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(54) Title: 18-20 MEMBER BI-POLYCYCLIC COMPOUNDS

(57) Abstract: The invention relates to 18-20 member bi-polycyclic compounds, methods of making these compounds, and methods of using them in treating hyperproliferative disorders (e.g., cancer) and non-malignant tumors; promoting muscle formation; inhibiting muscle degeneration or the loss of muscle mass or muscle function; and myofibers ex vivo.



WO 2015/188015 A1

**18-20 MEMBER BI-POLYCYCLIC COMPOUNDS****CROSS REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of the filing date of U.S. Provisional Application No. 62/007,673, filed June 4, 2014, and U.S. Provisional Application No. 62/007,686, filed  
 5 June 4, 2014, which applications are hereby incorporated by reference herein in their entireties.

**FIELD OF THE INVENTION**

The invention relates to 18-20 member bi-polycyclic compounds and methods of making and using these compounds to promote muscle formation, inhibit muscle degeneration, and treat  
 10 hyperproliferative disorders (*e.g.*, cancer).

**BACKGROUND OF THE INVENTION**

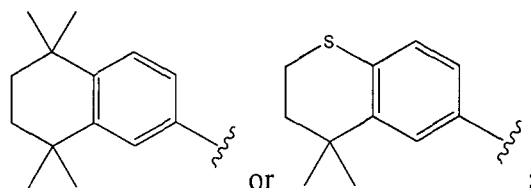
The disappearance of muscle mass associated with several pathological conditions is not effectively addressed by palliative or pharmacological therapies. Therefore there is a need to  
 15 develop therapeutics that delay or prevent the mechanisms of muscle atrophy and can therefore inhibit or help to prevent muscle degeneration and support muscle function in patients.

The following references may be of interest: Vannini *et al.*, *EMBO Rep.* **9**:879-84, 2007; Shibata *et al.*, *Recent Prog. Horm. Res.* **52**:141-64, 1997; Gronemeyer and Miturski, *Cell Mol. Biol. Lett.* **6**:3-52, 2001; Oehme *et al.*, *Clin. Cancer Res.* **15**(1):91-9, 2009; Pori, *Eur. J. Med. Chem.* **70**:857-63, 2013; Evans *et al.*, *J. Clin. Nutr.* **91**(suppl):1123S-7S, 2010; Abmayr and Pavlath, *Development* **139**:641-656, 2012; Macpherson *et al.*, *J. Cell. Biochem.* **112**(8):2149-59, 2010; Moresi *et al.* *Cell* **143**(1):35-45, 2010; Nebbioso *et al.*, *EMBO Rep.* **10**(7):776-82, 2009; Glenisson *et al.*, *Biochim. Biophys. Acta.* **1773**(10):1572-82, 2007 and WO/2011/097712.  
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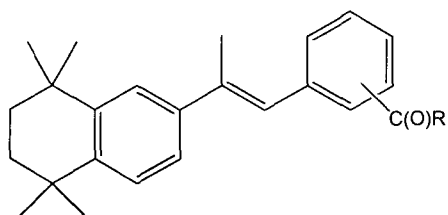
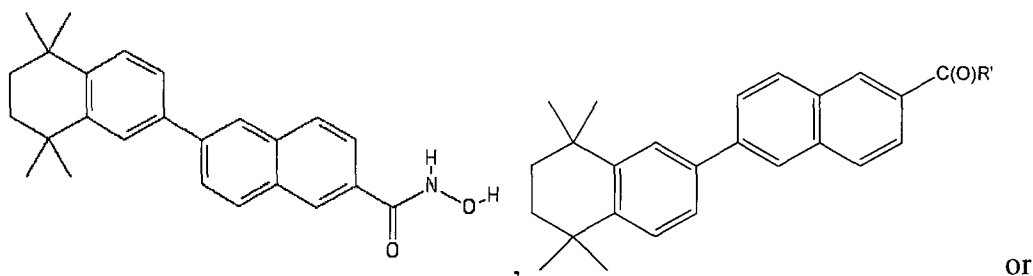
**SUMMARY OF THE INVENTION**

In a first aspect, the invention relates to a compound of Formula I: A-W-Z (I) or a pharmaceutically acceptable salt thereof, wherein A is



W is a heterocyclylene, arylene, heteroarylene, alkenylenearylene, arylenealkenylene alkenyleneheteroarylene, or heteroarylenealkenylene; and

Z is a hydrogen bond donor, with the proviso that the compound is not



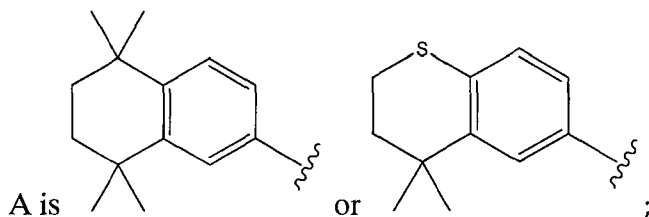
5 where R is -OH, -OCH<sub>3</sub> and -NHOH; and R' is -OH or -OCH<sub>3</sub>.

In another aspect, the invention features methods of treating a subject who has cancer or a non-malignant tumor by administering to the subject a therapeutically effective amount of a compound described above or a pharmaceutically acceptable composition containing such a compound or a mixture thereof.

The invention also relates, in part, to methods of inhibiting loss of muscle mass or muscle function in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I:

A-W-Z (I)

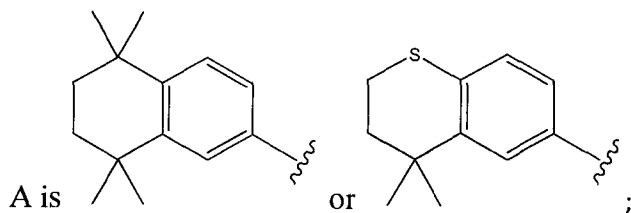
15 or a pharmaceutically acceptable salt thereof, wherein



W is a heterocyclylene, arylene, heteroarylene, alkenylenearylene, arylenealkenylene or alkenyleneheteroarylene, heteroarylenealkenylene; and

Z is a hydrogen bond donor.

In another aspect, the invention features methods for treating myofibers *ex vivo*. These methods can include the steps of providing an *ex vivo* preparation of myofibers, optionally comprising a natural or synthetic biological matrix; and contacting the preparation with an amount of a compound of Formula I: A-W-Z (I) or a pharmaceutically acceptable salt thereof,  
 5 that is sufficient to promote muscle mass or muscle function. Within Formula I,



W is a heterocyclylene, arylene, heteroarylene, alkenylenearylene, arylenealkenylene alkenyleneheteroarylene, or heteroarylenealkenylene; and Z is a hydrogen bond donor.

10 In another aspect, the invention features methods of making a compound as described herein, for example, as illustrated in the synthetic schemes shown below.

In other aspects, the invention features the use of one or more of the compounds described herein in the preparation of a medicament or in the preparation of a medicament for the treatment of cancer to for inhibiting the loss of muscle mass or muscle function.

15 Where elements are listed, it is to be understood that any one or more of the listed elements can be excluded from the compound, composition, or method. For example, the inventors have specified that W can be a heterocyclylene, arylene, heteroarylene, alkenylenearylene, arylenealkenylene alkenyleneheteroarylene, or heteroarylenealkenylene. Therefore, W can be any of these elements except heterocyclylene, for example.

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### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 exemplifies various compounds of the invention.

Figure 2 shows a proton NMR spectra for compound 5.

Figure 3 shows a proton NMR spectra for compound 8.

25 Figure 4 shows a proton NMR spectra for compound 13.

Figures 5A-B are graphs demonstrating dose-dependent inhibition of recombinant human HDAC-1 and HDAC-6 using compounds disclosed herein.

Figures 6A-B are graphs showing the induction of RAR-dependent transcriptional activity and lack of induction of RXR-dependent transcriptional activity in MCF7 cells.

Figures 7A-C are graphs depicting the cytotoxic effect of compounds disclosed herein in high risk neuroblastoma (IMR-32 and BE-2C) and triple negative breast cancer (MDA-MB-231) cell lines.

Figure 8 is a series of gels showing the effect of compound 13 on intracellular acetylation of p53 protein in IMR-32 neuroblastoma cells.

Figure 9 shows a series of gels demonstrating the effect of certain compound on intracellular acetylation of alpha-tubulin in BE-2C neuroblastoma cells.

Figure 10 is a series of photomicrographs showing immunohistochemically stained C2C12 cells in culture and the effect of certain compounds on fiber apparition and maintenance in long term culture.

Figure 11 shows how the certain compounds of the invention affect fusion of differentiated mononuclear C2C12 myoblasts in long term cultures.

Figures 12A-B are bar graphs showing the effect of compound 17 on the distribution of the length and diameter of myotubes in long term C2C12 culture.

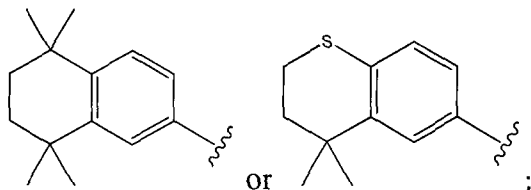
Figure 13 shows the effect of certain compounds on myotube degeneration in differentiated C2C12 cells.

Figures 14A-B are bar graphs showing the effect of compounds 13 and 17 on myofiber gene expression in C2C12 cells.

Figure 15 is a graph comparing the pharmacokinetic profile for compounds 13 and 17.

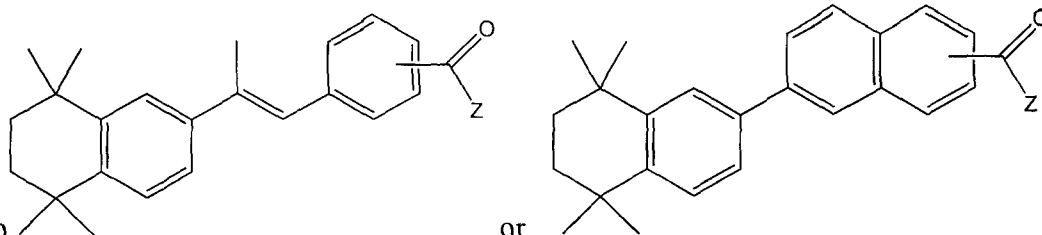
### DETAILED DESCRIPTION

*Compounds:* The invention relates to compounds of Formula I: A-W-Z (I) or a pharmaceutically acceptable salt thereof, wherein A is



W is a heterocyclylene, arylene, heteroarylene, alkenylenearylene, arylenealkenylene alkenyleneheteroarylene, or heteroarylenealkenylene; and

Z is a hydrogen bond donor, with the proviso that the compound is not a compound



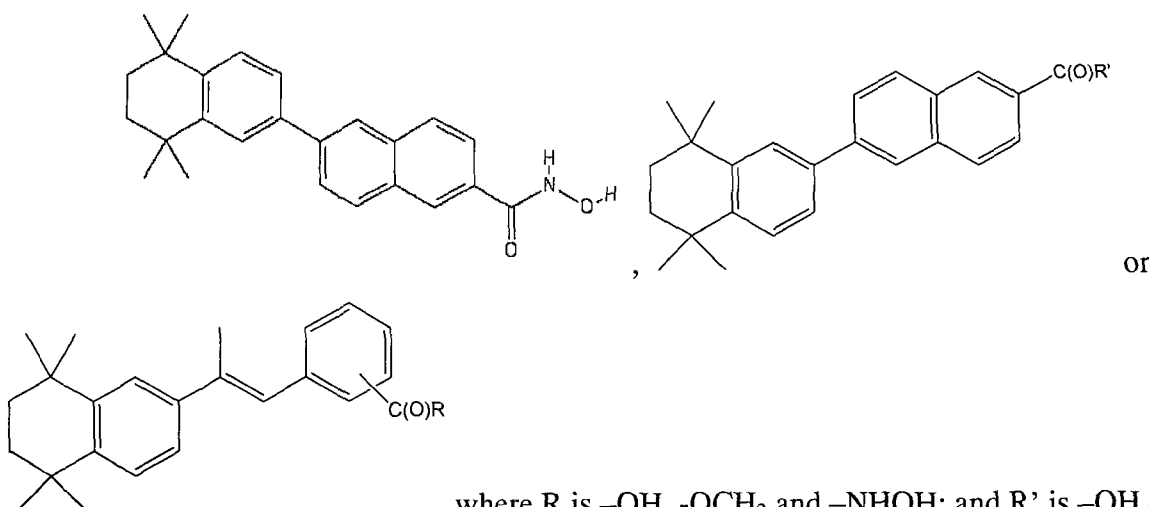
conforming to

or

wherein Z is a hydrogen bond donor (e.g., wherein Z is -OH, -O(C<sub>1-6</sub> alkyl), -NH<sub>2</sub>, and -NHOH).

For example, the invention relates to compounds of Formula I with the proviso that the

5 compound is not:

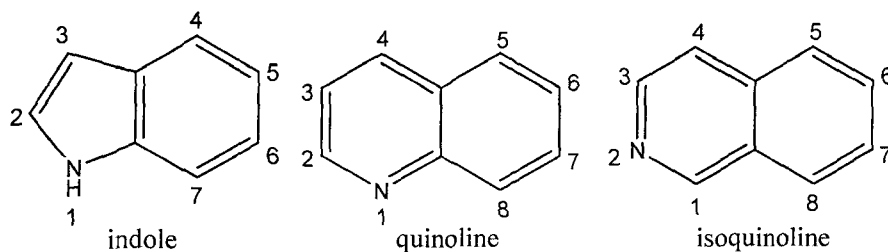


OCH<sub>3</sub>.

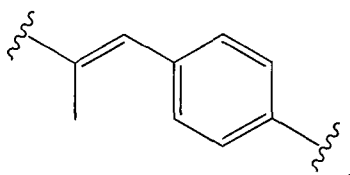
where R is -OH, -OCH<sub>3</sub> and -NHOH; and R' is -OH or -

10 In some embodiments, W is an indolinylene linked to A at any one of positions 2, 3, 4, 5, 6 or 7 of the indolinylene; a quinolinene linked to A at any one of positions 2, 3, 4, 5, 6, 7, or 8; or an isoquinolinene linked to A at any one of positions 1, 3, 4, 5, 6, 7, or 8. In other embodiments, W is -propylene-phenylene-.

15 In regard to the indolinylene, quinolinene and isoquinolinene moieties, the following numbering schemes apply:



The compounds of the invention are not limited to the indolinylene, quinolinene and isoquinolinene moieties for W. The nitrogen atom in these ring systems may have an oxygen or sulfur atom instead of nitrogen.



In some embodiments, W is

5 In some embodiments, Z is  $-C(O)NR^1R^2$  or  $-C(O)OR^3$ , where  $R^1$  and  $R^2$  are each independently hydrogen (H), hydroxyl (OH),  $C_{1-6}$  alkyl, hydroxy $C_{1-6}$  alkyl, amino $C_{1-6}$  alkyl, or aminoaryl; and  $R^3$  is H or  $C_{1-6}$  alkyl.

In some embodiments, Z is linked to the indolinylene, quinolinene, or isoquinolinene at any one of the positions of the indolinylene, quinolinene, or isoquinolinene that is not linked to A.

10 In some embodiments, W is an indolinylene linked to A at any one of positions 2, 3, 4, 5, 6 or 7 of the indolinylene; Z is  $-C(O)NR^1R^2$  or  $-C(O)OR^3$ , where  $R^1$  and  $R^2$  are each independently hydrogen, hydroxyl,  $C_{1-6}$  alkyl, hydroxy $C_{1-6}$  alkyl, amino $C_{1-6}$  alkyl, or aminoaryl; and  $R^3$  is H or  $C_{1-6}$  alkyl, and where Z is linked to the indolinylene at any one of positions 2, 3, 4, 5, 6 or 7 of the indolinylene not linked to A.

15 In other embodiments, W is a quinolinene linked to A at any one of positions 2, 3, 4, 5, 6, 7 or 8 of the quinolinene; Z is  $-C(O)NR^1R^2$  or  $-C(O)OR^3$ , where  $R^1$  and  $R^2$  are each independently hydrogen, hydroxyl,  $C_{1-6}$  alkyl, hydroxy $C_{1-6}$  alkyl, amino $C_{1-6}$  alkyl, or aminoaryl; and  $R^3$  is H or  $C_{1-6}$  alkyl, and where Z is linked to the quinolinene at any one of positions 2, 3, 4, 5, 6, 7 or 8 of the quinolinene.

20 In certain other embodiments, W is a isoquinolinene linked to A at one of positions 1, 3, 4, 5, 6, 7 or 8 of the isoquinolinene moiety; Z is  $-C(O)NR^1R^2$  or  $-C(O)OR^3$ , where  $R^1$  and  $R^2$  are each independently hydrogen, hydroxyl,  $C_{1-6}$  alkyl, hydroxy $C_{1-6}$  alkyl, amino $C_{1-6}$  alkyl, or aminoaryl; and  $R^3$  is H or  $C_{1-6}$  alkyl, and where Z is linked to the quinoline ring at any one of positions 2, 3, 4, 5, 6, 7 or 8 of the isoquinolinene.

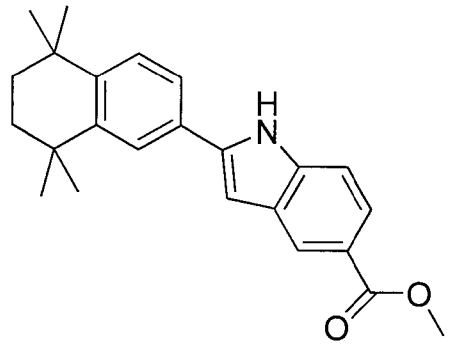
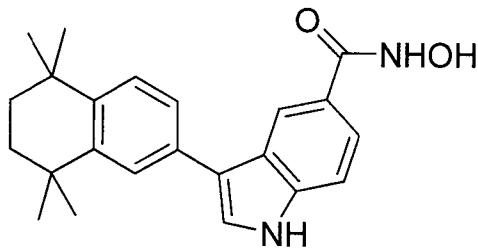
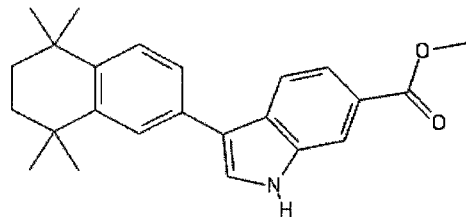
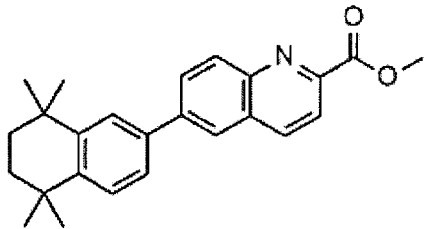
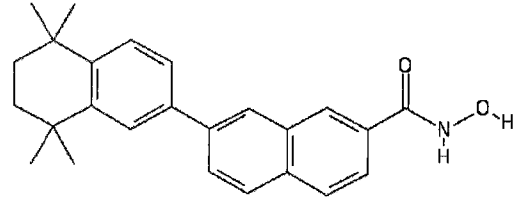
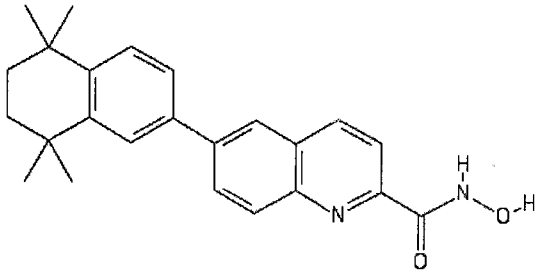
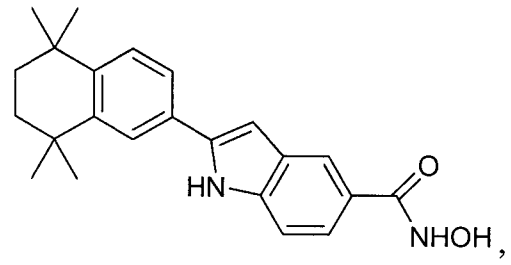
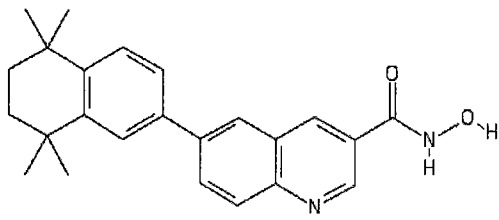
25 In one embodiment, Z is  $-C(O)NR^1R^2$ ;  $R^1$  is H; and  $R^2$  is OH.

In another embodiment, Z is  $-C(O)NR^1R^2$ ;  $R^1$  is H; and  $R^2$  is aminoaryl.

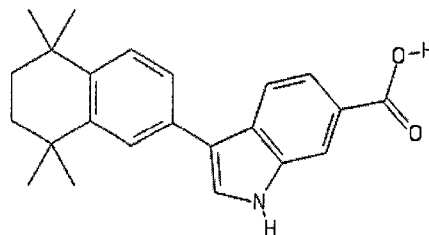
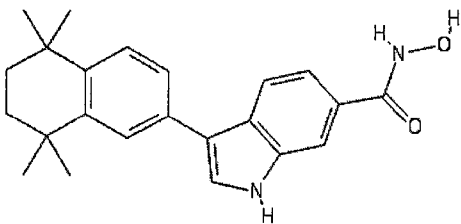
In yet another embodiment, Z is  $-C(O)OR^3$ ; and  $R^3$  is H.

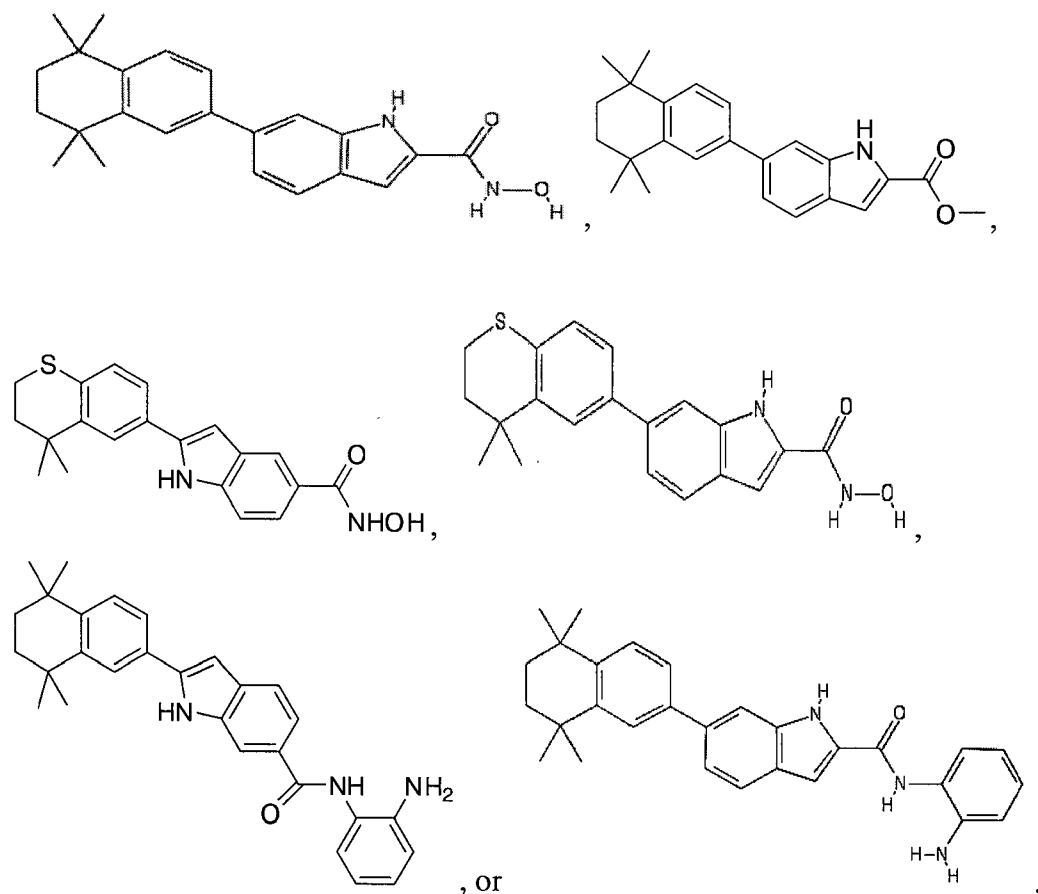
In another embodiment, Z is  $-C(O)OR^3$ ; and  $R^3$  is  $C_{1-6}$  alkyl.

The compound can be:



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5 It is to be understood that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can be combined in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

The compounds described herein can be asymmetric (*e.g.*, having one or more  
 10 stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Accordingly, the compositions of the invention (*e.g.*, pharmaceutical compositions) can include a compound or compounds in the R-form, the S-form, or a racemic or non-racemic mixture thereof. Compounds that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods for preparing optically active  
 15 forms from optically inactive starting materials are known in the art and include resolution of racemic mixtures and stereoselective synthesis. Stable, geometric isomers are also contemplated in the present invention. Cis and trans geometric isomers of the compounds are described and may be isolated as a mixture of isomers or as separate isomers.

Resolution of racemic mixtures can be carried out by any of the numerous methods known in the art. For example, compounds can be resolved by fractional recrystallization using a chiral resolving acid which is an optically active, salt forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the  
5 D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as 3-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of *ct*-methylbenzylamine (*e.g.*, S and R forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine,  
10 cyclohexylethylamine, 1,2-diaminocyclohexane, and the like. Racemic mixtures can also be resolved by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent compositions can be determined by one of ordinary skill in the art.

Compounds of the invention also include tautomeric forms, which result from the  
15 swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Examples of prototropic tautomers include ketone-enol pairs, amide-imidic acid pairs, lactam-lactim pairs, amide-imidic acid pairs, enamine-imine pairs, and annular forms where a proton can occupy two or more positions of a  
20 heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H-isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by an appropriate substitution.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number  
25 but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

As used herein, the term "alkyl" refers to a saturated hydrocarbon group which is straight-chained or branched. Examples of alkyl groups include methyl (Me), ethyl (Et), propyl (*e.g.*, *n*-propyl and isopropyl), butyl (*e.g.*, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl), pentyl (*e.g.*, *n*-pentyl, isopentyl, *sec*-pentyl, neopentyl), and the like. An alkyl group can contain from 1 to  
30 about 20 (*e.g.*, from 2 to about 20, from 1 to about 10, from 1 to about 8, from 1 to about 6, from 1 to about 4, or from 1 to about 3) carbon atoms. By "about," we mean  $\pm 10\%$  (*e.g.*, about 20

grams is 18-22 grams) or, where the referenced number of units is less than 10 or not readily useful in divided tenths, we mean  $\pm 1$  (e.g., about 6 carbon atoms is 5-7 carbon atoms; about 20 carbon atoms is 19-21 carbon atoms).

The term "alkoxy," when used alone or in combination with other groups, refers to a terminal oxy containing alkyl group, as defined above such as methoxy, ethoxy, propoxy, isopropoxy and the like.

The terms "alkenyl" and "alkynyl," when used alone or in combination with other groups, refer to mono- or polyunsaturated aliphatic hydrocarbon radicals containing from two to 15 carbon atoms and at least one double or triple bond, respectively. "Alkenyl" and "alkynyl" refer to both branched and unbranched alkenyl and alkynyl groups, respectively. The alkenyl and alkynyl groups include straight chained alkenyl or alkynyl groups containing from two to eight carbon atoms and branched alkenyl or alkynyl groups containing from five to ten carbon atoms. The alkenyl and alkynyl groups also include alkenyl and alkynyl groups containing from two to six carbon atoms and branched alkenyl and alkynyl groups containing from 5 to eight carbon atoms. Examples of alkenyl groups include ethenyl, 2-propenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, allyl, 1, 3-butadienyl, 1, 3-dipentenyl, 1,4 dipentenyl, 1-hexenyl, 1, 3-hexenyl, 1,4-hexenyl, 1, 3, 5-trihexenyl, 2, 4-dihexenyl, and the like.

Examples of alkynyl include ethynyl, 1-propynyl, 2-propynyl, 1 butynyl, 2-butynyl, 2-methyl-1-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 3 -methyl-1-pentynyl, 2-methyl-1-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, and the like. The alkenyl and alkynyl groups contain at least one double bond or one triple bond, respectively. In another embodiment, they each may contain up to 4 carbon-carbon multiple bonds, for example, 1, 2, 3, or 4, double bonds or triple bonds, respectively. The double bonds in the alkenyl groups may be conjugated, as in 1,3-butadienyl, or non-conjugated, as in 1,4-di pentenyl.

As used herein, "aryl" refers to monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings) aromatic hydrocarbons such as, for example, phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms. The term "aryl" includes aromatic rings fused to non-aromatic rings, as long as one of the fused rings is an aromatic hydrocarbon.

The term “heteroaryl” refers to an aryl group in which at least one of the ring atoms is a heteroatom (*i.e.*, oxygen, nitrogen, or sulfur). Heteroaryl groups include monocyclic and polycyclic (*e.g.*, having 2, 3 or 4 fused rings) systems. Examples of heteroaryl groups include without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, 5 isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrol, oxazolyl, benzodiazine, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, quinolinyl, isoquinolinyl purinyl, indolyl, and the like.

The term “heterocyclic” when used alone or in combination with other groups refers to a 10 5- to 8-membered (*e.g.*, 5- or 6-membered) monocyclic or 8- to 11-membered bicyclic heterocyclic radical that may be either saturated or unsaturated, aromatic or non-aromatic, and which may be optionally benzo- or pyrido-fused if monocyclic, containing at least one ring heteroatom. Each heterocycle consists of carbon atoms and from 1 to 4 ring heteroatoms selected from nitrogen, oxygen and sulfur.

15 As used herein, “nitrogen” and “sulfur” include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen.

“Alkylene” refers to a linear or branched saturated divalent hydrocarbon radical, which may optionally be substituted as described herein. In certain embodiments, the alkylene is a linear saturated divalent hydrocarbon radical that has 1 to 20 ( $C_{1-20}$ ), 1 to 15 ( $C_{1-15}$ ), 1 to 10 20 ( $C_{1-10}$ ), or 1 to 6 ( $C_{1-6}$ ) carbon atoms, or branched saturated divalent hydrocarbon radical of 3 to 20 ( $C_{3-20}$ ), 3 to 15 ( $C_{3-15}$ ), 3 to 10 ( $C_{3-10}$ ), or 3 to 6 ( $C_{3-6}$ ) carbon atoms. Linear  $C_{1-6}$  and branched  $C_{3-6}$  alkylene groups are also referred as “lower alkylene.” Examples of alkylene groups include, but are not limited to, methylene, ethylene, propylene (including all isomeric forms), n-propylene, isopropylene, butylene (including all isomeric forms), n-butylene, isobutylene, 25 t-butylene, pentylene (including all isomeric forms), and hexylene (including all isomeric forms). For example,  $C_{1-6}$  alkylene refers to a linear saturated divalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated divalent hydrocarbon radical of 3 to 6 carbon atoms.

The term “alkenylene” refers to a linear or branched divalent hydrocarbon radical that contains one or more carbon-carbon double bonds. The alkenylene may be optionally substituted 30 as described herein. The term “alkenylene” also embraces radicals having “cis” and “trans” configurations, or alternatively, “E” and “Z” configurations. As used herein, the term

“alkenylene” encompasses both linear and branched alkenylene, unless otherwise specified. For example, C<sub>2-6</sub> alkenylene refers to a linear unsaturated divalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated divalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkenylene is a linear divalent hydrocarbon radical of 2 to 20 (C<sub>2-20</sub>), 2 to 15 (C<sub>2-15</sub>), 2 to 10 (C<sub>2-10</sub>), or 2 to 6 (C<sub>2-6</sub>) carbon atoms, or a branched divalent hydrocarbon radical of 3 to 20 (C<sub>3-20</sub>), 3 to 15 (C<sub>3-15</sub>), 3 to 10 (C<sub>3-10</sub>), or 3 to 6 (C<sub>3-6</sub>) carbon atoms. Examples of alkenylene groups include, but are not limited to, ethenylene, allylene, propenylene, butenylene, and 4-methylbutenylene.

The term “cycloalkylene” refers to a cyclic saturated bridged and/or non-bridged divalent hydrocarbon radical, which may be optionally substituted as described herein. In certain embodiments, the cycloalkylene has from 3 to 20 (C<sub>3-20</sub>), from 3 to 15 (C<sub>3-15</sub>), from 3 to 10 (C<sub>3-10</sub>), or from 3 to 7 (C<sub>3-7</sub>) carbon atoms. Examples of cycloalkylene groups include, but are not limited to, cyclopropylene (*e.g.*, 1,1-cyclopropylene and 1,2-cyclopropylene), cyclobutylene (*e.g.*, 1,1-cyclobutylene, 1,2-cyclobutylene, or 1,3-cyclobutylene), cyclopentylene (*e.g.*, 1,1-cyclopentylene, 1,2-cyclopentylene, or 1,3-cyclopentylene), cyclohexylene (*e.g.*, 1,1-cyclohexylene, 1,2-cyclohexylene, 1,3-cyclohexylene, or 1,4-cyclohexylene), cycloheptylene (*e.g.*, 1,1-cycloheptylene, 1,2-cycloheptylene, 1,3-cycloheptylene, or 1,4-cycloheptylene), decalinylene, and adamantylene.

The term “heterocyclylene” refers to a divalent non-aromatic ring system and/or a multicyclic ring system that contains at least one non-aromatic ring, wherein one or more of the non-aromatic ring atoms are heteroatoms independently selected from O, S, or N, and the remaining ring atoms are carbon atoms. In certain embodiments, the heterocyclylene group has from 3 to 20 (*e.g.*, 3-15, 3-10, 3-8, 4-7, or 5-6) ring atoms. In certain embodiments, the heterocyclylene is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include a fused or bridged ring system, and in which the nitrogen or sulfur atoms may be optionally oxidized, the nitrogen atoms may be optionally quaternized, and some rings may be partially or fully saturated, or aromatic. The heterocyclylene may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclylene groups include, but are not limited to, azepinylene, benzodioxanylene, benzodioxolylene, benzofuranonylene, benzopyranonylene, benzopyranylene, benzotetrahydrofuranylene, benzotetrahydrothienylene, benzothiopyranylene, benzoxazinylene,

$\beta$ -carbolinylene, chromanylene, chromonylene, cinnolinylene, coumarinylene, decahydroisoquinolinylene, dihydrobenzothiazinylene, dihydrobenzoxazinylene, dihydrofurylene, dihydroisoindolylene, dihydropyranylene, dihydropyrazolylene, dihydropyrazinylene, dihydropyridinylene, dihydropyrimidinylene, dihydropyrrolylene, 5 dioxolanylene, 1,4-dithianylene, furanonylene, imidazolidinylene, imidazolinylene, indolinylene, isobenzotetrahydrofuranylene, isobenzotetrahydrothienylene, isochromanylene, isocoumarinylene, isoindolinylene, isothiazolidinylene, isoxazolidinylene, morpholinylene, octahydroindolylene, octahydroisoindolylene, oxazolidinonylene, oxazolidinylene, oxiranylene, piperazinylene, piperidinylene, 4-piperidonylene, pyrazolidinylene, pyrazolinylene, 10 pyrrolidinylene, pyrrolinylene, quinuclidinylene, tetrahydrofurylene, tetrahydroisoquinolinylene, tetrahydropyranylene, tetrahydrothienylene, thiamorpholinylene, thiazolidinylene, tetrahydroquinolinylene, and 1,3,5-trithianylene.

The terms, arylene, heteroarylene, alkenylenearylene, arylenealkenylene alkenyleneheteroarylene, or heteroarylenealkenylene all refer to divalent forms of aryl, 15 heteroaryl, alkenylaryl, arylalkenyl, alkenylheteroaryl and heteroarylalkenyl radicals.

As used herein, a "hydrogen bond donor" comprises a hydrogen atom attached to an electronegative atom (*e.g.*, fluorine, oxygen, sulfur or nitrogen). In some embodiments, the hydrogen bond donor is -OH, -O(C<sub>1-6</sub> alkyl), -NH<sub>2</sub>, or -NHOH.

The term "compound," as used herein is meant to include all stereoisomers, geometric 20 isomers, tautomers, and isotopes of the structures depicted, including structures conforming to a generic formula set out herein.

All compounds, and all pharmaceutically acceptable salts thereof, can be either found together with other substances such as water and solvents (*e.g.*, hydrates and solvates) or can be substantially isolated. A compound of the invention or a salt thereof is "substantially isolated" 25 when at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched to any extent in a compound of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of a compound or 30 compounds of the invention, or a salt or salts thereof. Methods for isolating compounds and their salts are routine in the art.

The phrase “pharmaceutically acceptable” is employed herein to refer 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 problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions “ambient temperature” and “room temperature,” as used herein, are understood in the art, and refer generally to a temperature, *e.g.* a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20°C to about 30°C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, “pharmaceutically acceptable salts” are derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention 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, alcohols (*e.g.*, methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in Remington’s Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p.1418 and Journal of Pharmaceutical Science, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

Synthesis: The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, *e.g.*, temperatures which can range from the solvent’s freezing temperature to the solvent’s boiling

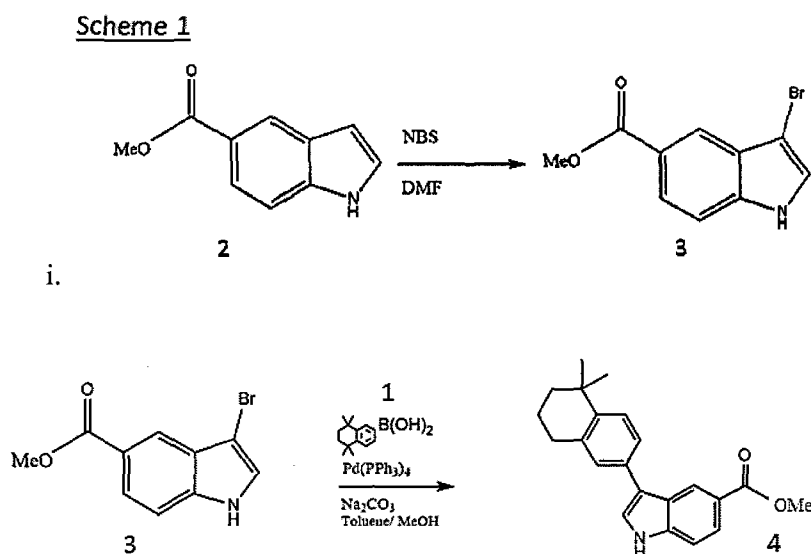
temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

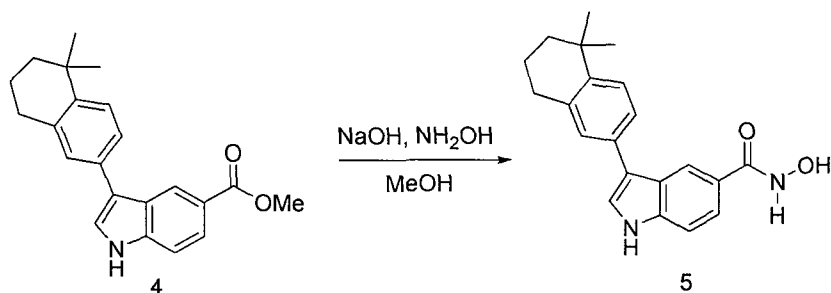
Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3<sup>rd</sup> Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (*e.g.*, <sup>1</sup>H or <sup>13</sup>C), infrared spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

An exemplary method for preparing certain compounds of the invention is provided in Scheme 1.

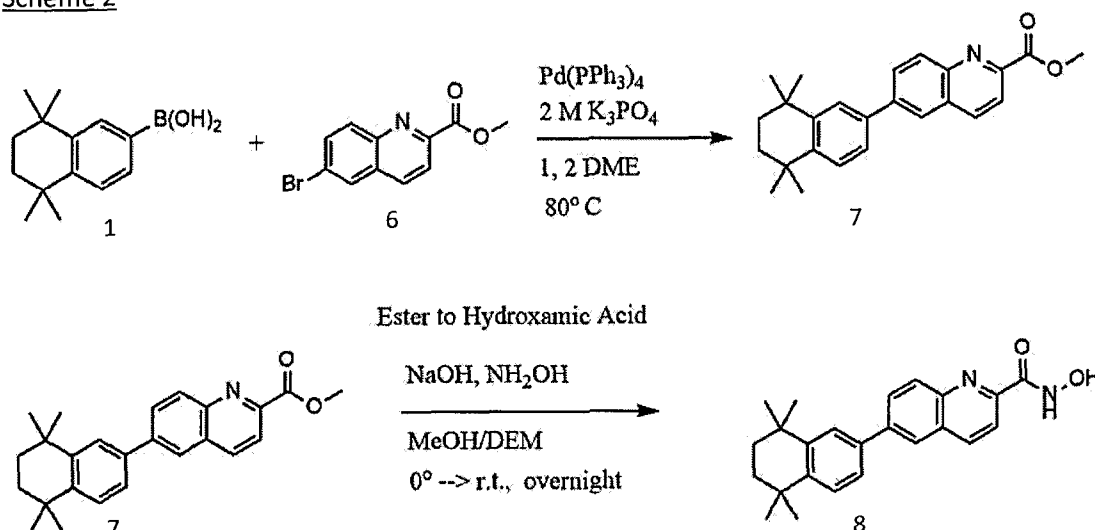
Compound **3** was produced by bromination of methyl indole-5-carboxylate, compound **2** (ACC Corporation). Compound **4** is then produced by reacting compound **1** with compound **3**. Compound **5** was prepared from the corresponding methyl carboxylic ester, compound **4**, by nucleophilic substitution with hydroxylamine in the presence of NaOH and MeOH.



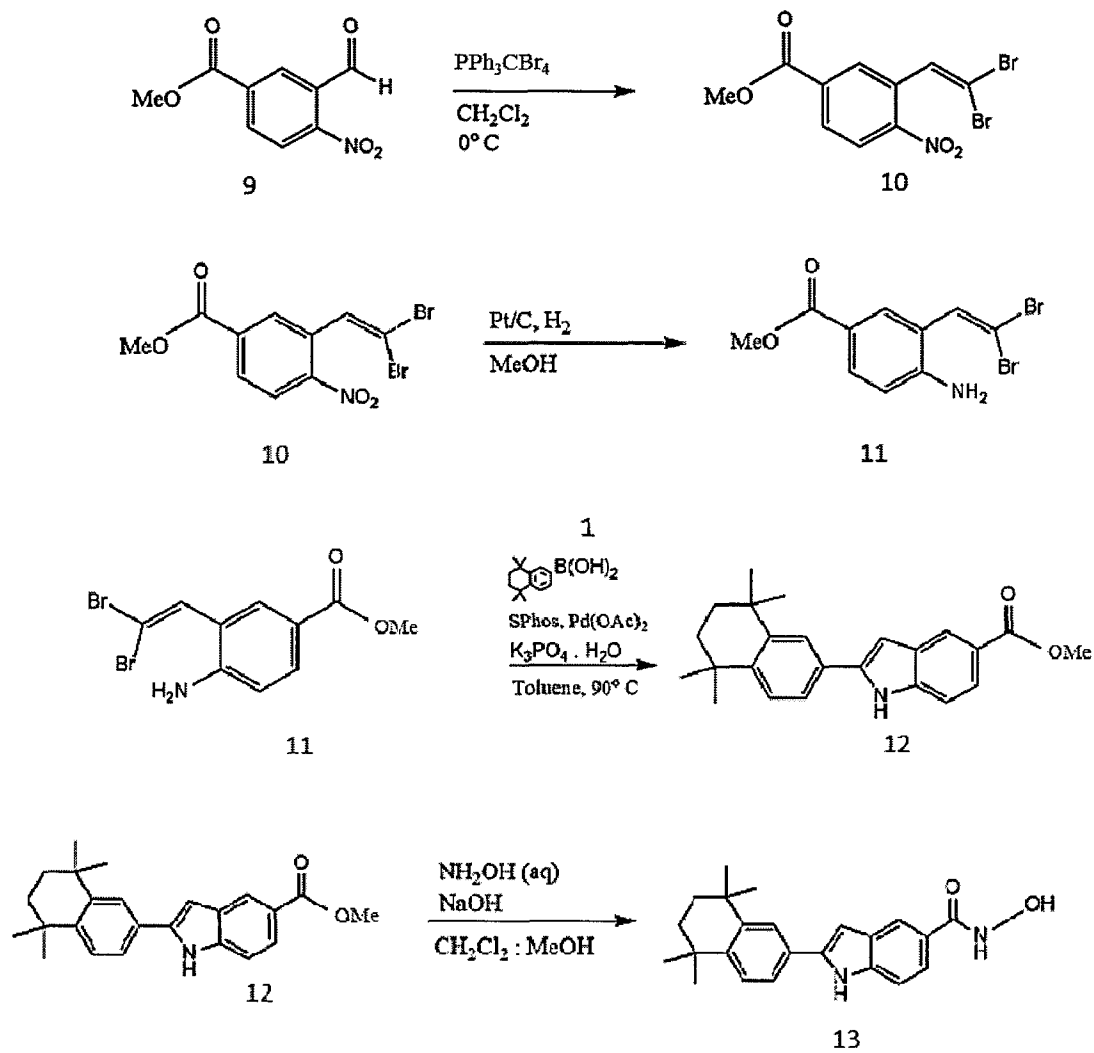


Scheme 2 shows the synthetic scheme for producing compound **8**, which was derived from compound **7** by replacement of methyl ester by hydroxamate in the presence of NaOH and MeOH/CH<sub>2</sub>Cl<sub>2</sub>. Compound **7** was the product of a Suzuki coupling between compound **1** and methyl 6-bromoquinoline-2-carboxylate, compound **6**.

#### Scheme 2



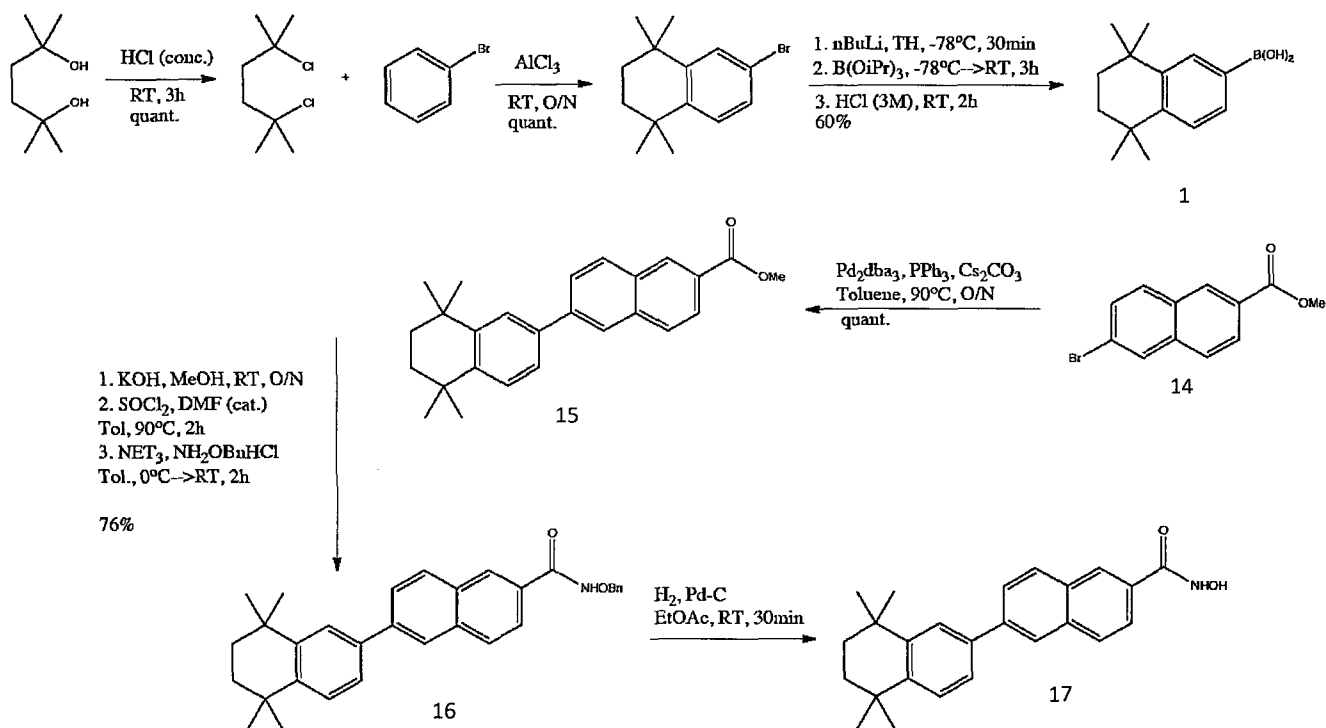
Further, Scheme 3 shows the synthetic scheme for preparing compound **13**, which is derived from compound **12** by replacement of the methyl ester by hydroxamate in the presence of NaOH and MeOH/CH<sub>2</sub>Cl<sub>2</sub>. Compound **12** was prepared by performing concomitant intramolecular Pd(OAc)<sub>2</sub>-catalysed Buchwald-Hartwig coupling of vinyl bromide and amine in compound **11** followed by intermolecular Suzuki cross coupling of the resulting 2-bromoindole with boronic acid, (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl) (compound **1**). Compound **11** was synthesized from compound **10** by platinumium/carbon catalytic hydrogenation of the nitro group. 1,1-Dibromoalkene compound **10** was synthesized by Corey-Fuchs reaction with aldehyde **9**.

**Scheme 3**

5 Scheme 4 shows a synthetic method for preparing compound 17.

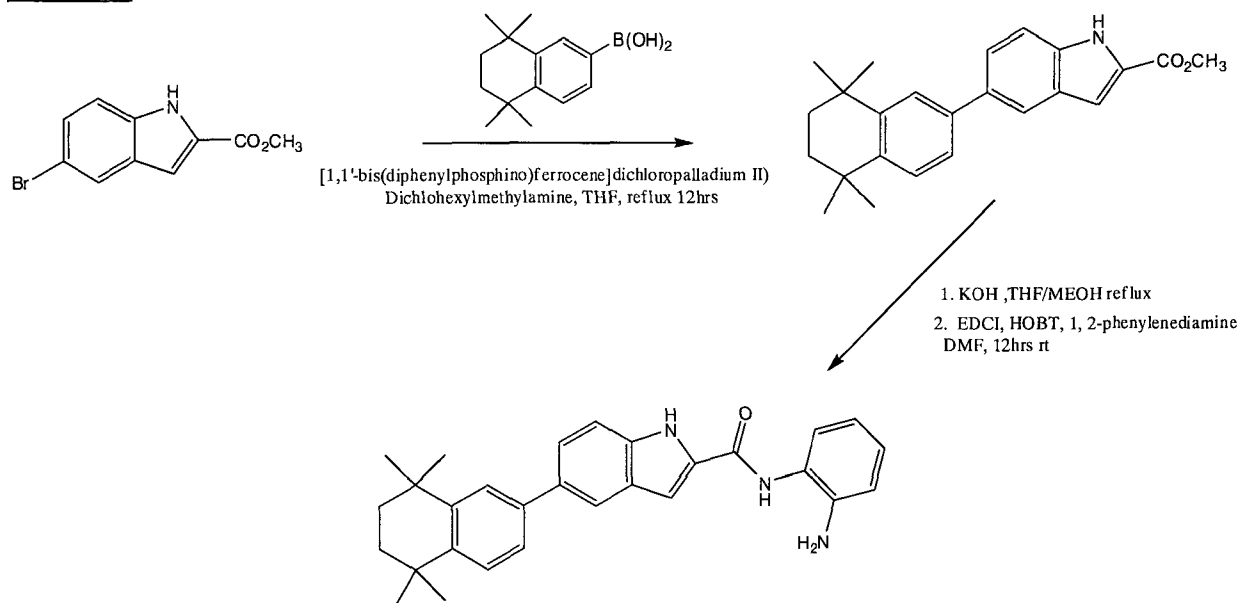
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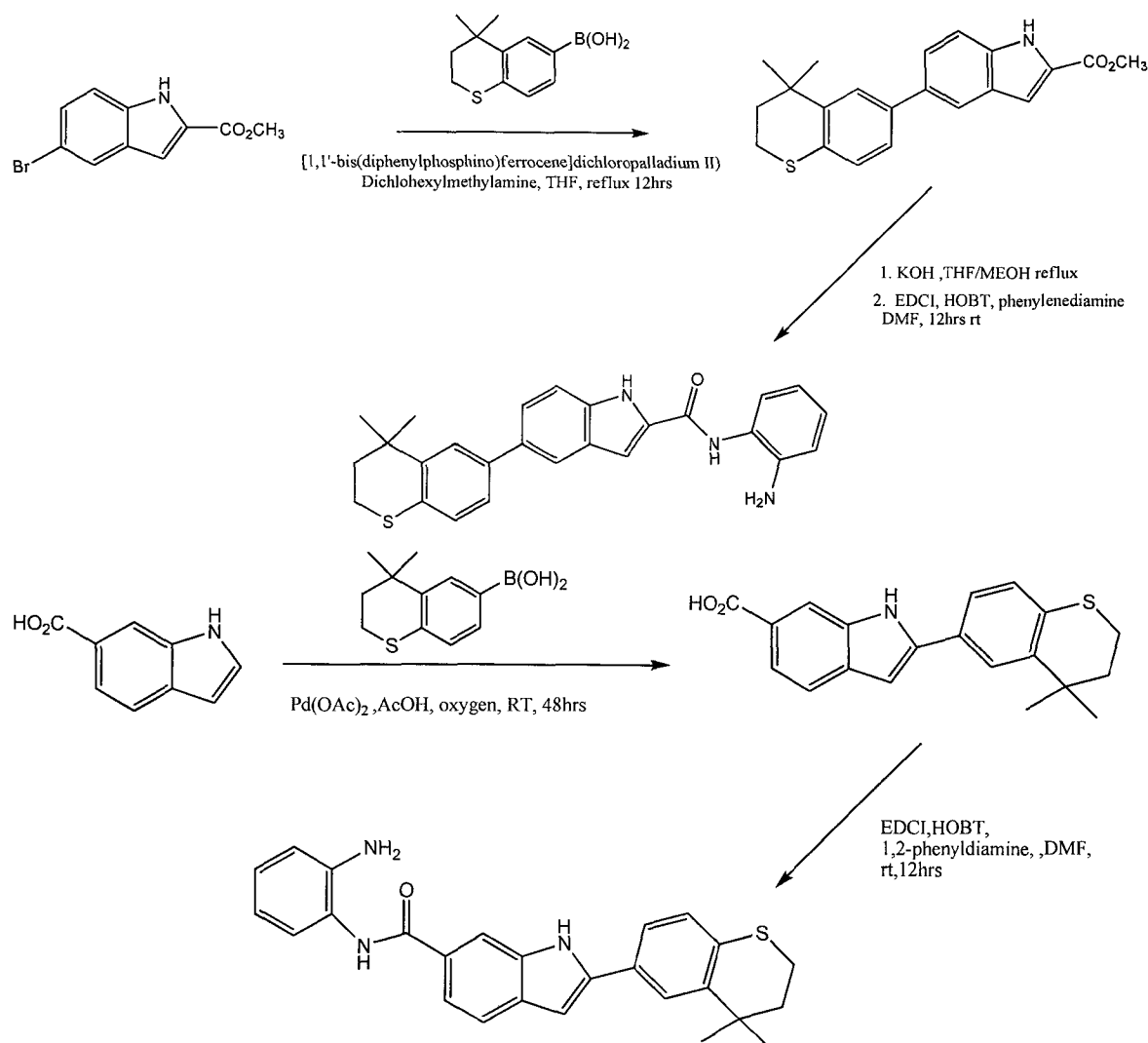
Scheme 4:



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Scheme 5



Scheme 6

- 5 *Methods and Use of the present compounds in the preparation of a medicament:* In another aspect, the invention features methods of use or methods of treatment for a patient who is suffering from a hyperproliferative disorder (*e.g.*, a cancer, including blood-borne cancers and cancers that manifest as solid tumors). The “use” or methods of use can include the preparation of a medicament or the preparation of a medicament for treating a hyperproliferative disorder,
- 10 non-malignant tumor, or muscle-related condition as described herein. The medicament(s) can include a compound or compounds as described herein (*e.g.*, for the treatment of a hyperproliferative disorder), and the methods of treating a patient can include a step of administering to the patient a therapeutically effective amount of a compound or compounds as

described herein. For ease of reading, we do not repeat the phrase “or a pharmaceutically acceptable salt thereof” at every opportunity. It is to be understood that where a compound of the invention can be used, a pharmaceutically acceptable salt thereof can also be used. In any method of treatment, the method can include a step of identifying a patient in need.

5 In one aspect, the invention relates to methods of treating a subject who has cancer or a non-malignant tumor, the method comprising administering to the subject a therapeutically effective amount of a compound described herein.

In various embodiments, the use can be directed to, or the methods of treating can be applied to, a subject who has been diagnosed with lung cancer (*e.g.*, a non-small cell lung  
10 cancer), a colon cancer, a melanoma, a breast cancer, a renal cancer, an ovarian cancer, a prostate cancer, a cancer of the nervous system (affecting the brain or spinal cord, such as a glioma), a neuroendocrine tumor (*e.g.*, a neuroblastoma), or a blood cancer (*e.g.*, a leukemia or lymphoma).

In one embodiment, the present invention features methods of treating pheochromocytoma in a subject comprising administering to the subject a therapeutically  
15 effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

In another embodiment, the invention features methods of treating neuroblastoma in a subject comprising administering to the subject a therapeutically effective amount of compound of Formula I or a pharmaceutically acceptable salt thereof.

As noted, the present invention further provides a compound of Formula I, or a  
20 pharmaceutically acceptable salt thereof for use in the preparation of a medicament or for the production of a medicament for use in therapy, including therapy for any condition or type of condition described herein.

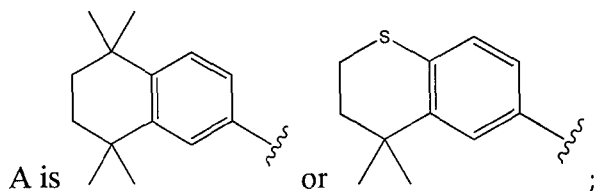
Although the invention is not limited to compounds that exert a beneficial effect through any particular mechanism of action, our studies indicate that the compounds of the invention can  
25 inhibit tumor growth or survival. Compounds of the invention can also be an effective treatment to reduce metastatic growth of tumors (metastasis).

The present invention further provides methods for treating a disease caused by or associated with the presence of a tumor in a mammalian subject, including identifying a subject  
30 in which reduction of tumor mass is desirable, and administering to the subject in need of such treatment a therapeutically effective amount or dose of a compound of the present invention or a pharmaceutical composition thereof. The subject can be a mammal (*e.g.*, a human or veterinary

subject). The compound(s) and composition(s) described herein can be administered orally or parenterally. The disease can be a solid extracranial tumor such as, but not limited to, neuroblastoma. The tumor can also be associated with a breast cancer or be an intracranial tumor such, but not limited to, a glioma. As noted, the disease can also be a blood borne cancer such as, but not limited to, leukemia. In some embodiments, the disease is localized to a tissue or organ while in other instances the disease has spread to multiple organs or tissues (e.g., as in metastasis).

As used herein, the term “contacting” refers to the bringing together of indicated moieties (e.g., a compound or composition of the invention) in an *in vitro* system (e.g., a culture system including muscle cells or precursors or progenitors thereof) or an *in vivo* system (e.g., within the body, either in the vicinity of or distant from a tumor) in a manner that produces a desired outcome (e.g., a treatment as described herein).

As noted, the present invention also relates to methods inhibiting the loss of muscle mass or muscle function in a subject, and such methods can be carried out by administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I: A-W-Z (I) or a pharmaceutically acceptable salt thereof, where

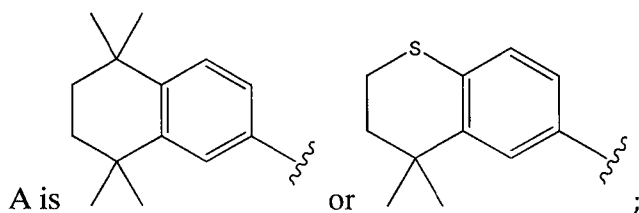


W is a heterocyclylene, arylene, heteroarylene, alkenylenearylene, arylenealkenylene or alkenyleneheteroarylene, heteroarylenealkenylene; and Z is a hydrogen bond donor.

In certain aspects, the loss of muscle mass is associated with an inherited myopathy. In other aspects, the loss of muscle mass is associated with muscular dystrophy, neuromyotonia, nemaline myopathy, multi/minicore myopathy, centronuclear myopathy, mitochondrial myopathy, inflammatory myopathy, metabolic myopathy. In yet another aspect, the loss of muscle mass is associated with intensive care unit-acquired weakness (ICUAW), chronic obstructive pulmonary disease (COPD), heart failure, traumatic injury or malignancy.

The invention also relates to methods for treating myofibers *ex vivo*. These methods can include the steps of providing an *ex vivo* preparation of myofibers, optionally comprising a natural or synthetic biological matrix; and contacting the preparation with an amount of a

compound of Formula I: A-W-Z (I) or a pharmaceutically acceptable salt thereof, where the amount of the compound is sufficient to promote muscle mass or muscle function and



W is a heterocyclylene, arylene, heteroarylene, alkenylenearylene, arylenealkenylene  
5 alkenyleneheteroarylene, or heteroarylenealkenylene; and Z is a hydrogen bond donor.

As used herein, the terms “individual” or “patient,” or “subject” are used interchangeably (unless the context clearly indicates otherwise) to refer to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

10 As used herein, the phrase “therapeutically effective amount” refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

As used herein, the term “treating” or “treatment” refers to one or more of (1) preventing  
15 the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*e.g.*, inhibiting the progression of the  
20 disease); and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

*Pharmaceutical Formulations and Dosage Forms:* The invention provides compositions  
25 (*e.g.*, pharmaceutical compositions) comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and at least one carrier (*e.g.*, a pharmaceutically acceptable carrier). Thus, the invention relates to pharmaceutical compositions comprising a compound as disclosed herein, and a pharmaceutically acceptable carrier. The compound can be present in an amount

that confers a clinically beneficial result on a patient to whom the compound has been administered (i.e., a therapeutically effective amount).

When employed as pharmaceuticals, the compounds of the invention can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. For example, the compositions may be administered orally or parenterally.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the invention or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for oral administration. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, and sterile packaged powders. In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.* about 40 mesh.

The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be prepared by processes known in the art, *e.g.*, see International Application No. WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, alimentary oils and methyl cellulose. The formulations can additionally include: lubricating agents such as talc,

magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1000 mg (1 g), more usually about 100 to about 500 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

In some embodiments, the compounds or compositions of the invention contain from about 5 to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 5 to about 10, about 10 to about 15, about 15 to about 20, about 20 to about 25, about 25 to about 30, about 30 to about 35, about 35 to about 40, about 40 to about 45, or about 45 to about 50 mg of the active ingredient.

In some embodiments, the compounds or compositions of the invention contain from about 50 to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 50 to about 100, about 100 to about 150, about 150 to about 200, about 200 to about 250, about 250 to about 300, about 350 to about 400, or about 450 to about 500 mg of the active ingredient.

In some embodiments, the compounds or compositions of the invention contain from about 500 to about 1000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 500 to about 550, about 550 to about 600, about 600 to about 650, about 650 to about 700, about 700 to about 750, about 750 to about 800, about 800 to about 850, about 850 to about 900, about 900 to about 950, or about 950 to about 1000 mg of the active ingredient.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that

the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

5 For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally  
10 effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, about 0.1 to about 1000 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or  
15 pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of  
20 polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as  
25 cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

In some embodiments, the compositions are administered by the oral route for local effect. Solution, suspension, or powder compositions can be administered orally from devices which deliver the formulation in an appropriate manner.

The amount of compound or composition administered to a patient will vary depending  
30 upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic

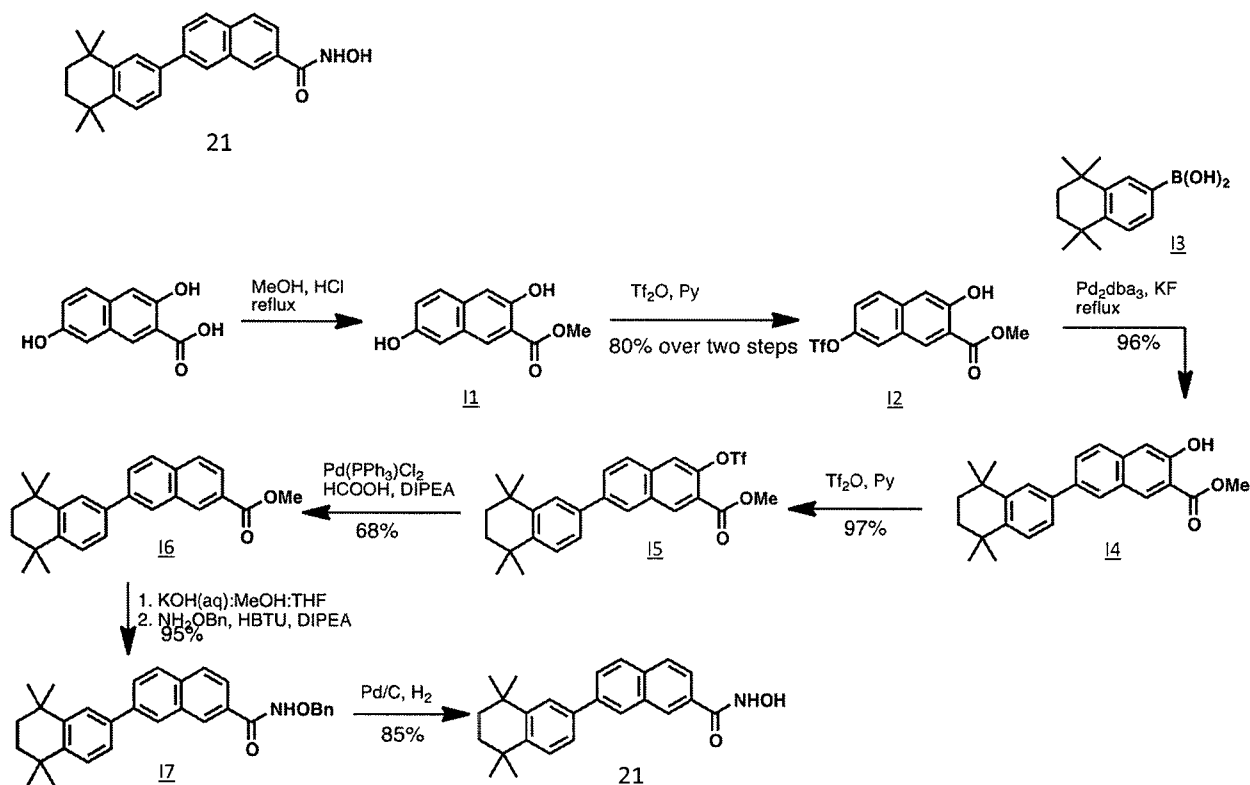
applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of a pharmaceutical composition as described herein. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of a compound of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1  $\mu\text{g}$ /kg to about 1 g/kg of body weight per day.

## EXAMPLES

## Example 1: Synthesis of Compound 21



*Methyl 3-hydroxy-7-((trifluoromethylsulfonyl)oxy)-2-naphthoate (II)*: 3,7-dihydroxy-2-naphthoic acid (200 mg, 0.980 mmol, 1 eq) was dissolved in methanol (5 mL) at room temperature. Concentrated HCl (7 drops, catalytic) was added, and the resulting mixture was stirred at reflux for 16 hours. The reaction mixture was concentrated *in vacuo* and partitioned between EtOAc (10 mL) and H<sub>2</sub>O (10 mL). The aqueous layer was further extracted with EtOAc (2 x 5 mL). The combined organic layer was washed with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give the corresponding methyl ester as a yellow solid. No further purification was performed (the crude product was used in the next step).

Characterization data for **II**:  $\delta_{\text{H}}$  (500MHz, CDCl<sub>3</sub>) 4.02 (s, 3H), 7.12-7.17 (m, 2H), 7.27 (s, 1H), 7.60 (d, 1H, *J* 9Hz), 10.28 (s, 1H).  $\delta_{\text{C}}$  (500MHz, CDCl<sub>3</sub>) 52.6, 110.1, 111.8, 114.6, 121.6, 127.8, 128.2, 130.4, 133.4, 151.8, 154.7, 170.3. HRMS (ESI) calculated for C<sub>12</sub>H<sub>9</sub>O<sub>4</sub> (M - H<sup>+</sup>), 217.0501, found 217.0506.

**II** (214 mg, 0.975 mmol, 1 eq) was dissolved in dry DCM (5 ml). The solution was cooled to 0°C and pyridine (158  $\mu$ L, 1.96 mmol, 5 eq) and triflic anhydride (165  $\mu$ L, 0.975

mmol, 1 eq) were added using syringes in a dropwise manner. The reaction was allowed to warm up to room temperature and stirred for 2 hours. The reaction solution was diluted with Et<sub>2</sub>O (5 mL) and quenched with excess HCl (aq., 3M). The aqueous layer was further extracted with Et<sub>2</sub>O (5 mL). The combined organic layer was washed with saturated NaHCO<sub>3</sub> and brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a brown oil. The crude mixture was purified using flash chromatography (20% EtOAc in hexanes) to give **I2** as an off-white solid (262 mg, 80% over 2 steps).

Characterization data for **I2**:  $\delta_{\text{H}}$  (500MHz, CDCl<sub>3</sub>) 4.04 (s, 3H), 7.34 (s, 1H), 7.35 (dd, 1H, *J* 2.5 Hz and 9.5 Hz), 7.69 (d, 1H, *J* 2.5 Hz), 7.72 (dd, 1H, *J* 0.5 Hz and 9.5 Hz), 8.49 (d, 1H, *J* 0.5 Hz), 10.54 (s, 1H).  $\delta_{\text{C}}$  (500MHz, CDCl<sub>3</sub>) 52.9, 112.1, 115.7, 120.3, 122.8, 126.3, 128.9, 132.4, 136.6, 145.5, 157.3, 169.7. HRMS (ESI) calculated for C<sub>13</sub>H<sub>8</sub>F<sub>3</sub>O<sub>6</sub>S (M – H<sup>+</sup>), 358.9994, found 348.9999.

*Methyl 6-hydroxy-5',5',8',8'-tetramethyl-5',6',7',8'-tetrahydro-[2,2'-binaphthalene]-7-carboxylate (I4)*: **I2** (13.0 mg, 0.0387 mmol, 1 eq) and **I3** (27.0 mg, 0.116 mmol, 3 eq) were dissolved in DME (3 mL) at room temperature. PPh<sub>3</sub> (2.03 mg, 0.00773 mmol, 20 mol%), KF dihydrate (11.0 mg, 0.116 mmol, 3 eq), and Pd<sub>2</sub>bda<sub>3</sub> (1.77 mg, 0.00193 mmol, 5 mol%) were added to the solution. Distilled water (0.4 mL) was added to the resulting mixture and the reaction was degassed and purged with argon. The reaction mixture was stirred at reflux for 16 hours. After cooling, the reaction mixture was filtered through a layer of Celite and the filtrate partitioned between EtOAc (5 mL) and H<sub>2</sub>O (5 mL). The aqueous layer was further extracted with EtOAc (5 mL). The combined organic layer was washed with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude mixture was purified using flash chromatography (20% EtOAc in hexanes) to give **I4** (14.4 mg, 96%).

Characterization data for **I4**:  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 1.34 (s, 6H), 1.37 (s, 6H), 1.74 (s, 2H), 4.04 (s, 3H), 7.33 (s, 1H), 7.43 (m, 2H), 7.61 (s, 1H), 7.76 (m, 2H), 7.97 (s, 2H), 8.56 (s, 1H), 10.45 (s, 1H).  $\delta_{\text{C}}$  (500MHz, CDCl<sub>3</sub>) 32.3, 32.5, 33.9, 34.1, 34.7, 34.9, 52.9, 125.2, 125.3, 125.6, 125.9, 126.8, 127.4, 128.5, 129.1, 131.2, 131.9, 136.4, 137.7, 141.7, 145.4, 145.7, 168.9.

*Methyl 5',5',8',8'-tetramethyl-6-((trifluoromethylsulfonyl)oxy)-5',6',7',8'-tetrahydro-[2,2'-binaphthalene]-7-carboxylate (I5)*: The phenol **I4** (20.0 mg, 0.0257 mmol, 1 eq) was dissolved in dry DCM (2 ml). This solution was cooled to 0°C and pyridine (20.8  $\mu$ L, 0.129 mmol, 5 eq) and triflic anhydride (13.0  $\mu$ L, 0.0386 mmol, 1.5 eq) were added using a

syringe. The reaction was allowed to warm up to room temperature and stirred for 2 hours. The reaction solution was diluted with Et<sub>2</sub>O (5 mL) and quenched with excess HCl (aq., 3M). The aqueous layer was further extracted with Et<sub>2</sub>O (5 mL). The combined organic layer was washed with saturated NaHCO<sub>3</sub> and brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude mixture was purified using flash chromatography (20% EtOAc in hexanes) to give **I5** (13.0 mg, 97%).

Characterization data for **I5**:  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 1.35 (s, 6H), 1.38 (s, 6H), 1.75 (s, 4H), 4.03 (s, 3H), 7.47 (s, 2H), 7.63 (s, 1H), 7.76 (s, 1H), 7.95 (s, 2H), 8.14 (s, 1H), 8.72 (s, 1H).

*Methyl 5',5',8',8'-tetramethyl-5',6',7',8'-tetrahydro-[2,2'-binaphthalene]-7-carboxylate*

**(I6)**: The triflate **I5** (29.4 mg, 0.0565 mmol, 1 eq) was dissolved in dry DMF (0.5 mL) at room temperature. DIPEA (29.5  $\mu$ L, 0.169 mmol, 3 eq), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (2 mg, 0.00283 mmol, 5 mol%), and HCOOH (43.0  $\mu$ L, 0.113 mmol, 2 eq) were added and the final solution was heated to 100°C for 6 hours. The cooled reaction mixture was filtered through a layer of Celite and partitioned between EtOAc (5 mL) and H<sub>2</sub>O (5 mL). The aqueous layer was further extracted with another portion of EtOAc (5 mL). The combined organic layer was washed with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude mixture was purified using flash chromatography (20% EtOAc in hexanes) to give **I6** (14.1 mg, 68%).

Characterization data for **I6**:  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 1.35 (s, 6H), 1.38 (s, 6H), 1.75 (s, 4H), 4.00 (s, 3H), 7.43 (dd, 2H,  $J_1$  8.1 Hz and 8.1 Hz), 7.65 (s, 1H), 7.84 (m, 3H), 8.04 (d, 1H,  $J$  8.4 Hz), 8.12 (s, 1H), 8.67 (s, 1H).

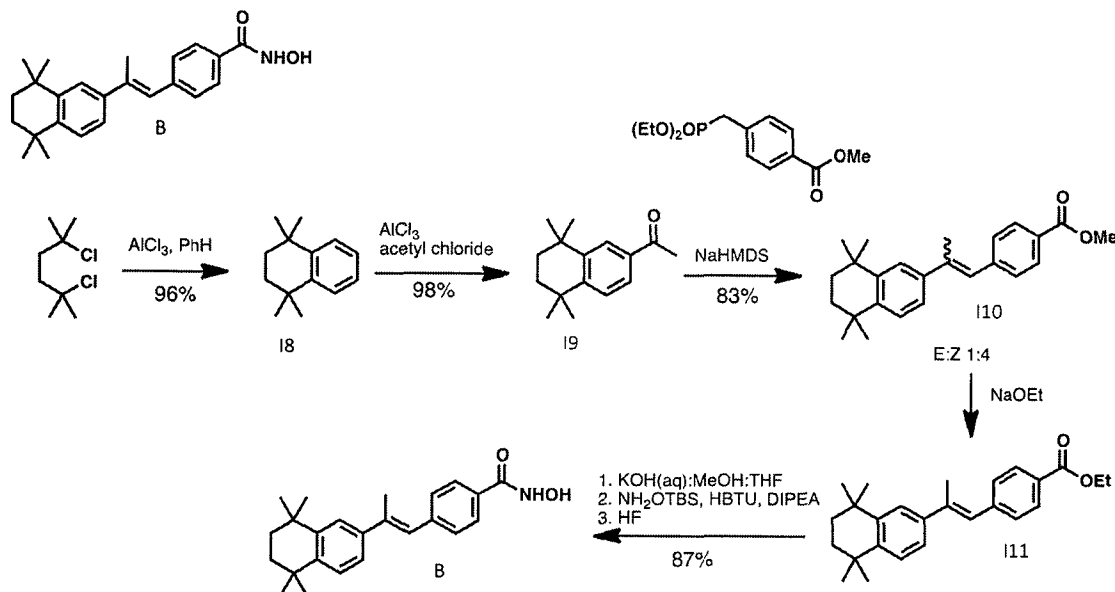
*N-(benzyloxy)-5',5',8',8'-tetramethyl-5',6',7',8'-tetrahydro-[2,2'-binaphthalene]-7-carboxamide (I7)*: To a solution of **I6** (14.1 mg, 0.0379 mmol, 1 eq) in dry THF (795  $\mu$ L) was added methanol (264  $\mu$ L) and 1M KOH (aqueous, 264  $\mu$ L, 7 eq). The solution was stirred at room temperature for 15 hours. The reaction mixture was acidified to around pH 3 with 3 M HCl, and extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to dryness to give the corresponding carboxylic acid. The crude acid (18.4 mg, 0.0513 mmol, 1 eq) was then dissolved in dry DMF (2 mL), and OBnNH<sub>2</sub> hydrochloride salt (9.01 mg, 0.0564 mmol, 1.1 eq) and DIPEA (26.8  $\mu$ L, 0.154 mmol, 3 eq) were added to the solution. HBTU (25.3 mg, 0.0667 mmol, 1.3 eq) was added. The resulting mixture was stirred at room temperature for 15 hours. The crude reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried with

Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude was purified by flash chromatography (6% EtOAc in toluene) to give **I7** as a white solid (22.6mg, 95% over 2 steps).

Characterization data for **I7**:  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 1.33 (s, 6H), 1.36 (s, 6H), 1.73 (s, 4H), 5.09 (s, 2H), 7.28 (m, 1H), 7.32-7.38 (m, 5H), 7.61 (d, 1H, *J* 1.2Hz), 7.74-7.90 (m, 4H),  
5 8.01 (s, 1H), 8.02 (s, 1H), 8.29 (s, 1H).

*N*-hydroxy-5',5',8',8',-tetramethyl-5',6',7',8'-tetrahydro-[2,2'-binaphthalene]-7-carboxamide (**A**): **I7** (25.0 mg, 0.0539 mmol) was dissolved in minimal amounts of EtOAc. A catalytic amount of Pd-C was added and the flask was purged with H<sub>2</sub> using a balloon. The reaction was further stirred at room temperature in presence of 1atm of H<sub>2</sub> gas with TLC  
10 monitoring until the starting material was completely consumed (about 20-30 min). The reaction mixture was filtered through a layer of Celite and the filtrate concentrated under reduced pressure to give an orange solid (15 mg, 85% before HPLC purification). The crude product was purified by reverse-phase HPLC (Agilent 1260 Infinity HPLC system equipped with an autosampler, a quaternary pump, a photodiode array detector, and an Agilent Zorbax SB-C18 analytical column,  
15 methanol/H<sub>2</sub>O). The final product **A** was obtained as a white crystalline solid.

Characterization data for **A**:  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 1.35 (s, 6H), 1.38 (s, 6H), 1.75 (s, 4H), 7.43 (d, 1H, *J* 8.1 Hz), 7.47 (dd, 1H, *J* 2.1 Hz and 8.7 Hz), 7.64 (d, 1H, *J* 2.1 Hz), 7.83 (d, 2H, *J* 8.7 Hz), 7.92 (dd, 2H, *J* 3.9 Hz and 8,1 Hz), 8.09 (m, 1H), 8.21 (s, 1H), 8.40 (s, 1H).  $\delta_{\text{C}}$   
20 (400MHz, CDCl<sub>3</sub>) 30.9, 31.2, 33.9, 34.3, 34.9, 35.2, 123.5, 124.4, 124.6, 124.7, 125.3, 126.1, 127.0, 128.5, 129.3, 129.7, 131.9, 135.2, 137.8, 140.7, 144.5, 145.1, 166.9. HRMS (ESI) calculated for C<sub>25</sub>H<sub>26</sub>NO<sub>2</sub> (M - H<sup>+</sup>), 372.1969, found 372.1941.

**Example 2: Synthesis of Compound B**

**1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene (18):** 2,5-dichloro-2,5-  
 5 dimethylhexane (300 mg, 1.64 mmol, 1 eq) was dissolved in dry benzene (25 mL).  $\text{AlCl}_3$  (22.0  
 mg, 0.164 mmol, 0.1 eq) was added to the solution, which was stirred at reflux for 16 hours. The  
 reaction was quenched with 3M HCl (5 mL) and extracted with hexanes (10 mL x 3). The  
 combined organic layer was washed with brine, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated  
*in vacuo*. The crude was purified by flash chromatography (100% hexanes) to give **18** (309 mg,  
 10 91% yield) as a colourless oil.

Characterization data for **18**:  $\delta_{\text{H}}$  (500MHz,  $\text{CDCl}_3$ ) 1.33 (s, 12H), 1.74 (s, 4H), 7.16-7.19  
 (m, 2H), 7.34-7.36 (m, 2H,  $J$  2 Hz and 8.4 Hz).  $\delta_{\text{C}}$  (500MHz,  $\text{CDCl}_3$ ) 31.9, 34.2, 35.1, 125.5,  
 126.5, 144.8.

**1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone (19):** **18** (37.0 mg,  
 15 0.197 mmol, 1 eq) was dissolved in dry DCM (5 mL), to which acetyl chloride (15.5  $\mu\text{L}$ , 0.216  
 mmol, 1.1 eq) and  $\text{AlCl}_3$  (26.2 mg, 0.216 mmol, 1.1 eq) were added sequentially. The reaction  
 mixture was refluxed for two hours then cooled to room temperature and quenched with water.  
 The crude mixture was extracted with EtOAc (3 mL x 3). The combined organic layer was  
 washed with  $\text{NaHCO}_3$  (saturated, aqueous) and brine, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and

concentrated *in vacuo*. The crude was purified by flash chromatography (10% EtOAc/hexanes) to give **I9** (44.8 mg, 98% yield).

Characterization data for **I9**:  $\delta_{\text{H}}$  (500MHz,  $\text{CDCl}_3$ ) 1.28 (s, 6H), 1.30 (s, 6H), 1.69 (s, 4H), 2.55 (s, 3H), 7.38 (d, 1H,  $J$  8.0 Hz), 7.70 (dd, 1H,  $J$  1.9 Hz and 8.0 Hz), 7.92 (d, 1H,  $J$  1.9 Hz). HRMS (ESI) calculated for  $\text{C}_{16}\text{H}_{23}\text{O}$  ( $\text{M} + \text{H}^+$ ), 231.1749, found 231.1767.

*Ethyl 4-(2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)benzoate (II2)*: The Horner Wardsworth Emmons reagent **I10** (316 mg, 1.10 mmol, 2 eq) was dissolved in dry THF (5 mL) and cooled to 0°C. NaHMDS (1M solution in THF, 1.10 mL, 2 eq) was added dropwise to the phosphonate reagent and the mixture stirred at low temperature for 30 minutes. **I9** (127 mg, 0.552 mmol, 1 eq) was dissolved in dry THF (5mL) in a separate flask and was slowly added to deprotonated HWE reagent through cannula. The mixture was allowed to slowly warm up to room temperature and stirred until disappearance of starting material. The reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  solution and extracted with EtOAc (5 mL x 3). The combined organic layer was washed with  $\text{NaHCO}_3$  (saturated, aqueous) and brine, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to give **I11** as a *E:Z* mixture (1:4, 166 mg, 83% yield). **I11** (166 mg, 0.458 mmol, 1 eq) was dissolved in dry EtOH, to which an excess of freshly prepared NaOEt solution was added. The mixture was stirred at room temperature for two hours. Neutralizing workup and removal of organic solvent yielded **I12** as mostly *E* isomer.

Characterization data for **I12** as an *E* isomer:  $\delta_{\text{H}}$  (300MHz,  $\text{CDCl}_3$ ) 1.32 (s, 6H), 1.35 (s, 6H), 1.39 (t, 3H,  $J$  7.1 Hz), 1.72 (s, 4H), 2.30 (d, 3H,  $J$  1.2 Hz), 4.36 (q, 2H,  $J$  7.1 Hz), 6.82 (s, 1H), 7.32 (m, 2H), 7.42 (d, 1H,  $J$  8.1 Hz), 7.47 (d, 1H,  $J$  1.2 Hz), 8.04 (d, 1H,  $J$  8.1 Hz).

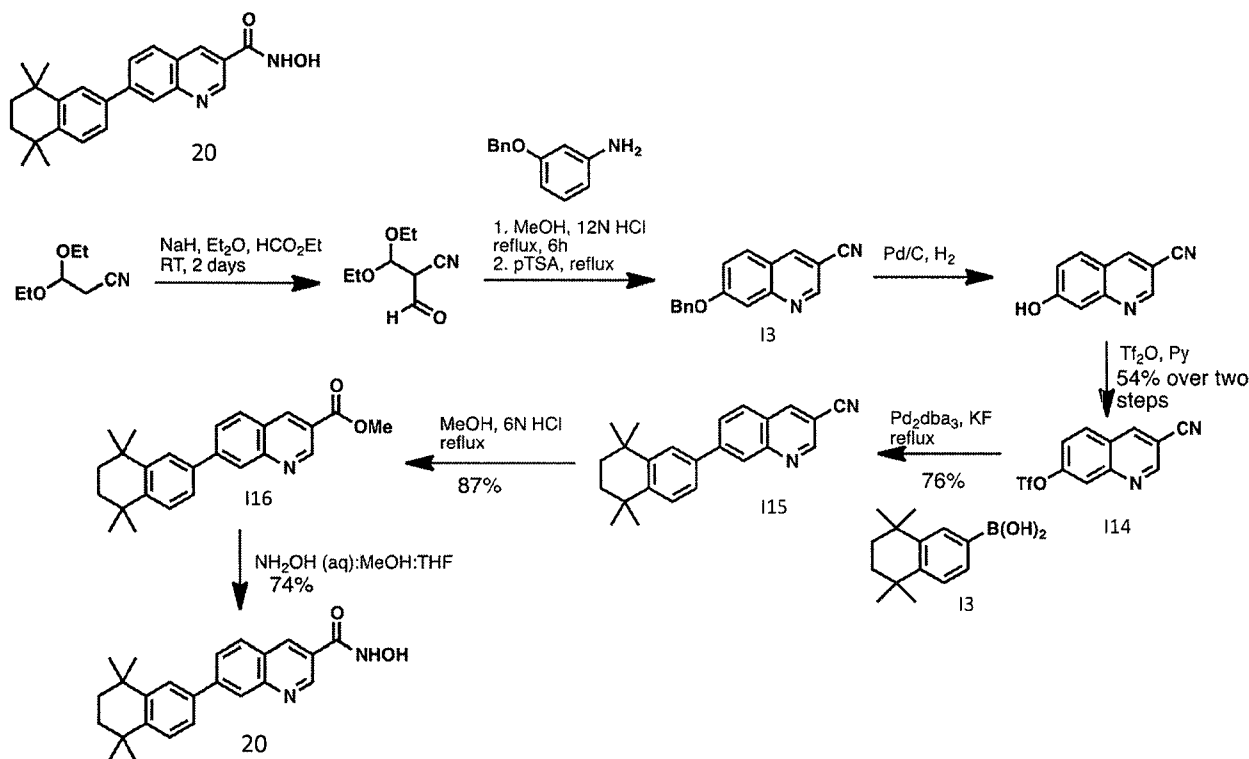
*(E)-N-hydroxy-4-(2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)prop-1-en-1-yl)benzamide (B)*:

**I12** (49 mg, 0.135 mmol) was dissolved in THF (1 mL), and KOH (1M, 0.5 mL) and MeOH (0.5 mL) were added. The reaction proceeded at room temperature for 5 hours until the starting material was not observable on TLC. The mixture was acidified with 3M HCl to pH 3 and extracted repeatedly with EtOAc. The combined organic layer was washed with brine, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The crude carboxylic acid was used without purification. The acid was subsequently dissolved in dry DMF (2 mL).  $\text{NH}_2\text{OTBS}$  (23.3 mg, 0.158 mmol, 1.1 eq), DIPEA (75.0  $\mu\text{L}$ , 0.430 mmol, 3 eq) were added with stirring at room

temperature, followed by HBTU (71 mg, 0.186 mmol, 1.3 eq). The reaction mixture was stirred at room temperature for 16 hours. A quick extraction with EtOAc was performed and the organic layer containing the *O*-TBS protected hydroxamic acid was concentrated *in vacuo* and redissolved in DCM (3 mL). An excess of concentrated HF (~20 eq) was added to the DCM solution and the biphasic mixture was stirred vigorously for two hours at room temperature. The reaction was neutralized with saturated NaHCO<sub>3</sub> and extracted with additional DCM. The organic layer was washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude product was purified by reverse-phase flash chromatography (20-95% MeOH in H<sub>2</sub>O) to yield **B** as a slightly yellow oil (43 mg, 87%).

Characterization data for **B**:  $\delta_H$  (500MHz, CD<sub>3</sub>OD) 1.31 (s, 6H), 1.34 (s, 6H), 1.74 (s, 4H), 2.28 (d, 1H, *J* 1.5 Hz), 6.82 (s, 1H), 7.02 (dd, 1H, *J* 2 Hz and 8.5 Hz), 7.31 (m, 2H), 7.45 (d, 2H, *J* 8.5 Hz), 7.77 (d, 2H, *J* 8.5 Hz).  $\delta_C$  (500MHz, CD<sub>3</sub>OD) 30.82, 30.84, 30.9, 33.7, 33.9, 34.8, 35.0, 64.0, 123.1, 123.6, 125.3, 126.2, 126.6, 128.7, 128.9, 129.7, 139.5, 140.7, 142.1, 144.0, 144.4, 166.6. HRMS (ESI) calculated for C<sub>24</sub>H<sub>28</sub>NO<sub>2</sub>, [M-H<sup>+</sup>] 362.2123, found 362.2132.

### Example 3: Synthesis of Compound 20



7-(benzyloxy)quinoline-3-carbonitrile (**I13**): **I13** was prepared according to the procedure of Cai T.B., *et al*, *Journal of Medicinal Chemistry*, **51**:1849-1860, 2008.

Characterization data for **I13**:  $\delta_{\text{H}}$  (500MHz,  $\text{CDCl}_3$ ) 5.28 (s, 2H), 7.39-7.51 (m, 5H), 7.65 (dd, 1H,  $J$  2.5 Hz and 9.0 Hz), 8.05 (d, 1H,  $J$  9.0 Hz), 8.14 (d, 1H,  $J$  2.5 Hz), 8.63 (d, 1H,  $J$  2.0 Hz), 9.15 (d, 1H,  $J$  2.0 Hz)  $\delta_{\text{C}}$  (500MHz,  $\text{CDCl}_3$ ) 70.6, 116.3, 121.7, 122.3, 122.8, 123.1, 123.3, 125.4, 127.7, 128.5, 129.5, 130.8, 141.2, 149.1, 151.4.

3-cyanoquinolin-7-yl trifluoromethanesulfonate (**I14**): **I13** (27.0 mg, 0.104 mmol, 1 eq) was dissolved in minimal EtOAc. A catalytic amount of Pd-C was added and the flask was purged with  $\text{H}_2$  using a balloon. The reaction was further stirred at room temperature in presence of 1atm of  $\text{H}_2$  gas with TLC monitoring until the starting material was completely consumed (about three hours). The reaction mixture was filtered through a layer of Celite and the filtrate concentrated under reduced pressure to give an orange oil. The crude product was used in the next step without purification. The crude hydroxyquinoline (17.7 mg, 0.104 mmol, 1 eq) was dissolved in dry DCM (1 mL), pyridine (42.0  $\mu\text{L}$ , 0.519 mmol, 5 eq) and triflic anhydride (27.0  $\mu\text{L}$ , 0.156 mmol, 1.5 eq) were added at room temperature. The mixture was stirred for 2.5 hours at which point the reaction was quenched with water and partitioned between EtOAc and water. The aqueous layer was extracted with additional EtOAc (5 mL x 3) and the organic layers combined. The latter was washed with sodium bicarbonate (saturated, aqueous) and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The purification using flash chromatography (20% EtOAc in hexanes) yielded **I14** as a waxy solid (13 mg, 54% over two steps).

Characterization data for **I14**:  $\delta_{\text{H}}$  (500MHz,  $\text{CDCl}_3$ ) 7.64 (dd, 1H,  $J$  2.5 Hz and 9.0 Hz), 8.05 (d, 1H,  $J$  9.0 Hz), 8.14 (d, 1H,  $J$  2.5 Hz), 8.63 (d, 1H,  $J$  2.0 Hz), 9.15 (d, 1H,  $J$  2.0 Hz)  $\delta_{\text{C}}$  (500MHz,  $\text{CDCl}_3$ ) 116.3, 117.5, 120.0, 121.7, 122.8, 125.4, 130.8, 141.2, 149.1, 151.4, 151.6.

7-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)quinoline-3-carbonitrile (**I15**): **I14** (5.7 mg, 0.0189 mmol, 1.0 eq) and **I3** (13 mg, 0.0567 mmol, 3.0 eq) were dissolved in DME (1 mL) at room temperature.  $\text{PPh}_3$  (1.00 mg, 0.00377 mmol, 20 mol%), KF dihydrate (5.30 mg, 0.0567mmol, 3.0 eq), and  $\text{Pd}_2\text{bda}_3$  (1.00 mg, 0.000943 mmol, 5 mol%) were added to the solution. Distilled water (10 drops) was added to the resulting mixture and the reaction was degassed and purged with argon. The reaction mixture was stirred at reflux for 16 hours. After cooling, the reaction mixture was filtered through a layer of Celite and the filtrate partitioned

between EtOAc (5 mL) and H<sub>2</sub>O (5 mL). The aqueous layer was further extracted with EtOAc (5 mL). The combined organic layer was washed with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude mixture was purified using flash chromatography (20% EtOAc in hexanes) to give **I15** (4.89 mg, 76%).

5 Characterization data for **I15**:  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 1.34 (s, 6H), 1.37 (s, 6H), 1.74 (s, 4H), 7.43 (d, 1H, *J* 8.1 Hz), 7.51 (dd, 1H, *J* 2.1 Hz and 8.1 Hz), 7.70 (d, 1H, *J* 2.1 Hz), 7.83 (bs, 2H), 8.02 (bs, 1H), 8.37 (s, 1H), 8.80 (d, 1H, *J* 1.5 Hz).  $\delta_{\text{C}}$  (300MHz, CDCl<sub>3</sub>) 31.9, 34.2, 35.1, 125.5, 126.5, 144.8, 116.3, 117.5, 120.0, 121.7, 122.8, 125.4, 130.8, 141.2, 149.1, 151.4, 151.6.

*Methyl 7-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)quinoline-3-carboxylate (I16)*: **I15** (10.0 mg, 0.0294 mmol) was dissolved in MeOH (2 mL) to which concentrated HCl (2 mL) was added. The mixture was heated to reflux with stirring for 16 hours then cooled in an ice bath. The pH was adjusted to neutral with 1M KOH. The reaction mixture was extracted with EtOAc (5 mL x 3). The combined organic layer was washed with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude mixture was purified using  
15 preparative thin layer chromatography (30% EtOAc in hexanes) to give **I16** (9.50 mg, 87%).

Characterization data for **I16**:  $\delta_{\text{H}}$  (300MHz, CDCl<sub>3</sub>) 1.34 (s, 6H), 1.37 (s, 6H), 1.74 (s, 4H), 4.03 (s, 3H), 7.46 (d, 1H, *J* 8.4 Hz), 7.53 (d, 1H, *J* 8.1 Hz), 7.73 (s, 1H), 7.89 (d, 1H, *J* 8.1 Hz), 7.98 (d, 1H, *J* 8.4 Hz), 8.39 (s, 1H), 8.87 (s, 1H), 9.46 (s, 1H).

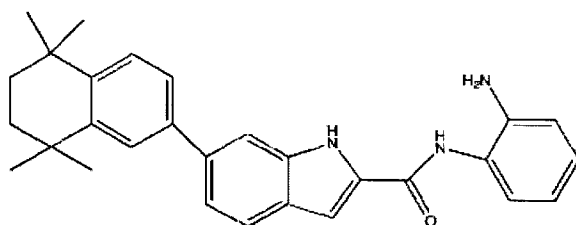
*N-hydroxy-7-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)quinoline-3-carboxamide (C)*: **I16** (9.50 mg, 0.0254 mmol, 1.00 eq) was dissolved in dry THF (2 mL) and cooled in an ice bath. To the solution were added MeOH (0.5 mL) and 50% v/v NH<sub>2</sub>OH (in water, 0.5 mL, excess). The mixture was allowed to warm up slowly to room temperature and stirred for three days. The pH was adjusted to approximately pH 3 with 1M KOH. The resulting solution was partitioned between water and EtOAc. The aqueous layer was further extracted  
25 with EtOAc (5mL x 3). The combined organic layer was washed with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by reverse-phase flash chromatography (20-95% MeOH in H<sub>2</sub>O) to yield **C** as a clear film (6.5 mg, 74%).

Characterization data for **C**:  $\delta_{\text{H}}$  (300MHz, CD<sub>3</sub>OD) 1.32 (s, 6H), 1.37 (s, 6H), 1.77 (s, 4H), 7.48 (d, 1H, *J* 8.4 Hz), 7.58 (d, 1H, *J* 8.1 Hz), 7.75 (s, 1H), 7.94 (d, 1H, *J* 8.1 Hz), 7.98 (d, 1H, *J* 8.4 Hz), 8.39 (s, 1H), 8.95 (s, 1H), 9.50 (s, 1H).  $\delta_{\text{C}}$  (300MHz, CD<sub>3</sub>OD) 31.3, 31.4, 34.1,

30

34.4, 35.2, 35.3, 123.5, 124.3, 124.5, 124.7, 125.20, 126.4, 127.8, 128.6, 128.9, 129.7, 131.6, 136.6, 137.5, 140.7, 148.3, 149.1, 167.9. HRMS (ESI) calcd for  $C_{24}H_{26}N_2O_2$ ,  $[M-H^+]$  373.1992, found 373.1978.

5 **Example 4: Synthesis of compounds 22, 23, and 24**

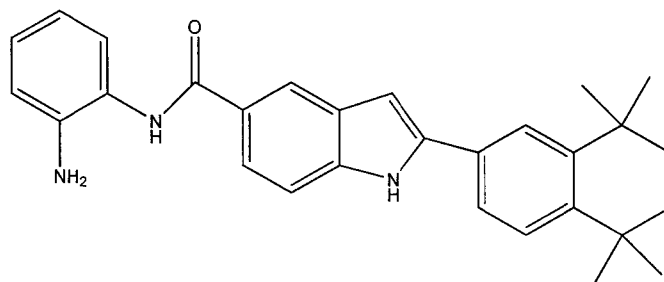


Compound 22

To 200 mg of 6-bromoindole 2-carboxylic acid methyl ester in THF 6ml was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (70mg), dicyclohexylmethylamine (1.2 ml) and boronic acid (300 mg). The mixture was stirred under reflux for 12 hours then  
10 cooled to room temperature. The reaction mixture was poured into water and extracted with ethyl acetate, and the resulting organic layer was dried and evaporated. The crude mixture was purified by flash chromatography (ISCO combiflash) using a 10-50% ethyl acetate gradient to afford 200 mg of product, which was dissolved in 10 ml methanol:THF (1:1) and 2 ml of 2N KOH was added to the resulting solution. The solution was heated for 12 hours at 60°C then  
15 cooled to room temperature. Water (50 ml) and 2N HCl (4 ml) was added to the solution, which was then extracted with ethyl acetate (100 ml). The organic layer was dried and evaporated. The crude product was purified by combiflash using 10-100% ethyl acetate gradient to afford the acid as a white solid (140 mg). The acid was dissolved in DMF (5 ml) to which EDCI (140 mg), HOBT (120 mg) and 1,2-phenylenediamine (120 mg) was added and the reaction mixture was  
20 stirred overnight at room temperature. The reaction solution was extracted with water (100 ml) and ethyl acetate (100 ml), and the isolated organic layer was dried and evaporated. This crude product was purified using combiflash with 0-100% ethyl acetate to give 70 mg of final product (22).

Characterization data: (300MHz,  $CD_3COCD_3$ ) 10.8 (s, 1H), 9.2 (s, 1H), 7.8 (s, 1H), 7.75  
25 (d, 1H), 7.65 (s, 1H). 7.45-7.5 (m, 5H), 7.1 (m, 1H), 6.9 (m, 1H), 4.7 (bs, 2H), 1.75 (s, 4H), 1.4 (d.6H). MS:  $[M+1]$  438.

## Synthesis of compound 23

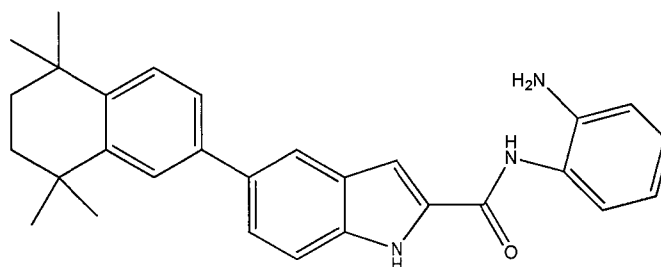


To 250 mg of indole-5-carboxylic acid was added 16 ml of acetic acid, 300 mg of boronic acid and 70 mg palladium acetate. The reaction was flushed with oxygen, and then stirred for 48 hrs. The solvent was evaporated, and the resulting product purified by flash chromatography (ISCO combiflash) using a 10-50% ethyl acetate/hexane gradient. The purified acid product was dissolved in 5ml of DMF, and HOBt (150 mg), EDCI (150 mg), and 1,2-phenylenediamine (150 mg) was added to the solution. The reaction was stirred overnight at room temperature. This reaction mixture was poured into water, extracted with ethyl acetate, dried and evaporated. A 5:1 hexane/ethyl acetate solution was added to the crude product, and the suspension was filtered to afford 100 mg of product (**23**).

Characterization data: NMR (600MHz, CD<sub>3</sub>COCD<sub>3</sub>): 11.7 (s,1H), 9.5 (s,1H), 8.35 (s,1H), 7.8 (s,1H), 7.74 (d,1H), 7.66 (d,1H), 7.47 (d,1H), 7.2 (d,1H), 7.01 (m,2H), 6.8 (d,1H), 6.63 (m,1H), 4.9 (s,2H), 1.66 (s,4H) and 1.3 (d,12H).

15

## Synthesis of compound 24



To a solution of 5-bromoindole-2-carboxylic acid methyl ester (250 mg) in THF (6 ml) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (70 mg) and boronic acid (300 mg). This reaction mixture was placed degassed with argon and heated at 60°C for 48 hours. The solvent was evaporated, and the resulting product purified by flash chromatography (ISCO combiflash) using a 10-50% ethyl acetate/hexane gradient. The resulting

product (purified ester) was hydrolyzed by heating at 60° C overnight in a solution of methanol/THF/2N NaOH (1:1:1, 9 ml). This solution was poured into a solution of 5 ml 2N HCl and 50 ml water, and the extracted with ethyl acetate. The organic layer was dried and evaporated. The crude acid (100 mg) was dissolved in DMF (10 ml) to which EDCI (150 mg),  
5 HOBt (150 mg) and 1,2-phenylenediamine (150 mg) was added, and this solution was stirred overnight. The solvent was evaporated off, and the resulting product purified by flash chromatography (ISCO combiflash) using a 10-50% ethyl acetate/hexane gradient to provide compound 24.

Characterization data: NMR(600MHz, CD<sub>3</sub>SOCD<sub>3</sub>): 11.6 (s, 1H), 9.75 (s, 1H), 7.9  
10 (s, 1H), 7.4-7.7 (m, 6H), 7.25 (9d, 1H), 7.0(m, 1H), 6.8 (s, 1H), 6.6(s, 1H), 4.95 (s, 2H), 1.75 (s, 4H) and 1.3 (d, 12H).

### Example 5

The effect of compounds on the enzymatic activity of purified recombinant human  
15 HDAC-1, -2, -3, -6, and -8 activity and of purified rat liver HDAC was examined by measuring the deacetylation of synthetic peptides in various preparations of HDACs. HDAC assays were performed using a two-step enzymatic reaction where enzyme activity is correlated to the release of 4-amino-7-methylcoumarin (AMC). AMC fluorescence is measured in a fluorescent plate reading using  $\lambda_{\text{ex}}$ 380nm and  $\lambda_{\text{em}}$ 440nm. The assay was run in a 96-well format using an assay  
20 buffer (50 mM Tris-HCl, pH 8, 137 mM NaCl, 2.7 mM KCl, 1 mM MgCl<sub>2</sub> and 50 ug/mL ultra-pure, non-acetylated BSA. Purified human recombinant HDAC-1, HDAC-2, HDAC-3/NCOR and HDAC-6 were assayed using Ac-Arg-Gly-Lys (Ac)-AMC (Bachem 4044046) as a substrate. Purified human recombinant HDAC-8 was assayed using Boc-Lys(Tfa)-AMC (Bachem 4060676) as a substrate. Both substrates were used at a final concentration of 10  $\mu$ M. Final enzyme  
25 concentrations in the assays were as follows: 0.38  $\mu$ g/mL HDAC-2 (Cayman Chem 10009377), 1.37  $\mu$ g/mL HDAC-6 (Cayman Chem 10009465), HDAC-8 (Cayman Chem 10009465, 150  $\mu$ l, diluted 100x), purified rat liver HDAC (Millipore 382165, 0.8 mg/mL proteins diluted 50x).

HDAC-8, HDAC-9, HDAC-10 and HDAC-11 were assayed using HDAC-Glo™ I/II Kit (Promega Corporation G6421) in a total volume of 110  $\mu$ l following the manufacturer's  
30 instructions. Enzyme concentrations were as follows: 230 ng/ $\mu$ L HDAC-8 (Cayman Chem

19380), 100 ng/mL HDAC-9 (Sigma SRP5268), 460 ng/ml HDAC-10 (Axxora/Enzo BML-SE99), 600 ng/mL HDAC- 11 (Axxora/Enzo BML-SE560).

Benchmark compounds, including, entinostat, panabinostat, ricolinostat, romidepsin, and suberoylanilide hydroxamic acid (SAHA) were run alongside the test compounds. The compounds were dissolved in DMSO and tested in duplicate using 1/3 dilution concentration curve. Typically, HDAC preparations were pre-incubated with compounds or DMSO in assay buffer on ice for 5 min prior to substrate addition. The reaction was allowed to proceed for 40 min at 37° C, after which developer solution (0.5% trypsin, 10µM trichostatin A (TSA)) was added to obtain a final concentration of 0.1% trypsin, 2 µM TSA. After 30 minutes at room temperature, the amount of free fluorogenic AMC was measured as described above. Data showing the effect of various compounds of the invention on HDAC-1 and HDAC-6 are presented in Figures 5A and 5B, respectively, and data for all HDACs are summarized in Table 1.

**Table 1:**

	1	2	3	6	8	9	10	11	Rat liver		
5	+/-	++	++	+++	++++	+/-	+/-	+/-	++	-	-
8		-	-	+++	++	-	-	-	-	++	-
13	+/-	++	++	++++	+++	+/-	+/-	+/-	+++	+++	-
17	-	-	-	++	++	-	-	-	-	++	-
18	+/-	++	-	+++	++	NT	NT	NT	NT	+	-
19	-	++	-	+++	-	NT	NT	NT	NT	-	-
20	-	-	-	++	++	NT	NT	NT	+/-	+++	-
21	-	-	-	-	-	-	NT	NT	-	-	-
Entinostat	+++	++++	+++	-	+	+++	++	+++	NT	-	NT
Panobinostat	++++	++++	++++	++++	++++	++++	++++	++++	NT	-	++++
Ricolinostat	++++	++++	++++	++++	++++	NT	++	+++	NT	-	+++
Romidepsin	+/-	+/-	+++	-	++	++++	+++	+++	NT	-	+++
SAHA	++++	++++	++++	++++	++++	++++	++++	++++	++++	-	++++

Because absolute IC<sub>50</sub> values vary with different assay systems or substrates, the relative activity of each compound is represented using the symbols "+" or "-". A greater number of "+" signs denotes a greater potency (IC<sub>50</sub>) the inhibition of the respective HDACs. The symbol "+/-" denotes that 100% inhibition of the enzyme could not be reached in the condition used. "NT" = not tested.

*Results:* Under the experimental conditions, the compounds were mostly inactive active against HDAC-1. However, compounds 5, 13, and 18 inhibited up to ~50% HDAC-1 activity. All of the compounds tested demonstrated an apparent lack of inhibition of HDAC-1, -2, -3, -9, -10 and -11 under the experimental conditions. Surprisingly, compound 5 was shown to be over 200 times more potent than compound 17 in the HDAC-8 inhibition assay. Likewise, compound 13 was shown to be at least 50-fold more potent than compound 17 in the HDAC-6

inhibition assay (Figure 5A and Table 1), and at least 13-fold more potent than compound 17 in HDAC-8 inhibition assay (Table 1).

When measuring inhibition of purified rat hepatic HDAC, compound 8 was at least three times more potent than compound 17, and compounds 5 and 13 were six and seventy times more  
5 potent than compound 17, respectively (Table 1).

### Example 6

The effect of various compounds of the invention on RAR-mediated transcription in MCF7 breast cancer cells was examined by measuring their effect on the transcription of a  
10 luciferase reporter gene under the control of a TK promoter placed downstream of a RAR response element (RARE: PuGGTCAnnnnnPuGGTCA (SEQ ID NO:1)). In addition, the effect of the compounds on the closely related RXR-mediated transcription was examined by measuring their effect on the transcription of a luciferase reporter gene under the control of a TK promoter placed downstream of a RXR response element (RXRE: PuGGTCAnPuGGTCA (SEQ  
15 ID NO:2))

Typically, 10,000 cells were plated in 96 wells plates in phenol red-free RPMI medium supplemented with 10% charcoal-stripped Fetal Bovine Serum. After 24 hours, cells were transfected with 0.1 µg of luciferase reporter plasmid and 0.01µg of a reporter plasmid expressing renilla luciferase (RLuc) gene under the control of a SV40 promoter, using Fugene 6  
20 transfection reagent (0.5 µl/well Promega Corporation). Cells were treated in triplicate with compounds or vehicle (DMSO) for 24 hours. Luciferase and renilla luciferase activities were measured using Dual-Glo reagent (Promega Corporation). Luciferase activity was normalized in each well for renilla activity.

*Results:* As shown in Figure 6A and summarized in Table 2, compounds 8, 13, 18, 19  
25 and 20 activated RARE-dependent luciferase expression in MCF7 cells. Compound 13 was five to ten times more potent than compound 17 in activating a RARE-tk\_luc reporter plasmid transfected in MCF7 cells. Surprisingly, while all benchmark HDAC inhibitors activated transcription from an RXRE-promoter, none of compounds 5, 8, 13, 17, 18, 19, 20 and 21 demonstrated transcriptional activation of RXR (Figure 6B; Table 2).

30

**Table 2:** Summary of compounds' ability to activate RARE-dependent transcription in MCF7 cells

<i>Compound</i>	<i>RAR</i>	<i>RXR</i>
5	-	-
8	++	-
13	+++	-
17	++	-
18	+	-
19	-	-
20	+++	-
21	-	-
Entinostat	-	NT
Panobinostat	-	+++++
Ricolinostat	-	+++
Romidepsin	-	++++
SAHA	-	+++++

**Example 7**

The cytotoxicity of compounds was examined and directly compared to compound 17, by measuring cell survival of clonal tumor cell lines IMR-32, BE2C (neuroblastoma), as well as MDA-MB-231, BT20, HCC-38 (Basal) and MCF7 (luminal) breast cancer cells (ATCC). Cells were cultured in phenol red-free RPMI medium supplemented with 10% FBS and 1mM Ala-Glu. Typically, 10,000-20,000 cells/well were plated in a 96 well plate (Costar 3197). Cells were exposed to compounds or vehicle (1% DMSO final). Cells were maintained in the presence of compound for four or five days. Media and compounds were renewed every 48 hours. Cell survival was measured using the luminescence CellTiterGlo kit (Promega Corporation) and expressed as relative light unit as fold over DMSO.

*Results:* The data show that compounds were cytotoxic in a variety of cancer cell lines (Figures 7A-C). In IMR-32 neuroblastoma cells, the compounds tested were cytotoxic in the 30 nM to 300 nM range. Strikingly, compounds 5 and 13 were ten-fold more potent than compounds 17 and 8 in killing IMR-32 cells (Figure 7A). Strikingly, in both BE-2C and MDA-MB-231 cancer cell lines, compounds 13 and 18 were more potent than compound 17, SAHA or Ricolinostat (Figures 7B-C).

**Example 8**

The effect of certain compounds on intracellular acetylation of target proteins was tested in high risk neuroblastoma cells, BE-2C and IMR-32 cells.

BE-2C cells were grown to confluence in phenol-red-free RPMI media supplemented with 10% FBS and 2.5 mM Ala-Glu. The cells were treated with DMSO or 5  $\mu$ M compound 13, Ricolinostat (2  $\mu$ M), SAHA (2  $\mu$ M), or TSA (1  $\mu$ M), in DMSO for 16 hours. Total and Lys 40 acetylated alpha tubulin were detected using specific antibodies.

5 IMR32 cells were grown to confluence in phenol-red-free RPMI media supplemented with 10% es grade FBS and 2.5 mM Ala-Glu. Cells were treated with DMSO or 1  $\mu$ M or 5  $\mu$ M compound 13 in DMSO for 16 hours. Protein extracts were prepared in RIPA buffer in the presence of protease and phosphatase inhibitors. Proteins were separated on a 4-20% gel by PAGE and transferred to a nitrocellulose membrane.

10 Beta actin, total and Lys382 acetylated p53, and Lys40 acetylated alpha, and total tubulin were detected using antibodies (Cell Signaling #8557, #2524 #2525, #12152 and #2144 respectively) using manufacturer recommended conditions.

*Results:* The data show that, consistent with the HDAC inhibitory activity observed *in vitro* (Table 1), under conditions where neither the level of total p53 nor that of total beta actin were affected, addition of 1  $\mu$ M or 5  $\mu$ M compound 13 resulted in a pronounced accumulation of lysine acetylated p53 (Figure 8). Surprisingly, while treatment with ricolinostat, SAHA and TSA all resulted in a pronounced Lysin (K) 40 alpha-Tubulin acetylation, no significant acetylation was observed in compound 13-treated cells at 5  $\mu$ M, a concentration greater than IC<sub>50</sub> (Figure 9). The lack of increased alpha tubulin acetylation was confirmed using LC-MS analysis. These findings confirm that compound 13 acts as a *bona fide* inhibitor of HDAC activity, and suggests that the cytotoxicity of this compound does not result from tubulin acetylation.

### Example 9

The effect of compounds on myoblast fusion was examined in C2C12 cells maintained in RPMI media supplemented with 2% horse serum. C2C12 myoblastic cells were purchased from the American Type Culture Collection (ATCC) and maintained undifferentiated in RPMI media (Corning) supplemented with 2 mM L-Alanine-L-Glutamine (ATCC) and 1 mM pyruvate (Corning). Undifferentiated cells were maintained below 70% confluence. For long term cultures and compound treatment, cells were plated at high density CellBIND Culture Dishes (Corning 3294, 3296, 3337) and in RPMI supplemented with 2% Horse Serum (Gibco) and 2 mM L-Alanine-L-Glutamine (ATCC) and 1mM pyruvate (Corning). Compounds were

dissolved in DMSO at 1000 times the final concentration and diluted 1-in-1000 in the media covering the cells. Media and compounds were changed daily. For immunocytochemistry, cells were fixed in 2% PFA in HBSS for 10 minutes and left in HBSS at 4° under humidified atmosphere and processed for immunocytochemistry. For myosin heavy chain detection (MHC),  
5 cells were first incubated in 100 ul -1 ml 0.15 M Glycine in DPBS for 10 minutes, rinse with DPBS. 100 ul-1 ml 0.5% Triton-X in DPBS was added for 10 minutes, rinsed with DPBS, and followed by incubation with 100 ul blocking agent (10% goat serum in DPBS) for 30 min at room temperature. MF20 primary antibody in 10% goat serum in DPBS was added at 1/60 dilution for 30 min at room temperature and rinsed three times with 100ul DPBS. IgG2b goat  
10 anti mouse secondary antibody (Jackson Immuno-Research) was added at 1: 1000 in 10% goat serum in DPBS for exactly 30 min at room temperature then rinsed 3 times with 100ul DPBS. A final rinse in H<sub>2</sub>O was performed and cells were covered with two drops of Elvanol and covered gently with cover slip and allowed to dry in the dark for 24-48 hours.

*Results:* Surprisingly, our data suggest that under long-term cultures in suboptimal  
15 RPMI-containing media, addition of compounds 13, 17 or B enhances the fusion of single cells into large multinucleated, elongated C2C12 myotubes (Figure 10). Immunohistochemistry staining assays suggest that the compounds promote the fusion and/or maintenance of myosin heavy chain (MHC)-expressing differentiated myoblasts. In DMSO-treated C2C12 cells cultured for 10 days, myotube formation does not occur despite the presence of a large number  
20 of almost exclusively mononucleated MHC-expressing differentiated myoblasts with a single polynucleated-MHC-expressing myotube. Under the same conditions, using 300 nM of compound 17 resulted in the majority of MHC-expressing cells being polynucleated myotubes with an average of 5-10 nuclei per cell, suggesting that fusion was promoted (Figure 11).

The quantitation of the average distribution of myotubes' length and diameter  
25 demonstrate that in the presence of 300 nM of compound 17 are longer and larger than when treated with DMSO (Figures 12A and B).

Taken together, our data suggest that the compounds tested significantly improve myoblast fusion and/or myotube survival in long-term cultures.

**Example 10**

C2C12 myoblasts were seeded at 100,000 in 30 mm plate in growth medium (Phenol red –free RMPI containing 10% FBS, Sodium pyruvate and Ala-Glu), and “pre-treated” with DMSO or 200 nM of compounds 13 or 17 . At confluence cells were shifted to differentiation media (high glucose DMEM, + 0.2%HS + 1x Insulin/Transferrin/Selenium (Life Tech 41400-045) + Glutamine, without Pyruvate). Fully differentiated C2C12-derived myotubes were left in culture without media renewal for 8 days followed by media renewal and microscopic examination.

*Results:* The data show that extensive cellular fusion was observed after 72 hours differentiation in cells that were treated with compounds 13 or 17 versus DMSO (Figure 13 top).

In addition, when left in exhausted media for over 8 days, DMSO-treated myotubes, but not myotubes treated with compounds 13 or 17, underwent severe structural atrophy and cell death. In contrast, myotubes treated with compounds 13 or 17 withstood culture stress conditions with very little structural alteration (Figure 13 bottom).

**Example 11**

Treatment with compounds 13 or 17 down regulates the expression muscle-atrophy genes myogenin and Atrogin in long term C2C12 cultures (Figure 14A and B).

Quantitative RT-PCR was performed on RNA prepared from cell treated as in Example 9. At day 10 of the experiment, cells were rinsed in HBSS (without calcium or magnesium) and RNA was prepared using FastLane Cell cDNA Kit (Qiagen). Quantitative PCR was performed using Eppendorf and SYBR amplification mix (Sigma-Aldrich) using the gene specific primer combination given in Table 3. Data were normalized for ribosomal housekeeping gene RPLP0

*Results:* Consistent with a role in preserving myotube integrity during long term cultures, compounds 13 and 17 down-regulated the expression of genes implicated in myofiber degradation.

Table 3: Sequence of gene-specific primers used in Q-RT PCR quantitation of myofiber-degradation associated genes.

	ATROGIN	MYOGENIN	RPLP0
Forward Primer	CTTCTCAGAGAGGCAGATT (SEQ ID NO:3)	CCCAACCCAGGAGATCAT (SEQ ID NO:4)	CGGAGGAATCAGATGAGGATA (SEQ ID NO:5)
Reverse Primer	TCTTCTTGGGTAACATCGTACA (SEQ ID NO:6)	CTGGGAAGGCAACAGACATA (SEQ ID NO:7)	CAGACCGGAGTTTTAAGAGAAG (SEQ ID NO:8)

### Example 11

5 Mouse Pharmacokinetics studies were conducted in female athymic nude or male C57/B6 mice (n=3). Due to its very poor aqueous solubility, compound 17 was formulated in 66% PEG-400/33% H<sub>2</sub>O-1% Tween-80. In contrast compound 13 was formulated in 66% PEG-400/33% H<sub>2</sub>O. Compounds were administered PO (30 mg/kg) or IV (5mg/kg), and plasma concentrations were measured by UV/HPLC. The results are presented in Figure 15 and pharmacokinetic parameters for each compounds are summarized in Table 4.

Table 4

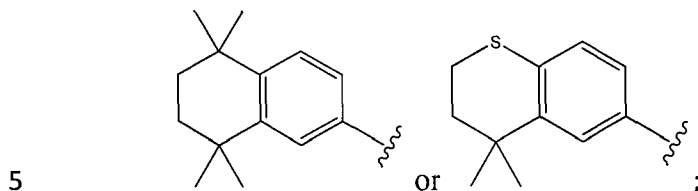
	Compound 17	Compound 13
<b>AUC<sub>0-∞</sub> (μM·h)</b>	28.71	42.00
<b>C<sub>max</sub> (μM)</b>	2.08	5.54
<b>T<sub>max</sub> (h)</b>	4.3	1.4
<b>F (%)</b>	19.7	~40
<b>CL<sub>p</sub> (mL/min/kg)</b>	10.2	0.24
<b>V<sub>d,ss</sub> (L/kg)</b>	4.6	8
<b>MRT (h)</b>	7.1	6.9

15 *Results:* Compound 13 displayed improved aqueous solubility and pharmacokinetics properties compared with compound 17. Notably, oral bioavailability, AUC, C<sub>max</sub> were markedly higher for compound 13, while T<sub>max</sub> was markedly reduced (Figure 15 and Table 4).

## WHAT IS CLAIMED IS:

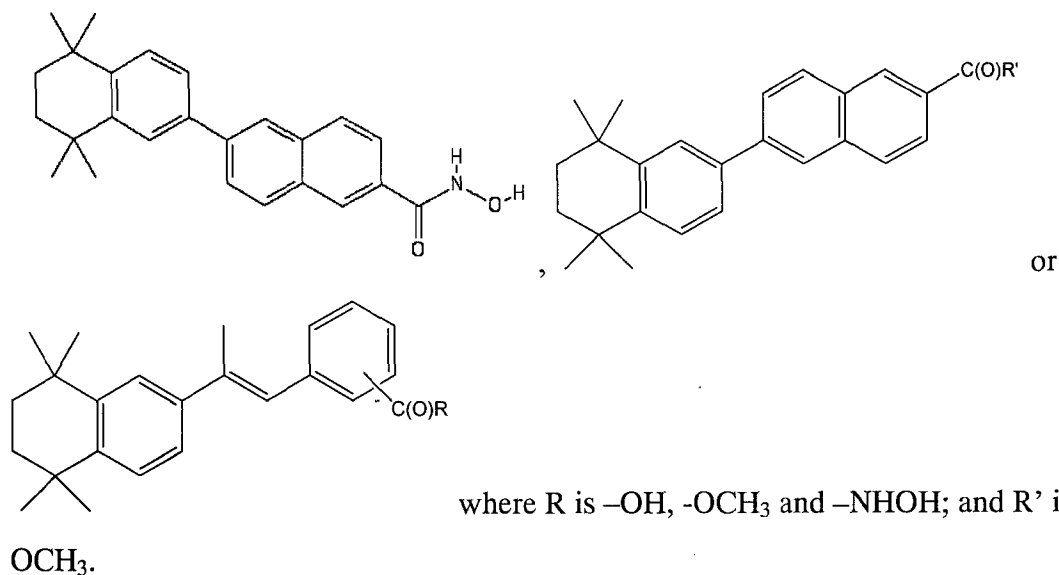
1. A compound of Formula I: A-W-Z (I)

or a pharmaceutically acceptable salt thereof, wherein A is



W is a heterocyclylene, arylene, heteroarylene, alkenylenearylene, arylenealkenylene, alkenyleneheteroarylene, or heteroarylenealkenylene; and

Z is a hydrogen bond donor, with the proviso that the compound is not

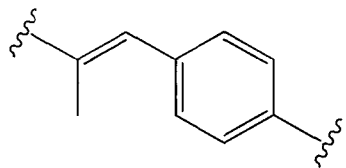


2. The compound of claim 1, wherein W is an indolinylene linked to A at any one of positions 2, 3, 4, 5, 6 or 7 of the indolinylene; a quinolinene linked to A at any one of positions 2, 3, 4, 5, 6, 7, or 8; or an isoquinolinene linked to A at any one of positions 1, 3, 4, 5, 6, 7, or 8.

3. The compound of claim 1, wherein W is -propylene-phenylene-.

4. The compound of claim 1, wherein Z is -C(O)NR<sup>1</sup>R<sup>2</sup> or -C(O)OR<sup>3</sup>, wherein R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen (H), hydroxyl (OH), C<sub>1-6</sub> alkyl, hydroxyC<sub>1-6</sub> alkyl, aminoC<sub>1-6</sub> alkyl, or aminoaryl; and R<sup>3</sup> is H or C<sub>1-6</sub> alkyl.

5. The compound of claim 2, wherein Z is linked to the indolinylene, quinolinene, or isoquinolinene at any one of the positions that is not linked to A.



5 6. The compound of claim 4, wherein W is

7. The compound of claim 1, wherein W is an indolinylene linked to A at any one of positions 2, 3, 4, 5, 6 or 7 of the indolinylene; Z is  $-C(O)NR^1R^2$  or  $-C(O)OR^3$ , wherein  $R^1$  and  $R^2$  are each independently hydrogen, hydroxyl,  $C_{1-6}$  alkyl, hydroxy $C_{1-6}$  alkyl, amino $C_{1-6}$  alkyl, or aminoaryl; and  $R^3$  is H or  $C_{1-6}$  alkyl, and wherein Z is linked to the indolinylene at any one of positions 2, 3, 4, 5, 6 or 7 of the indolinylene not linked to A.

8. The compound of claim 1, wherein W is a quinolinene linked to A at any one of positions 2, 3, 4, 5, 6, 7 or 8 of the quinolinene; Z is  $-C(O)NR^1R^2$  or  $-C(O)OR^3$ , wherein  $R^1$  and  $R^2$  are each independently hydrogen, hydroxyl,  $C_{1-6}$  alkyl, hydroxy $C_{1-6}$  alkyl, amino $C_{1-6}$  alkyl, or aminoaryl; and  $R^3$  is H or  $C_{1-6}$  alkyl, and wherein Z is linked to the quinolinene at any one of positions 2, 3, 4, 5, 6, 7 or 8 of the quinolinene.

9. The compound of claim 1, W is a isoquinolinene linked to A at one of positions 1, 3, 4, 5, 6, 7 or 8 of the isoquinolinene moiety; Z is  $-C(O)NR^1R^2$  or  $-C(O)OR^3$ , wherein  $R^1$  and  $R^2$  are each independently hydrogen, hydroxyl,  $C_{1-6}$  alkyl, hydroxy $C_{1-6}$  alkyl, amino $C_{1-6}$  alkyl, or aminoaryl; and  $R^3$  is H or  $C_{1-6}$  alkyl, and wherein Z is linked to the quinoline ring at any one of positions 2, 3, 4, 5, 6, 7 or 8 of the isoquinolinene.

10. The compound of any one of claims 7-9, wherein Z is  $-C(O)NR^1R^2$ ;  $R^1$  is H; and  $R^2$  is OH.

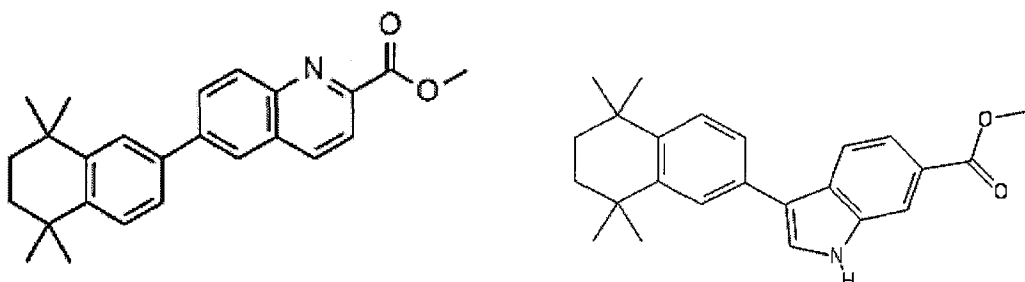
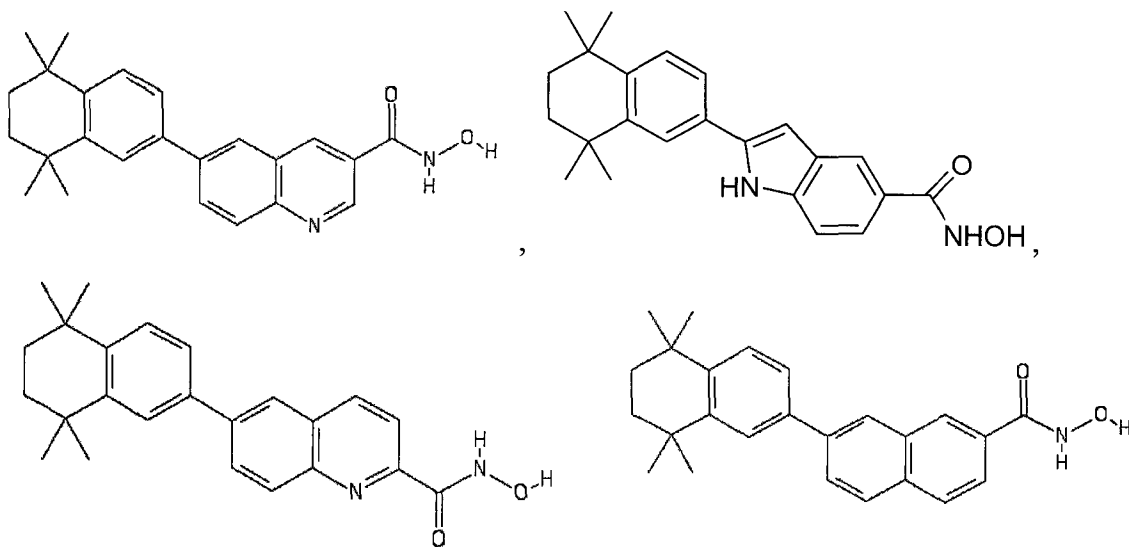
11. The compound of any one of claims 7-9, wherein Z is  $-C(O)NR^1R^2$ ;  $R^1$  is H; and  $R^2$  is aminoaryl.

12. The compound of any one of claims 7-9, wherein Z is  $-C(O)OR^3$ ; and  $R^3$  is H.

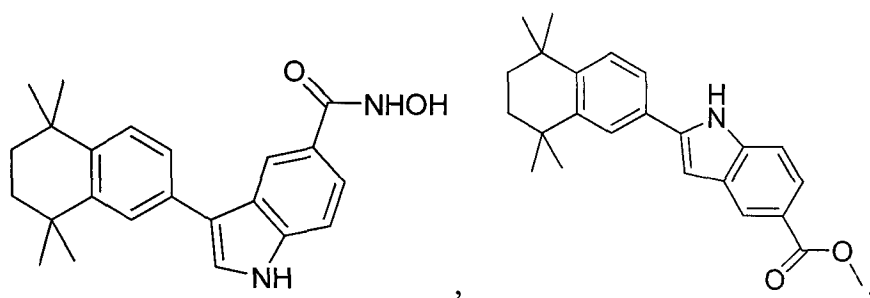
13. The compound of any one of claims 7-9, wherein Z is  $-C(O)OR^3$ ; and  $R^3$  is  $C_{1-6}$  alkyl.

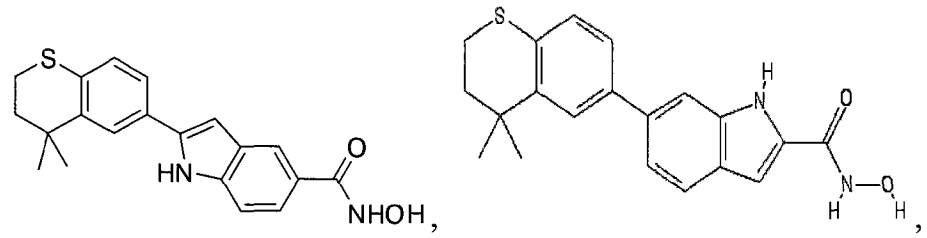
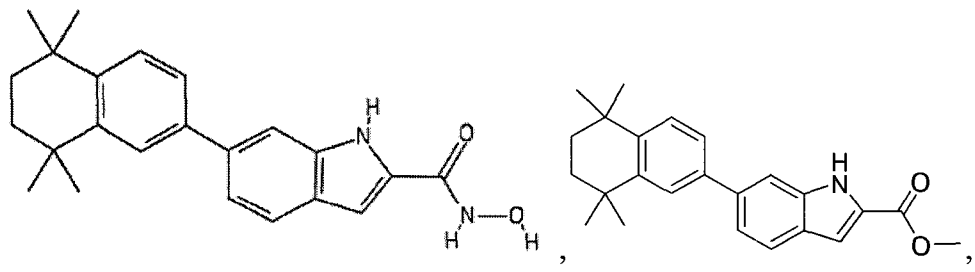
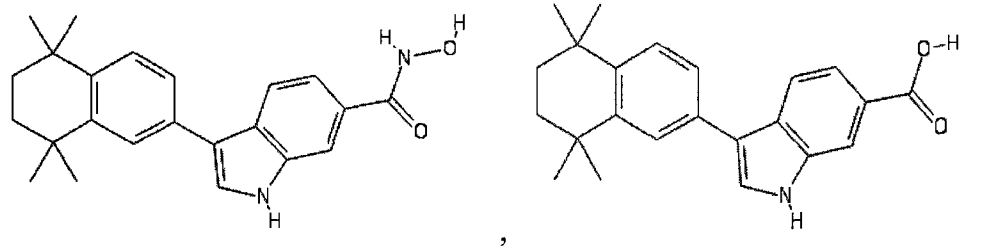
5

14. The compound of claim 1, wherein the compound is

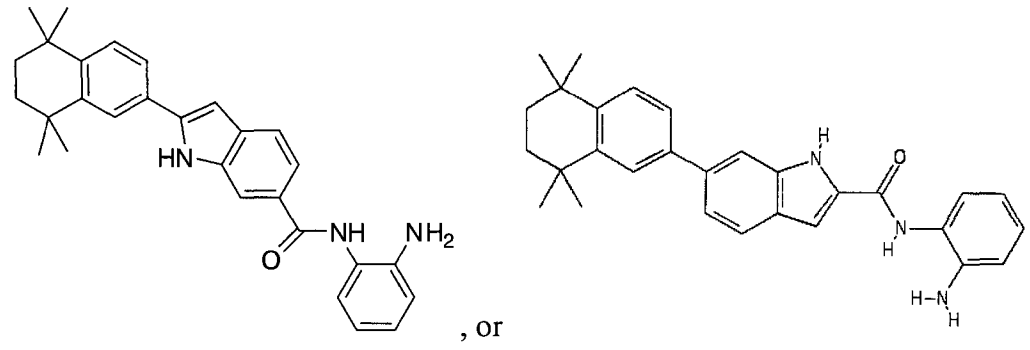


10





5



, or

15. A pharmaceutical composition comprising a compound of any one of claims 1-14, and a pharmaceutically acceptable carrier.

10

16. A method of treating a subject who has cancer or a non-malignant tumor, the method comprising administering to the subject a therapeutically effective amount of a compound of claim 1 or a composition of claim 15.

17. The method of claim 16, wherein the cancer is non-small cell lung cancer, colon cancer, melanoma, breast cancer, renal cancer, ovarian cancer, prostate cancer, cancer of the central nervous system, a blood cancer, or a neuroblastoma.

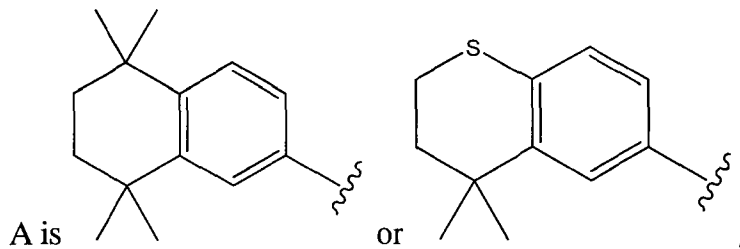
5 18. The method of claim 16, wherein the non-malignant tumor is a pheochromocytoma.

19. A method of inhibiting loss of muscle mass or muscle function in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I:

10

A-W-Z (I)

or a pharmaceutically acceptable salt thereof, wherein



W is a heterocyclylene, arylene, heteroarylene, alkenylenearylene, arylenealkenylene or alkenyleneheteroarylene, heteroarylenealkenylene; and

15

Z is a hydrogen bond donor.

20. The method of claim 19, wherein the loss of muscle mass is associated with an inherited myopathy.

20

21. The method of claim 19, wherein the loss of muscle mass is associated with muscular dystrophy, neuromyotonia, nemaline myopathy, multi/minicore myopathy, centronuclear myopathy, mitochondrial myopathy, inflammatory myopathy, metabolic myopathy.

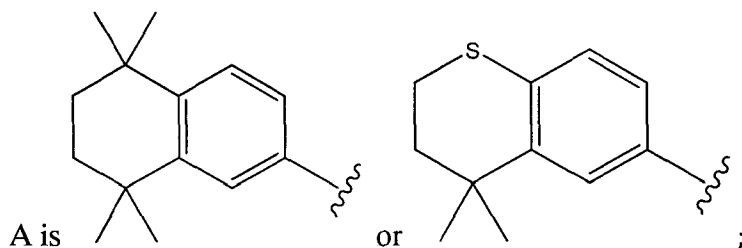
25

22. The method of claim 19, wherein the loss of muscle mass is associated with intensive care unit-acquired weakness (ICUAW), chronic obstructive pulmonary disease (COPD), heart failure, traumatic injury or malignancy.

23. A method for treating myofibers *ex vivo*, the method comprising:

providing an *ex vivo* preparation of myofibers, optionally comprising a natural or synthetic biological matrix; and

contacting the preparation with an amount of a compound of Formula I: A-W-Z (I) or a pharmaceutically acceptable salt thereof, wherein the amount of the compound is sufficient to promote muscle mass or muscle function and



W is a heterocyclylene, arylene, heteroarylene, alkenylenearylene, arylenealkenylene alkenyleneheteroarylene, or heteroarylenealkenylene; and

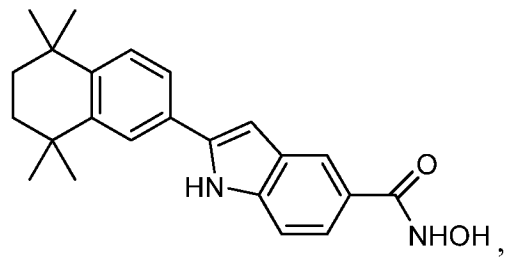
Z is a hydrogen bond donor.

15

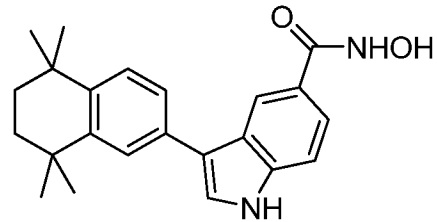
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25

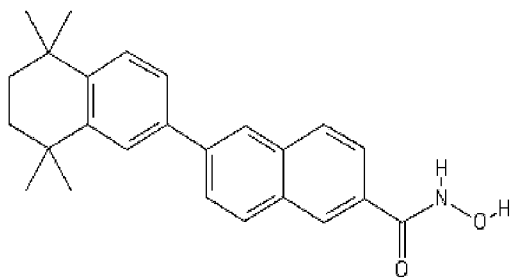
Figure 1



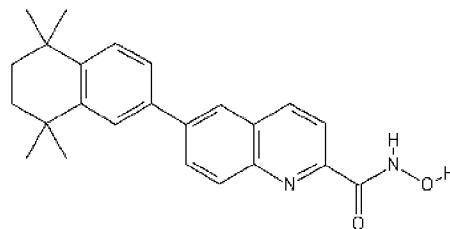
Compound 13



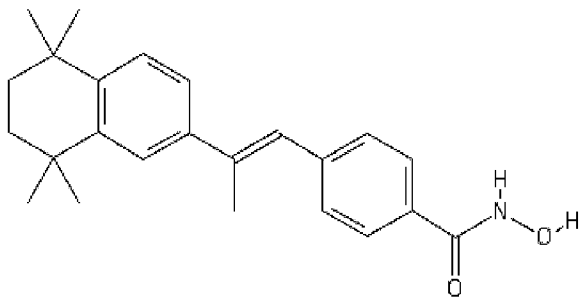
Compound 5



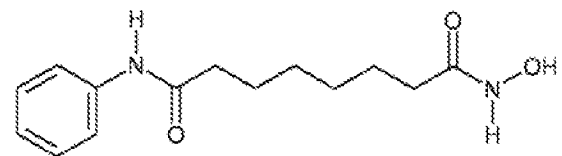
Compound 17



Compound 8

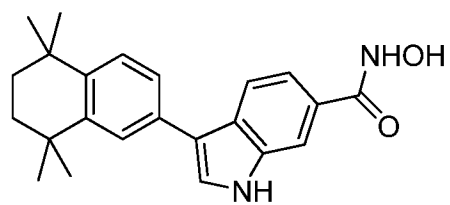


Compound B

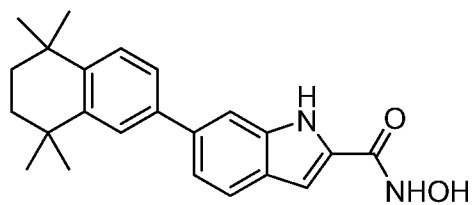


SAHA

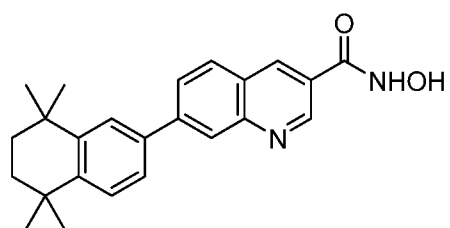
Figure 1 (cont.)



Compound 18

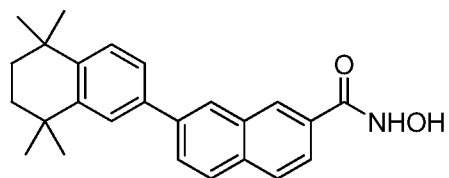


Compound 19



Compound 20

, and



Compound 21



Current Data Parameters  
NAME md\_80\_p64\_recryst  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20131211  
Time 11.51  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
ID 65536  
SOLVENT MeOD  
NS 64  
DS 2  
SWH 8223.685 Hz  
FIDRES 0.125483 Hz  
AQ 3.9845889 sec  
RG 203  
DW 60.800 usec  
DE 6.50 usec  
TE 298.2 K  
D1 1.00000000 sec  
TD0 1

==== CHANNEL f1 =====  
NUC1 1H  
P1 12.75 usec  
PL1 -2.00 dB  
PL1W 12.14226913 W  
SF01 400.1524711 MHz

F2 - Processing parameters  
SI 32768  
SF 400.1500000 MHz  
EM  
WDW 0  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

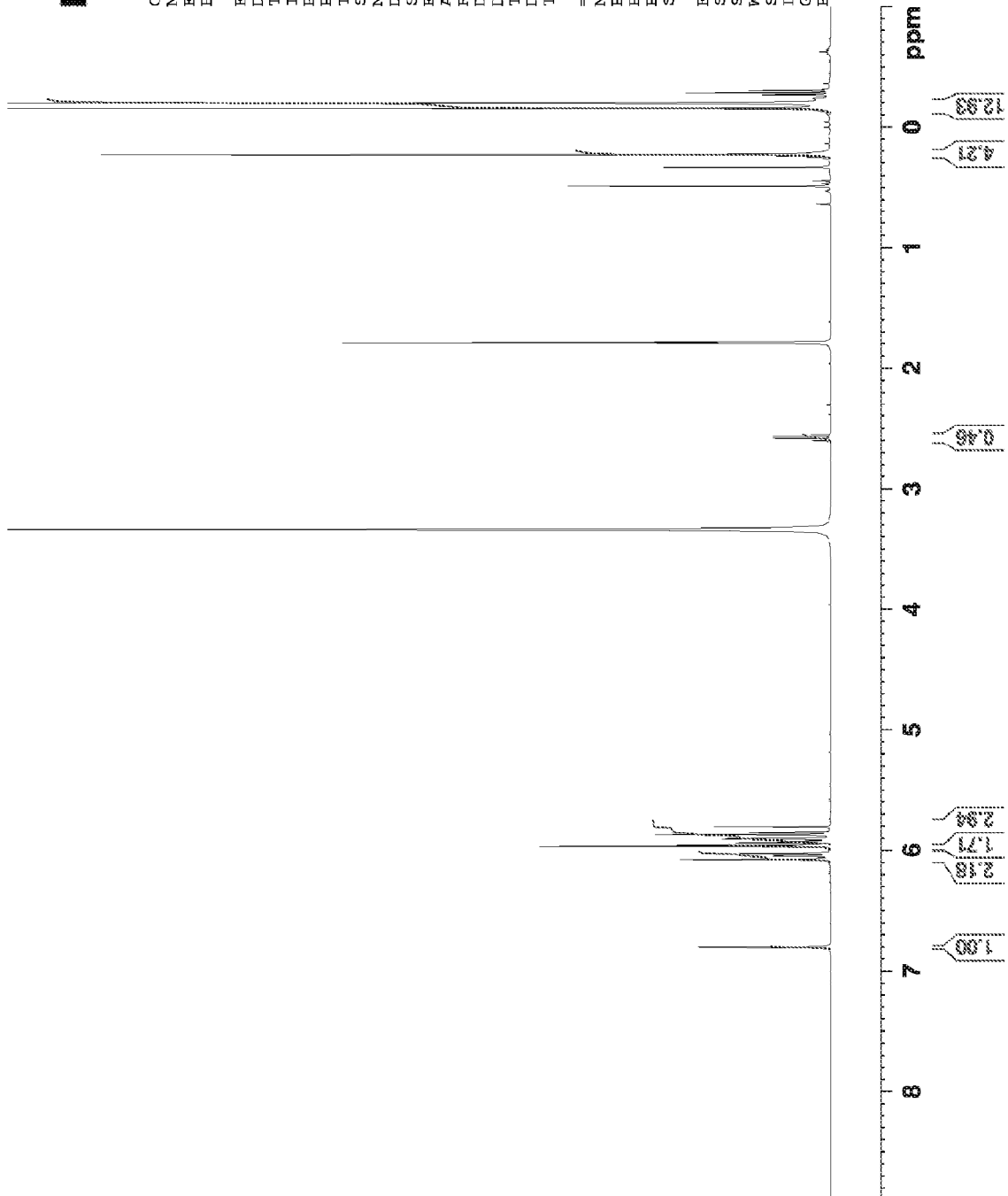


FIGURE 2

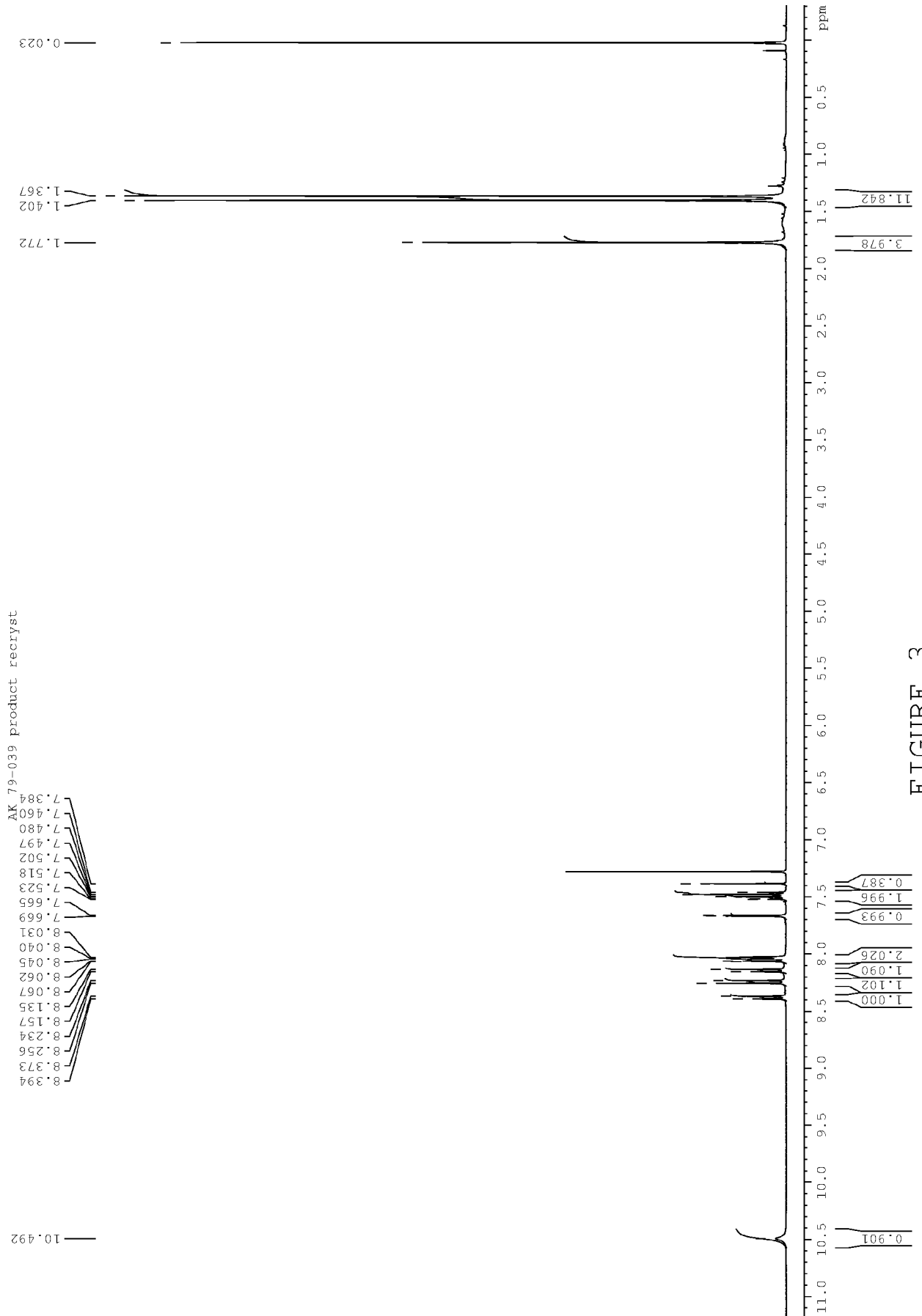


FIGURE 3



Current Data Parameters  
NAME md\_80\_p48  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20131112  
Time\_ 10.20  
INSTRUM SPECT  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
ID 65536  
SOLVENT MeOD  
NS 32  
DS 2  
SWH 8223.685 Hz  
FIDRES 0.125483 Hz  
AQ 3.9845889 sec  
RG 203  
DE 60.800 usec  
TE 6.50 usec  
TD 300.0 K  
D1 1.0000000 sec  
TD0 1

==== CHANNEL f1 =====  
NUC1 1H  
P1 12.75 usec  
PL1 -2.00 dB  
PL1W 12.14226913 W  
SF01 400.1524711 MHz

F2 - Processing parameters  
SI 32768  
SF 400.1500000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

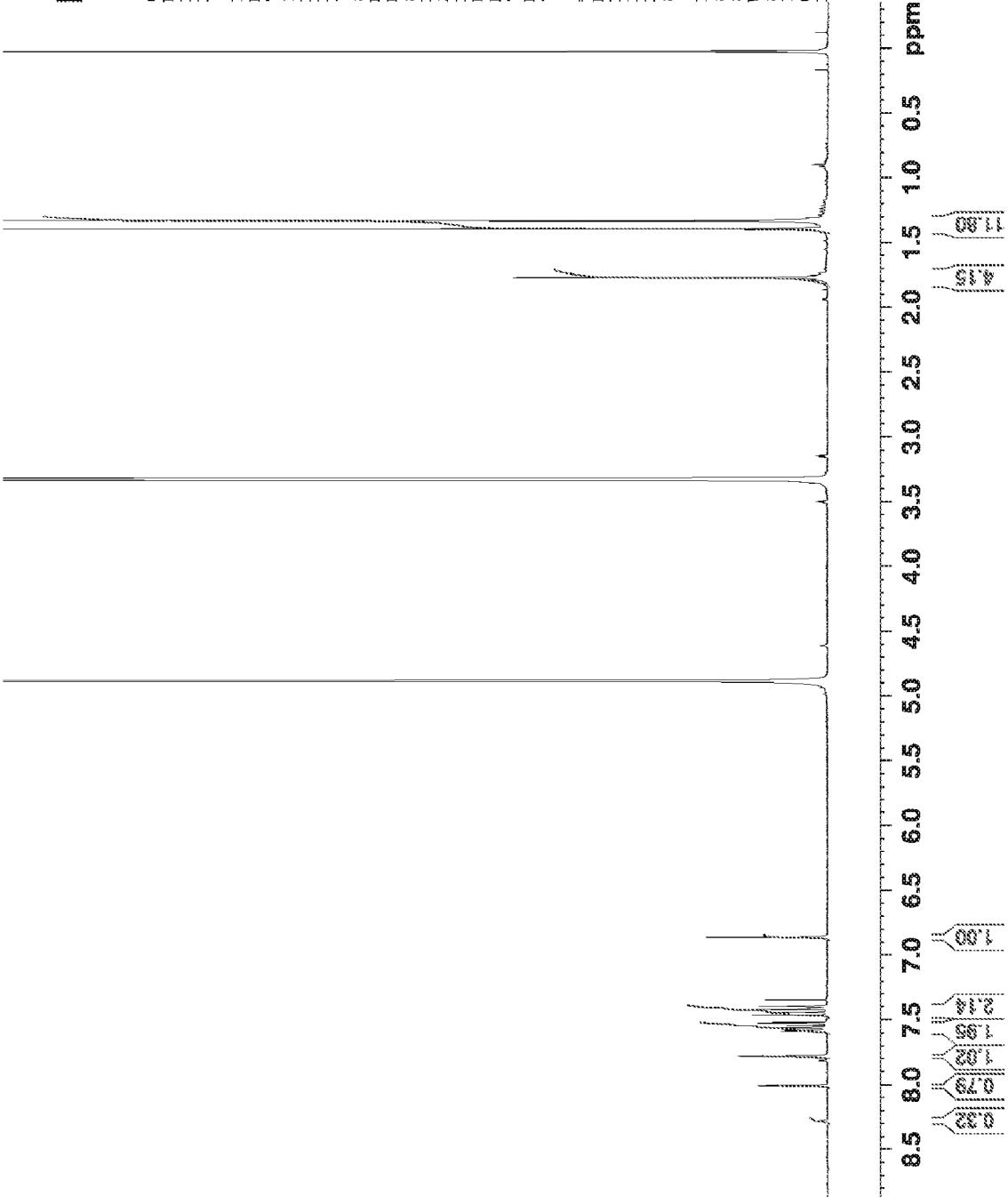
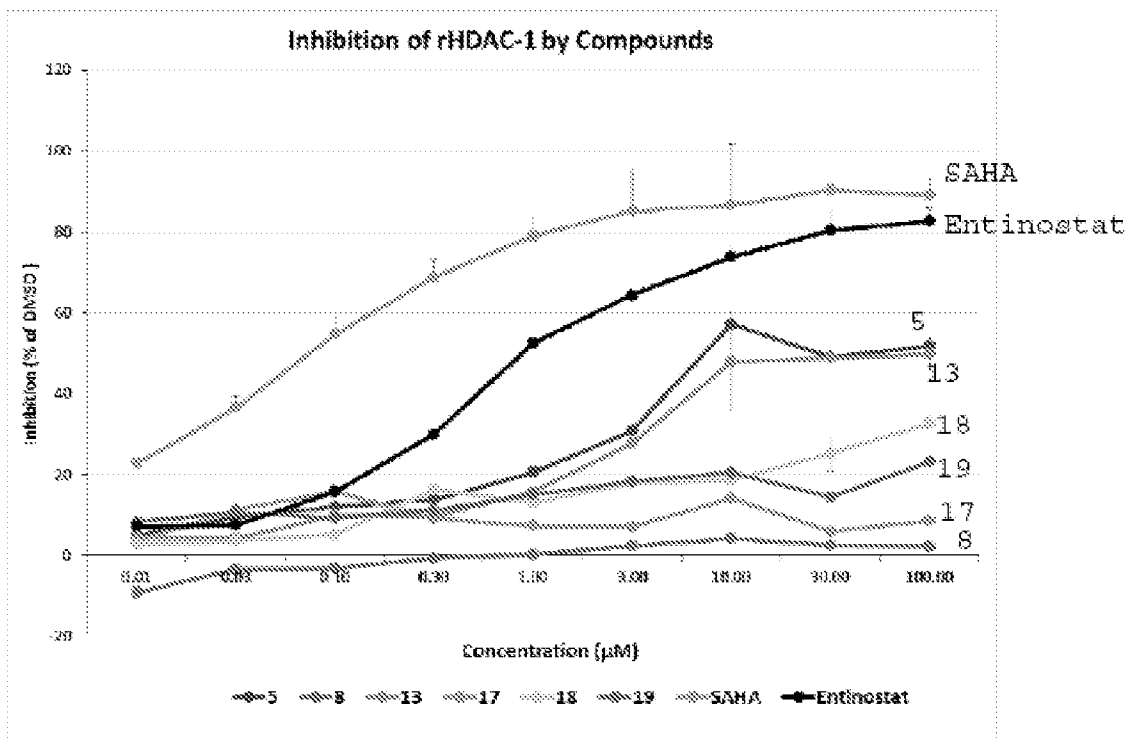


FIGURE 4

Figure 5

A



B

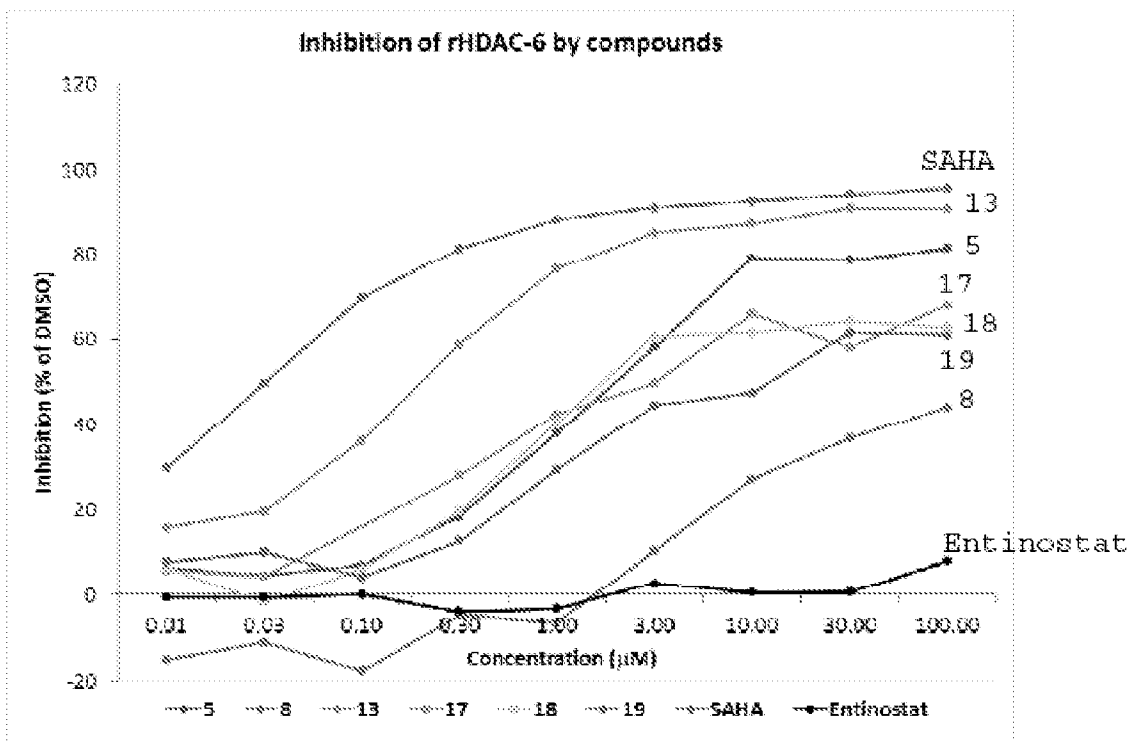
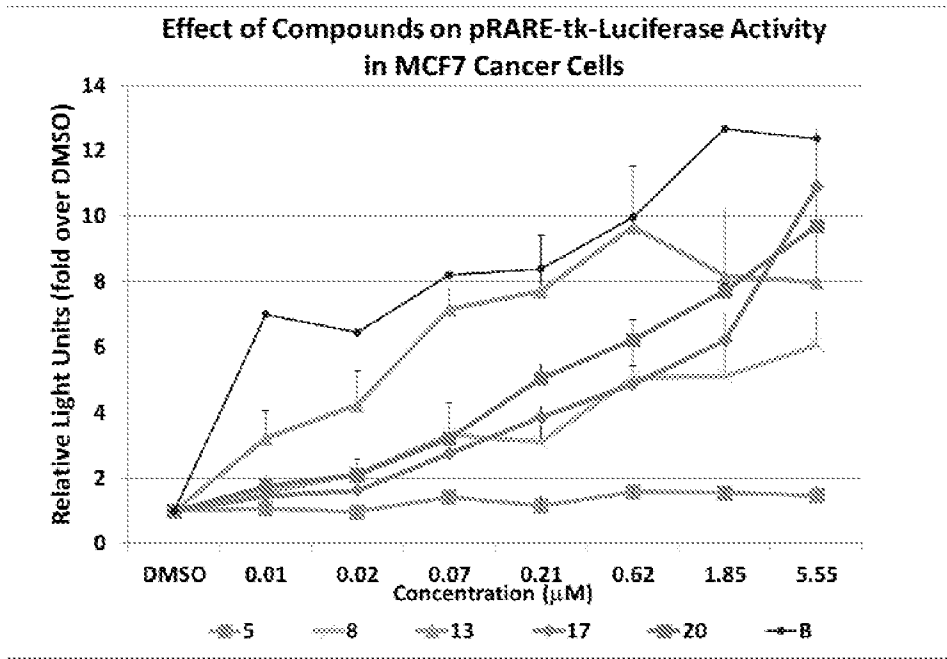


Figure 6

A



B

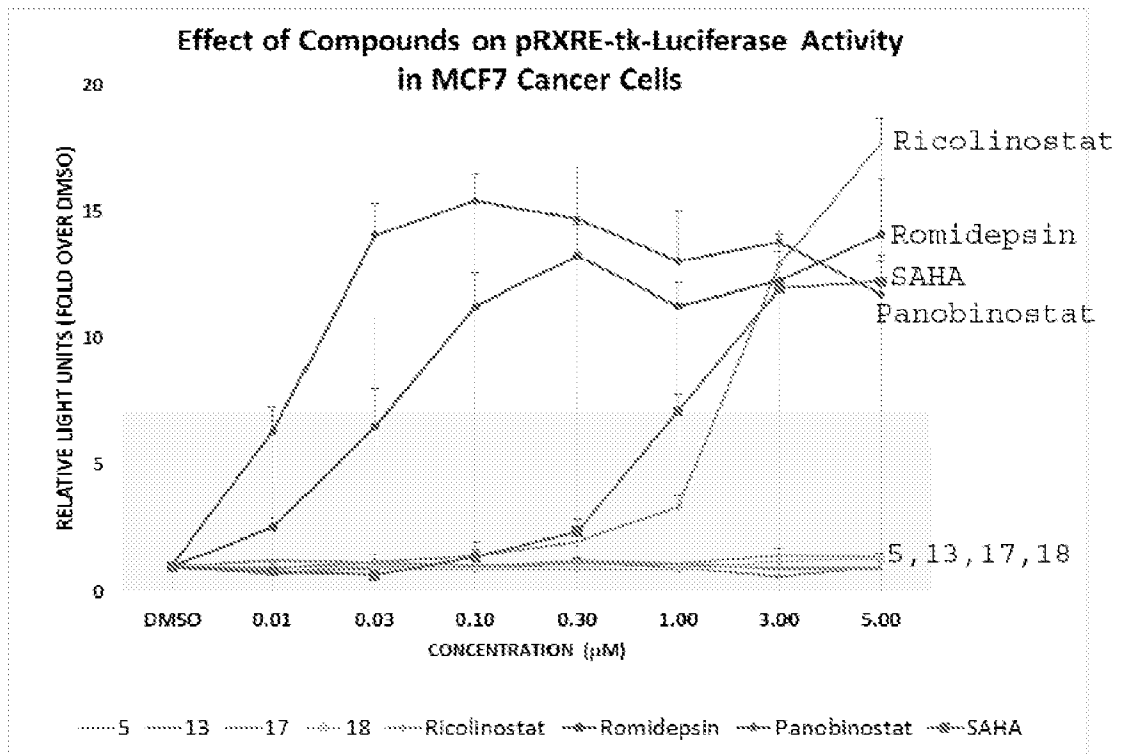
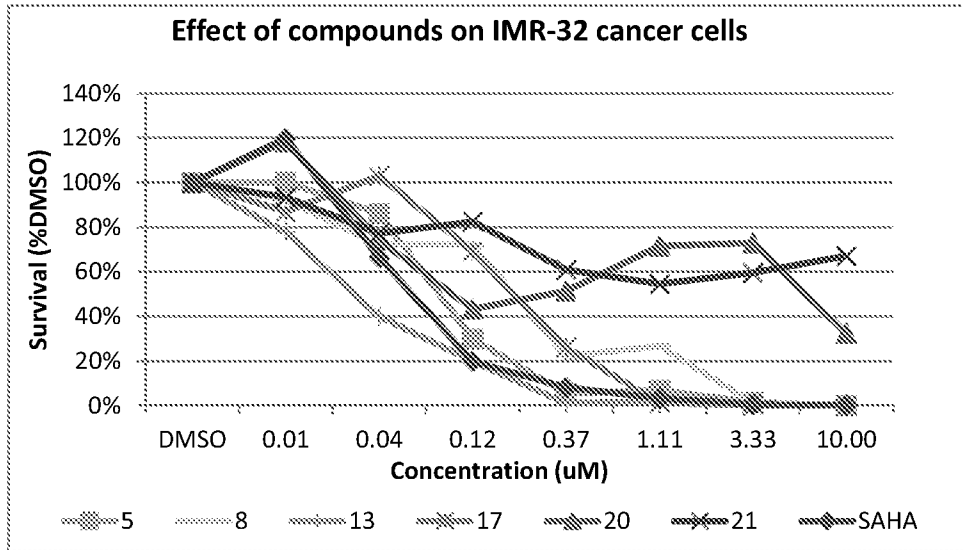


Figure 7

A



B

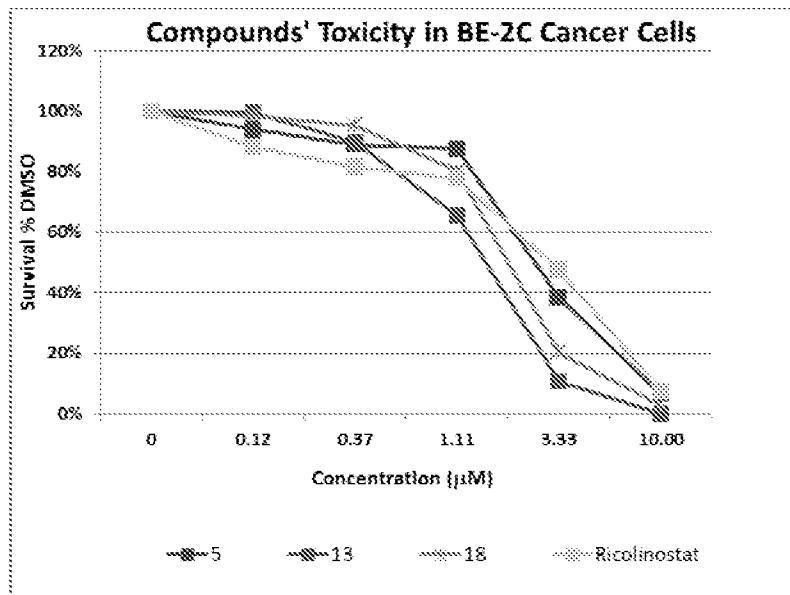


Figure 7 (cont.)

C

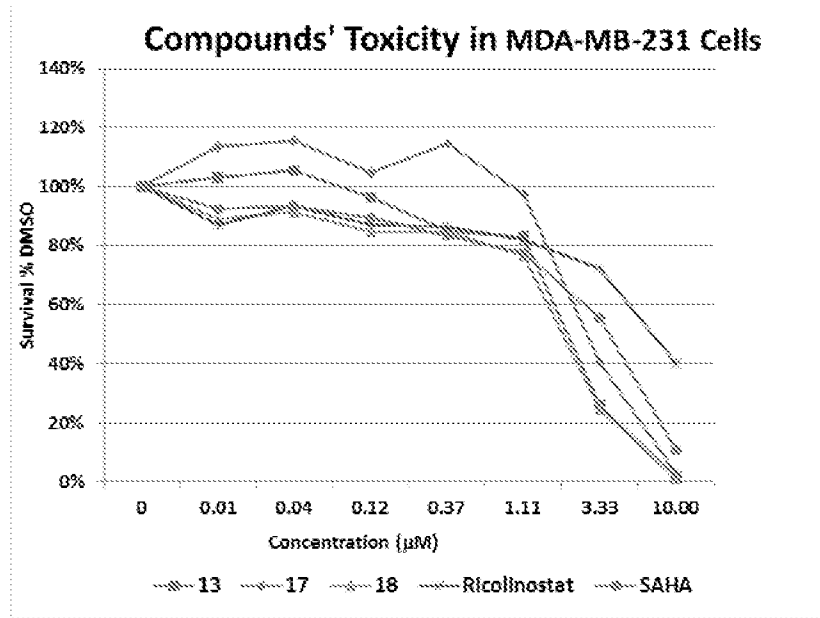


Figure 8

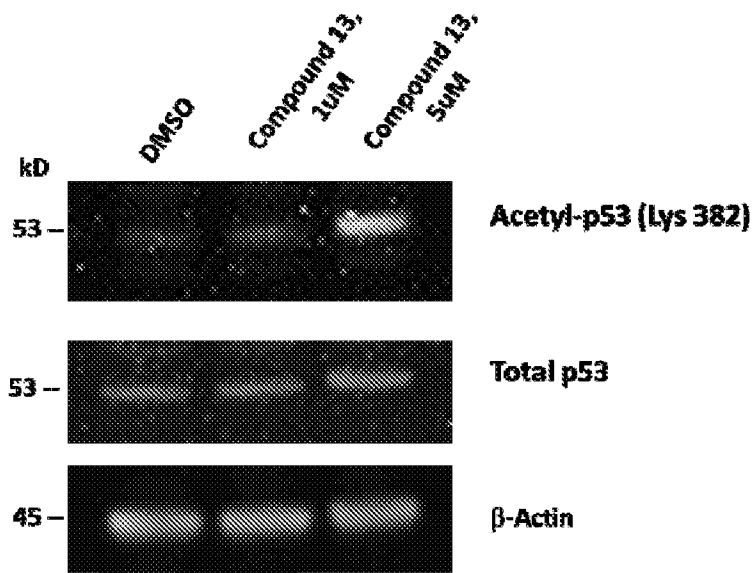


Figure 9

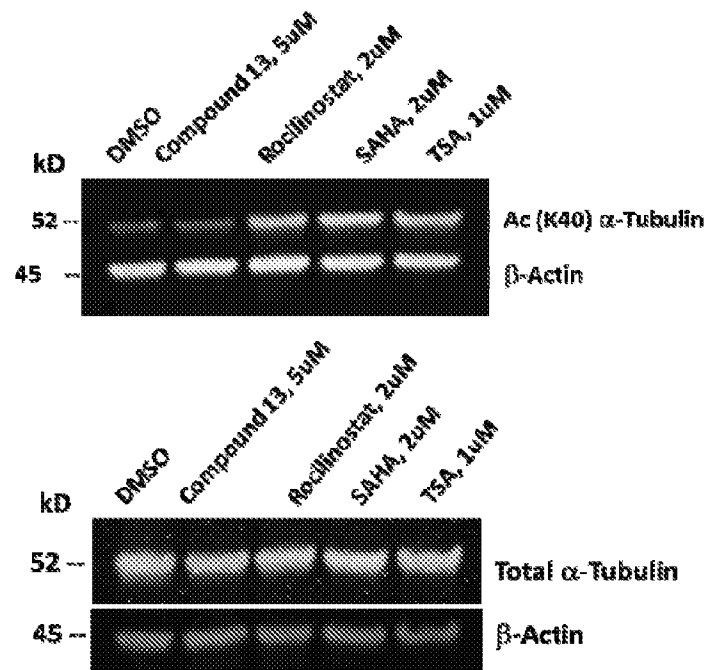


Figure 10

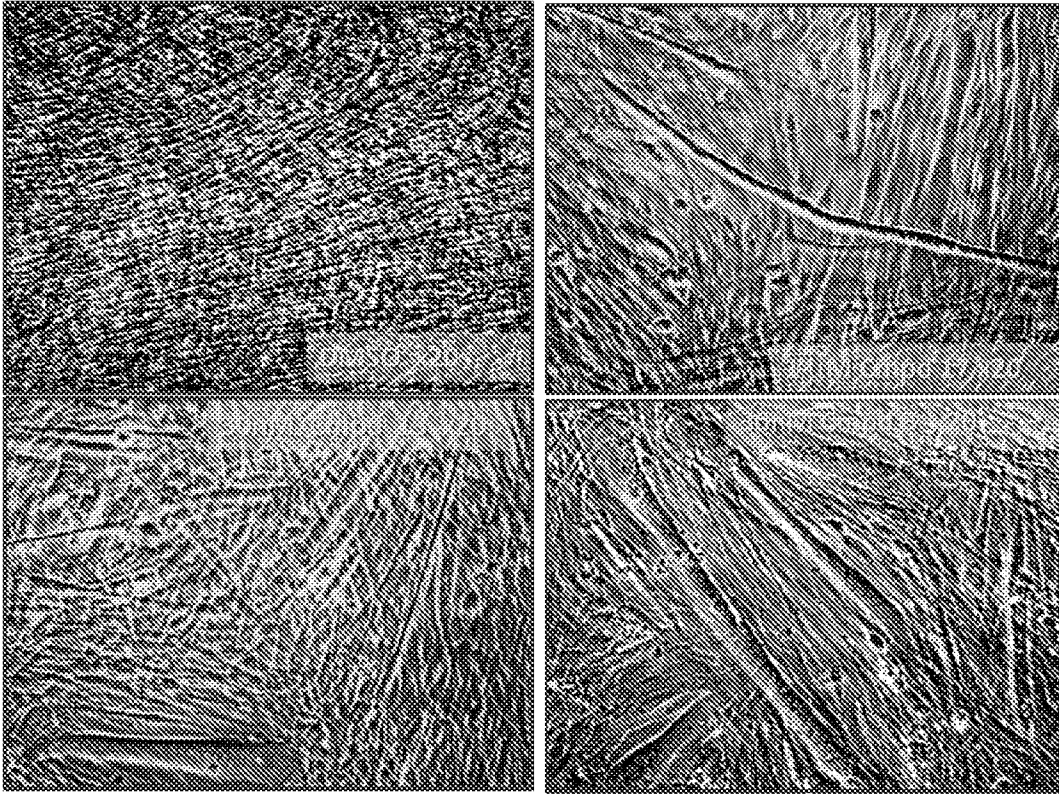
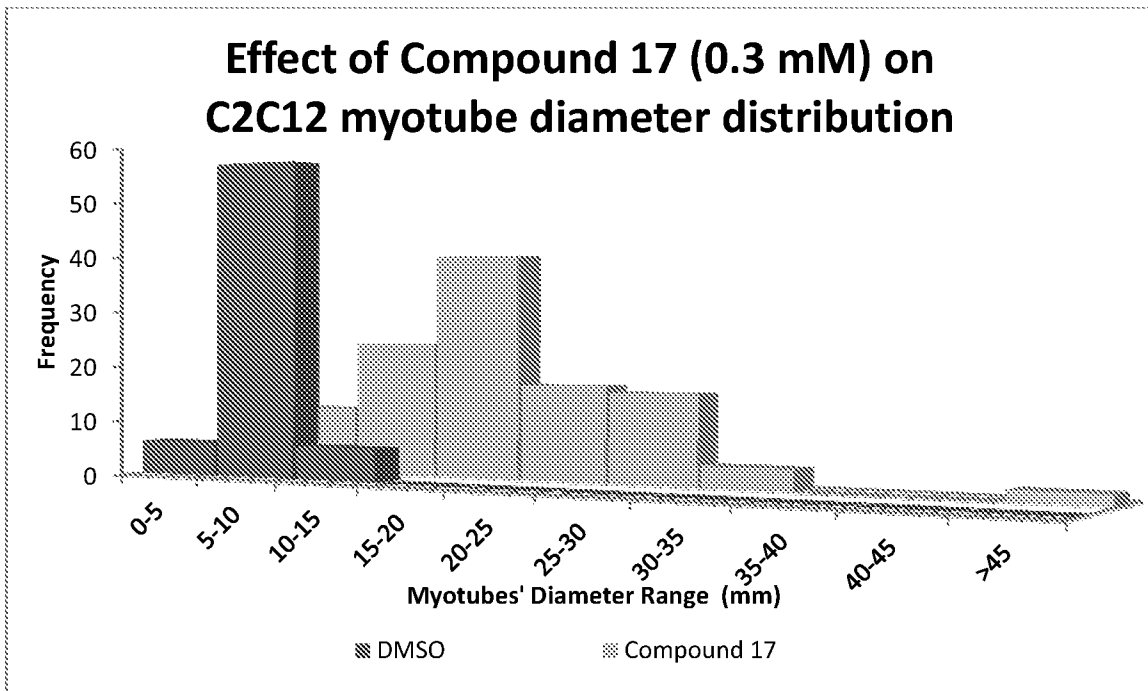


Figure 11



Figure 12

A



B

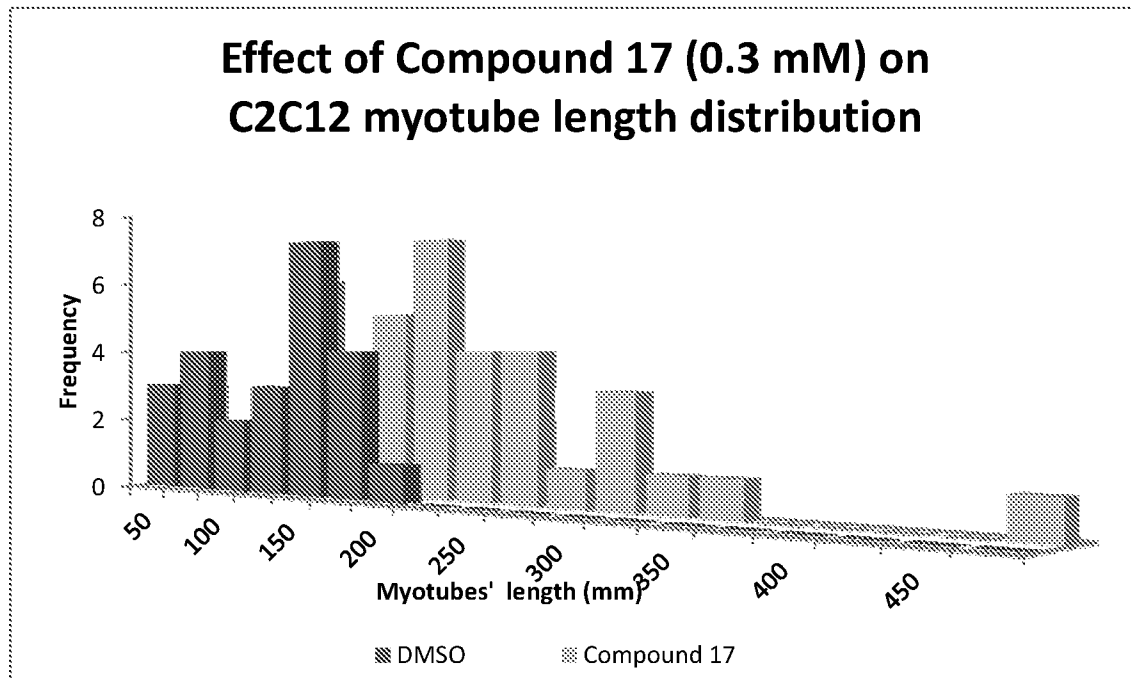


Figure 13

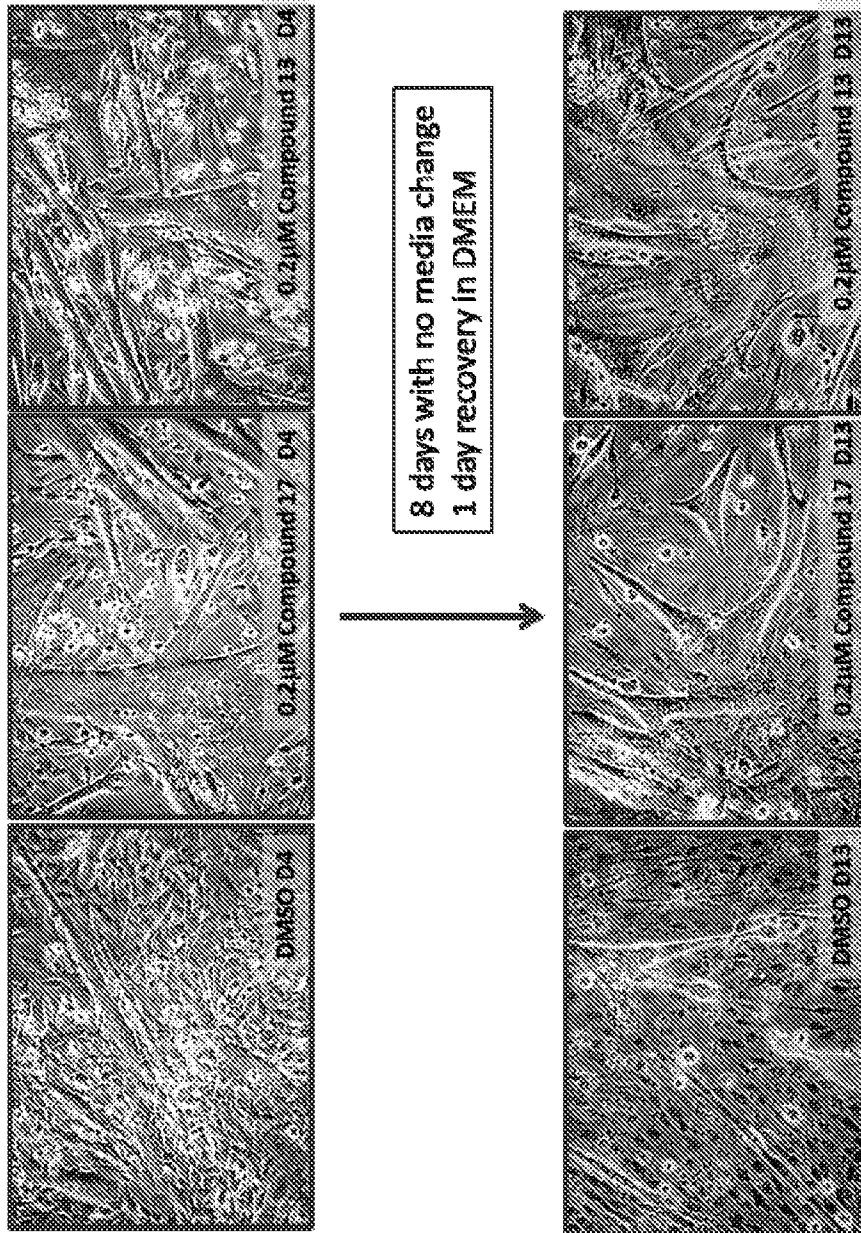
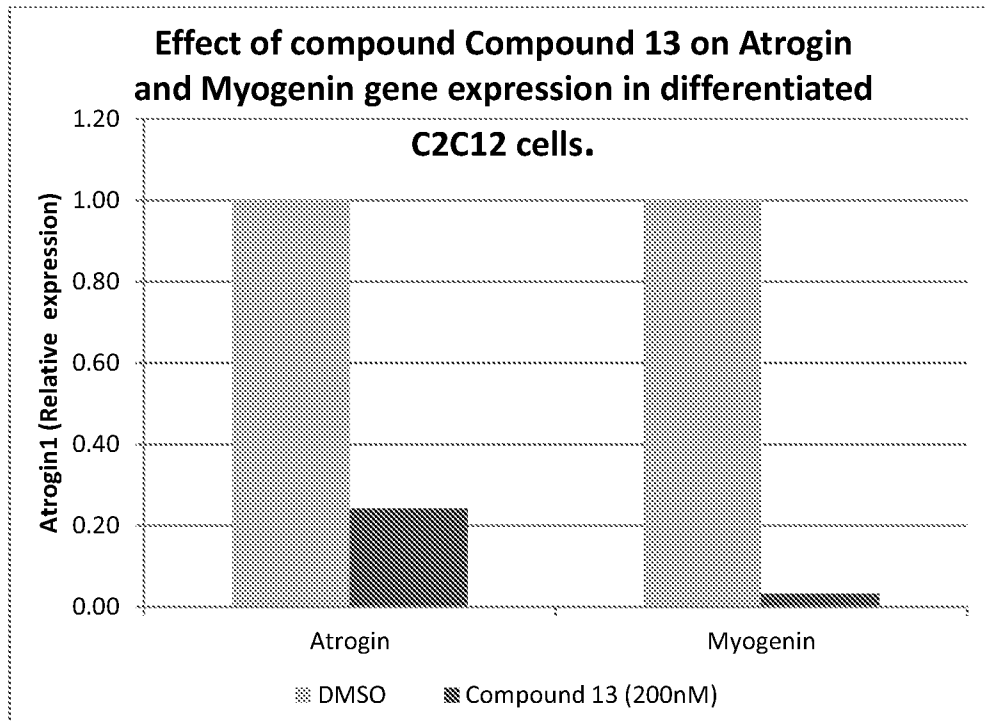


Figure 14

A



B

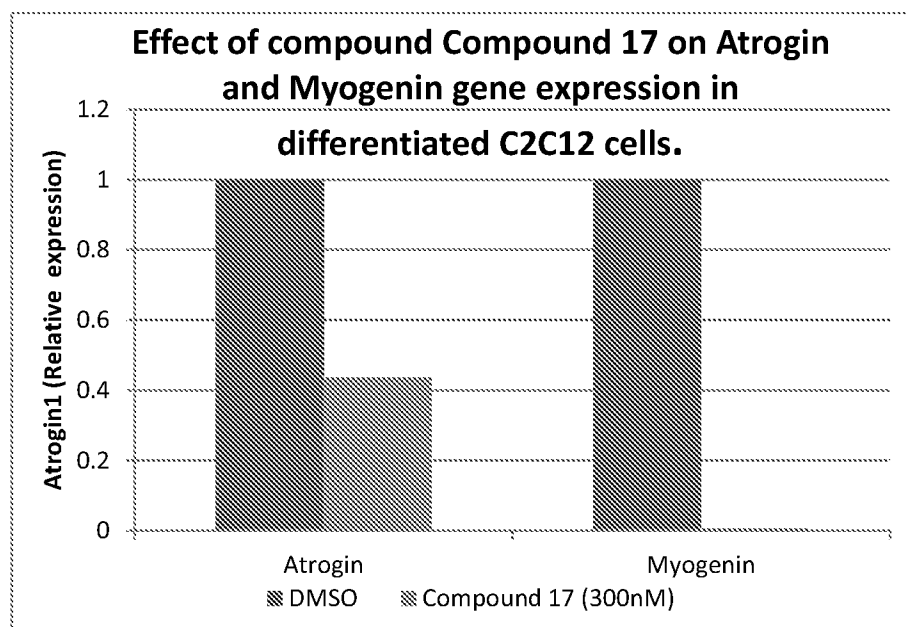
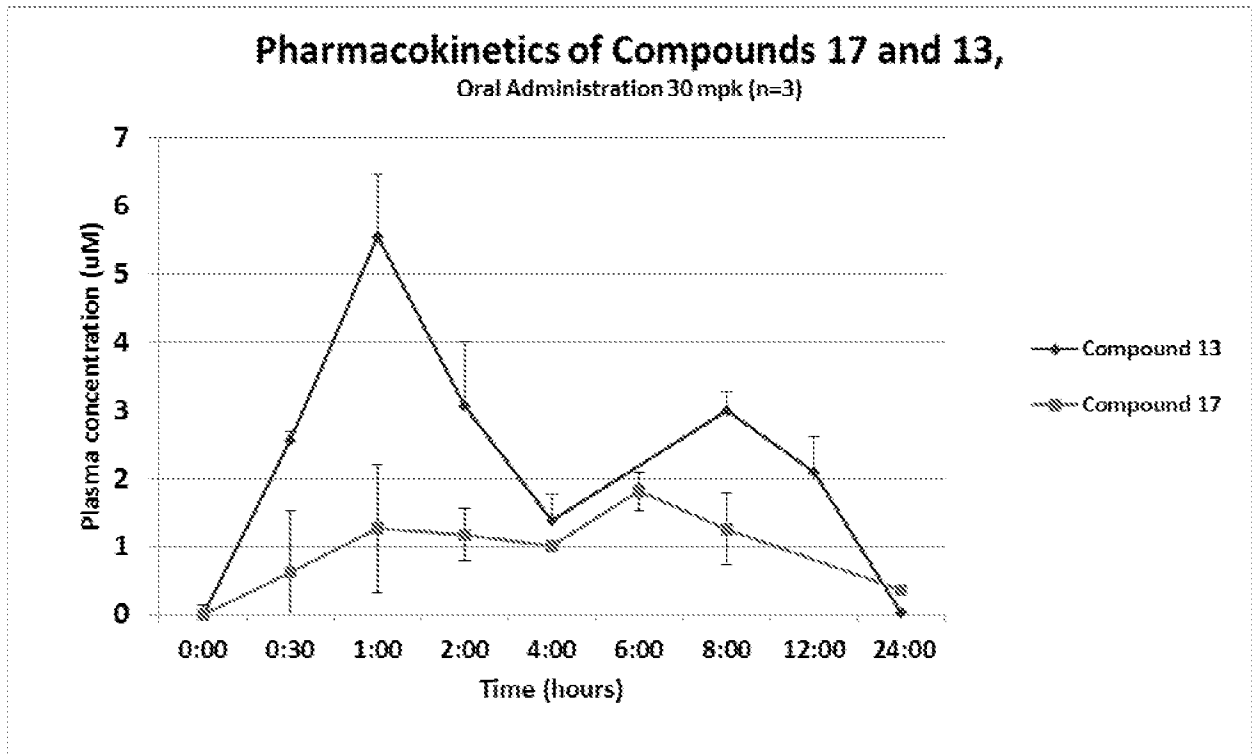


Figure 15



**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US 2015/034303

**A. CLASSIFICATION OF SUBJECT MATTER**

(see extra sheet)

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D 209/04, 409/04, 217/26, C07C 15/24, A61K 31/404, 31/03, A61P 35/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Espacenet, PatSearch, STN Online, USPTO

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0963981 A1 (GALDERMA RESEARCH & DEVELOPMENT, S.N.C.) 15.12.1999, p. 14, example 13, claims	1, 2, 4, 7-10, 14-18
X	DE 3443230 A1 (CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES C.I.R.D.) 05.06.1985, pp. 25-29, examples 1-4, claim 1	1-5, 7-10, 14
X	US 4454341 A1 (SRI INTERNATIONAL) 12.06.1984, col. 7-8, example 1, claim 1	1-5, 7-10, 14
X Y	Database CA [online] DOUGUET, Dominique et al. "Quantitative structure-activity relationship studies of RAR $\alpha$ , $\beta$ , $\gamma$ retinoid agonists." Quantitative Structure-Activity Relationships, 18 (2), 107-123 1999 (abstract) [online] Retrieved from STN, AN: 131:194472; RN 104249-87-8	1-5, 7-10, 14 19-23

Further documents are listed in the continuation of Box C.

See patent family annex.

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

Date of the actual completion of the international search

21 August 2015 (21.08.2015)

Date of mailing of the international search report

10 September 2015 (10.09.2015)

Name and mailing address of the ISA/RU:  
Federal Institute of Industrial Property,  
Berezhkovskaya nab., 30-1, Moscow, G-59,  
GSP-3, Russia, 125993  
Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37

Authorized officer  
  
I. Tumko  
  
Telephone No. (495) 531-64-81

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: 1, 15-23 (all partially)  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Claim 1 refers to an extreme large number of possible compounds due to the huge breadth of radical definitions and a meaningful search over the whole breadth of the claim is impossible. Moreover support and disclosure in the sense of Articles 5 and 6 is to be found for a very small proportion of the compounds claimed. Consequently, the search has been restricted to those claimed compounds, which appear to be supported, i.e. compounds defined in dependent claims 2-14.
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US 2015/034303

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2012/030919 A2 (THOMAS JEFFERSON UNIVERSITY) 08.03.2012, pp. 49-50, example 7, claims	19-23
X	WO 2003/043998 A1 (MAXIA PHARMACEUTICALS. INC.) 30.05.2003, abstract, paragraphs [0008], [0026]-[0027]	1-18

**INTERNATIONAL SEARCH REPORT**  
Classification of subject matter

International application No.

PCT/US 2015/034303

*C07D 209/04 (2006.01)*  
*C07D 409/04 (2006.01)*  
*C07D 217/26 (2006.01)*  
*C07C 15/24 (2006.01)*  
*A61K 31/03 (2006.01)*  
*A61K 31/404 (2006.01)*  
*A61P 35/00 (2006.01)*