mmol), 2-bromoethyl acetate (1.89 g, 11.3 mmol) and anhydrous DMF (50 mL) was stirred for 2 h at 50 °C. The solvent was removed under high vacuum and the crude purified by column chromatography on silica gel (CH_2Cl_2/MeOH=60/1) to provide target compound 401-38 as a pale yellow solid (2.95 g, 62.8%): LCMS: 500 $[M+1]^+$.

Step 14c. 2-(6-Amino-8-(6-iodobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethanol (Compound 402-38)

A suspension of compound 401-38 (2.95 g, 5.91 mmol) in MeOH (70 mL) was treated with K_2CO_3 (0.98 g, 7.1 mmol) at 50 °C for 1 h. The reaction was filtered and concentrated to afforded the title compound 402-38 as a pale white solid (1.33 g, 49.3%): LCMS: 458 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 3.72 (t, 2H, *J*= 5.4 Hz), 4.27 (t, 2H, *J*= 5.4 Hz), 5.02 (t, 1H, *J*=5.4 Hz), 6.07 (s, 2H), 6.88 (s, 1H), 7.34 (s, 2H), 7.47(s, 1H), 8.15 (s, 1H).

Step 14d. 2-(6-Amino-8-(6-iodobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethyl methanesulfonate (Compound 403-38)

The compound 402-38 (0.52 g, 1.13 mmol) was dissolved in hot anhydrous dioxane (25 mL). The solution was cooled to 45 °C and was treated with NEt_3 (0.47 mL, 3.39 mmol) and MsCl (194 mg, 1.70 mmol) for 20 min. The mixture was concentrated and purified by column chromatography on silica gel (CH_2Cl_2/MeOH=60/1) to provide compound 403-38 as a pale yellow solid (585 mg, 96.7%): LCMS: 536 $[M+1]^+$.

Step 14e. Methyl 6-(2-(6-amino-8-(6-iodobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)hexanoate (Compound 404-38)

A solution of KOH (785 mg, 14 mmol) in MeOH (4 ml) was added dropwise into a solution of methyl 6-aminohexanoate hydrochloride (2543 mg, 14 mmol) in MeOH (4 ml) at 0°C. The mixture was stirred for 0.5 h at 0 °C, filtrated and the filtrate was used directly in next step. The compound 403-38 (500 mg, 0.934 mmol) and NEt_3 (472 mg, 4.67 mmol) was added to the above filtrate. The resulting mixture was stirred at 65 °C overnight. The solution was concentrated and purified by column chromatography on silica gel (CH_2Cl_2/MeOH=150/1) to provide compound 404-38 as a pale white solid (77 mg, 14%): LCMS: 585 $[M+1]^+$.

Step 14f. 6-(2-(6-Amino-8-(6-iodobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)-N-hydroxyhexanamide (Compound 38)

The title compound 38 was prepared as a pale white solid (17 mg, 22 %) from compound 404-38 (77 mg, 0.13 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 3 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 154~160 °C, LCMS: 586 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 1.23 (m, 4H) 1.44 (m, 2H), 1.91 (t, 2H, *J* = 7.4 Hz), 2.45 (t, 2H), 2.81 (t, 2H, *J* = 6.3 Hz), 4.21 (t, 2H, *J* = 6.8 Hz), 6.06 (s, 2H), 6.82 (s, 1H), 7.35 (s, 2H), 7.47 (s, 1H), 8.15 (s, 1H), 8.64 (s, 1H).

EXAMPLE 15: Preparation of 7-(2-(6-amino-8-(6-iodobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)-N-hydroxyheptanamide (Compound 39)

Step 15a. Ethyl 7-(2-(6-amino-8-(6-iodobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)heptanoate (Compound 404-39)

The title compound 404-39 was prepared as a pale white solid (100 mg, 17 %) from compound 403-14 (500 mg, 0.93 mmol), ethyl 7-aminoheptanoate hydrochloride (2936 mg, 14 mmol) and KOH (785 mg, 14 mmol) in MeOH (8.0 mL) using a procedure similar to that described for compound 404-38 (Example 14): LCMS: 613 $[M+1]^+$.

Step 15b. 7-(2-(6-Amino-8-(6-iodobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)-N-hydroxyheptanamide (Compound 39)

The title compound 39 was prepared as a pale white solid (30 mg, 31 %) from compound 404-39 (100 mg, 0.16 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 3 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 106~115 °C LCMS: 600 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 1.26 (m, 6H) 1.47 (m, 2H), 1.69 (s, 1H),1.91 (t, 2H, J = 7.4 Hz), 2.44 (t, 2H), 2.81 (t, 2H, J = 6.6 Hz), 4.21 (t, 2H, J = 6.3 Hz), 6.06 (s, 2H), 6.82 (s, 1H), 7.36 (s, 2H), 7.47 (s, 1H), 8.15 (s, 1H), 8.65 (s, 1H), 10.30 (s, 1H).

EXAMPLE 16: Preparation of 8-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)-*N*-hydroxyoctanamide (Compound 41)

Step 16a. Methyl 8-(2-(6-amino-8-(6-bromobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)octanoate (Compound 404-41)

The title compound 404-41 was prepared as a viscous pale yellow solid (210 mg, 44 %) from compound 403-20 (410 mg, 0.84 mmol), Methyl 8-aminooctanoate hydrochloride (760 mg, 3.63 mmol) and KOH (203 mg, 3.63 mmol) in MeOH (6.0 mL) using a procedure similar to that described for compound 404-20 (Example 11): LC-MS: 566.8 $[M+1]^+$.

Step 16b. 8-(2-(6-Amino-8-(6-bromobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethylamino)-N-hydroxyoctanamide (Compound 41)

The title compound 41 was prepared as a pale white solid (50 mg, 24 %) from compound 404-41 (210 mg, 0.37 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 3.5 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 173~175 °C, LC-MS: 567.8 $[M+1]^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.18 (m, 6H), 1.26 (m, 2H), 1.45 (m, 2H), 1.69 (s, 1H), 1.91 (t, 2H, J= 7.2 Hz), 2.44 (t, 2H, J= 6.3 Hz), 2.82 (t, 2H, J= 6.3 Hz), 4.22 (t, 2H, *J*= 6.3 Hz), 6.08 (s, 2H), 6.83 (s, 1H), 7.34 (s, 1H), 7.35 (s, 2H), 8.15 (s, 1H), 8.64 (s, 1H), 10.30 (s, 1H).

EXAMPLE 17: Preparation of 4-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethoxy)-*N*-hydroxybutanamide (Compound 27)

Step 17a. Ethyl 4-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethoxy)butanoate (Compound 501-27)

To a solution of compound 402-20 (82 mg, 0.2 mmol) in DMSO (1.2 mL) was added KOH (13 mg, 0.22 mmol). The mixture was stirred for 1 hour at room temperature and then ethyl 4-bromobutanoate (39 mg, 0.2 mmol) and Bu_4NI (3 mg) was added. The mixture was heated to 55 °C and stirred overnight. The solution was cooled to room temperature and diluted with CH_2Cl_2 (10 mL), washed with H_2O (3 mL x 5). The organic layer was separated and dried over Na_2SO_4, filtered, and concentrated to leave a residue which was purified by column chromatography on silica gel (CH_2Cl_2/MeOH=180/1 with 0.5% Et_3N) to provide 501-27 (64 mg, 61%) as a pale yellow solid. LC-MS: 525.7 $[M+1]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (t, 3H, *J*= 7.2 Hz), 1.81 (m, 2H), 2.35 (t, 2H, *J*= 7.2 Hz), 3.29 (m, 2H), 4.00 (m, 6H), 6.08 (s, 2H), 6.61 (s, 2H), 7.16 (s, 1H), 7.19 (s, 1H), 8.01 (s, 1H).

Step 17b. 4-(2-(6-Amino-8-(6-bromobenzo[d][1,3]dioxol-5-ylthio)-9H-purin-9-yl)ethoxy)-N-hydroxybutanamide (Compound 27)

The title compound 37 was prepared as a white solid (34 mg, 35 %) from compound 501-27 (98 mg, 0.19 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 4 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 209~211 °C, LC-MS: 512.8 $[M+1]^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.77 (m, 2H), 2.06 (t, 2H, *J*= 7.2 Hz), 3.29 (m, 2H), 3.89 (t, 2H, *J*= 7.2 Hz), 3.98 (t, 2H, *J*= 6.9 Hz), 6.08 (s, 2H), 6.77 (s, 2H), 7.16 (s, 1H), 7.20 (s, 1H), 8.01 (s, 1H), 8.78 (s, 1H), 10.46 (s, 1H).

EXAMPLE 18: Preparation of 5-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethoxy)-*N*-hydroxypentanamide (Compound 28)

Step 18a. Methyl 5-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethoxy)pentanoate (Compound 501-28)

The title compound 501-28 was prepared as a pale yellow solid (180 mg, 56 %) from compound 402-20 (250 mg, 0.61 mmol), KOH (38 mg, 0.67 mmol), Methyl 5-bromopentanoate (119 mg, 0.61 mmol) and Bu_4NI (10 mg) using a procedure similar to that described for compound 27 (Example 17): LC-MS: 525.8 $[M+1]^+$.

Step 18b. 5-(2-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethoxy)-*N*-hydroxypentanamide (Compound 28)

The title compound 28 was prepared as a white solid (120 mg, 66 %) from compound 501-28 (180 mg, 0.19 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 6 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 181~183 °C, LC-MS: 526.8 $[M+1]^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.49 (m, 4H), 1.94 (t, 2H, J= 6.9 Hz), 3.29 (m, 2H), 3.96 (m, 4H), 6.08 (s, 2H), 6.59 (s, 2H), 7.17 (s, 1H), 7.19 (s, 1H), 8.01 (s, 1H), 8.67 (s, 1H), 10.32 (s, 1H).

EXAMPLE 19: Preparation of 6-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethoxy)-*N*-hydroxyhexanamide (compound 29)

Step 19a. Ethyl 6-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethoxy)hexanoate (Compound 501-29)

The title compound 501-29 was prepared as a pale white solid (200 mg, 59 %) from compound 402-20 (250 mg, 0.61 mmol), KOH (38 mg, 0.67 mmol), Ethyl 6-bromohexanoate (136 mg, 0.61 mmol) and Bu_4NI (10 mg) using a procedure similar to that described for compound 27 (Example 17): LCMS: 552 $[M+1]^+$.

Step 19b. 6-(2-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethoxy)-*N*-hydroxyhexanamide (Compound 29)

The title compound 29 was prepared as a pale white solid (45 mg, 23 %) from compound 501-29 (200 mg, 0.36 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 5 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 168~177 °C, LCMS: 539 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 1.21 (m, 2H) 1.50 (m, 4H), 1.90 (t, 2H, J = 7.3 Hz), 3.96 (m, 4H), 6.08 (s, 2H), 6.57 (s, 2H), 7.17 (s, 1H), 7.21 (s, 1H), 8.01 (s, 1H), 8.64 (s, 1H), 10.31 (s, 1H).

EXAMPLE 20: Preparation of 7-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethoxy)-*N*-hydroxyheptanamide (Compound 30)

Step 20a. Ethyl 7-(2-(6-amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethoxy)heptanoate (Compound 501-30)

The title compound 501-30 was prepared as a pale white solid (200 mg, 58 %) from compound 402-20 (250 mg, 0.61 mmol), KOH (38 mg, 0.67 mmol), ethyl 7-bromoheptanoate (145 mg, 0.61 mmol) and Bu_4NI (10 mg, 0.027 mmol) using a procedure similar to that described for compound 27 (Example 17): LCMS: 566 $[M+1]^+$.

Step 20b. 7-(2-(6-Amino-8-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)ethoxy)-*N*-hydroxyheptanamide (Compound 30)

The title compound 30 was prepared as a pale white solid (45 mg, 23 %) from compound 501-30 (200 mg, 0.35 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 5 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 107~111 ^oC, LCMS: 553 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 1.22 (m, 4H) 1.46 (m, 4H), 1.90 (t, 2H, J = 7.4 Hz), 3.92 (m, 4H), 6.08 (s, 2H), 6.57 (s, 2H), 7.16 (s, 1H), 7.20 (s, 1H), 8.01 (s, 1H); ^1H NMR (DMSO-d_6+D_2O): δ 1.20(m, 4H) 1.45 (m, 4H), 1.88 (t, 2H, J = 7.4 Hz), 3.30(t, 2H) 3.92 (m, 4H), 6.06 (s, 2H), 7.13 (s, 1H), 7.18 (s, 1H), 8.02 (s, 1H).

EXAMPLE 21: Preparation of 7-(6-amino-8-(6-chlorobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)-*N*-hydroxyheptanamide (Compound 31)

Step 21a. 8-(6-Chlorobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (compound 105-31)

A mixture of compound 104 (0.5 g, 3.64 mmol), 5-chloro-6-iodobenzo[*d*][1,3] dioxole (1.27 g, 5.47 mmol), neocuproine hydrate (62.3 mg, 0.36 mmol), CuI (57 mg, 0.36 mmol) and NaO-*t*-Bu (345 mg, 4.37 mmol) in anhydrous DMF (25 mL) was stirred for 24 h at 110 ^oC (oil bath) under nitrogen atmosphere. The solvent was removed under high vacuum and the crude purified by column chromatography on silica gel (CH_2Cl_2/MeOH=30/1) to provide target compound 105-31 as a yellow solid (281 mg, 24%): LCMS: 322 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 6.12 (s, 2H), 7.05 (s, 1H), 7.22 (s, 2H), 7.27 (s, 1H), 8.07 (s, 1H), 13.23 (s, 1H).

Step 21b. Ethyl 7-(6-amino-8-(6-chlorobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl) heptanoate (Compound 106-31)

A mixture of compound 105-31 (403 mg, 1.25 mmol), Cs_2CO_3 (692.2 mg, 2.13 mmol), ethyl 7-bromoheptanoate (446 mg, 1.88 mol) and anhydrous DMF (25 mL) was stirred for 6 h at 85 °C. The solvent was removed under high vacuum and the crude purified by column chromatography on silica gel (CH_2Cl_2/MeOH=100/1) to provide target compound 106-31 as a yellow viscous solid (230 mg, 38.5%): LCMS: 478 $[M+1]^+$. ^1H NMR (DMSO-d_6): δ 1.16 (m, 7H), 1.44 (m, 2H), 1.65 (m, 2H), 2.24 (t, 2H, J=7.2 Hz), 4.02 (q, 2H, J_1= 6.9 Hz, J_2= 14.1 Hz), 4.14 (t, 2H, J= 6.9 Hz), 6.11 (s, 2H), 6.88 (s, 1H), 7.27 (s, 1H), 7.40 (s, 2H), 8.15 (s, 1H).

Step 21c. 7-(6-Amino-8-(6-chlorobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)-*N*-hydroxyheptanamide (Compound 31)

The title compound 31 was prepared as a pale white solid (75 mg, 55.5 %) from compoundd 106-31 (140 mg, 0.29 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 4 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 128~134 °C, LCMS: 465 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 1.20 (m, 4H), 1.40 (m, 2H), 1.65 (m, 2H), 1.90 (t, 2H, J= 7.5 Hz), 4.13 (t, 2H, J= 6.9 Hz), 6.11 (s, 2H), 6.89 (s, 1H), 7.28 (s, 1H), 7.40 (s, 2H), 8.15 (s, 1H), 8.66 (s, 1H), 10.33 (s, 1H).

EXAMPLE 22: Preparation of 7-(6-amino-8-(6-iodobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)-*N*-hydroxyheptanamide (Compound 32)

Step 22a. 8-(6-Iodobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-6-amine (compound 105-32)

A mixture of compound 104 (0.8 g, 4.78 mmol), 5,6-diiodobenzo[*d*][1,3]dioxole (2.68 g, 7.18 mmol), neocuproine hydrate (100 mg, 0.48 mmol), CuI (91.1 mg, 0.48 mmol) and NaO-*t*-Bu (0.55 g, 5.74 mmol) in anhydrous DMF (40 mL) was stirred for 24 h at 110 °C (oil bath) under nitrogen atmosphere. The solvent was removed under high vacuum and the crude purified by column chromatography on silica gel (CH_2Cl_2/MeOH=30/1) to provide target compound 105-32 as a yellow solid (348 mg, 17.6%): LCMS: 414 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 6.09 (s, 2H), 7.01 (s, 1H), 7.22 (s, 2H), 7.51 (s, 1H), 8.08 (s, 1H), 13.20 (s, 1H).

Step 22b. Ethyl 7-(6-amino-8-(6-iodobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)heptanoate (Compound 106-32)

The title compound 106-32 was prepared as a yellow viscous solid (250 mg, 53.5 %) from compoundd 105-32 (300 mg, 0.82 mmol), Cs_2CO_3 (454.7 mg, 1.40 mmol), ethyl 7-bromoheptanoate (292.7 mg, 1.23 mol) and anhydrous DMF (15 mL) using a procedure similar to that described for compound 106-31 (Example 21): LCMS: 570 [M+1] $^+$. ^{1}H NMR (DMSO-d_6): δ 1.20 (m, 7H), 1.44 (m, 2H), 1.65 (m, 2H), 2.23 (t, 2H, J=7.2 Hz), 4.02 (q, 2H, J_1= 6.9 Hz, J_2= 14.1Hz), 4.13 (t, 2H, J= 6.9 Hz), 6.08 (s, 2H), 6.82 (s, 1H), 7.44 (s, 2H), 7.50 (s, 1H), 8.16 (s, 1H).

Step 22c. 7-(6-Amino-8-(6-iodobenzo[*d*][1,3]dioxol-5-ylthio)-9*H*-purin-9-yl)-*N*-hydroxyheptanamide (Compound 32)

The title compound 32 was prepared as a pale white solid (135 mg, 36.8 %) from compound 106-32 (244 mg, 0.43 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 6 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 200~203 °C, LCMS: 557 [M+1]$^+$; ^{1}H NMR (DMSO-d_6): δ 1.20 (m, 4H), 1.43 (m, 2H), 1.62 (m, 2H), 1.90 (t, 2H, J= 7.5 Hz), 4.11 (t, 2H, J= 6.9 Hz), 6.07 (s, 2H), 7.00 (s, 1H), 6.82 (s, 1H), 7.42 (s, 2H), 7.50 (s, 1H), 8.15 (s, 1H), 8.66 (s, 1H), 10.32 (s, 1H).

EXAMPLE 23: Preparation of 7-(4-amino-2-(6-chlorobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-*N*-hydroxyheptanamide (Compound 34)

Step 23a. 2-Chloro-N-(4-methoxybenzyl)-3-nitropyridin-4-amine (Compound 602)

To a stirred solution of compound 601 (1 g, 5.18 mmol) in DMF (8.6 mL) was added (4-methoxyphenyl)methanamine (0.71 g□ 5.18 mmol) and triethylamine (0.644 mL). The reaction mixture was stirred at room temperature for 2 h. The mixture was evaporated to remove DMF and purified by column chromatography on silica gel (EtOAc/petroleum at 10:1) to obtain 602 as a yellow solid (1.32 g, 87%): LCMS: 294 [M+1]$^+$; ^{1}H NMR (DMSO-d_6): δ 3.72 (s, 3H), 4.40 (d, 2H, J = 6.3 Hz), 6.81 (d, 1H, J = 5.7 Hz), 6.91 (d, 2H, J = 9.0 Hz), 7.25 (d, 2H, J = 8.4 Hz), 7.95 (d, 1H, J = 5.4 Hz), 8.02 (t, 1H, J = 5.7 Hz).

Step 23b. 2-Chloro-N^4-(4-methoxybenzyl)pyridine-3,4-diamine (603)

To a stirred solution of compound 602 (1.32 g, 4.49 mmol) in methanol (66 mL) was added water (6.6 mL), iron powder (2.51 g, 44.9 mmol) and concentrated HCl solution (1 mL). The reaction mixture was stirred at room temperature for 30 min, and then heated to reflux overnight. The mixture was adjusted to pH 11 with 6N NaOH. The resulting solid was filtered and washed with methanol (10 mL). The combined filtrate was concentrated to leave a residue which was purified by column chromatography on silica gel (EtOAc/petroleum at 2:1) to obtain 603 as a light green solid (712 mg, 60%): LCMS: 264 [M+1]$^+$; ^{1}H NMR (DMSO-d_6): δ 3.73 (s, 3H), 4.31

(d, 2H, J = 5.7 Hz), 4.81 (s, 2H), 6.33 (m, 2H), 6.90 (d, 2H, J = 8.7 Hz), 7.26 (d, 2H, J = 9.0 Hz), 7.34 (d, 1H, J = 5.1 Hz).

Step 23c. 4-Chloro-1-(4-methoxybenzyl)-1*H*-imidazo[4,5-*c*]pyridine-2(3*H*)-thione (Compound 604)

A mixture of compound 603 (2 g, 7.6 mmol), carbon disulfide (2.88 g, 37.9 mmol), potassium hydroxide (2.12 g, 37.9 mmol) in ethanol (11.5 mL) and water (1.5 mL) was heated at reflux overnight. The reaction was cooled down to room temperature and 100 mL of water was added. The mixture was adjusted to pH 7 with acetic acid and then extracted with two portions of methylene chloride. The extract was concentrated at reduced pressure and purified by column chromatography on silica gel (EtOAc/petroleum at 5:1) to obtain compound 604 as a white solid (2 g, 86%): LCMS: 306 $[M]^+$; ^{1}H NMR (DMSO-d_6): δ 3.68 (s, 3H), 6.41 (s, 2H), 6.86 (d, 2H, J = 8.7 Hz), 7.36 (m, 3H), 8.07 (d, 1H, J = 5.4 Hz), 13.74 (s, 1H).

Step 23d. 4-Amino-1-(4-methoxybenzyl)-1*H*-imidazo[4,5-*c*]pyridine-2(3*H*)-thione (Compound 605)

A mixture of compound 604 (1 g, 3.25 mmol) and sodium amide (3g, 77 mmol) in 25 mL liquid ammonia was charged in a no air sealed tube, and stirred at room temperature for 30 h. The mixture was cooled to –40 °C and the tube was opened. Ethanol was added carefully to the reaction until no gas generated. 200 mL of water was added and adjusted the mixture to pH 7 with acetic acid. The resulting mixture was filtered to obtain crude which was purified by column chromatography on silica gel (methylene chloride/methanol at 50:1) to obtain compound 605 as a white solid (718 mg, 77%): LCMS: 287 $[M]^+$; ^{1}H NMR (DMSO-d_6): δ 3.68 (s, 3H), 5.31 (s, 2H), 6.06 (s, 2H), 6.59 (d, 1H, J = 6.3 Hz), 6.85 (d, 2H, J = 9.0 Hz), 7.33 (d, 2H, J = 8.4 Hz), 7.64 (d, 1H, J = 5.7 Hz), 12.53 (s, 1H).

Step 23e. 2-(6-Chlorobenzo[*d*][1,3]dioxol-5-ylthio)-1-(4-methoxybenzyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine (Compound 606-34)

A mixture of compound 605 (543 mg, 1.9 mmol), 5-chloro-6-iodobenzo[*d*][1,3] dioxole (1.07 g, 3.79 mmol), neocuproine hydrate (40 mg, 0.19 mmol), CuI (36 mg, 0.19 mmol) and NaO*t*-Bu (273 mg, 2.84 mmol) in anhydrous DMF (24 mL) was stirred for 24 h at 110 °C (oil bath) under nitrogen atmosphere. The solvent was removed under high vacuum and the crude purified by column chromatography on silica gel (CH_2Cl_2/MeOH at 100/1) to obtain target compound 606-34 as a brown solid (506 mg, 61%): LCMS: 441 $[M+1]^+$; ^{1}H NMR (DMSO-d_6):

δ 3.69 (s, 3H), 5.37 (s, 2H), 6.04 (s, 2H), 6.41 (s, 2H), 6.55 (s, 1H), 6.80 (d, 2H, J = 8.7 Hz), 7.04 (d, 2H, J = 9.3 Hz), 7.17 (s, 1H), 7.73 (s, 1H).

Step 23f. 2-(6-Chlorobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo[4,5-*c*]pyridin-4-amine (607-34)

Compound 606-34 (506 mg, 1.14 mmol) was dissolved in TFA (4 mL) and stirred for 2 h at 80 °C. The solution was evaporated and the residual was adjust to pH 7 with saturated $NaHCO_3$ and filtered. The precipitate was purified by column chromatography on silica gel (CH_2Cl_2/MeOH at 30/1) to obtain target compound 607-34 as a yellow solid (300 mg, 82%): LCMS: 321 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 6.11 (s, 2H), 6.56 (m, 3H), 7.04 (s, 1H), 7.26 (s, 1H), 7.49 (s, 2H), 12.25 (s, 1H).

Step 23g. Ethyl 7-(4-amino-2-(6-chlorobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo [4,5-*c*]pyridin-1-yl)heptanoate (Compound 608-34)

A mixture of compound 607-34 (300 mg, 0.935 mmol), ethyl 7-bromoheptanoate (333 mg, 1.403 mmol), Cs_2CO_3 (517 mg, 1.59 mmol) in DMF (12 mL) was stirred at 85 °C for 2 h. DMF was evaporated under vacuum, and the residue was purified by column chromatography on silica gel (methylene chloride / methanol at 100:1) to yield compound 608-34 as a white solid (300 mg, 67%): LCMS: 477 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 1.15 (m, 7H), 1.42 (m, 2H), 1.58 (m, 2H), 2.21 (t, 2H, J = 7.2 Hz), 4.02 (q, 2H, J = 7.5 Hz), 4.16 (t, 2H, J = 7.2 Hz), 6.08 (s, 2H), 6.37 (s, 2H), 6.73 (s, 1H), 6.80 (d, 1H, J = 5.1 Hz), 7.25 (s, 1H), 7.70 (d, 1H, J = 6.0 Hz).

Step 23h. 7-(4-Amino-2-(6-chlorobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo[4,5-*c*] pyridin-1-yl)-*N*-hydroxyheptanamide (Compound 34)

The title compound 34 was prepared as a white solid (98 mg, 34 %) from compound 608-34 (300 mg, 0.63 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 3 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 144 ~ 148 °C, LCMS: 464 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 1.22 (m, 4H), 1.42 (m, 2H), 1.65 (m, 2H), 1.90 (t, 2H, J = 7.2 Hz), 4.29 (t, 2H, J = 6.9 Hz), 6.14 (s, 2H), 7.07 (s, 1H), 7.31 (m, 2H), 7.73 (d, 1H, J = 6.9 Hz), 8.51 (s, 2H), 10.32 (s, 1H), 13.04 (s, 1H).

EXAMPLE 24: Preparation of 7-(4-amino-2-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-*N*-hydroxyheptanamide (Compound 35)

Step 24a. 2-(6-Bromobenzo[*d*][1,3]dioxol-5-ylthio)-1-(4-methoxybenzyl)-1*H*-imidazo[4,5-*c*]pyridin-4-amine (606-35)

The title compound 606-35 was prepared as a brown solid (584 mg, 49 %) from compound 605 (700 mg, 2.44 mmol), 5-bromo-6-iodobenzo[*d*][1,3] dioxole (1.20 g, 3.66 mmol), neocuproine hydrate (51 mg, 0.244 mmol), CuI (46 mg, 0.244 mmol) and NaO*t*-Bu (234 mg, 2.44 mmol) in anhydrous DMF (31 mL) using a procedure similar to that described for compound 606-34 (Example 23): LCMS: 485 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 3.29 (s, 3H), 5.39 (s, 2H), 6.04 (s, 2H), 6.54 (s, 1H), 6.81 (m, 3H), 6.91 (d, 1H, J = 5.4 Hz), 7.06 (d, 2H, J = 8.6 Hz), 7.29 (s, 1H), 7.71 (d, 1H, J = 6.0 Hz).

Step 24b. 2-(6-Bromobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo[4,5-*c*] pyridin-4-amine (Compound 607-35)

Compound 606-35 (557 mg, 1.15 mmol) was dissolved in TFA (4 mL) and stirred for 2 h at 80 °C. The solution was evaporated and the residual was adjusted to pH 7 with saturated $NaHCO_3$ and filter. The precipitate was purified by column chromatography on silica gel (CH_2Cl_2/MeOH at 30/1) to obtain target compound 607-35 as a white solid (308 mg, 74%): LCMS: 365 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 6.07 (s, 2H), 6.58 (s, 2H), 6.69 (d, 1H, J = 6.0 Hz), 6.98 (s, 1H), 7.34(s, 1H), 7.47 (d, 1H, J = 5.7 Hz).

Step 24c. Ethyl 7-(4-amino-2-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo [4,5-*c*]pyridin-1-yl)heptanoate (Compound 608-35)

The title compound 608-35 was prepared as a white solid (240 mg, 56%) from compound 607-35 (302 mg, 0.827 mmol), ethyl 7-bromoheptanoate (294 mg, 1.24 mmol), Cs_2CO_3 (457 mg, 1.406 mmol) in DMF (12 mL) using a procedure similar to that described for compound 608-34 (Example 23): LCMS: 521 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 1.16 (m, 7H), 1.41 (m, 2H), 1.58 (m, 2H), 2.21 (t, 2H, J = 7.5 Hz), 4.02 (q, 2H, J = 6.9 Hz), 4.16 (t, 2H, J = 6.9 Hz), 6.07 (s, 2H), 6.40 (s, 2H), 6.67 (s, 1H), 6.80 (d, 1H, J = 5.7 Hz), 7.36 (s, 1H), 7.71 (d, 1H, J = 5.7 Hz).

Step 24d. 7-(4-Amino-2-(6-bromobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo[4,5-*c*] pyridin-1-yl)-*N*-hydroxyheptanamide (Compound 35)

The title compound 35 was prepared as a white solid (182 mg, 79%) from compound 608-35 (236 mg, 0.453 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 3 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 179 ~ 181 °C, LCMS: 508 $[M+1]^+$; ^1H NMR (DMSO-d_6): δ 1.17 (m, 4H), 1.36 (m, 2H), 1.57 (m, 2H), 1.88 (t, 2H, J =

6.9 Hz), 4.15 (t, 2H, *J* = 7.2 Hz), 6.08 (s, 2H), 6.43 (s, 2H), 6.67 (s, 1H), 6.81 (d, 1H, *J* = 5.4 Hz), 7.36 (s, 1H), 7.71 (d, 1H, *J* = 5.7 Hz), 8.66 (s, 1H), 10.32 (s, 1H).

EXAMPLE 25: Preparation of 7-(4-amino-2-(6-iodobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-*N*-hydroxyheptanamide (Compound 36)

Step 25a. 2-(6-Iodobenzo[*d*][1,3]dioxol-5-ylthio)-1-(4-methoxybenzyl)-1*H*-imidazo [4,5-*c*]pyridin-4-amine (Compound 606-36)

The title compound 606-36 was prepared as a brown solid (734 mg, 55%) from compound 605 (725 mg, 2.53 mmol), 5,6-diiodobenzo[*d*][1,3] dioxole (1.89 g, 5.06 mmol), neocuproine hydrate (53 mg, 0.253 mmol), CuI (48 mg, 0.253 mmol) and NaO*t*-Bu (365 mg, 3.80 mmol) in anhydrous DMF (32 mL) using a procedure similar to that described for compound 606-34 (Example 23): LCMS: 533 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 3.69 (s, 3H), 5.35 (s, 2H), 6.01 (s, 2H), 6.47 (s, 1H), 6.80 (d, 2H, *J* = 9.0 Hz), 7.06 (d, 2H, *J* = 8.6 Hz), 7.41 (s, 1H).

Step 25b. 2-(6-Iodobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo[4,5-*c*]pyridin-4-amine (Compound 607-36)

Compound 606-36 (730 mg, 1.37 mmol) was dissolved in TFA (4.8 mL) and stirred for 2 h at 80 °C. The solution was evaporated and the residual was adjust to pH 7 with saturated $NaHCO_3$ and filter. The precipitate was purified by column chromatography on silica gel (CH_2Cl_2/MeOH at 30/1) to obtain target compound 607-36 as a yellow solid (526 mg, 93%): LCMS: 413 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 6.09 (s, 2H), 6.73 (m, 3H), 7.03 (s, 1H), 7.52 (m, 2H), 12.45 (s, 1H).

Step 25c. Ethyl 7-(4-amino-2-(6-iodobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo[4,5-*c*] pyridin-1-yl)heptanoate (Compound 608-36)

The title compound 608-36 was prepared as a white solid (149 mg, 61%) from compound 607-36 (178 mg, 0.432 mmol), ethyl 7-bromoheptanoate (154 mg, 0.648 mmol), Cs_2CO_3 (239 mg, 0.734 mmol) in DMF (6.3 mL) using a procedure similar to that described for compound 608-34 (Example 23): LCMS: 569 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 1.16 (m, 7H), 1.42 (m, 2H), 1.57 (m, 2H), 2.22 (t, 2H, *J* = 7.2 Hz), 4.03 (q, 2H, *J* = 7.5 Hz), 4.15 (t, 2H, *J* = 7.2 Hz), 6.04 (s, 2H), 6.39 (s, 2H), 6.65 (s, 1H), 6.80 (d, 1H, *J* = 6.0 Hz), 7.48 (s, 1H), 7.71 (d, 1H, *J* = 5.7 Hz).

Step 25d. 7-(4-Amino-2-(6-iodobenzo[*d*][1,3]dioxol-5-ylthio)-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-*N*-hydroxyheptanamide (Compound 36)

The title compound 36 was prepared as a white solid (45 mg, 33%) from compound 608-36 (140 mg, 0.246 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 3 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 191 ~193 °C, LCMS: 556 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 1.18 (m, 4H), 1.37 (m, 2H), 1.57 (m, 2H), 1.89 (t, 2H, J = 6.9 Hz), 4.14 (t, 2H, J = 7.2 Hz), 6.04 (s, 2H), 6.42 (s, 2H), 6.66 (s, 1H), 6.80 (d, 1H, J = 5.7 Hz), 7.49 (s, 1H), 7.71 (d, 1H, J = 5.7 Hz), 8.66 (s, 1H), 10.31 (s, 1H).

EXAMPLE 26: Preparation of 6-(4-amino-2-(6-iodobenzo[d][1,3]dioxol-5-ylthio)-1H-imidazo[4,5-c]pyridin-1-yl)-N-hydroxyhexanamide (Compound 42)

Step 26a. Ethyl 6-(4-amino-2-(6-iodobenzo[d][1,3]dioxol-5-ylthio)-1H-imidazo[4,5-c]pyridin-1-yl)hexanoate (Compound 608-42)

The title compound 608-42 was prepared as a white solid (260 mg, 64%) from compound 607-36 (300 mg, 0.73 mmol), ethyl 6-bromohexanoate (243 mg, 1.09 mmol), Cs_2CO_3 (404 mg, 1.24 mmol) in DMF (4.0 mL) using a procedure similar to that described for compound 608-34 (Example 23): LCMS: 555 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 1.14 (t, 2H, J = 7.2 Hz), 1.19 (m, 2H), 1.47 (m, 2H), 1.57 (m, 2H), 2.19 (t, 2H, J = 7.2 Hz), 4.01 (q, 2H, J = 7.2 Hz), 4.16 (t, 2H, J = 6.9 Hz), 6.05 (s, 2H), 6.55 (s, 2H), 6.68 (s, 1H), 6.83 (d, 1H, J = 6.0 Hz), 7.48 (s, 1H), 7.70 (d, 1H, J = 6.0 Hz).

Step 26b. 6-(4-Amino-2-(6-iodobenzo[d][1,3]dioxol-5-ylthio)-1H-imidazo[4,5-c]pyridin-1-yl)-N-hydroxyhexanamide (Compound 42)

The title compound 42 was prepared as a white solid (107 mg, 42%) from compound 608-42 (260 mg, 0.47 mmol) and freshly prepared NH_2OH methanol solution (1.77 M, 6 mL) using a procedure similar to that described for compound 11 (Example 6): m.p. 189 ~193 °C, LCMS: 542 $[M+1]^+$; ^{1}H NMR (DMSO-d_6): δ 1.20 (m, 2H), 1.44 (m, 2H), 1.56 (m, 2H), 1.87 (t, 2H, J = 7.2 Hz), 4.13 (t, 2H, J = 7.2 Hz), 6.05 (s, 2H), 6.36 (s, 2H), 6.67 (s, 1H), 6.78 (d, 1H, J = 6.0 Hz), 7.48 (s, 1H), 7.70 (d, 1H, J = 5.7 Hz).

Biological Assays:

As stated hereinbefore the derivatives defined in the present invention possess anti-proliferation activity. These properties may 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 Hsp90 chaperone activity.

The Hsp90 chaperone assay was performed to measure the ability of HSP90 protein to refold the heat-denatured luciferase protein. HSP90 was 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 was added to denaturation mix and incubated at 50 ^{0}C for 8 min. The final concentration of HSP90 and luciferase in denaturation mixture were 0.375 μM and 0.125 μM respectively. A 5 μl sample of the denatured mix was 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 was 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 was incubated at dark for 5 min before reading the luminescence signal on a TopCount plate reader (PerkinElmer Life Science).

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

HDAC inhibitors were screened using an HDAC fluorimetric assay kit (AK-500, Biomol, Plymouth Meeting, PA). Test compounds were dissolved in dimethylsulphoxide (DMSO) to give a 20 mM working stock concentration. Fluorescence was measured on a WALLAC Victor 2 plate reader and reported as relative fluorescence units (RFU). Data were plotted using GraphPad Prism (v4.0a) and IC50's calculated using a sigmoidal dose response curve fitting algorithm.

Each assay was 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 following TABLE B lists compounds representative of the invention and their activity in HDAC and HSP90 assays. In these assays, the following grading was used: **I** ≥ 10 µM, 10 µM > **II** > 1 µM, 1 µM > **III** > 0.1 µM, and **IV** ≤ 0.1 µM for IC_{50}.

TABLE B

Compound No.	HDAC	HSP90
5	III	III
6	IV	III
12	IV	
13	I	I
14	III	
16	IV	I
18	IV	I
20	I	III
23	IV	III
24	IV	III
27	I	I
28	II	I
29	II	I
30	IV	I
31	IV	II
32	IV	IV
33	I	III
34	IV	II
35	IV	II
36	IV	III
37	I	III
38	III	III
39	IV	III
40	I	I
41	IV	

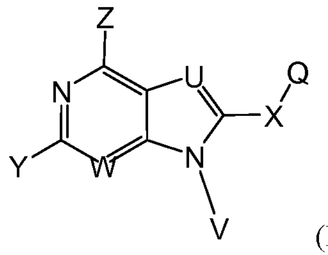
The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent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

U is N or CH;

W is N or CH;

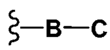
X is absent, O, S, S(O), $S(O)_2$, $N(R_8)$, CF_2 or C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, in which one or more methylene can be interrupted or terminated by O, S, SO, SO_2, $N(R_8)$., R_8 is hydrogen, acyl, aliphatic or substituted aliphatic;

Y is independently hydrogen, halogen, NO_2, CN, or lower alkyl;

Z is amino, alkylamino, or dialkylamino;

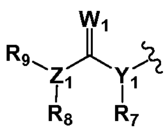
Q is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, or heterocycloalkyl;

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 one or more O, S, S(O), SO_2, $N(R_8)$, C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; substituted or unsubstituted cycloalkyl;

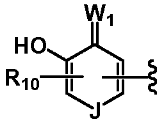
and wherein Q and/or V is further substituted by 

, where

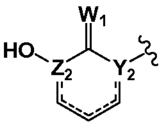
C is selected from:

(a) 

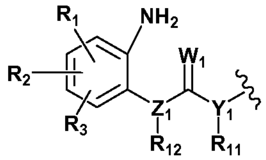
; where W_1 is O or S; Y_1 is absent, N, or CH; Z_1 is N or CH; R_7 and R_9 are independently hydrogen, OR', aliphatic or substituted aliphatic, wherein R' is hydrogen, aliphatic, substituted aliphatic or acyl; provided that if R_7 and R_9 are both present, one of R_7 or R_9 must be OR' and if Y is absent, R_9 must be OR'; and R_8 is hydrogen, acyl, aliphatic or substituted aliphatic;

(b) 

; where W_1 is O or S; J is O, NH or NCH_3; and R_{10} is hydrogen or lower alkyl;

(c) 

; where W_1 is O or S; Y_1 and Z_1 are independently N, C or CH; and

(d) 

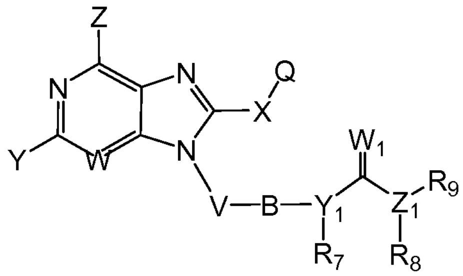
; where Z_1, Y_1, and W_1 are as previously defined; R_{11} and R_{12} are independently selected from hydrogen or aliphatic; R_1, R_2 and R_3 are independently selected from hydrogen, hydroxy, amino, halogen, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, substituted or unsubstituted alkylthio, substituted or unsubstituted alkylsulfonyl, CF_3, CN, NO_2, N_3, sulfonyl, acyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

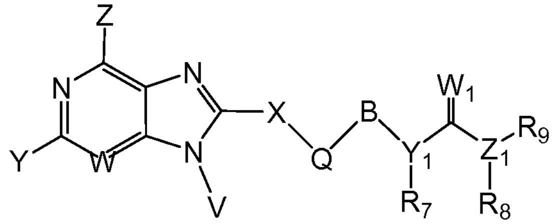
B is a linker.

2. A compound according to claim 1, wherein B is a direct bond or straight- or branched-, 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, $N(R_8)$, C(O), substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic; where R_8 is hydrogen, acyl, aliphatic or substituted aliphatic.

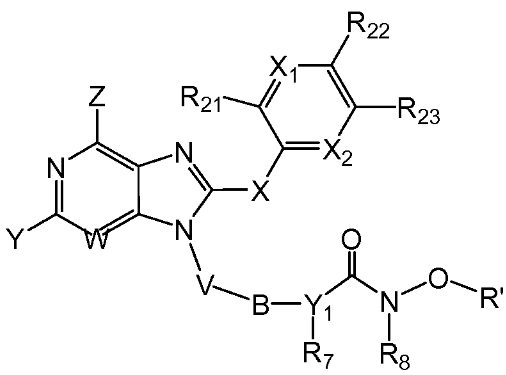
3. A compound according to Claim 1 represented by formula (II) or (III):


(II)


(III)

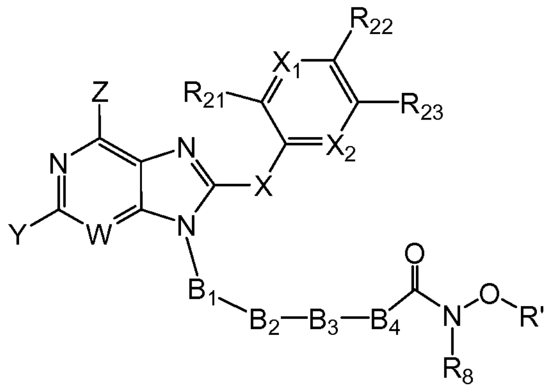
or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein Y, Z, W, X, Q, V, B, Z_1, Y_1, W_1 and R_7-R_9 are as previously defined in Claim 1.

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


(IV)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein X_1 and X_2 are independently CH or N; R_{21}-R_{23} are 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_{22} and R_{23} can be taken together from the carbon to which they are attached to form a fused heterocyclic ring or fused heteroaryl optionally substituted with 1-3 heteroatom; and B, X, Y, Z, W, V, Y_1, R', R_7, and R_8 are as previously defined in Claim 1.

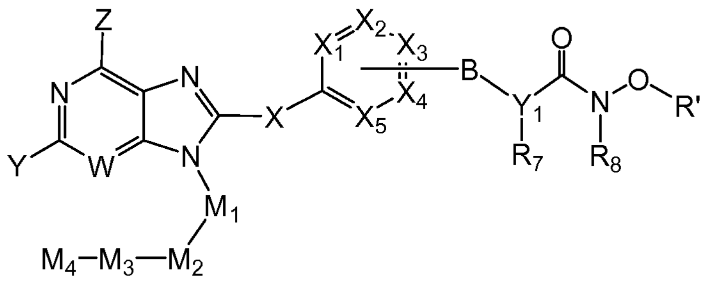
5. A compound according to Claim 1 represented by formula (V)



(V)

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein X_1 and X_2 are independently CH or N; R_{21}-R_{23} are 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_{22} and R_{23} can be taken together from the carbon to which they are attached to form a fused heterocyclic ring or fused heteroaryl optionally substituted with 1-3 heteroatom; B_1 is absent, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl or aryl; B_2 is absent, O, S, SO, SO_2, $N(R_8)$ or CO; B_3 is absent, O, S, SO, SO_2, $N(R_8)$ or CO C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; B_4 is absent C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; X, Y, Z, W, R' and R_8 are as previously defined in Claim 1.

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

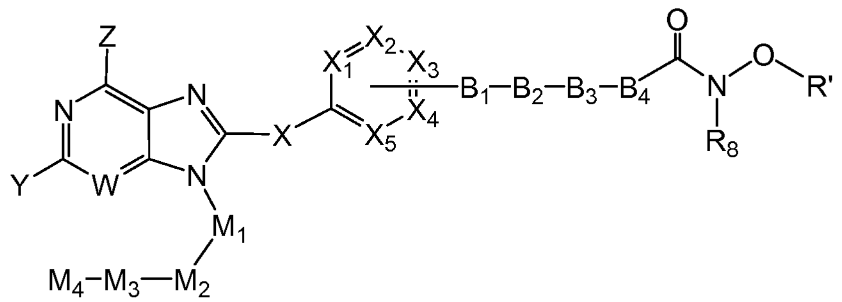


(VI)

wherein X_1-X_5 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; M_1 is absent, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-

C_6 alkynyl; M_2 is absent, O, S, SO, SO_2, $N(R_8)$ or C=O; M_3 is absent, O, S, SO, SO_2, $N(R_8)$, C=O, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocyclic, aryl or heteroaryl; M_4 is absent, O, S, SO, SO_2, $N(R_8)$, C=O, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocyclic, aryl or heteroaryl; B, X, Z, Y, Y_1, R', R_7 and R_8 are as previously defined in Claim 1.

7. A compound according to Claim 1 represented by formula (VII):

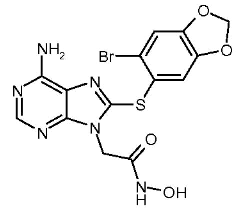
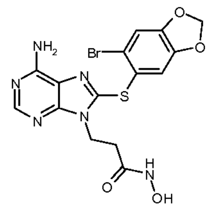
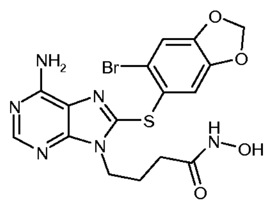
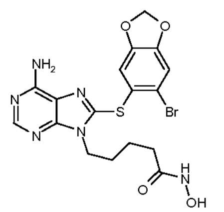
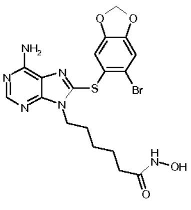
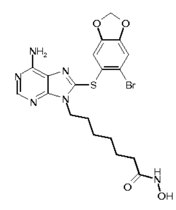
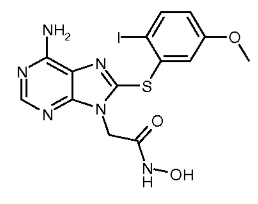


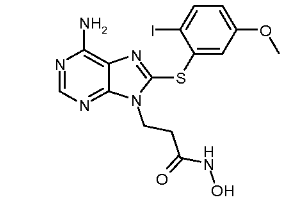
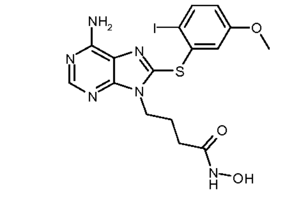
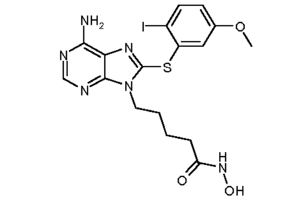
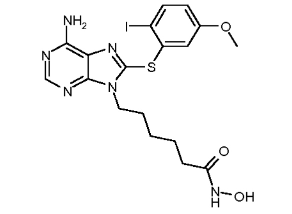
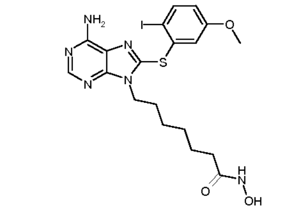
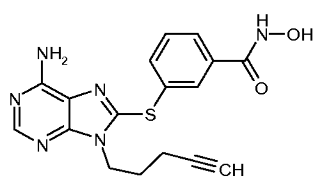
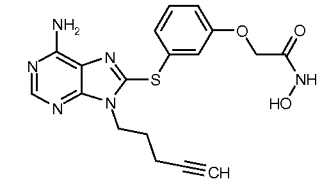
(VII)

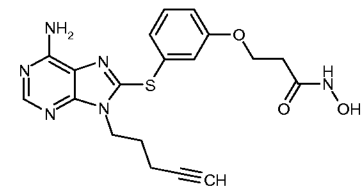
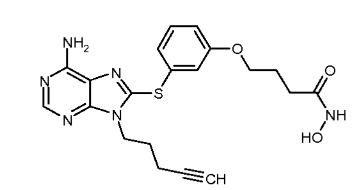
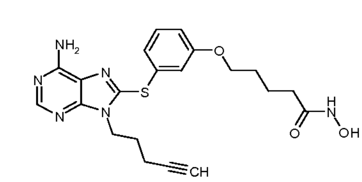
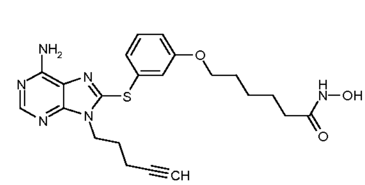
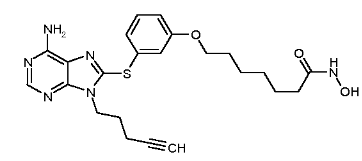
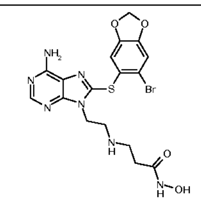
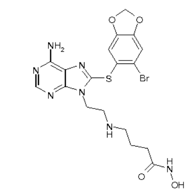
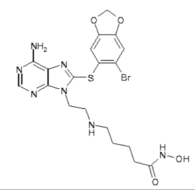
or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof, wherein X_1-X_5 are independently N or CR_{21}, where R_{21} is independently selected from hydrogen, hydroxy, amino, halogen, substituted or unsubstituted alkoxy, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, CF_3, CN, NO_2, N_3, sulfonyl, acyl, aliphatic, and substituted aliphatic; B_1 is absent, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl or aryl; B_2 is absent, O, S, SO, SO_2, $N(R_8)$ or CO; B_3 is absent, O, S, SO, SO_2, $N(R_8)$ or CO C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; B_4 is absent , C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroary; M_1 is absent, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl; M_2 is absent, O, S, SO, SO_2, $N(R_8)$ or C=O; M_3 is absent, O, S, SO, SO_2, $N(R_8)$, C=O, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocyclic, aryl or heteroaryl; M_4 is absent, O, S, SO, SO_2, $N(R_8)$, C=O, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, cycloalkyl, heterocyclic, aryl or heteroaryl; X, Z, Y and R_8 are as previously defined in Claim 1.

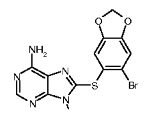
8. A compound according to Claim 1 selected from the compounds delineated in Table A or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts, prodrugs and solvates thereof:

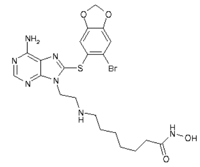
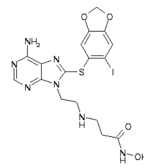
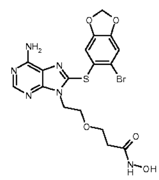
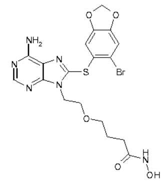
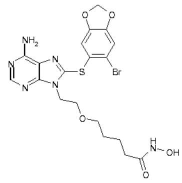
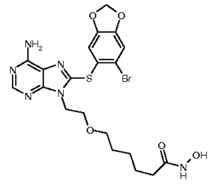
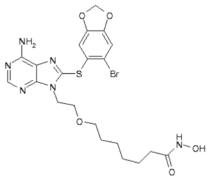
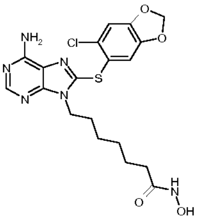
TABLE A

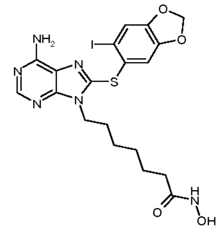
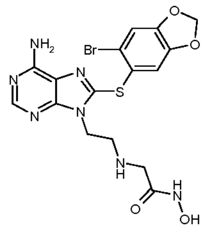
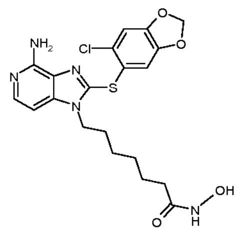
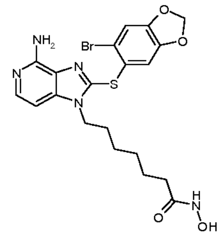
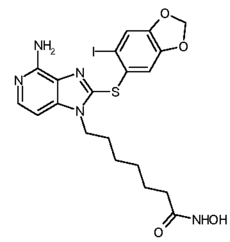
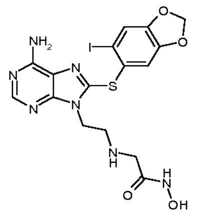
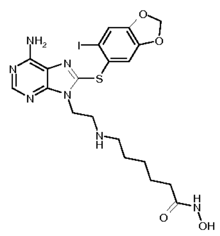
Compound #	Structure
1	
2	
3	
4	
5	
6	
7	

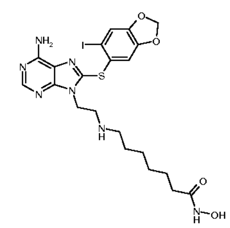
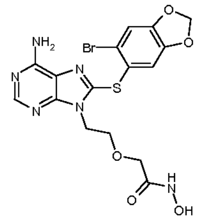
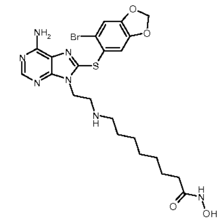
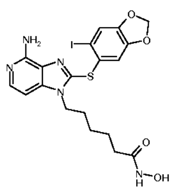
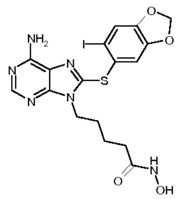
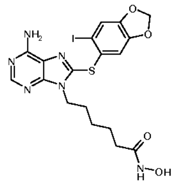
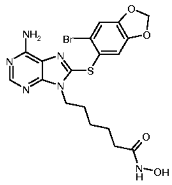
8	
9	
10	
11	
12	
13	
14	

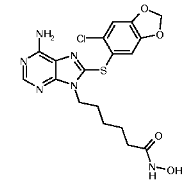
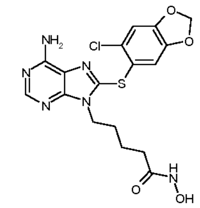
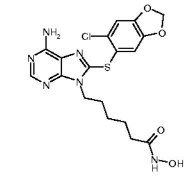
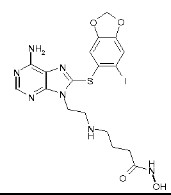
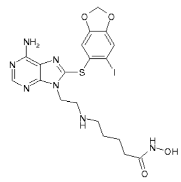
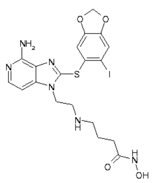
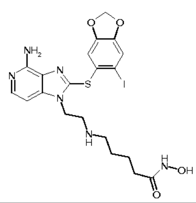
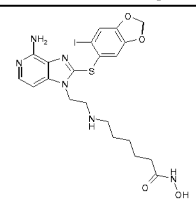
15	
16	
17	
18	
19	
20	
21	
22	

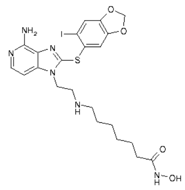


23	
24	
25	
26	
27	
28	
29	
30	
31	

32	
33	
34	
35	
36	
37	
38	

39	
40	
41	
42	
43	
44	
45	

46	
47	
48	
49	
50	
51	
52	
53	

54	

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

10. A method of treating cell proliferative disorder that requires or is facilitated by expression of an HSP90 protein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the of Claim 8.

11. The method of Claim 10, wherein said cell proliferative disorder is selected from the group consisting of papilloma, blastoglioma, Kaposi's sarcoma, melanoma, non-small cell lung cancer, ovarian cancer, prostate cancer, colon cancer, squamous cell carcinoma, astrocytoma, head cancer, neck cancer, bladder cancer, breast cancer, lung cancer, colorectal cancer, thyroid cancer, pancreatic cancer, renal cell carcinoma, gastric cancer, hepatocellular carcinoma, neuroblastoma, leukemia, lymphoma, vulcar cancer, Hodgkin's disease and Burkitt's disease.

12. A method of treating an HDAC-mediated disease comprising administering to a subject in need thereof a pharmaceutical composition of Claim 8.

13. A method of treating cell proliferative disorder that relates to expression of an HSP90 protein and HDAC comprising administering to a subject in need thereof a pharmaceutical composition of Claim 8.