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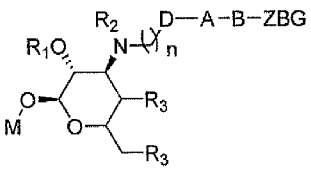
(54) **Title:** NON-PEPTIDE MACROCYCLIC HISTONE DEACETYLASE (HDAC) INHIBITORS AND METHODS OF MAKING AND USING THEREOF

(I)



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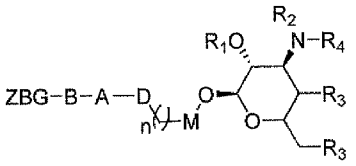

(57) **Abstract:** Compounds of Formula (I) or (II), and methods of making and using thereof, are described herein. wherein M represents a macrolide subunit, n is a C_{1-6} group, optionally containing one or more heteroatoms, wherein the carbon atoms and/or heteroatoms are in a linear and/or cyclic arrangement, D is an alkyl or aryl group, A is a linking group connected to D, B is an alkyl, wherein M represents a macrolide subunit, R_1, R_2 and R_4 are independently are selected from hydrogen, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{1-6} alkanoate group, a C_{2-6} carbamate group, a C_{2-6} carbonate group, a C_{2-6} carbamate group, or a C_{2-6} thiocarbamate group, R_3 is hydrogen or $-OR_5$, R_5 is selected from a group consisting of Hydrogen, a C_{1-6} alkyl hgroup, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, C_{1-6} alkanoate group, C_{2-6} carbamate group, C_{2-6} carbonate group, C_{2-6} carbamate group, or C_{2-6} thiocarbamate group.

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NON-PEPTIDE MACROCYCLIC HISTONE DEACETYLASE (HDAC) INHIBITORS AND METHODS OF MAKING AND USING THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. Provisional Application No. 60/947,036, entitled "Non-Peptide Macrocyclic Histone Deacetylase (HDAC) Inhibitors and Methods of Making and Using Thereof", filed June 29, 2007, by Adegboyega Oyelere.

FIELD OF THE INVENTION

The present invention generally relates to non-peptide macrocyclic histone deacetylase (HDAC) inhibitors and methods of making and using thereof.

BACKGROUND OF THE INVENTION

HDACs and histone acetyltransferases (HATs) are two functionally opposing enzymes, which tightly regulate the chromatin structure and function via sustenance of equilibrium between the acetylated- and deacetylated-states of nucleosomal histones (Grunstein, M., *Nature* 389, 349-352 (1997)). Aberrations in intracellular histone acetylation-deacetylation equilibrium have been linked to the repression of a subset of genes resulting in excessive proliferation and are implicated in a number of malignant diseases (Jenuwein, T.; Allis, C. D., *Science* 293, 1074-1080 (2001); Marks, P.; Rifkind, R. A.; Richon, V. M.; Breslow, R.; Miller, T.; Kelly, W. K., *Nat. Rev. Cancer*, 1, 194-202 (2001)). HDACs function as part of multiprotein complexes that catalyze the removal of acetyl groups from the ε-amino groups of specific lysine residues located near the N-termini of nucleosomal core histones (Rundlett, S. E.; Carmen, A. A.; Kobayashi, R.; Bavykin, S.; Turner, B. M.; Grunstein, M., *Proc. Natl. Acad. Sci. U.S.A.*, 93, 14503-14508 (1996); Grozinger, C. M.; Schreiber, S. L., *Chem. Biol.* 9, 3-16 (2002)). HDAC-catalyzed deacetylation results in positively charged, hypoacetylated histones which bind tightly to the phosphate backbone of DNA, thus inducing gene-specific repression of transcription. Inhibition of HDAC

deacetylase function results in the weakening of the bond between histones and DNA, thus increasing DNA accessibility and gene transcription.

Eighteen distinct human HDACs have been identified to date. They are classified into three major HDAC families based on their homology to three Saccharomyces cerevisiae HDACs (RPD3, HDA1, and SIR2). Class I include HDACs 1, 2, 3 and 8. Class II consists of HDACs 4, 5, 6, 7, 9, 10 and 11. The third class of HDACs consists of the sirtuins, which are homologically distinct from all the currently known HDACs. Early observations of HDAC inhibition by small molecules came from Yoshida *et al.* who reported that the natural product (R)-trichostatin A induced cell differentiation of murine erythroleukemia cells and hyperacetylation of histone proteins at nanomolar concentrations (Yoshida, M.; Kijima, M.; Akita, M.; Beppu, T., *J. Biol. Chem.* 265, 17174-17179 (1990); Yoshida, M.; Hoshikawa, Y.; Koseki, K.; Mori, K.; Beppu, T., *J. Antibiot.* 43, 1101-1106 (1990)). Subsequently, Breslow and co-workers described suberoylanilide hydroxamic acid (SAHA) as a potent HDAC inhibitor (Richon, V. M.; Webb, Y.; Merger, R.; Sheppard, T.; Jursic, B. *et al.*, *Proc. Natl. Acad. Sci. USA.* 93, 5705-5708 (1996); Richon, V. M.; Emiliani, S.; Verdin, E.; Webb, Y.; Breslow, R. *et al.*, *Proc. Natl. Acad. Sci. USA.* 95, 3003-3007 (1998); Breslow, R.; Belvedere, S.; Gershell, L., *Helv. Chim. Acta* 83, 1685-1692 (2000)).

Inhibition of HDACs is an emerging therapeutic strategy in cancer therapy. HDAC inhibitors have demonstrated ability to arrest proliferation of nearly all transformed cell types, including epithelial (melanoma, lung, breast, pancreas, ovary, prostate, colon and bladder) and hematological (lymphoma, leukemia and multiple myeloma) tumors (Kelly, W. K; O'Connor, O. A.; Marks, P. A., *Expert. Opin. Investig. Drugs*, 11, 1695-1713 (2002)). Additionally, HDAC inhibitors have demonstrated other biological activity including anti-inflammatory, anti-arthritic, anti-infective, anti-malarial, cytoprotective, neuroprotective, chemopreventive and/or cognitive enhancing effects.

All HDAC inhibitors so far reported typically fit a three-motif pharmacophoric model namely, a zinc-binding group (ZBG), a hydrophobic linker and a recognition cap-group (Miller, T. A.; Witter, D. J.; Belvedere, S., *J. Med. Chem.*, 46, 5097-5116 (2003)). Structural modifications of the ZBG yielding hydroxamate isosteres such as benzamide, α-ketoesters, electrophilic ketones, mercaptoamide and phosphonates have been reported. The cap-group may present better opportunities to discover potent and possibly even selective HDAC inhibitors. Toward this end, recent work by Schreiber and co-workers has led to the identification of cap group-modified agents that display differential inhibition against specific HDAC sub-types (Wong, J.; Hong, R.; Schreiber, S., *J. Am. Chem. Soc.* 125, 5586–5587 (2003); Haggarty, S. J.; Koeller, K. M.; Wong, J. C.; Grozinger, C. M.; Schreiber, S. L., *Proc. Natl. Acad. Sci. USA*, 100, 4389-4394 (2003)).

Cyclic-peptide moieties are the most complex of all HDAC inhibitor cap-groups and present an opportunity for the modulation of the biological activities of HDAC inhibitors. The macrocycle group is made up of hydrophobic amino acids and the prominent difference among the members of this class is in the amino acid side-chain substitution on the ring. Mechanistically, cyclic-peptide HDAC inhibitors could be divided into two classes: (i) reversible HDAC inhibitors and (ii) irreversible HDAC inhibitors, due to the alkylative modification of HDAC enzyme by the epoxy-ketone moiety on their side-chain. HDAC inhibitory activity and selectivity varied significantly by changing the side-chain of each amino acid and the pattern of the combination of amino acid chirality (Komatsu, Y.; Tomizaki, K.; Tsukamoto, M.; Kato, T. *et al.*, *Cancer Res.* 61, 4459–4466 (2001); Furumai, R.; Komatsu, Y.; Nishino, N.; Khochbin, S.; Yoshida, M. *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 98, 87-92 (2001); Nishino, H.; Tomizaki, K.; Kato, T.; Nishino, N.; Yoshida, M.; Komatsu, Y., *Peptide Sci.- Symp.*, 189-192 (1998)).

Although cyclic-peptide HDAC inhibitors may possess potent HDAC inhibitory activity (nanomolar range), their broad application in specific therapies, such as cancer therapy, currently remains largely unproven. The

absence of clinically effective cyclic-peptide HDAC inhibitors may be in part due to development problems characteristic of large peptides, most especially poor oral bioavailability. In fact, the overall *in vivo* efficacy of cyclic-peptide HDAC inhibitors is complicated by their membrane penetration ability. HDAC inhibitory potency has been noted to increase with increase in the hydrophobicity of the macrocyclic ring (Meinke, P. T.; Liberator, P., *Curr. Med. Chem.*, 8, 211-235 (2001)). Unfortunately, SAR studies for this class of compounds have been impaired largely because most macrocyclic HDAC inhibitors known to date contain peptide macrocycles. In addition to retaining the pharmacologically disadvantaged peptidyl-backbone, they offer only limited opportunity for side-chain modifications.

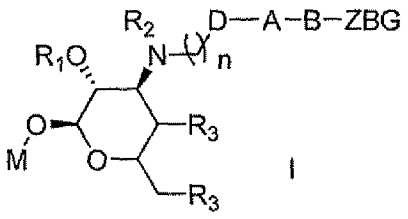
To date, several other structurally distinct small molecule HDAC inhibitors have been reported including hydroxamates, benzamides, short-chain fatty acids, electrophilic ketones and cyclic-peptides (Miller, T. A.; Witter, D. J.; Belvedere, S., *J. Med. Chem.* 46, 5097-5116 (2003); Rosato, R. R.; Grant, S., *Expert Opin. Invest. Drugs*, 13, 21-38 (2004); Monneret, C., *Eur. J. of Med. Chem.*, 40, 1–13 (2005); Yoo, C. B.; Jones, P. A., *Nature Reviews Drug Discovery*, 5, 37-50 (2006)). Most of these agents have been shown to non-selectively inhibit the deacetylase activity of class I/II HDAC enzymes. The HDAC inhibitor SAHA has been approved by the FDA for the treatment of cutaneous T cell lymphoma. However, a large number of the identified HDAC inhibitors have elicited only limited *in vivo* antitumor activities and have not progressed beyond preclinical characterizations.

Therefore, there is a need to develop new HDAC inhibitors with improved efficacy, and better pharmacokinetic properties for use as therapeutic agents, such as anti-cancer agents.

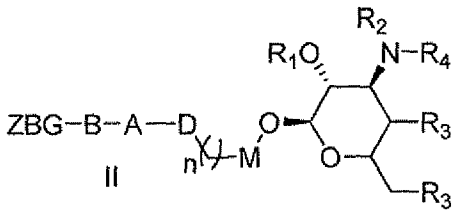
It is therefore an object of the invention to provide non-peptide macrocyclic HDAC inhibitors having improved efficacy and methods of making and using thereof.

SUMMARY OF THE INVENTION

Compounds of Formula I or II, and methods of making and using thereof, are described herein.



I



II

wherein M represents a macrolide subunit,

n consists of C_{1-6} group, optionally containing one or more heteroatoms, wherein the carbon atoms and/or heteroatoms are in a linear and/or cyclic arrangement,

D is an alkyl or aryl group,

A is a linking group connected to D,

B is an alkyl, alkylaryl or alkylheteroaryl spacer group,

ZBG is a Zinc Binding Group,

R_1, R_2 and R_4 are independently are selected from the group consisting of hydrogen, a C1-6 alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, C_{1-6} alkanoate group, C_{2-6} carbamate group, C_{2-6} carbonate group, C_{2-6} carbamate group, or C_{2-6} thiocarbamate group,

R_3 is hydrogen or -OR_5,

R_5 is selected from a group consisting of Hydrogen, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, C_{1-6} alkanoate group, C_{2-6} carbamate group, C_{2-6} carbonate group, C_{2-6} carbamate group, or C_{2-6} thiocarbamate group.

The compounds can be administered as the free acid or base, or as a pharmaceutically acceptable salt, prodrug, or solvate. The compounds may be useful as anti-cancer agents, anti-inflammatory agents, anti-infective agents, anti-malarial agents, cytoprotective agents, chemopreventive agents, prokinetic agents, and/or cognitive enhancing agents. The presence of the marolide group allows for the targeted delivery of the HDAC inhibitor in view on the ability of macrolides to accumulate in specific tissues. The compounds described herein can be formulated with a pharmaceutically acceptable carrier and, optionally one or more pharmaceutically acceptable excipients, for enteral, parenteral, or topical administration. The compounds

can be formulated for immediate release and/or controlled release. Examples of controlled release formulations include sustained release, delayed release, pulsatile release, and combinations thereof.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

"Macrolide", as used herein, includes, but is not limited to, multi-member lactonic ring molecules, wherein "member" refers to the carbon atoms or heteroatoms in the ring, and "multi" is a number greater than about 10, preferably from 10 to about 20, more preferably 12-, 14-, 15-, 16-, 17- or 18-member lactonic rings. Suitable macrolides include, but are not limited to, azithromycin and its derivatives; clarithromycin and its derivatives; erythromycin and its derivatives; bridged bicyclic macrolides, such as EDP-420 and its derivatives; dirithromycin, 9-dihydro-9-deoxo-9a-aza-9a-homoerythromycin; HMR 3004, HMR 3647; HMR 3787; josamycin; erythromycylamine; ABT 773; TE 802; flurithromycin; tylosin; tilmicosin; oleandomycin; desmycosin; CP- 163505; EDP-420; roxithromycin; miocamycin; rokitamycin and derivatives thereof, such as ketolides (e.g., 3-ketone), lactams (e.g., 8a- or 9a-lactams) and derivatives lacking one or more sugar moieties.

"Aryl", as used herein, refers to 5-, 6- and 7-membered aromatic, heterocyclic, fused aromatic, fused heterocyclic, biaromatic, or bihetereocyclic ring systems, optionally substituted, for example, by halogens, alkyl-, alkenyl-, and alkynyl-groups. Broadly defined, "Ar", as used herein, includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate,

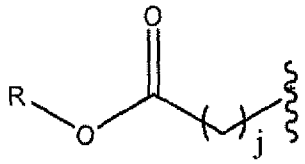
phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, --CF_3, --CN, or the like. The term "Ar" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (i.e., "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic ring or rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocycles. Examples of heterocyclic ring include, but are not limited to, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3 b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl and xanthenyl.

"Zinc binding group" or "ZBG", as used herein, refers to a moiety of moieties capable of inhibiting the activity of zinc metalloenzymes including,

but not limited to, HDAC and matrix metalloproteinase (MMP) activity. Suitable examples include, but are not limited to, hydroxamates, N-formyl hydroxylamine (or retro-hydroxamate), carboxylates, thiols, dithiols, trithiocarbonates, thioesters, benzamide, keto, mercaptoacetamides, 2-ketoamides, epoxides, epoxyketones, trifluoromethyl ketones, hydroxypyridinones, pyrones, hydroxylpyridinethiones, and thiopyrones.

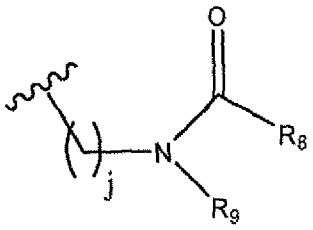
"Alkyl", as used herein, refers to the radical of saturated or unsaturated aliphatic groups, including straight-chain alkyl, alkenyl, or alkynyl groups, branched-chain alkyl, alkenyl, or alkynyl groups, cycloalkyl, cycloalkenyl, or cycloalkynyl (alicyclic) groups, alkyl substituted cycloalkyl, cycloalkenyl, or cycloalkynyl groups, and cycloalkyl substituted alkyl, alkenyl, or alkynyl groups. Unless otherwise indicated, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C1-C30 for straight chain, C3-C30 for branched chain), and more preferably 20 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure.

"Alkoxycarbonyl", as used herein, refers to a substituent having the following chemical formula:



wherein R is a linear, branched, or cyclic alkyl group, wherein j is from about 1 to about 12.

"Alkoxycarbamido", as used herein, refers to a substituent having the following chemical formula:



wherein R_8 is alkoxy and R_9 is hydrogen, alkoxy-alkyl, or alkanoyl, and j is from about 1 to about 12.

"Alkylaryl", as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or hetero aromatic group).

"Heterocycle" or "heterocyclic", as used herein, refers to a cyclic radical attached via a ring carbon or nitrogen of a monocyclic or bicyclic ring containing 3-10 ring atoms, and preferably from 5-6 ring atoms, consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) wherein Y is absent or is H, O, $(C_1$- $_4)$alkyl, phenyl or benzyl, and optionally containing 1-3 double bonds and optionally substituted with one or more substituents. Examples of heterocyclic ring include, but are not limited to, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole,

pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl and xanthenyl.

"Heteroaryl", as used herein, refers to a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and 1, 2, 3, or 4 heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(Y) where Y is absent or is H, O, (C_1-C_8) alkyl, phenyl or benzyl. Non-limiting examples of heteroaryl groups include furyl, imidazolyl, triazolyl, triazinyl, oxazoyl, isoxazoyl, thiazolyl, isothiazoyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide), quinolyl (or its N-oxide) and the like. The term "heteroaryl" can include radicals of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto. Examples of heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazoyl, isoxazoyl, thiazolyl, isothiazoyl, pyraxolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl (or its N-oxide), thientyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide), quinolyl (or its N-oxide), and the like.

"Halogen", as used herein, refers to fluorine, chlorine, bromine, or iodine.

The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The terms ortho, meta and para apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

"Pharmaceutically acceptable salt", as used herein, refer to derivatives of the compounds defined by Formula I and II wherein the parent compound is modified by making acid or base salts thereof. Example of pharmaceutically acceptable salts include but are not limited to mineral or organic acid salts of basic residues such as amines; and alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. Such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, tolunesulfonic, naphthalenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic salts.

The pharmaceutically acceptable salts of the compounds can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000, p. 704; and "Handbook of Pharmaceutical Salts: Properties, Selection, and Use," P. Heinrich Stahl and Camille G. Wermuth, Eds., Wiley-VCH, Weinheim, 2002.

As generally used herein "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity,

irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

"Prodrug", as used herein, refers to a pharmacological substance (drug) which is administered in an inactive (or significantly less active) form. Once administered, the prodrug is metabolized in the body (in vivo) into the active compound.

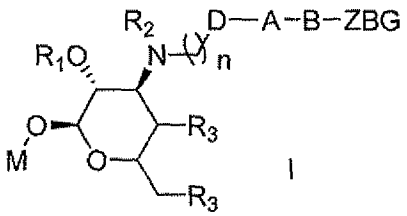
"Solvate", as used herein, refers to a compound which is formed by the interaction of molecules of a solute with molecules of a solvent.

"Reverse ester", as used herein, refers to the interchange of the positions of the oxygen and carbon groups in a series of structurally related compounds

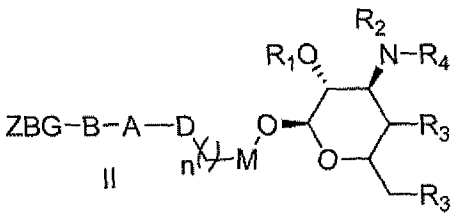
"Reverse amide", as used herein, refers to the interchange of the positions of the nitrogen and carbon groups in a series of structurally related compounds.

II. Compounds

Compounds of Formula I or II, and methods of making and using thereof, are described herein.



I



II

wherein M represents a macrolide subunit,

n is a C_{1-6} group, optionally containing one or more heteroatoms, wherein the carbon atoms and/or heteroatoms are in a linear and/or cyclic arrangement,

D is an alkyl or aryl group,

A is a linking group connected to D,

B is an alkyl, alkylaryl or alkylheteroaryl spacer group,

ZBG is a Zinc Binding Group,

R_1, R_2 and R_4 are independently are selected from hydrogen, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{1-6} alkanoate

group, a C_{2-6} carbamate group, a C_{2-6} carbonate group, a C_{2-6} carbamate group, or C_{2-6} thiocarbamate group,

R_3 is hydrogen or $-OR_5$, wherein

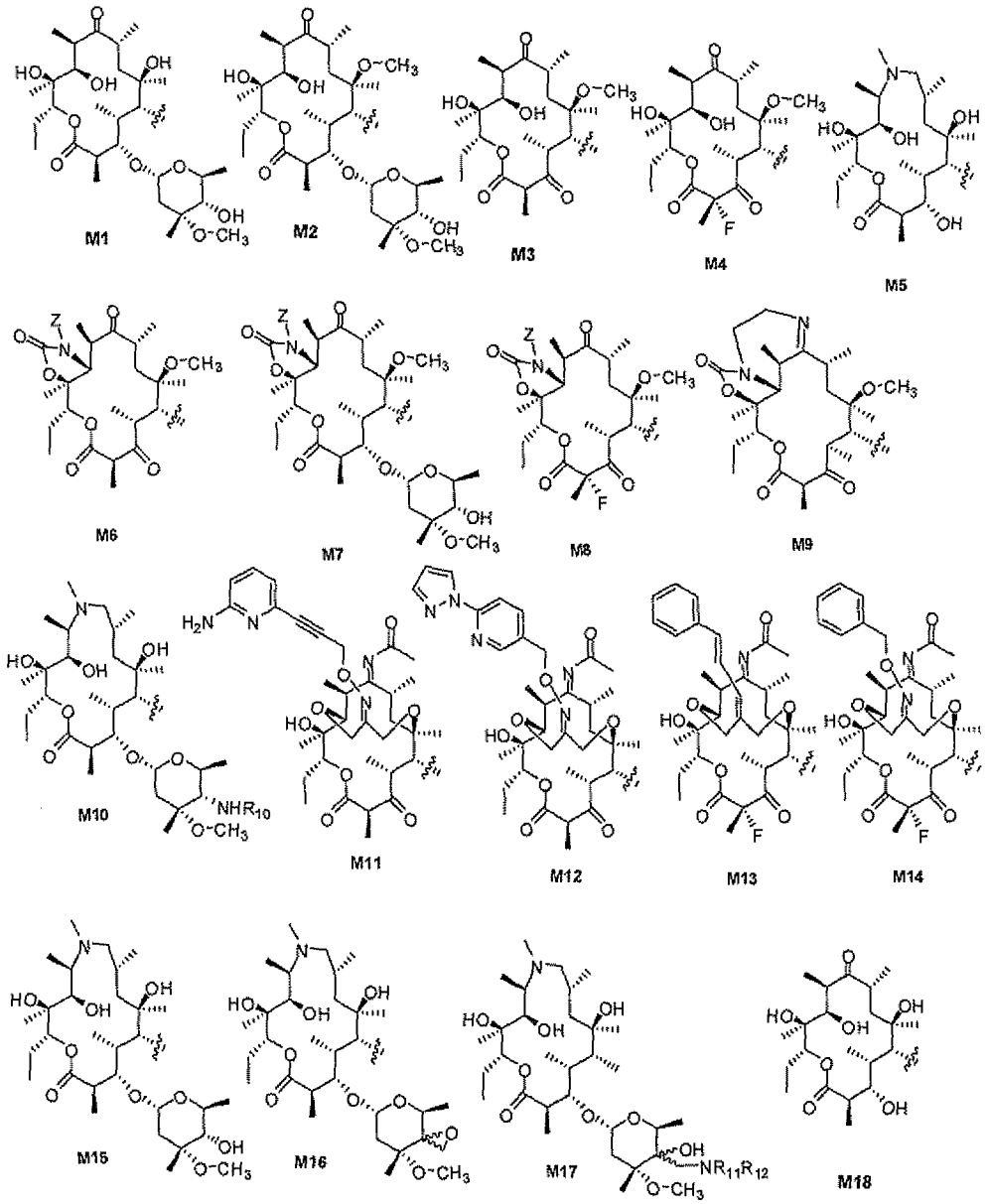
R_5 is selected from hydrogen, a C_{1-6} alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, C_{1-6} alkanoate group, C_{2-6} carbamate group, C_{2-6} carbonate group, C_{2-6} carbamate group, or C_{2-6} thiocarbamate group.

Examples of the linking group A include, but are not limited to, amide, reverse amide, ester, reverse ester, alkoxyl, sulfanyl, sulfinyl, sulfonyl, sulfonamido, ketone, sp^3 hybridized carbon, sp^2 hybridized carbon, sp hybridized carbon, 5 or 6 membered heterocyclic rings including but not limiting to 1,2,3-triazolyl, l,2,4-triazolyl, 1-tetrazolyl, 1-indolyl, 1- indazolyl, 2-isoindolyl, 7-oxo-2-isoimdolyl,1-pirinyl, 3-isothiazolyl, 4-isothiazolyl and 5- isothiazolyl, 1,3,4,-oxadiazole, 4-oxo-2-thiazolinyl or 5-rnethyl-l.3,4-thiadiazol-2-yl, thiazoledione, 1,2,3,4-thiatriazole, 1,2,4-dithiazolone, pyridine, thiophene, furan, pyrazoline, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazolyl, 2-quinolyl. 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxalinyl, 1-phthalazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyI, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 4,5-dihydrooxazole, 1,2,3-oxathiole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, benzoisothiazole. benzisoxazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3-oxathiazole-1-oxide, l,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-l,2,4-oxadiazol-3-yl, l,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 1-pyrrolyl, l-pyrazolyl. Each of these moieties may be substituted as appropriate.

B is an alkyl, alkylaryl or alkylheteroaryl spacer group. Suitable alkyl spacer group chain length ranges from about C_4 to about C_{12}, optionally substituted by one or more double and/or triple bonds. The total number of atoms in the alkylaryl and alkylheteroaryl groups is from about 6 to about 50.

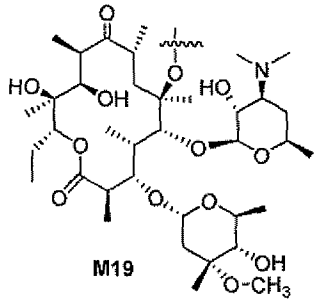
M is a macrolide subunit. Suitable macrolide subunits include, but are not limited to, multi-member lactonic ring molecules, wherein "member" refers to the carbon atoms or heteroatoms in the ring, and "multi" is a number greater than about 10, preferably from 10 to about 20, more preferably 12-, 14-, 15-, 16-, 17- or 18-member lactonic rings. Exemplary macrolides include, but are not limited to, azithromycin and its derivatives; clarithromycin and its derivatives; erythromycin and its derivatives; bridged bicyclic macrolide, such as EDP-420 and its derivatives; dirithromycin, 9-dihydro-9-deoxo-9a-aza-9a-homoerythromycin; HMR 3004, HMR 3647; HMR 3787; josamycin; erythromycylamine; ABT 773; flurithromycin; tylosin; tilmicosin; oleandomycin; desmycosin; CP- 163505; EDP-420; roxithromycin; miocamycin; rokitamycin and derivatives thereof, such as ketolides (e.g., 3-ketone), lactams (e.g., 8a- or 9a-lactams) and derivatives lacking one or more sugar moieties. Other suitable macrolides are shown in Table 1:

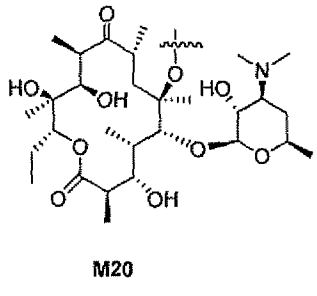
Table 1. Macrolide Subunits

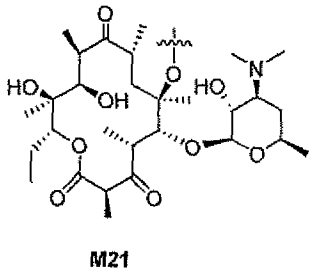


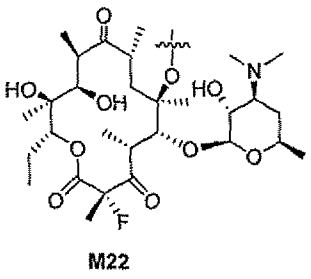
In another embodiment, the points of attachment of the ZBG are O6 and O9 in the 14-membered macrolides shown in Table 2:

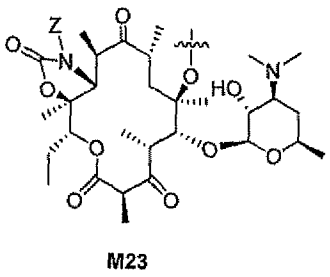
Table 2. 14-Membered Macrolides

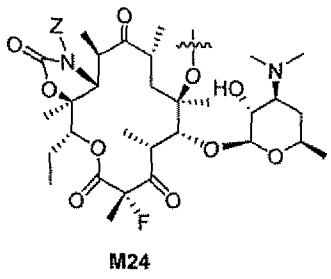


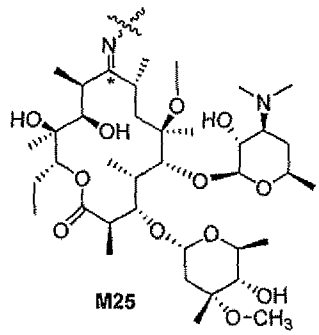


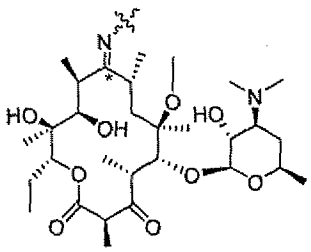








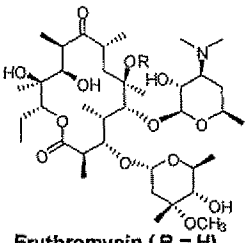




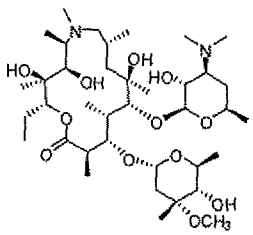
In M25 and M26, the bond between the starred carbon and the nitrogen can be a single bond or a double bond. This is represented by a dashed line in the structures of M25 and M26.

Macrolide antibiotics have been in use for over 50 years for the treatment of respiratory tract infections. Over the past 20 years, macrolides have also been shown to have other non-antibiotic properties. For example, they have demonstrated anti-inflammatory and immunomodulatory effects making them potential candidates for the management of diseases of chronic airway inflammation. Fourteen-membered and fifteen-membered macrolides, such as erythromycin, clarithromycin, and azithromycin, the

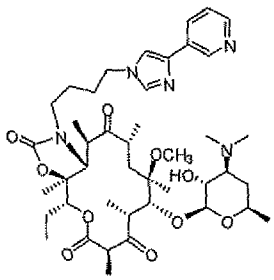
structures of which are shown below, have shown improved pulmonary function, and decrease morbidity and mortality in patients with diffuse panbronchiolitis (DPB).



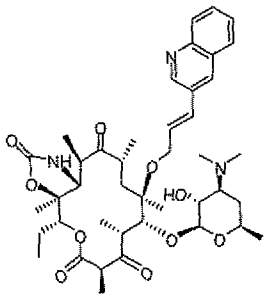
Erythromycin (R = H)
Clarithomycin (R = Me)



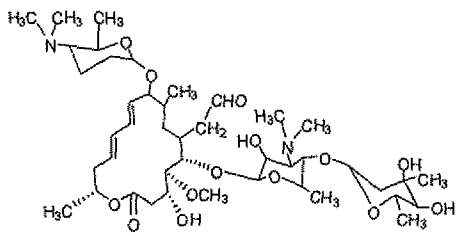
Azithromycin



Telithromycin (Ketek)



Cethromycin (ABT-773)



Spiramycin

Additionally, clarithromycin and azithromycin a positive immunomodulatory effects in patients with non-small-cell cancer. However, a direct role of macrolides in cancer therapy is still being investigated. Earlier observations by Parajuli et al. showed that clarithromycin alone did not have a therapeutic effect on the growth and organ metastasis of human non-small cell lung cancer cells in severe combined immunodeficient (SCID) mouse models (*see* also Sassa, K.; Mizushima, Y.; Fujishita, T.; Oosaki, R.; Kobayashi, M., *Antimicrob. Agents Chemother.*, 43, 67-72 (1999)). Yatsunami *et al.* investigated the effects of macrolide antibiotics on tumor angiogenesis and found that two 14-membered ring macrolide antibiotics, roxithromycin and clarithromycin, significantly reduced the dense capillary network area in a mouse dorsal air sac angiogenesis model (Yatsunami, J.; Fukuno, Y.; Nagata, M.; Tominaga, M.; Aoki, S.; Tsuruta, N. *et al.*, *Clin. Exp. Metastasis*, 17, 361-367 (1999)). Also, evidence has begun to emerge on the beneficial effect of azithromycin in cystic fibrosis (CF) management.

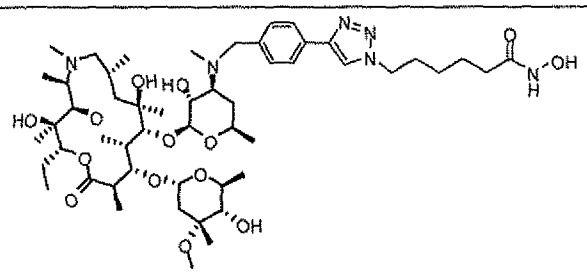
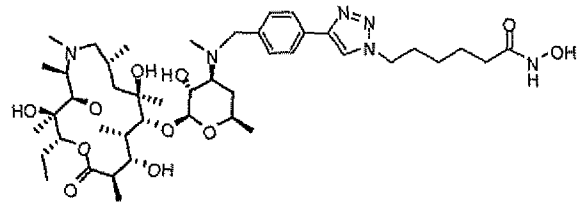
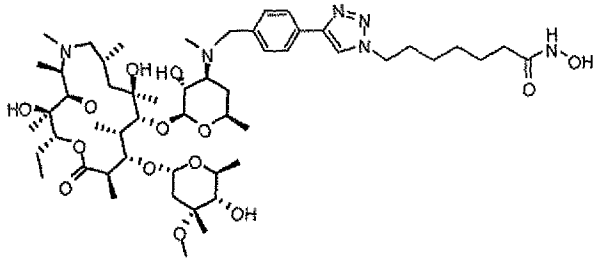
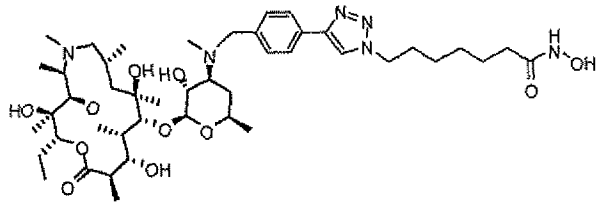
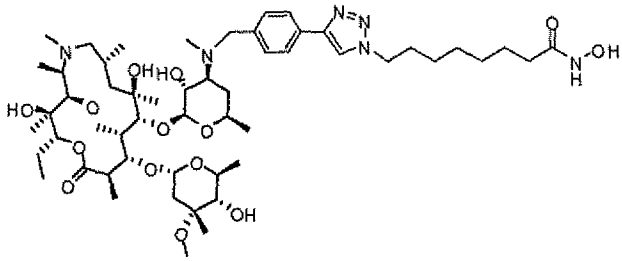
The compounds described herein may have one or more chiral centers and thus exist as one or more stereoisomers. Such stereoisomers can

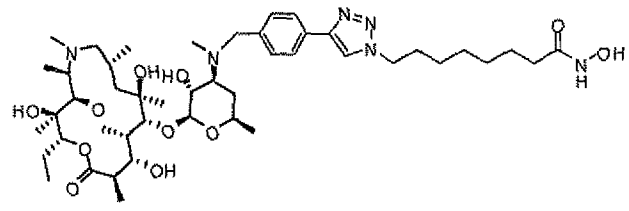
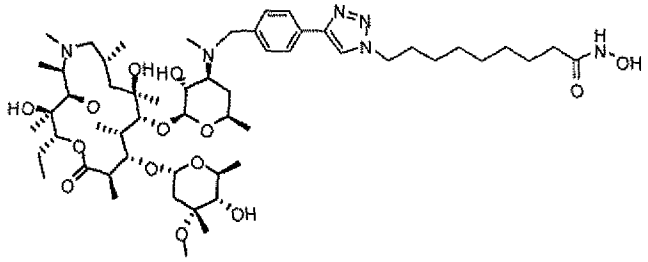
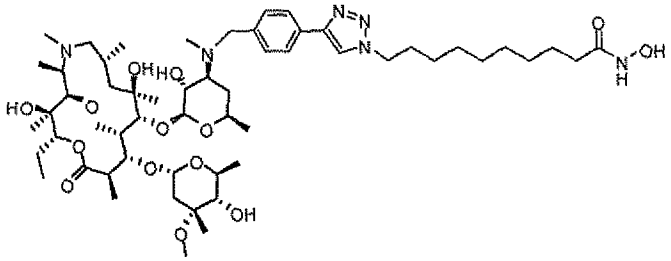
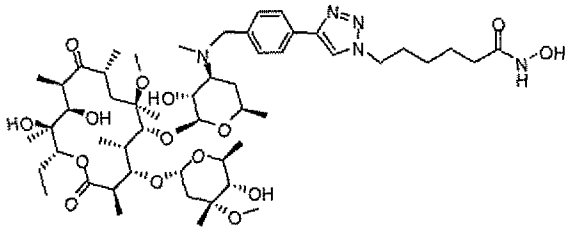
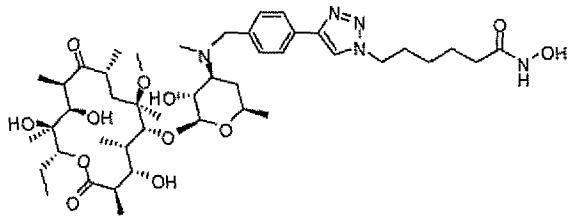
exist as a single enantiomer, a mixture of diastereomers or a racemic mixture.

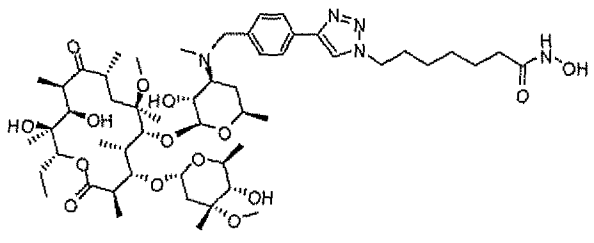
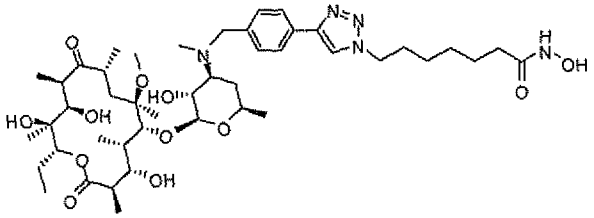
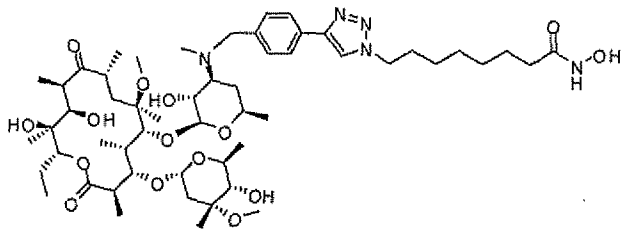
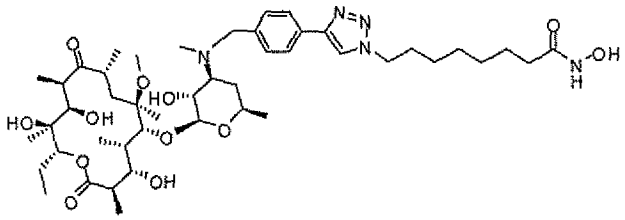
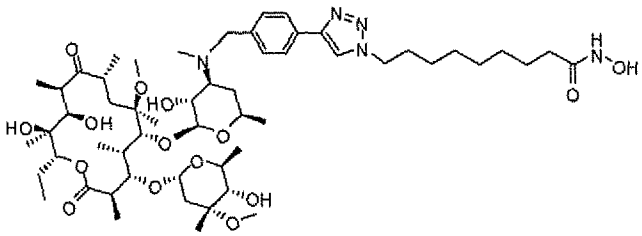
As used herein, the term "stereoisomers" refers to compounds made up of the same atoms having the same bond order but having different three-dimensional arrangements of atoms which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomers" refers to two stereoisomers which are non-superimposable mirror images of one another. As used herein, the term "optical isomer" is equivalent to the term "enantiomer". As used herein the term "diastereomer" refers to two stereoisomers which are not mirror images but also not superimposable. The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers. The term "chiral center" refers to a carbon atom to which four different groups are attached. Choice of the appropriate chiral column, eluent, and conditions necessary to effect separation of the pair of enantiomers is well known to one of ordinary skill in the art using standard techniques (see e.g. Jacques, J. et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc. 1981).

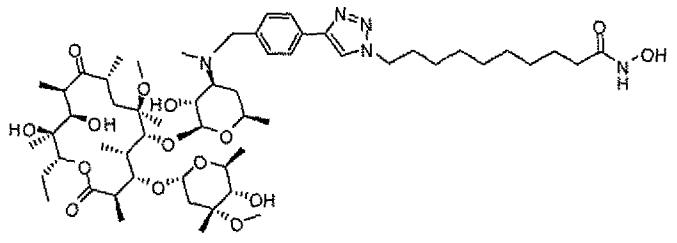
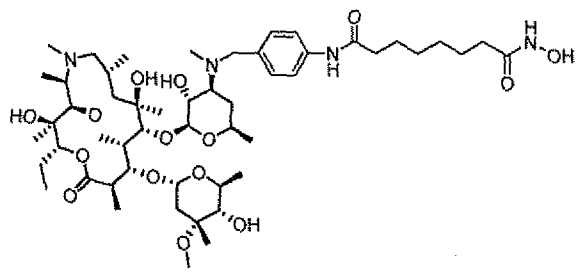
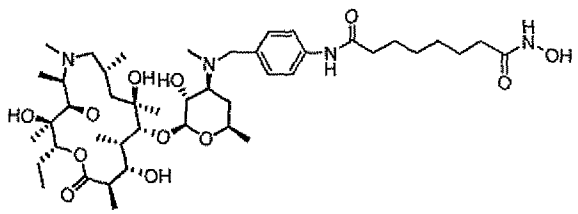
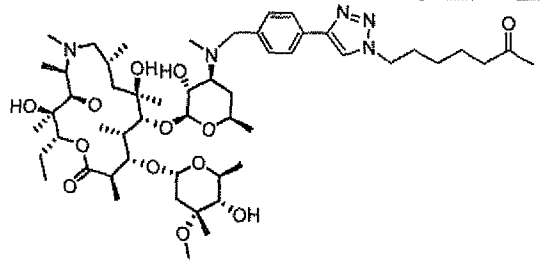
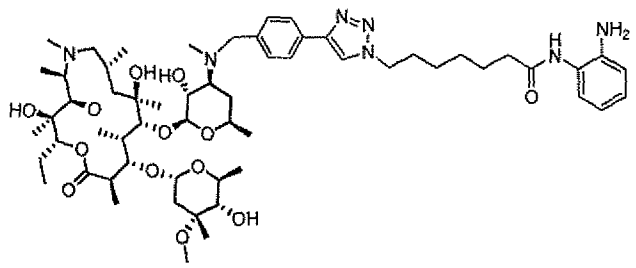
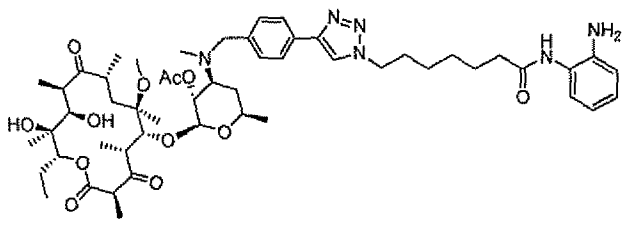
Non-limiting examples of HDAC inhibitors of Formula I and II are shown in Table 3.

Table 3. Additional HDAC Inhibitors

COMPOUND NUMBER	STRUCTURE
7	
8	
9	
10	
11	

12	
13	
14	
23	
24	

25	
26	
27	
28	
29	

30	
36	
38	
40	
44	
47	

It is believed that substitution of the cyclic peptide moiety of a prototypical cyclic-peptide HDAC inhibitor with macrolide skeletons will generate a new class of potent HDAC inhibitors. Furthermore, this class of HDAC inhibitors may possess targeted activity, such as targeted anti-cancer activity due to selective tissue distribution conferred by the macrolide moiety. The biological effects of macrolides are aided by their high distribution into target tissues. Macrolides accumulate in higher concentration within leukocytes as compared to levels found in serum (Labro, M. T. Effects of macrolides on leukocytes and inflammation. In Expanding Indications of the New Macrolides, Azalides and Streptogramins (Zinner, S., Young, S. & Acar, J., Eds), Marcel Dekker, Inc., New York, NY, USA. pp. 101–116 (1997)).

III. Formulations

Formulations containing one or more of the compounds described herein may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, diluents, binders, lubricants, disintegrators, fillers, pH modifying agents, preservatives, antioxidants, solubility enhancers, and coating compositions.

Carrier also includes all components of coating compositions which may include plasticizers, pigments, colorants, stabilizing agents, and glidants. Delayed release, extended release, and/or pulsatile release dosage formulations may be prepared as described in standard references such as "Pharmaceutical dosage form tablets", eds. Liberman et. al. (New York, Marcel Dekker, Inc., 1989), "Remington – The science and practice of pharmacy", 20th ed., Lippincott Williams & Wilkins, Baltimore, MD, 2000, and "Pharmaceutical dosage forms and drug delivery systems", 6th Edition, Ansel et al., (Media, PA: Williams and Wilkins, 1995). These references

provide information on carriers, materials, equipment and process for preparing tablets and capsules and delayed release dosage forms of tablets, capsules, and granules.

Examples of suitable coating materials include, but are not limited to, cellulose polymers such as cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate; polyvinyl acetate phthalate, acrylic acid polymers and copolymers, and methacrylic resins that are commercially available under the trade name EUDRAGIT® (Roth Pharma, Westerstadt, Germany), zein, shellac, and polysaccharides.

Additionally, the coating material may contain conventional carriers such as plasticizers, pigments, colorants, glidants, stabilization agents, pore formers and surfactants.

Optional pharmaceutically acceptable excipients present in the drug-containing tablets, beads, granules or particles include, but are not limited to, diluents, binders, lubricants, disintegrants, colorants, stabilizers, and surfactants. Diluents, also referred to as "fillers," are typically necessary to increase the bulk of a solid dosage form so that a practical size is provided for compression of tablets or formation of beads and granules. Suitable diluents include, but are not limited to, dicalcium phosphate dihydrate, calcium sulfate, lactose, sucrose, mannitol, sorbitol, cellulose, microcrystalline cellulose, kaolin, sodium chloride, dry starch, hydrolyzed starches, pregelatinized starch, silicone dioxide, titanium oxide, magnesium aluminum silicate and powdered sugar.

Binders are used to impart cohesive qualities to a solid dosage formulation, and thus ensure that a tablet or bead or granule remains intact after the formation of the dosage forms. Suitable binder materials include, but are not limited to, starch, pregelatinized starch, gelatin, sugars (including sucrose, glucose, dextrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums such as acacia, tragacanth, sodium alginate, cellulose, including hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, and veegum, and synthetic polymers such as acrylic acid and

methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, aminoalkyl methacrylate copolymers, polyacrylic acid/polymethacrylic acid and polyvinylpyrrolidone.

Lubricants are used to facilitate tablet manufacture. Examples of suitable lubricants include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, glycerol behenate, polyethylene glycol, talc, and mineral oil.

Disintegrants are used to facilitate dosage form disintegration or "breakup" after administration, and generally include, but are not limited to, starch, sodium starch glycolate, sodium carboxymethyl starch, sodium carboxymethylcellulose, hydroxypropyl cellulose, pregelatinized starch, clays, cellulose, alginine, gums or cross linked polymers, such as cross-linked PVP (Polyplasdone XL from GAF Chemical Corp).

Stabilizers are used to inhibit or retard drug decomposition reactions which include, by way of example, oxidative reactions.

Surfactants may be anionic, cationic, amphoteric or nonionic surface active agents. Suitable anionic surfactants include, but are not limited to, those containing carboxylate, sulfonate and sulfate ions. Examples of anionic surfactants include sodium, potassium, ammonium of long chain alkyl sulfonates and alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylthioxyl)-sulfosuccinate; and alkyl sulfates such as sodium lauryl sulfate. Cationic surfactants include, but are not limited to, quaternary ammonium compounds such as benzalkonium chloride, benzethonium chloride, cetrimonium bromide, stearyl dimethylbenzyl ammonium chloride, polyoxyethylene and coconut amine. Examples of nonionic surfactants include ethylene glycol monostearate, propylene glycol myristate, glyceryl monostearate, glyceryl stearate, polyglyceryl-4-oleate, sorbitan acylate, sucrose acylate, PEG-150 laurate, PEG-400 monolaurate, polyoxyethylene monolaurate, polysorbates, polyoxyethylene octylphenylether, PEG-1000 cetyl ether, polyoxyethylene tridecyl ether, polypropylene glycol butyl ether,

Poloxamer® 401, stearoyl monoisopropanolamide, and polyoxyethylene hydrogenated tallow amide. Examples of amphoteric surfactants include sodium N-dodecyl-.beta.-alanine, sodium N-lauryl-.beta.-iminodipropionate, myristoamphoacetate, lauryl betaine and lauryl sulfobetaine.

If desired, the tablets, beads, granules, or particles may also contain minor amount of nontoxic auxiliary substances such as wetting or emulsifying agents, dyes, pH buffering agents, or preservatives.

A. Other Active Agents

The HDAC inhibitors described herein can be administered adjunctively with other active compounds. These compounds include but are not limited to analgesics, anti-inflammatory drugs, antipyretics, antidepressants, antiepileptics, antihistamines, antimigraine drugs, antimuscarinics, anxioltyics, sedatives, hypnotics, antipsychotics, bronchodilators, anti-asthma drugs, cardiovascular drugs, corticosteroids, dopaminergics, electrolytes, gastro-intestinal drugs, muscle relaxants, nutritional agents, vitamins, parasympathomimetics, stimulants, anorectics and anti-narcoleptics. "Adjunctive administration", as used herein, means the HDAC inhibitors can be administered in the same dosage form or in separate dosage forms with one or more other active agents.

Specific examples of compounds that can be adjunctively administered with the GDAC inhibitors include, but are not limited to, aceclofenac, acetaminophen, adomexetine, almotriptan, alprazolam, amantadine, amcinonide, aminocyclopropane, amitriptyline, amolodipine, amoxapine, amphetamine, aripiprazole, aspirin, atomoxetine, azasetron, azatadine, beclomethasone, benactyzine, benoxaprofen, bermoprofen, betamethasone, bicifadine, bromocriptine, budesonide, buprenorphine, bupropion, buspirone, butorphanol, butriptyline, caffeine, carbamazepine, carbidopa, carisoprodol, celecoxib, chlordiazepoxide, chlorpromazine, choline salicylate, citalopram, clomipramine, clonazepam, clonidine, clonitazene, clorazepate, clotiazepam, cloxazolam, clozapine, codeine, corticosterone, cortisone, cyclobenzaprine, cyproheptadine, demexiptiline, desipramine, desomorphine, dexamethasone, dexanabinol,

dextroamphetamine sulfate, dextromoramide, dextropropoxyphene, dezocine, diazepam, dibenzepin, diclofenac sodium, diflunisal, dihydrocodeine, dihydroergotamine, dihydromorphine, dimetacrine, divalproxex, dizatriptan, dolasetron, donepezil, dothiepin, doxepin, duloxetine, ergotamine, escitalopram, estazolam, ethosuximide, etodolac, femoxetine, fenamates, fenoprofen, fentanyl, fludiazepam, fluoxetine, fluphenazine, flurazepam, flurbiprofen, flutazolam, fluvoxamine, frovatriptan, gabapentin, galantamine, gepirone, ginko bilboa, granisetron, haloperidol, huperzine A, hydrocodone, hydrocortisone, hydromorphone, hydroxyzine, ibuprofen, imipramine, indiplon, indomethacin, indoprofen, iprindole, ipsapirone, ketaserin, ketoprofen, ketorolac, lesopitron, levodopa, lipase, lofepramine, lorazepam, loxapine, maprotiline, mazindol, mefenamic acid, melatonin, melitracen, memantine, meperidine, meprobamate, mesalamine, metapramine, metaxalone, methadone, methadone, methamphetamine, methocarbamol, methyldopa, methylphenidate, methylsalicylate, methysergid(e), metoclopramide, mianserin, mifepristone, milnacipran, minaprine, mirtazapine, moclobemide, modafinil (an anti-narcoleptic), molindone, morphine, morphine hydrochloride, nabumetone, nadolol, naproxen, naratriptan, nefazodone, neurontin, nomifensine, nortriptyline, olanzapine, olsalazine, ondansetron, opipramol, orphenadrine, oxaflozane, oxaprazin, oxazepam, oxitriptan, oxycodone, oxymorphone, pancrelipase, parecoxib, paroxetine, pemoline, pentazocine, pepsin, perphenazine, phenacetin, phendimetrazine, phenmetrazine, phenylbutazone, phenytoin, phosphatidylserine, pimozide, pirlindole, piroxicam, pizotifen, pizotyline, pramipexole, prednisolone, prednisone, pregabalin, propanolol, propizepine, propoxyphene, protriptyline, quazepam, quinupramine, reboxitine, reserpine, risperidone, ritanserin, rivastigmine, rizatriptan, rofecoxib, ropinirole, rotigotine, salsalate, sertraline, sibutramine, sildenafil, sulfasalazine, sulindac, sumatriptan, tacrine, temazepam, tetrabenozine, thiazides, thioridazine, thiothixene, tiapride, tiasipirone, tizanidine, tofenacin, tolmetin, toloxatone, topiramate, tramadol, trazodone, triazolam, trifluoperazine, trimethobenzamide, trimipramine, tropisetron, valdecoxib,

valproic acid, venlafaxine, viloxazine, vitamin E, zimeldine, ziprasidone, zolmitriptan, zolpidem, zopiclone and isomers, salts, and combinations thereof.

IV. Methods of Preparation

Compound numberings, e.g., **1**, **2**, **3**, etc. as used below are for reference within this section only are not to be confused with any similar numberings in the synthetic schemes described below or in the examples.

The schemes below describe exemplary chemistries that can be used to synthesize the compounds described herein. It is to be appreciated the compounds described herein may be synthesized by other methods known in the art.

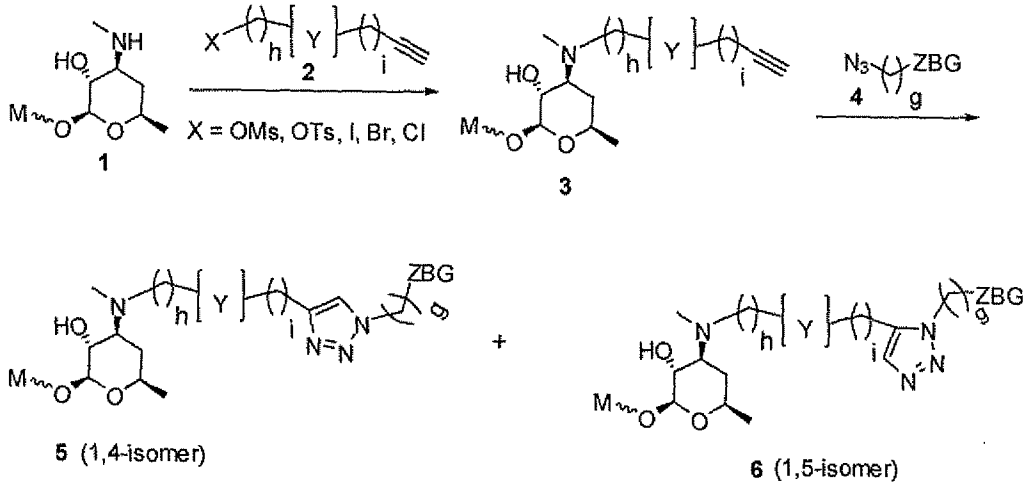
General Synthetic Schemes

Scheme 1a-c illustrates representative general syntheses of compounds of types **5** and **6**, **9** and **10**, and **12** and **13**. The starting des-N-methyl macrolide **1** could be sourced from a variety of N-demethylation reactions of the tertiary amines of basic sugars on macrolides known in the art (*see* Flynn *et al.* (1954) *J. Am. Chem. Soc.*, 76: 3121; U.S. Patent No. 3,725,385; Ku *et al.* (1997) *Bioorg. Med. Chem. Lett.*, 7: 1203; Stenmark *et al.* (2000) *J. Org. Chem.*, 65: 3875; Randolph *et al.* (2004) *J. Med. Chem.*, 47, 1085; and U.S. Patent No. 7,335,753).

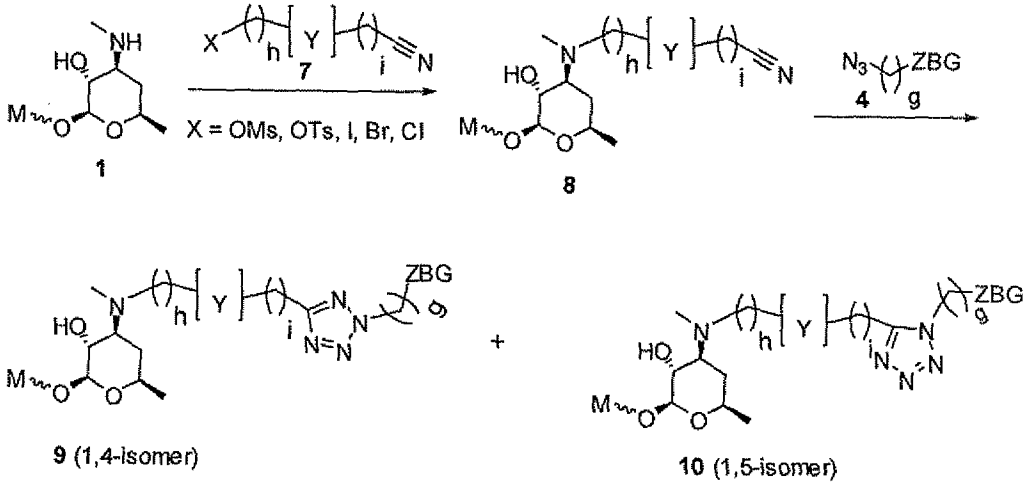
Reaction of **1** with electrophiles **2** and **7** yields alkynes and nitriles **3** and **8** respectively. Reactions of azide **4** and nitrile oxide **11** with alkynes **3** generate two regioisomeric triazole and isoxazole products **5** and **6** and **12** and **13** respectively. The triazole products' regioisomeric ratios and reaction rates could be altered by heating the reaction and/or by the use of catalysts (such as, but not limited to, copper (I) and Ru (II) salts and complexes: see Rostovtsev *et al.* (2002) *Angew. Chem. Int. Ed.*, 41: 2596; Tornoe *et al.* (2002) *J. Org. Chem.*, 67: 3057; Zhang *et al.* (2005) *J. Am. Chem. Soc.*, 127: 15998). Similarly, reaction of nitrile **8** and azide **4** generates two regioisomeric tetrazole products, **9** and **10**. The ZBG in azide **4** can be protected if necessary. Suitable ZBG protecting groups include are described herein.

Scheme 1

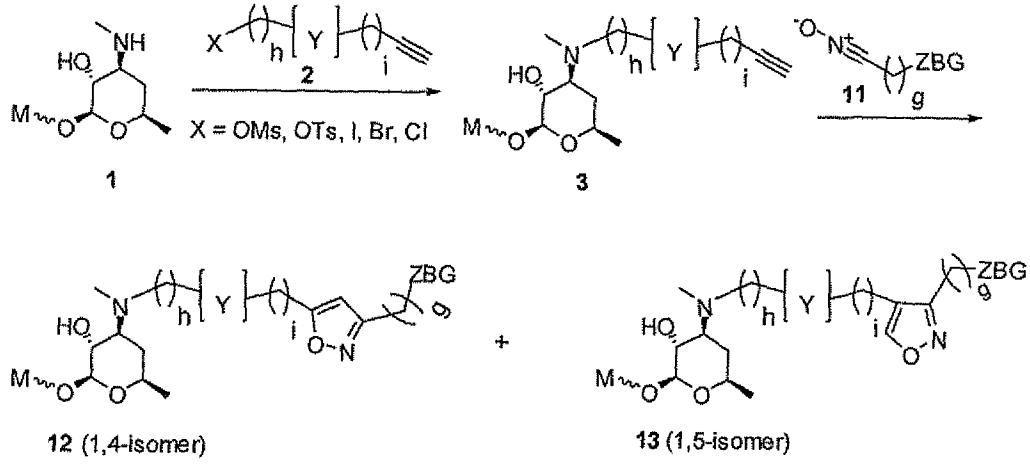
a)


X = OMs, OTs, I, Br, Cl
1
2
3
4
5 (1,4-isomer)
6 (1,5-isomer)

b)

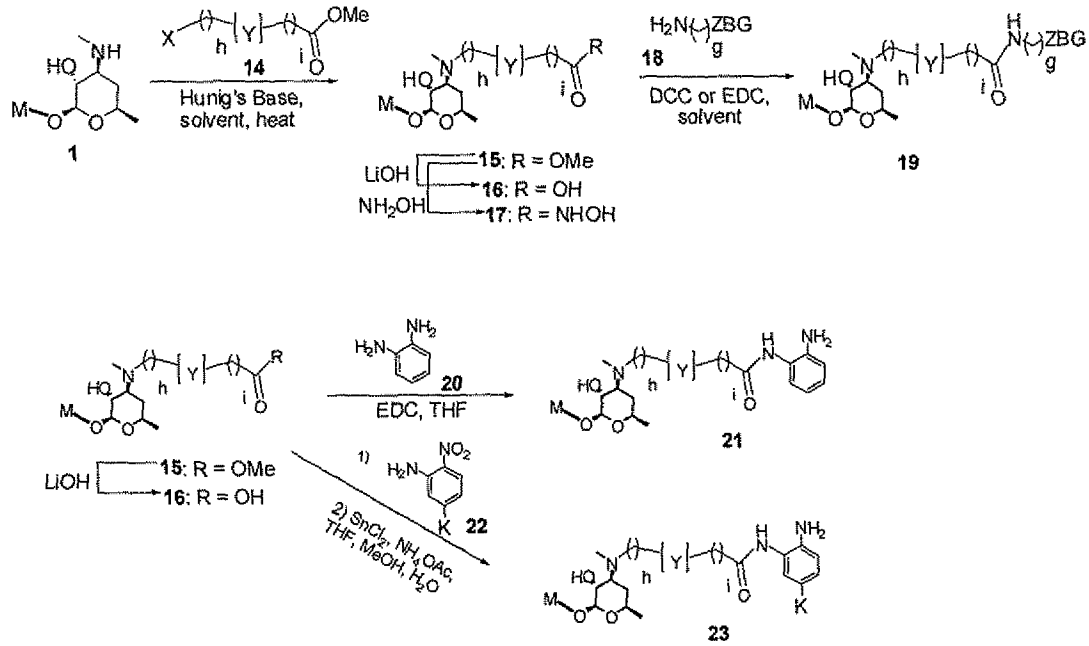

X = OMs, OTs, I, Br, Cl
1
7
8
4
9 (1,4-isomer)
10 (1,5-isomer)

c)


X = OMs, OTs, I, Br, Cl
1
2
3
11
12 (1,4-isomer)
13 (1,5-isomer)

Scheme 2 illustrates representative general syntheses of compounds with amide as the linker-cap group connection moiety and benzamide compounds of types **17** and **19** and **21** and **23** respectively. Reaction of **1** with electrophile **14** yields ester **15**. Compound **15** can be directly reacted with ZBG amine **18** to yield compound **19**. Alternatively, **19** can be obtained from acid **16** and ZBG amine **18** through carbodiimide coupling. Additionally, hydroxamate **17**, containing an appropriate aromatic moiety and appropriate alkyl chain length can be obtained from the reaction of hydroxylamine with ester **15**. Similarly, benzamide compounds **21** and **23** can be prepared from the reaction of ester **15** or acid **16** with anilines **20** and **22**. In the case of the para-substituted benzamide **23**, the intermediate nitro anilide must be reduced to obtain the desired benzamide **23**. The synthesis of para-substituted nitro aniline **22** is known in the art (for example, see Moradei *et al.* (2007) *J. Med. Chem.*, 45, 5543).

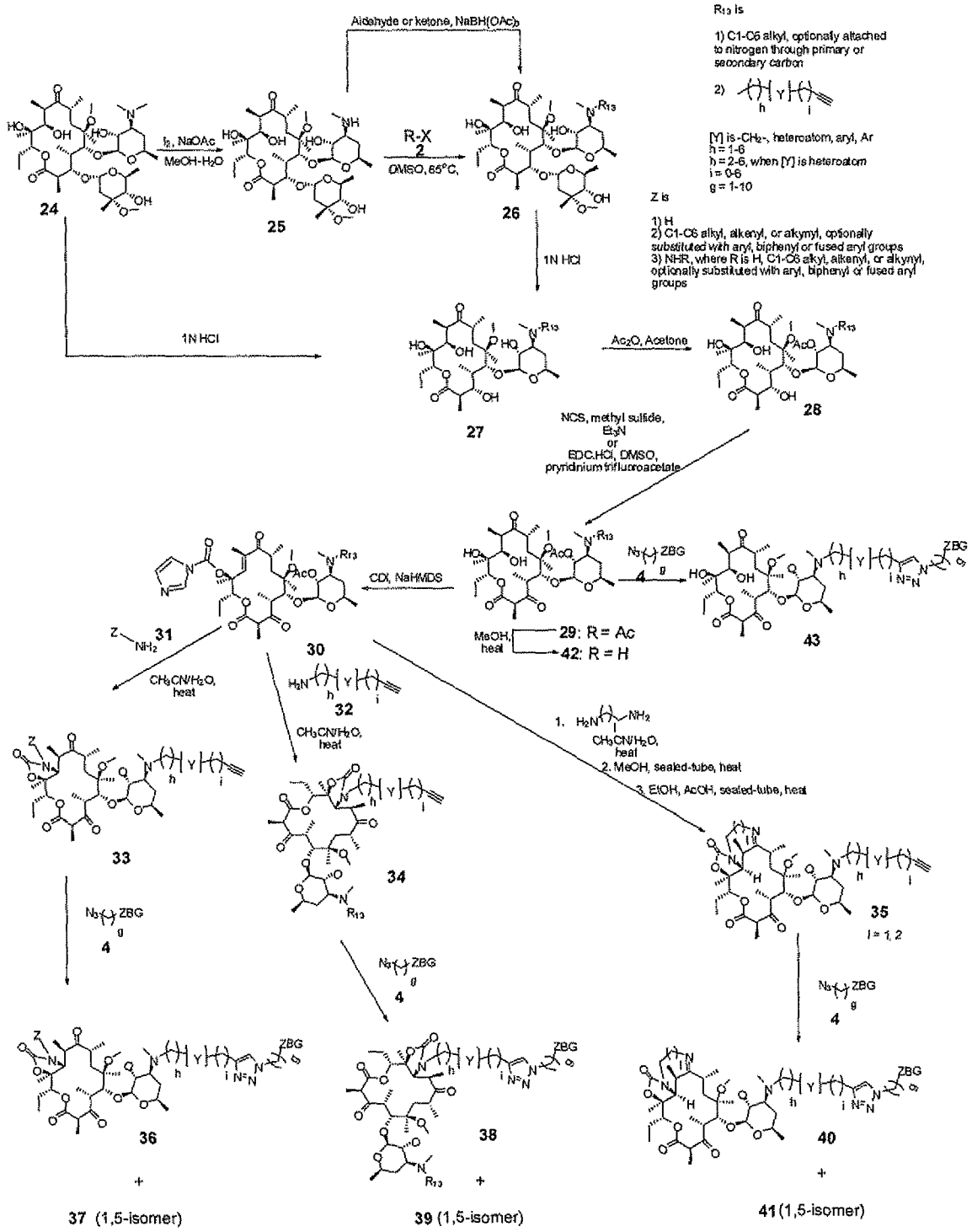
Scheme 2



Scheme 3 illustrates representative general syntheses of ketolide and bridged-ketolide based triazole derivatives. Clarithromycin **24** can be N-

demethylated to give des-N-methyl clarithromycin **25**. Reaction of **25** with electrophile **2** yields alkyne **26**. Alternatively, alkyne **26 can** be obtained by reductive amination of appropriate aldehydes and ketones. Descladinose **27** can be prepared from the treatment of alkyne **26** with dilute mineral acid, such as HCl. Compound **27,** whereR_{13} is CH_3, can be similarly obtained from reaction of **24** with dilute mineral acid. Selective acylation of the hydroxyl group of the amine sugar can be achieved by treatment of compound **27** with acetic anhydride in appropriate non-protic solvents such as, but not limited to, acetone, in the absence of base to yield compound **28**. Oxidation of **28** under Corey-Kim or similar conditions (see Corey & Kim (1972) *J. Am. Chem. Soc.*, 94: 7586; Pfitzner & Moffatt (1965) *J. Am. Chem. Soc.*, 87: 5661; Ley *et al.* (1994) *Synthesis*, 639) leads to ketolide **29**. Treatment of **29** with carbonyldiimidazole and NaHMDS will give carbamate **30**. Reaction of **30** with amines **31**, **32** and ethane-1,2-diamine will afford intermediate **33**, **34**, and **35**, respectively (see U.S. Patent No. 5,631,355; Kashimura *et al.* (2003), *J. Antibiot.*, 56: 1062; Randolph *et al.* (2004) *J. Med. Chem.*, 47, 1085; Plata *et al.* (2004) *Tetr.*, 60: 10171). Subsequent reactions of intermediates **33**, **34**, and **35** with azide **4** will lead to bridged-ketolides **36** and **37**, **38** and **39**, and **40** and **41**, respectively. When R_{13} contains an appropriate aromatic moiety and alkyl chain length, ketolide **29** can be modified to form compound **30** by methanolysis at elevated temperatures. Subsequent reaction of **30** with azide **4** will furnish ketolide **43**. Again, it should be appreciated that the ZBG in azides of type **4** can be appropriately protected. Moreover, similar chemistries can be applied for the synthesis of the tetrazoles and oxazoles analogs of the ketolide and bridged-ketolide exemplified in scheme 3.

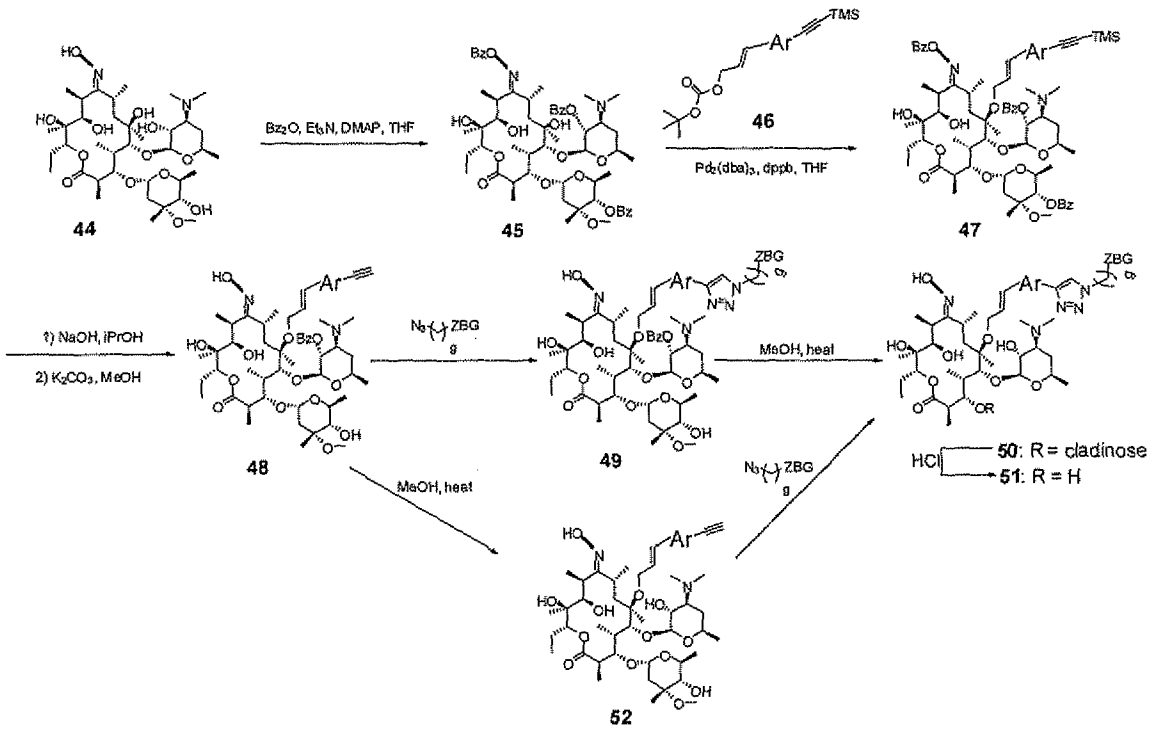
Scheme 3



Scheme 4 illustrates representative general synthesis of triazole compounds with HDAC recognition cap-group connected to the macrocyclic ring at O6 position of 14-membered macrolide such as, but not limiting to, erythromycin. Adapting known protocols (see, Plata *et al.* (2004) *Tetra.*, 60:

10171), the aryl alkyne **47** can be obtained from readily available erythromycin A-9-oxime (see, Morimoto *et al.* (1990) *J. Antibiot.*, 43:286) through the intermediacy of **45**. Sequential base treatment with aqueous alkali and potassium carbonate in methanol will lead to alkyne **48** which can be reacted with azide **4** to give triazole **49**. Methanolysis of **49** will afford triazole **50**. Triazole **50** can be modified to form compound **51** by treatment with dilute mineral acid. Alternatively, methanolysis of alkyne **48** yields alkyne **51**. Reaction of **51** with azide **4** will yield triazole **50**.

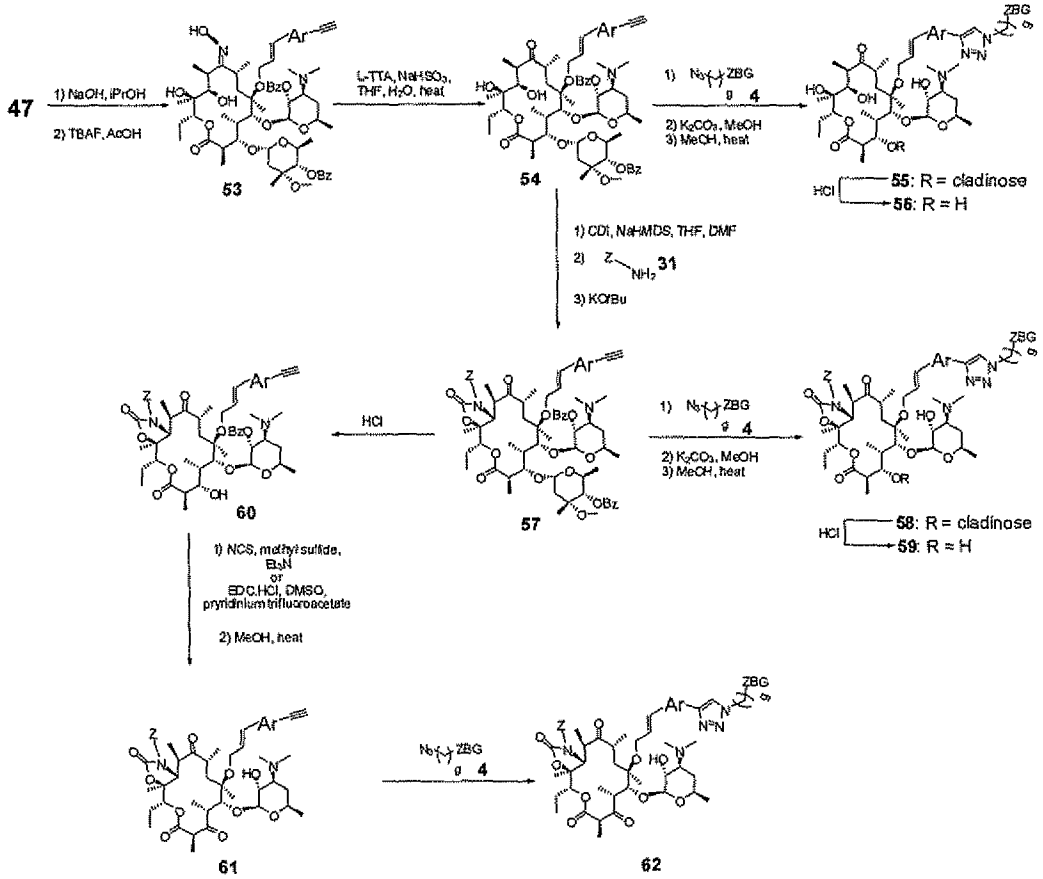
Scheme 4



Scheme 5 illustrates representative general syntheses of triazole compounds with HDAC recognition cap-groups connected to the macrocyclic ring at the O6 position of 14-membered ketolides and carbamate modified macrolides. Selective benzoyl deprotection and silyl group removal will afford aryl alkyne **53**. The oxime group in **53** can be removed by heating **53** in a THF/H_2O containing $NaHSO_3$ and L-tartaric acid to afford aryl alkyne **54** (adapting protocols described by Plata *et al.* (2004) *Tetra.*, 60: 10171). Reaction of **54** with azide **4** followed by debenzoylation by sequential treatment with potassium carbonate in methanol and methanolysis

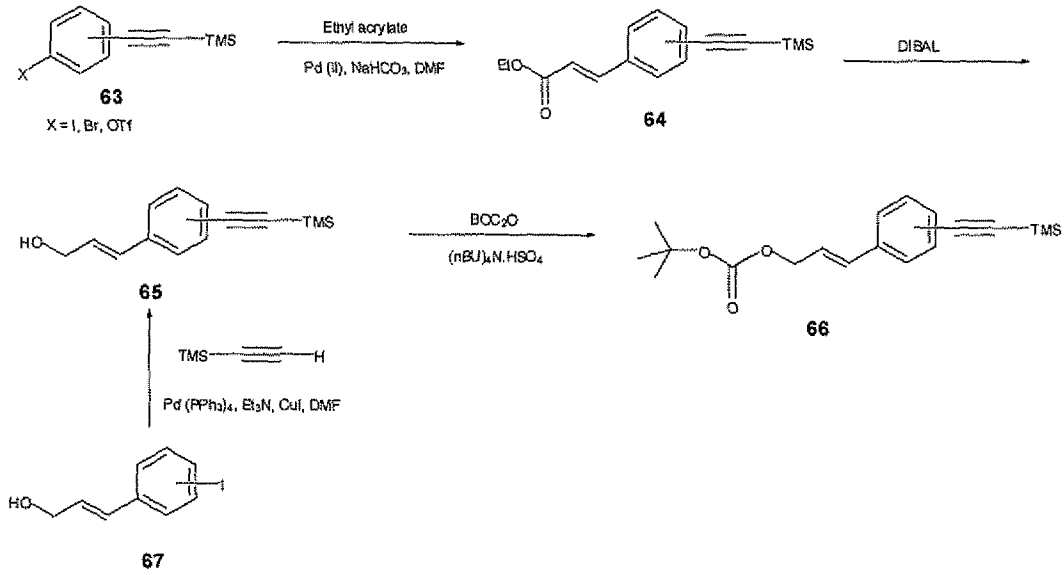
at elevated temperatures will yield triazole **55**. Triazole **55** can be modified to form compound **56** by treatment with dilute mineral acid. Aryl alkyne **54** can be modified to form aryl alkyne **57** by adapting procedures exemplified for similar transformations in scheme 3 or alternative protocols described in the art (see U.S. Patent No. 5,631,355; Kashimura *et al.* (2003), *J. Antibiot.*, 56: 1062; Randolph *et al.* (2004) *J. Med. Chem.*, 47, 1085; Plata *et al.* (2004) *Tetra.*, 60: 10171). Reaction of **57** with azide **4** followed by debenzoylation by sequential treatment with potassium carbonate in methanol and methanolysis at elevated temperatures will yield triazole **58**. Triazole **58** can be converted to compound **59** by treatment with dilute mineral acid. A direct treatment of **57** with dilute mineral acid will afford alcohol **60**. Oxidation of **60** under Corey-Kim or similar conditions followed by methanolysis at elevated temperatures will yield alkyne ketolide **61**. Reaction of **61** with azide **4** will yield triazole **62**.

Scheme 5

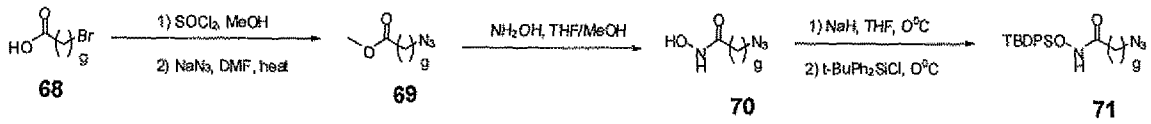


Intermediates such as electrophiles **2**, **7** and **14**, azide **4**, nitrile oxide **11**, amine **30** and carbonate alkyne **46** are all easily accessible by synthetic protocols known in the art. Exemplary examples for the synthesis of compounds whose general structures fit the forgoing are illustrated in schemes 6, 7, 8, and 9. Halogenated aryl alkyne **63** can undergo Heck coupling with ethyl acrylate to furnish α,β-unsaturated ester **64**. Reduction of **64** with DIBAL should generate alkenol **65**, which can be transformed to carbonate **66** using methods known in the art (*see* US Patent No. 6,579,986; Plata *et al.* (2004), *Tetra.*, 60: 10171). Alternatively, alkenol **65** can be prepared from alkenol **67** through Hagihara-Sonogashira coupling (Belema *et al. Tet. Lett.*, (2004), 45: 1693). Reactions of carboxylic acid **68** with thionyl chloride in methanol follow by treatment with sodium azide should furnish azido methyl ester **69**. Treatment of **69** with hydroxylamine should provide azido hydroxamate **70** (Ho *et al.*, (2005), *J. Org, Chem.*, 70, 4873). The hydroxamate group of **70** can be appropriately protected with a silyl group to provide silyl azide **71** (Muri *et al. Org. Lett.*, (2000) 2: 539). Hagihara-Sonogashira coupling between alcohol **72** and TMS-acetylene should yield alkyne **73**. TMS deprotection should furnish alkyne **74**, which can be reacted with MsCl to provide mesylate **75**. Reaction of phthalimide salt with **75** should provide phthalimide **76**, which can be converted to amine **77** by hydrazinolysis or other suitable protocol known in the art. Treatment of alcohol **78**, incorporating ZBG (appropriately protected when necessary), with oxidants such as PDC, should provide aldehyde **79**. Reaction of **79** with hydroxylamine should furnish oxime **80**, which can be converted to nitrile oxide **81** by treatment with NBS or other reagents such NCS, chloramine T, etc. Because of the likely instability of nitrile oxides, the generation of nitrile oxide can be performed in the presence of the appropriate alkyne **3** (scheme 1) to furnish the regioisomeric mixture of the isoxazoles.

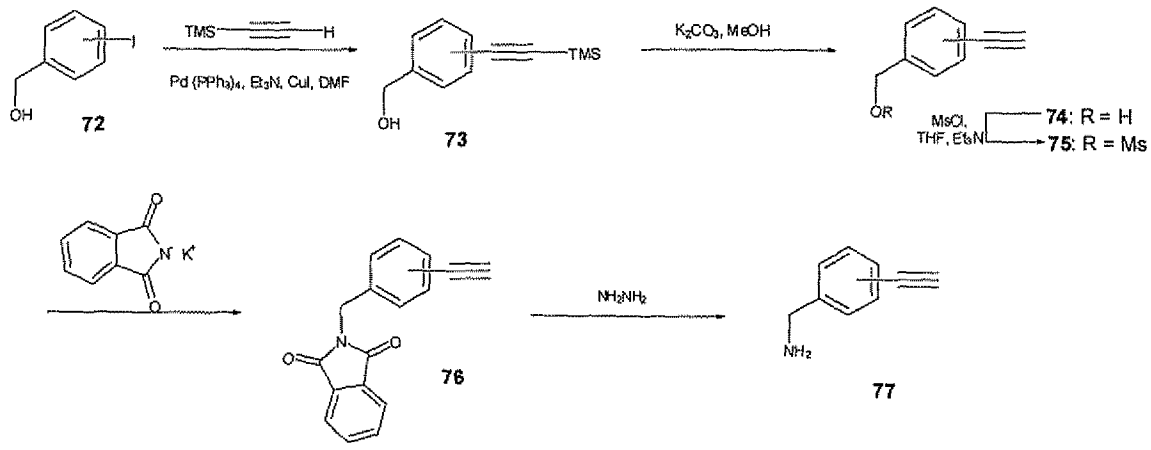
Scheme 6



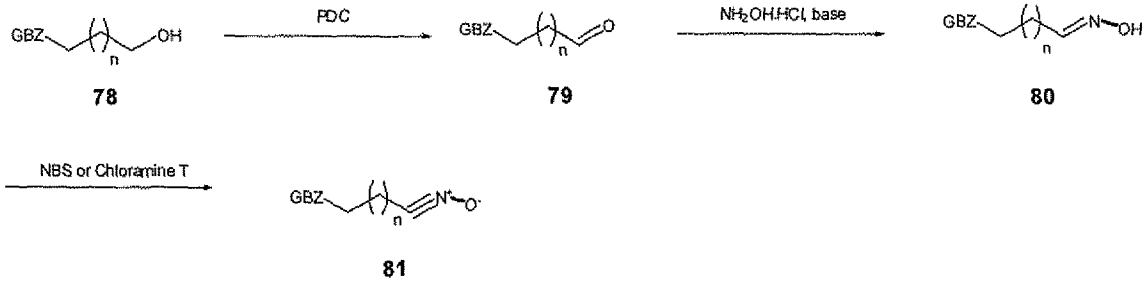
Scheme 7



Scheme 8

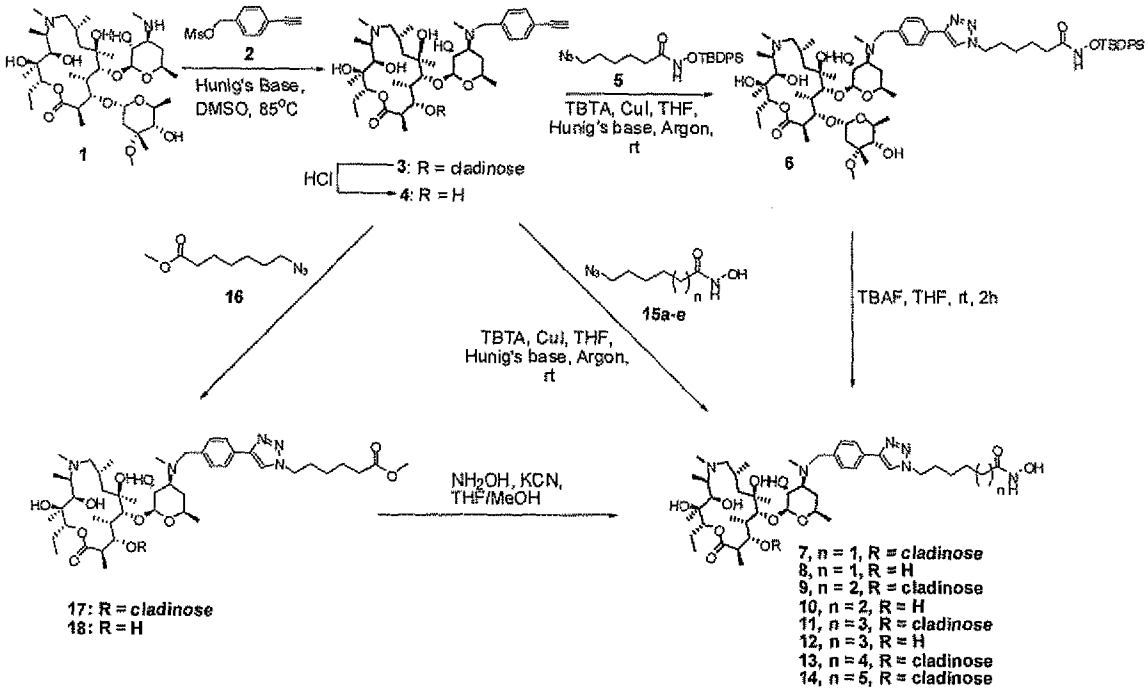


Scheme 9

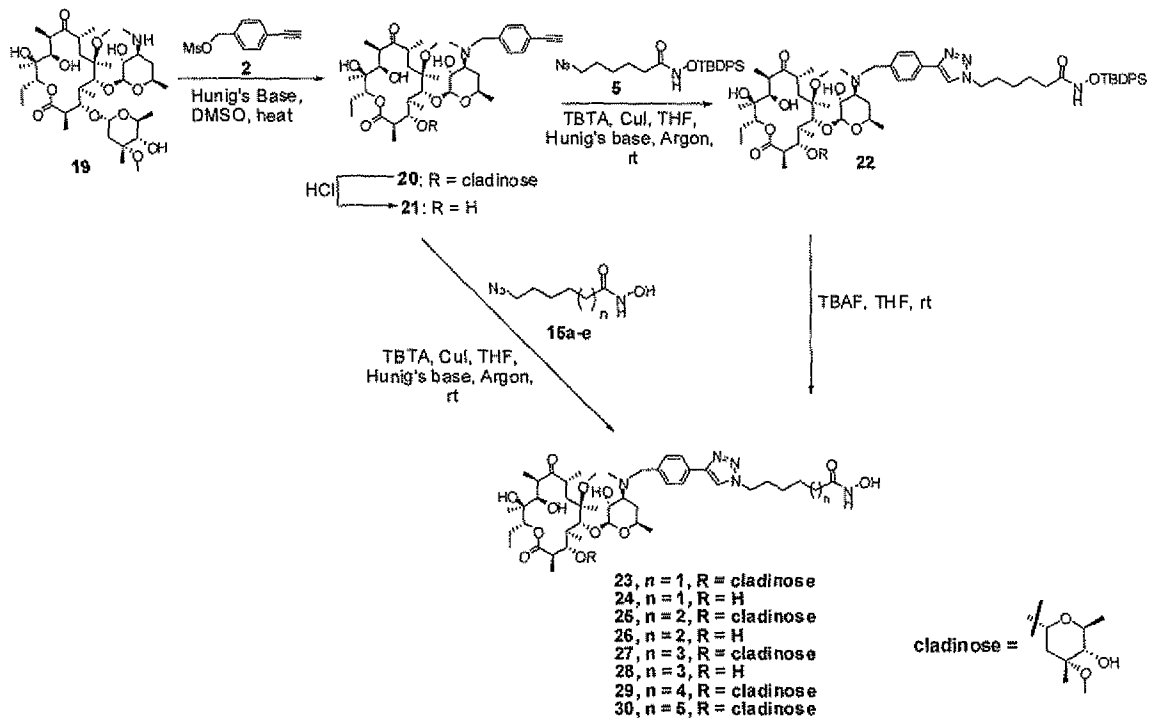


Schemes 10 and 11 illustrate the synthesis of compounds **7-14** and **23-30** in Table 3.

Scheme 10: Synthesis of compounds 7-14

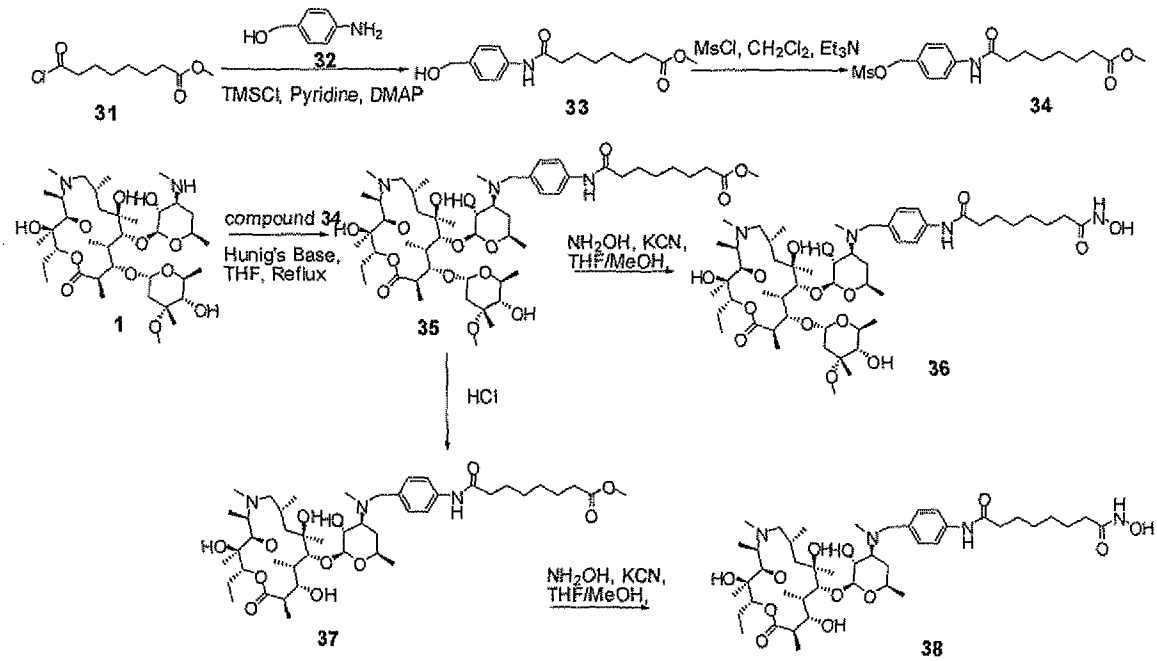


Scheme 11: Synthesis of compounds 23-30



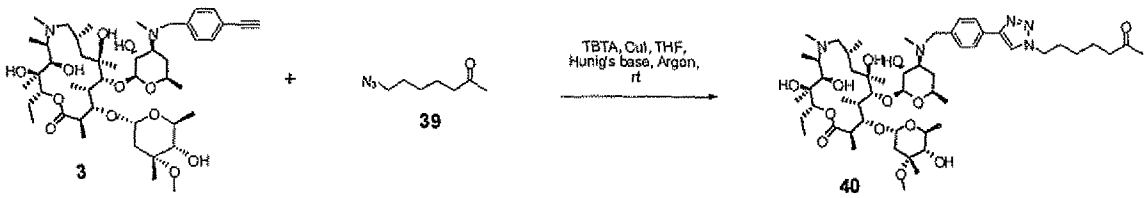
Scheme 12 illustrates the synthesis of compounds **36** and **38** in Table 3.

Scheme 12: Synthesis of compounds 36 and 38



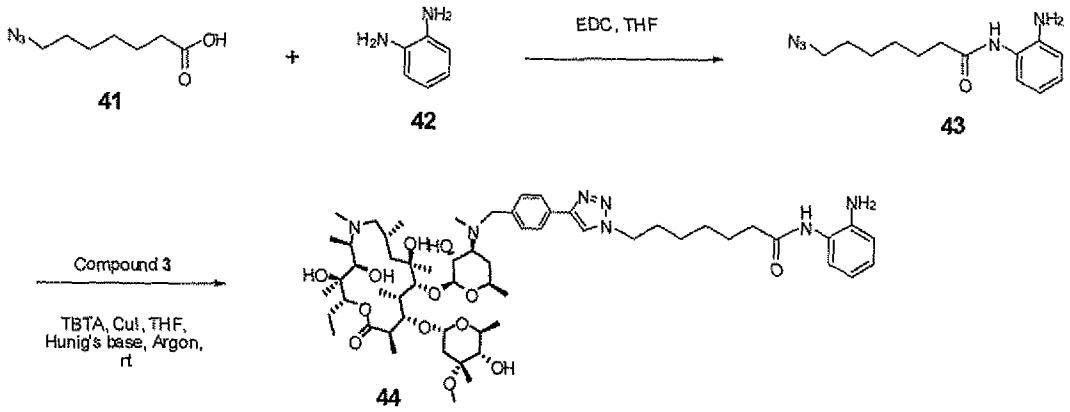
Schemes 13, 14 and 15 below illustrate the synthesis of compounds **40, 44** and **47** in Table 3.

Scheme 13: Synthesis of compound 40



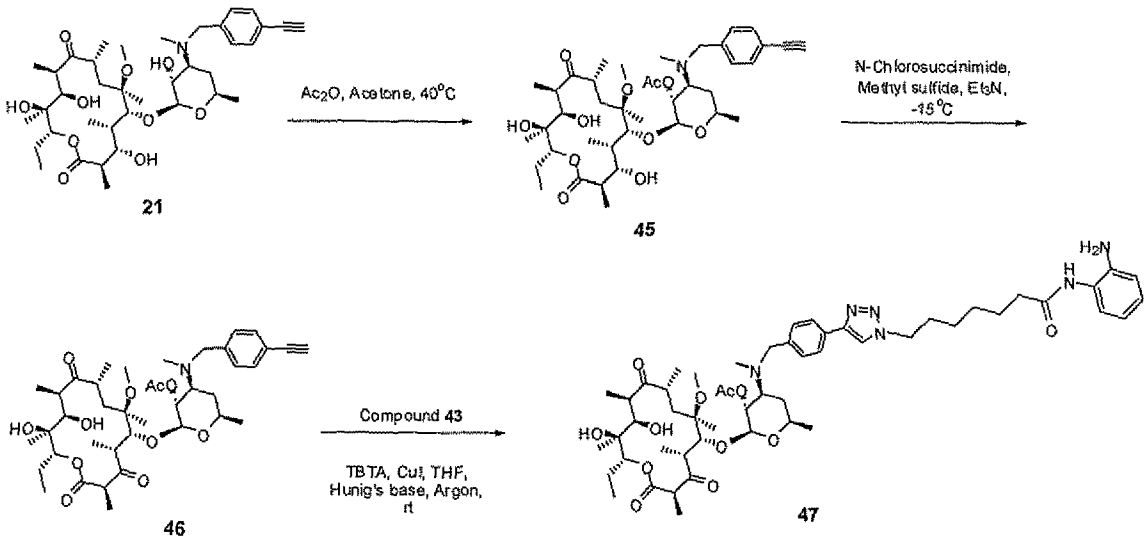
3 39 40

Scheme 14: Synthesis of compound 44



41 42 43 44

Scheme 15: Synthesis of compound 47



21 45 46 47

V. Methods of Use and Administration

The compounds described herein may be used as anti-cancer agents, anti-inflammatory agents, anti-infective agents, anti-malarial agents, cytoprotective agents, neuroprotective agents, chemopreventive agents, prokinetic agents, and/or cognitive enhancing agents. Examples of cancer which may be treated include, but are not limited to, lung cancer, myeloma,

leukemia, lymphoma, breast cancer, prostate cancer, pancreatic cancer, cervical cancer, ovarian cancer, and liver cancer. The compounds can be formulated for enteral, parenteral, and/or topical (e.g., transdermal, mucosal, etc.) administration.

The compounds of general formula I and II and their pharmaceutically-acceptable addition salts, prodrugs, and/or solvates can also be used in the form of pharmaceutical preparations which facilitate bioavailability. One or more compounds of Formula I and II may be administered in a single dosage form or in multiple dosage forms

Enteral Formulations

Pharmaceutical compositions for oral administration can be liquid or solid. Liquid dosage forms suitable for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to an encapsulated or unencapsulated HDAC inhibitor, 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, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants, wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents. As used herein, the term "adjuvant" refers to any compound which is a nonspecific modulator of the immune response. In certain preferred embodiments, the adjuvant stimulates the immune response. Any adjuvant may be used in accordance with the present invention. A large number of adjuvant compounds are known in the art (Allison, *Dev. Biol. Stand.* 92:3, 1998; Unkeless et al., *Annu. Rev. Immunol.* 6:251, 1998; and Phillips et al., Vaccine 10: 151, 1992).

Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, caplets, dragees, powders and granules. In such solid dosage forms, the encapsulated or unencapsulated compound is typically 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 contain buffering agents.

Solid compositions of a similar type may also be employed as fill materials 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.

Parenteral Formulations

Pharmaceutical preparations in the form suitable for injection are subjected to conventional pharmaceutical operations such as sterilization and/or may contain adjuvants including, but not limited to, preservatives, stabilizers, wetting or emulsifying agents, and buffers.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated as known in the 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 can be 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 can be used in the preparation of injectable formulations. In a particularly preferred embodiment, the compound is suspended in a carrier fluid containing 1% (w/v) sodium carboxymethyl cellulose and 0.1% (v/v) TWEEN™ 80. The injectable formulations can be sterilized, for example, by filtration through a bacteria-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.

Topical Formulations.

The compounds described here can also be formulated for topical, transdermal, or mucosal delivery. Dosage forms for topical or transdermal administration include, but are not limited to, ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, or patches. The compounds are typically admixed under sterile conditions with a pharmaceutically acceptable carrier and any excipients (e.g., preservatives, buffers, etc.) that may be required. Ophthalmic formulations, ear drops and eye drops can also be prepared. The ointments, pastes, creams and gels may contain, in addition to the active agent, 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.

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 compounds described herein in a 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(s) in a polymer matrix or gel.

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

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds described herein 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 compound(s).

The formulations contain an effective amount of one or more HDAC inhibitors. The doses in which the HDAC inhibitors and their salts, prodrugs, or solvates can be administered may vary widely depending on the condition of the patient and the symptoms to be treated. One of ordinary skill in the art can readily determine the necessary dosage based on the condition of the patient and the disease to be treated.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Publications cited herein and the materials for which they are cited are specifically incorporated by reference.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

Examples

Materials

"Preparative TLC" or "prep TLC" refers to preparative thin layer chromatography and was performed on Analtech preparative TLC plates

(UV 254, 2000 μm), unless otherwise stated. "Column chromatography" or "flash column chromatography" was performed with 200-400 Mesh silica gel, unless otherwise noted.

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian-Gemini 400 magnetic resonance spectrometer. ^{1}H NMR spectra were recorded in parts per million (ppm) relative to the peak of $CDCl_3$, (7.24 ppm), CD_3OD (3.31 ppm), or DMSO-d_6 (2.49 ppm). ^{13}C spectra were recorded relative to the central peak of the $CDCl_3$ triplet (77.0 ppm), CD_3OD (49.0 ppm), or the DMSO-d_6 septet (39.7 ppm), and were recorded with complete hetero-decoupling.

Common reaction solvents were either high performance liquid chromatography (HPLC) grade or American Chemical Society (ACS) grade, and used without further purification. Anhydrous solvents and other reagents were purchased and used without further purification.

Fluor de Lys™ is a fluorescence based HDAC activity assay comprising a combination of fluorogenic Histone deAcetylase Lysyl substrate and a developer. The kit is a highly sensitive and convenient alternative to radiolabeled, acetylated histones or peptide/HPLC methods for the assay of histone deacetylases. This assay is based on the ability of HeLa nuclear extract, which is enriched in HDAC activity, to mediate the deacetylation of the acetylated lysine side chain of the *Fluor de Lys* substrate. The assay procedure requires two steps. First, incubation of the HeLa nuclear extract with the *Fluor de Lys* substrate results in substrate deacetylation and thus sensitizes it to the second step. In the second step, treatment of the deacetylated substrate with the *Fluor de Lys* developer produces a fluorophore. The substrate-developer reaction, under normal circumstances goes to completion in less than 1 min at 25°C. The kit used was the Fluorimetric Assay/Drug Discovery Kit - AK-500 Manual Fluorescent Assay System available from BIOMOL® International, Plymouth Meeting, PA.

The numbers used to identify the compounds described in the examples correspond to the references numbers in Table 4 and/or reaction schemes 10-15.

Example 1. Synthesis of Compounds 7-14 and 23-30 in Table 3

Synthesis of Azithromycin-*N*-phenylacetylene (3)

To a solution of *N*-demethylated azithromycin **1** (2.0 g, 2.56 mmol) in anhydrous DMSO (30 ml) was added Hunig's base (4 ml) and 4-ethynylbenzyl methanesulfonate **2** (0.760 g, 3.60 mmol). The reaction mixture was heated with stirring under argon at 85°C for 2.5 h. The reaction was cooled and diluted with ethyl acetate (EtOAc, 100 mL) and washed with saturated $NaHCO_3$ (3 x 60 mL) and saturated brine (60 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, 12:1:0.05 CH_2Cl_2/MeOH/conc. NH_4OH) to give 1.2 g (52%) of **3** as a brownish white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.84 (m), 0.97 (d, J = 7.6 Hz), 1.04 (m), 1.12-1.32 (m), 1.36-1.53 (m), 1.66-1.75 (m), 1.81-2.07 (m), 2.19 (s), 2.25-2.29 (m), 2.48 (m), 2.63-2.73 (m), 2.89 (bs), 2.96 (t, J = 9.8 Hz), 3.02 (s), 3.08 (s), 3.27-3.32 (m), 3.38-3.45 (m), 3.56 (d, J = 6.8 Hz), 3.63 (s), 3.72 (d, J = 13.2 Hz), 3.97 (m), 4.19 (m), 4.36 (d, J = 7.2Hz), 4.63 (d, J = 10 Hz), 5.04 (d, J = 4.4 Hz), 7.21 (d, J = 8 Hz), 7.39 (d, J = 8 Hz) ; ^{13}C-NMR ($CDCl_3$, 100MHz) δ 7.5, 9.2, 11.3, 14.9, 16.3, 18.3, 21.3, 21.4, 21.6, 22.0, 26.8, 27.6, 29.6, 34.7, 36.3, 36.9, 42.0, 42.3, 45.2, 49.2, 57.7, 62.3, 63.7, 65.4, 68.5, 70.0, 70.6, 72.7, 73.5, 73.8, 74.2, 77.1, 77.9, 78.0, 83.4, 83.7, 94.5, 102.6, 120.8, 128.5, 132.0, 139.6, 178.3; HRMS (FAB, mnba) calc for $[C_{46}H_{76}N_2O_{12} + H]^+$ 849.5476, found 849.5411.

Synthesis of Azithromycin-arylalkyltriazolyl methyl ester (17)

Azithromycin-*N*-phenylacetylene **3** (0.045 g, 0.053 mmol) and azido-ester **16** (0.014 g, 0.080 mmol) were dissolved in anhydrous THF (5 mL) and stirred under argon at room temperature. Copper (I) iodide (0.010 g, 0.053 mmol), and Hunig's base (0.05 mL) were then added to the reaction mixture, and stirring continued for 12 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 1:4 NH_4OH/saturated NH_4Cl (3 x 25 mL)

and again with saturated NH_4Cl (25 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by preparative TLC, eluting with Hexane/EtOAc/Et_3N 3:2:0.1 to give 50 mg (92%) of **17** as a white-brown solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.82-0.90 (m), 0.98 (d, J = 7.6 Hz), 1.05-1.13 (m), 1.19-1.23 (m), 1.25-1.30 (m), 1.40-1.52 (m), 1.60-1.74 (m), 1.80-1.96 (m), 2.00-2.06 (m), 2.22-2.37 (m), 2.56 (m), 2.67 (m), 2.95 (t, J = 9.8 Hz), 3.07 (s), 3.29-3.34 (m), 3.46 (bs), 3.54 (d, J = 6.8 Hz), 3.61 (s), 3.68 (bs), 3.77 (m), 3.97 (m), 4.18 (m), 4.34-4.38 (m), 4.69 (m), 5.06 (d, J = 4 Hz), 7.32 (d, J = 6.4 Hz), 7.73-7.75 (m); ^{13}C-NMR ($CDCl_3$, 100MHz) δ 8.7, 9.2, 11.3, 14.2, 14.7, 16.5, 18.2, 21.4, 21.5, 22.2, 24.2, 25.9, 26.6, 27.3, 29.7, 30.0, 33.6, 34.6, 36.4, 36.9, 42.4, 45.3, 45.8, 49.3, 50.0, 51.5, 57.7, 63.9, 65.5, 68.6, 69.4, 70.5, 72.7, 73.8, 74.2, 77.2, 77.6, 78.0, 83.4, 94.4, 102.7, 119.3, 125.5, 129.1, 129.4, 147.2, 173.4, 178.1. MS (FAB, mnba) 1020.3 $(M+H)^+$.

Synthesis of Descladinoseazithromycin-arylalkyltriazolyl methyl ester (18)

A mixture of compound **3** (0.12 g, 0.14 mmol) in 0.25 N HCl (15 mL) was stirred at room temperature for 20 h and poured into EtOAc (20 mL). The two layers were separated and the aqueous layer was washed with EtOAc (2 x 20 mL), basified with concentrated NH_4OH and then extracted with 5 % MeOH in CH_2Cl_2 (2 x 30 mL). The combined organic layer was washed with saturated brine (30 mL) and dried over Na_2SO_4. Solvent was evaporated off to give 89 mg (91%) of descladinose compound **4** as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.81-0.87 (m), 0.90-1.07 (m), 1.17-1.27 (m), 1.31-1.59 (m), 1.68-1.71 (m), 1.80-1.87 (m), 1.99-2.03 (m), 2.08 (s), 2.23-2.27 (m), 2.31 (s), 2.44-2.48 (m), 2.59-2.73 (m), 3.32-3.39 (m), 3.48-3.53 (m), 3.60-3.65 (m), 3.73 (d, J = 9.6 Hz), 3.84-3.91 (m), 4.43 (d, J = 7.2 Hz), 4.69-4.72 (m), 7.16 (d, J = 8.0 Hz), 7.39 (d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ 7.7, 7.9, 10.9, 14.2, 16.1, 20.9, 21.1, 21.2, 25.9, 26.6, 29.3, 36.0, 36.4, 37.1, 42.1, 44.5, 57.6, 60.3, 62.5, 65.3, 69.9, 70.5, 70.9, 73.0, 74.1, 75.4, 77.2, 79.5, 83.3, 94.9, 106.5, 120.8, 128.3, 132.0, 139.3, 177.2. MS (FAB, mnba) 691.2 $(M+H)^+$.

The descladinose compound **4** (0.080 g, 0.115 mmol) and azido-ester **16** (0.030 g, 0.173 mmol) were dissolved in anhydrous THF (5 mL) and stirred under argon at room temperature. Copper (I) iodide (0.010 g, 0.053 mmol), and Hunig's base (0.05 mL) were then added to the reaction mixture, and stirring continued for 12 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with 1:4 NH_4OH/saturated NH_4Cl (3 x 25 mL) and again with saturated NH_4Cl (25 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by preparative TLC, eluting with Hexane/EtOAc/Et_3N 3:2:0.1 to give 65 mg (65%) of **18** as a white-brown solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.79-0.86 (m), 1.00-1.07 (m), 1.17-1.35 (m), 1.42-1.51 (m), 1.55-1.72 (m), 1.80-1.94 (m), 2.00-2.05 (m), 2.1 (s), 2.23-2.27 (m), 2.33 (s), 2.47 (d, J = 10.4 Hz), 2.58-2.72 (m), 3.32-3.41 (m), 3.52-3.73 (m), 3.92-4.00 (m), 4.34 (t, J = 7.0 Hz), 4.41 (d, J = 7.6 Hz), 4.69 (d, J = 10.8 Hz), 7.24 (d, J = 8.4 Hz), 7.71(d, J = 8 Hz), 7.73 (s); ^{13}C NMR ($CDCl_3$, 100MHz) δ 7.7, 7.9, 8.7, 10.9, 16.1, 16.1, 20.9, 21.2, 24.2, 25.8, 25.9, 26.6, 29.2, 29.6, 30.0, 33.6, 36.0, 36.3, 37.1, 42.0, 44.5, 45.8, 50.0, 51.5, 57.7, 62.6, 65.1, 69.9, 70.4, 73.1, 74.1, 75.3, 79.4, 94.8, 106.4, 119.3, 125.5, 128.9, 129.6, 138.2, 147.1, 173.4, 177.2. MS (FAB, mnba) 862.2 $(M+H)^+$.

Synthesis of Azithromycin-*N*-phenyltriazolylhexahydroxamic acid (7)

Method A

To a solution of compound **17** (0.04 g, 0.04 mmol) in 1:1 THF/MeOH (3 mL) was added hydroxylamine (50 % in H_2O) (0.03 mL, 0.54 mmol) and a catalytic amount of KCN. The mixture was stirred at room temperature for 24 h. The reaction was partitioned between 5 % MeOH in CH_2Cl_2 (30 mL) and saturated sodium bicarbonate (25 mL), the two layers were separated and the aqueous layer was extracted with 5 % MeOH in CH_2Cl_2 (2 x 20 mL). The combined organic layer was washed with saturated brine (40 mL) and dried over Na_2SO_4. Solvent was evaporated off and the crude was purified by preparative TLC, eluting with CH_2Cl_2/ MeOH/NH4OH 10:1:0.1 to give compound **7** (6.5 mg, 16 %) as brown-white solid.

Method B

Azithromycin-*N*-phenylacetylene **3** (0.100 g, 0.109 mmol) and 6-azidohexahydroxamic acid **15a** (0.081 g, 0.117 mmol) were dissolved in anhydrous THF (5 mL) and stirred under argon at room temperature. Copper (I) iodide (0.011 g, 0.07 mmol) and Hunig's base (0.5 mL) were then added to the reaction mixture, and stirring continued for 4 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 1:4 NH_4OH/saturated NH_4Cl (3 x 30 mL) and saturated NH_4Cl (30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) to give 71 mg (59%) of **7** as a brownish white solid.

Method C

Azithromycin-*N*-phenylacetylene **3** (0.045 g, 0.050 mmol) and 6-azido-*O*-silyl hexahydroxamate **6** (0.060 g, 0.146 mmol) were dissolved in anhydrous THF (5 mL) and stirred under argon at room temperature (**Note:** compound **6** was prepared from the corresponding azido carboxylic acid, t-$BuPh_2SiCl$ and NaH, according to the procedure described by Muri *et al.* ORG. LETT (2000) 2: 539). Copper (I) iodide (0.010 g, 0.05 mmol), Hunig's base (0.5 mL) and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine, (TBTA) (0.016 g, 0.030 mmol) were then added to the reaction mixture, and stirring continued for 2 h (**Note:** TBTA was synthesized according to Chen *et al. Org. Lett.*, (2004) 6: 2853). The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 1:4 NH_4OH/saturated NH_4Cl (2 x 30 mL) and saturated NH_4Cl (30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) to give 38 mg (60%) of silyl protected compound **6** as a brownish white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.82-0.92 (m), 1.00-1.14 (m), 1.17-1.27 (m), 1.30-1.32 (m), 1.35-1.59 (m), 1.73-1.92 (m), 2.01-2.15 (m), 2.24-2.32 (m), 2.36 (br s), 2.56 (d, J = 10.4 Hz), 2.69 (m), 2.98 (d, J = 10 Hz), 3.07-3.09 (m), 3.32-3.36 (m), 3.42-3.46 (m), 3.55-3.63 (m), 3.66 (s),

3.78 (d, J = 13.2 Hz), 4.01 (m), 4.15-4.25 (m), 4.40 (d, J = 6.8 Hz), 4.63 (d, J = 7.2 Hz), 4.69 (s), 5.10 (d, J = 4.4 Hz), 7.31-7.43 (m), 7.65-7.75 (m).

To a solution of silyl protected compound **6** (0.025 g, 0.02 mmol) in THF (1 mL) was added 1 M TBAF in THF (0.030 mL, 0.030 mmol) and the mixture was stirred at room temperature for 2 h during which TLC revealed a near quantitative conversion to a lower Rf product. The reaction was partitioned between CH_2Cl_2 (30 mL) and saturated NH_4Cl (25 mL), the two layers were separated and the organic layer dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/Et_3N) to give 15 mg (73%) of 7 as a brownish white solid.

^{1}H-NMR (Acetone-d6, 400MHz) δ 0.83-0.92 (m), 1.02 (d, J = 7.6 Hz), 1.08-1.11 (m), 1.14 (d, J = 7.6 Hz), 1.18 (d, J = 6 Hz), 1.24-1.29 (m), 1.33-1.47 (m), 1.54 (dd, J = 4.8 Hz, 15.2 Hz), 1.66 (m), 1.80-2.01 (m), 2.06-2.12 (m), 2.18-2.24 (m), 2.26 (s), 2.28-2.31 (m), 2.35-2.41 (m), 2.51 (d, J = 10 Hz), 2.65-2.96 (m), 3.12 (s), 3.22-3.29 (m), 3.41-3.47 (m), 3.54-3.69 (m), 3.81 (d, J = 13.2 Hz), 4.11 (m), 4.24 (m), 4.45 (t, J = 7.0 Hz), 4.50 (d, J = 6.8 Hz), 4.75 (d, J = 7.2 Hz), 4.97 (d, J = 5.2 Hz), 7.42 (d, J = 8.0 Hz), 7.84 (d, J = 8.0 Hz), 8.35 (s). MS (FAB, mnba) 1021.2 $(M+H)^+$.

Synthesis of Descladinose-Azithromycin-*N*-phenyltriazolylhexa-hydroxamic acid (8)

Method A

To a solution of compound **18** (0.04 g, 0.05 mmol) in 1:1 THF/MeOH (3 mL) was added hydroxylamine (50 % in H_2O) (0.04 mL, 0.54 mmol) and a catalytic amount of KCN. The mixture was stirred at room temperature for 24 h. The reaction was partitioned between 5 % MeOH in CH_2Cl_2 (30 mL) and saturated sodium bicarbonate (25 mL), the two layers were separated and the aqueous layer was extracted with 5 % MeOH in CH_2Cl_2 (2 x 20 mL). The combined organic layer was washed with saturated brine (40 mL) and dried over Na_2SO_4. Solvent was evaporated off and the crude was purified by preparative TLC, eluting with CH_2Cl_2/MeOH/NH4OH 10:1:0.1 to give compound **8** (9.0 mg, 23 %) as brown-white solid.

Method B

Reaction of descladinose-azithromycin-*N*-phenylacetylene **4** (0.134 g, 0.188 mmol) and 6-azidohexahydroxamic acid **15a** (0.130 g, 0.755 mmol) within 8 h (according to the protocols of **Method B** described for the synthesis of compound **7** above), followed by prep TLC (silica, 10:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 73 mg (43%) of **8** as a brownish white solid.

^{1}H-NMR (Acetone-d6, 400MHz) δ 0.82-0.90 (m), 1.02 (d, J = 7.2 Hz), 1.07 (s), 1.09 (d, J = 6.8 Hz), 1.18-1.23 (m), 1.28 (bs), 1.31-1.39 (m), 1.46-1.56 (m), 1.65 (m), 1.81-1.83 (m), 1.87-1.99 (m), 2.05-2.11 (m), 2.18-2.21 (m), 2.18-2.21 (m), 2.24 (s), 2.25-2.29 (m), 2.35 (s), 4.47 (d, J = 9.2 Hz), 2.61-2.67 (m), 2.70-2.77 (m), 3.30-3.34 (m), 3.41 (m), 3.52-3.65 (m), 2.81 (d, J = 13.2 Hz), 4.44 (t, J = 7.0 Hz), 4.59 (d, J = 7.6 Hz), 4.87 (dd, J = 1.8 Hz, 11.0 Hz), 7.43 (d, J = 8.4 Hz), 7.83 (d, J = 8.4 Hz), 8.34 (m); HMRS (ESI) calcd for $[C_{44}H_{74}N_6O_{11} + H]^+$ 863.5488, found 863.5528.

Accordingly, compounds **9-14** and **23-30** (in this section) were synthesized according to the protocols of Method B described for the synthesis of compound **7** above.

Synthesis of Azithromycin-N-phenyltriazolylheptahydroxamic acid (9)

Reaction of azithromycin-*N*-phenylacetylene **3** (0.134 g, 0.158 mmol) and 7-azidoheptahydroxamic acid **15b** (0.125 g, 0.672 mmol) within 4 h, followed by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 93 mg (56%) of **9** as a brownish white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.81-1.51 (m), 1.54-1.65 (m), 1.70-2.14 (m), 2.20-2.38 (m), 2.46-2.56 (m), 2.60-2.70 (m), 3.00 (s), 3.31 (t, J = 8.8 Hz), 3.38-3.54 (m), 3.60 (s), 3.78 (d, J = 12.8 Hz), 3.98-4.20 (m), 4.36 (d, J = 7.2 Hz), 4.49 (d, J = 7.2 Hz), 5.11 (d, J = 4.0 Hz), 7.32 (d, J = 7.6 Hz), 7.73 (s), 7.75 (d, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.6, 8.8, 11.5, 14.4, 16.6, 17.7, 21.3, 21.6, 21.8, 25.1, 26.0, 26.7, 27.1, 28.2, 29.2, 29.6, 30.0, 33.1, 34.5, 35.7, 36.7, 41.8, 42.7, 45.3, 49.3, 50.3, 50.7, 57.9, 62.7, 63.0, 65.8, 68.6, 69.4, 70.4, 72.6, 73.2, 73.8, 77.8, 78.1, 78.2, 83.5, 94.4, 102.8, 119.3, 125.7, 129.4, 129.7, 138.4,

147.4, 171.3, 178.4; HMRS (ESI) calcd for $[C_{53}H_{90}N_6O_{14} + H]^+$ 1035.6587, found 1035.6628.

Synthesis of Descladinose-Azithromycin-*N*-phenyltriazolylhepta-hydroxamic acid (10)

Reaction of descladinose-azithromycin-*N*-phenylacetylene **4** (0.130 g, 0.188 mmol) and 7-azidoheptahydroxamic acid **15b** (0.130 g, 0.755 mmol) within 8 h, followed by prep TLC (silica, 10:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 78 mg (47%) of **10** as a brownish white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.66-2.32 (m), 2.47 (d, J = 10.8 Hz), 2.63-2.70 (m), 3.34-3.51 (m), 3.62-3.69 (m), 4.20-4.40 (m), 4.74 (br s), 7.26 (br s), 7.73 (br s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.4, 7.9, 10.7, 16.0, 16.1, 20.9, 21.1, 25.0, 25.7, 26.5, 28.0, 28.9, 29.8, 35.8, 36.3, 36.9, 42.0, 44.4, 50.1, 57.9, 62.7, 63.9, 69.9, 70.4, 70.8, 73.3, 74.1, 75.2, 79.5, 94.9, 106.6, 119.7, 125.7, 129.2, 129.6, 138.4, 147.3, 177.5; HMRS (ESI) calcd for $[C_{45}H_{76}N_6O_{11} + H]^+$ 877.5645, found 877.5665.

Synthesis of Azithromycin-*N*-phenyltriazolyloctahydroxamic acid (11)

Reaction of azithromycin-*N*-phenylacetylene **3** (0.10 g, 0.120 mmol) and 8-azidooctahydroxamic acid **15c** (0.047 g, 0.24 mmol) within 2.5 h, followed by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 72 mg (58 %) of **11** as a brownish white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 4.0 Hz), 0.87-1.22 (m), 1.29 (s), 1.30-2.28 (m), 2.29 (s), 2.30-3.00 (m), 3.10 (s), 3.20-3.79 (m), 3.99-4.03 (m), 4.35-4.40 (m), 4.65 (d, J = 8.0 Hz), 5.11 (d, J = 4.8 Hz), 7.34 (d, J = 8.0 Hz), 7.72 (s), 7.77 (d, J = 8.0 Hz); ^{13}C NMR (DMSO-d_6, 400MHz) δ 7.5, 9.8, 11.6, 15.4, 18.2, 19.1, 21.5, 22.1, 22.7, 25.6, 26.3, 26.6, 28.7, 29.0, 29.6, 30.2, 32.0, 32.8, 35.2, 36.4, 37.2, 42.2, 45.3, 49.2, 50.1, 58.3, 63.2, 65.4, 67.7, 70.8, 73.3, 74.2, 77.0, 78.4, 83.4, 102.8, 121.6, 125.6, 129.7, 130.0, 135.0, 147.0, 177.8; HRMS (FAB, thioglycerol) calc for $[C_{54}H_{92}N_6O_{14} + H]^+$ 1049.6749, found 1049.6648.

Synthesis of Descladinose-Azithromycin-*N*-phenyltriazolyloctahydroxamic acid (12)

Reaction of azithromycin-*N*-phenylacetylene **4** (0.10 g, 0.144 mmol) and 8-azidooctahydroxamic acid **15c** (0.049 g, 0.246 mmol) within 2.5 h, followed by prep TLC (silica, 10:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 94 mg (73 %) of **12** as a brownish white solid. HRMS (FAB, thioglycerol) calc for $[C_{46}H_{79}N_6O_{11} + H]^+$ 891.5806, found 891.5910.

Synthesis of Azithromycin-*N*-phenyltriazolylnonahydroxamic acid (13)

Reaction of azithromycin-*N*-phenylacetylene **3** (0.10 g, 0.120 mmol) and 9-azidononahydroxamic acid **15d** (0.043 g, 0.20 mmol) within 2.5 h, followed by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 64 mg (51 %) of **13** as a brownish white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84- 1.30 (m), 1.33-2.26 (m), 2.30 (s), 2.38-2.68 (m), 2.99 (s), 3.32-3.84 (m), 4.03-4.08 (m), 4.35-4.41 (m), 4.53 (d, J = 8.0 Hz), 5.13 (d, J = 4.0 Hz), 7.35 (d, J = 8.0 Hz), 7.75 (s), 7.78 (d, J = 8.0 Hz); ^{13}C NMR (DMSO-d_6, 400MHz) δ 6.9, 9.0, 11.6, 14.7, 16.9, 18.0, 21.6, 21.8, 22.1, 25.6, 26.4, 26.9, 27.3, 28.8, 29.0, 29.1, 29.5, 29.9, 30.4, 34.8, 36.0, 37.0, 42.1, 43.0, 45.6, 49.5, 50.5, 58.1, 63.5, 66.1, 68.8, 70.7, 72.9, 74.1, 78.1, 78.3, 78.5, 83.7, 94.4, 94.7, 103.1, 119.6, 126.0, 129.7, 130.0, 147.6, 178.7; LRMS (MALDI) calc for $[C_{55}H_{94}N_6O_{14} + H]^+$ 1063.6, found 1063.7.

Synthesis of Azithromycin-*N*-phenyltriazolyldecahydroxamic acid (14)

Reaction of azithromycin-*N*-phenylacetylene **3** (0.10 g, 0.120 mmol) and 10-azido-decahydroxamic acid **15e** (0.045 g, 0.20 mmol) within 4.5 h, followed by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 70 mg (56 %) of **14** as a brownish white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85-1.36 (m), 1.41-2.24 (m), 2.28, 2.36 (s), 2.33-3.10 (m), 3.05 (s), 3.23-3.82 (m), 4.06-4.10 (m), 4.36-4.41 (m), 4.49 (d, J = 8.0 Hz), 5.15 (d, J = 4.0 Hz), 7.34 (d, J = 8 Hz), 7.75 (s), 7.78 (d, J = 8.0 Hz); ^{13}C NMR (DMSO-d_6, 400MHz) δ6.7, 9.0, 11.7, 14.6, 16.9, 17.9, 21.6, 21.9, 22.0, 25.6, 26.4, 26.8, 27.0, 27.3, 28.8, 29.0, 21.9, 29.3, 29.5, 29.9, 30.3, 33.6, 34.9, 35.8, 37.0,

42.1, 43.0, 45.6, 49.6, 50.6, 51.6, 58.0, 62.8, 63.9, 66.2, 68.9, 69.6, 70.7, 72.9, 73.5, 74.0, 74.1, 78.2, 78.6, 83.6, 94.6, 103.0, 119.6, 126.0, 129.6, 129.9, 138.9, 147.6, 178.6; HRMS (MALDI) calc for $[C_{56}H_{96}N_6O_{14} + H]^+$ 1077.7057, found 1077.6971.

Synthesis of Clarithromycin-*N*-phenylacetylene (20)

To a solution of *N*-demethylated clarithromycin **19** (2.40 g, 3.34 mmol) in anhydrous DMSO (30 ml) was added Hunig's base (3 ml) and 4-ethynylbenzyl methanesulfonate **2** (0.920 g, 4.34 mmol). The reaction mixture was then heated with stirring under argon at 85°C for 2.5 h. The reaction was cooled and diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (3 x 60 mL) and saturated brine (60 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica, gradient 12:1; 10:1; 8:1; CH_2Cl_2/acetone) to give 1.8 g (63%) of **20** as a brownish white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.82 (t, J = 7.2 Hz), 1.03-1.28 (m), 1.37 (s), 1.40-1.55 (m), 1.65-1.90 (m), 2.03 (d, J = 10.0 Hz), 2.22 (s), 2.30 (d, J = 15.2 Hz), 2.40-2.60 (m), 2.80-2.90 (m), 2.94-3.00 (m), 3.04 (s), 3.09 (s), 3.16 (s), 3.24-3.29 (m), 3.38-3.46 (m), 3.59 (d, J = 6.8 Hz), 3.70-3.75 (m), 3.88-3.95 (m), 4.37 (d, J = 7.2 Hz), 4.88 (d, J = 4.4 Hz), 5.02 (dd, J = 11.6, 2.4 Hz), 7.23 (d, J = 12.0 Hz), 7.42 (d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.2, 10.7, 12.4, 16.1, 18.1, 18.7, 19.9, 21.1, 21.5, 29.3, 32.4, 34.8, 36.9, 37.2, 39.2, 45.0, 45.2, 49.3, 50.6, 53.4, 57.6, 63.3, 65.6, 68.5, 69.0, 70.6, 72.5, 74.2,76.5, 77.8, 78.1, 78.2, 80.8, 95.8, 102.5, 120.9, 128.6, 132.0, 133.5, 139.4, 175.4; HRMS (ESI) calc for $[C_{46}H_{73}NO_{13} + H]^+$ 848.5155, found 848.5181.

Synthesis of Descladinose-Clarithromycin-*N*-phenylacetylene (21)

To a solution of clarithromycin-*N*-phenylacetylene **20** (0.500 g, mmol) in ethanol (20 mL) was added 1N HCl (20 mL), and stirring continued for 22 h at room temperature. The reaction mixture was basified with concentrated NH_4OH to about pH = 9. The reaction mixture was diluted with distilled water (40 mL) and extracted with EtOAc (3 x 60 mL). The combined organic layers were washed with saturated brine (40 mL),

dried over Na_2SO_4, and concentrated *in vauo*. The crude product was purifed by flash chromatography (silica, 8:1 CH_2Cl_2/acetone) to give 320 mg (79%) of **21** as a brownish white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.82 (t, J = 7.6 Hz), 1.09-1.28 (m), 1.34 (s), 1.40-1.55 (m), 1.70-1.74 (m),1.87-1.94 (m), 2.08-2.15 (m), 2.54-2.66 (m), 2.94-2.98 (m), 3.05 (s), 3.25 (s), 3.31-3.42 (m), 3.48-3.56 (m), 3.66 (d, J = 10.0 Hz), 3.82 (s), 3.90 (s), 4.35 (d, J = 7.6 Hz), 5.14 (dd, J = 10.8, 2.0 Hz), 7.18 (d, J = 8.0 Hz), 7.42 (d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.4, 10.5, 12.7, 15.3, 16.3, 17.8, 18.8, 21.4, 29.2, 35.9, 36.6, 37.5, 38.7, 44.5, 45.5, 49.6, 57.8, 65.0, 69.7, 70.1, 70.6, 74.1, 77.9, 78.9, 83.3, 88.5, 106.5, 121.0, 128.4, 132.1, 139.1, 174.7; HRMS (ESI) calc for $[C_{38}H_{59}NO_{10} + H]^+$ 690.4212, found 690.4259.

Synthesis of Clarithromycin-*N*-phenyltriazolylhexahydroxamic acid (23)

Reaction of clarithromycin-*N*-phenylacetylene **20** (0.100 g, 0.120 mmol) and 6-azidohexahydroxamic acid **15a** (0.080 g, 0.470 mmol) within 2.5 h, followed by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 70 mg (58%) of **23** as a brownish white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.81 (t, J = 7.6 Hz), 1.03-1.52 (m), 1.62-1.92 (m) 2.04-2.29 (m), 2.48-2.60 (m), 2.82-2.90 (m), 2.93-2.99 (m), 3.09 (s), 3.19 (s), 3.28-3.33 (m), 3.42-3.46 (m), 3.60 (d, J = 7.6 Hz), 3.70-3.80 (m), 3.90-3.98 (m), 4.37-4.40 (m), 4.87 (d, J = 4.8 Hz), 5.03 (dd, J = 11.6, 2.4 Hz), 7.34 (d, J = 7.6 Hz), 7.77 (d, J = 7.6 Hz), 7.82 (s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.1, 10.5, 12.2, 15.9, 17.9, 18.5, 19.7, 20.9, 21.2, 21.4, 24.3, 25.5, 29.4, 29.6, 34.7, 36.8, 37.1, 39.0, 39.1, 45.0, 45.1, 49.3, 49.9, 50.5, 53.3, 57.5, 63.6, 65.5, 68.5, 69.0, 70.7, 72.4, 74.2, 77.8, 78.2, 80.9, 95.9, 102.6, 119.8, 125.6, 129.4, 147.4, 175.8; HMRS (ESI) calcd for $[C_{52}H_{85}N_5O_{15} + H]^+$ 1020.6114, found 1020.6121.

Synthesis of Descladinose-Clarithromycin-*N*-phenyltriazolylhexa-hydroxamic acid (24)

Reaction of descladinose-clarithromycin-*N*-phenylacetylene **21** (0.075 g, 0.109 mmol) and 6-azidohexahydroxamic acid **15a** (0.040 g, 0.233 mmol) within 4 h, followed by prep TLC (silica, 10:1:0.1

CH_2Cl_2/MeOH/conc. NH_4OH) gave 47 mg (51%) of **24** as a brownish white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.79 (t, J = 7.2 Hz), 1.08-1.32 (m), 1.39-1.64 (m), 1.71-1.81 (m), 1.82-1.96 (m), 2.04-2.18 (m), 2.51-2.70 (m), 2.92-2.98 (m), 3.18-3.38 (m), 3.45-3.55 (m), 3.60-3.74 (m), 3.81 (s), 3.90 (s), 4.33 (br s), 5.13 (d, J = 10.4 Hz), 7.29 (br s), 7.74 (br s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.6, 10.7, 12.9, 15.5, 16.4, 18.0, 19.0, 21.5, 21.6, 29.5, 29.9, 36.1, 36.7, 37.7, 39.0, 44.7, 45.7, 49.8, 50.3, 58.2, 64.6, 70.0, 70.3, 70.9, 74.4, 78.3, 79.1, 88.5, 106.7, 120.3, 126.1, 129.6, 129.9, 147.7, 175.4; HMRS (ESI) calcd for $[C_{44}H_{71}N_5O_{12} + H]^+$ 862.5172, found 862.5155.

Synthesis of Clarithromycin-*N*-phenyltriazolylheptahydroxamic acid (25)

Reaction of clarithromycin-*N*-phenylacetylene **20** (0.130 g, 0.153 mmol) and 7-azidoheptahydroxamic acid **15b** (0.105 g, 0.565 mmol) within 2.5 h, followed by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 105 mg (67%) of **25** as yellowish solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.82 (t, J = 8.0 Hz), 1.04-1.52 (m), 1.67-1.92 (m), 2.14-2.29 (m), 2.52-2.60 (m), 2.82-2.90 (m), 2.95-3.00 (m), 3.10 (s), 3.16 (s), 3.27-3.32 (m), 3.41-3.46 (m), 3.59 (d, J = 6.8 Hz), 3.69-3.79 (m), 3.90-3.95 (m), 4.34-4.39 (m), 4.87 (d, J = 4.4 Hz), 5.02 (d, J = 9.2 Hz), 7.33 (d, J = 6.4 Hz), 7.77 (d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.1, 10.5, 12.2, 15.9, 17.9, 18.5, 19.8, 20.9, 21.2 , 21.4, 24.7, 25.5, 27.7, 29.8, 34.7, 36.8, 37.1, 39.1, 45.0, 45.2, 49.3, 50.0, 50.5, 57.6, 63.6, 65.6, 68.6, 69.0, 70.7, 72.4, 74.2, 77.8, 78.3, 80.9, 95.9, 102.7, 119.5, 125.7, 129.4, 147.5, 175.8; HMRS (ESI) calcd for $[C_{53}H_{87}N_5O_{15} + H]^+$ 1034.6271, found 1034.6246.

Synthesis of Descladinose-Clarithromycin-*N*-phenyltriazolyl-heptahydroxamic acid (26)

Reaction of descladinose-clarithromycin-*N*-phenylacetylene **21** (0.075 g, 0.109 mmol) and 7-azidoheptahydroxamic acid **15b** (0.040 g, 0.233 mmol) within 4 h, followed by prep TLC (silica, 10:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 80 mg (84%) of **26** as a brownish white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.78 (t, J = 7.2 Hz), 1.06-1.31 (m), 1.40-1.53 (m), 1.71 (d, J = 11.6 Hz), 1.80-1.91 (m), 2.01-2.20 (m), 2.50-2.65

(m), 2.91-2.97 (m), 3.16 (t, J = 6.4 Hz), 3.26-3.35 (m), 3.42-3.54 (m), 3.64-3.71 (m), 3.80 (br s), 3.90 (br s), 4.30-4.34 (m), 5.12 (dd, J = 11.6, 2.4 Hz), 7.27 (d, J = 8.0 Hz), 7.72 (d, J = 7.2 Hz), 7.80 (s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.3, 10.3, 12.5, 15.2, 16.1, 17.6, 18.6, 21.1, 21.3, 24.8, 25.1, 25.5, 26.2, 27.8, 28.5, 29.1, 29.6, 29.7, 32.3, 35.8, 36.3, 37.4, 38.6, 44.3, 45.4, 49.5, 50.0, 51.2, 57.8, 64.2, 69.7, 69.9, 70.6, 74.1, 77.9, 78.7, 88.0, 106.3, 119.9, 125.7, 129.3, 129.5, 138.3, 147.3, 175.1; HMRS (ESI) calcd for $[C_{45}H_{73}N_5O_{12} + H]^+$ 876.5329, found 876.5301.

Synthesis of Clarithromycin- *N*-Phenyltriazolyloctahydroxamic acid (27)

Reaction of clarithromycin- *N*-phenylacetylene **20** (0.101 g, 0.120 mmol) and 8-azidooctahydroxamic acid **15c** (0.047 g, 0.24 mmol) within 2.5 h, followed by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 92 mg (74%) of **27** as a brownish white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (t, J = 7.2 Hz), 1.04-2.05 (m), 2.22 (s), 2.19-2.82 (m), 3.00 (s), 3.08 (s), 2.91-3.80 (m), 3.95 (m), 4.38 (m), 4.88 (d, J = 4.4 Hz), 5.04 (dd, J = 10.8, 2.0 Hz), 7.33 (d, J = 7.6 Hz), 7.71 (s), 7.77 (d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 400MHz) δ 8.8, 9.4, 10.8, 12.5, 16.2, 18.2, 18.8, 20.0, 21.2, 21.5, 21.6, 25.1, 26.0, 26.7, 28.2, 28.6, 28.9, 29.9, 30.1, 35.0, 36.9, 37.4, 39.2, 39.4, 45.2, 45.4, 46.1, 49.6, 50.4, 50.8, 51.6, 58.1, 63.6, 65.9, 68.4, 69.3, 70.9, 72.8, 74.4, 78.0, 78.5, 81.2, 96.1, 120.1, 102.6, 126.1, 130.2, 147.4, 176.0 ; HRMS (ESI) calc for $[C_{54}H_{90}N_5O_{15} + H]^+$ 1048.6427, found 1048.6486.

Synthesis of Descladinose-Clarithromycin- *N*-Phenyltriazolyl-octahydroxamic acid (28)

Reaction of clarithromycin- *N*-phenylacetylene **21** (0.10 g, 0.144 mmol) and 8-azidooctahydroxamic acid **15c** (0.049 g, 0.246 mmol) within 2.5 h, followed by prep TLC (silica, 10:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 117 mg (90 %) of **28** as a brownish white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (t, J = 7.2 Hz), 1.10-2.09 (m), 2.18 (s), 2.19-2.68 (m), 2.98-3.73 (m), 3.83 (s), 3.93 (m), 4.36 (m), 5.16 (d, J = 8.0 Hz), 7.31 (d, J = 8.0 Hz), 7.77 (2H, d, J = 8.0 Hz), 7.79 (1H, s); ^{13}C NMR ($CDCl_3$, 400MHz) δ 8.5,

10.6, 12.8, 15.4, 16.4, 17.9, 18.9, 21.4, 21.6, 29.4, 36.1, 36.7, 37.7, 38.9, 44.7, 45.7, 49.8, 58.0, 65.2, 70.0, 70.4, 70.8, 74.4, 76.8, 78.2, 79.2, 83.6, 88.8, 106.9, 121.3, 128.7, 132.5, 139.6, 175.2 ; HRMS (FAB, thioglycerol) calc for $[C_{46}H_{76}N_5O_{12} + H]^+$ 890.5490, found 890.5562.

Synthesis of Clarithromycin- *N*-Phenyltriazolylnonahydroxamic acid (29)

Reaction of clarithromycin- *N*-phenylacetylene **20** (0.100 g, 0.120 mmol) and 9-azidononahydroxamic acid **15d** (0.043 g, 0.20 mmol) within 2.5 h, followed by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 54 mg (42%) of **29** as a brownish white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.81 (t, J = 7.2 Hz), 1.04-2.02 (m), 2.24 (s), 2.10-2.97 (m), 3.00 (s), 3.09 (s), 3.20-3.82 (m), 3.88 (m), 4.39 (m), 4.88 (d, J = 4.0 Hz), 5.05 (d, J = 10.0 Hz), 7.35 (d, J = 8.0 Hz), 7.77 (d, J = 4.0 Hz); ^{13}C NMR ($CDCl_3$, 400MHz) δ 9.0, 9.3, 10.8, 12.5, 16.1, 18.2, 18.8, 21.2, 21.5, 21.6, 21.7, 21.8, 26.3, 26.8, 28.7, 28.9, 29.1, 29.9, 30.3, 35.0, 37.0, 37.4, 39.3, 39.4, 45.2, 45.4, 49.6, 50.5, 50.8, 51.6, 57.8, 63.8, 65.8, 68.8, 69.2, 70.9, 72.7, 74.5, 76.8, 78.1, 78.4, 78.5, 81.1, 96.1, 102.9, 119.7, 125.9, 129.6, 129.9, 138.7, 147.6, 176.1; HRMS (ESI) calc for $[C_{55}H_{91}N_5O_{15} + H]^+$ 1062.6584, found 1062.6586.

Synthesis of Clarithromycin- *N*-Phenyltriazolyldecahydroxamic acid (30)

Reaction of clarithromycin- *N*-phenylacetylene **20** (0.10 g, 0.120 mmol) and 10-azidodecahydroxamic acid **15e** (0.045 g, 0.197 mmol) within 2.5 h, followed by prep TLC (silica, 12:1:0.1 CH_2Cl_2/MeOH/conc. NH_4OH) gave 68 mg (53 %) of **30** as a brownish white solid. ^1H NMR ($CDCl_3$, 400 MHz) 0.82 (t, J = 7.2 Hz), 1.05-2.12 (m), 2.24 (s), 2.26-2.97 (m), 3.01, 3.10 (s), 3.19-3.80 (m), 3.95 (m), 4.39 (m), 4.89 (d, J = 4.0 Hz), 5.04 (d, J = 8.0 Hz), 7.35 (d, J = 8.0 Hz), 7.76 (s), 7.79 (d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 400MHz) δ 9.3, 10.8, 12.5, 16.1, 18.2, 18.8, 20.0, 21.2, 21.5, 21.7, 25.4, 26.2, 28.9, 29.0, 29.3, 29.6, 29.9, 30.2, 35.0, 37.0, 37.4, 39.3, 39.4, 45.2, 45.4, 49.6, 50.5, 50.8, 51.6, 57.8, 63.8, 65.8, 68.8, 69.2, 70.9, 72.7, 74.5, 76.8, 78.1, 78.5, 81.1, 96.1, 102.9, 119.7, 125.9, 129.6, 129.8, 138.9, 147.6,

176.1 ; HRMS (ESI) calc for $[C_{56}H_{93}N_5O_{15} + H]^+$ 1076.6740, found 1076. 6667.

Example 2. Synthesis of Compounds 36 and 38 in Table 3

Synthesis of Methyl 8-(4-(hydroxymethyl)phenylamino)-8-oxooctanoate (33):

To a mixture of 8-methoxy-8-oxooctanoic acid (0.40 g, 2.10 mmol), benzotriazole (0.28 g, 2.23 mmol) in anhydrous CH_2Cl_2 (15 mL) was added $SOCl_2$ (0.17 mL, 2.23 mmol) at 0°C, the mixture was kept stirring at 0°C for 2.5 h and then filtered. The solvent was evaporated off to give crude acid chloride **31** which was used without further purification.

To a solution of (4-aminophenyl)methanol **32** (0.31 g, 2.50 mmol) in anhydrous pyridine (8 mL) was added chlorotrimethylsilane (0.32 mL, 2.50 mmol) at room temperature and stirring continued for 2 h. The mixture, together with a catalytic amount of DMAP, was added to a mixture of crude chloride **31** (obtained as described above) in pyridine at 0°C. The reaction was allowed to warm to room temperature and stirring continued overnight. Water (5 mL) and 1 M TBAF in tetrahydrofuran (THF) (0.25 mL, 0.25 mmol) were added and stirring continued for additional 30 min. EtOAc (50 mL) and 1N HCl (30 mL) were added, the two layers were separated, the organic layer was washed with 1N HCl (30 mL) and saturated brine (30 mL) and dried over Na_2SO_4. Solvent was evaporated off and the crude was purified by preparative TLC, eluting with acetone/hexanes 1:1 to give compound **33** (195 mg, 30 %) as yellow-white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1. 24 (4H, m), 1.49-1.59 (4H, m), 2.17-2.25 (4H, m), 3.58 (3H, s), 4.50 (2H, s), 7.13 (2H, d, J = 8.4 Hz), 7.37 (2H, d, J = 8.4 Hz).

Synthesis of Azithromycin-arylalkyl methyl ester (35)

To a solution of crude preparation of compound **33** (0.64 g, 2.20 mmol) in CH_2Cl_2 (15 mL) and triethylamine (Et_3N) (0.90 mL, 6.60 mmol) was added mesyl chloride (0.70 mL, 8.85 mmol) at 0°C and the reaction was allowed to warm to room temperature. Stirring continued for 2h, CH_2Cl_2 (40 mL) and saturated sodium bicarbonate (30 mL) were added. The two layers were separated; the organic layer was washed with sodium bicarbonate (1 x

30 mL), saturated brine (30 mL) and dried over Na_2SO_4. Solvent was evaporated off and the crude was purified by flash chromatography (silica gel, eluting with Hexane/EtOAc, gradient 3:1, 2:1, 1:1) to give compound **34** (320 mg, 40 %) as white solid.

A mixture of 4'-Desmethylazithromycin **1** (0.45 g, 0.62 mmol), compound **34** (0.32 g, 0.86 mmol), catalytic amount of potassium iodide in THF (15 mL) and Hunig's base (3 mL) was heated under refluxing condition for 48 h. CH_2Cl_2 (80 mL) and saturated sodium bicarbonate (40 mL) were added and the two layers were separated. The organic layer was washed with sodium bicarbonate (40 mL), saturated brine (40 mL) and dried over Na_2SO_4. Solvent was evaporated off and the crude was purified by preparative TLC, eluting with EtOAc/hexanes/ Et_3N 3:2:0.1 to give compound **35** (176 mg, 28 %) as brown-white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ 0.79-0.83 (m), 0.94-1.01 (m), 1.09-1.20 (m), 1.22-1.32 (m), 1.37-1.59 (m), 1.62- 1.73 (m), 1.77-2.01 (m), 2.08-2.28 (m), 2.38-2.52 (m), 2.61-2.71 (m), 2.91-3.01 (m), 3.11 (s), 3.25-3.33 (m), 3.42 (m), 3.54-3.65 (m), 3.97 (m), 4.18 (m), 4.36 (d, J = 6.8 Hz), 4.61 (m), 5.03 (d, J = 4.4 Hz), 7.14 (d, J = 8.4 Hz), 7.42 (d, J = 8.4 Hz), 7.73 (s), 8.97 (bs) ; ^{13}C-NMR (CDCl3, 100MHz) δ 7.5, 9.1, 11.3, 14.8, 16.2, 16.9, 18.2, 20.5, 21.2, 21.4, 21.5, 21.9, 24.6, 25.3, 26.7, 27.5, 28.7, 29.6, 33.9, 34.7, 36.2, 36.7, 37.3, 39.1, 41.9, 42.2, 45.1, 48.5, 49.3, 51.4, 57.3, 62.2, 64.3, 65.4, 68.5, 69.9, 70.5, 72.7, 73.5, 73.8, 74.1, 77.7, 77.9, 83.4, 94.4, 102.6, 119.5, 129.0, 134.2, 137.0, 171.0, 173.8, 178.4. MS (FAB, mnba) 1010.3 $(M+H)^+$.

Synthesis of Azithromycin-arylalkyl hydroxamic acid (36)

To a solution of compound **35** (0.09 g, 0.09 mmol) in 1:1 THF/MeOH (3 mL) was added hydroxylamine (50 % in H_2O) (0.03 mL, 0.54 mmol) and a catalytic amount of KCN. The mixture was stirred at room temperature for 24 h. The reaction was partitioned between 5 % MeOH in CH_2Cl_2 (30 mL) and saturated sodium bicarbonate (25 mL), the two layers were separated and the aqueous layer was extracted with 5 % MeOH in CH_2Cl_2 (2 x 20 mL). The combined organic layer was washed with saturated brine (40 mL) and dried over Na_2SO_4. Solvent was evaporated off and the crude was purified by

preparative TLC, eluting with CH_2Cl_2/MeOH/NH_4OH 10:1:0.1 to give compound **36** (22 mg, 25 %) as brown-white solid. ^{1}H-NMR (CD_3OD, 400MHz) δ 0.87-0.92 (m), 1.02-1.12 (m), 1.17-1.37 (m), 1.43-1.69 (m), 1.75-1.88 (m), 1.99 (m). 2.08 (m), 2.13-2.19 (m), 2.24 (s), 2.30 (s), 2.33-2.41 (m), 2.54 (d, J = 11.2 Hz), 2.75-2.80 (m) , 3.00 (d, J = 9.6 Hz), 3.19 (bs), 3.47-3.51 (m), 3.60 (bs), 3.63-3.78 (m), 4.14-4.22 (m), 4.50 (d, J = 7.2 Hz), 5.02 (d, J = 4.8 Hz), 7.29 (d, J = 8.0 Hz), 7.49 (d, J = 8.4 Hz). MS (FAB, mnba) 1011.3 $(M+H)^+$.

Synthesis of Desclasinose-azithromycin-arylalkyl hydroxamic acid (38)

A mixture of compound **35** (0.05 g, 0.05 mmol) in 0.25 N HCl (15 mL) was stirred at room temperature for 20 h and poured into EtOAc (20 mL). The two layers were separated and the aqueous layer was washed with EtOAc (2 x 20 mL), basified with concentrated NH_4OH and then extracted with 5 % MeOH in CH_2Cl_2 (2 x 30 mL). The combined organic layer was washed with saturated brine (30 mL) and dried over Na_2SO_4. Solvent was evaporated off to give compound **37** which was used for the next reaction without further purification.

To a solution of compound **37** (obtained as described above) in 1:1 THF/MeOH (2 mL) was added hydroxylamine (50 % in H_2O) (0.05 mL, 0.79 mmol) and a catalytic amount of KCN. The mixture was stirred at room temperature for 24 h. The reaction was partitioned between 5 % MeOH in CH_2Cl_2 (30 mL) and saturated brine (20 mL), the two layers were separated and the organic layer was dried over Na_2SO_4. Solvent was evaporated off and the crude was purified by preparative TLC, eluting with CH_2Cl_2/ MeOH/NH_4OH 9:1:0.1 to give compound **38** (7 mg, 16 %) as brown-white solid. ^{1}H-NMR (CD_3OD, 400MHz) δ 0.78 (m), 0.85 (d, J = 7.2 Hz), 0.91 (d, J = 8.0 Hz), 0.99 (s), 1.11 (m), 1.26-1.76 (m), 1.98 (t, J = 7.4 Hz), 2.08 (m), 2.17 (s), 2.25 (t, J = 7.4 Hz), 2.40 (bs), 2.58 (m), 2.95 (bs), 3.24 (m), 3.37-3.56 (m), 3.67 (d, J = 13.2 Hz), 4.53 (d, J = 7.6 Hz), 7.19 (d, J = 8.4 Hz), 7.39 (d, J = 8.4 Hz). MS (FAB, mnba) 853.3 $(M+H)^+$.

Example 3. Synthesis of Compounds 40, 44 and 47 in Table 3

Synthesis of Azithromycin-*N*-phenyltriazolylhepta-2-methyl ketone (40)

Compound **3** (0.040 g, 0.047 mmol) and azido-2-methyl ketone **39** (0.011g, 0.071 mmol) were dissolved in anhydrous THF (7 mL) and stirred under argon at room temperature. Copper (I) iodide (0.010 g, 0.053 mmol) and Hunigs' base (0.1 mL) were then added to reaction mixture and stirring continued for 2 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 1:4 NH_4OH/saturated NH_4Cl (3 x 30 mL) and saturated NH_4Cl (30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by preparative TLC (12:1 CH_2Cl_2: MeOH) to give 38 mg (81%) of **40** as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86-0.89 (t, J = 7.2 Hz), 0.92-0.98 (m), 1.01-1.02 (d, J = 7.2 Hz), 1.086 (s), 1.12-1.24 (m), 1.29-1.34 (m), 1.42-1.66 (m), 1.74-1.78 (d, J = 16 Hz), 1.84-2.08 (m), 2.11 (s), 2.15 (m), 2.26-2.48 (m), 2.56-2.74 (m), 2.84 (s), 2.74-3.08 (m), 3.11 (s), 3.32-3.40 (m), 3.46-3.84 (m), 3.98-4.46 (m), 4.23 (broad singlet), 4.38-4.51 (m), 4.72 (broad singlet), 5.06-5.12 (m), 7.31-7.38 (m), 7.75 (s), 7.77-7.79 (d, J = 8 Hz); HRMS (ESI) calc for $[C_{53}H_{89}N_5O_{13} + H]^+$ 1004.6529, found 1004.6482.

Synthesis of Azidobenzamide (43)

A solution of azido acid **41** (0.150 g, 0.877 mmol) in dry THF (10 mL) was treated with 1,2-diaminobenzene **42** (0.568 g, 5.26 mmol) and EDC (0.219 g, 1.14 mmol) . The resulting mixture was stirred at room temperature for about 24 h and then concentrated *in vacuo*. The crude was diluted with EtOAc (40 mL), washed in succession with water (30 mL) and brine (30 mL) and the organic layer was dried over Na_2SO_4. Solvent was evaporated off and the crude was purified by flash chromatography (silica, Hexanes/ EtOAc 1:2) to give 79 mg (35%) of **43** as a yellow solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34-1.68 (m), 2.27-2.31 (m), 3.84 (s), 6.72-6.75 (m), 7.00-7.05 (m), 7.09-7.11 (d, J = 8 Hz); HRMS (ESI) calcd for $[C_{13}H_{19}N_5O + H]^+$ 262.1662, found 262.1635.

Synthesis of Azithromycin-*N*-phenyltriazolylheptabenzamide (44)

Compound **3** (0.050 g, 0.059 mmol) and azido benzamide **43** (0.023 g, 0.088 mmol) were dissolved in anhydrous THF (10 mL) and stirred under argon at room temperature. Copper (I) iodide (0.010 g, 0.0526 mmol) and Hunigs' base (0.1 mL) were then added to reaction mixture and stirring continued for 2 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with 1:4 NH_4OH/saturated NH_4Cl (3 x 30 mL) and saturated NH_4Cl (30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product is purified by prep TLC (12:1 CH_2Cl_2/MeOH) to give 38 mg (59%) of **44** as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80-1.57 (m), 1.70-1.75 (m), 1.85-1.91 (m), 2.01-2.07 (m), 2.13 (s), 2.22-2.26(m), 2.36-2.41 (m), 2.58 (br s), 2.68 (br s), 2.75-3.07 (m), 3.25-3.62 (m), 3.69 (s), 3.81 (br s), 3.98 (br s), 4.17 (s), 4.32-4.48 (m), 4.72 (br s) 5.05 (s), 6.70-6.76 (m), 6.92-7.02 (m), 7.18-7.21 (d, J = 12 Hz), 7.32 (br s), 7.71-7.73 (d, J = 8 Hz), 7.78 (s). 7.87 (br s); HRMS (ESI) calcd for $[C_{59}H_{95}N_7O_{13}$ + $H]^+$ 1110.7060, found 1110.7012.

Synthesis of Descladinose-clarithromycin- *N*-phenylacetylene-*O*-Acetate (45)

Descladinose-clarithromycin- *N*-phenylacetylene **21** (3.80 g, 5.5 mmol) was dissolved in acetone (20 ml) followed by addition of acetic anhydride (0.62 g, 6.0 mmol) and stirred at 40°C for 36 h. The reaction mixture was diluted with EtOAc (100 mL), washed with aqueous $NaHCO_3$ and brine, and then purified on silica column eluting with 6:1 CH_2Cl_2/Acetone to obtain 2.8g (70%) of **45** as a brownish white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, J = 7.2 Hz), 0.90 (d, J = 7.2 Hz), 1.08-1.47 (m), 1.58 (s), 1.63-2.05 (m), 2.08 (s), 2.16 (s), 2.42-2.80 (m), 2.92 (s), 2.94-3.00 (m), 3.03-3.68 (m), 3.79 (s), 3.94 (s), 4.08 (m), 4.54 (d, J = 8.0 Hz), 4.80 (m), 5.15 (dd, J = 11.6, 2.4 Hz), 7.17 (d, J = 8.4 Hz), 7.38 (d, J = 8.0 Hz).

Synthesis of clarithromycin- *N*-phenylacetylene ketolide (46)

Methyl sulfide (0.35 g, 5.7 mmol), was added to a mixture of *N*-chlorosuccinimide (0.65 g, 4.8 mmol) and CH_2Cl_2 (3 mL) while maintaining

the temperature at -15°C. Compound **45** (2.5 g, 3.4 mmol) dissolved in CH_2Cl_2 (20 mL) was added to the reaction mixture, followed by triethylamine (0.39 g, 3.8 mmol). The mixture was stirred at -15°C for 3.5 h and partitioned between EtOAc (100 mL) and 0.5 N aqueous NaOH (150 mL). The organic layer was separated, washed with brine (70 mL), and dried over Na_2SO_4. Solvent was evaporated off and the crude was purified on silica column eluting with 1:4:0.1 EtOAc/Hexane/Et_3N, increasing solvent polarity to 2:3:0.1, to afford 2.0 g (80%) of **46** as off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80-0.86 (m), 1.09-1.57 (m), 1.58 (s), 1.62-2.02 (m), 2.05 (s), 2.15 (s), 2.44-2.80 (m), 2.92 (s), 2.95-3.00 (m), 3.05-3.82 (m), 4.12 (m), 4.38 (d, J = 8.0 Hz), 4.79-4.83 (m), 5.14 (dd, J = 11.2, 2.0 Hz), 7.16 (d, J = 7.6 Hz), 7.38 (d, J = 7.6 Hz).

Synthesis of Ketolide-*N*-phenyltriazolylheptabenzamide (47)

Ketolide **46** (0.050 g, 0.069 mmol) and azido benzamide **43** (0.027 g, 0.103 mmol) were dissolved in anhydrous THF (10 mL) and stirred under argon at room temperature. Copper (I) iodide (0.010 g, 0.0526 mmol) and Hunigs' base (0.1 mL) were then added to reaction mixture and stirring continued for 2 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 1:4 NH_4OH/saturated NH_4Cl (3 x 30 mL) and saturated NH_4Cl (30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified by prep TLC (3:2 CH_2Cl_2/Acetone) to give 51 mg (75%) of **47** as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78-0.88 (m), 1.18-1.25 (m), 1.31-1.70 (m), 1.87-2.00 (m), 2.14 (s), 2.28-2.35 (m), 2.42-2.51(m), 2.62-2.75 (m), 3.12 (s), 3.31-3.35 (t, J = 8 Hz), 3.42 (s), 3.47 (br s), 3.62-3.82 (m), 4.32-4.40 (m), 5.05-5.09 (d, J = 16 Hz), 5.44 (s), 5.77 (s), 6.64-6.74 (m), 6.95-7.00 (m), 7.10-7.15 (m), 7.18-7.21 (m), 7.27-7.31 (m), 7.60 (s) 7.72-7.74 (d, J = 8 Hz), 7.77 (s).

Example 4. Anti-HDAC activity of nonpeptide macrocyclic HDAC inhibitors

Inhibition of HeLa nuclear extract HDAC 1/2 and HDAC8 by compounds 7-14, 23-30, 36, and 38 was evaluated in a *Fluor de Lys assay* according to the manufacture's protocol. Each IC_{50} value was obtained by

averaging three independent experiments. This data is shown in Table 4. The compounds displayed both linker-length and macrolide-type dependent HDAC inhibition activities with IC_{50} in low nanomolar range.

Table 4. Inhibitory activity of HDAC inhibitors

	HDAC 1/2 (nM)	HDAC 8 (nM)
Compound		
7	91.6	4,730
8	88.8	3,740
9	13.85	994
10	10.56	1,020
11	58.88	7,130
12	72.44	6,780
13	145.50	11,050
14	226.73	N.D.
23	36.98	3,990
24	44.26	4,750
25	4.09	1,890
26	1.87	1,390
27	55.59	5,880
28	123.03	4,420
29	169.80	10,550
30	223.36	N.D
36	107.1	6,680
38	109.8	2,320

Example 4. Evaluating *in vitro* anti-cancer activity of HDAC inhibitors

The potency of compounds in Table 5 were investigated by determining the drug concentrations necessary for 50 % inhibition of cell viability (IC_{50}) in SKMES 1, NCI-H69, DU 145 cells, lung fibroblasts, and HMEC. Drug concentrations necessary for 50 % inhibition of cell viability (EC_{50}) were quantitatively measured using trypan blue exclusion according to literature protocol (Mosmann, T. (1983) *J. Immunol. Methods 65*: 55; Chen *et al.* (2008) Bioorg. Med. Chem. 16: 4839). Table 5 shows the EC_{50}

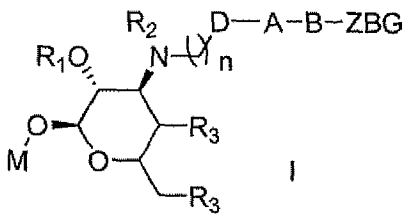
values for each compound. All compounds inhibit the proliferation of the transformed cells studied with EC_{50} in low micromolar range. Most importantly, these compounds are less toxic to untransformed cell-lines (lung fibroblast and HMEC) that we have studied to date.

Table 5. Cell growth inhibitory data

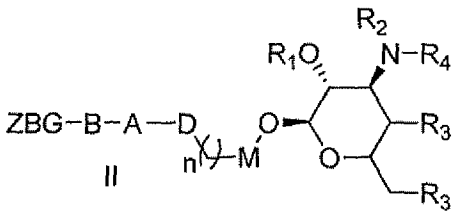
Compound	SKMES 1 (uM)	NCI-H69 (uM)	DU-145 (uM)	Lung fibroblast (uM)	HMEC (uM)
7	1.79	1.92	1.45	>10	>10
8	1.68	1.77	1.24	>10	>10
9	2.33	3.45	1.88	>10	>10
10	2.56	3.01	1.97	>10	>10
11	4.89	4.56	5.89	>10	>10
12	4.67	3.99	5.68	>10	>10
13	7.54	8.45	>10	>10	>10
23	2.15	2.67	2.98	>10	>10
24	1.95	1.92	3.29	>10	>10
25	1.33	1.45	1.12	>10	>10
26	1.28	1.49	1.05	>10	>10
27	4.89	5.67	6.97	>10	>10
28	4.45	5.09	5.78	>10	>10
29	7.12	7.29	8.14	>10	>10

I claim:

1. A compound of Formula I or II:



I



II

wherein M represents a macrolide subunit,

n is a C_{1-6} group, optionally containing one or more heteroatoms, wherein the carbon atoms and/or heteroatoms are in a linear and/or cyclic arrangement,

D is an alkyl or aryl group,

A is a linking group connected to D,

B is an alkyl, alkylaryl or alkylheteroaryl spacer group,

ZBG is a Zinc Binding Group,

R_1, R_2 and R_4 are independently selected from the group consisting of hydrogen, a C1-6 alkyl group, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{1-6} alkanoate group, a C_{2-6} carbamate group, a C_{2-6} carbonate group, a C_{2-6} carbamate group, or a C_{2-6} thiocarbamate group,

R_3 is hydrogen or $-OR_5$,

R_5 is selected from the group consisting of hydrogen, a C_{1-6} alkyl hgroup, a C_{2-6} alkenyl group, a C_{2-6} alkynyl group, a C_{1-6} alkanoate group, a C_{2-6} carbamate group, a C_{2-6} carbonate group, a C_{2-6} carbamate group, or a C_{2-6} thiocarbamate group.

2. The compound of claim 1, wherein the macrolide subunit is a multi-member lactonic ring structure.

3. The compound of claim 2, wherein the multi-member lactonic ring structure is selected from the group consisting of the compounds in Table 1.

4. The compound of claim 2, wherein the multi-member lactonic ring structure is selected from the group consisting of the compounds in Table 2.

5. The compound of any one of claims 1 to 4, wherein R_1-R_3 is hydrogen.

6. The compound of any one of claims 1-5, wherein n is 1, 2, or 3.

7. The compound of any one of claims 1-6, wherein D is a phenyl, biphenyl, or naphthyl group.

8. The compound of any one of claims 1-7, wherein A is an amide or 1,2,3-triazolyl group.

9. The compound of any one of claims 1-8, wherein B is an alkyl group having from 4-6 carbon atoms.

10. The compound of any one of claims 1-9, wherein the zinc binding group is selected from the group consisting of hydroxamate and N-formyl hydroxylamine.

11. The compound of any one of claims 1-10 selected from the group consisting of the compounds in Table 3.

12. The compound of claim 11, wherein the compound is azithromycin-arylalkyltriazolyl hydroxamate or clarithromycin-arylalkyltriazolyl hydroxamate.

13. The compound of claim 11, wherein the compound is desclasinoseazithromycin-arylalkyltriazolyl hydroxamate or desclasinoseclarithromycin-arylalkyltriazolyl hydroxamate.

14. A pharmaceutical composition comprising an effective amount of the compound of any one of claims 1-13 in combination with a pharmaceutically acceptable diluent, excipient, or carrier.

15. The composition of claim 14, wherein the composition is administered enterally.

16. The composition of claim 14, wherein the composition is administered parenterally.

17. The composition of claim 14, wherein the composition is formulated for immediate release, modified release, and combinations thereof.

18. The composition of claim 17, wherein the formulation is selected from the group consisting of delayed release, extended release, pulsatile release, and combinations thereof.

19. A method of treating a disease or disorder in a human or animal comprising administering an effective amount of a compound of any one of claims 1-13.

20. The method of claim 19 wherein the disease or disorder to be treated is selected from the group consisting of cancer, inflammation, infections, and cognitive disorders.

21. The method of claim 20, wherein the disease or disorder to be treated is cancer.

22. The method of claim 21, wherein the cancer is selected from the group consisting of lung cancer, myeloma, leukemia, lymphoma, breast cancer, prostate cancer, pancreatic cancer, cervical cancer, ovarian cancer, and liver cancer.

23. The method of claim 19 wherein the compound is administered enterally.

24. The method of claim 23, wherein the compound is formulated in a solid oral dosage form selected from the group consisting of tablets, capsules, dragees, and caplets.

25. The method of claim 23, wherein the compound is formulated in a liquid oral dosage form selected from the group consisting of solutions, suspensions, and syrups.

26. The method of claim 19, wherein the compound is administered parenterally.