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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

(54) Title: METHODS RELATED TO ACTIVATION OF THE BONE MORPHOGENIC PROTEIN SIGNALING PATHWAY

(57) Abstract: In one aspect, compounds and compositions that activate BMP signaling and methods of making and using same are disclosed. The disclosed compounds and compositions can be useful for disorders associated with diminished BMP signaling such as, for example, cancer, juvenile polyposis syndrome, hereditary pulmonary arterial hypertension, obesity osteosporosis, and chronic kidney disease. The disclosed compounds and compositions can also be useful in cartilage repair and bone formation. This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.

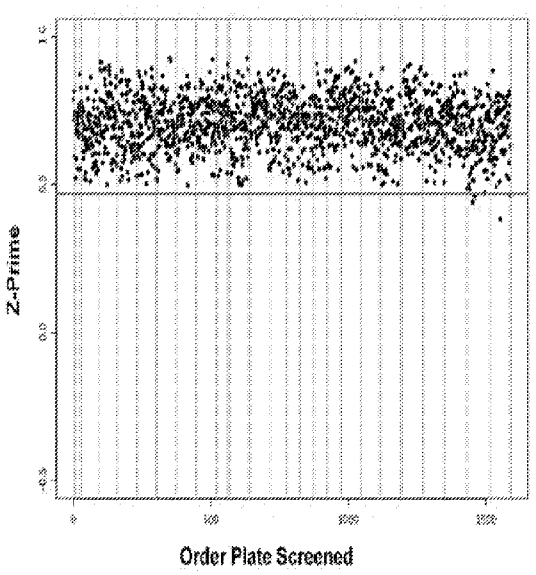


FIG. 1A

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— *with sequence listing part of description (Rule 5.2(a))*

METHODS RELATED TO ACTIVATION OF THE BONE MORPHOGENIC PROTEIN SIGNALING PATHWAY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/525,598, filed on June 27, 2017, which is incorporated herein fully by reference in its entirety.

REFERENCE TO SEQUENCE LISTING

[0002] The Sequence Listing submitted June 20, 2018 as a text file named "19116_0030P1_ST25.txt," created on June 19, 2018, and having a size of 1,696 bytes is hereby incorporated by reference pursuant to 37 C.F.R. § 1.52(e)(5).

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0003] This invention was made with government support under grant number CA096832 (MFR), awarded by the National Cancer Institute (NCI). The government has certain rights in the invention.

BACKGROUND

[0004] Bone Morphogenetic Proteins (BMPs) are members of the Transforming Growth Factor Beta (TGFβ) family of secreted signaling molecules, which also includes Activin and Nodal. BMPs were originally described as molecules that induce bone and cartilage formation (Wozney et al. (1988) *Science* **242**: 1528-1534) and are widely conserved across phyla with family members found in vertebrates, arthropods and nematodes (von Bubnoff and Cho (2001) *Dev. Biol.* **239**: 1-14). BMP signaling governs diverse biological processes including embryonic patterning and development (von Bubnoff and Cho (2001) *Dev. Biol.* **239**: 1-14; Raftery and Sutherland (1999) *Dev. Biol.* **210**: 251-268; Wang et al. (2014) *Genes Dis.* **1**: 87-105), stem cell renewal and differentiation (Wang et al. (2014) *Genes Dis.* **1**: 87-105; Morikawa et al. (2016) *Stem Cell Reports* **6**: 64-73), tissue homeostasis (Wang et al. (2014) *Genes Dis.* **1**: 87-105; Aubin and Soriano (2004) *Genes Dev.* **18**: 1482-1494), and bone development (Wang et al. (2014) *Genes Dis.* **1**: 87-105). The twelve BMP family members form homo- and heterodimers that bind to type I and type II serine-threonine kinase

transmembrane receptors (Koenig et al. (1994) *Mol. Cell Biol.* **14**: 5961-5974; ten Dijke et al. (1994) *J. Biol. Chem.* **269**: 16985-16988). BMP-2 and BMP-4 bind with high affinity to the type I receptors BMPR-IA (ALK3) or BMPR-IB (ALK6) receptors, while TGFβ and activins bind to the type IA activin receptor (ALK2) (Koenig et al. (1994) *Mol. Cell Biol.* **14**: 5961-5974; ten Dijke et al. (1994) *J. Biol. Chem.* **269**: 16985-16988). BMP-2 and BMP-4 binding induces the formation of a heterotetrameric complex composed of two BMPR-IA and/or BMPR-IB receptors and two BMPR-II receptors. In turn, constitutively activated BMPR-II trans-phosphorylates BMPR-IA activating its serine-threonine kinase activity (Moustakas and Heldin (2002) *Genes Dev.* **16**: 1867-1871). The activated heterotetrameric complex recruits intracellular signal transduction proteins of the Similar to Mothers Against Decapentaplegic (SMAD) family, SMAD1, SMAD5, and SMAD8, which are phosphorylated at the C-terminus (Chen et al. (1997) *Proc. Natl. Acad. Sci. USA* **94**: 12938-12943; Hoodless et al. (1996) *Cell* **85**: 489-500). Phospho-SMAD1/5/8s interact with SMAD4 and translocate to the nucleus where they activate transcription of target genes such as *Inhibitor of DNA Binding 1* (*ID1*) and *ID2* (Peng et al. (2004) *J. Biol.Chem.* **279**: 32941-32949).

[0005] Medulloblastoma is the most common malignant pediatric tumor that occurs in the cerebellum. It is divided into 4 subgroups, one of which displays constitutively activated Sonic Hedgehog (SHH) signaling (Pinho et al. (2011) *J. Pediatr. Hematol. Oncol.***33**: 605-609; Thompson et al. (2006) *J. Clin. Oncol.* **24**: 1924-1931; Kieran et al. (2010) *J. Clin. Oncol.* **28**: 4783-4789). BMP-2 and BMP-4 antagonize SHH (Rios et al. (2004) *Development* **131**: 3159-3168), and BMP-4 signaling induces irreversible differentiation of cerebellar granule neuronal progenitors and tumor cells from the SHH medulloblastoma subgroup (Zhao et al. (2008) *Gene Dev.* **22**: 722-727). This finding suggested that BMP agonists might be useful as a differentiation therapy for this pediatric cerebellar tumor. Because BMP homodimers do not cross the blood brain barrier, their use as a potential therapy for medulloblastoma is not an option.

[0006] Although agonists of BMP signaling have been previously identified, the effects of these compounds are modest at best. Rapamycin, a mTOR inhibitor, causes upregulation of BMP2 that promotes osteoblastic differentiation (Lee et al. (2010) *Stem Cells Dev* **19**: 557-568). Spiekerkoetter et al. identified an activator of BMPR2, FK506 (tacrolimus), using a low-throughput compound screen (Spiekerkoetter et al. (2013) *J Clin Invest* **123**: 3600-3613).

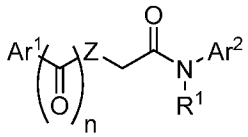
Isoliquiritigenin (SJ000286237) was previously identified as an agonist of BMP signaling (Vrijens et al. (2013) *PLoS One* **8**: e59045); however, this chalcone scaffold raised concerns for further chemical optimization since it is from a pan assay interference compound (PAINS) class (Baell and Holloway (2010) *J Med Chem***53**: 2719-2740).

[0007] Despite the key role of BMP signaling in significant biological process including embryonic development and stem cell differentiation, small molecules that target this pathway have remained elusive. Accordingly, there remains a need for small molecule activators of the BMP signaling pathway and methods of making and using same.

SUMMARY

[0008] In accordance with the purpose(s) of the invention, as embodied and broadly described herein, the invention, in one aspect, relates to compositions and methods for use in the prevention and treatment of disorders associated with diminished BMP signaling such as, for example, cancer, juvenile polyposis syndrome, hereditary pulmonary arterial hypertension, obesity osteoporosis, and chronic kidney disease. In a further aspect, the invention relates to compositions and methods for use in cartilage repair or bone formation.

[0009] Disclosed are methods of treating a disorder associated with diminished BMP signaling in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula:

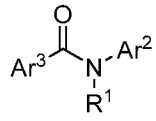


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wherein n is selected from 0 and 1; wherein Z is selected from O, CH_2, and NR^2; wherein R^2 is selected from hydrogen and C1-C4 alkyl; wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4

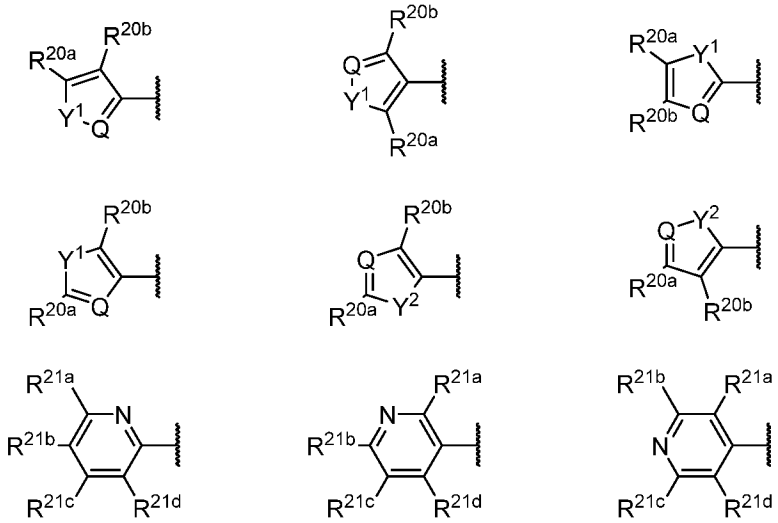
haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl); or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with diminished BMP signaling.

[0010] Also disclosed are methods of treating a disorder associated with diminished BMP signaling in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula:



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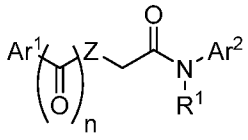
wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl); and wherein Ar^3 is a 5- or 6-membered heteroaryl selected from:



wherein Q, when present, is selected from $CR^{30a}R^{30b}$ and NR^{31}; wherein each of R^{30a}, R^{30b}, and R^{31}, when present, is independently selected from hydrogen and C1-C4 alkyl; wherein Y^1, when present, is selected from O, S, and NR^{31}; wherein Y^2, when present, is selected from O and NR^{31}; wherein each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently

selected from hydrogen, halogen, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl; or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with diminished BMP signaling.

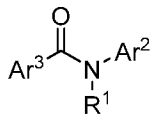
[0011] Also disclosed are methods of activating the BMP signaling pathway in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula:



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wherein n is selected from 0 and 1; wherein Z is selected from O, CH_2, and NR^2; wherein R^2 is selected from hydrogen and C1-C4 alkyl; wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and $–CO_2$(C1-C4 alkyl); wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and $–CO_2$(C1-C4 alkyl); or a pharmaceutically acceptable salt thereof, thereby activating the bone morphogenic pathway in a subject.

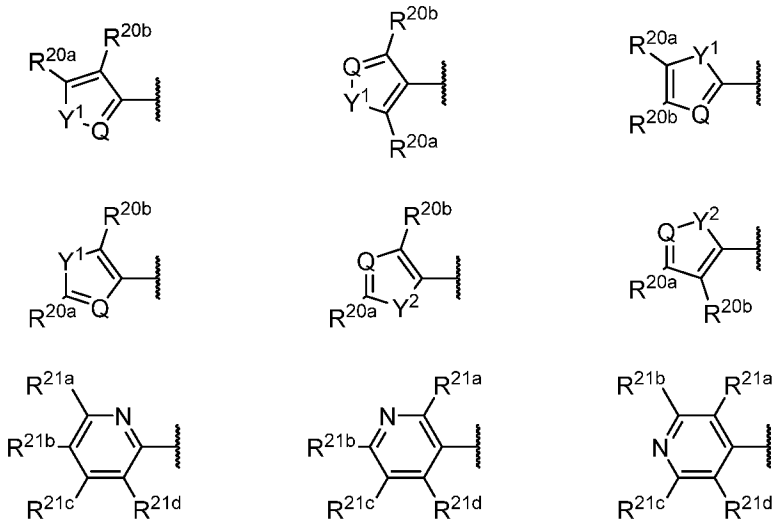
[0012] Also disclosed are methods of activating the BMP signaling pathway in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula:



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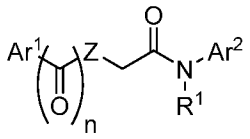
wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4)

dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl); and wherein Ar^3 is a 5- or 6-membered heteroaryl selected from:



wherein Q, when present, is selected from $CR^{30a}R^{30b}$ and NR^{31}; wherein each of R^{30a}, R^{30b}, and R^{31}, when present, is independently selected from hydrogen and C1-C4 alkyl; wherein Y^1, when present, is selected from O, S, and NR^{31}; wherein Y^2, when present, is selected from O and NR^{31}; wherein each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl; or a pharmaceutically acceptable salt thereof, thereby activating the bone morphogenic pathway in a subject.

[0013] Also disclosed are methods of activating the bone morphogenic pathway (BMP) in at least one cell, the method comprising the step of contacting at least one cell with an effective amount of at least one compound having a structure represented by a formula:

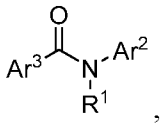


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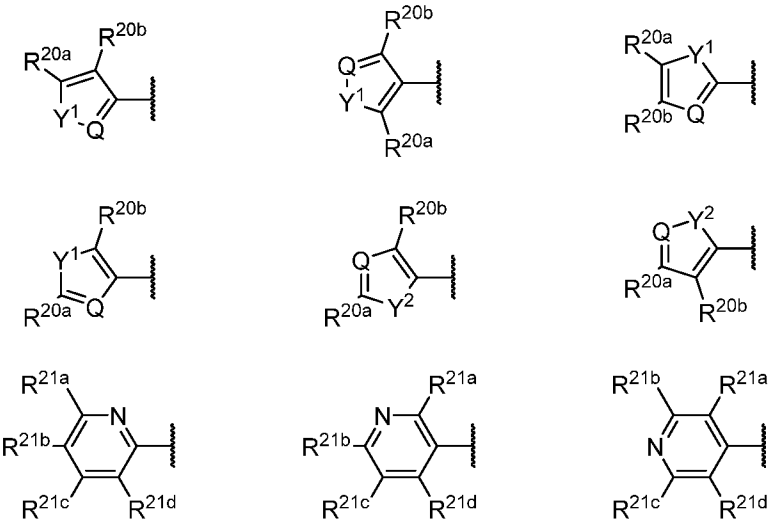
wherein n is selected from 0 and 1; wherein Z is selected from O, CH_2, and NR^2; wherein R^2 is selected from hydrogen and C1-C4 alkyl; wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4

haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and $-CO_2$(C1-C4 alkyl); wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and $-CO_2$(C1-C4 alkyl); or a pharmaceutically acceptable salt thereof, thereby activating the bone morphogenic pathway in at least one cell.

[0014] Also disclosed are methods of activating the bone morphogenic pathway (BMP) in at least one cell, the method comprising the step of contacting at least one cell with an effective amount of at least one compound having a structure represented by a formula:

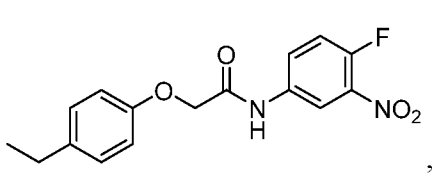


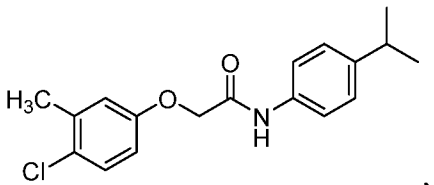
wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl); and wherein Ar^3 is a 5- or 6-membered heteroaryl selected from:

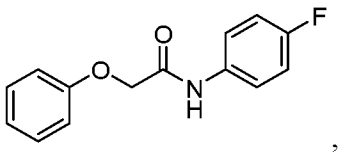


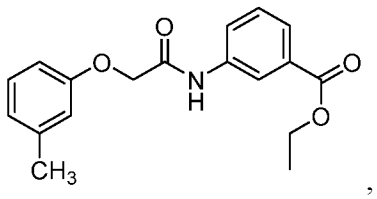
wherein Q, when present, is selected from $CR^{30a}R^{30b}$ and NR^{31}; wherein each of R^{30a}, R^{30b}, and R^{31}, when present, is independently selected from hydrogen and C1-C4 alkyl; wherein Y^1, when present, is selected from O, S, and NR^{31}; wherein Y^2, when present, is selected from O and NR^{31}; wherein each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl; or a pharmaceutically acceptable salt thereof, thereby activating the bone morphogenic pathway in at least one cell.

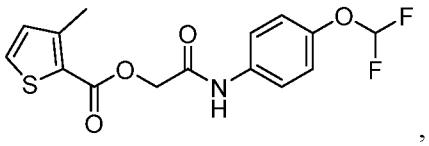
[0015] Also disclosed are pharmaceutical compositions comprising pharmaceutical composition comprising an effective amount of a compound having a structure selected from:

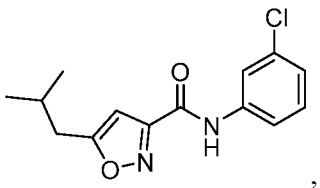

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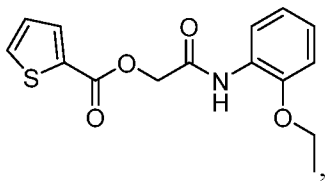

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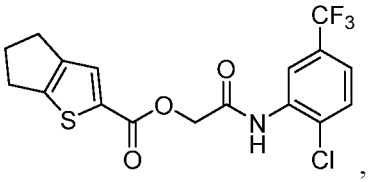

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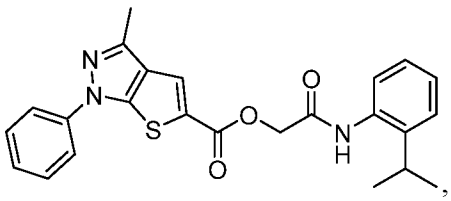

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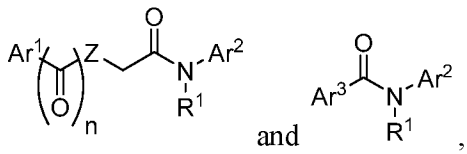

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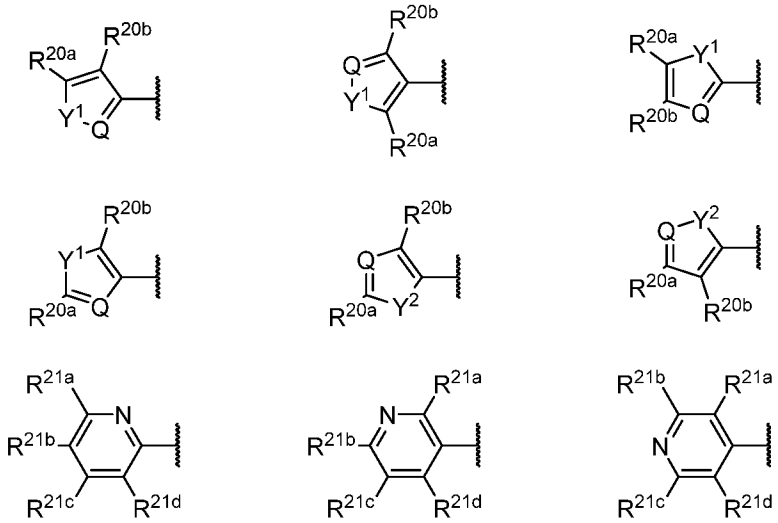

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or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

[0016] Also disclosed are kits comprising an effective amount of a compound having a structure represented by a formula selected from:



wherein n is selected from 0 and 1; wherein Z is selected from O, CH_2, and NR^2; wherein R^2 is selected from hydrogen and C1-C4 alkyl; wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl); wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl); and wherein Ar^3 is a 5- or 6-membered heteroaryl selected from:



wherein Q, when present, is selected from $CR^{30a}R^{30b}$ and NR^{31}; wherein each of R^{30a}, R^{30b}, and R^{31}, when present, is independently selected from hydrogen and C1-C4 alkyl; wherein Y^1, when present, is selected from O, S, and NR^{31}; wherein Y^2, when present, is selected from O and NR^{31}; and wherein each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently

selected from hydrogen, halogen, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl; or a pharmaceutically acceptable salt thereof, and one or more of: (a) at least one agent known to treat a disorder associated with diminished BMP signaling; (b) at least one agent known to diminish the BMP signaling pathway; and (c) instructions for treating a disorder associated with diminished BMP signaling.

[0017] Also disclosed are uses of a disclosed compound in cartilage repair or bone formation.

[0018] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several aspects and together with the description serve to explain the principles of the invention.

[0020] **FIG. 1A** and **FIG. 1B** show a representative summary of the high-throughput screening (HTS assay).

[0021] **FIG. 2** shows a representative summary of the high-throughput screen and hit identification.

[0022] **FIG. 3** shows a representative screening cascade for the discovery of small molecule activators of the BMP signaling pathway.

[0023] FIG. 4 shows a representative structure activity relationship (SAR) study using cScore, EC_{50}, and zebrafish phenotypic screen.

[0024] FIG. 5A-C show representative dose-response curves of the three lead compounds in ventralization of zebrafish embryos.

[0025] FIG. 6 show representative images of dose-response of leflunomide and teriflunomide on zebrafish.

[0026] FIG. 7A-G show representative data pertaining to the expression of BMP target genes in gastrula stage embryos.

[0027] FIG. 8A-I show representative data pertaining to activation of the canonical BMP signaling pathway.

[0028] FIG. 9A-C show representative full gel images corresponding to FIG. 8A-I.

[0029] FIG. 10A-I show representative data pertaining to the detection of p-SMAD1/5/8 with serum-free treatment.

[0030] FIG. 11A-C show representative data pertaining to the detection of ERK1/2 and phosphorylated ERK2 (pERK) by immunoblotting.

[0031] FIG. 12A-C show representative data pertaining to the detection of phosphorylated SMAD2 by immunoblotting.

[0032] FIG. 13A-J show representative data pertaining to differentiation of myoblastic C2C12 cells to osteoblasts.

[0033] FIG. 14A-F show representative data pertaining to transcriptional profiling by Affymetrix assay.

[0034] FIG. 15A-F show a representative regression analysis comparing low (10 ng; **15A**, **15C**, and **15E**) or high dose (300 ng; **15B**, **15D**, and **15F**) of BMP4 to 25 μM of compounds 1-3, respectively.

[0035] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION

[0036] The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples included therein.

[0037] Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

[0038] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

[0039] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application

in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein may be different from the actual publication dates, which can require independent confirmation.

A. DEFINITIONS

[0040] As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a functional group," "an alkyl," or "a residue" includes mixtures of two or more such functional groups, alkyls, or residues, and the like.

[0041] As used in the specification and in the claims, the term "comprising" can include the aspects "consisting of" and "consisting essentially of."

[0042] Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0043] As used herein, the terms "about" and "at or about" mean that the amount or value in question can be the value designated some other value approximately or about the same. It is generally understood, as used herein, that it is the nominal value indicated ±10% variation unless otherwise indicated or inferred. The term is intended to convey that similar values promote equivalent results or effects recited in the claims. That is, it is understood that

amounts, sizes, formulations, parameters, and other quantities and characteristics are not and need not be exact, but can be approximate and/or larger or smaller, as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art. In general, an amount, size, formulation, parameter or other quantity or characteristic is "about" or "approximate" whether or not expressly stated to be such. It is understood that where "about" is used before a quantitative value, the parameter also includes the specific quantitative value itself, unless specifically stated otherwise.

[0044] References in the specification and concluding claims to parts by weight of a particular element or component in a composition denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

[0045] A weight percent (wt. %) of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the component is included.

[0046] As used herein, "IC_{50}," is intended to refer to the concentration of a substance (*e.g.*, a compound or a drug) that is required for 50% inhibition of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an IC_{50} can refer to the concentration of a substance that is required for 50% inhibition *in vivo*, as further defined elsewhere herein. In a further aspect, IC_{50} refers to the half maximal (50%) inhibitory concentration (IC) of a substance.

[0047] As used herein, "EC_{50}," is intended to refer to the concentration of a substance (*e.g.*, a compound or a drug) that is required for 50% agonism of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an EC_{50} can refer to the concentration of a substance that is required for 50% agonism *in vivo*, as further defined elsewhere herein. In a further aspect, EC_{50} refers to the concentration of agonist that provokes a response halfway between the baseline and maximum response.

[0048] As used herein, the terms "optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0049] As used herein, the term "subject" can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. In one aspect, the subject is a mammal. A patient refers to a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects.

[0050] As used herein, the term "treatment" refers to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder. In various aspects, the term covers any treatment of a subject, including a mammal (*e.g.*, a human), and includes: (i) preventing the disease from occurring in a subject that can be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease, *i.e.*, arresting its development; or (iii) relieving the disease, *i.e.*, causing regression of the disease. In one aspect, the subject is a mammal such as a primate, and, in a further aspect, the subject is a human. The term "subject" also includes domesticated animals (*e.g.*, cats, dogs, etc.), livestock (*e.g.*, cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (*e.g.*, mouse, rabbit, rat, guinea pig, fruit fly, etc.).

[0051] As used herein, the term "prevent" or "preventing" refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action. It is understood that where reduce, inhibit or prevent are used herein, unless specifically indicated otherwise, the use of the other two words is also expressly disclosed.

[0052] As used herein, the term "diagnosed" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by the compounds, compositions, or methods disclosed herein.

[0053] As used herein, the terms "administering" and "administration" refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[0054] As used herein, the terms "effective amount" and "amount effective" refer to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a "therapeutically effective amount" refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at

levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In further various aspects, a preparation can be administered in a "prophylactically effective amount"; that is, an amount effective for prevention of a disease or condition.

[0055] As used herein, "dosage form" means a pharmacologically active material in a medium, carrier, vehicle, or device suitable for administration to a subject. A dosage forms can comprise inventive a disclosed compound, a product of a disclosed method of making, or a salt, solvate, or polymorph thereof, in combination with a pharmaceutically acceptable excipient, such as a preservative, buffer, saline, or phosphate buffered saline. Dosage forms can be made using conventional pharmaceutical manufacturing and compounding techniques. Dosage forms can comprise inorganic or organic buffers (*e.g.*, sodium or potassium salts of phosphate, carbonate, acetate, or citrate) and pH adjustment agents (*e.g.*, hydrochloric acid, sodium or potassium hydroxide, salts of citrate or acetate, amino acids and their salts) antioxidants (*e.g.*, ascorbic acid, alpha-tocopherol), surfactants (*e.g.*, polysorbate 20, polysorbate 80, polyoxyethylene9-10 nonyl phenol, sodium desoxycholate), solution and/or cryo/lyo stabilizers (*e.g.*, sucrose, lactose, mannitol, trehalose), osmotic adjustment agents (*e.g.*, salts or sugars), antibacterial agents (*e.g.*, benzoic acid, phenol, gentamicin), antifoaming agents (*e.g.*, polydimethylsilozone), preservatives (*e.g.*, thimerosal, 2-phenoxyethanol, EDTA), polymeric stabilizers and viscosity-adjustment agents (*e.g.*, polyvinylpyrrolidone, poloxamer 488, carboxymethylcellulose) and co-solvents (*e.g.*, glycerol, polyethylene glycol, ethanol). A dosage form formulated for injectable use can have a disclosed compound, a product of a disclosed method of making, or a salt, solvate, or polymorph thereof, suspended in sterile saline solution for injection together with a preservative.

[0056] As used herein, "kit" means a collection of at least two components constituting the kit. Together, the components constitute a functional unit for a given purpose. Individual member components may be physically packaged together or separately. For example, a kit comprising an instruction for using the kit may or may not physically include the instruction with other individual member components. Instead, the instruction can be supplied as a separate member component, either in a paper form or an electronic form which may be supplied on computer readable memory device or downloaded from an internet website, or as recorded presentation.

[0057] As used herein, "instruction(s)" means documents describing relevant materials or methodologies pertaining to a kit. These materials may include any combination of the following: background information, list of components and their availability information (purchase information, etc.), brief or detailed protocols for using the kit, trouble-shooting, references, technical support, and any other related documents. Instructions can be supplied with the kit or as a separate member component, either as a paper form or an electronic form which may be supplied on computer readable memory device or downloaded from an internet website, or as recorded presentation. Instructions can comprise one or multiple documents, and are meant to include future updates.

[0058] As used herein, the terms "therapeutic agent" include any synthetic or naturally occurring biologically active compound or composition of matter which, when administered to an organism (human or nonhuman animal), induces a desired pharmacologic, immunogenic, and/or physiologic effect by local and/or systemic action. The term therefore encompasses those compounds or chemicals traditionally regarded as drugs, vaccines, and biopharmaceuticals including molecules such as proteins, peptides, hormones, nucleic acids, gene constructs and the like. Examples of therapeutic agents are described in well-known literature references such as the Merck Index (14^{th} edition), the Physicians' Desk Reference (64^{th} edition), and The Pharmacological Basis of Therapeutics (12^{th} edition) , and they include, without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of a disease or illness; substances that affect the structure or function of the body, or pro-drugs, which become biologically active or more active after they have been placed in a physiological environment. For example, the term "therapeutic agent" includes compounds or compositions for use in all of the major

therapeutic areas including, but not limited to, adjuvants; anti-infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations, anorexics, anti-inflammatory agents, anti-epileptics, local and general anesthetics, hypnotics, sedatives, antipsychotic agents, neuroleptic agents, antidepressants, anxiolytics, antagonists, neuron blocking agents, anticholinergic and cholinomimetic agents, antimuscarinic and muscarinic agents, antiadrenergics, antiarrhythmics, antihypertensive agents, hormones, and nutrients, antiarthritics, antiasthmatic agents, anticonvulsants, antihistamines, antinauseants, antineoplastics, antipruritics, antipyretics; antispasmodics, cardiovascular preparations (including calcium channel blockers, beta-blockers, beta-agonists and antiarrythmics), antihypertensives, diuretics, vasodilators; central nervous system stimulants; cough and cold preparations; decongestants; diagnostics; hormones; bone growth stimulants and bone resorption inhibitors; immunosuppressives; muscle relaxants; psychostimulants; sedatives; tranquilizers; proteins, peptides, and fragments thereof (whether naturally occurring, chemically synthesized or recombinantly produced); and nucleic acid molecules (polymeric forms of two or more nucleotides, either ribonucleotides (RNA) or deoxyribonucleotides (DNA) including both double- and single-stranded molecules, gene constructs, expression vectors, antisense molecules and the like), small molecules (*e.g.*, doxorubicin) and other biologically active macromolecules such as, for example, proteins and enzymes. The agent may be a biologically active agent used in medical, including veterinary, applications and in agriculture, such as with plants, as well as other areas. The term "therapeutic agent" also includes without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of disease or illness; or substances which affect the structure or function of the body; or pro- drugs, which become biologically active or more active after they have been placed in a predetermined physiological environment.

[0059] The term “pharmaceutically acceptable” describes a material that is not biologically or otherwise undesirable, *i.e.*, without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

[0060] As used herein, the term “derivative” refers to a compound having a structure derived from the structure of a parent compound (*e.g.*, a compound disclosed herein) and whose structure is sufficiently similar to those disclosed herein and based upon that similarity,

would be expected by one skilled in the art to exhibit the same or similar activities and utilities as the claimed compounds, or to induce, as a precursor, the same or similar activities and utilities as the claimed compounds. Exemplary derivatives include salts, esters, amides, salts of esters or amides, and N-oxides of a parent compound.

[0061] As used herein, the term "pharmaceutically acceptable carrier" refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents, such as aluminum monostearate and gelatin, which delay absorption. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use. Suitable inert carriers can include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

[0062] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (*i.e.*, further substituted or unsubstituted).

[0063] In defining various terms, "A^1," "A^2," "A^3," and "A^4" are used herein as generic symbols to represent various specific substituents. These symbols can be any substituent, not limited to those disclosed herein, and when they are defined to be certain substituents in one instance, they can, in another instance, be defined as some other substituents.

[0064] The term "aliphatic" or "aliphatic group," as used herein, denotes a hydrocarbon moiety that may be straight-chain (*i.e.*, unbranched), branched, or cyclic (including fused, bridging, and spirofused polycyclic) and may be completely saturated or may contain one or more units of unsaturation, but which is not aromatic. Unless otherwise specified, aliphatic groups contain 1-20 carbon atoms. Aliphatic groups include, but are not limited to, linear or branched, alkyl, alkenyl, and alkynyl groups, and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0065] The term "alkyl" as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl, *t*-butyl, *n*-pentyl, isopentyl, *s*-pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, eicosyl, tetracosyl, and the like. The alkyl group can be

cyclic or acyclic. The alkyl group can be branched or unbranched. The alkyl group can also be substituted or unsubstituted. For example, the alkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol, as described herein. A "lower alkyl" group is an alkyl group containing from one to six (*e.g.*, from one to four) carbon atoms. The term alkyl group can also be a C1 alkyl, C1-C2 alkyl, C1-C3 alkyl, C1-C4 alkyl, C1-C5 alkyl, C1-C6 alkyl, C1-C7 alkyl, C1-C8 alkyl, C1-C9 alkyl, C1-C10 alkyl, and the like up to and including a C1-C24 alkyl.

[0066] Throughout the specification "alkyl" is generally used to refer to both unsubstituted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term "halogenated alkyl" or "haloalkyl" specifically refers to an alkyl group that is substituted with one or more halide, *e.g.*, fluorine, chlorine, bromine, or iodine. Alternatively, the term "monohaloalkyl" specifically refers to an alkyl group that is substituted with a single halide, *e.g.* fluorine, chlorine, bromine, or iodine. The term "polyhaloalkyl" specifically refers to an alkyl group that is independently substituted with two or more halides, *i.e.* each halide substituent need not be the same halide as another halide substituent, nor do the multiple instances of a halide substituent need to be on the same carbon. The term "alkoxyalkyl" specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term "aminoalkyl" specifically refers to an alkyl group that is substituted with one or more amino groups. The term "hydroxyalkyl" specifically refers to an alkyl group that is substituted with one or more hydroxy groups. When "alkyl" is used in one instance and a specific term such as "hydroxyalkyl" is used in another, it is not meant to imply that the term "alkyl" does not also refer to specific terms such as "hydroxyalkyl" and the like.

[0067] This practice is also used for other groups described herein. That is, while a term such as "cycloalkyl" refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, *e.g.*, an "alkylcycloalkyl." Similarly, a substituted alkoxy can be specifically referred to as, *e.g.*, a "halogenated alkoxy," a particular substituted alkenyl can be, *e.g.*, an "alkenylalcohol," and the like. Again, the practice of

using a general term, such as "cycloalkyl," and a specific term, such as "alkylcycloalkyl," is not meant to imply that the general term does not also include the specific term.

[0068] The term "cycloalkyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The term "heterocycloalkyl" is a type of cycloalkyl group as defined above, and is included within the meaning of the term "cycloalkyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0069] The term "polyalkylene group" as used herein is a group having two or more CH_2 groups linked to one another. The polyalkylene group can be represented by the formula —$(CH_2)_a$—, where "a" is an integer of from 2 to 500.

[0070] The terms "alkoxy" and "alkoxyl" as used herein to refer to an alkyl or cycloalkyl group bonded through an ether linkage; that is, an "alkoxy" group can be defined as —OA^1 where A^1 is alkyl or cycloalkyl as defined above. "Alkoxy" also includes polymers of alkoxy groups as just described; that is, an alkoxy can be a polyether such as —OA^1—OA^2 or —OA^1—$(OA^2)_a$—OA^3, where "a" is an integer of from 1 to 200 and A^1, A^2, and A^3 are alkyl and/or cycloalkyl groups.

[0071] The term "alkenyl" as used herein is a hydrocarbon group of from 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon double bond. Asymmetric structures such as $(A^1A^2)C=C(A^3A^4)$ are intended to include both the *E* and *Z* isomers. This can be presumed in structural formulae herein wherein an asymmetric alkene is present, or it can be explicitly indicated by the bond symbol C=C. The alkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0072] The term "cycloalkenyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms and containing at least one carbon-carbon double bound, *i.e.*, C=C. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, norbornenyl, and the like. The term "heterocycloalkenyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkenyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkenyl group and heterocycloalkenyl group can be substituted or unsubstituted. The cycloalkenyl group and heterocycloalkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0073] The term "alkynyl" as used herein is a hydrocarbon group of 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon triple bond. The alkynyl group can be unsubstituted or substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0074] The term "cycloalkynyl" as used herein is a non-aromatic carbon-based ring composed of at least seven carbon atoms and containing at least one carbon-carbon triple bound. Examples of cycloalkynyl groups include, but are not limited to, cycloheptynyl, cyclooctynyl, cyclononynyl, and the like. The term "heterocycloalkynyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkynyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkynyl group and heterocycloalkynyl group can be substituted or unsubstituted. The cycloalkynyl group and heterocycloalkynyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0075] The term "aromatic group" as used herein refers to a ring structure having cyclic clouds of delocalized π electrons above and below the plane of the molecule, where the π clouds contain (4n+2) π electrons. A further discussion of aromaticity is found in Morrison and Boyd, Organic Chemistry, (5th Ed., 1987), Chapter 13, entitled "Aromaticity," pages 477-497, incorporated herein by reference. The term "aromatic group" is inclusive of both aryl and heteroaryl groups.

[0076] The term "aryl" as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, anthracene, and the like. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, $-NH_2$, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein. The term "biaryl" is a specific type of aryl group and is included in the definition of "aryl." In addition, the aryl group can be a single ring structure or comprise multiple ring structures that are either fused ring structures or attached via one or more bridging groups such as a carbon-carbon bond. For example, biaryl can be two aryl groups that are bound together via a fused ring structure, as in naphthalene, or are attached via one or more carbon-carbon bonds, as in biphenyl.

[0077] The term "aldehyde" as used herein is represented by the formula —C(O)H. Throughout this specification "C(O)" is a short hand notation for a carbonyl group, *i.e.*, C=O.

[0078] The terms "amine" or "amino" as used herein are represented by the formula —NA^1A^2, where A^1 and A^2 can be, independently, hydrogen or alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. A specific example of amino is $-NH_2$.

[0079] The term "alkylamino" as used herein is represented by the formula —NH(-alkyl) where alkyl is a described herein. Representative examples include, but are not limited to, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, (sec-butyl)amino group, (tert-butyl)amino group, pentylamino group, isopentylamino group, (tert-pentyl)amino group, hexylamino group, and the like.

[0080] The term "dialkylamino" as used herein is represented by the formula —N(-alkyl)$_2$ where alkyl is a described herein. Representative examples include, but are not limited to, dimethylamino group, diethylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group, di(sec-butyl)amino group, di(tert-butyl)amino group, dipentylamino group, diisopentylamino group, di(tert-pentyl)amino group, dihexylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-ethyl-N-propylamino group and the like.

[0081] The term "carboxylic acid" as used herein is represented by the formula —C(O)OH.

[0082] The term "ester" as used herein is represented by the formula —OC(O)A^1 or —C(O)OA^1, where A^1 can be alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "polyester" as used herein is represented by the formula —(A^1O(O)C-A^2-C(O)O)$_a$— or —(A^1O(O)C-A^2-OC(O))$_a$—, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer from 1 to 500. "Polyester" is as the term used to describe a group that is produced by the reaction between a compound having at least two carboxylic acid groups with a compound having at least two hydroxyl groups.

[0083] The term "ether" as used herein is represented by the formula A^1OA^2, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein. The term "polyether" as used herein is represented by the formula —(A^1O-A^2O)$_a$—, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer of from 1 to 500. Examples of polyether groups include polyethylene oxide, polypropylene oxide, and polybutylene oxide.

[0084] The terms "halo," "halogen," or "halide," as used herein can be used interchangeably and refer to F, Cl, Br, or I.

[0085] The terms "pseudohalide," "pseudohalogen," or "pseudohalo," as used herein can be used interchangeably and refer to functional groups that behave substantially similar to halides. Such functional groups include, by way of example, cyano, thiocyanato, azido, trifluoromethyl, trifluoromethoxy, perfluoroalkyl, and perfluoroalkoxy groups.

[0086] The term "heteroalkyl," as used herein refers to an alkyl group containing at least one heteroatom. Suitable heteroatoms include, but are not limited to, O, N, Si, P and S, wherein the nitrogen, phosphorous and sulfur atoms are optionally oxidized, and the nitrogen heteroatom is optionally quaternized. Heteroalkyls can be substituted as defined above for alkyl groups.

[0087] The term "heteroaryl," as used herein refers to an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus, where N-oxides, sulfur oxides, and dioxides are permissible heteroatom substitutions. The heteroaryl group can be substituted or unsubstituted. The heteroaryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein. Heteroaryl groups can be monocyclic, or alternatively fused ring systems. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrimidinyl, tetrazolyl, thienyl, pyridinyl, pyrrolyl, *N*-methylpyrrolyl, quinolinyl, isoquinolinyl, pyrazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridazinyl, pyrazinyl, benzofuranyl, benzodioxolyl, benzothiophenyl, indolyl, indazolyl, benzimidazolyl, imidazopyridinyl, pyrazolopyridinyl, and pyrazolopyrimidinyl. Further not limiting examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, benzo[*d*]oxazolyl, benzo[*d*]thiazolyl, quinolinyl, quinazolinyl, indazolyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, benzo[c][1,2,5]thiadiazolyl, benzo[c][1,2,5]oxadiazolyl, and pyrido[2,3-b]pyrazinyl.

[0088] The terms "heterocycle" or "heterocyclyl," as used herein can be used interchangeably and refer to single and multi-cyclic aromatic or non-aromatic ring systems in which at least one of the ring members is other than carbon. Thus, the term is inclusive of, but not limited to, "heterocycloalkyl", "heteroaryl", "bicyclic heterocycle" and "polycyclic heterocycle." Heterocycle includes pyridine, pyrimidine, furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, oxazole, including, 1,2,3-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole, thiadiazole, including, 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, triazole, including, 1,2,3-triazole, 1,3,4-triazole, tetrazole, including 1,2,3,4-tetrazole and 1,2,4,5-tetrazole, pyridazine, pyrazine, triazine,

including 1,2,4-triazine and 1,3,5-triazine, tetrazine, including 1,2,4,5-tetrazine, pyrrolidine, piperidine, piperazine, morpholine, azetidine, tetrahydropyran, tetrahydrofuran, dioxane, and the like. The term heterocyclyl group can also be a C2 heterocyclyl, C2-C3 heterocyclyl, C2-C4 heterocyclyl, C2-C5 heterocyclyl, C2-C6 heterocyclyl, C2-C7 heterocyclyl, C2-C8 heterocyclyl, C2-C9 heterocyclyl, C2-C10 heterocyclyl, C2-C11 heterocyclyl, and the like up to and including a C2-C18 heterocyclyl. For example, a C2 heterocyclyl comprises a group which has two carbon atoms and at least one heteroatom, including, but not limited to, aziridinyl, diazetidinyl, dihydrodiazetyl, oxiranyl, thiiranyl, and the like. Alternatively, for example, a C5 heterocyclyl comprises a group which has five carbon atoms and at least one heteroatom, including, but not limited to, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, diazepanyl, pyridinyl, and the like. It is understood that a heterocyclyl group may be bound either through a heteroatom in the ring, where chemically possible, or one of carbons comprising the heterocyclyl ring.

[0089] The term "bicyclic heterocycle" or "bicyclic heterocyclyl," as used herein refers to a ring system in which at least one of the ring members is other than carbon. Bicyclic heterocyclyl encompasses ring systems wherein an aromatic ring is fused with another aromatic ring, or wherein an aromatic ring is fused with a non-aromatic ring. Bicyclic heterocyclyl encompasses ring systems wherein a benzene ring is fused to a 5- or a 6-membered ring containing 1, 2 or 3 ring heteroatoms or wherein a pyridine ring is fused to a 5- or a 6-membered ring containing 1, 2 or 3 ring heteroatoms. Bicyclic heterocyclic groups include, but are not limited to, indolyl, indazolyl, pyrazolo[1,5-a]pyridinyl, benzofuranyl, quinolinyl, quinoxalinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 3,4-dihydro-2H-chromenyl, 1H-pyrazolo[4,3-c]pyridin-3-yl; 1H-pyrrolo[3,2-b]pyridin-3-yl; and 1H-pyrazolo[3,2-b]pyridin-3-yl.

[0090] The term "heterocycloalkyl" as used herein refers to an aliphatic, partially unsaturated or fully saturated, 3- to 14-membered ring system, including single rings of 3 to 8 atoms and bi- and tricyclic ring systems. The heterocycloalkyl ring-systems include one to four heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein a nitrogen and sulfur heteroatom optionally can be oxidized and a nitrogen heteroatom optionally can be substituted. Representative heterocycloalkyl groups include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl,

piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

[0091] The term "hydroxyl" or "hydroxyl" as used herein is represented by the formula —OH.

[0092] The term "ketone" as used herein is represented by the formula $A^1C(O)A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0093] The term "azide" or "azido" as used herein is represented by the formula $—N_3$.

[0094] The term "nitro" as used herein is represented by the formula $—NO_2$.

[0095] The term "nitrile" or "cyano" as used herein is represented by the formula —CN.

[0096] The term "silyl" as used herein is represented by the formula $—SiA^1A^2A^3$, where A^1, A^2, and A^3 can be, independently, hydrogen or an alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0097] The term "sulfo-oxo" as used herein is represented by the formulas $—S(O)A^1$, $—S(O)_2A^1$, $—OS(O)_2A^1$, or $—OS(O)_2OA^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. Throughout this specification "S(O)" is a short hand notation for S=O. The term "sulfonyl" is used herein to refer to the sulfo-oxo group represented by the formula $—S(O)_2A^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfone" as used herein is represented by the formula $A^1S(O)_2A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfoxide" as used herein is represented by the formula $A^1S(O)A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0098] The term "thiol" as used herein is represented by the formula —SH.

[0099] "R^1," "R^2," "R^3," "R^n," where n is an integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R^1 is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can optionally be substituted with a hydroxyl group, an alkoxy group, an alkyl group, a halide, and the like. Depending upon the groups that are selected, a first group can be incorporated within second group or, alternatively, the first group can be pendant (*i.e.*, attached) to the second group. For example, with the phrase "an alkyl group comprising an amino group," the amino group can be incorporated within the backbone of the alkyl group. Alternatively, the amino group can be attached to the backbone of the alkyl group. The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

[00100] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogen of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. In is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (*i.e.*, further substituted or unsubstituted).

[00101] The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain aspects, their recovery, purification, and use for one or more of the purposes disclosed herein.

[00102] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R°$; $-(CH_2)_{0-4}OR°$; $-O(CH_2)_{0-4}R^o$, $-O-(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}CH(OR°)_2$; $-(CH_2)_{0-4}SR°$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be

substituted with R°; –NO_2; –CN; –N_3; -$(CH_2)_{0-4}N(R°)_2$; –$(CH_2)_{0-4}N(R°)C(O)R°$; –$N(R°)C(S)R°$; –$(CH_2)_{0-4}N(R°)C(O)NR°_2$; -$N(R°)C(S)NR°_2$; –$(CH_2)_{0-4}N(R°)C(O)OR°$; –$N(R°)N(R°)C(O)R°$; -$N(R°)N(R°)C(O)NR°_2$; -$N(R°)N(R°)C(O)OR°$; –$(CH_2)_{0-4}C(O)R°$; –$C(S)R°$; –$(CH_2)_{0-4}C(O)OR°$; –$(CH_2)_{0-4}C(O)SR°$; -$(CH_2)_{0-4}C(O)OSiR°_3$; –$(CH_2)_{0-4}OC(O)R°$; –$OC(O)(CH_2)_{0-4}SR$–, $SC(S)SR°$; –$(CH_2)_{0-4}SC(O)R°$; –$(CH_2)_{0-4}C(O)NR°_2$; –$C(S)NR°_2$; –$C(S)SR°$; -$(CH_2)_{0-4}OC(O)NR°_2$; -$C(O)N(OR°)R°$; –$C(O)C(O)R°$; –$C(O)CH_2C(O)R°$; –$C(NOR°)R°$; -$(CH_2)_{0-4}SSR°$; –$(CH_2)_{0-4}S(O)_2R°$; –$(CH_2)_{0-4}S(O)_2OR°$; –$(CH_2)_{0-4}OS(O)_2R°$; –$S(O)_2NR°_2$; -$(CH_2)_{0-4}S(O)R°$; -$N(R°)S(O)_2NR°_2$; –$N(R°)S(O)_2R°$; –$N(OR°)R°$; –$C(NH)NR°_2$; –$P(O)_2R°$; -$P(O)R°_2$; -$OP(O)R°_2$; –$OP(O)(OR°)_2$; $SiR°_3$; –(C_{1-4} straight or branched alkylene)O–$N(R°)_2$; or –(C_{1-4} straight or branched alkylene)C(O)O–$N(R°)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, –CH_2Ph, –$O(CH_2)_{0-1}Ph$, -CH_2-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[00103] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, –$(CH_2)_{0-2}R^•$, –(halo$R^•$), –$(CH_2)_{0-2}OH$, –$(CH_2)_{0-2}OR^•$, –$(CH_2)_{0-2}CH(OR^•)_2$; -O(halo$R^•$), –CN, –N_3, –$(CH_2)_{0-2}C(O)R^•$, –$(CH_2)_{0-2}C(O)OH$, –$(CH_2)_{0-2}C(O)OR^•$, –$(CH_2)_{0-2}SR^•$, –$(CH_2)_{0-2}SH$, –$(CH_2)_{0-2}NH_2$, –$(CH_2)_{0-2}NHR^•$, –$(CH_2)_{0-2}NR^•_2$, –NO_2, –$SiR^•_3$, –$OSiR^•_3$, -$C(O)SR^•$, –(C_{1-4} straight or branched alkylene)$C(O)OR^•$, or –$SSR^•$ wherein each $R^•$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, –CH_2Ph, –$O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[00104] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, =NNR$^*_2$, =NNHC(O)R*, =NNHC(O)OR*, =NNHS(O)$_2$R*, =NR*, =NOR*, –O(C(R$^*_2$))$_{2–3}$O–, or –S(C(R$^*_2$))$_{2–3}$S–, wherein each independent occurrence of R* is selected from hydrogen, C$_{1–6}$ aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: –O(CR$^*_2$)$_{2–3}$O–, wherein each independent occurrence of R* is selected from hydrogen, C$_{1–6}$ aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00105] Suitable substituents on the aliphatic group of R* include halogen, –R$^\bullet$, -(haloR$^\bullet$), -OH, –OR$^\bullet$, –O(haloR$^\bullet$), –CN, –C(O)OH, –C(O)OR$^\bullet$, –NH$_2$, –NHR$^\bullet$, –NR$^\bullet_2$, or –NO$_2$, wherein each R$^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C$_{1–4}$ aliphatic, –CH$_2$Ph, –O(CH$_2$)$_{0–1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00106] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include –R†, –NR$^\dagger_2$, –C(O)R†, –C(O)OR†, –C(O)C(O)R†, –C(O)CH$_2$C(O)R†, –S(O)$_2$R†, -S(O)$_2$NR$^\dagger_2$, –C(S)NR$^\dagger_2$, –C(NH)NR$^\dagger_2$, or –N(R†)S(O)$_2$R†; wherein each R† is independently hydrogen, C$_{1–6}$ aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R†, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00107] Suitable substituents on the aliphatic group of R† are independently halogen, –R$^\bullet$, -(haloR$^\bullet$), –OH, –OR$^\bullet$, –O(haloR$^\bullet$), –CN, –C(O)OH, –C(O)OR$^\bullet$, –NH$_2$, –NHR$^\bullet$, –NR$^\bullet_2$, or –NO$_2$, wherein each R$^\bullet$ is unsubstituted or where preceded by "halo" is substituted only

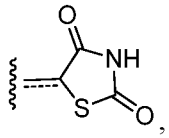
with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00108] The term "leaving group" refers to an atom (or a group of atoms) with electron withdrawing ability that can be displaced as a stable species, taking with it the bonding electrons. Examples of suitable leaving groups include halides and sulfonate esters, including, but not limited to, triflate, mesylate, tosylate, and brosylate.

[00109] The terms "hydrolysable group" and "hydrolysable moiety" refer to a functional group capable of undergoing hydrolysis, *e.g.*, under basic or acidic conditions. Examples of hydrolysable residues include, without limitation, acid halides, activated carboxylic acids, and various protecting groups known in the art (see, for example, "Protective Groups in Organic Synthesis," T. W. Greene, P. G. M. Wuts, Wiley-Interscience, 1999).

[00110] The term "organic residue" defines a carbon containing residue, *i.e.*, a residue comprising at least one carbon atom, and includes but is not limited to the carbon-containing groups, residues, or radicals defined hereinabove. Organic residues can contain various heteroatoms, or be bonded to another molecule through a heteroatom, including oxygen, nitrogen, sulfur, phosphorus, or the like. Examples of organic residues include but are not limited alkyl or substituted alkyls, alkoxy or substituted alkoxy, mono or di-substituted amino, amide groups, etc. Organic residues can preferably comprise 1 to 18 carbon atoms, 1 to 15, carbon atoms, 1 to 12 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. In a further aspect, an organic residue can comprise 2 to 18 carbon atoms, 2 to 15, carbon atoms, 2 to 12 carbon atoms, 2 to 8 carbon atoms, 2 to 4 carbon atoms, or 2 to 4 carbon atoms.

[00111] A very close synonym of the term "residue" is the term "radical," which as used in the specification and concluding claims, refers to a fragment, group, or substructure of a molecule described herein, regardless of how the molecule is prepared. For example, a 2,4-thiazolidinedione radical in a particular compound has the structure:



regardless of whether thiazolidinedione is used to prepare the compound. In some embodiments the radical (for example an alkyl) can be further modified (*i.e.*, substituted alkyl) by having bonded thereto one or more "substituent radicals." The number of atoms in a given radical is not critical to the present invention unless it is indicated to the contrary elsewhere herein.

[00112] "Organic radicals," as the term is defined and used herein, contain one or more carbon atoms. An organic radical can have, for example, 1-26 carbon atoms, 1-18 carbon atoms, 1-12 carbon atoms, 1-8 carbon atoms, 1-6 carbon atoms, or 1-4 carbon atoms. In a further aspect, an organic radical can have 2-26 carbon atoms, 2-18 carbon atoms, 2-12 carbon atoms, 2-8 carbon atoms, 2-6 carbon atoms, or 2-4 carbon atoms. Organic radicals often have hydrogen bound to at least some of the carbon atoms of the organic radical. One example, of an organic radical that comprises no inorganic atoms is a 5, 6, 7, 8-tetrahydro-2-naphthyl radical. In some embodiments, an organic radical can contain 1-10 inorganic heteroatoms bound thereto or therein, including halogens, oxygen, sulfur, nitrogen, phosphorus, and the like. Examples of organic radicals include but are not limited to an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, mono-substituted amino, di-substituted amino, acyloxy, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkyl, haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic, or substituted heterocyclic radicals, wherein the terms are defined elsewhere herein. A few non-limiting examples of organic radicals that include heteroatoms include alkoxy radicals, trifluoromethoxy radicals, acetoxy radicals, dimethylamino radicals and the like.

[00113] Compounds described herein can contain one or more double bonds and, thus, potentially give rise to cis/trans (E/Z) isomers, as well as other conformational isomers. Unless stated to the contrary, the invention includes all such possible isomers, as well as mixtures of such isomers.

[00114] Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, *e.g.*, each enantiomer and diastereomer, and a mixture of isomers, such as a racemic or scalemic mixture. Compounds described herein can contain one or more asymmetric centers and, thus, potentially give rise to diastereomers and optical isomers. Unless stated to the contrary, the present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. Mixtures of stereoisomers, as well as isolated specific stereoisomers, are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[00115] Many organic compounds exist in optically active forms having the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the disclosed formulas, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines is (bonds to atoms below the plane). The Cahn-Ingold-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

[00116] When the disclosed compounds contain one chiral center, the compounds exist in two enantiomeric forms. Unless specifically stated to the contrary, a disclosed compound includes both enantiomers and mixtures of enantiomers, such as the specific 50:50 mixture referred to as a racemic mixture. The enantiomers can be resolved by methods known to those skilled in the art, such as formation of diastereoisomeric salts which may be separated, for example, by crystallization (see, CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation by David Kozma (CRC Press, 2001)); formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step can liberate the desired enantiomeric form. Alternatively, specific enantiomers can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

[00117] Designation of a specific absolute configuration at a chiral carbon in a disclosed compound is understood to mean that the designated enantiomeric form of the compounds can be provided in enantiomeric excess (*e.e.*). Enantiomeric excess, as used herein, is the presence of a particular enantiomer at greater than 50%, for example, greater than 60%, greater than 70%, greater than 75%, greater than 80%, greater than 85%, greater than 90%, greater than 95%, greater than 98%, or greater than 99%. In one aspect, the designated enantiomer is substantially free from the other enantiomer. For example, the "R" forms of the compounds can be substantially free from the "S" forms of the compounds and are, thus, in enantiomeric excess of the "S" forms. Conversely, "S" forms of the compounds can be substantially free of "R" forms of the compounds and are, thus, in enantiomeric excess of the "R" forms.

[00118] When a disclosed compound has two or more chiral carbons, it can have more than two optical isomers and can exist in diastereoisomeric forms. For example, when there are two chiral carbons, the compound can have up to four optical isomers and two pairs of

enantiomers ((S,S)/(R,R) and (R,S)/(S,R)). The pairs of enantiomers (e.g., (S,S)/(R,R)) are mirror image stereoisomers of one another. The stereoisomers that are not mirror-images (e.g., (S,S) and (R,S)) are diastereomers. The diastereoisomeric pairs can be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. Unless otherwise specifically excluded, a disclosed compound includes each diastereoisomer of such compounds and mixtures thereof.

[00119] The compounds according to this disclosure may form prodrugs at hydroxyl or amino functionalities using alkoxy, amino acids, etc., groups as the prodrug forming moieties. For instance, the hydroxymethyl position may form mono-, di- or triphosphates and again these phosphates can form prodrugs. Preparations of such prodrug derivatives are discussed in various literature sources (examples are: Alexander et al., J. Med. Chem. 1988, 31, 318; Aligas-Martin et al., PCT WO 2000/041531, p. 30). The nitrogen function converted in preparing these derivatives is one (or more) of the nitrogen atoms of a compound of the disclosure.

[00120] "Derivatives" of the compounds disclosed herein are pharmaceutically acceptable salts, prodrugs, deuterated forms, radio-actively labeled forms, isomers, solvates and combinations thereof. The "combinations" mentioned in this context are refer to derivatives falling within at least two of the groups: pharmaceutically acceptable salts, prodrugs, deuterated forms, radio-actively labeled forms, isomers, and solvates. Examples of radio-actively labeled forms include compounds labeled with tritium, phosphorous-32, iodine-129, carbon-11, fluorine-18, and the like.

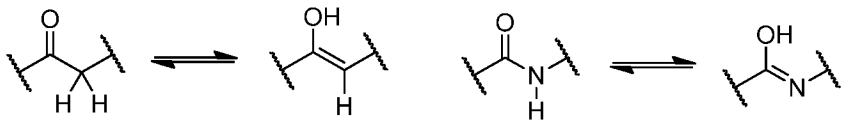
[00121] Compounds described herein comprise atoms in both their natural isotopic abundance and in non-natural abundance. The disclosed compounds can be isotopically-labeled or isotopically-substituted compounds identical to those described, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds further comprise prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said

prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, *i.e.*, ^{3}H, and carbon-14, *i.e.*, ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, *i.e.*, ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of the present invention and prodrugs thereof can generally be prepared by carrying out the procedures below, by substituting a readily available isotopically labeled reagent for a non- isotopically labeled reagent.

[00122] The compounds described in the invention can be present as a solvate. In some cases, the solvent used to prepare the solvate is an aqueous solution, and the solvate is then often referred to as a hydrate. The compounds can be present as a hydrate, which can be obtained, for example, by crystallization from a solvent or from aqueous solution. In this connection, one, two, three or any arbitrary number of solvent or water molecules can combine with the compounds according to the invention to form solvates and hydrates. Unless stated to the contrary, the invention includes all such possible solvates.

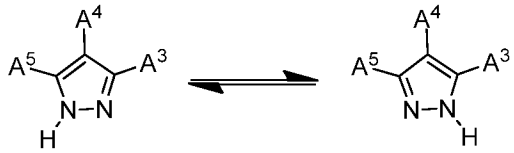
[00123] The term "co-crystal" means a physical association of two or more molecules which owe their stability through non-covalent interaction. One or more components of this molecular complex provide a stable framework in the crystalline lattice. In certain instances, the guest molecules are incorporated in the crystalline lattice as anhydrates or solvates, see *e.g.* "Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-crystals Represent a New Path to Improved Medicines?" Almarasson, O., et. al., The Royal Society of Chemistry, 1889-1896, 2004. Examples of co-crystals include p-toluenesulfonic acid and benzenesulfonic acid.

[00124] It is also appreciated that certain compounds described herein can be present as an equilibrium of tautomers. For example, ketones with an α-hydrogen can exist in an equilibrium of the keto form and the enol form.



keto form enol form amide form imidic acid form

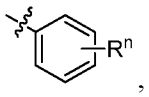
[00125] Likewise, amides with an N-hydrogen can exist in an equilibrium of the amide form and the imidic acid form. As another example, pyrazoles can exist in two tautomeric forms, N^1-unsubstituted, 3-A^3 and N^1-unsubstituted, 5-A^3 as shown below.



Unless stated to the contrary, the invention includes all such possible tautomers.

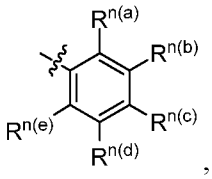
[00126] It is known that chemical substances form solids which are present in different states of order which are termed polymorphic forms or modifications. The different modifications of a polymorphic substance can differ greatly in their physical properties. The compounds according to the invention can be present in different polymorphic forms, with it being possible for particular modifications to be metastable. Unless stated to the contrary, the invention includes all such possible polymorphic forms.

[00127] In some aspects, a structure of a compound can be represented by a formula:



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which is understood to be equivalent to a formula:



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wherein n is typically an integer. That is, R^n is understood to represent five independent substituents, $R^{n(a)}$, $R^{n(b)}$, $R^{n(c)}$, $R^{n(d)}$, $R^{n(e)}$. By "independent substituents," it is meant that each R substituent can be independently defined. For example, if in one instance $R^{n(a)}$ is halogen, then $R^{n(b)}$ is not necessarily halogen in that instance.

[00128] Certain materials, compounds, compositions, and components disclosed herein can be obtained commercially or readily synthesized using techniques generally known to those of skill in the art. For example, the starting materials and reagents used in preparing the disclosed compounds and compositions are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Acros Organics (Morris Plains, N.J.), Strem Chemicals (Newburyport, MA), Fisher Scientific (Pittsburgh, Pa.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and supplemental volumes (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[00129] Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; and the number or type of embodiments described in the specification.

[00130] Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these compounds cannot be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and

permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the compositions of the invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the methods of the invention.

[00131] It is understood that the compositions disclosed herein have certain functions. Disclosed herein are certain structural requirements for performing the disclosed functions, and it is understood that there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

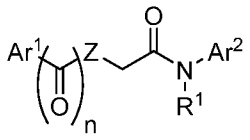
B. COMPOUNDS

[00132] In one aspect, disclosed are compounds useful in treating or preventing a disorder associated with diminished BMP signaling such as, for example, cancer, juvenile polyposis syndrome, hereditary pulmonary arterial hypertension, obesity osteoporosis, and chronic kidney disease. In a further aspect, the invention relates to compounds for use in cartilage repair or bone formation. In a further aspect, the disclosed compounds exhibit modulation of the BMP signaling pathway. In a still further aspect, the disclosed compounds exhibit activation of the BMP signaling pathway.

[00133] It is contemplated that each disclosed derivative can be optionally further substituted. It is also contemplated that any one or more derivative can be optionally omitted from the invention. It is understood that a disclosed compound can be provided by the disclosed methods. It is also understood that the disclosed compounds can be employed in the disclosed methods of using.

1. STRUCTURE

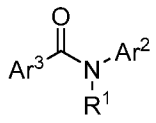
[00134] In one aspect, disclosed are compounds having a structure represented by a formula:



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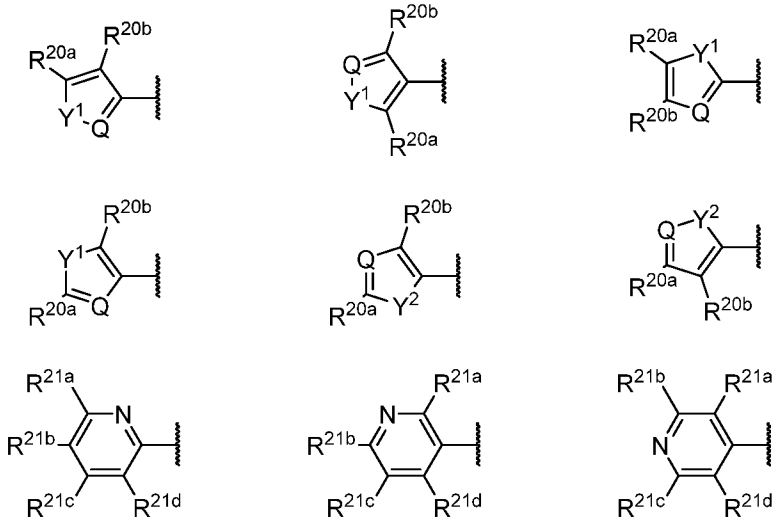
wherein n is selected from 0 and 1; wherein Z is selected from O, CH_2, and NR^2; wherein R^2 is selected from hydrogen and C1-C4 alkyl; wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); or a pharmaceutically acceptable salt thereof.

[00135] In one aspect, disclosed are compounds having a structure represented by a formula:



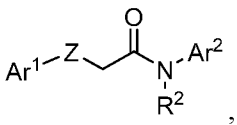
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wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); and wherein Ar^3 is a 5- or 6-membered heteroaryl selected from:



wherein Q, when present, is selected from $CR^{30a}R^{30b}$ and NR^{31}; wherein each of R^{30a}, R^{30b}, and R^{31}, when present, is independently selected from hydrogen and C1-C4 alkyl; wherein Y^1, when present, is selected from O, S, and NR^{31}; wherein Y^2, when present, is selected from O and NR^{31}; wherein each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl; or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with diminished BMP signaling.

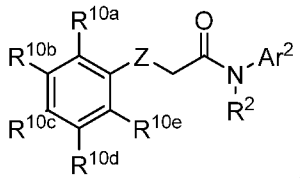
[00136] In a further aspect, the compound has a structure represented by a formula:



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or a pharmaceutically acceptable salt thereof.

[00137] In a further aspect, the compound has a structure represented by a formula:

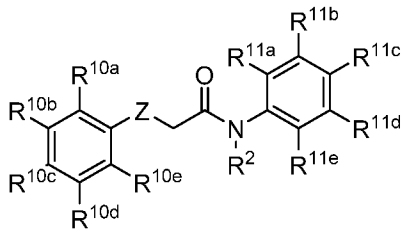


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wherein each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-

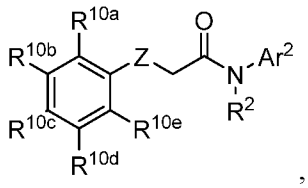
C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl), provided that at least two of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is hydrogen, or a pharmaceutically acceptable salt thereof.

[00138] In a further aspect, the compound has a structure represented by a formula:



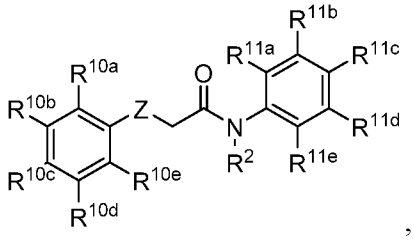
wherein each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl), or wherein each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl substituted with 0-3 groups independently selected from hydrogen, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl), provided that at least two of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is hydrogen, or a pharmaceutically acceptable salt thereof.

[00139] In a further aspect, the compound has a structure represented by a formula:



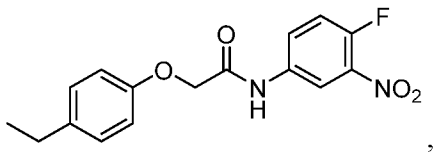
wherein each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and –C(O)(C1-C4 alkyl), provided that two, three, or four of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is hydrogen.

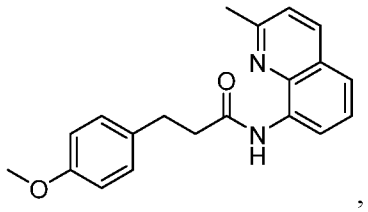
[00140] In a further aspect, the compound has a structure represented by a formula:

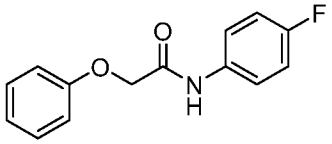


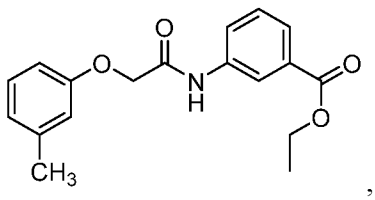
wherein each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl), or wherein each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl substituted with 0-3 groups independently selected from hydrogen, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl), provided that at least two of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is hydrogen.

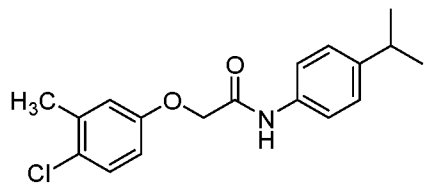
[00141] In a further aspect, the compound is selected from:



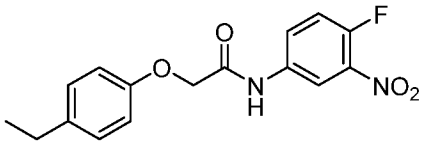




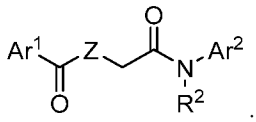


and 

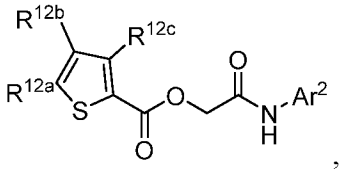
[00142] In a further aspect, the compound is:



[00143] In a further aspect, the compound has a structure represented by a formula:

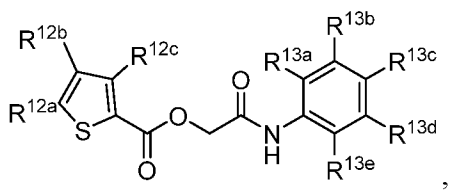


[00144] In a further aspect, the compound has a structure represented by a formula:



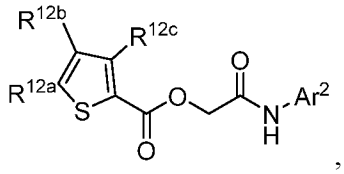
wherein each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), provided that at least two of R^{12a}, R^{12b}, and R^{12c} is hydrogen, or wherein each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, a 5-membered heteroaryl, a 6-membered aryl, or a 6-membered heterocycloalkyl, and are substituted with 0-3 groups independently selected from hydrogen, phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl).

[00145] In a further aspect, the compound has a structure represented by a formula:



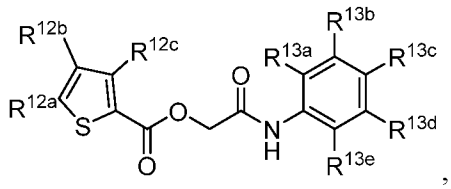
wherein each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), provided that at least two of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is hydrogen.

[00146] In a further aspect, the compound has a structure represented by a formula:



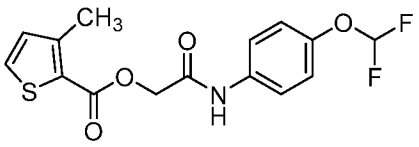
wherein each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, $-NH_2$, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), provided that at least two of R^{12a}, R^{12b}, and R^{12c} is hydrogen, or wherein each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, a 5-membered heteroaryl, a 6-membered aryl, or a 6-membered heterocycloalkyl, and are substituted with 0-3 groups independently selected from hydrogen, phenyl, $-NH_2$, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl).

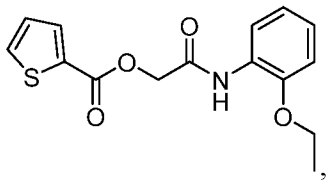
[00147] In a further aspect, the compound has a structure represented by a formula:

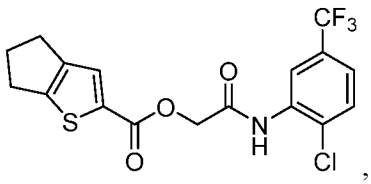


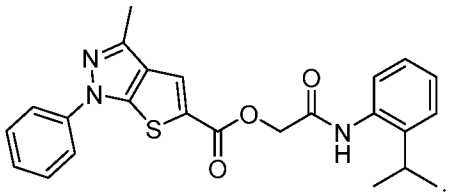
wherein each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, halogen, $-NH_2$, –OH, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino, provided that at least two of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is hydrogen.

[00148] In a further aspect, the compound is selected from:

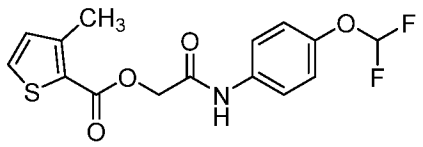

,


,

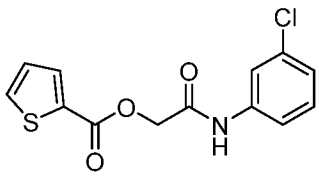

, and

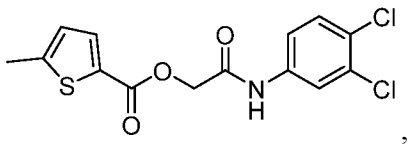

.

[00149] In a further aspect, the compound is:

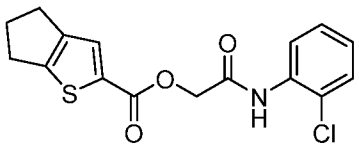

.

[00150] In a further aspect, the compound is not:

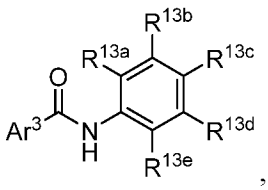

,


,

and


.

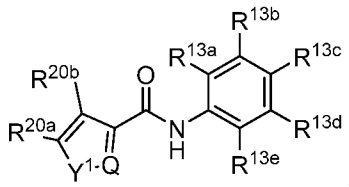
[00151] In a further aspect, the compound has a structure represented by a formula:


,

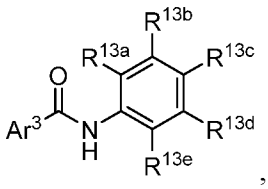
wherein each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, halogen, $-NH_2$, $-OH$, $-CN$, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-

C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), provided that at least two of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} are hydrogen.

[00152] In a further aspect, the compound has a structure represented by a formula:

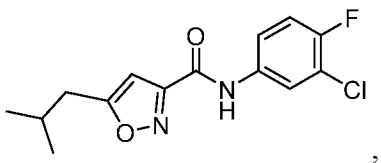


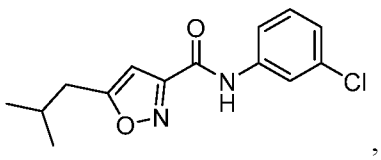
[00153] In a further aspect, the compound has a structure represented by a formula:

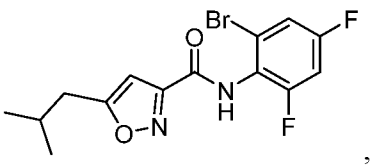


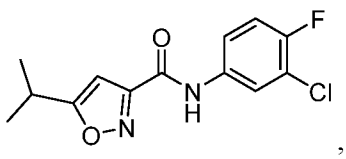
wherein each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, halogen, $-NH_2$, –CN, $-NO_2$, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), provided that at least two of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} are hydrogen.

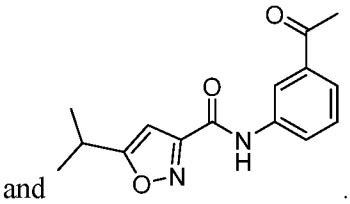
[00154] In a further aspect, the compound is selected from:



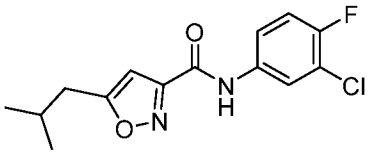




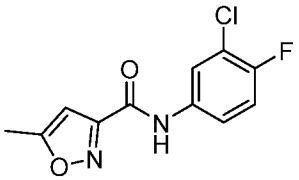


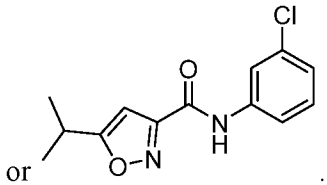
and 

[00155] In a further aspect, the compound is:



[00156] In a further aspect, the compound is not:



or 

[00157] In one aspect, n is selected from 0 and 1. In a further aspect, n is 1. In a still further aspect, n is 0.

a. Z Groups

[00158] In one aspect, Z is selected from O, CH_2, and NR^2. In a further aspect, Z is selected from O and NR^2. In a still further aspect, Z is selected from CH_2 and NR^2. In yet a further aspect, Z is selected from O and CH_2. In an even further aspect, Z is O. In a still further aspect, Z is CH_2. In yet a further aspect, Z is NR^2.

b. Q Groups

[00159] In one aspect, Q, when present, is selected from CR^{30} and N. In a further aspect, Q, when present, is selected from CH and M. In a still further aspect, Q, when present, is CR^{30}. In yet a further aspect, Q, when present, is CH. In an even further aspect, Q, when present, is N.

c. Y^1 GROUPS

[00160] In one aspect, Y^1, when present, is selected from O, S, and NR^{31}. In a further aspect, Y^1, when present, is selected from O and S. In a still further aspect, Y^1, when present, is selected from O and NR^{31}. In yet a further aspect, Y^1, when present, is selected from S and NR^{31}. In an even further aspect, Y^1, when present, is O. In a still further aspect, Y^1, when present, is S. In yet a further aspect, Y^1, when present, is NR^{31}.

d. Y^2 GROUPS

[00161] In one aspect, Y^2, when present, is selected from O and NR^{31}. In a further aspect, Y^2, when present, is O. In a still further aspect, Y^2, when present, is NR^{31}.

e. R^1 GROUPS

[00162] In one aspect, R^1 is selected from hydrogen and C1-C4 alkyl. In a further aspect, R^1 is hydrogen.

[00163] In a further aspect, R^1 is selected from hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, and *t*-butyl. In a still further aspect, R^1 is selected from hydrogen, methyl, ethyl, *n*-propyl, and *i*-propyl. In yet a further aspect, R^1 is selected from hydrogen, methyl, and ethyl. In an even further aspect, R^1 is selected from hydrogen and ethyl. In a still further aspect, R^1 is selected from hydrogen and methyl.

[00164] In a further aspect, R^1 is C1-C4 alkyl. In a still further aspect, R^1 is selected from methyl, ethyl, *n*-propyl, and *i*-propyl. In yet a further aspect, R^1 is selected from methyl and ethyl. In an even further aspect, R^1 is ethyl. In a still further aspect, R^1 is methyl.

f. R^2 GROUPS

[00165] In one aspect, R^2, when present, is selected from hydrogen and C1-C4 alkyl. In a further aspect, R^2, when present, is hydrogen.

[00166] In a further aspect, R^2, when present, is selected from hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, and *t*-butyl. In a still further aspect, R^2, when present, is selected from hydrogen, methyl, ethyl, *n*-propyl, and *i*-propyl. In yet a further aspect, R^2, when present, is selected from hydrogen, methyl, and ethyl. In an even further

aspect, R^2, when present, is selected from hydrogen and ethyl. In a still further aspect, R^2, when present, is selected from hydrogen and methyl.

[00167] In a further aspect, R^2, when present, C1-C4 alkyl. In a still further aspect, R^2, when present, is selected from methyl, ethyl, *n*-propyl, and *i*-propyl. In yet a further aspect, R^2, when present, is selected from methyl and ethyl. In an even further aspect, R^2, when present, is ethyl. In a still further aspect, R^2, when present, is methyl.

g. R^{10A}, R^{10B}, R^{10C}, R^{10D}, AND R^{10E} GROUPS

[00168] In one aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, halogen, $-NH_2$, $-OH$, $-CN$, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), provided that at least two of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is hydrogen. In a still further aspect, each of each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is hydrogen.

[00169] In a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, $-OH$, $-CN$, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, $-OH$, $-CN$, $-NO_2$, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CH_2F$, $-CH(CH_3)CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCH_2CH_2CH_2F$, $-OCH(CH_3)CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-OCH_2CH_2CHF_2$, $-OCH(CH_3)CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)_2$, $-N(CH(CH_3)CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)CH_2CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, $-OH$, $-CN$, $-NO_2$, methyl, ethyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-NHCH_3$, –

$NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-CO_2CH_3$, and $-CO_2CH_2CH_3$. In an even further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, $-CH_2F$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-OCH_2F$, $-OCHF_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(O)CH_3$, and $-CO_2CH_3$.

[00170] In a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, halogen, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CH_2F$, $-CH(CH_3)CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCH_2CH_2CH_2F$, $-OCH(CH_3)CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-OCH_2CH_2CHF_2$, $-OCH(CH_3)CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)_2$, $-N(CH(CH_3)CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)CH_2CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, methyl, ethyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-CO_2CH_3$, and $-CO_2CH_2CH_3$. In an even further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, methyl, $-CH_2F$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-OCH_2F$, $-OCHF_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(O)CH_3$, and $-CO_2CH_3$.

[00171] In a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, –

$CH(CH_3)CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)_2$, $-N(CH(CH_3)CH_3)_2$, and $-N(CH_3)(CH_2CH_3)$. In yet a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, ethyl, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and $-N(CH_3)(CH_2CH_3)$. In an even further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, $-CH_2OH$, $-CH_2OCH_3$, $-NHCH_3$, and $-N(CH_3)_2$.

[00172] In a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, and C1-C4 alkoxy. In a still further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2CH_2OCH_2CH_3$. In yet a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, ethyl, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, and $-CH_2OCH_2CH_3$. In an even further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, and $-CH_2OCH_3$.

[00173] In a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, halogen, C1-C4 alkyl, C1-C4 haloalkyl, and C1-C4 alkoxy. In a still further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CH_2F$, $-CH(CH_3)CH_2Cl$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2CH_2OCH_2CH_3$. In yet a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, methyl, ethyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, and $-CH_2OCH_2CH_3$. In an even further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, methyl, $-CH_2F$, $-CH_2Cl$, and $-CH_2OCH_3$.

[00174] In a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, halogen, and C1-C4 alkyl. In a still further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, methyl, ethyl, *n*-propyl, and *i*-propyl. In yet a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, methyl, and ethyl. In an even further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, –F, –Cl, and methyl.

[00175] In a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, methyl, ethyl, *n*-propyl, and *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, and *t*-butyl. In yet a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, methyl, ethyl, *n*-propyl, and *i*-propyl. In an even further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, methyl, and ethyl. In a still further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen and ethyl. In yet a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen and methyl.

In a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen and C1-C4 alkoxy. In a still further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, $–CH_2OCH_3$, $–CH_2CH_2OCH_3$, $–CH_2CH_2CH_2OCH_3$, $–CH(CH_3)CH_2OCH_3$, $–CH_2OCH_2CH_3$, and $–CH_2CH_2OCH_2CH_3$. In yet a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, $–CH_2OCH_3$, $–CH_2CH_2OCH_3$, and $–CH_2OCH_2CH_3$. In an even further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen and $–CH_2OCH_3$.

[00176] In a further aspect, each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and –C(O)(C1-C4 alkyl), provided that two, three, or four of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is hydrogen.

h. R^{11A}, R^{11B}, R^{11C}, R^{11D}, AND R^{11E} GROUPS

[00177] In one aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), or each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl substituted with 0-3 groups independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), provided that at least two of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is hydrogen. In a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is hydrogen.

[00178] In a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In yet a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CH_2F$, $-CH(CH_3)CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCH_2CH_2CH_2F$, $-OCH(CH_3)CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-OCH_2CH_2CHF_2$, $-OCH(CH_3)CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)_2$, $-N(CH(CH_3)CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)CH_2CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl,

ethyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-CO_2CH_3$, and $-CO_2CH_2CH_3$. In an even further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, $-CH_2F$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-OCH_2F$, $-OCHF_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(O)CH_3$, and $-CO_2CH_3$.

[00179] In a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)_2$, $-N(CH(CH_3)CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)CH_2CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, ethyl, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-CO_2CH_3$, and $-CO_2CH_2CH_3$. In an even further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, $-CH_2OH$, $-CH_2OCH_3$, $-NHCH_3$, $-N(CH_3)_2$, $-C(O)CH_3$, and $-CO_2CH_3$.

[00180] In a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, halogen, $-NO_2$, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NO_2$, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, –

$N(CH_2CH_2CH_3)_2$, $-N(CH(CH_3)CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)CH_2CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NO_2$, methyl, ethyl, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-CO_2CH_3$, and $-CO_2CH_2CH_3$. In an even further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NO_2$, methyl, $-CH_2OCH_3$, $-NHCH_3$, $-N(CH_3)_2$, $-C(O)CH_3$, and $-CO_2CH_3$.

[00181] In a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, halogen, $-NO_2$, C1-C4 alkyl, and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NO_2$, methyl, ethyl, *n*-propyl, *i*-propyl, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NO_2$, methyl, ethyl, $-CO_2CH_3$, and $-CO_2CH_2CH_3$. In an even further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $-NO_2$, methyl, and $-CO_2CH_3$.

[00182] In a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, halogen, and $-NO_2$. In a still further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, and $-NO_2$. In yet a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, and $-NO_2$. In an even further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –Cl, and $-NO_2$.

[00183] In a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen and halogen. In a still further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, and –Cl. In yet a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen and –F. In an even further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen and –Cl.

[00184] In a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, and *t*-butyl. In yet a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, methyl, ethyl, *n*-propyl, and *i*-propyl. In an even further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, methyl, and ethyl. In a still further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen and ethyl. In yet a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen and methyl.

[00185] In a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, $-CO_2CH_3$, and $-CO_2CH_2CH_3$. In an even further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen and $-CO_2CH_3$.

[00186] In a further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl substituted with 0-3 groups independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl substituted with 0-2 groups independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In yet a further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl substituted with 0-1 group selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In

an even further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl monosubstituted with a group selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise an unsubstituted 6-membered heterocycloalkyl.

[00187] In a further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a pyridinyl substituted with 0-3 groups independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a pyridinyl substituted with 0-2 groups independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In yet a further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a pyridinyl substituted with 0-1 group selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In an even further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a pyridinyl monosubstituted with a group selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise an unsubstituted pyridinyl.

[00188] In a further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl substituted with 0-3 groups independently selected from hydrogen and C1-C4 alkyl. In a still further

aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl substituted with 0-2 groups independently selected from hydrogen and C1-C4 alkyl. In yet a further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl substituted with 0-1 group selected from hydrogen and C1-C4 alkyl. In an even further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl monosubstituted with a group selected from hydrogen and C1-C4 alkyl.

[00189] In a further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a pyridinyl substituted with 0-3 groups independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a pyridinyl substituted with 0-2 groups independently selected from hydrogen and C1-C4 alkyl. In yet a further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a pyridinyl substituted with 0-1 group selected from hydrogen and C1-C4 alkyl. In an even further aspect, each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a pyridinyl monosubstituted with a group selected from hydrogen and C1-C4 alkyl.

[00190] In a further aspect, each of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is independently selected from hydrogen, –F, –Cl, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl), or wherein each of R^{11a} and R^{11b} are covalently bonded together and, together with the intermediate atoms, comprise a 6-membered heterocycloalkyl substituted with 0-3 groups independently selected from hydrogen, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl), provided that at least two of R^{11a}, R^{11b}, R^{11c}, R^{11d}, and R^{11e} is hydrogen.

i. R^{12A}, R^{12B}, AND R^{12C} GROUPS

[00191] In one aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), provided that at least two of R^{12a}, R^{12b}, and R^{12c} is hydrogen, or each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, a 5-membered heteroaryl, a 6-membered aryl, or a 6-membered heterocycloalkyl, and are substituted with 0-3 groups independently selected from hydrogen, phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is hydrogen.

[00192] In a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In yet a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CH_2F$, $-CH(CH_3)CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCH_2CH_2CH_2F$, $-OCH(CH_3)CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-OCH_2CH_2CHF_2$, $-OCH(CH_3)CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)_2$, $-N(CH(CH_3)CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)CH_2CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, ethyl, $-CH_2F$, $-CH_2Cl$, –

CH_2CH_2F, $-CH_2CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-CO_2CH_3$, and $-CO_2CH_2CH_3$. In an even further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, $-CH_2F$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-OCH_2F$, $-OCHF_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(O)CH_3$, and $-CO_2CH_3$.

[00193] In a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, halogen, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CH_2F$, $-CH(CH_3)CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCH_2CH_2CH_2F$, $-OCH(CH_3)CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-OCH_2CH_2CHF_2$, $-OCH(CH_3)CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)_2$, $-N(CH(CH_3)CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)CH_2CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$, and $-CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, methyl, ethyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-CO_2CH_3$, and $-CO_2CH_2CH_3$. In an even further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, methyl, $-CH_2F$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-OCH_2F$, $-OCHF_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(O)CH_3$, and $-CO_2CH_3$.

[00194] In a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently

selected from hydrogen, –F, –Cl, $–NH_2$, –OH, –CN, $–NO_2$, methyl, ethyl, *n*-propyl, *i*-propyl, $–CH_2OH$, $–CH_2CH_2OH$, $–CH_2CH_2CH_2OH$, $–CH(CH_3)CH_2OH$, $–CH_2OCH_3$, $–CH_2CH_2OCH_3$, $–CH_2CH_2CH_2OCH_3$, $–CH(CH_3)CH_2OCH_3$, $–CH_2OCH_2CH_3$, $–CH_2CH_2OCH_2CH_3$, $–NHCH_3$, $–NHCH_2CH_3$, $–NHCH_2CH_2CH_3$, $–NHCH(CH_3)CH_3$, $–N(CH_3)_2$, $–N(CH_2CH_3)_2$, $–N(CH_2CH_2CH_3)_2$, $–N(CH(CH_3)CH_3)_2$, $–N(CH_3)(CH_2CH_3)$, $–C(O)CH_3$, $–C(O)CH_2CH_3$, $–C(O)CH_2CH_2CH_3$, $–C(O)CH(CH_3)_2$, $–CO_2CH_3$, $–CO_2CH_2CH_3$, $–CO_2CH_2CH_2CH_3$, and $–CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, –F, –Cl, $–NH_2$, –OH, –CN, $–NO_2$, methyl, ethyl, $–CH_2OH$, $–CH_2CH_2OH$, $–CH_2OCH_3$, $–CH_2CH_2OCH_3$, $–CH_2OCH_2CH_3$, $–NHCH_3$, $–NHCH_2CH_3$, $–N(CH_3)_2$, $–N(CH_2CH_3)_2$, $–N(CH_3)(CH_2CH_3)$, $–C(O)CH_3$, $–C(O)CH_2CH_3$, $–CO_2CH_3$, and $–CO_2CH_2CH_3$. In an even further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, –F, –Cl, $–NH_2$, –OH, –CN, $–NO_2$, methyl, $–CH_2OH$, $–CH_2OCH_3$, $–NHCH_3$, $–N(CH_3)_2$, $–C(O)CH_3$, and $–CO_2CH_3$.

[00195] In a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, halogen, and C1-C4 alkyl. In a still further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, –F, –Cl, methyl, ethyl, *n*-propyl, and *i*-propyl. In yet a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, –F, –Cl, methyl, and ethyl. In an even further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, –F, –Cl, and methyl.

[00196] In a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, and *t*-butyl. In yet a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, methyl, ethyl, *n*-propyl, and *i*-propyl. In an even further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, methyl, and ethyl. In a still further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen and ethyl. In yet a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen and methyl.

[00197] In a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, a 5-membered heteroaryl, a 6-membered aryl, or a 6-membered heterocycloalkyl,

and are substituted with 0-3 groups independently selected from hydrogen, phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, a 5-membered heteroaryl, a 6-membered aryl, or a 6-membered heterocycloalkyl, and are substituted with 0-2 groups independently selected from hydrogen, phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In yet a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, a 5-membered heteroaryl, a 6-membered aryl, or a 6-membered heterocycloalkyl, and are substituted with 0-1 group selected from hydrogen, phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In an even further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, a 5-membered heteroaryl, a 6-membered aryl, or a 6-membered heterocycloalkyl, and are monosubstituted with a group selected from hydrogen, phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, a 5-membered heteroaryl, a 6-membered aryl, or a 6-membered heterocycloalkyl, and are unsubstituted.

[00198] In a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, or a 6-membered heterocycloalkyl, and are substituted with 0-3 groups independently selected from hydrogen, phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In

a still further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, or a 6-membered heterocycloalkyl, and are substituted with 0-2 groups independently selected from hydrogen, phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In yet a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, or a 6-membered heterocycloalkyl, and are substituted with 0-1 group selected from hydrogen, phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In an even further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, or a 6-membered heterocycloalkyl, and are monosubstituted with a group selected from hydrogen, phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, or a 6-membered heterocycloalkyl, and are unsubstituted.

[00199] In a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl substituted with 0-3 groups independently selected from hydrogen, phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl substituted with 0-2 groups independently selected from hydrogen, phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In yet a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl substituted with 0-1 group

selected from hydrogen, phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In an even further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl monosubstituted with a group selected from hydrogen, phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise an unsubstituted 5-membered cycloalkyl.

[00200] In a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered heteroaryl or a 6-membered aryl, and are substituted with 0-3 groups independently selected from hydrogen, phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered heteroaryl or a 6-membered aryl, and are substituted with 0-2 groups independently selected from hydrogen, phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In yet a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered heteroaryl or a 6-membered aryl, and are substituted with 0-1 group selected from hydrogen, phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In an even further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered heteroaryl or a 6-membered aryl, and are monosubstituted with a group selected from hydrogen, phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, each of

R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered heteroaryl or a 6-membered aryl, and are unsubstituted.

[00201] In a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a pyrazolyl substituted with 0-3 groups independently selected from hydrogen, phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a pyrazolyl substituted with 0-2 groups independently selected from hydrogen, phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In yet a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a pyrazolyl substituted with 0-1 group selected from hydrogen, phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In an even further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a pyrazolyl monosubstituted with a group selected from hydrogen, phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise an unsubstituted pyrazolyl.

[00202] In a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, a 5-membered heteroaryl, a 6-membered aryl, or a 6-membered heterocycloalkyl, and are substituted with 0-3 groups independently selected from hydrogen, C1-C4 alkyl, and phenyl. In a still further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, or a 6-membered heterocycloalkyl, and are substituted with 0-3 groups

independently selected from hydrogen, C1-C4 alkyl, and phenyl. In yet a further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl substituted with 0-3 groups independently selected from hydrogen, C1-C4 alkyl, and phenyl. In an even further aspect, each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered heteroaryl or a 6-membered aryl, and are substituted with 0-3 groups independently selected from hydrogen, C1-C4 alkyl, and phenyl.

[00203] In a further aspect, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, $-NH_2$, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), provided that at least two of R^{12a}, R^{12b}, and R^{12c} is hydrogen, or wherein each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, a 5-membered heteroaryl, a 6-membered aryl, or a 6-membered heterocycloalkyl, and are substituted with 0-3 groups independently selected from hydrogen, phenyl, $-NH_2$, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl).

j. R^{13A}, R^{13B}, R^{13C}, R^{13D}, AND R^{13E} GROUPS

[00204] In one aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), provided that at least two of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is hydrogen. In a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is hydrogen.

[00205] In a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F,–Cl, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –

Cl, –NH_2, –OH, –CN, –NO_2, methyl, ethyl, *n*-propyl, *i*-propyl, –CH_2F, –CH_2Cl, –CH_2CH_2F, –CH_2CH_2Cl, –$CH_2CH_2CH_2F$, –$CH_2CH_2CH_2Cl$, –$CH(CH_3)CH_2F$, –$CH(CH_3)CH_2Cl$, –CH_2OH, –CH_2CH_2OH, –$CH_2CH_2CH_2OH$, –$CH(CH_3)CH_2OH$, –CH_2OCH_3, –$CH_2CH_2OCH_3$, –$CH_2CH_2CH_2OCH_3$, –$CH(CH_3)CH_2OCH_3$, –$CH_2OCH_2CH_3$, –$CH_2CH_2OCH_2CH_3$, –OCH_2F, –OCH_2CH_2F, –$OCH_2CH_2CH_2F$, –$OCH(CH_3)CH_2F$, –$OCHF_2$, –OCH_2CHF_2, –$OCH_2CH_2CHF_2$, –$OCH(CH_3)CHF_2$, –$NHCH_3$, –$NHCH_2CH_3$, –$NHCH_2CH_2CH_3$, –$NHCH(CH_3)CH_3$, –$N(CH_3)_2$, –$N(CH_2CH_3)_2$, –$N(CH_2CH_2CH_3)_2$, –$N(CH(CH_3)CH_3)_2$, –$N(CH_3)(CH_2CH_3)$, –$C(O)CH_3$, –$C(O)CH_2CH_3$, –$C(O)CH_2CH_2CH_3$, –$C(O)CH(CH_3)_2$, –CO_2CH_3, –$CO_2CH_2CH_3$, –$CO_2CH_2CH_2CH_3$, and –$CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, –NH_2, –OH, –CN, –NO_2, methyl, ethyl, –CH_2F, –CH_2Cl, –CH_2CH_2F, –CH_2CH_2Cl, –CH_2OH, –CH_2CH_2OH, –CH_2OCH_3, –$CH_2CH_2OCH_3$, –$CH_2OCH_2CH_3$, –OCH_2F, –OCH_2CH_2F, –$OCHF_2$, –OCH_2CHF_2, –$NHCH_3$, –$NHCH_2CH_3$, –$N(CH_3)_2$, –$N(CH_2CH_3)_2$, –$N(CH_3)(CH_2CH_3)$, –$C(O)CH_3$, –$C(O)CH_2CH_3$, –CO_2CH_3, and –$CO_2CH_2CH_3$. In an even further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, –NH_2, –OH, –CN, –NO_2, methyl, –CH_2F, –CH_2Cl, –CH_2OH, –CH_2OCH_3, –OCH_2F, –$OCHF_2$, –$NHCH_3$, –$N(CH_3)_2$, –$C(O)CH_3$, and –CO_2CH_3.

[00206] In a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, halogen, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, methyl, ethyl, *n*-propyl, *i*-propyl, –CH_2F, –CH_2Cl, –CH_2CH_2F, –CH_2CH_2Cl, –$CH_2CH_2CH_2F$, –$CH_2CH_2CH_2Cl$, –$CH(CH_3)CH_2F$, –$CH(CH_3)CH_2Cl$, –CH_2OH, –CH_2CH_2OH, –$CH_2CH_2CH_2OH$, –$CH(CH_3)CH_2OH$, –CH_2OCH_3, –$CH_2CH_2OCH_3$, –$CH_2CH_2CH_2OCH_3$, –$CH(CH_3)CH_2OCH_3$, –$CH_2OCH_2CH_3$, –$CH_2CH_2OCH_2CH_3$, –OCH_2F, –OCH_2CH_2F, –$OCH_2CH_2CH_2F$, –$OCH(CH_3)CH_2F$, –$OCHF_2$, –OCH_2CHF_2, –$OCH_2CH_2CHF_2$, –$OCH(CH_3)CHF_2$, –$NHCH_3$, –$NHCH_2CH_3$, –$NHCH_2CH_2CH_3$, –$NHCH(CH_3)CH_3$, –$N(CH_3)_2$, –$N(CH_2CH_3)_2$, –$N(CH_2CH_2CH_3)_2$, –$N(CH(CH_3)CH_3)_2$, –$N(CH_3)(CH_2CH_3)$, –$C(O)CH_3$, –$C(O)CH_2CH_3$, –$C(O)CH_2CH_2CH_3$, –$C(O)CH(CH_3)_2$, –CO_2CH_3, –$CO_2CH_2CH_3$, –$CO_2CH_2CH_2CH_3$, and –$CO_2CH(CH_3)_2$. In yet a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, methyl, ethyl, –CH_2F, –CH_2Cl, –CH_2CH_2F, –

CH_2CH_2Cl, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-CO_2CH_3$, and $-CO_2CH_2CH_3$. In an even further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, methyl, $-CH_2F$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-OCH_2F$, $-OCHF_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(O)CH_3$, and $-CO_2CH_3$.

[00207] In a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CH_2F$, $-CH(CH_3)CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCH_2CH_2CH_2F$, $-OCH(CH_3)CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-OCH_2CH_2CHF_2$, $-OCH(CH_3)CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-N(CH_2CH_2CH_3)_2$, $-N(CH(CH_3)CH_3)_2$, and $-N(CH_3)(CH_2CH_3)$. In yet a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, ethyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and $-N(CH_3)(CH_2CH_3)$. In an even further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, methyl, $-CH_2F$, $-CH_2Cl$, $-CH_2OH$, $-CH_2OCH_3$, $-OCH_2F$, $-OCHF_2$, $-NHCH_3$, and $-N(CH_3)_2$.

[00208] In a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, halogen, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl. In a still further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, methyl, ethyl, *n*-propyl, *i*-propyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CH_2Cl$, $-CH(CH_3)CH_2F$, $-CH(CH_3)CH_2Cl$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, –

$CH_2OCH_2CH_3$, $-CH_2CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCH_2CH_2CH_2F$, $-OCH(CH_3)CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-OCH_2CH_2CHF_2$, and $-OCH(CH_3)CHF_2$. In yet a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, methyl, ethyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-OCH_2F$, $-OCH_2CH_2F$, $-OCHF_2$, and $-OCH_2CHF_2$. In an even further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, methyl, $-CH_2F$, $-CH_2Cl$, $-CH_2OCH_3$, $-OCH_2F$, and $-OCHF_2$.

[00209] In a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, and *t*-butyl. In yet a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, methyl, ethyl, *n*-propyl, and *i*-propyl. In an even further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, methyl, and ethyl. In a still further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen and ethyl. In yet a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen and methyl.

[00210] In a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen and C1-C4 haloalkoxyalkyl. In a still further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, $-OCH_2F$, $-OCH_2CH_2F$, $-OCH_2CH_2CH_2F$, $-OCH(CH_3)CH_2F$, $-OCHF_2$, $-OCH_2CHF_2$, $-OCH_2CH_2CHF_2$, and $-OCH(CH_3)CHF_2$. In yet a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, $-OCH_2F$, $-OCH_2CH_2F$, $-OCHF_2$, and $-OCH_2CHF_2$. In an even further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, $-OCH_2F$, and $-OCHF_2$.

[00211] In a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen and C1-C4 alkoxy. In a still further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH(CH_3)CH_2OCH_3$, $-CH_2OCH_2CH_3$, and $-CH_2CH_2OCH_2CH_3$. In yet a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, and $-CH_2OCH_2CH_3$. In an even further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen and $-CH_2OCH_3$.

[00212] In a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, halogen, and C1-C4 haloalkyl. In a still further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, $–CH_2F$, $–CH_2Cl$, $–CH_2CH_2F$, $–CH_2CH_2Cl$, $–CH_2CH_2CH_2F$, $–CH_2CH_2CH_2Cl$, $–CH(CH_3)CH_2F$, and $–CH(CH_3)CH_2Cl$. In yet a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, –F, –Cl, $–CH_2F$, $–CH_2Cl$, $–CH_2CH_2F$, and $–CH_2CH_2Cl$. In an even further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, $–CH_2F$, and $–CH_2Cl$.

[00213] In a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, halogen, $–NH_2$, –CN, $–NO_2$, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl), provided that at least two of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} are hydrogen.

[00214] In a further aspect, each of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is independently selected from hydrogen, halogen, $–NH_2$, –OH, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino, provided that at least two of R^{13a}, R^{13b}, R^{13c}, R^{13d}, and R^{13e} is hydrogen.

k. R^{20A}, R^{20B}, R^{21A}, R^{21B}, R^{21C}, AND R^{21D} GROUPS

[00215] In one aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl. In a further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is hydrogen.

[00216] In a further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl. In a still further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, –F, –Cl, methyl, ethyl, *n*-propyl, *i*-propyl, $–CH_2F$, $–CH_2Cl$, $–CH_2CH_2F$, $–CH_2CH_2Cl$, $–CH_2CH_2CH_2F$, $–CH_2CH_2CH_2Cl$, $–CH(CH_3)CH_2F$, $–CH(CH_3)CH_2Cl$, $–CH_2OCH_3$, $–CH_2CH_2OCH_3$, $–CH_2CH_2CH_2OCH_3$, $–CH(CH_3)CH_2OCH_3$, $–CH_2OCH_2CH_3$, $–CH_2CH_2OCH_2CH_3$, $–OCH_2F$, $–OCH_2CH_2F$, $–OCH_2CH_2CH_2F$, $–OCH(CH_3)CH_2F$, $–OCHF_2$, $–OCH_2CHF_2$, $–OCH_2CH_2CHF_2$, and $–OCH(CH_3)CHF_2$. In yet a further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is

independently selected from hydrogen, –F, –Cl, methyl, ethyl, $–CH_2F$, $–CH_2Cl$, $–CH_2CH_2F$, $–CH_2CH_2Cl$, $–CH_2OCH_3$, $–CH_2CH_2OCH_3$, $–CH_2OCH_2CH_3$, $–OCH_2F$, $–OCH_2CH_2F$, $–OCHF_2$, and $–OCH_2CHF_2$. In an even further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, –F, –Cl, methyl, $–CH_2F$, $–CH_2Cl$, $–CH_2OCH_3$, $–OCH_2F$, and $–OCHF_2$.

[00217] In a further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, –OH, –CN, and C1-C4 alkyl. In a still further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, –F, –Cl, –OH, –CN, methyl, ethyl, *n*-propyl, and *i*-propyl. In yet a further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, –F, –Cl, –OH, –CN, methyl, and ethyl. In an even further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, –F, –Cl, –OH, –CN, and methyl.

[00218] In a further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen and halogen. In a still further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, –F, and –Cl. In yet a further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen and –F. In an even further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen and –Cl.

[00219] In a further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, and *t*-butyl. In yet a further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, methyl, ethyl, *n*-propyl, and *i*-propyl. In an even further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, methyl, and ethyl. In a still further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen and ethyl. In yet a further aspect, each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen and methyl.

l. R^{30} GROUPS

[00220] In one aspect, R^{30}, when present, is selected from hydrogen and C1-C4 alkyl. In a further aspect, R^{30}, when present, is hydrogen.

[00221] In a further aspect, R^{30}, when present, is selected from hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, and *t*-butyl. In a still further aspect, R^{30}, when present, is selected from hydrogen, methyl, ethyl, *n*-propyl, and *i*-propyl. In yet a further aspect, R^{30}, when present, is selected from hydrogen, methyl, and ethyl. In an even further aspect, R^{30}, when present, is selected from hydrogen and ethyl. In a still further aspect, R^{30}, when present, is selected from hydrogen and methyl.

[00222] In a further aspect, R^{30}, when present, is C1-C4 alkyl. In a still further aspect, R^{30}, when present, is selected from methyl, ethyl, *n*-propyl, and *i*-propyl. In yet a further aspect, R^{30}, when present, is selected from methyl and ethyl. In an even further aspect, R^{30}, when present, is ethyl. In a still further aspect, R^{30}, when present, is methyl.

m. R^{31} GROUPS

[00223] In one aspect, R^{31}, when present, is selected from hydrogen and C1-C4 alkyl. In a further aspect, R^{31}, when present, is hydrogen.

[00224] In a further aspect, R^{31}, when present, is selected from hydrogen, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, and *t*-butyl. In a still further aspect, R^{31}, when present, is selected from hydrogen, methyl, ethyl, *n*-propyl, and *i*-propyl. In yet a further aspect, R^{31}, when present, is selected from hydrogen, methyl, and ethyl. In an even further aspect, R^{31}, when present, is selected from hydrogen and ethyl. In a still further aspect, R^{31}, when present, is selected from hydrogen and methyl.

[00225] In a further aspect, R^{31}, when present, is C1-C4 alkyl. In a still further aspect, R^{31}, when present, is selected from methyl, ethyl, *n*-propyl, and *i*-propyl. In yet a further aspect, R^{31}, when present, is selected from methyl and ethyl. In an even further aspect, R^{31}, when present, is ethyl. In a still further aspect, R^{31}, when present, is methyl.

n. Ar^1 Groups

[00226] In one aspect, Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a further aspect, Ar^1 is selected from aryl and heteroaryl and substituted with 0-2 groups independently selected from phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, Ar^1 is selected from aryl and heteroaryl and substituted with 0-1 group selected from phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In yet a further aspect, Ar^1 is selected from aryl and heteroaryl and substituted with a group selected from phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In an even further aspect, Ar^1 is selected from aryl and heteroaryl and is unsubstituted.

[00227] In a further aspect, Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, halogen, C1-C4 alkyl, and C1-C4 alkoxy. In a still further aspect, Ar^1 is selected from aryl and heteroaryl and substituted with 0-2 groups independently selected from phenyl, halogen, C1-C4 alkyl, and C1-C4 alkoxy. In yet a further aspect, Ar^1 is selected from aryl and heteroaryl and substituted with 0-1 group selected from halogen, C1-C4 alkyl, and C1-C4 alkoxy. In an even further aspect, Ar^1 is selected from aryl and heteroaryl and substituted with a group selected from phenyl, halogen, C1-C4 alkyl, and C1-C4 alkoxy.

[00228] In a further aspect, Ar^1 is aryl substituted with 0-3 groups independently selected from phenyl, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, Ar^1 is aryl substituted with 0-2 groups independently selected from phenyl, halogen, $-NH_2$, –OH,

–CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In yet a further aspect, Ar^1 is aryl substituted with 0-1 group selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In an even further aspect, Ar^1 is aryl monosubstituted with a group selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^1 is unsubstituted aryl.

[00229] In a further aspect, Ar^1 is aryl substituted with 0-3 groups independently selected from phenyl, halogen, C1-C4 alkyl, and C1-C4 alkoxy. In a still further aspect, Ar^1 is aryl substituted with 0-2 groups independently selected from halogen, C1-C4 alkyl, and C1-C4 alkoxy. In yet a further aspect, Ar^1 is aryl substituted with 0-1 group selected from phenyl, halogen, C1-C4 alkyl, and C1-C4 alkoxy. In an even further aspect, Ar^1 is aryl monosubstituted with a group selected from phenyl, halogen, C1-C4 alkyl, and C1-C4 alkoxy.

[00230] In a further aspect, Ar^1 is phenyl substituted with 0-3 groups independently selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^1 is phenyl substituted with 0-2 groups independently selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In yet a further aspect, Ar^1 is phenyl substituted with 0-1 group selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In an even further aspect, Ar^1 is phenyl monosubstituted with a group selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4

haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^1 is unsubstituted phenyl.

[00231] In a further aspect, Ar^1 is phenyl substituted with 0-3 groups independently selected from halogen, C1-C4 alkyl, and C1-C4 alkoxy. In a still further aspect, Ar^1 is phenyl substituted with 0-2 groups independently selected from halogen, C1-C4 alkyl, and C1-C4 alkoxy. In yet a further aspect, Ar^1 is phenyl substituted with 0-1 group selected from halogen, C1-C4 alkyl, and C1-C4 alkoxy. In an even further aspect, Ar^1 is phenyl monosubstituted with a group selected from halogen, C1-C4 alkyl, and C1-C4 alkoxy.

[00232] In a further aspect, Ar^1 is heteroaryl substituted with 0-3 groups independently selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^1 is heteroaryl substituted with 0-2 groups independently selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In yet a further aspect, Ar^1 is heteroaryl substituted with 0-1 group selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In an even further aspect, Ar^1 is heteroaryl monosubstituted with a group selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^1 is unsubstituted heteroaryl.

[00233] In a further aspect, Ar^1 is heteroaryl substituted with 0-3 groups independently selected from C1-C4 alkyl and phenyl. In a still further aspect, Ar^1 is heteroaryl substituted with 0-2 groups independently selected from C1-C4 alkyl and phenyl. In yet a further aspect, Ar^1 is heteroaryl substituted with 0-1 group selected from C1-C4 alkyl and phenyl. In an even further aspect, Ar^1 is heteroaryl monosubstituted with a group selected from C1-C4 alkyl and phenyl.

[00234] In a further aspect, Ar^1 is thiophenyl substituted with 0-3 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In a still further aspect, Ar^1 is thiophenyl substituted with 0-2 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In yet a further aspect, Ar^1 is thiophenyl substituted with 0-1 group selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In an even further aspect, Ar^1 is thiophenyl monosubstituted with a group selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In a still further aspect, Ar^1 is unsubstituted thiophenyl.

[00235] In a further aspect, Ar^1 is thiophenyl substituted with 0-3 groups independently selected from C1-C4 alkyl. In a still further aspect, Ar^1 is thiophenyl substituted with 0-2 groups independently selected from C1-C4 alkyl. In yet a further aspect, Ar^1 is thiophenyl substituted with 0-1 group selected from C1-C4 alkyl. In an even further aspect, Ar^1 is thiophenyl monosubstituted with a group selected from C1-C4 alkyl.

[00236] In a further aspect, Ar^1 is 1H-thieno[2,3-c]pyrazolyl substituted with 0-3 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In a still further aspect, Ar^1 is 1H-thieno[2,3-c]pyrazolyl substituted with 0-2 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In yet a further aspect, Ar^1 is 1H-thieno[2,3-c]pyrazolyl substituted with 0-1 group selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-

C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In an even further aspect, Ar^1 is 1H-thieno[2,3-c]pyrazolyl monosubstituted with a group selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^1 is unsubstituted 1H-thieno[2,3-c]pyrazolyl.

[00237] In a further aspect, Ar^1 is 1H-thieno[2,3-c]pyrazolyl substituted with 0-3 groups independently selected from C1-C4 alkyl and phenyl. In a still further aspect, Ar^1 is 1H-thieno[2,3-c]pyrazolyl substituted with 0-2 groups independently selected from C1-C4 alkyl and phenyl. In yet a further aspect, Ar^1 is 1H-thieno[2,3-c]pyrazolyl substituted with 0-1 group selected from C1-C4 alkyl and phenyl. In an even further aspect, Ar^1 is 1H-thieno[2,3-c]pyrazolyl monosubstituted with a group selected from C1-C4 alkyl and phenyl.

[00238] In a further aspect, Ar^1 is 5,6-dihydro-4H-cyclopenta[b]thiophenyl substituted with 0-3 groups independently selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^1 is 5,6-dihydro-4H-cyclopenta[b]thiophenyl substituted with 0-2 groups independently selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In yet a further aspect, Ar^1 is 5,6-dihydro-4H-cyclopenta[b]thiophenyl substituted with 0-1 group selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In an even further aspect, Ar^1 is 5,6-dihydro-4H-cyclopenta[b]thiophenyl monosubstituted with a group selected from phenyl, halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^1 is unsubstituted 5,6-dihydro-4H-cyclopenta[b]thiophenyl.

[00239] In a further aspect, Ar^1 is selected from aryl and heteroaryl and substituted with 1-3 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino.

[00240] In a further aspect, Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, $–NH_2$, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl).

o. Ar^2 Groups

[00241] In one aspect, Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In a further aspect, Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-2 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In a still further aspect, Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-1 group selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In yet a further aspect, Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with a group selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl). In an even further aspect, Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and is unsubstituted.

[00242] In a further aspect, Ar^2 is aryl substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4)

dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^2 is aryl substituted with 0-2 groups independently selected from halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In yet a further aspect, Ar^2 is aryl substituted with 0-1 group selected from halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In an even further aspect, Ar^2 is aryl substituted with a group selected from halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^2 is unsubstituted aryl.

[00243] In a further aspect, Ar^2 is phenyl substituted with 0-3 groups independently selected from halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^2 is phenyl substituted with 0-2 groups independently selected from halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In yet a further aspect, Ar^2 is phenyl substituted with 0-1 group selected from halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In an even further aspect, Ar^2 is phenyl substituted with a group selected from halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl). In a still further aspect, Ar^2 is unsubstituted phenyl.

[00244] In a further aspect, Ar^2 is 6- to 10-membered N-containing heteroaryl substituted with 0-3 groups independently selected from halogen, –NH_2, –OH, –CN, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4

alkyl). In a still further aspect, Ar^2 is 6- to 10-membered N-containing heteroaryl substituted with 0-2 groups independently selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In yet a further aspect, Ar^2 is 6- to 10-membered N-containing heteroaryl substituted with 0-1 group selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In an even further aspect, Ar^2 is 6- to 10-membered N-containing heteroaryl substituted with a group selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, Ar^2 is unsubstituted 6- to 10-membered N-containing heteroaryl.

[00245] In a further aspect, Ar^2 is quinolinyl substituted with 0-3 groups independently selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, Ar^2 is quinolinyl substituted with 0-2 groups independently selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In yet a further aspect, Ar^2 is quinolinyl substituted with 0-1 group selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In an even further aspect, Ar^2 is quinolinyl substituted with a group selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl). In a still further aspect, Ar^2 is unsubstituted quinolinyl.

[00246] In a further aspect, Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from –F, –Cl, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4

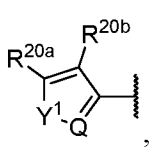
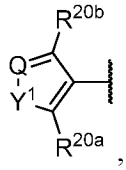
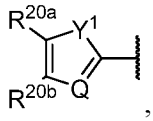
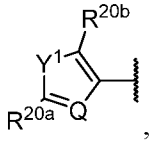
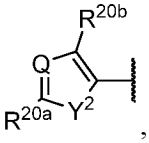
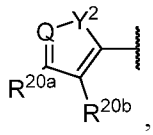
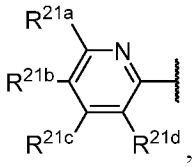
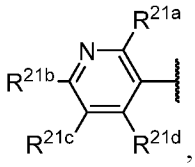
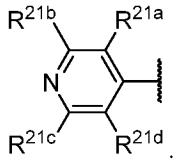
haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl).

[00247] In a further aspect, Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, –NH_2, –CN, –NO_2, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and –CO_2(C1-C4 alkyl).

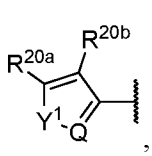
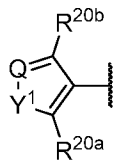
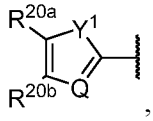
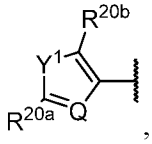
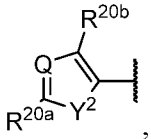
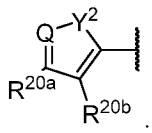
[00248] In a further aspect, Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, –NH_2, –OH, –NO_2, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino.

p. Ar^3 Groups

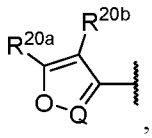
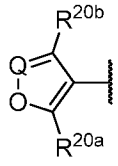
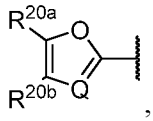
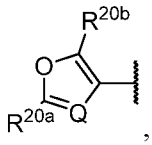
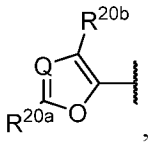
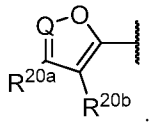
[00249] In one aspect, Ar^3 is a 5- or 6-membered heteroaryl selected from:


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and

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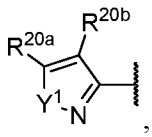
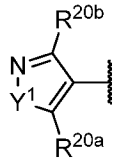
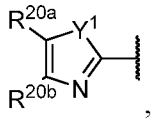
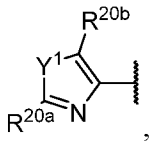
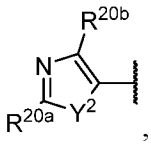
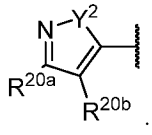
[00250] In a further aspect, Ar^3 is a 5-membered heteroaryl selected from:

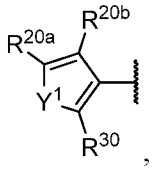
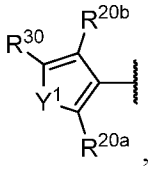
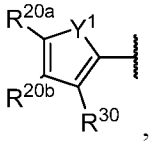
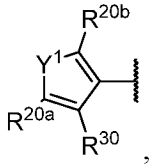
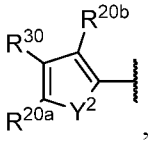
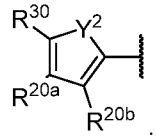
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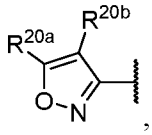
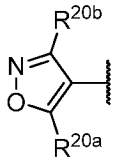
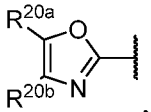
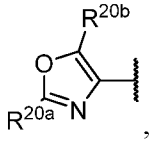
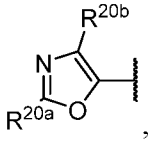
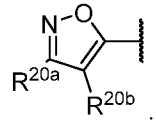
[00252] In a further aspect, Ar^3 is a 5-membered heteroaryl selected from:

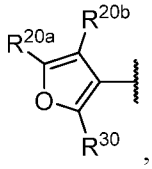
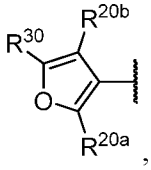
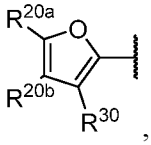
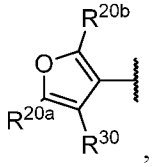
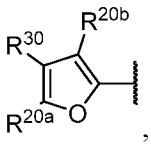
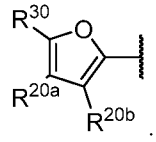
[00253] In a further aspect, Ar^3 is a 5-membered heteroaryl selected from:

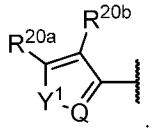
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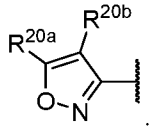
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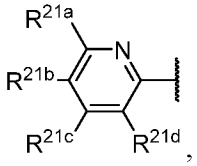
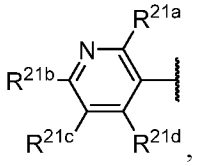
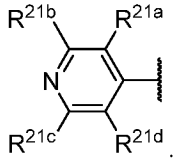
[00256] In a further aspect, Ar^3 is:



[00257] In a further aspect, Ar^3 is:

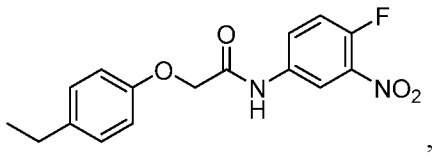
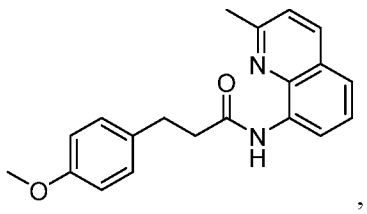


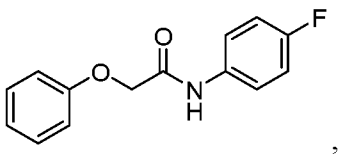
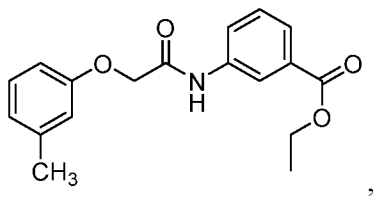
[00258] In a further aspect, Ar^3 is a 6-membered heteroaryl selected from:

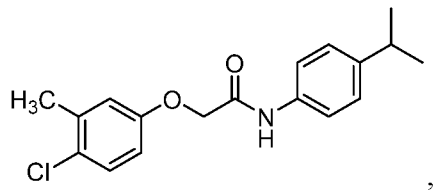
, , and .

2. EXAMPLE COMPOUNDS

[00259] In one aspect, a compound can be present as one or more of the following structures:

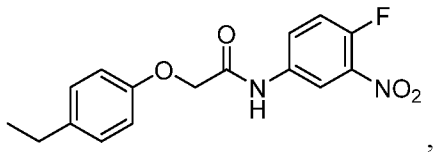
, ,

, ,

and ,

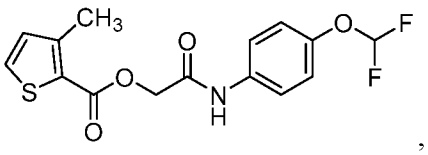
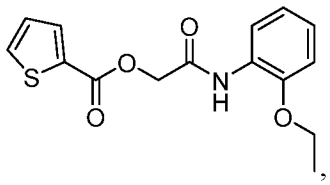
or a pharmaceutically acceptable salt thereof.

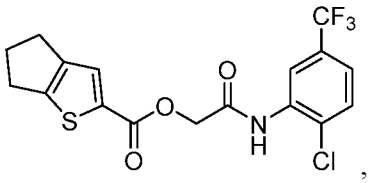
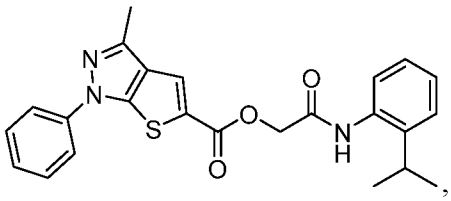
[00260] In a further aspect, a compound can be present as:

,

or a pharmaceutically acceptable salt thereof.

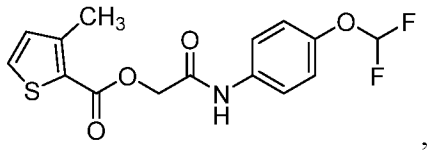
[00261] In one aspect, a compound can be present as one or more of the following structures:

, ,

, and ,

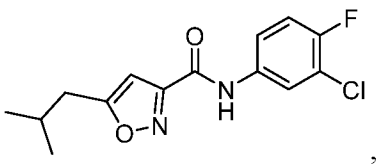
or a pharmaceutically acceptable salt thereof.

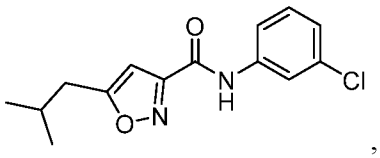
[00262] In one aspect, a compound can be present as:

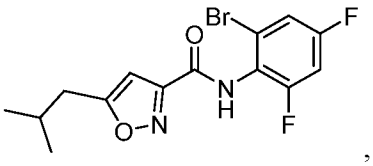
,

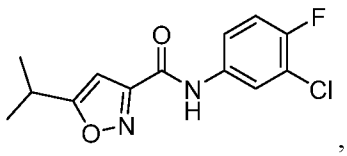
or a pharmaceutically acceptable salt thereof.

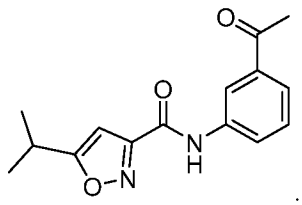
[00263] In one aspect, a compound can be present as one or more of the following structures:


,


,

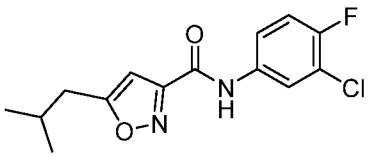

,


,

and 
.

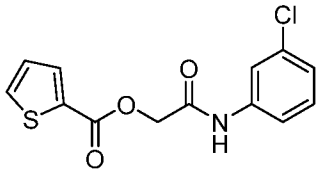
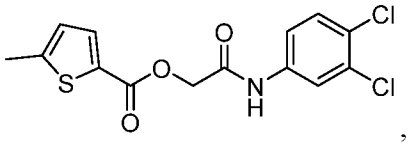
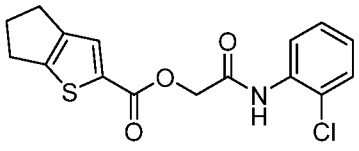
or a pharmaceutically acceptable salt thereof.

[00264] In one aspect, a compound can be present as:


,

or a pharmaceutically acceptable salt thereof.

[00265] In a further aspect, the compound is not:

and .

C. METHODS OF MAKING A COMPOUND

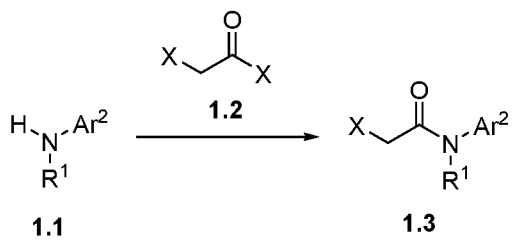
[00266] The compounds of this invention can be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature, exemplified in the experimental sections or clear to one skilled in the art. For clarity, examples having a single substituent are shown where multiple substituents are allowed under the definitions disclosed herein.

[00267] Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the following Reaction Schemes, as described and exemplified below. In certain specific examples, the disclosed compounds can be prepared by Routes I-IV, as described and exemplified below. The following examples are provided so that the invention might be more fully understood, are illustrative only, and should not be construed as limiting.

1. ROUTE I

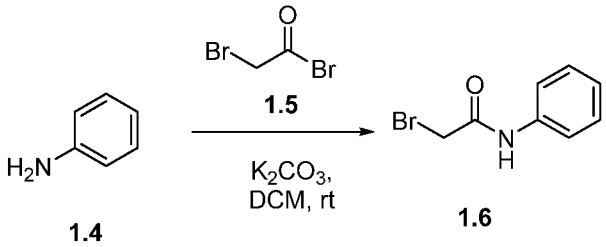
[00268] In one aspect, substituted activators of BMP can be prepared as shown below.

SCHEME 1A.



[00269] Compounds are represented in generic form, wherein each X is selected from Cl and Br and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 1B.

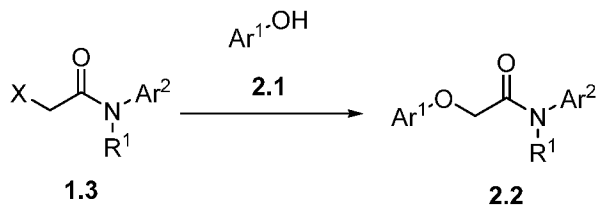


[00270] In one aspect, compounds of type **1.6**, and similar compounds, can be prepared according to reaction **Scheme 1B** above. Thus, compounds of type **1.6** can be prepared by acylation of an appropriate amine, e.g., **1.4** as shown above, and an appropriate acyl halide, e.g., 2-bromoacetyl bromide as shown above. Appropriate amines and appropriate acyl halides are commercially available or prepared by methods known to one skilled in the art. The acylation is carried out in the presence of an appropriate base, e.g., potassium carbonate, in an appropriate solvent, e.g., dichloromethane (DCM). As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **1.1** and **1.2**), can be substituted in the reaction to provide substituted amide derivatives similar to Formula **1.3**.

2. ROUTE II

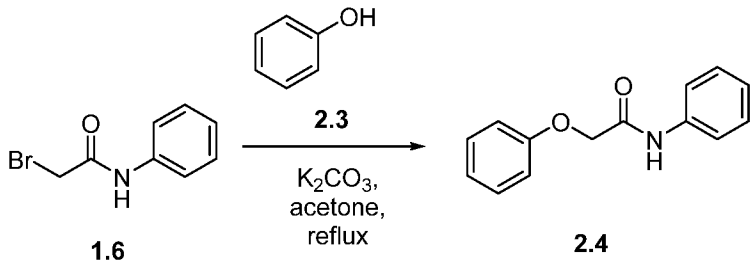
[00271] In one aspect, substituted activators of BMP can be prepared as shown below.

SCHEME 2A.



[00272] Compounds are represented in generic form, wherein X is selected from Cl and Br and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 2B.



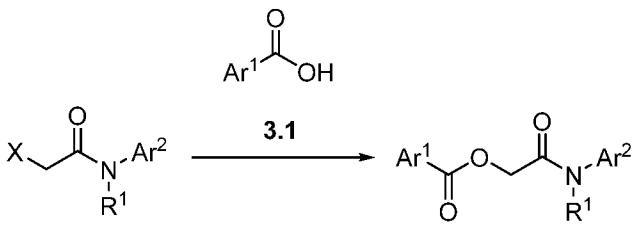
1.6 2.4

[00273] In one aspect, compounds of type **2.4**, and similar compounds, can be prepared according to reaction **Scheme 2B** above. Thus, compounds of type **2.4** can be prepared by a substitution reaction of an appropriate alkyl halide, e.g., **1.6** as shown above, and an appropriate alcohol, e.g., phenol as shown above. Appropriate alcohols are commercially available or prepared by methods known to one skilled in the art. The substitution reaction is carried out in the presence of an appropriate base, e.g., potassium carbonate, in an appropriate solvent, e.g., acetone. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **1.3** and **2.1**), can be substituted in the reaction to provide substituted amide derivatives similar to Formula **2.2**.

3. ROUTE III

[00274] In one aspect, substituted activators of BMP can be prepared as shown below.

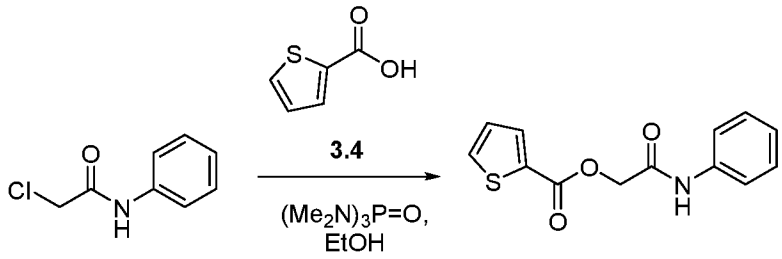
SCHEME 3A.



1.3 3.2

[00275] Compounds are represented in generic form, wherein X is selected from Cl and Br and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 3B.



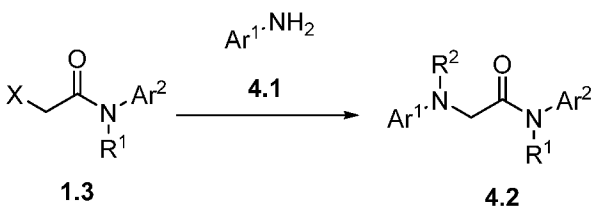
3.3 3.5

[00276] In one aspect, compounds of type **3.5**, and similar compounds, can be prepared according to reaction **Scheme 3B** above. Thus, compounds of type **3.5** can be prepared by a coupling reaction of an appropriate alkyl halide, e.g., **3.3** as shown above, and an appropriate carboxylic acid, e.g., thiophene-2-carboxylic acid as shown above. Appropriate carboxylic acids are commercially available or prepared by methods known to one skilled in the art. The coupling reaction is carried out in the presence of an appropriate phosphine oxide, e.g., hexamethylphosphoramide (HMPA), in an appropriate solvent, e.g., ethanol. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **1.3** and **3.1**), can be substituted in the reaction to provide substituted amide derivatives similar to Formula **3.2**.

4. ROUTE IV

[00277] In one aspect, substituted activators of BMP can be prepared as shown below.

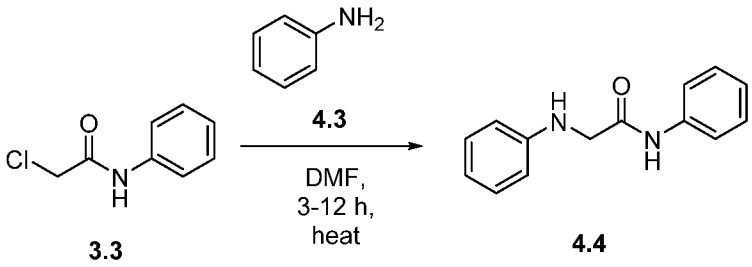
SCHEME 4A.



1.3 4.2

[00278] Compounds are represented in generic form, wherein X is selected from Cl and Br and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 4B.



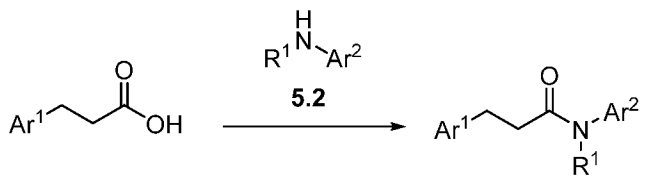
3.3 4.4

[00279] In one aspect, compounds of type **4.4**, and similar compounds, can be prepared according to reaction **Scheme 4B** above. Thus, compounds of type **4.4** can be prepared by alkylation of an appropriate amine, e.g., **4.3** as shown above, and an appropriate alkyl halide, e.g., **3.3** as shown above. Appropriate amines and appropriate alkyl halides are commercially available or prepared by methods known to one skilled in the art. The alkylation is carried out in an appropriate solvent, e.g., dimethylformamide (DMF), for an appropriate period of time, e.g., 3-12 h. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **1.3** and **4.1**), can be substituted in the reaction to provide substituted amide derivatives similar to Formula **4.2**.

5. ROUTE V

[00280] In one aspect, substituted activators of BMP can be prepared as shown below.

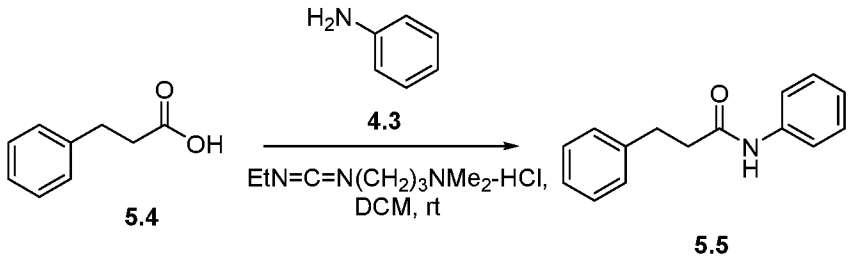
SCHEME 5A.



5.1 5.3

[00281] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 5B.

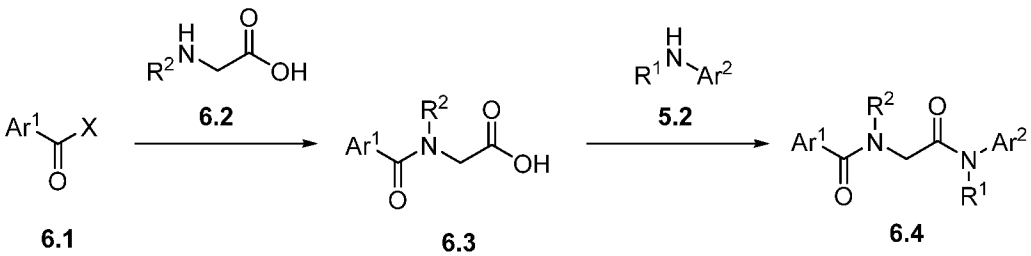


[00282] In one aspect, compounds of type **5.5**, and similar compounds, can be prepared according to reaction **Scheme 5B** above. Thus, compounds of type **5.5** can be prepared by a coupling reaction of an appropriate carboxylic acid, e.g., **5.4** as shown above, and an appropriate amine, e.g., **4.3** as shown above. Appropriate carboxylic acids and appropriate amines are commercially available or prepared by methods known to one skilled in the art. The coupling reaction is carried out in the presence of an appropriate imine, e.g., 3-(((ethylimino)methylene)amino)-N,N-dimethylpropan-1-amine hydrochloride, in an appropriate solvent, e.g., dichloromethane (DCM). As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **5.1** and **5.2**), can be substituted in the reaction to provide substituted amide derivatives similar to Formula **5.3**.

6. ROUTE VI

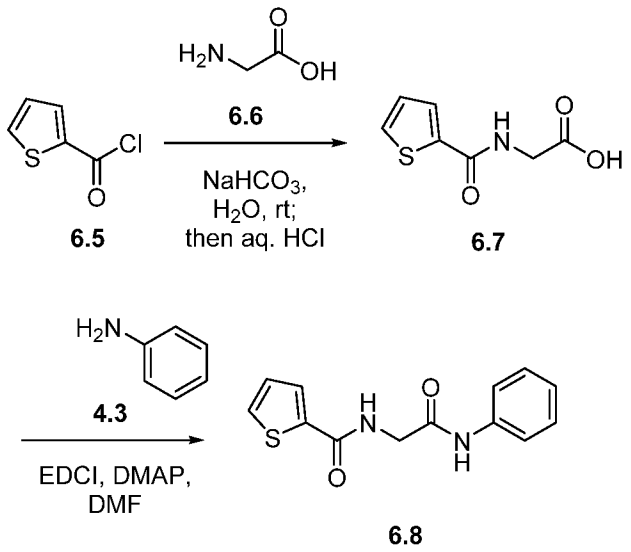
[00283] In one aspect, substituted activators of BMP can be prepared as shown below.

SCHEME 6A.



[00284] Compounds are represented in generic form, wherein X is selected from Cl and Br and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 6B.

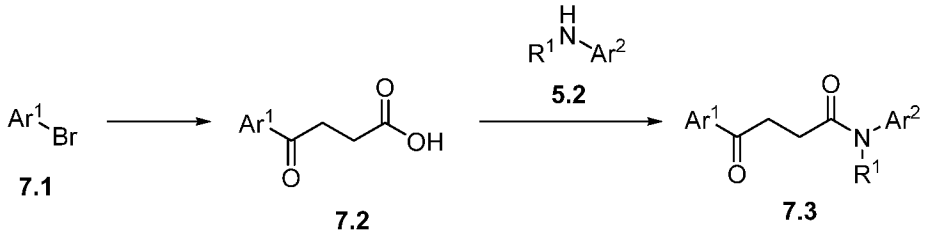


[00285] In one aspect, compounds of type **6.8**, and similar compounds, can be prepared according to reaction **Scheme 6B** above. Thus, compounds of type **6.7** can be prepared by acylation of an appropriate acyl halide, e.g., **6.5** as shown above, and an appropriate amine, e.g., **6.6** as shown above. Appropriate acyl halides and appropriate amides are commercially available or prepared by methods known to one skilled in the art. The acylation is carried out in the presence of an appropriate base, e.g., sodium bicarbonate, followed by addition of an appropriate acid, e.g., hydrochloric acid. Compounds of type **6.8** can be prepared by a coupling reaction to an appropriate carboxylic acid, e.g., **6.7** as shown above, with an appropriate amine, e.g., **4.3** as shown above. Appropriate amines are commercially available or prepared by methods known to one skilled in the art. The coupling reaction is carried out in the presence of an appropriate coupling agent, e.g., 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), and an appropriate activating agent, e.g., 4-dimethylaminopyridine (DMAP), in an appropriate solvent, e.g., dimethylformamide (DMF). As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **5.2**, **6.1**, **6.2**, and **6.3**), can be substituted in the reaction to provide substituted tetrahydroquinoline derivatives similar to Formula **6.4**.

7. ROUTE VII

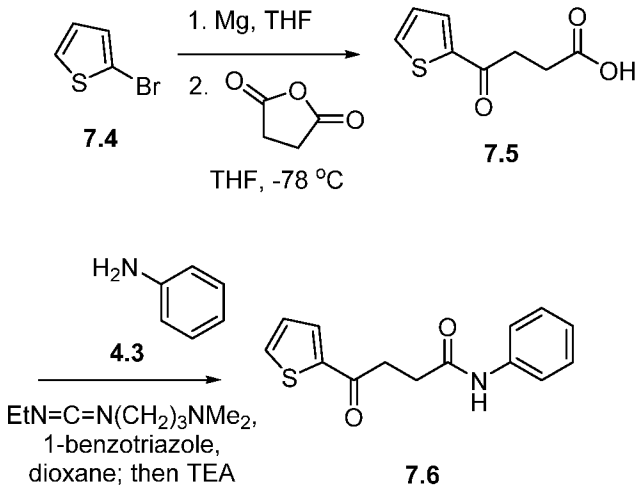
[00286] In one aspect, substituted activators of BMP can be prepared as shown below.

SCHEME 7A.



[00287] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 7B.



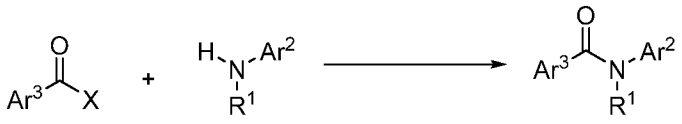
[00288] In one aspect, compounds of type **7.6**, and similar compounds, can be prepared according to reaction **Scheme 7B** above. Thus, compounds of type **7.5** can be prepared by a Grignard reaction of an appropriate aryl bromide, e.g., **7.4** as shown above. Appropriate aryl bromides are commercially available or prepared by methods known to one skilled in the art. The Grignard reaction is carried out in the presence of an appropriate magnesium source, e.g., magnesium metal, in an appropriate solvent, e.g., tetrahydrofuran (THF), followed by addition of dihydrofuran-2,5-dione in an appropriate solvent, e.g., tetrahydrofuran (THF), at an appropriate temperature, e.g., -78 °C. Compounds of type **7.6** can be prepared by a coupling reaction to an appropriate carboxylic acid, e.g., **7.5** as shown above, with an appropriate amine, e.g., **4.3** as shown above. Appropriate amines are commercially available or prepared by methods known to one skilled in the art. The coupling reaction is carried out in the presence of an appropriate imine, e.g., 3-(((ethylimino)methylene)amino)-N,N-

dimethylpropan-1-amine, and an appropriate ligand, e.g., 1-benzotriazole, in an appropriate solvent, e.g., dioxane, followed by addition of an appropriate base, e.g., triethylamine (TEA). As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **5.2**, **7.1**, and **7.2**), can be substituted in the reaction to provide substituted amide derivatives similar to Formula **7.3**.

8. ROUTE VIII

[00289] In one aspect, substituted activators of BMP can be prepared as shown below.

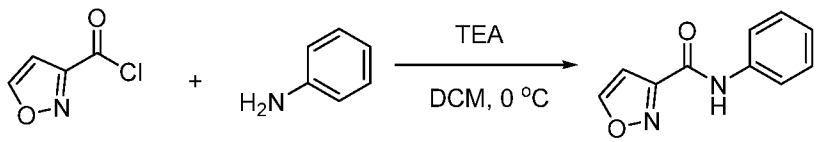
SCHEME 8A.



8.1 **1.1** **8.2**

[00290] Compounds are represented in generic form, wherein X is selected from Cl and Br and with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 8B.



8.3 **4.3** **8.4**

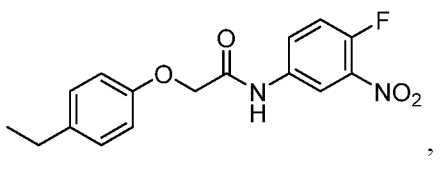
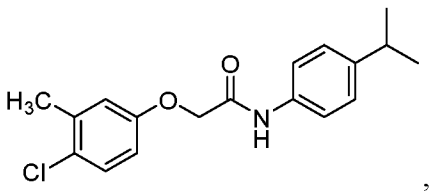
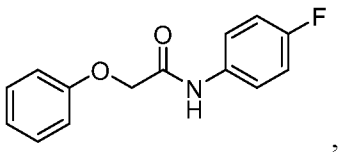
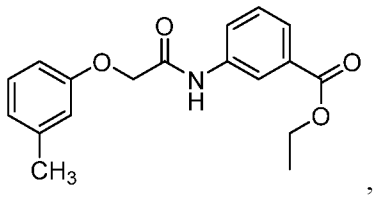
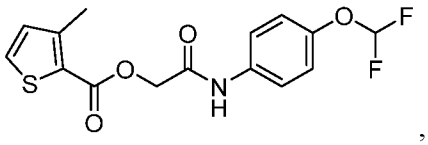
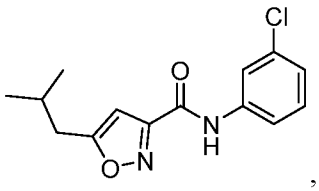
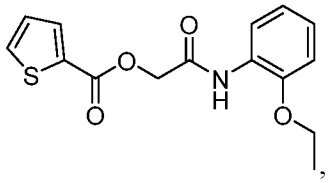
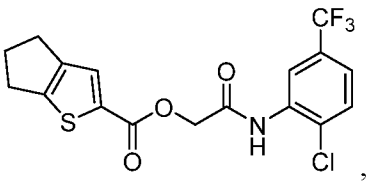
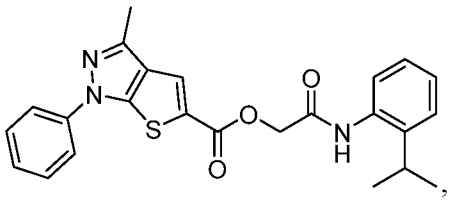
[00291] In one aspect, compounds of type **8.4**, and similar compounds, can be prepared according to reaction **Scheme 8B** above. Thus, compounds of type **8.4** can be prepared by acylation of an appropriate acyl halide, e.g., **8.3** as shown above, and an appropriate amine, e.g., **4.3** as shown above. Appropriate acyl halides and appropriate amines are commercially available or prepared by methods known to one skilled in the art. The acylation is carried out in the presence of an appropriate base, e.g., triethylamine (TEA), in an appropriate solvent, e.g., dichloromethane (DCM), at an appropriate temperature, e.g., 0 °C. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized

approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **8.1** and **1.1**), can be substituted in the reaction to provide substituted amide derivatives similar to Formula **8.4**.

D. PHARMACEUTICAL COMPOSITIONS

[00292] In one aspect, disclosed are pharmaceutical compositions comprising a disclosed compound, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[00293] In one aspect, disclosed are pharmaceutical compositions comprising an effective amount of a compound having a structure selected from:


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and

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or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

[00294] In various aspects, the compounds and compositions of the invention can be administered in pharmaceutical compositions, which are formulated according to the intended method of administration. The compounds and compositions described herein can be formulated in a conventional manner using one or more physiologically acceptable carriers or excipients. For example, a pharmaceutical composition can be formulated for local or systemic administration, *e.g.*, administration by drops or injection into the ear, insufflation (such as into the ear), intravenous, topical, or oral administration.

[00295] In a further aspect, the composition further comprises an effective amount of at least one chemotherapeutic agent.

[00296] The nature of the pharmaceutical compositions for administration is dependent on the mode of administration and can readily be determined by one of ordinary skill in the art. In various aspects, the pharmaceutical composition is sterile or sterilizable. The therapeutic compositions featured in the invention can contain carriers or excipients, many of which are known to skilled artisans. Excipients that can be used include buffers (for example, citrate buffer, phosphate buffer, acetate buffer, and bicarbonate buffer), amino acids, urea, alcohols, ascorbic acid, phospholipids, polypeptides (for example, serum albumin), EDTA, sodium chloride, liposomes, mannitol, sorbitol, water, and glycerol. The nucleic acids, polypeptides, small molecules, and other modulatory compounds featured in the invention can be administered by any standard route of administration. For example, administration can be parenteral, intravenous, subcutaneous, or oral. A modulatory compound can be formulated in various ways, according to the corresponding route of administration. For example, liquid solutions can be made for administration by drops into the ear, for injection, or for ingestion; gels or powders can be made for ingestion or topical application. Methods for making such formulations are well known and can be found in, for example, Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, PA 1990.

[00297] In various aspects, the disclosed pharmaceutical compositions comprise the disclosed compounds (including pharmaceutically acceptable salt(s) thereof) as an active ingredient, a pharmaceutically acceptable carrier, and, optionally, other therapeutic

ingredients or adjuvants. The instant compositions include those suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00298] In various aspects, the pharmaceutical compositions of this invention can include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of the compounds of the invention. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

[00299] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[00300] In preparing the compositions for oral dosage form, any convenient pharmaceutical media can be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets can be coated by standard aqueous or nonaqueous techniques.

[00301] A tablet containing the composition of this invention can be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets can be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets can be made by

molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

[00302] The pharmaceutical compositions of the present invention comprise a compound of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00303] Pharmaceutical compositions of the present invention suitable for parenteral administration can be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[00304] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[00305] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, mouth washes, gargles, and the like. Further, the compositions can be in a form suitable for

use in transdermal devices. These formulations can be prepared, utilizing a compound of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

[00306] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories can be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

[00307] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, and/or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

[00308] In a further aspect, an effective amount is a therapeutically effective amount. In a still further aspect, an effective amount is a prophylactically effective amount.

[00309] In a further aspect, the pharmaceutical composition is administered to a mammal. In a still further aspect, the mammal is a human. In an even further aspect, the human is a patient.

[00310] In a further aspect, the pharmaceutical composition is used to treat a disorder associated with BMP signaling such as, for example, juvenile polyposis syndrome (JPS), hereditary pulmonary arterial hypertension (HPAH), obesity osteoporosis, and chronic kidney disease.

[00311] In a further aspect, the pharmaceutical composition is used to increase extracellular matrix production and chondrocyte differentiation as in, for example, cartilage

repair for osteoarthritis. In a still further aspect, the pharmaceutical composition is used to induce bone formation as in, for example, a bone fracture.

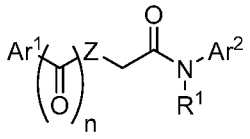
[00312] In a further aspect, the pharmaceutical composition is used to treat a disease of cellular proliferation. In a still further aspect, the disease of cellular proliferation is a cancer. In yet a further aspect, the cancer is selected from leukemia, breast cancer, prostate cancer, Ewing sarcoma, gastric cancer, melanoma, multiple myeloma, blastic plasmacytoid dendritic cell neoplasm, human squamous carcinoma, NUT midline carcinoma, lymphoma, angiogenesis, bladder cancer, thyroid cancer, childhood rhabdomyosarcoma, ovarian cancer, neurofibromatosis, lung cancer, colorectal cancer, IDH1-mutant glioma, uveal melanoma, pancreatic cancer, glioblastoma, neuroblastoma, advanced systemic mastocytosis, osteosarcoma, Merkel cell carcinoma, medulloblastoma, and malignant peripheral nerve sheath tumors. In a further aspect, the disorder associated with diminished BMP signaling is a cancer.

[00313] It is understood that the disclosed compositions can be prepared from the disclosed compounds. It is also understood that the disclosed compositions can be employed in the disclosed methods of using.

E. METHODS OF TREATING A DISORDER ASSOCIATED WITH DIMINISHED BMP SIGNALING

[00314] In various aspects, the compounds and compositions disclosed herein are useful for treating, preventing, ameliorating, controlling or reducing the risk of a variety of disorders associated with BMP signaling, including, for example, juvenile polyposis syndrome (JPS), hereditary pulmonary arterial hypertension (HPAH), obesity osteoporosis, chronic kidney disease, and cancer. Thus, in one aspect, disclosed are methods of treating a disorder associated with diminished BMP signaling in a subject, the method comprising the step of administering to the subject an effective amount of at least one disclosed compound or a pharmaceutically acceptable salt thereof.

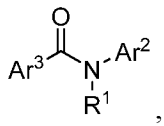
[00315] In one aspect, disclosed are methods of treating a disorder associated with diminished BMP signaling in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula:



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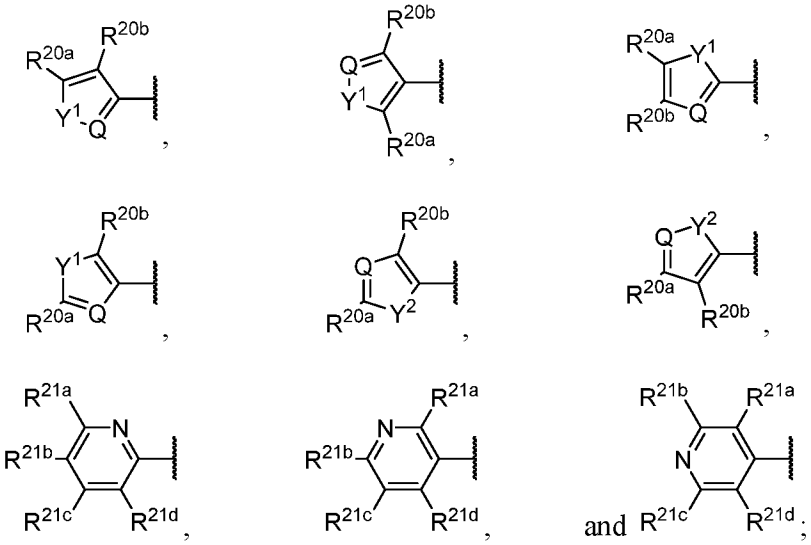
wherein n is selected from 0 and 1; wherein Z is selected from O, CH_2, and NR^2; wherein R^2 is selected from hydrogen and C1-C4 alkyl; wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with diminished BMP signaling.

[00316] In one aspect, disclosed are methods of treating a disorder associated with diminished BMP signaling in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula:



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wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); and wherein Ar^3 is a 5- or 6-membered heteroaryl selected from:



wherein Q, when present, is selected from CR^{30} and N; wherein R^{30}, when present, is selected from hydrogen and C1-C4 alkyl; wherein Y^1, when present, is selected from O, S, and NR^{31}; wherein R^{31}, when present, is selected from hydrogen and C1-C4 alkyl; wherein Y^2, when present, is selected from O and NR^{31}; wherein each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl; or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with diminished BMP signaling.

[00317] In a further aspect, the disorder is selected from juvenile polyposis syndrome (JPS), hereditary pulmonary arterial hypertension (HPAH), obesity osteoporosis, and chronic kidney disease.

[00318] In a further aspect, the disorder associated with diminished BMP signaling is a disease of cellular proliferation. In a still further aspect, the disease of cellular proliferation is cancer. In yet a further aspect, the cancer is selected from leukemia, breast cancer, prostate cancer, Ewing sarcoma, gastric cancer, melanoma, multiple myeloma, blastic plasmacytoid dendritic cell neoplasm, human squamous carcinoma, NUT midline carcinoma, lymphoma, angiogenesis, bladder cancer, thyroid cancer, childhood rhabdomyosarcoma, ovarian cancer, neurofibromatosis, lung cancer, colorectal cancer, IDH1-mutant glioma, uveal melanoma, pancreatic cancer, glioblastoma, neuroblastoma, advanced systemic mastocytosis, osteosarcoma, Merkel cell carcinoma, medulloblastoma, and malignant peripheral nerve

sheath tumors. In a further aspect, the disorder associated with diminished BMP signaling is a cancer.

[00319] In various aspects, the disclosed compounds can be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of disorders associated with diminished BMP signaling for which disclosed compounds or the other drugs can have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) can be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and a disclosed compound is preferred. However, the combination therapy can also include therapies in which a disclosed compound and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the disclosed compounds and the other active ingredients can be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions include those that contain one or more other active ingredients, in addition to a compound of the present invention.

[00320] In a further aspect, the compound exhibits activation of BMP signaling. In a still further aspect, the compound exhibits an increase in BMP signaling.

[00321] In a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 25 μM. In a still further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 15 μM. In yet a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 10 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 5 μM. In a still further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 1 μM. In yet a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 0.5 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 0.1 μM. In a still further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 0.05 μM. In yet a further aspect, the compound

exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 0.01 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 0.005 μM. In a still further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.005 μM to about 25 μM. In yet a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.01 μM to about 25 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.05 μM to about 25 μM. In a still further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.1 μM to about 25 μM. In yet a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.5 μM to about 25 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 1 μM to about 25 μM. In a still further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 5 μM to about 25 μM. In yet a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 10 μM to about 25 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 15 μM to about 25 μM.

[00322] In a further aspect, the subject is a mammal. In a still further aspect, the mammal is a human.

[00323] In a further aspect, the subject has been diagnosed with a need for treatment of the disorder associated with diminished BMP signaling prior to the administering step. In a still further aspect, the subject is at risk for developing the disorder prior to the administering step.

[00324] In a further aspect, the effective amount is a therapeutically effective amount. In a still further aspect, the effective amount is a prophylactically effective amount.

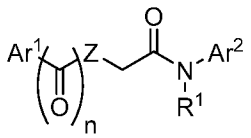
[00325] In a further aspect, the method further comprises identifying a subject at risk for developing the disorder prior to the administering step.

[00326] In a further aspect, the method further comprises the step of identifying a subject in need of treatment of a disorder associated with diminished BMP signaling.

F. METHODS OF ACTIVATING THE BMP SIGNALING PATHWAY IN A SUBJECT

[00327] In various aspects, disclosed are methods of activating the BMP signaling pathway in a subject, the method comprising the step of administering to the subject an effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

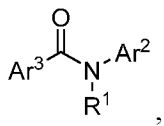
[00328] In one aspect, disclosed are methods of activating the BMP signaling pathway in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula:



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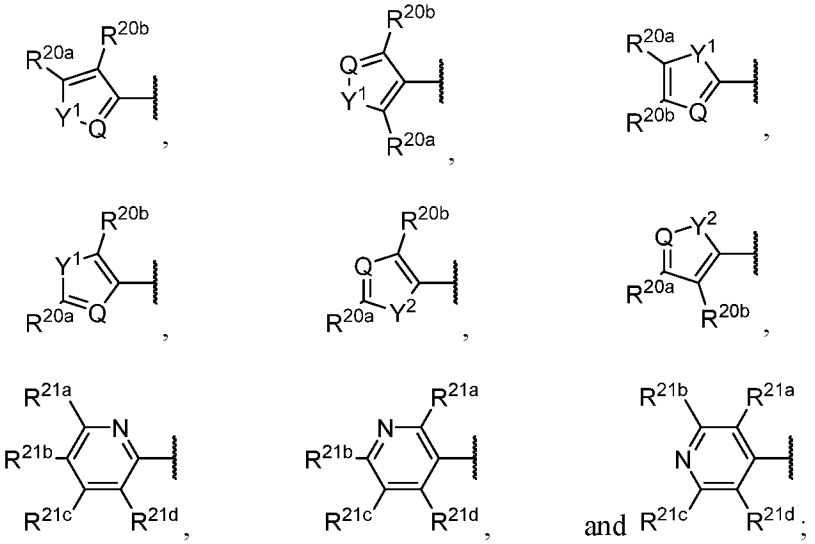
wherein n is selected from 0 and 1; wherein Z is selected from O, CH_2, and NR^2; wherein R^2 is selected from hydrogen and C1-C4 alkyl; wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); or a pharmaceutically acceptable salt thereof, thereby activating the bone morphogenic pathway in a subject.

[00329] In one aspect, disclosed are methods of activating the BMP signaling pathway in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula:



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wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); and wherein Ar^3 is a 5- or 6-membered heteroaryl selected from:



wherein Q, when present, is selected from CR^{30} and N; wherein R^{30}, when present, is selected from hydrogen and C1-C4 alkyl; wherein Y^1, when present, is selected from O, S, and NR^{31}; wherein R^{31}, when present, is selected from hydrogen and C1-C4 alkyl; wherein Y^2, when present, is selected from O and NR^{31}; wherein each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl; or a pharmaceutically acceptable salt thereof, thereby activating the bone morphogenic pathway in a subject.

[00330] In a further aspect, the subject has been diagnosed with osteoarthritis prior to the administering step. In a still further aspect, the subject has been diagnosed with having a bone fracture prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a subject in need of cartilage repair or bone formation.

[00331] In a further aspect, the subject has been diagnosed with a need for activation of the BMP signaling pathway prior to the administering step. In a still further aspect, the subject has been diagnosed with a need for treatment of a disorder associated with diminished

BMP signaling prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a subject in need of treatment of a disorder associated with diminished BMP signaling.

[00332] In a further aspect, the disorder is selected from juvenile polyposis syndrome (JPS), hereditary pulmonary arterial hypertension (HPAH), obesity osteoporosis, and chronic kidney disease.

[00333] In a further aspect, the disorder associated with diminished BMP signaling is a disease of cellular proliferation. In a still further aspect, the disease of cellular proliferation is cancer. In yet a further aspect, the cancer is selected from leukemia, breast cancer, prostate cancer, Ewing sarcoma, gastric cancer, melanoma, multiple myeloma, blastic plasmacytoid dendritic cell neoplasm, human squamous carcinoma, NUT midline carcinoma, lymphoma, angiogenesis, bladder cancer, thyroid cancer, childhood rhabdomyosarcoma, ovarian cancer, neurofibromatosis, lung cancer, colorectal cancer, IDH1-mutant glioma, uveal melanoma, pancreatic cancer, glioblastoma, neuroblastoma, advanced systemic mastocytosis, osteosarcoma, Merkel cell carcinoma, medulloblastoma, and malignant peripheral nerve sheath tumors.

[00334] In a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 25 μM. In a still further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 15 μM. In yet a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 10 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 5 μM. In a still further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 1 μM. In yet a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 0.5 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 0.1 μM. In a still further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 0.05 μM. In yet a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 0.01 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.001 μM to about 0.005 μM. In a still further aspect, the compound exhibits

activation of BMP signaling with a EC_{50} of from about 0.005 μM to about 25 μM. In yet a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.01 μM to about 25 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.05 μM to about 25 μM. In a still further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.1 μM to about 25 μM. In yet a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 0.5 μM to about 25 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 1 μM to about 25 μM. In a still further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 5 μM to about 25 μM. In yet a further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 10 μM to about 25 μM. In an even further aspect, the compound exhibits activation of BMP signaling with a EC_{50} of from about 15 μM to about 25 μM.

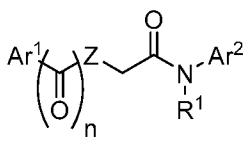
[00335] In a further aspect, the subject is a mammal. In a still further aspect, the mammal is a human.

[00336] In a further aspect, the effective amount is a therapeutically effective amount. In a still further aspect, the effective amount is a prophylactically effective amount.

G. METHODS OF ACTIVATING THE BMP SIGNALING PATHWAY IN AT LEAST ONE CELL

[00337] In one aspect, disclosed are methods of activating BMP signaling in at least one cell, the method comprising the step of contacting the at least one cell with an effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

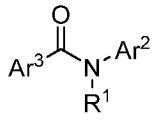
[00338] In one aspect, disclosed are methods of activating the BMP signaling pathway in at least one cell, the method comprising the step of contacting at least one cell with an effective amount of at least one compound having a structure represented by a formula:



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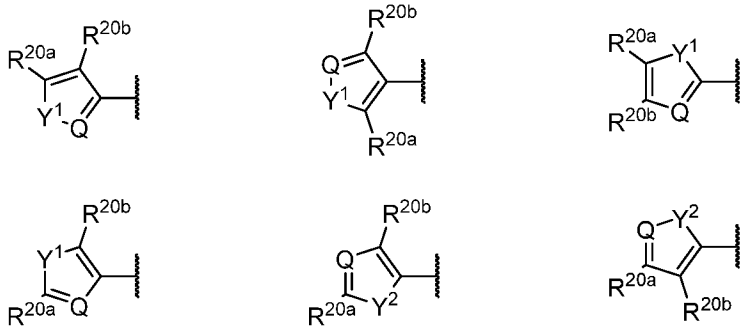
wherein n is selected from 0 and 1; wherein Z is selected from O, CH_2, and NR^2; wherein R^2 is selected from hydrogen and C1-C4 alkyl; wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and $-CO_2$(C1-C4 alkyl); wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and $-CO_2$(C1-C4 alkyl); or a pharmaceutically acceptable salt thereof, thereby activating the bone morphogenic pathway in at least one cell.

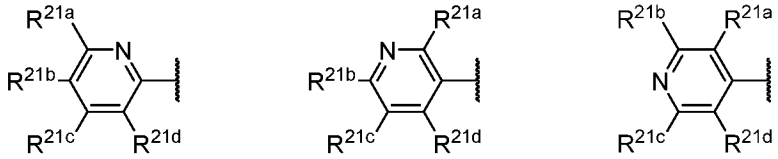
[00339] In one aspect, disclosed are methods of activating the BMP signaling pathway in at least one cell, the method comprising the step of contacting at least one cell with an effective amount of at least one compound having a structure represented by a formula:



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wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl); and wherein Ar^3 is a 5- or 6-membered heteroaryl selected from:





wherein Q, when present, is selected from $CR^{30a}R^{30b}$ and NR^{31}; wherein each of R^{30a}, R^{30b}, and R^{31}, when present, is independently selected from hydrogen and C1-C4 alkyl; wherein Y^1, when present, is selected from O, S, and NR^{31}; wherein Y^2, when present, is selected from O and NR^{31}; wherein each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl; or a pharmaceutically acceptable salt thereof, thereby activating the bone morphogenic pathway in at least one cell.

[00340] In a further aspect, the cell is a cancer cell.

[00341] In a further aspect, the cell is mammalian. In a still further aspect, the mammalian cell is human. In yet a further aspect, the cell has been isolated from a human prior to the contacting step.

[00342] In a further aspect, contacting is via administration to a subject. In a still further aspect, the subject has been diagnosed with a need for activation of the BMP signaling pathway prior to the administering step. In yet a further aspect, the subject has been diagnosed with a need for treatment of a disorder associated with diminished BMP signaling prior to the administering step.

H. METHODS OF USING THE COMPOSITIONS

[00343] Provided are methods of using of a disclosed composition or medicament. In one aspect, the method of use is directed to the treatment of a disorder. In a further aspect, the disclosed compounds can be used as single agents or in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions for which the compound or the other drugs have utility, where the combination of drugs together are safer or more effective than either drug alone. The other drug(s) can be administered by a route and in an amount commonly used therefore, contemporaneously or sequentially with a disclosed compound. When a disclosed compound is used contemporaneously with one or more other drugs, a

pharmaceutical composition in unit dosage form containing such drugs and the disclosed compound is preferred. However, the combination therapy can also be administered on overlapping schedules. It is also envisioned that the combination of one or more active ingredients and a disclosed compound can be more efficacious than either as a single agent.

[00344] The pharmaceutical compositions and methods of the present invention can further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

1. MANUFACTURE OF A MEDICAMENT

[00345] In one aspect, the invention relates to a method for the manufacture of a medicament for treating a disorder associated with BMP signaling in a mammal, the method comprising combining a therapeutically effective amount of a disclosed compound or product of a disclosed method with a pharmaceutically acceptable carrier or diluent.

[00346] In a further aspect, the disorder associated with diminished BMP signaling is selected from juvenile polyposis syndrome (JPS), hereditary pulmonary arterial hypertension (HPAH), obesity osteoporosis, and chronic kidney disease.

[00347] In a further aspect, the disorder associated with diminished BMP signaling is a disease of cellular proliferation. In a still further aspect, the disease of cellular proliferation is a cancer. In yet a further aspect, the cancer is selected from leukemia, breast cancer, prostate cancer, Ewing sarcoma, gastric cancer, melanoma, multiple myeloma, blastic plasmacytoid dendritic cell neoplasm, human squamous carcinoma, NUT midline carcinoma, lymphoma, angiogenesis, bladder cancer, thyroid cancer, childhood rhabdomyosarcoma, ovarian cancer, neurofibromatosis, lung cancer, colorectal cancer, IDH1-mutant glioma, uveal melanoma, pancreatic cancer, glioblastoma, neuroblastoma, advanced systemic mastocytosis, osteosarcoma, Merkel cell carcinoma, medulloblastoma, and malignant peripheral nerve sheath tumors. In a further aspect, the disorder associated with diminished BMP signaling is a cancer.

[00348] As regards these applications, the present method includes the administration to an animal, particularly a mammal, and more particularly a human, of a therapeutically effective amount of the compound effective in the activation of protein signaling and

especially BMP signaling. The dose administered to an animal, particularly a human, in the context of the present invention should be sufficient to affect a therapeutic response in the animal over a reasonable time frame. One skilled in the art will recognize that dosage will depend upon a variety of factors including the condition of the animal, the body weight of the animal, as well as the severity and stage of the disorder.

[00349] Thus, in one aspect, the invention relates to the manufacture of a medicament comprising combining a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, with a pharmaceutically acceptable carrier or diluent.

2. USE OF COMPOUNDS AND COMPOSITIONS

[00350] Also provided are the uses of the disclosed compounds and compositions. Thus, in one aspect, the invention relates to the uses of activators of BMP signaling. In a further aspect, the use is for cartilage repair or to induce bone formation for use in, for example, repairing a bone fracture. In a still further aspect, the use is to increase extracellular matrix production and chondrocyte differentiation for use, for example, cartilage repair for osteoarthritis.

[00351] In a further aspect, the invention relates to the use of a disclosed compound or product of a disclosed method in the manufacture of a medicament for the treatment of a disorder associated with BMP signaling such as, for example, juvenile polyposis syndrome (JPS), hereditary pulmonary arterial hypertension (HPAH), obesity osteoporosis, chronic kidney disease, and cancer.

[00352] In a further aspect, the disorder is selected from juvenile polyposis syndrome (JPS), hereditary pulmonary arterial hypertension (HPAH), obesity osteoporosis, and chronic kidney disease.

[00353] In a further aspect, the disorder associated with diminished BMP signaling is a disease of cellular proliferation. In a still further aspect, the disease of cellular proliferation is a cancer. In yet a further aspect, the cancer is selected from leukemia, breast cancer, prostate cancer, Ewing sarcoma, gastric cancer, melanoma, multiple myeloma, blastic plasmacytoid dendritic cell neoplasm, human squamous carcinoma, NUT midline carcinoma, lymphoma,

angiogenesis, bladder cancer, thyroid cancer, childhood rhabdomyosarcoma, ovarian cancer, neurofibromatosis, lung cancer, colorectal cancer, IDH1-mutant glioma, uveal melanoma, pancreatic cancer, glioblastoma, neuroblastoma, advanced systemic mastocytosis, osteosarcoma, Merkel cell carcinoma, medulloblastoma, and malignant peripheral nerve sheath tumors. In a further aspect, the disorder associated with diminished BMP signaling is a cancer.

[00354] In a further aspect, the use relates to a process for preparing a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound or a product of a disclosed method, and a pharmaceutically acceptable carrier, for use as a medicament.

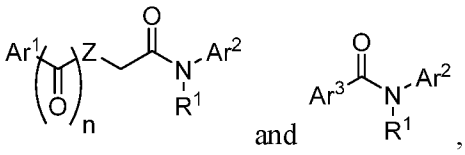
[00355] In a further aspect, the use relates to a process for preparing a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound or a product of a disclosed method, wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of the disclosed compound or the product of a disclosed method.

[00356] In various aspects, the use relates to the treatment of a disorder in a vertebrate animal. In a further aspect, the use relates to the treatment of a disorder in a human subject.

[00357] It is understood that the disclosed uses can be employed in connection with the disclosed compounds, methods, compositions, and kits. In a further aspect, the invention relates to the use of a disclosed compound or composition of a medicament for the treatment of a disorder associated with diminished BMP signaling in a mammal.

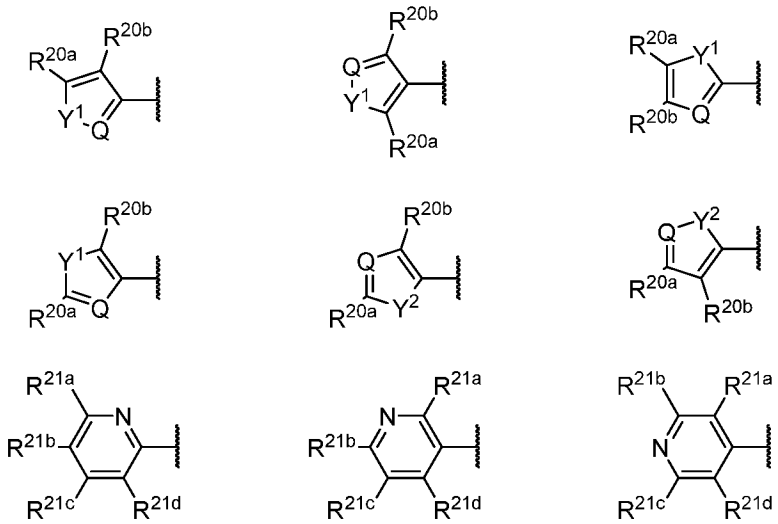
3. KITS

[00358] In one aspect, disclosed are kits comprising an effective amount of a compound having a structure represented by a formula selected from:



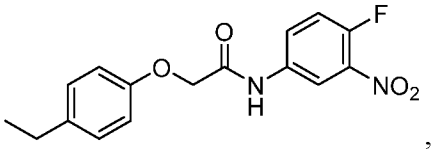
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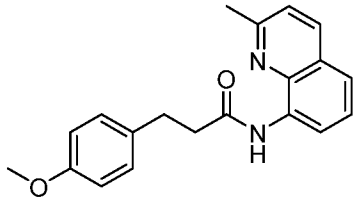
wherein n is selected from 0 and 1; wherein Z is selected from O, CH_2, and NR^2; wherein R^2 is selected from hydrogen and C1-C4 alkyl; wherein R^1 is selected from hydrogen and C1-C4 alkyl; wherein Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); and wherein Ar^3 is a 5- or 6-membered heteroaryl selected from:

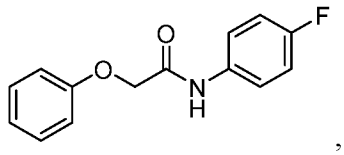


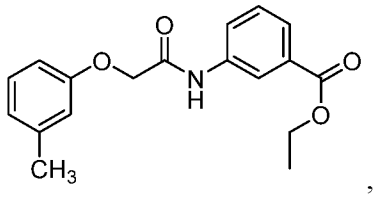
wherein Q, when present, is selected from $CR^{30a}R^{30b}$ and NR^{31}; wherein each of R^{30a}, R^{30b}, and R^{31}, when present, is independently selected from hydrogen and C1-C4 alkyl; wherein Y^1, when present, is selected from O, S, and NR^{31}; wherein Y^2, when present, is selected from O and NR^{31}; and wherein each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl; or a pharmaceutically acceptable salt thereof, and one or more of: (a) at least one agent known to treat a disorder associated with diminished BMP signaling; (b) at least one agent known to diminish the BMP signaling pathway; and (c) instructions for treating a disorder associated with diminished BMP signaling.

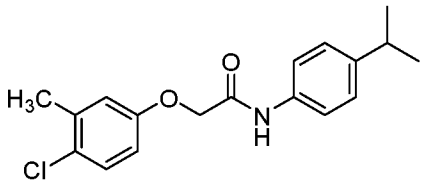
[00359] In various aspects, the compound is selected from:

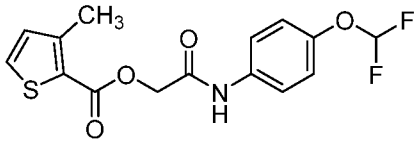

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and 
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[00360] In various aspects, the agents and pharmaceutical compositions described herein can be provided in a kit. The kit can also include combinations of the agents and pharmaceutical compositions described herein.

[00361] In various aspects, the informational material can be descriptive, instructional, marketing or other material that relates to the methods described herein and/or to the use of the agents for the methods described herein. For example, the informational material may relate to the use of the agents herein to treat a subject who has, or who is at risk for developing, a disorder associated with diminished BMP signaling. The kits can also include paraphernalia for administering the agents of this invention to a cell (in culture or *in vivo*) and/or for administering a cell to a patient.

[00362] In various aspects, the informational material can include instructions for administering the pharmaceutical composition and/or cell(s) in a suitable manner to treat a human, *e.g.*, in a suitable dose, dosage form, or mode of administration (*e.g.*, a dose, dosage form, or mode of administration described herein). In a further aspect, the informational material can include instructions to administer the pharmaceutical composition to a suitable subject, *e.g.*, a human having, or at risk for developing, a disorder associated with diminished BMP signaling.

[00363] In various aspects, the composition of the kit can include other ingredients, such as a solvent or buffer, a stabilizer, a preservative, a fragrance or other cosmetic ingredient. In such aspects, the kit can include instructions for admixing the agent and the other ingredients, or for using one or more compounds together with the other ingredients.

[00364] In a further aspect, the compound and the at least one agent known are co-formulated. In a still further aspect, the compound and the at least one agent are co-packaged.

[00365] In a further aspect, the kit further comprises a plurality of dosage forms, the plurality comprising one or more doses; wherein each dose comprises an effective amount of the compound and the at least one agent. In a still further aspect, the effective amount is a therapeutically effective amount. In yet a further aspect, the effective amount is a prophylactically effective amount. In an even further aspect, each dose of the compound and the at least one agent are co-packaged. In a still further aspect, each dose of the compound and the at least one agent are co-formulated.

4. SUBJECTS

[00366] In various aspects, the subject of the herein disclosed methods is a vertebrate, *e.g.*, a mammal. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. A patient refers to a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects.

[00367] In some aspects of the disclosed methods, the subject has been diagnosed with a need for treatment prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a disorder associated with diminished BMP signaling prior to the administering step. In some aspects of the disclosed methods, the subject has been identified with a need for treatment prior to the administering step. In one aspect, a subject can be treated prophylactically with a compound or composition disclosed herein, as discussed herein elsewhere.

a. DOSAGE

[00368] Toxicity and therapeutic efficacy of the agents and pharmaceutical compositions described herein can be determined by standard pharmaceutical procedures, using either cells in culture or experimental animals to determine the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and can be expressed as the ratio LD_{50}/ED_{50}.

[00369] Data obtained from cell culture assays and further animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity, and with little or no adverse effect on a human's ability to hear. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any agents used in the methods described herein, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (that is, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Exemplary dosage amounts of a differentiation agent are at least from about 0.01 to 3000 mg per day, *e.g.*, at least about 0.00001, 0.0001, 0.001, 0.01, 0.1, 1, 2, 5, 10, 25, 50, 100, 200, 500, 1000, 2000, or 3000 mg per kg per day, or more.

[00370] The formulations and routes of administration can be tailored to the disease or disorder being treated, and for the specific human being treated. For example, a subject can receive a dose of the agent once or twice or more daily for one week, one month, six months, one year, or more. The treatment can continue indefinitely, such as throughout the lifetime of the human. Treatment can be administered at regular or irregular intervals (once every other day or twice per week), and the dosage and timing of the administration can be adjusted throughout the course of the treatment. The dosage can remain constant over the course of the treatment regimen, or it can be decreased or increased over the course of the treatment.

[00371] In various aspects, the dosage facilitates an intended purpose for both prophylaxis and treatment without undesirable side effects, such as toxicity, irritation or allergic response. Although individual needs may vary, the determination of optimal ranges for effective amounts of formulations is within the skill of the art. Human doses can readily be extrapolated from animal studies (Katocs et al., (1990) Chapter 27 in Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, PA). In general, the dosage required to provide an effective amount of a formulation, which can be adjusted by one skilled in the art, will vary depending on several factors, including the age, health, physical condition, weight, type and extent of the disease or disorder of the recipient, frequency of treatment, the nature of concurrent therapy, if required, and the nature and scope of the desired effect(s) (Nies et al., (1996) Chapter 3, In: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., Hardman et al., eds., McGraw-Hill, New York, NY).

b. ROUTES OF ADMINISTRATION

[00372] Also provided are routes of administering the disclosed compounds and compositions. The compounds and compositions of the present invention can be administered by direct therapy using systemic administration and/or local administration. In various aspects, the route of administration can be determined by a patient's health care provider or clinician, for example following an evaluation of the patient. In various aspects, an individual patient's therapy may be customized, *e.g.*, the type of agent used, the routes of administration, and the frequency of administration can be personalized. Alternatively, therapy may be performed using a standard course of treatment, *e.g.*, using pre-selected agents and pre-selected routes of administration and frequency of administration.

[00373] Systemic routes of administration can include, but are not limited to, parenteral routes of administration, *e.g.*, intravenous injection, intramuscular injection, and intraperitoneal injection; enteral routes of administration *e.g.*, administration by the oral route, lozenges, compressed tablets, pills, tablets, capsules, drops (*e.g.*, ear drops), syrups, suspensions and emulsions; rectal administration, *e.g.*, a rectal suppository or enema; a vaginal suppository; a urethral suppository; transdermal routes of administration; and inhalation (*e.g.*, nasal sprays).

[00374] In various aspects, the modes of administration described above may be combined in any order.

I. EXAMPLES

[00375] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

[00376] The Examples are provided herein to illustrate the invention, and should not be construed as limiting the invention in any way. Examples are provided herein to illustrate the invention and should not be construed as limiting the invention in any way.

1. BIOLOGY EXPERIMENTALS

a. CELL LINES AND TISSUE CULTURE

[00377] The generation of the human cervical carcinoma C33A-2D2 subclone was previously described (Vrijens et al. (2013) *PLoS One 8*, e59045). Briefly, a construct containing the BMP-responsive element (BRE) of the ID1 promoter linked to the luciferase gene in C33A cells was stably expressed (Korchynskyi and ten Dijke (2002) *J Biol Chem 277*, 4883-4891). Cells were maintained in Eagle's medium essential medium (EMEM) supplemented with 10% fetal bovine serum (FBS), 2 mM glutamine, 500 units/mL penicillin and 500 μg/mL streptomycin and grown at 37 °C and 8% CO_2. The mouse myoblast cell line C2C12 was grown in DMEM supplemented with 5% FBS, 2 mM glutamine, 500 units/mL penicillin and 500 μg/mL streptomycin and grown at 37 °C and 8% CO_2. To avoid depletion of the myoblastic population, C2C12 cells were not allowed to grow to confluence and were passaged at a density less than 70%.

b. Compound Library Selection and High Throughput Screening (HTS)

[00378] The entire content of the St. Jude compound library (N = 643,432 unique) was screened in the primary high-throughput screening (HTS) using a human cervical carcinoma clonal reporter cell line, C33A-2D2, that provided a robust BMP-4 response for the high throughput cell-based assay system. Details of the method for the HTS were reported previously (Vrijens et al. (2013) *PLoS One 8*, e59045). Briefly, cells were plated and drug diluted in DMSO were added approximately 0.5 hours later. The assay plates were then incubated overnight followed by luminescence assay for luciferase reporter activity with SteadyLite HTS reagent (PerkinElmer, Waltham, MA). The library was composed as follows: ~80% from commercial 'diversity' libraries designed to broadly sample from available scaffold space while abiding by drug-like/lead-like criteria (Lipinski, C. A. (2004) *Drug discovery today. Technologies 1*, 337-341) ~10% from in-house focused libraries which are based on scaffolds from major therapeutic target classes such as kinases, G-protein-coupled receptors (GPCRs), and proteases; ~5% natural product fractions from an in-house program (Yang et al. (2014) *J Nat Prod 77*, 902-909); and the remaining ~5% from external collaborators and in-house lead optimization projects. CScore was determined as previously described (Ouwang et al. (2011) *J Bioinform Comput Biol 9 Suppl 1*, 1-14).

c. Fish Maintenance and Compound Administration

[00379] Wild-type zebrafish (Wik - *Danio rerio*) embryos were obtained and maintained in accordance with standard husbandry procedures (Westerfield, M. (2007) *The Zebrafish Book: A guide for the laboratory use of zebrafish (Danio rerio)*, University of Oregon Press, Eugene, OR) and in compliance IACUC guidelines. Embryos at approximately 2 hours post fertilization (hpf) were placed into a 6- or 12-well flat bottom dish and treated with DMSO or compounds at a concentration of 0.1 μM to 50 μM as indicated in the text. The treatments were as followed: 1) no treatment [E3 media (5 mM NaCl, 0.17 mM KCl, 0.33 mM $CaCl_2$, 0.33 mM $MgSO_4$], 2) vehicle (1% DMSO in E3), 3) SJ000286273, 4) 1, 5) 3, 6) 2. Embryos were treated until either shield stage (6 hpf) or the onset of circulation (24 hpf). For *in situ* hybridization, shield stage embryos were fixed in 4% paraformaldehyde for 24 hrs. Circulation stage embryos were manually dechorionated and assessed for

ventralization as previously described (Kishimoto et al. (1997) *Development 124*, 4457-4466).

d. WHOLE MOUNT *IN SITU* HYBRIDIZATION AND QUANTIFICATION

[00380] Probe synthesis and whole mount *in situ* hybridization was performed as described previously (Clements et al. (2009) *Dev Dyn 238*, 1788-1795). The following probe constructs were used: pGenTeasa-bmp2b (*bmp2b*, gift of A. Lekven), pBS SK+ *chordin* (*chd*, gift of D. Kimelman), eve1 (*eve1*, gift of A. Lekven), pZL1-szl-BamHI (*szl*, gift of A. Lekven), pBS SK- *vent* (*vent*, gift of D. Kimelman), and pBS SK- vox (*vox*, gift of D. Kimelman). The *in-situ* hybridizations were quantified using ImageJ (http://imagej.nih.gov/ij) by tracing the area of generated stain, correlating to mRNA expression of the indicated gene. Embryos were equivalent sizes, permitting quantification of signal alterations as a general measure of altered transcript abundance, as has been used previously (Clements et al. (2009) *Dev Dyn 238*, 1788-1795).

e. IMMUNOBLOTTING

[00381] 1.8 x 10^6 C33A-2D2 cells were plated on 100 mm plates, and grown for 24 hrs in EMEM media supplemented with 10 % FBS, 2 mM glutamine, 500 units/mL penicillin and 500 µg/mL streptomycin at 37 °C and 8% CO_2. After 24 hrs, the medium was changed to serum-free EMEM supplemented with 2 mM glutamine, 500 units/mL penicillin and 500 µg/mL streptomycin and grown overnight. The next day medium was replaced with fresh serum-free medium containing the compounds dissolved in methanol for 0.5, 1, 3, 6, 9, and 12 hrs. Cells treated for 0.5 hrs with 10 ng/mL of human recombinant BMP-4 (R&D Systems, Minneapolis, MN) and methanol (MeOH) concentrations ranging from 0.034% to 0.38% for 0.5, 1, and 3 hrs were used as positive and negative control, respectively. After collection, cells were lyzed (RIPA lysis buffer) and sonication (VirSonic 475 dismembranator). Proteins were quantified using a bicinchoninic acid (BCA) protein assay reagent (Pierce, Rockford, IL) per manufacturer's instructions. 20 µg of protein lysate per sample were loaded on a 10% SDS-PAGE gel for phosphorylated (P)-SMAD1/5/8 and a 12% SDS PAGE gel for the inhibitor of DNA binding protein ID1, as previously published (Vrijens et al. (2013) *PLoS One 8*, e59045). Antibodies used were rabbit polyclonal antibodies to human phospho-(P)-SMAD1/5/8 (homemade; 1:2500 dilution) (Vrijens et al.

(2013) *PLoS One 8*, e59045), SMAD1/5/8 (Santa Cruz sc-6031-R; 1:500 dilution), ID1 (Abcam cat. # EPR7098; 1:1000 dilution), P-ERK1/2 (Santa Cruz sc-101760; 1:500 dilution), ERK1/2 (Santa Cruz sc-135900; 1:1000 dilution), P-SMAD2 (Cell Signaling #3108; 1:1000 dilution), SMAD2 (Cell Signaling #3122; 1:1000 dilution) and ACTIN (Santa Cruz sc-1615; 1:2000 dilution). Secondary antibody used was anti-rabbit IgG HRP (Cell Signaling, cat. # 7074; 1:2000 dilution), anti-mouse IgG HRP (ECL/GE Healthcare NA931V, 1:2000 dilution), and anti-goat IgG HRP (Life Technologies A16005, 1:2000 – 1:3000 dilution).

f. MYOBLAST DIFFERENTIATION

[00382] Evaluation of myoblast differentiation activity was previously described (Vrijens et al. (2013) *PLoS One 8*, e59045). Briefly, $2x10^4$ C2C12 cells were plated in 24-well plates and allowed to grow O/N at 37 °C. The next morning medium was replaced with fresh medium containing 5% FBS and individual wells were treated with MeOH, 6.25 μM or 25 μM of each compound or recombinant BMP-4 (10, 300 ng/mL). Cells were treated for 6 days and fixed for 10 minutes with 3.7% formaldehyde at room temperature (RT), washed with PBS and cells were washed with PBS and counterstained with Neutral Red Solution (from Sigma-Aldrich, St. Louis, MO). 20X magnification images were taken on a Nikon TE 2000 E2 (20X, 0.5 Plan Fluor objective; DS-Fi1 camera).

g. GENE EXPRESSION PROFILING AND GO ANALYSIS

[00383] The RNA expression profile of BMP-4, 942, 178, 181, or vehicle treated C2C12 cells were assayed using MoGene-2_0-st-v1 Affymetrix microarrays (Mountain View, CA). Data was RMA summarized and quality controlled using Partek Genomics Suite 6.6 (St. Louis, MO). Gene expression responses to each drug were modeled by linear regression. Those genes which were concordantly positively or negatively correlated with drug dose for BMP-4 and 942 at the .9 level or greater with a nominal regression p value < .05 were visualized in an unsupervised heat map using Partek Genomics Suite 6.6. Arrays from wild type primary osteoblasts data from GEO (GSE57195) were downloaded, RMA summarized and normalized together with the other arrays to facilitate comparison in the heat map. For GO analysis in KEGG the logFC of max dose vs control was found for each drug and those 94 genes that were induced by at least 0.5 by both BMP-4 and 942 were tested in Enrichr (Chen et al. (2013) *BMC Bioinformatics 14*, 128; Kuleshov et al. (2016) *Nucleic*

Acids Res 44, W90-97). Scatterplots of log ratios were regressed and visualized using STATA/MP 14.2 (College Station, Texas).

h. QUANTITATIVE REAL-TIME PCR (QRT-PCR)

[00384] Total RNA was extracted from C2C12 cells (untreated, treated with vehicle (0.036% MeOH), stimulated with 10 ng BMP-4, or 12.5 μM and 25 μM of 942). RNA was extracted with TRIzol reagent (Ambion by Life Technologies). cDNA was synthetized using High Capacity cDNA Reverse Transcription Kit (Applied Biosystems by Thermo Fisher Scientific. Cat # 4374966), per the manufacturer's instructions. Quantitative RT-PCR was performed using TaqMan Fast Advance Master Kit (Applied Biosystems by Thermo Fisher Scientific Cat # 4444557), according manufacturer's procedures and performed in a QuantStudio3 machine (Applied Biosystems by Thermo Fisher Scientific). The context sequences of the primers used were listed as follows: Mouse Adh7, 5' TCGGGGAAAAGCATTCGGACTGTCC-3' (Assay ID Mm00507750_m1; SEQ ID NO: 1); Mouse Ptgfr, 5'-CTGGAGTCCCTTTCTGGTAACAATG-3' (Assay ID Mm00436055_m1; SEQ ID NO: 2); Mouse Ankrd2, 5'-GTGATGAGTTCCGTCGGACAGCACT-3' (Assay ID Mm00508030_m1: SEQ ID NO: 3); Mouse GAPDH, 5'-GGTGTGAACGGATTTGGCCGTATTG-3' (Assay ID Mm99999915_g1; SEQ ID NO: 4). All the primers were FAM-Labeled TaqMan (Applied Biosystems by Thermo Fisher Scientific). Threshold cycle (CT) values from triplicate measurements were averaged and normalized to those obtained from an internal control gene, GAPDH. Relative gene expression was determined by the $2^{-\Delta\Delta CT}$ method (Livak, K. J., and Schmittgen, T. D. (2001) *Methods 25*, 402-408). Data are expressed as the mean ± SEM. Statistical analyses were performed in GraphPad Prism Software v. 6.0. Statistical significance was determined by one way ANOVA with Tukey's multiple comparison test ($p \leq 0.05$).

2. CELL-BASED HTS ASSAY

[00385] To find new compounds that act as BMP-4 signaling agonists, a high throughput screen of a library of 643,432 compounds was completed using a BMP-responsive luciferase cell-based assay in a 384-well plate format. Results of the primary screen are shown in FIG. 1A and FIG. 1B). The average Z-prime was 0.71. Relative compound activity was calculated by subtracting the background from the DMSO negative

control [compound – median (DMSO)], using log2-transformed luciferase Relative Luminescence Units (RLUs). A hit was defined as any compound displaying activity greater than two standard deviations from the median DMSO negative control signal. This generated a list of 5,287 actives for hit validation.

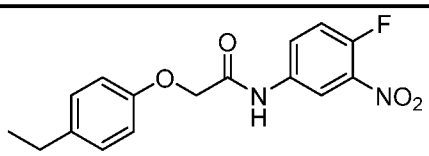
[00386] For further chemical structure analysis, topology mapping and clustering was performed (Shelat, A. A., and Guy, R. K. (2007) *Nature Chemical Biology 3*, 442-446). Of the 5,287 actives, 267 were natural product fractions and had no defined scaffold. The remaining set of molecules were abstracted into 3,247 Bemis-Murcko scaffolds (Bemis, G. W., and Murcko, M. A. (1996) *J Med Chem 39*, 2887-2893), which indicated sparse sampling among closely related structural analogs (1.6 molecules per scaffold). Further abstraction and clustering of the resulting scaffolds yielded the scaffold network diagram in FIG. 2.

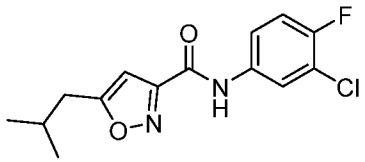
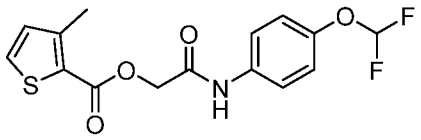
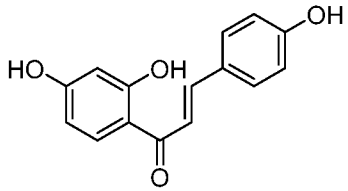
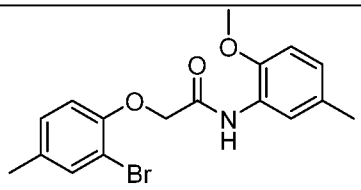
[00387] Referring to FIG. 1A, Z-prime values per plate from the primary HTS assay performed in a 384-well format are shown. The average Z-prime observed was 0.71 (black lineO.

[00388] Referring to FIG. 1B, a primary HTS scattergram of 643,432 compounds screened in single concentration at 10 μM is shown.

[00389] Referring to FIG. 2, a Network Graph showing the chemical structures of 5,287 hits selected based on it criteria from the primary screen is shown. Similar structures cluster together in the branches of the network based on their molecular topology. The structures of the three hits [1 (**1**), 2 (**2**), and SJ00037178 (**3**)] are gouped in cluster 5 and highlighted (see also Table 1 below).

TABLE 1.

Compound No.	Structure
1	

Compound No.	Structure
2	
3	
4	
5	

3. SELECTION OF BMP SIGNALING ACTIVATORS 1, 2, AND 3.

[00390] The dose response of 5,287 compounds was determined using a 10-point, 3-fold serial dilution performed in triplicate with top compounds at a concentration ~50 μM. From the actives, 2,534 compounds produced reliable ($R^2 > 0.8$) fits to the Hill equation giving a sigmoidal concentration-response curve. Of these, 1,604 compounds had an $EC_{50} \leq$ 1 μM and were designated validated hits. The natural product fractions and the five largest scaffold clusters (numbered 1-5 and annotated with the structure of the cluster head) accounted for 53% of all compounds tested in dose-response. The largest cluster, represented by the diphenylsuccinamide scaffold (cluster 5), contained 834 compounds. A summary of the screening cascade is shown in FIG. 3.

[00391] Referring to FIG. 3, the research work flow was initiated with a cell-based luciferase assay in C33A-2D2 cell lines followed by a zebrafish phenotypic screen and further evaluation by immunoblotting.

[00392] Despite identifying a significant number of potent, validated hits ($EC_{50} \leq 1$ μM), ~94% of all compounds tested in dose-response had low to modest efficacy (magniture of response ≤ 4-fold the DMSO signal). Although such responses were statistically significant, their biological consequence was unclear. Furthermore, certain compounds produced non-sigmoidal dose-response curves that suggested pathway activation at low concentration and cytotoxicity at higher concentrations. As no non-protein agonists of BMP signaling exist, it is difficult to define a reasonable minimal response.

4. BMP-SIGNALING ACTIVATORS VENTRALIZE ZEBRAFISH EMBRYOS

[00393] Zebrafish have previously proven to be a useful platform for identifying compounds that modulate signaling pathways including the Bmp signaling pathway (Vrijens et al. (2013) *PLoS One 8*, e59045; Yu et al. (2008) *Nat Chem Biol 4*, 33-41; Hao et al. (2012) *Nature 485*, 195-200; Kaufman et al. (2009) *Nat Protoc 4*, 1422-1432). BMP signaling in vertebrates, including zebrafish, directs the formation of ventral tissues and genetic markers. Stereotypical phenotypes and gene expression resulting from increased or decreased specification of ventral tissue can provide a means to preliminarily identify compounds that modulate BMP signaling activity, or validate compounds identified by other means.

[00394] A zebrafish phenotypic screen was utilized to access the ability of 97 validated hits to activate the BMP pathway and produce a ventralized phenotype. The set of 97 compounds sampled from 16 of the 27 scaffold clusters, with over 70% of compounds coming from the five largest clusters, labeled 1-5 (see FIG. 2). Of the tested validated hits, four showed activity at all concentrations tested but failed to fit to the Hill equation ('Super Active'); 62 compounds demonstrated sigmoidal dose-response behavior and good potency (EC50≤1μM, 'Sigmoidal'); 18 had non-sigmoidal behavior ('Inverse'); six were only active at the highest concentration tested ('Single-Point'); and seven showed no response at any concentration tested ('Inactive') (FIG. 4). The 'Single-Point' and 'Inactive' classes were expected to be inactive in the phenotypic assay and were considered negative controls. 'Super Actives' tend to be either highly potent compounds that were screened at too high a concentration, or the result of assay artifacts. Most true positives in the zebrafish assay were expected to be from the 'Sigmoidal' and 'Inverse' classes. The HTS and phenotypic screening results are reported in Table 2. This screen identified three compounds, 1 (compound **1**), 2 (compound **2**), and 3 (compound **3**) as positive hits at 1μM (FIG. 5A-D).

[00395] Referring to FIG. 4, three validated hits in the zebrafish assay, compounds **1**, **2**, and **3**, exhibited well-behaved dose-response curves (the 'Sigmoidal' class) in the cell-based assay by cScore.

[00396] Referring to FIG. 5A, representative images (i-v) of increasing ventralized phenotrypes at 24 hpf are shown. Arrows indicate major areas of ventralization (ii-v).

[00397] Referring to FIG. 5B-D, the distribution of phenotypes caused by compound **1** (FIG. 5B), **2** (FIG. 5C), and **3** (FIG. 5D), at the indicated doses following treatment of embryos beginning at 2 hpf and scored at 24 hpf ar shown. Graphs represent percent ± SEM of embryos displaying a given phenotype in three independent experiments, with 20-60 embryos per condition.

TABLE 2.

sample	primary cScore	primary r2	primary EC_{50}	primary EC_{50}_l	primary EC_{50}_u	Zebrafish assay @1 μM
SJ000024224-2	Inactive	NA	NA	NA	NA	inactive
SJ000031311-2	Inactive	NA	NA	NA	NA	inactive
SJ000338276-2	Inactive	NA	NA	NA	NA	inactive
SJ000122872-2	Inactive	NA	NA	NA	NA	inactive
SJ000460846-2	Inactive	NA	NA	NA	NA	inactive
SJ000251743-2	Inactive	NA	NA	NA	NA	inactive
SJ000049059-2	Inactive	NA	NA	NA	NA	inactive
SJ000338514-2	Inverse	0.92	-3.823908741	-4.013228266	-3.552841969	inactive
SJ000184	Inverse	0.97	-3.5376020	-3.7212463	-3.3665315	inactive

sample	primary cScore	primary r2	primary EC_{50}	primary EC_{50}_l	primary EC_{50}_u	Zebrafish assay @1 µM
291-2			02	99	44	
SJ000518754-2	Inverse	0.86	-3.48148606	-3.958607315	-3.48148606	inactive
SJ000007551-2	Inverse	0.74	-3.420216403	-4	-3.420216403	inactive
SJ000208458-2	Inverse	0.64	-3.292429824	-3.920818754	-3.301029996	inactive
SJ000517298-2	Inverse	0.8	-3.537602002	-3.958607315	-3.318758763	inactive
SJ000337803-2	Inverse	0.24	-3.22184875	-4.096910013	-3.22184875	inactive
SJ000292370-3	Inverse	0.67	-3.356547324	-4.055517328	-3.356547324	inactive
SJ000161809-3	Inverse	0.57	-3.366531544	-4	-3.207608311	inactive
SJ000124514-2	Inverse	-2.20E-16	-6.721246399	-10.14874165	-4.124938737	inactive
SJ000081990-2	Inverse	0.4	-4.060480747	-4.853871964	-4.060480747	inactive
SJ000097754-2	Inverse	0.72	-4.214670165	-4.37675071	-3.721246399	inactive
SJ000369908-2	Inverse	0.59	-3.37675071	-4	-3.193820026	inactive

sample	primary cScore	primary r2	primary EC_{50}	primary EC_{50}_l	primary EC_{50}_u	Zebrafish assay @1 µM
SJ000108033-2	Inverse	0.87	-4.13667714	-4.27572413	-3.958607315	inactive
SJ000304667-2	Inverse	0.91	-3.744727495	-3.853871964	-3.602059991	toxic
SJ000516965-2	Inverse	0.93	-3.568636236	-3.602059991	-3.508638306	toxic
SJ000151680-2	Inverse	0.68	-3.420216403	-4.113509275	-3.420216403	toxic
SJ000184121-2	Inverse	0.58	-3.886056648	-4.096910013	-3.522878745	toxic
1	Sigmoidal	0.98	-6.619788758	-6.853871964	-6.30980392	active
3	Sigmoidal	0.93	-6	-6.346787486	-5.744727495	active
2	Sigmoidal	0.85	-7.443697499	-7.795880017	-7.017728767	active
SJ000024045-2	Sigmoidal	0.91	-8.920818754	-9.070581074	-8.769551079	inactive
SJ000029514-2	Sigmoidal	0.97	-8.301029996	-8.443697499	-8.173925197	inactive
SJ000026852-2	Sigmoidal	0.94	-8.173925197	-8.356547324	-8	inactive
SJ000298	Sigmoidal	0.93	-7.9586073	-8.1366771	-7.7958800	inactive

sample	primary cScore	primary r2	primary EC_{50}	primary EC_{50}_l	primary EC_{50}_u	Zebrafish assay @1 µM
151-2			15	4	17	
SJ000340178-2	Sigmoidal	0.92	-7.853871964	-8.022276395	-7.619788758	inactive
SJ000293035-2	Sigmoidal	0.96	-7.823908741	-7.958607315	-7.698970004	inactive
SJ000055839-2	Sigmoidal	0.91	-7.744727495	-7.920818754	-7.522878745	inactive
SJ000063028-2	Sigmoidal	0.91	-7.619788758	-7.769551079	-7.537602002	inactive
SJ000031471-2	Sigmoidal	0.94	-7.585026652	-7.744727495	-7.397940009	inactive
SJ000207974-2	Sigmoidal	0.93	-7.327902142	-7.481486066	-7.187086643	inactive
SJ000208514-2	Sigmoidal	0.95	-7.292429824	-7.468521083	-7.13076828	inactive
SJ000045485-2	Sigmoidal	0.99	-7.207608311	-7.292429824	-7.124938737	inactive
SJ000063138-2	Sigmoidal	0.92	-7.070581074	-7.200659451	-6.920818754	inactive
SJ000354312-2	Sigmoidal	0.96	-7.060480747	-7.229147988	-6.920818754	inactive
SJ000017426-3	Sigmoidal	0.96	-6.958607315	-7.173925197	-6.744727495	inactive

sample	primary cScore	primary r2	primary EC_{50}	primary EC_{50}_l	primary EC_{50}_u	Zebrafish assay @1 μM
SJ000062591-2	Sigmoidal	0.93	-6.886056648	-7.036212173	-6.769551079	inactive
SJ000162243-3	Sigmoidal	0.94	-6.795880017	-6.886056648	-6.638272164	inactive
SJ000367650-2	Sigmoidal	0.9	-6.769551079	-6.958607315	-6.619788758	inactive
SJ000063180-2	Sigmoidal	0.94	-6.769551079	-7	-6.522878745	inactive
SJ000154298-2	Sigmoidal	0.91	-6.744727495	-7.13667714	-6.124938737	inactive
SJ000062600-2	Sigmoidal	0.95	-6.568636236	-6.744727495	-6.408935393	inactive
SJ000370379-2	Sigmoidal	0.95	-6.552841969	-6.769551079	-6.102372909	inactive
SJ000444978-2	Sigmoidal	0.95	-6.537602002	-6.677780705	-6.337242168	inactive
SJ000316928-2	Sigmoidal	0.92	-6.508638306	-6.721246399	-6.086186148	inactive
SJ000295844-2	Sigmoidal	-1.5	-8.853871964	-44.02687215	-4.602059991	inactive
SJ000121199-2	Sigmoidal	0.81	-8.494850022	-8.744727495	-8.22184875	inactive
SJ000338	Sigmoidal	0.82	-8.1938200	-8.4317982	-8	inactive

sample	primary cScore	primary r2	primary EC_{50}	primary EC_{50}_l	primary EC_{50}_u	Zebrafish assay @1 μM
565-2			26	76		
SJ000056835-2	Sigmoidal	0.9	-8.148741651	-8.30980392	-7.958607315	inactive
SJ000124445-2	Sigmoidal	0.9	-8	-8.200659451	-7.744727495	inactive
SJ000143378-2	Sigmoidal	0.74	-7.958607315	-8.27572413	-7.602059991	inactive
SJ000063040-2	Sigmoidal	0.85	-7.920818754	-8.102372909	-7.657577319	inactive
SJ000518716-2	Sigmoidal	0.89	-7.886056648	-8.15490196	-7.508638306	inactive
SJ000294921-2	Sigmoidal	0.83	-7.853871964	-8.107905397	-7.602059991	inactive
SJ000394353-2	Sigmoidal	0.83	-7.795880017	-7.886056648	-7.602059991	inactive
SJ000208831-2	Sigmoidal	0.83	-7.698970004	-7.958607315	-7.346787486	inactive
SJ000007707-2	Sigmoidal	0.8	-7.552841969	-7.958607315	-7.065501549	inactive
SJ000045486-2	Sigmoidal	0.88	-7.508638306	-7.769551079	-7.086186148	inactive
SJ000139983-2	Sigmoidal	0.87	-7.431798276	-7.677780705	-7.200659451	inactive

sample	primary cScore	primary r2	primary EC_{50}	primary EC_{50}_l	primary EC_{50}_u	Zebrafish assay @1 μM
SJ000441894-2	Sigmoidal	0.82	-7.408935393	-7.585026652	-6.958607315	inactive
SJ000161544-3	Sigmoidal	0.86	-7.408935393	-7.744727495	-7.008773924	inactive
SJ000390741-2	Sigmoidal	0.81	-7	-7.327902142	-6.366531544	inactive
SJ000451891-2	Sigmoidal	0.74	-6.958607315	-7.292429824	-6.420216403	inactive
SJ000294743-2	Sigmoidal	0.87	-6.886056648	-7.494850022	-6.193820026	inactive
SJ000208133-2	Sigmoidal	0.88	-6.638272164	-6.769551079	-6.251811973	inactive
SJ000414020-2	Sigmoidal	0.86	-3.744727495	-4.075720714	-3.744727495	inactive
SJ000421218-2	Sigmoidal	0.7	-3.744727495	-4.167491087	-3.744727495	inactive
SJ000063022-2	Sigmoidal	0.8	-3.677780705	-4.22184875	-3.698970004	inactive
SJ000339592-2	Sigmoidal	0.92	-8.050609993	-8.161150909	-7.920818754	toxic
SJ000013778-2	Sigmoidal	0.93	-7.823908741	-7.958607315	-7.721246399	toxic
SJ000296	Sigmoidal	0.91	-7.2146701	-7.4559319	-6.9208187	toxic

sample	primary cScore	primary r2	primary EC_{50}	primary EC_{50}_l	primary EC_{50}_u	Zebrafish assay @1 μM
667-2			65	56	54	
SJ000293006-2	Sigmoidal	0.93	-7.207608311	-7.508638306	-6.744727495	toxic
SJ000433644-2	Sigmoidal	0.91	-6.823908741	-7.075720714	-6.657577319	toxic
SJ000368630-2	Sigmoidal	0.96	-5.958607315	-6.13667714	-5.744727495	toxic
SJ000007499-2	Sigmoidal	0.83	-8.346787486	-8.619788758	-8.107905397	toxic
SJ000154959-2	Sigmoidal	0.78	-8.096910013	-8.397940009	-7.769551079	toxic
5	Sigmoidal	0.86	-8.091514981	-8.292429824	-7.886056648	toxic
SJ000290800-2	Sigmoidal	0.83	-7.823908741	-8.119186408	-7.431798276	toxic
SJ000121296-3	Sigmoidal	0.84	-7.795880017	-8.031517051	-7.552841969	toxic
SJ000207559-2	Sigmoidal	0.9	-7.200659451	-7.443697499	-7.013228266	toxic
SJ000105009-2	Single-Point	NA	NA	NA	NA	inactive
SJ000449712-2	Single-Point	NA	NA	NA	NA	inactive
SJ000106942-2	Single-Point	NA	NA	NA	NA	inactive

sample	primary cScore	primary r2	primary EC_{50}	primary EC_{50}_l	primary EC_{50}_u	Zebrafish assay @1 μM
SJ000338685-2	Single-Point	NA	NA	NA	NA	inactive
SJ000195722-2	Single-Point	NA	NA	NA	NA	inactive
SJ000208919-2	Single-Point	NA	NA	NA	NA	inactive
SJ000339517-2	Super Active	NA	-9	NA	NA	inactive
SJ000294876-2	Super Active	NA	-9	NA	NA	inactive
SJ000157784-2	Super Active	NA	-9	NA	NA	inactive
SJ000338428-2	Super Active	NA	-9	NA	NA	inactive
SJ000286673-2	Supplement	NA	NA	NA	NA	toxic
SJ000287098-9	Supplement	NA	NA	NA	NA	inactive
SJ000286237-8	Supplement	NA	NA	NA	NA	inactive
SJ000821588-2	Supplement	NA	NA	NA	NA	inactive

[00398] During early axis patterning Bmp signaling directs ventral tissue formation in zebrafish. Ectopic activation of the Bmp pathway leads to a spectrum of ventralized phenotypes (see FIG. 5A i-v) ranging from mild cyclopia (V1, FIG. 5A ii) and headlessness (V3, FIG. 5A iv) to loss of all dorsoanterior tissues (V4, FIG. 5A v). The phenotypes of embryos treated with dose escalations of the test set of validated hits, including the BMP activator SJ000286237 (Isoliquiritigenin, compound **4**) as a positive control, were examined and scored using this scheme (Vrijens et al. (2013) *PLoS One 8*, e59045). All three compounds tested caused a dose-dependent ventralization of the zebrafish embryo at 24 hours

post fertilization (hpf). Embryos treated with **1** displayed the most severe ventralization and this compound was also the most potent. Interestingly, **1** also caused more mortality, and at lower than controls and the other two compounds. These results demonstrate that these compounds cause ventralization of embryos consistent with increased BMP signaling activity. All three new compounds ventralized zebrafish embryos and based on this effect, were termed "ventromorphins."

[00399] Interestingly, while all compounds in the 'Single-point' and 'Inactive' classes were inactive in the zebrafish assay, the three phenotypically active compounds all belonged to the class producing well-behaved dose-response curves ('Sigmoidal') in the cell-based assay (see FIG. 4). However, these three compounds were not among the most potent compounds in that screen. Sixteen compounds, all from the 'Sigmoidal' and 'Inverse' classes, were toxic. It was previously reported that the chalcones, compound **4** and 4-hydroxychalcone, induced a ventralization phenotype at concentrations ≥5 μM, whereas the 2 flavones, Diosmetin and Apigenin, did not (Vrijens et al. (2013) *PLoS One 8*, e59045). Both chalcones failed to show any appreciable phenotype at 1 μM, suggesting that the compounds **1**, **2**, and **3** have higher potency *in vivo*. Compounds **1**, **2**, and **3** were topologically similar N-phenylamides representing scaffold cluster 5 (see FIG. 4). Several close analogs in the set of 97 compounds which were assayed in the phenotypic screen were all inactive except for compound **5** which was toxic. Interestingly, this chemotype has been found to be an agonist in several unrelated luciferase screens including a SMN2 screen that identified compound, LDN-75654(Fuentealba et al. (2012) *Hum Mol Genet* **21**: 664-680; O'Donnell et al. (2010) *PLoS One* **5**; Cherry et al. (2013) *EMBO Mol Med* **5**: 1103-1118). The FDA-approved drug leflunomide and its active form teriflunomide have also been previously studied (O'Donnell et al. (2010) *PLoS One* **5**; White et al. (2011) *Nature* **471**: 518-522); however, leflunomide, which was in the initial compound screen disclosed herein, did not meet the EC_{50} cut off value. Both leflunomide and teriflunomide were tested in zebrafish, but neither caused ventralization in zebrafish embryos (see FIG. 6) (although they did show the previously observed ability to inhibit neural crest differentiation to pigment).

[00400] Referring to FIG. 6, representative images of zebrafish embryos at 24 h.p.f. (a-f) or 48 h.p.f. (g-l) are shown. Embryos were untreated (a, g), vehicle treated (1% DMSO; b,

h), or treated with 3 μM leflunomide (c, i), 6 μM leflunomide (d, j), 1 μM teriflunomide (e, k), or 2 μM teriflunomide (e, k), respectively.

5. VENTROMORPHINS PRODUCE BMP GENETIC RESPONSES IN ZEBRAFISH EMBRYOS

[00401] The experiments indicated that compounds **1**, **2**, and **3** produce embryonic phenotypes consistent with activated Bmp signaling. To evaluate these responses in more detail, the expression of genes that are established direct targets of Bmp signaling were analyzed (*bone morphogenetic protein 2b* (*bmp2b)*, *even-skipped-like 1 (eve1)*, and *sizzled* (*szl*)) in embryos treated with compound and controls, by whole mount *in situ* hybridization. Compounds **1**, **2**, and **3** all caused an increase in *bmp2b* (FIG. 7A, a-e), as well as an increase in *szl* expression (FIG. 7A, f-j). However, an increase in *eve1* expression was not observed (FIG. 7A, k-o). Without wishing to be bound by theory, these data indicate that in embryos, ventromorphins activate a subset of Bmp signaling responses, suggesting that they act at a level upstream of receptor activation (for example by inducing additional pathways that modulate eventual Bmp responsiveness) or downstream to specifically engage only specific elements of the Bmp signal transduction machinery.

[00402] Indirect or cooperatively induced Bmp genetic targets were also examined. These included the transcriptional repressors *vox* (also known as *vega1*) and *vent* (also known as *vega2*), as well as *chd*, which encodes a secreted Bmp inhibitor, and is repressed by vent and vox (Kawahara et al. (2000) *Genesis 28*, 58-67; Kawahara et al. (2000) *Proc Natl Acad Sci U S A 97*, 12121-12126; Imai et al. (2001) *Development 128*, 2407-2420; Melby et al. (2000) *Dev Biol 224*, 275-285). As would be expected for embryos with ectopic Bmp signaling, all three compounds expanded expression of the ventralization markers, *vent* (FIG. 7B and FIG. 7C) and *vox* (FIG. 7D and FIG. 7E), and decreased expression of *chd* compared to controls (FIG. 7F and FIG. 7G). Without wishing to be bound by theory, this data reveal that the ventromorphins induce phenotypic and genetic ventralization, largely consistent with activation of the Bmp pathway.

[00403] Referring to FIG. 7A-G, zebrafish embryos were treated with 6.25 μM of each compound beginning at 2 hours post fertilization (hpf) and examined for RNA expression patterns by *in situ* hybridization at 8 hpf (FIG. 7A, a-o) or 6 hpf (FIG. 7A, q, s, u). 8 hpf

(75% epiboly) embryos were examined for *bmp2b* (FIG. 7A, a-e), *szl* (FIG. 7A, f-j), and *eve1* (FIG. 7A, k-o) expression. At 6 hpf (shield stage) embryos were fixed and expression of the positive BMP targets *vent* (FIG. 7B and FIG. 7C) and *vox* (FIG. 7D and FIG. 7E) and the negative target *chd* (FIG. 7F and FIG. 7G) were examined by whole mount *in situ* hybridization and quantified using ImageJ. Representative untreated and compound treated expression shown right (FIG. 7C, FIG. 7E, and FIG. 7G). Data represents average area of mRNA expression in three independent experiments and a total of 40-70 embryos per treatment.

6. VENTROMORPHINS ACTIVATE BMP SIGNALING RESPONSES IN CELL CULTURE

[00404] The zebrafish assays suggested that compounds **1**, **2**, and **3** activate the canonical BMP signaling pathway. To extend these observations, immunoblotting of protein lysates from C33A-2D2 cells stimulated with the compounds at different times was performed. All three compounds activated phosphorylation of SMAD1/5/8 (FIG. 8A-I and FIG. 9A-C) in serum-free medium (FIG. 10A-I). As in zebrafish embryos, compound **1** was most active. It induced P-SMAD1/5/8 maximally at 1 hr following treatment (FIG. 8A-C). In contrast, compound **2** (FIG. 8D-F) and **3** (FIG. 8G-I) achieved peak activity 0.5 hrs after stimulation. Compound **2** was the weakest activator of SMAD phosphorylation, with minimal increase in p-SMAD1/5/8 over control.

[00405] BMPs can also signal through SMAD-independent mechanisms, including the MAPK pathway (Jeong et al. (2010) *Korean J Urol 51*, 511-517). Immunoblotting analysis of lysates from C33A-2D2 treated with compounds revealed clear induction of the phosphorylated Extracellular Signal-regulated Protein Kinase, ERK1/2 (P-ERK1/2) by compound **1** (FIG. 11A-C) but not by **2** or **3** (data not shown). None of the compounds were able to stimulate SMAD2 phosphorylation (FIG. 12A-C), which responds to non-BMP TGFβ family members. Without wishing to be bound by theory, these data demonstrate that in cell culture, as in embryos, the three compounds activate selective BMP signaling responses.

[00406] Referring to FIG. 8A-I, immunoblot analysis of C33A-2D2 cells are shown. Specifically, the cells were untreated (U) or treated with Vehicle (V, 0.034% - 0.038% Methanol), 10 ng BMP-4 (B) or **1** (FIG. 8A), **2** (FIG. 8D), or **3** (FIG. 8G) for 0.5 to 12 hrs as

indicated. Proteins were separated on either 10% or 12% PAGE gels and immunoblotted with antibodies to phosphorylated SMAD1/5/8 (pSMAD1/5/8) or total SMAD1/5/8. Actin was used as loading control. Quantification of protein signal for pSMAD1/5/8 (FIG. 8B, FIG. 8E, and FIG. 8H) and Smad1/5/8 (FIG. 8C, FIG. 8F, and FIG. 8I) is indicated as the ratio of signal to actin expression ± standard deviation.

[00407] Referring to FIG. 9A-C, the full gel images for FIG. 8A-I are shown. Specifically, FIG. 9A corresponds to FIG. 8A-C including replicates (i, ii, and iii), FIG. 9B corresponds to FIG. 8D-F including replicates (i, ii, and iii), and FIG. 9C corresponds to FIG. 8G-I including replicates (i, ii, and iii).

[00408] Referring to FIG. 10A-I, an immunoblot analysis of protein lysates from C33A-2D2 cells treated with a 15-hour starvation in serum-free media prior to treatment with 6.25 μM compound **1**, **2**, or **3** are shown (U = untreated; V = 0.34-0.38% Methanol; B = 10 ng BMP4 for 3 hours). Additionally, quantification of p-SMAD1/5/8 (FIG. 10B, FIG. 10E, and FIG. 10H) and SMAD1/5/8 (FIG. 10C, FIG. 10F, and FIG. 10I) signal by ratio to Actin, used as loading control, are also illustrated.

[00409] Referring to FIG. 11A-C, protein lysates from C33A-2D2 cells were treated with compound **1** for varying timepoints as indicated (U = untreated; V = treated; B = 10 ng BMP4). Quantification of pERK (FIG. 11B) and ERK (11C) signal by ratio of Id1 to Actin are also shown.

[00410] Referring to FIG. 12A-C, protein lysates from C33A-2D2 cells were treated with compound **1** (FIG. 12A), **2** (FIG. 12B), **3** (FIG. 12C), or NIH3T3 (N) cells treated with TGF-β used as positive control (U = untreated; V = 0.036% methanol; B = 10 ng BMP4).

7. VENTROMORPHINS INDUCE OSTEOBLASTIC DIFFERENTIATION OF MYOBLASTS

[00411] C2C12 is a mouse myoblast cell line that differentiates into osteoblasts in response to treatment with BMP4 (Yaffe, D., and Saxel, O. (1977) *Nature 270*, 725-727; Blau et al. (1985) *Science 230*, 758-766; Li et al. (2005) *J Bone Miner Res 20*, 1611-1623). A hallmark of osteoblast induction by BMP is development of cellular "cobblestone" morphology. All three compounds were able to induce morphological osteoblast

differentiation of C2C12 cells (FIG. 13A-J), consistent with the idea that ventromorphins are capable of stimulating BMP-4 signaling.

[00412] Referring to FIG. 13A-J, mouse C2C12 myoblastic cells were untreated (FIG. 13A i, ii) or treated for 6 days with: vehicle (0.03% DMSO, FIG. 13B i, ii), 19 ng BMP-4 (FIG. 13C i, ii), 300 ng BMP-4 (FIG. 13D i, ii), 6.25 μM **1** (FIG. 13E i, ii), 25 μM **1** (FIG. 13F i, ii), 6.25 μM **2** (FIG. 13G i, ii), 25 μM **2** (FIG. 13H i, ii), 6.25 μM **3** (FIG. 13I i, ii), or 25 μM **3** (FIG. 13J i, ii). For each treatment, one 20X magnification representative image (i) is displayed along with a zoomed in image (ii) displaying cell morphology. Scale bar for 100 μM is represented in FIG. 13A. Dashed lines indicate the outline of cells.

[00413] Differentiation of myoblasts to osteoblast by the three compounds was confirmed by Affymetrix gene expression array, in which it was found that all three compounds and BMP-4 directed expression of a set of common genes (FIG. 14A). The highest dose (100 and 300 ng) BMP-4 treatments generated a gene expression signature most similar to osteoblast expression. Low dose (10 ng) BMP-4 treatment aligned closely with 25μM of compound **3** treatment and with 25μM 942 (although separated in the heat map, see FIG. 14A). GO analysis confirmed that genes induced by BMP-4 and compound **1** correspond to those found in osteoblasts (FIG. 14B). In addition, regression analysis confirmed a significant linear correlation between BMP-4 and compound **1** (FIG. 14C and FIG. 15A-F) but not between BMP-4 and compounds **2** or **3** (FIG. 15). Expression of three targets: *Alcohol dehydrogenase 7* (*Adh7*), *Prostaglandin F receptor* (*Ptgfr*), and *Ankyrin repeat domain-containing protein 2* (*Ankrd2*) was confirmed by qRT-PCR. Both *Adh7* and *Ptgfr* displayed significant increase in expression following BMP-4 or 942 treatment compared to control (FIG. 14D and FIG. 14E). *Ankrd2* had decreased expression in cells treated with BMP-4 or 942 as compared to controls, although BMP-4 had a more potent effect (FIG. 14F). Without wishing to be bound by theory, these data show that ventromorphins direct multiple BMP signaling responses.

[00414] Referring to FIG. 14A-F, RNA expression from C2C12 myoblasts treated for 6 days with BMP-4 10, 100, 300 ng/mL or the compounds at 6.25, 12.5, or 25 μg/mL, or vehicle are shown. FIG. 14A shows an unsupervised heat map of genes, which were positively or negatively correlated with BMP-4 and compound **1**. FIG. 14B shows a GO analysis of 94 genes induced by at least 0.5 fold by both BMP-4 and 25 μM compound **1**.

FIG. 14C shows a scatter plot with regression analysis for 10 ng BMP-4 and 25 μM compound **1**. qRT-PCR for *Adh7* (FIG. 14D), *Ptgfr* (FIG. 14E), and *Ankrd2* (FIG. 14F) from C2C12 cells untreated, or treated with vehicle, 10 or 300 ng BMP-4, or 12.5 or 25 μM compound **1** are also shown. *= significantly different than untreated ($p \leq 0.0169$). #= significantly different than vehicle ($p \leq 0.0209$). $= treatmens significantly different ($p \leq 0.05$).

[00415] Referring to FIG. 15A-F, regression analysis comparing low (10 ng) or high (300 ng) dose of BMP4 to 25 μM of compounds **1** (low, high; FIG. 15A and FIG. 15B), **2** (low, high; FIG. 15C and FIG. 15D), and **3** (low, high; FIG. 15E and FIG. 15F).

9. SMALL MOLECULE ACTIVATORS OF BMP SIGNALING

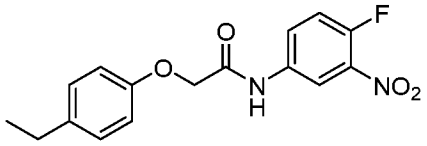
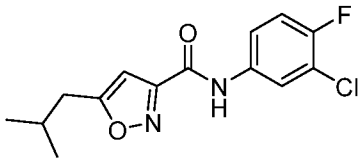
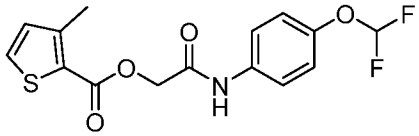
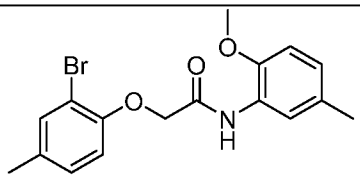
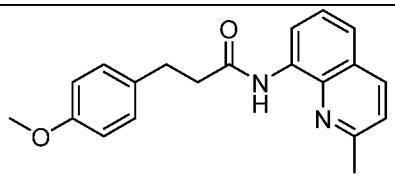
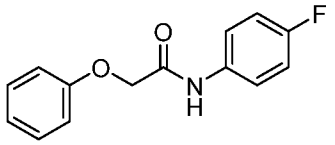
[00416] BMPs are metabologens currently used for the treatment of bone regeneration and kidney disorders. Unfortunately, BMPs are expensive to produce, bulky, and do not cross the blood-brain barrier. Their clinical use is also limited due to the supra-physiological doses required for therapeutic efficacy, which cause severe side effects (Gottfried and Dailey (2008) *Neurosurgery* **64**: 380-391). Without wishing to be bound by theory, the disclosed small molecule activators of the BMP signaling pathway can be a more cost-effective alternative and would also be potentially more deliverable to the brain than BMP molecules.

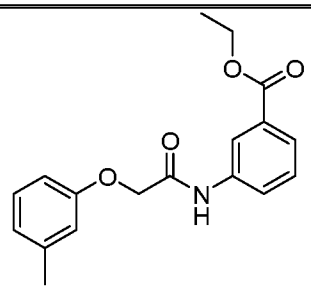
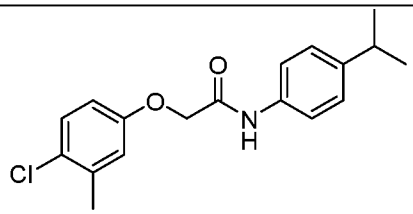
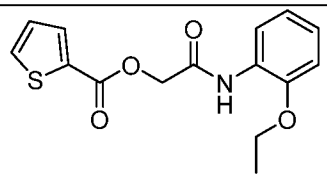
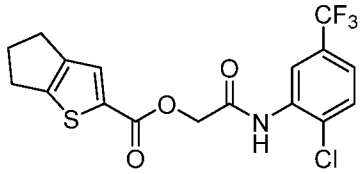
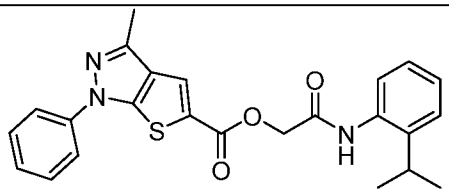
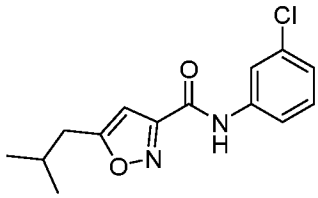
[00417] It was previously found that BMPs can induce differentiation of GNPs and SHH medulloblastoma tumor cells, suggesting that activators of BMP signaling could be used as differentiation therapy of SHH medulloblastoma (Vrijens et al. (2013) *PLoS One* **8**: e59045). Improved potency of BMP activators might eventually lead to their use in tissue engineering efforts, including bone repair with less toxic effects than those described for BMP2 and BMP4. Their use could also be more cost-effective and potentially more easily deliverable. Finally, without wishing to be bound by theory, because compounds **1**, **2**, and **3** can penetrate zebrafish embryos, they might be useful as chemical probes to interrogate BMP signaling.

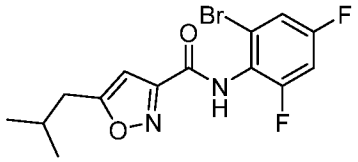
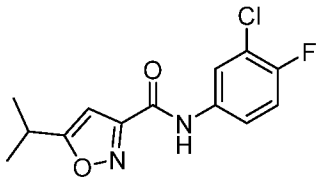
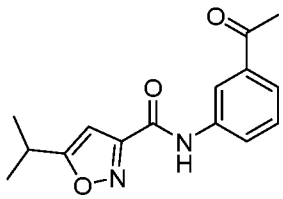
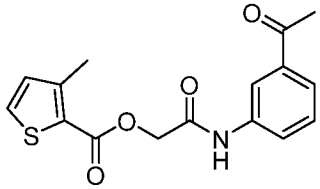
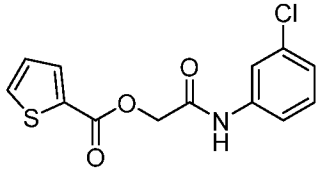
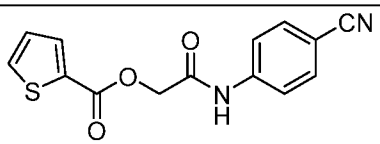
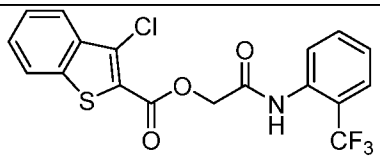
10. CHARACTERIZATION OF BMP SIGNALING ACTIVATORS

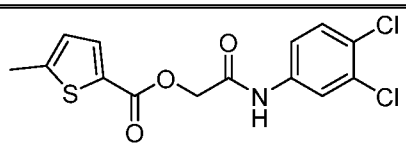
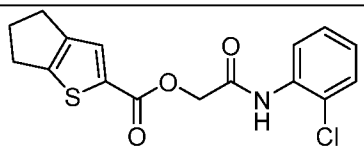
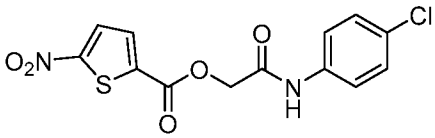
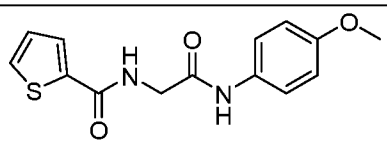
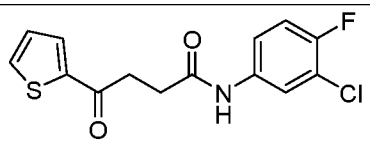
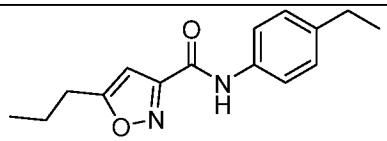
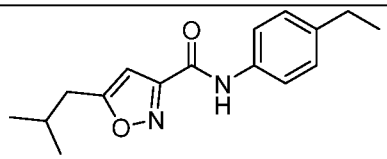
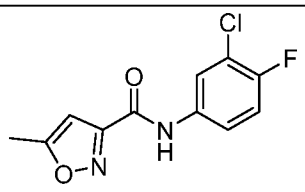
[00418] A list of compounds evaluated for their ability to activate BMP signaling is shown in Table 3 below.

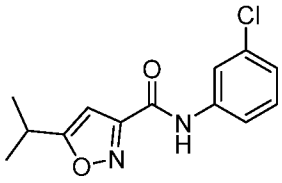
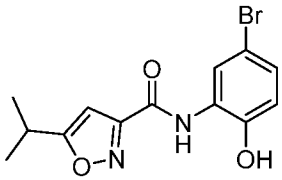
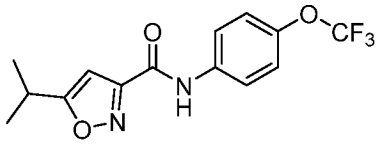
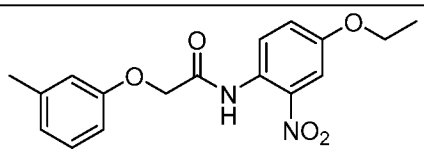
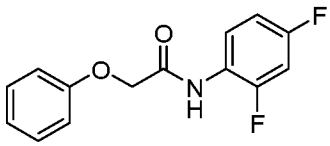
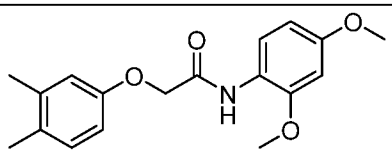
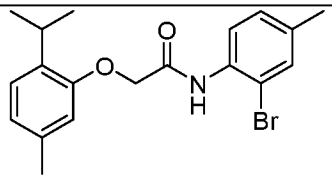
TABLE 3.

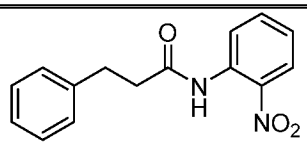
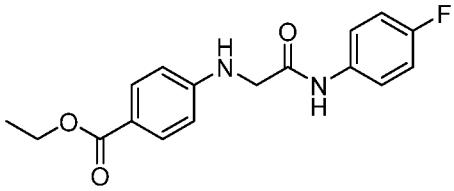
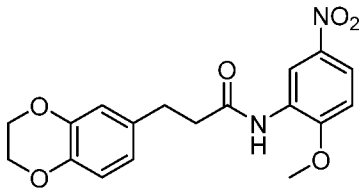
No.	Structure	Zebrafish Activity (SP at 6 μM)	Luciferase Assay in C33A cells EC_{50} (μM)
1		active	0.240
2		active	0.036
3		active	1.000
5		toxic	0.008
6		active	NT
7		active	NT

No.	Structure	Zebrafish Activity (SP at 6 µM)	Luciferase Assay in C33A cells EC_{50} (µM)
8		active	NT
9		active	NT
10		active	NT
11		active	NT
12		active	NT
13		active	>50

No.	Structure	Zebrafish Activity (SP at 6 µM)	Luciferase Assay in C33A cells EC_{50} (µM)
14		active	NT
15		active	NT
16		active	NT
17		inactive	>50
18		inactive	NT
19		inactive	NT
20		inactive	NT

No.	Structure	Zebrafish Activity (SP at 6 μM)	Luciferase Assay in C33A cells EC_{50} (μM)
21		inactive	NT
22		inactive	NT
23		inactive	NT
24		inactive	NT
25		inactive	NT
26		inactive	0.085
27		inactive	0.170
28		inactive	NT

No.	Structure	Zebrafish Activity (SP at 6 μM)	Luciferase Assay in C33A cells EC_{50} (μM)
29		inactive	NT
30		inactive	NT
31		inactive	NT
32		inactive	NT
33		inactive	NT
34		toxic	NT
35		inactive	NT

No.	Structure	Zebrafish Activity (SP at 6 μM)	Luciferase Assay in C33A cells EC_{50} (μM)
36		inactive	NT
37		inactive	NT
38		inactive	NT

NT = Not Tested

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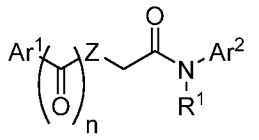
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[00479] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

What is claimed is:

1. A method for treating a disorder associated with diminished BMP signaling in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula:



,

wherein n is selected from 0 and 1;

wherein Z is selected from O, CH_2, and NR^2;

wherein R^2 is selected from hydrogen and C1-C4 alkyl;

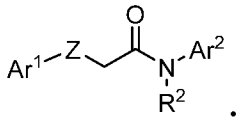
wherein R^1 is selected from hydrogen and C1-C4 alkyl;

wherein Ar^1 is selected from aryl and heteroaryl and substituted with 0-3 groups independently selected from phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl);

wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl);

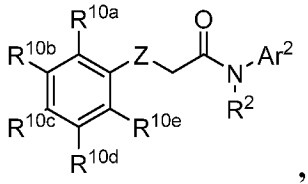
or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with diminished BMP signaling.

2. The method of claim 1, wherein the compound has a structure represented by a formula:



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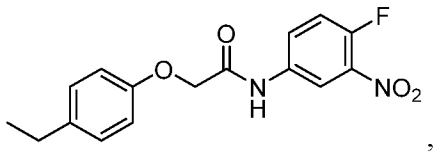
3. The method of claim 2, wherein the compound has a structure represented by a formula:



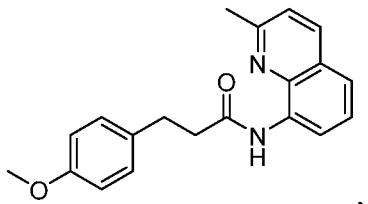
,

wherein each of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is independently selected from hydrogen, halogen, $-NH_2$, –OH, –CN, $-NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $-CO_2$(C1-C4 alkyl), provided that at least two of R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e} is hydrogen.

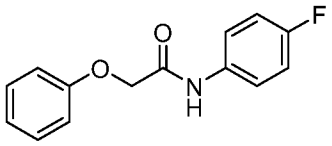
4. The method of claim 2, wherein the compound is selected from:



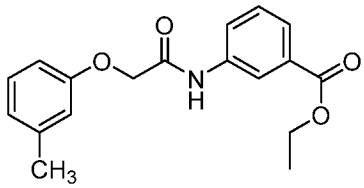
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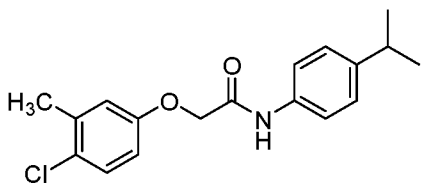
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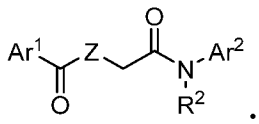


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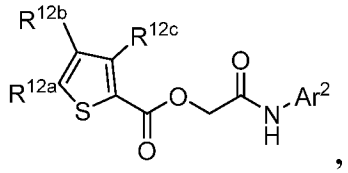


and .

5. The method of claim 1, wherein the compound has a structure represented by a formula:



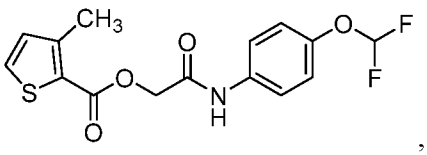
6. The method of claim 5, wherein the compound has a structure represented by a formula:

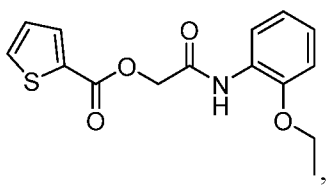


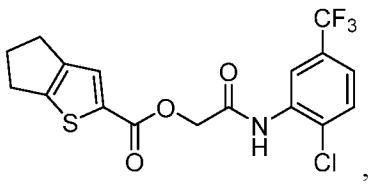
wherein each of R^{12a}, R^{12b}, and R^{12c} is independently selected from hydrogen, phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl), provided that at least two of R^{12a}, R^{12b}, and R^{12c} is hydrogen,

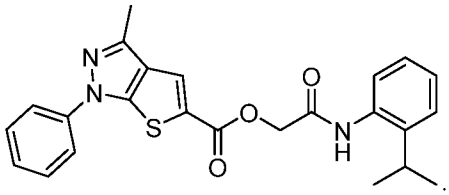
or wherein each of R^{12a} and R^{12b} are covalently bonded together and, together with the intermediate atoms, comprise a 5-membered cycloalkyl, a 6-membered cycloalkyl, a 5-membered heteroaryl, a 6-membered aryl, or a 6-membered heterocycloalkyl, and are substituted with 0-3 groups independently selected from hydrogen, phenyl, halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl).

7. The method of claim 5, wherein the compound is selected from:

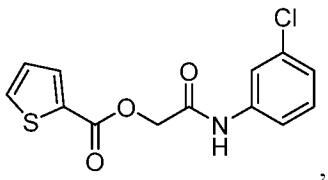


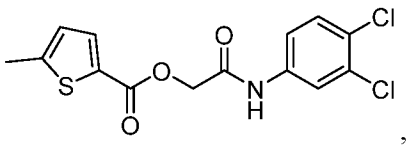


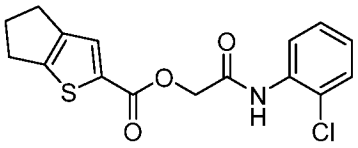

,

and 
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8. The method of claim 5, wherein the compound is not:


,

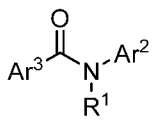

,

and 
.

9. The method of claim 1, wherein the disorder associated with diminished BMP signaling is selected from juvenile polyposis syndrome (JPS), hereditary pulmonary arterial hypertension (HPAH), obesity osteoporosis, and chronic kidney disease.

10. The method of claim 1, wherein the disorder associated with diminished BMP signaling is a cancer.

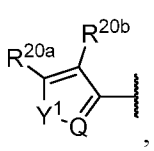
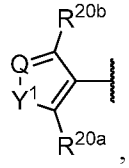
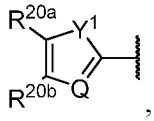
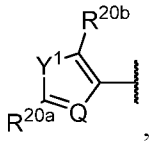
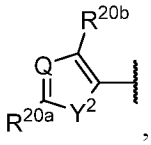
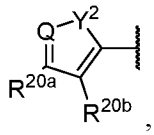
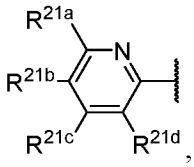
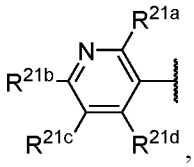
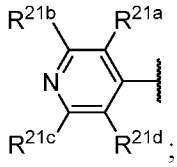
11. A method for treating a disorder associated with diminished BMP signaling in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula:


,

wherein R^1 is selected from hydrogen and C1-C4 alkyl;

wherein Ar^2 is selected from aryl and 6- to 10-membered N-containing heteroaryl and substituted with 0-3 groups independently selected from halogen, $–NH_2$, –OH, –CN, $–NO_2$, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, C1-C4 haloalkoxyalkyl, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, –C(O)(C1-C4 alkyl), and $–CO_2$(C1-C4 alkyl); and

wherein Ar^3 is a 5- or 6-membered heteroaryl selected from:


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and

;

wherein Q, when present, is selected from CR^{30} and N;

wherein R^{30}, when present, is selected from hydrogen and C1-C4 alkyl;

wherein Y^1, when present, is selected from O, S, and NR^{31};

wherein R^{31}, when present, is selected from hydrogen and C1-C4 alkyl;

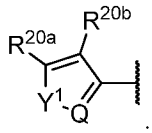
wherein Y^2, when present, is selected from O and NR^{31};

wherein each of R^{20a}, R^{20b}, R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, –OH, –CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, and C1-C4 haloalkoxyalkyl;

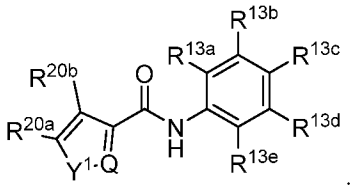
or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with diminished BMP signaling.

12. The method of claim 11, wherein Ar^3 is a 5-membered heteroaryl.

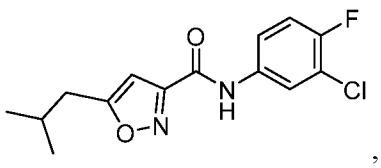
13. The method of claim 11, wherein Ar^3 is:

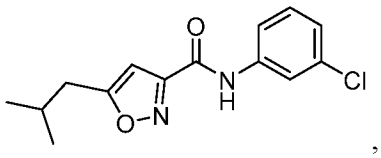


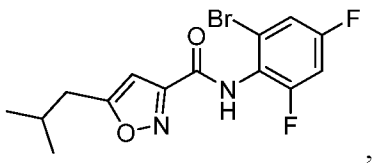
14. The method of claim 11, wherein the compound has a structure represented by a formula:

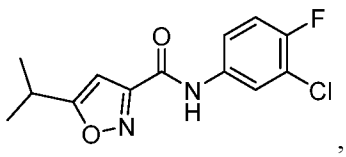


15. The method of claim 11, wherein the compound is selected from:

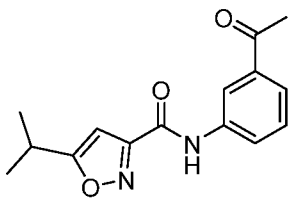
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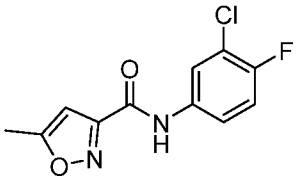
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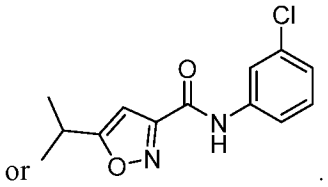
and

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16. The method of claim 11, wherein the compound is not:



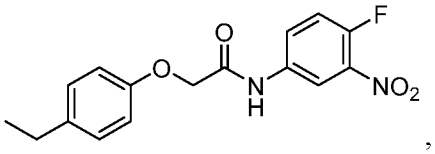
or

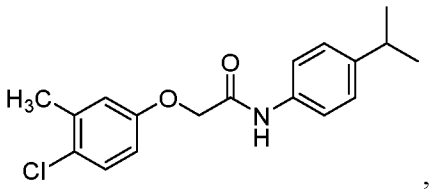


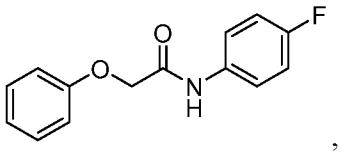
17. The method of claim 11, wherein the disorder associated with diminished BMP signaling is selected from juvenile polyposis syndrome (JPS), hereditary pulmonary arterial hypertension (HPAH), obesity osteoporosis, and chronic kidney disease.

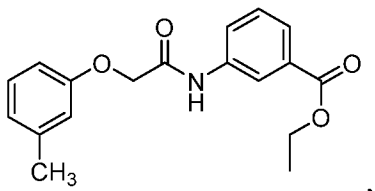
18. The method of claim 11, wherein the disorder associated with diminished BMP signaling is a cancer.

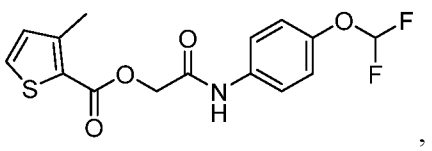
19. A pharmaceutical composition comprising an effective amount of a compound having a structure selected from:

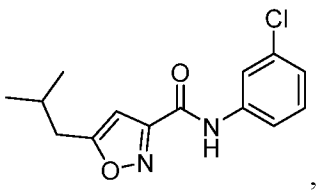


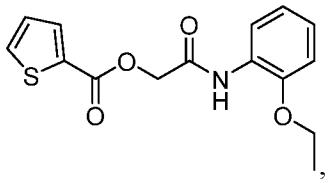


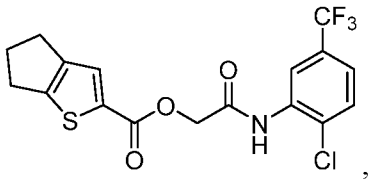


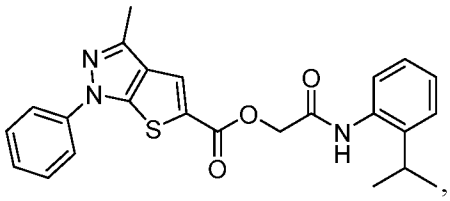












or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

20. The composition of claim 19, further comprising an effective amount of at least one chemotherapeutic agent.

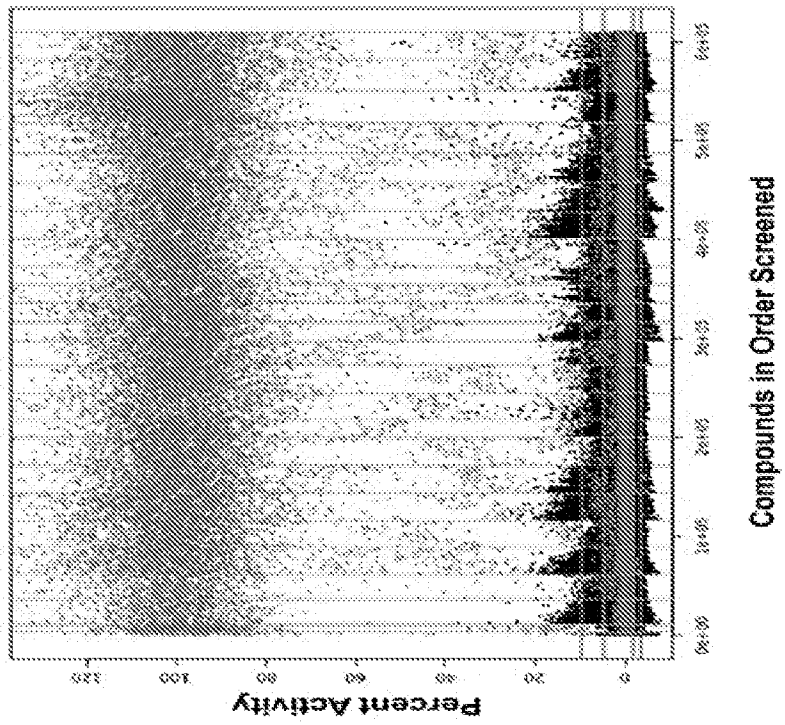

Percent Activity
Compounds in Order Screened

FIG. 1B

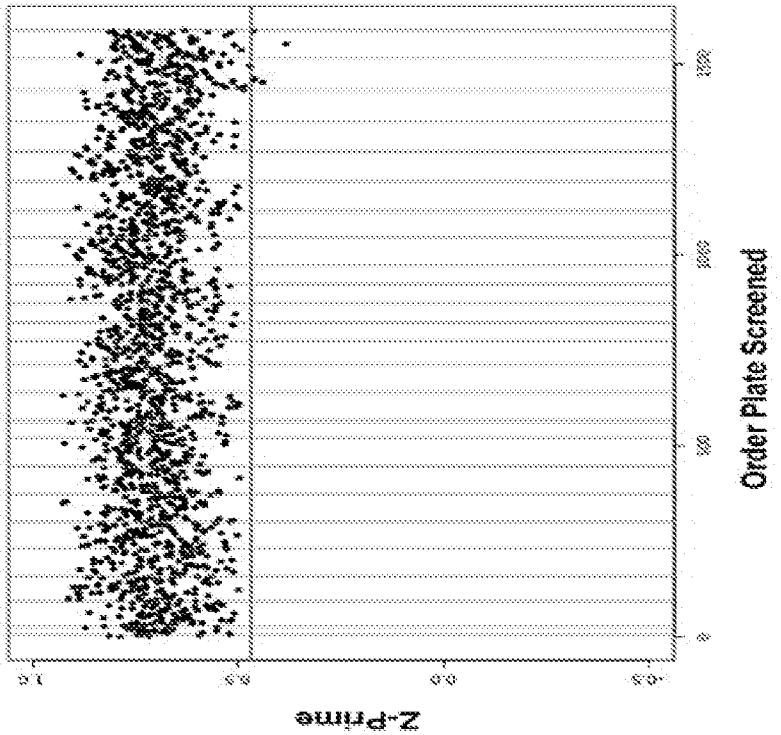

Z-Prime
Order Plate Screened

FIG. 1A

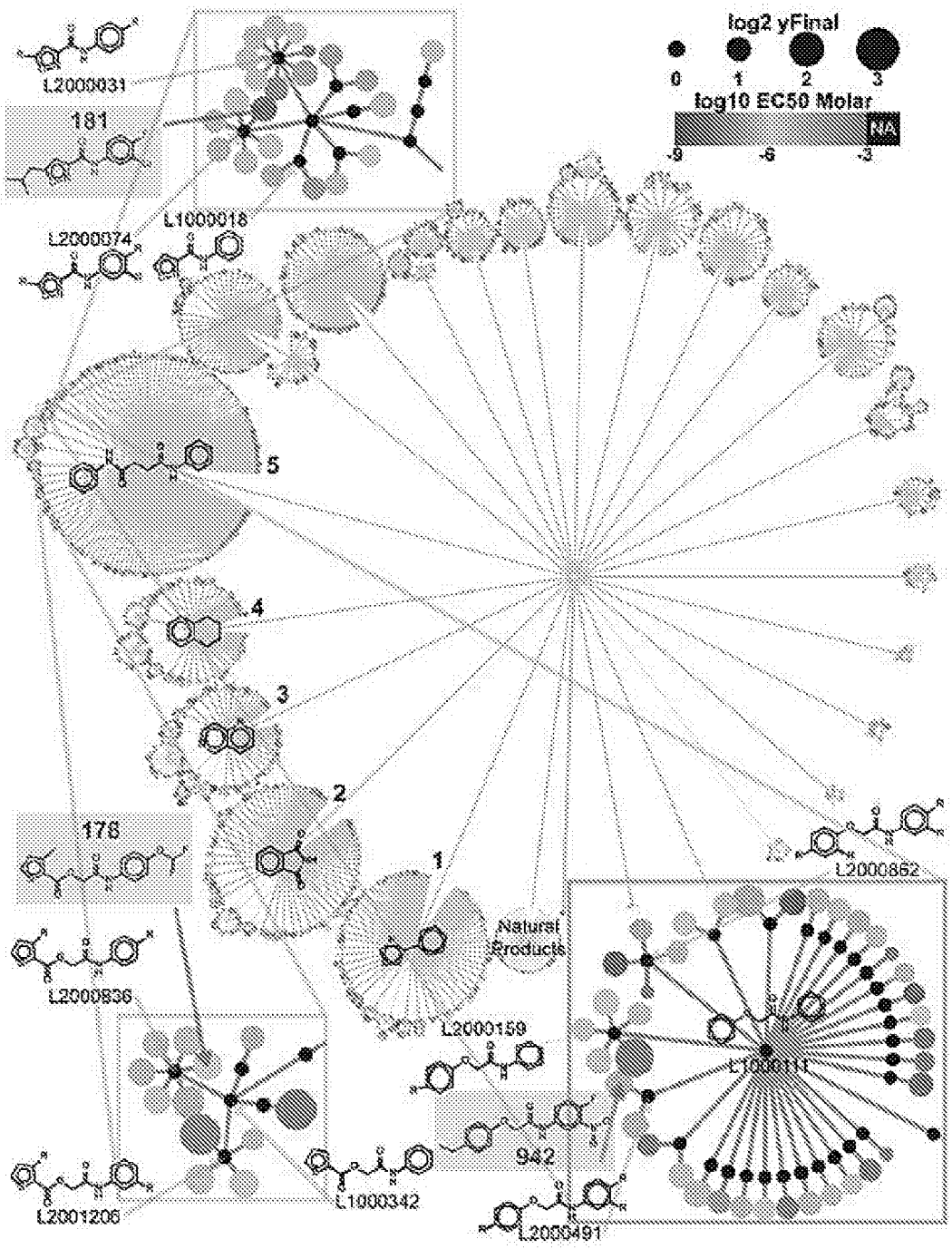

log2 yFinal
0
1
2
3
log10 EC50 Molar
NA
-9
-6
-3
L2000031
181
L1000018
L2000074
5
4
3
2
1
178
L2000836
L2001206
L1000342
L2000159
Natural Products
942
L2000491
L2000862
L1000111

FIG. 2

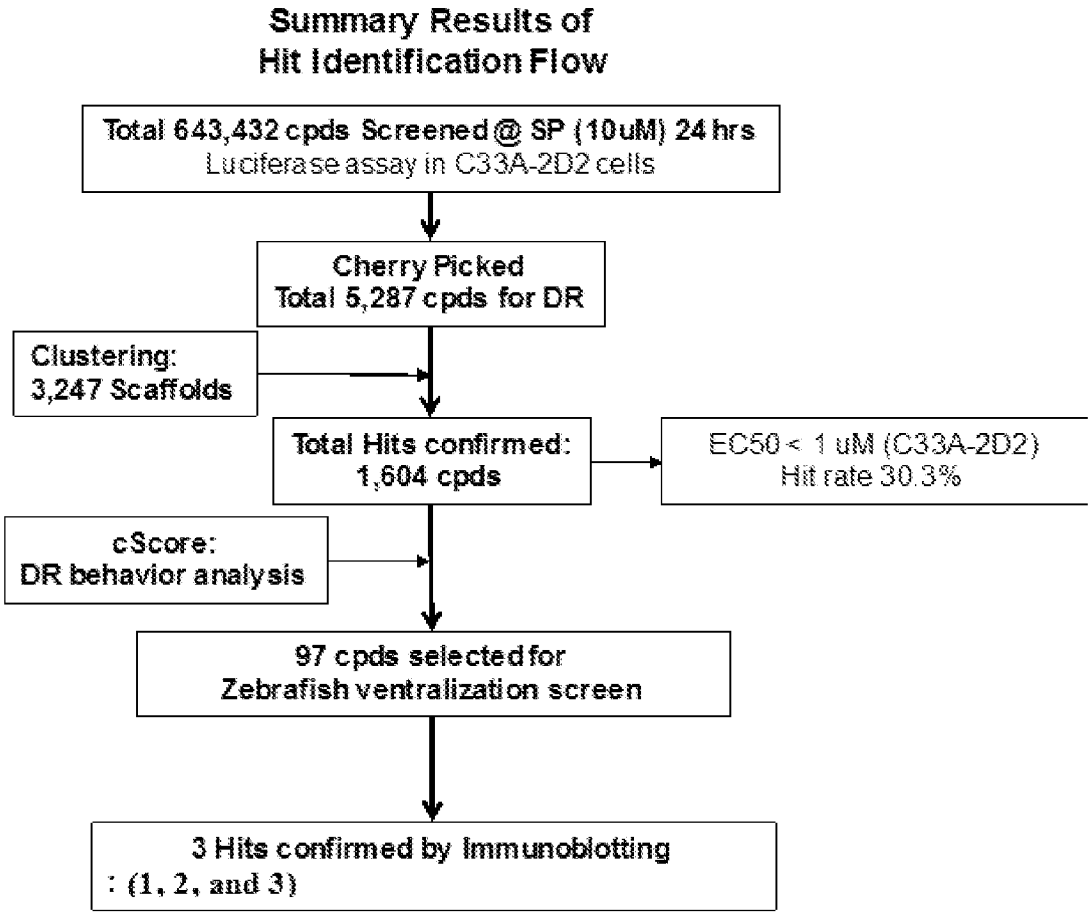

Summary Results of
Hit Identification Flow
Total 643,432 cpds Screened @ SP (10uM) 24 hrs
Luciferase assay in C33A-2D2 cells
Cherry Picked
Total 5,287 cpds for DR
Clustering:
3,247 Scaffolds
Total Hits confirmed:
1,604 cpds
EC50 < 1 uM (C33A-2D2)
Hit rate 30.3%
cScore:
DR behavior analysis
97 cpds selected for
Zebrafish ventralization screen
3 Hits confirmed by Immunoblotting
: (1, 2, and 3)

FIG. 3

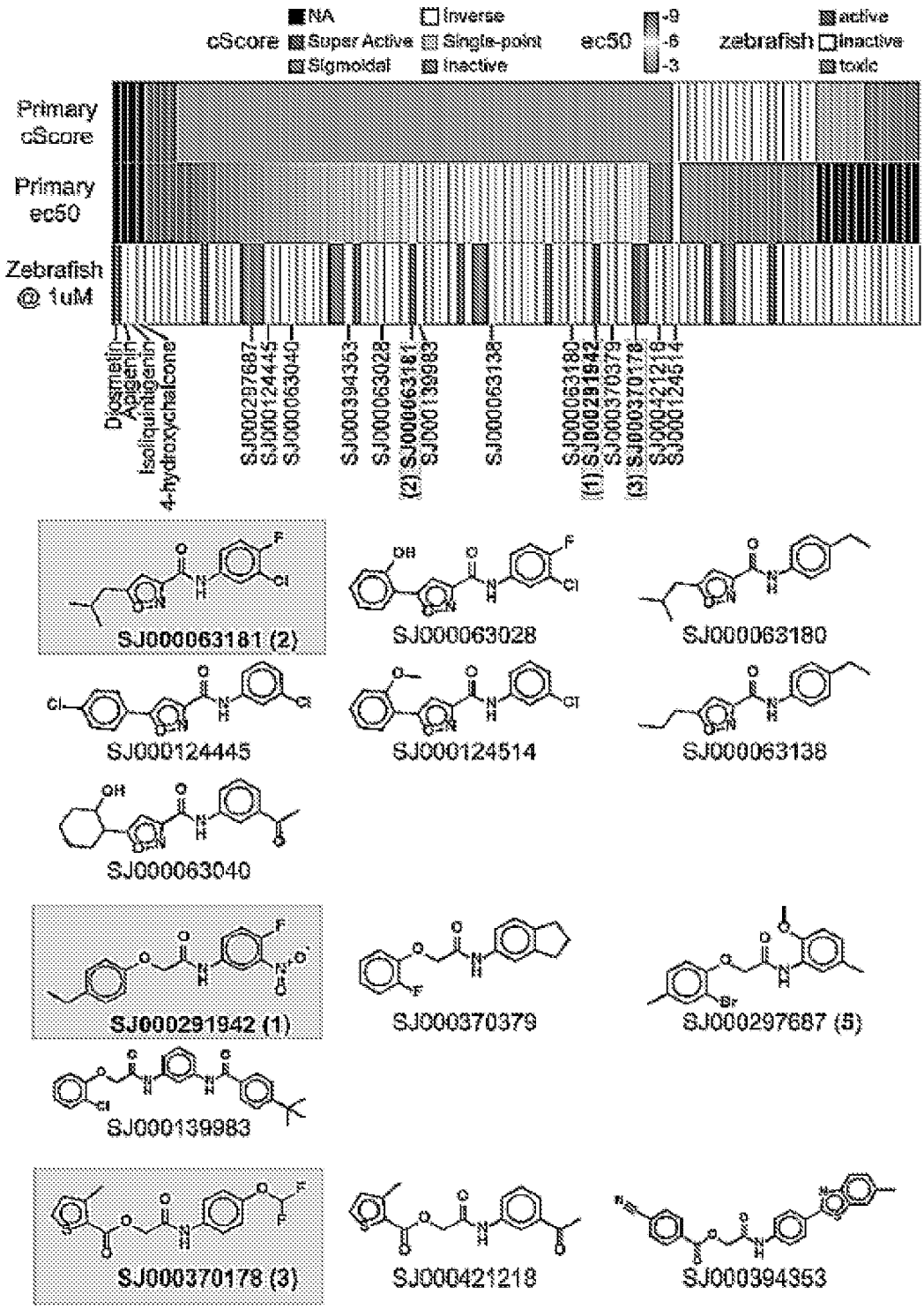

cScore
NA
Super Active
Sigmoidal
Inverse
Single-point
Inactive
ec50
-9
-6
-3
zebrafish
active
inactive
toxic
Primary cScore
Primary ec50
Zebrafish @ 1uM
Diosmetin
Apigenin
Isoliquiritigenin
4-hydroxychalcone
SJ000297687
SJ000124445
SJ000063040
SJ000394353
SJ000063028
(2) SJ000063181
SJ000139983
SJ000063138
SJ000063180
(1) SJ000291942
SJ000370379
(3) SJ000370178
SJ000421218
SJ000124514
SJ000063181 (2)
SJ000063028
SJ000063180
SJ000124445
SJ000124514
SJ000063138
SJ000063040
SJ000291942 (1)
SJ000370379
SJ000297687 (5)
SJ000139983
SJ000370178 (3)
SJ000421218
SJ000394353

FIG. 4

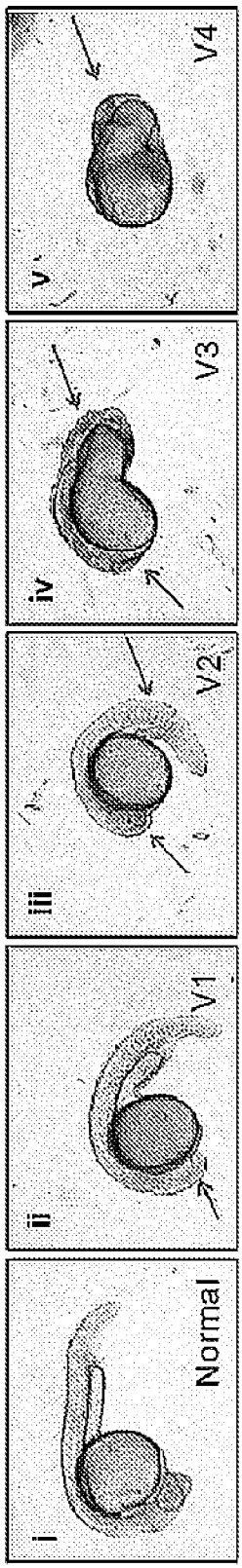


FIG. 5A

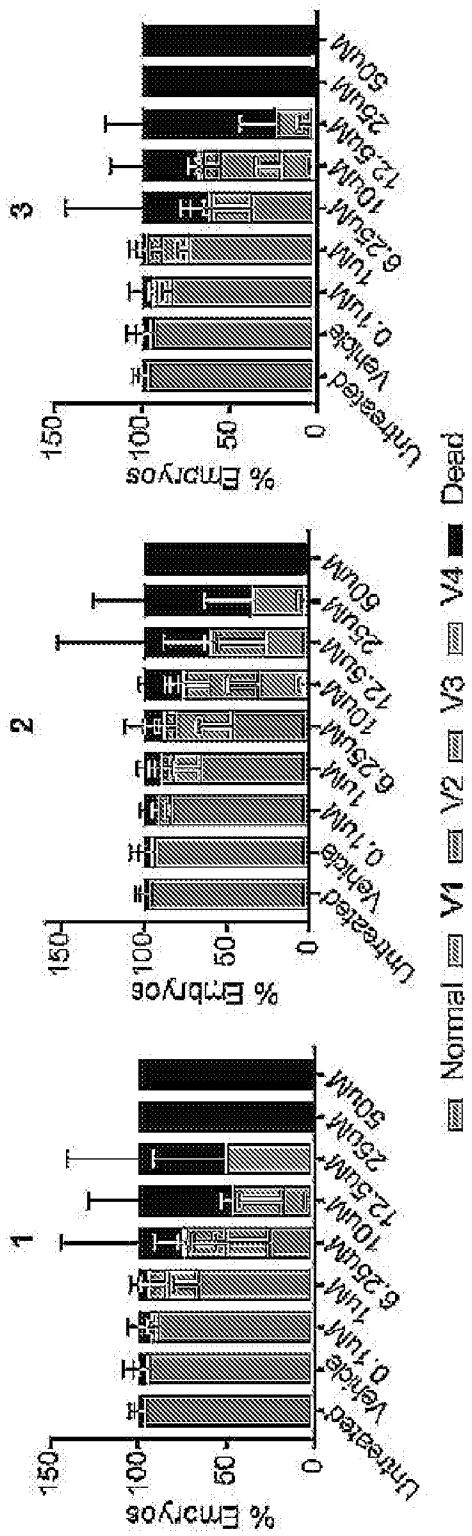


FIG. 5B

FIG. 5C

FIG. 5D

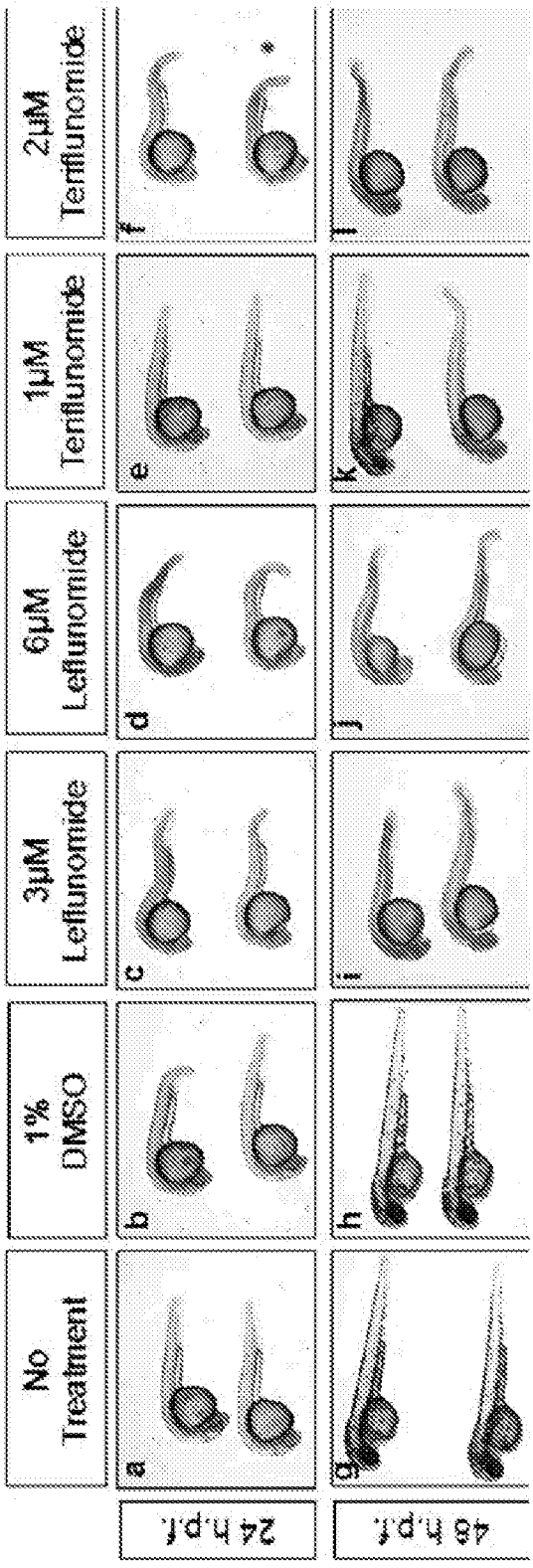

No Treatment
1% DMSO
3μM Leflunomide
6μM Leflunomide
1μM Teriflunomide
2μM Teriflunomide
24 h.p.f.
48 h.p.f.
a
b
c
d
e
f
g
h
i
j
k
l
*

FIG. 6

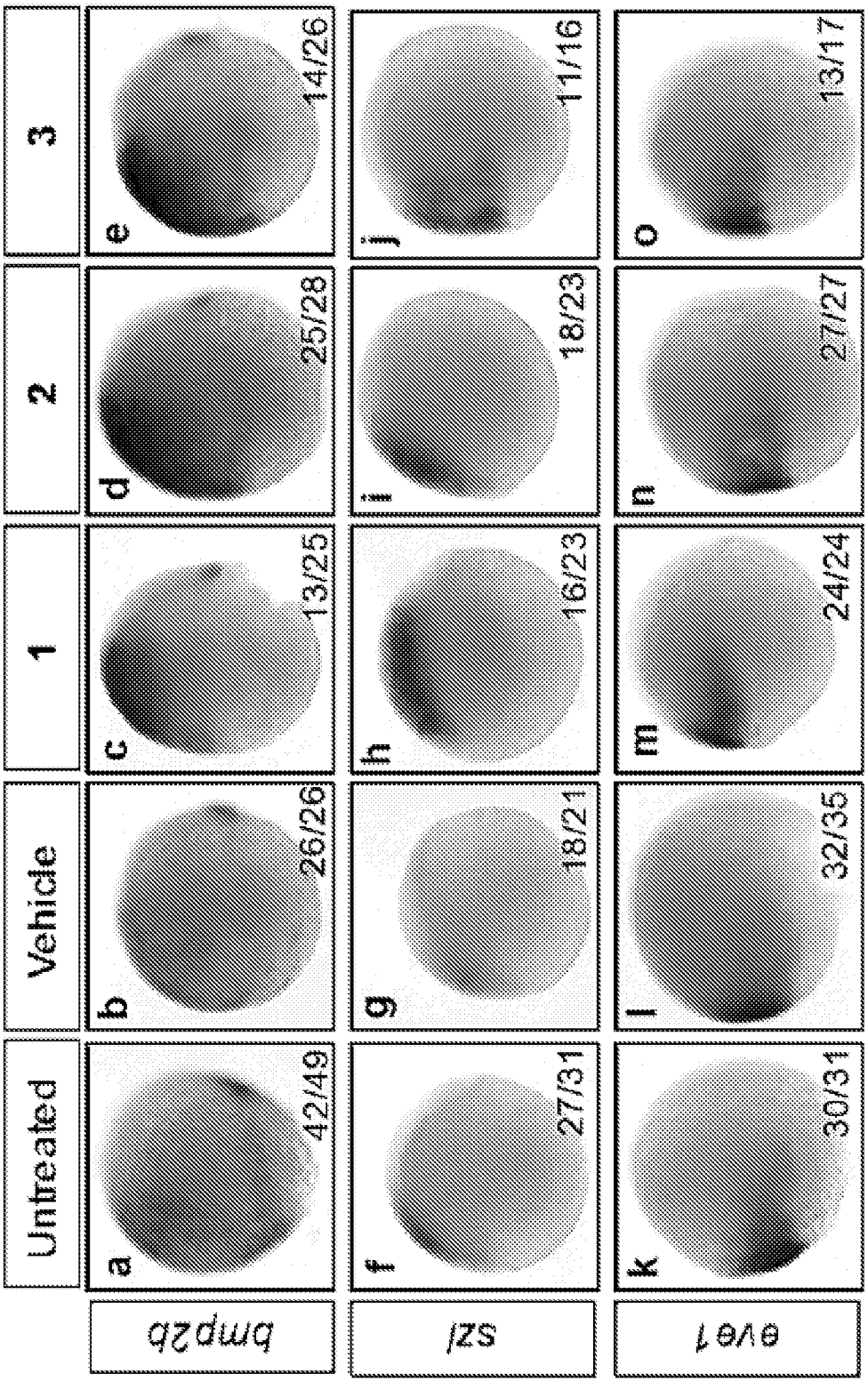

Untreated
Vehicle
1
2
3
bmp2b
szl
evel
a
42/49
b
26/26
c
13/25
d
25/28
e
14/26
f
27/31
g
18/21
h
16/23
i
18/23
j
11/16
k
30/31
l
32/35
m
24/24
n
27/27
o
13/17

FIG. 7A

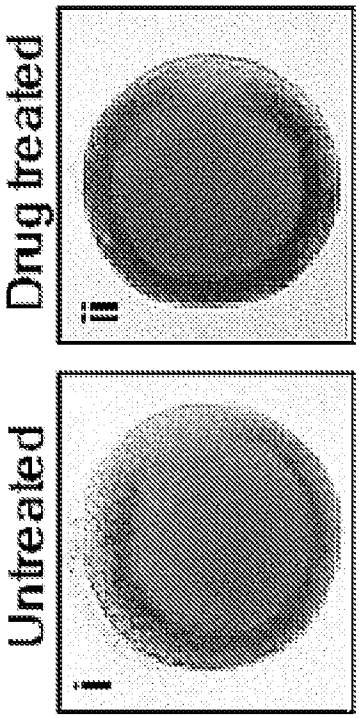

Untreated
Drug treated
i
ii

FIG. 7C

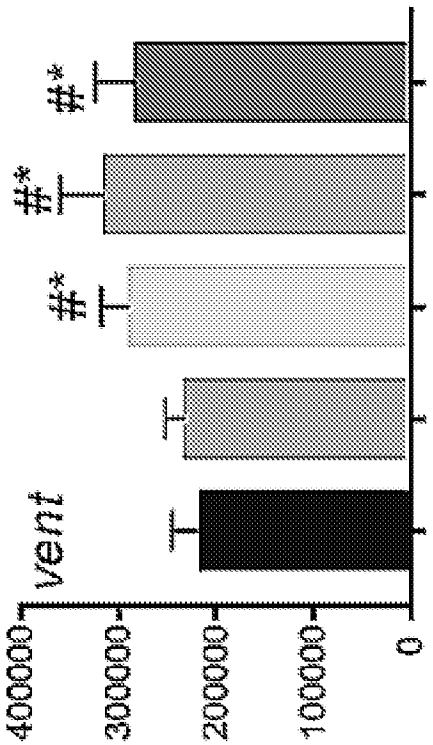

400000
300000
200000
100000
0
vent
#*
#*
#*

FIG. 7B

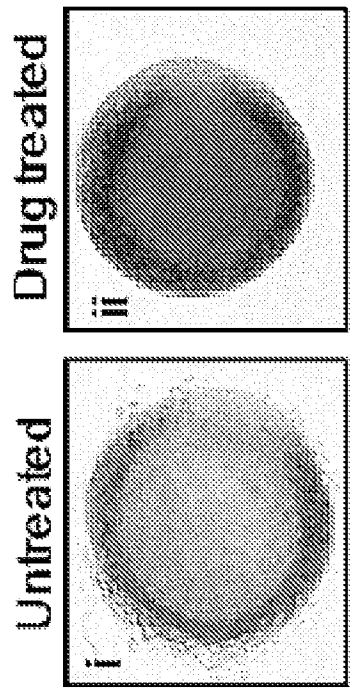

Untreated
Drug treated
i
ii

FIG. 7E

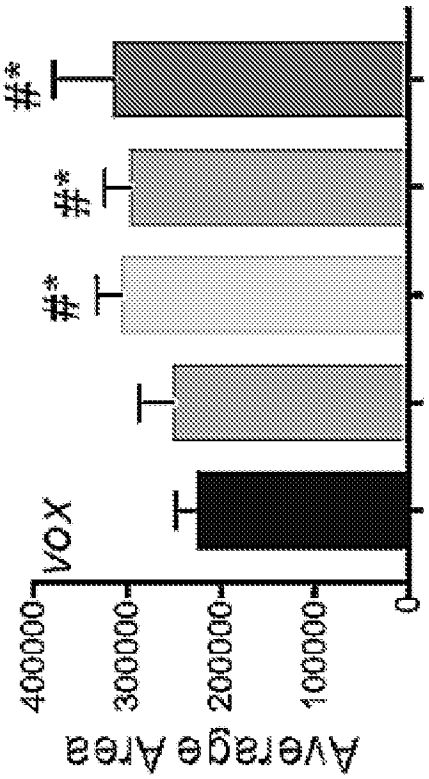

Average Area
400000
300000
200000
100000
0
VOX
#*
#*
#*

FIG. 7D

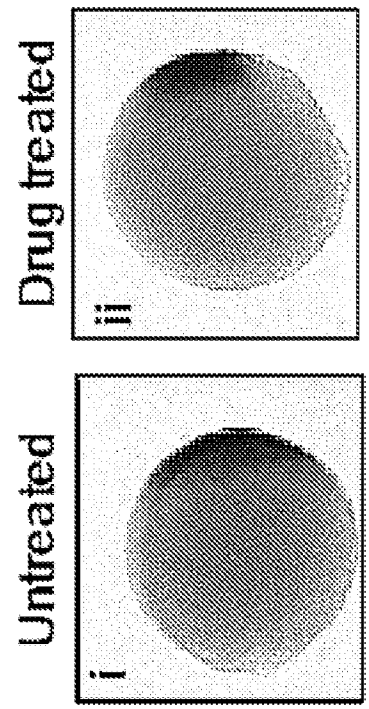

Untreated
i
Drug treated
ii

FIG. 7G

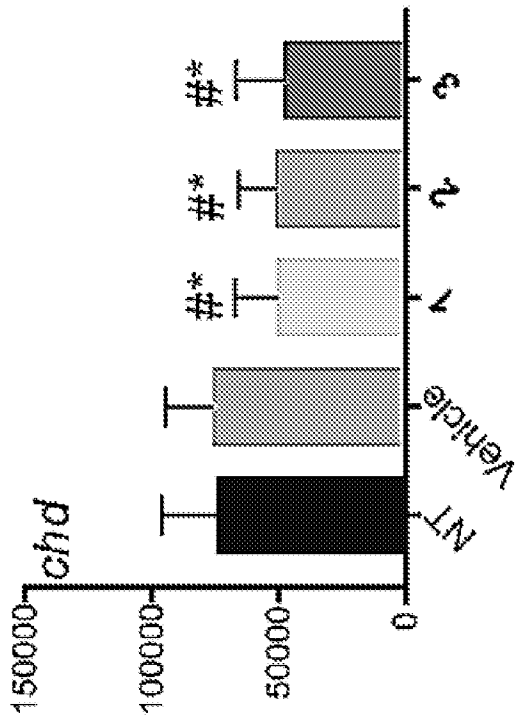

chd
150000
100000
50000
0
NT
Vehicle
1
2
3
#*
#*
#*

FIG. 7F

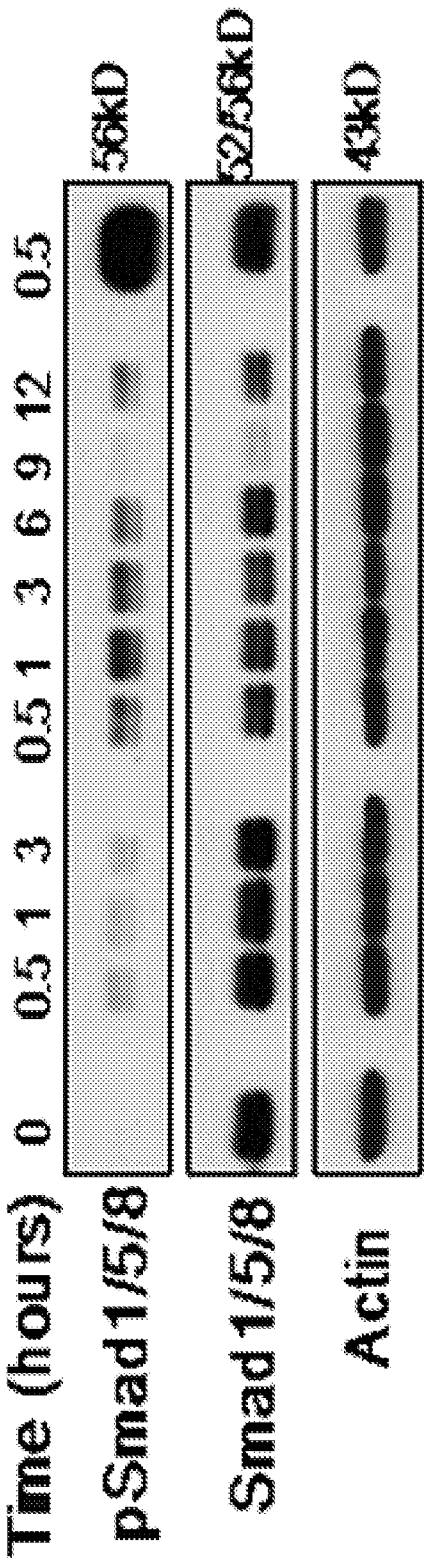

U
V
1
B
Time (hours)
0
0.5
1
3
0.5
1
3
6
9
12
0.5
pSmad1/5/8
Smad1/5/8
Actin
56kD
52/56kD
43kD

FIG. 8A

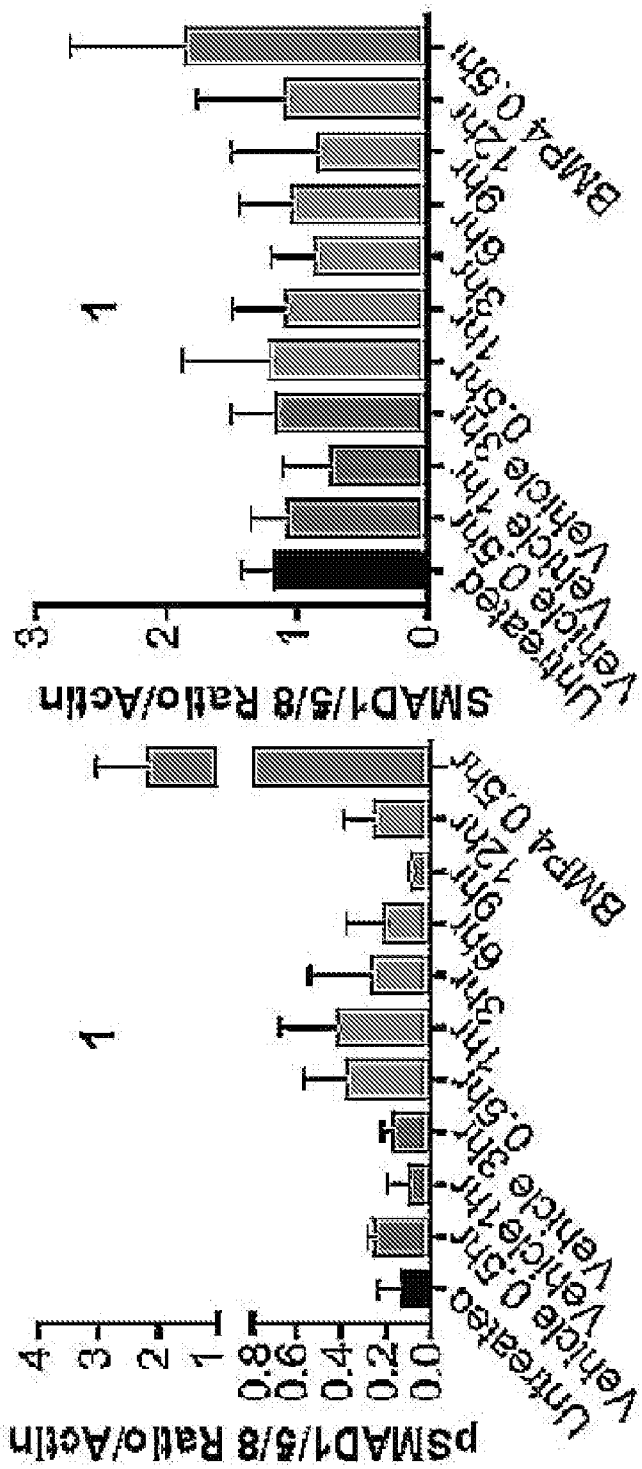

pSMAD1/5/8 Ratio/Actin
0.0
0.2
0.4
0.6
0.8
1
2
3
4
1
Untreated
Vehicle 0.5hr
Vehicle 1hr
Vehicle 3hr
Vehicle 0.5hr
1hr 3hr 6hr 9hr 12hr
BMP4 0.5hr
SMAD1/5/8 Ratio/Actin
0
1
2
3
1
Untreated
Vehicle 0.5hr
Vehicle 1hr
Vehicle 3hr
Vehicle 0.5hr
1hr 3hr 6hr 9hr 12hr
BMP4 0.5hr

FIG. 8B

FIG. 8C

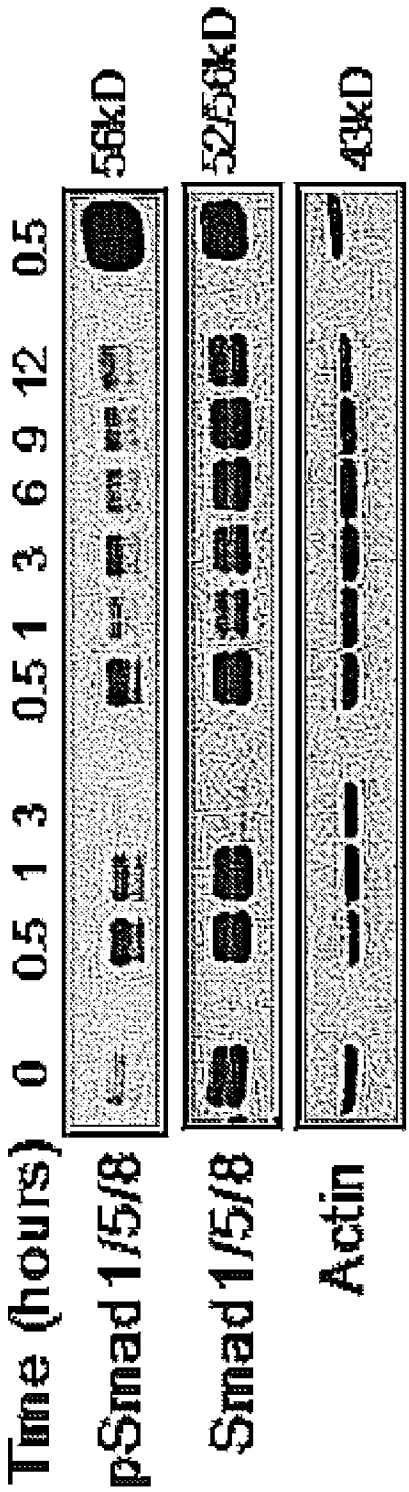

U
V
2
B
Time (hours)
0
0.5
1
3
0.5
1
3
6
9
12
0.5
pSmad1/5/8
Smad1/5/8
Actin
56kD
52/56kD
43kD

FIG. 8D

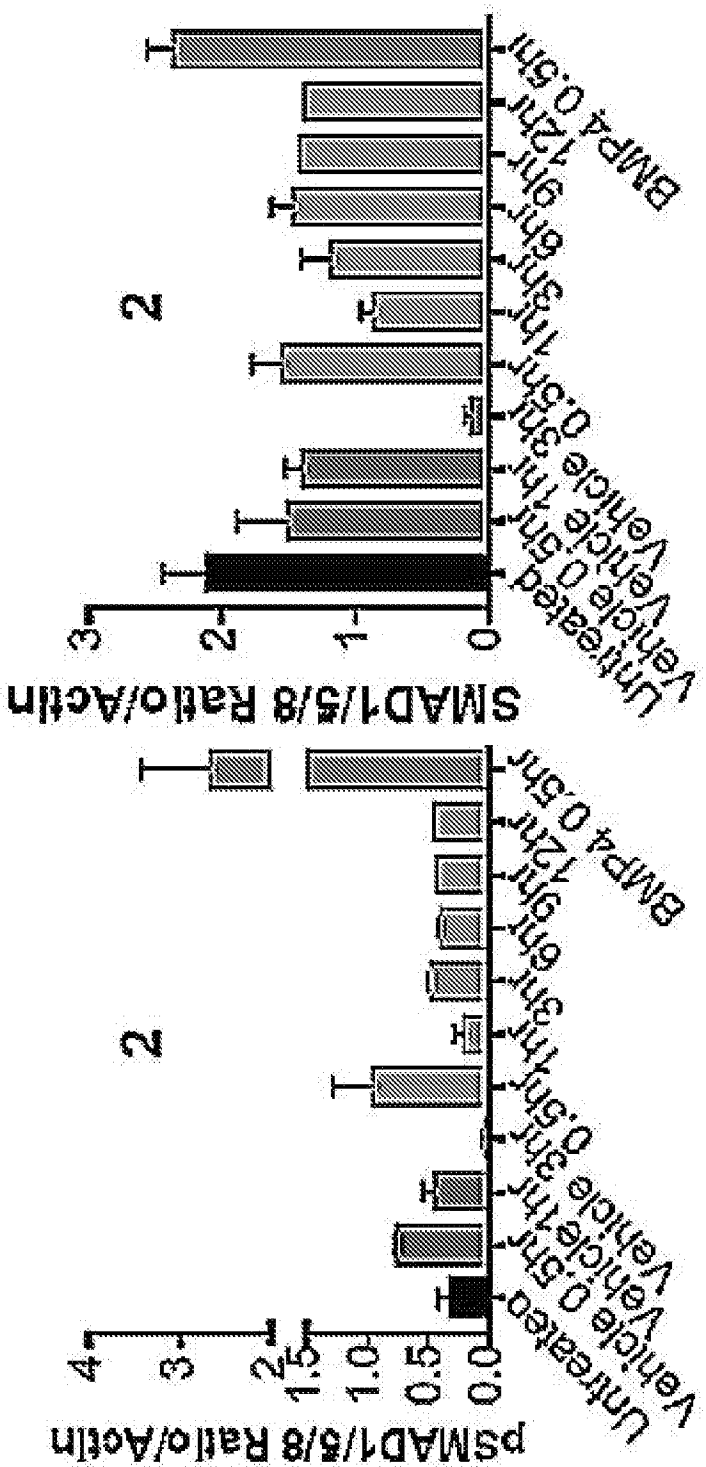

pSMAD1/5/8 Ratio/Actin
4
3
2.5
2.0
1.5
1.0
0.5
0.0
2
Untreated
Vehicle 0.5hr
Vehicle 1hr
Vehicle 3hr
0.5hr
1hr
3hr
6hr
9hr
12hr
BMP4 0.5hr

FIG. 8E

SMAD1/5/8 Ratio/Actin
3
2
1
0
2
Untreated
Vehicle 0.5hr
Vehicle 1hr
Vehicle 3hr
0.5hr
1hr
3hr
6hr
9hr
12hr
BMP4 0.5hr

FIG. 8F

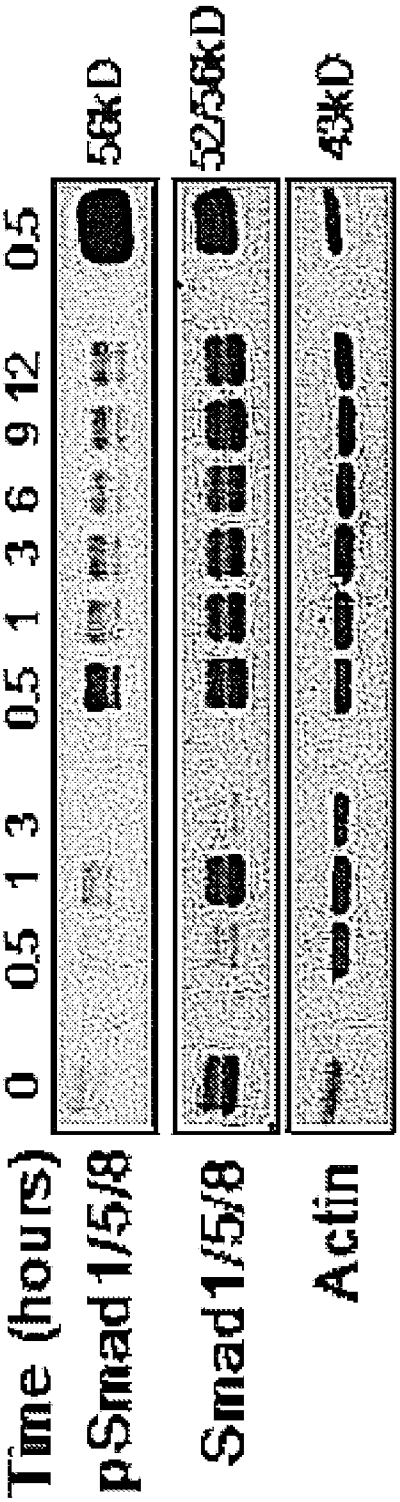

U
V
3
B
0
0.5
1
3
0.5
1
3
6
9
12
0.5
Time (hours)
pSmad1/5/8
Smad1/5/8
Actin
56kD
52/56kD
43kD

FIG. 8G

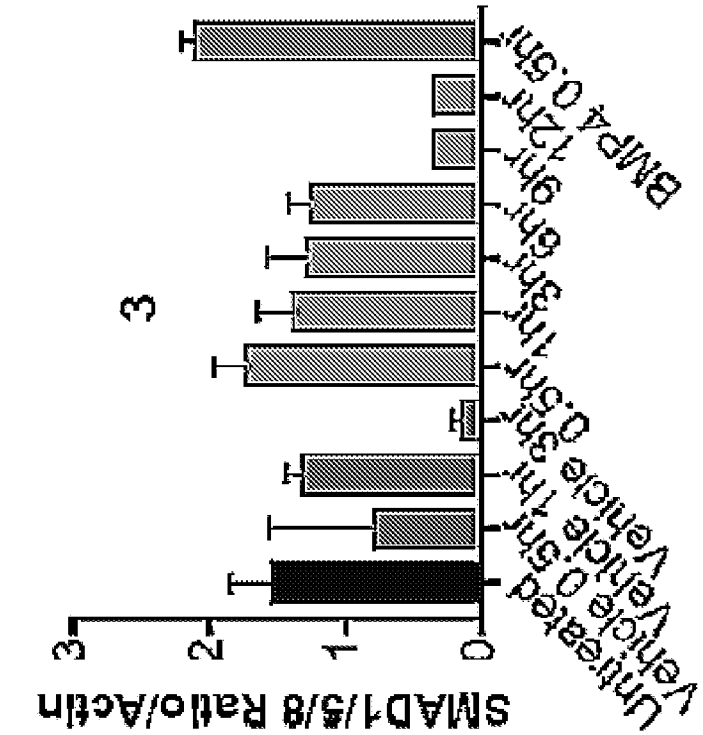

SMAD1/5/8 Ratio/Actin
3
2
1
0
Untreated
Vehicle 0.5hr
Vehicle 1hr
Vehicle 3hr
0.5hr
1hr
3hr
6hr
9hr
12hr
BMP4 0.5hr

FIG. 8I

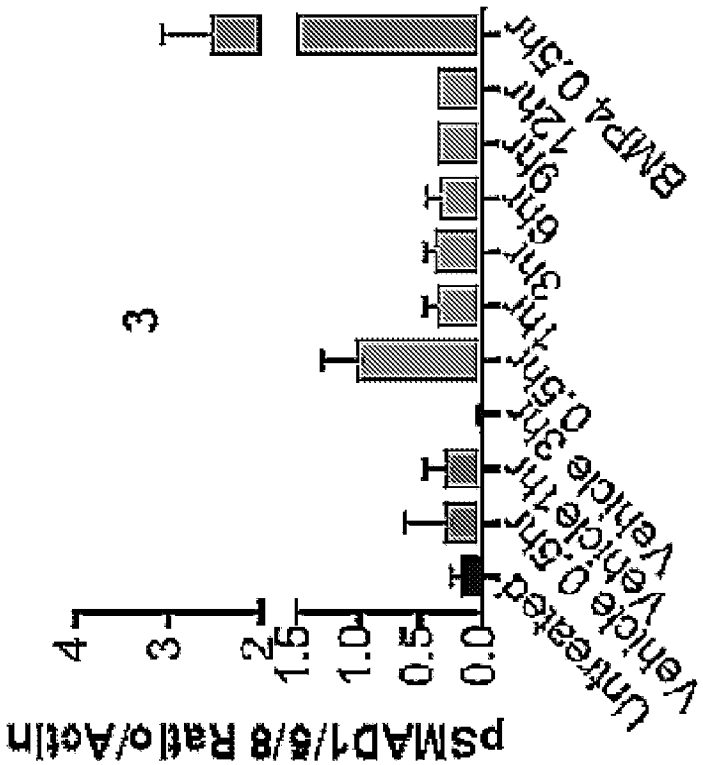

pSMAD1/5/8 Ratio/Actin
4
3
2
1.5
1.0
0.5
0.0
Untreated
Vehicle 0.5hr
Vehicle 1hr
Vehicle 3hr
0.5hr
1hr
3hr
6hr
9hr
12hr
BMP4 0.5hr

FIG. 8H

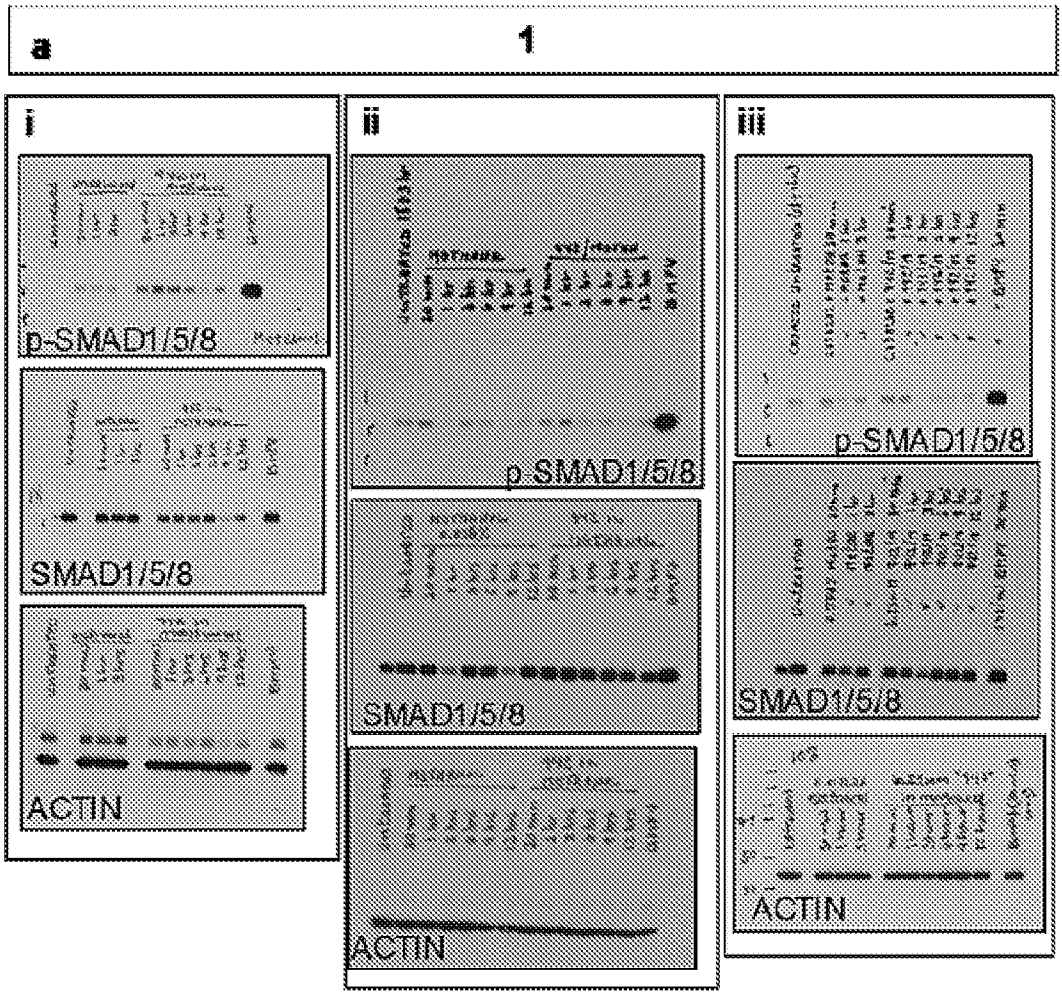

a
1
i
p-SMAD1/5/8
SMAD1/5/8
ACTIN
ii
p-SMAD1/5/8
SMAD1/5/8
ACTIN
iii
p-SMAD1/5/8
SMAD1/5/8
ACTIN

FIG. 9A

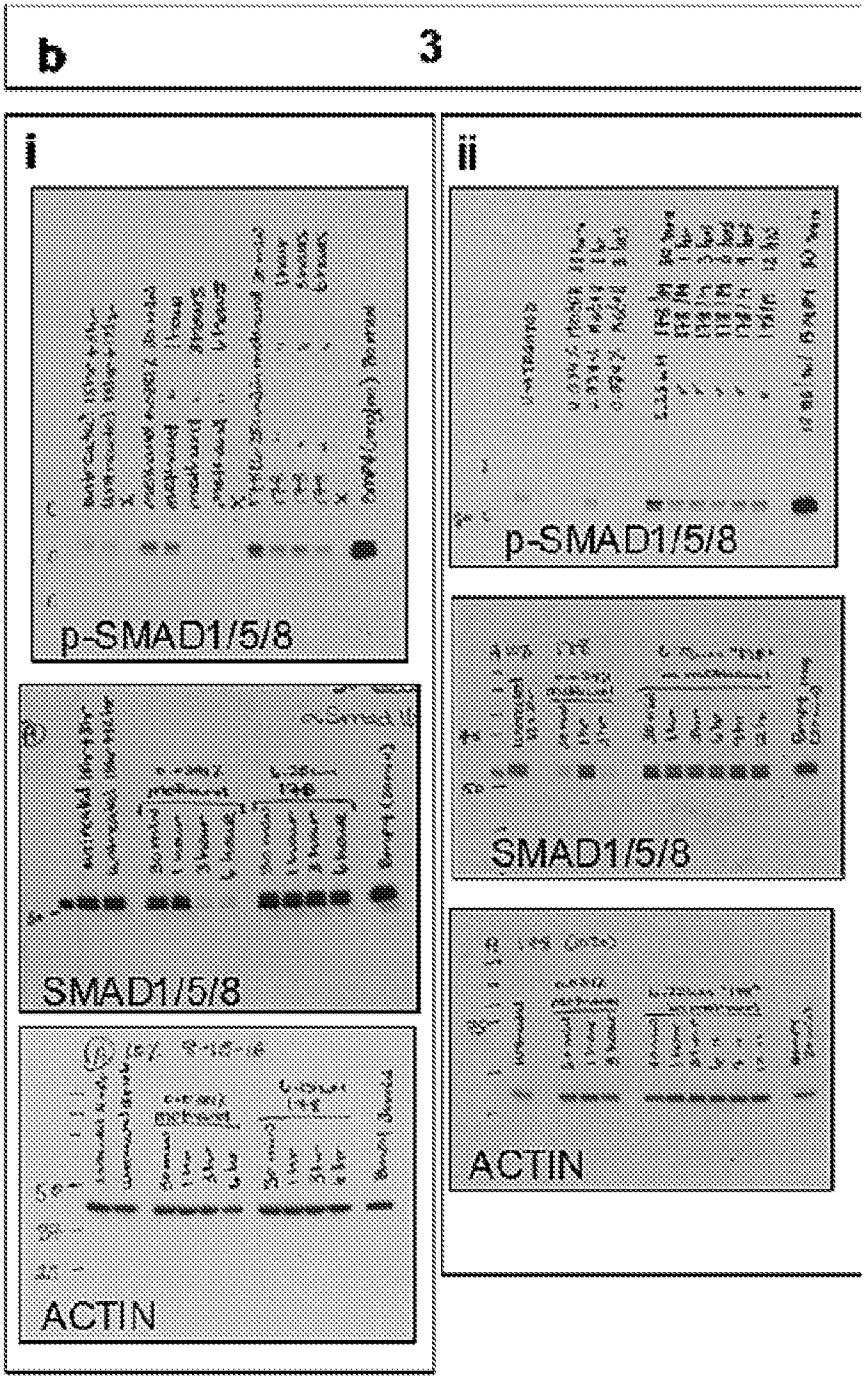


FIG. 9B

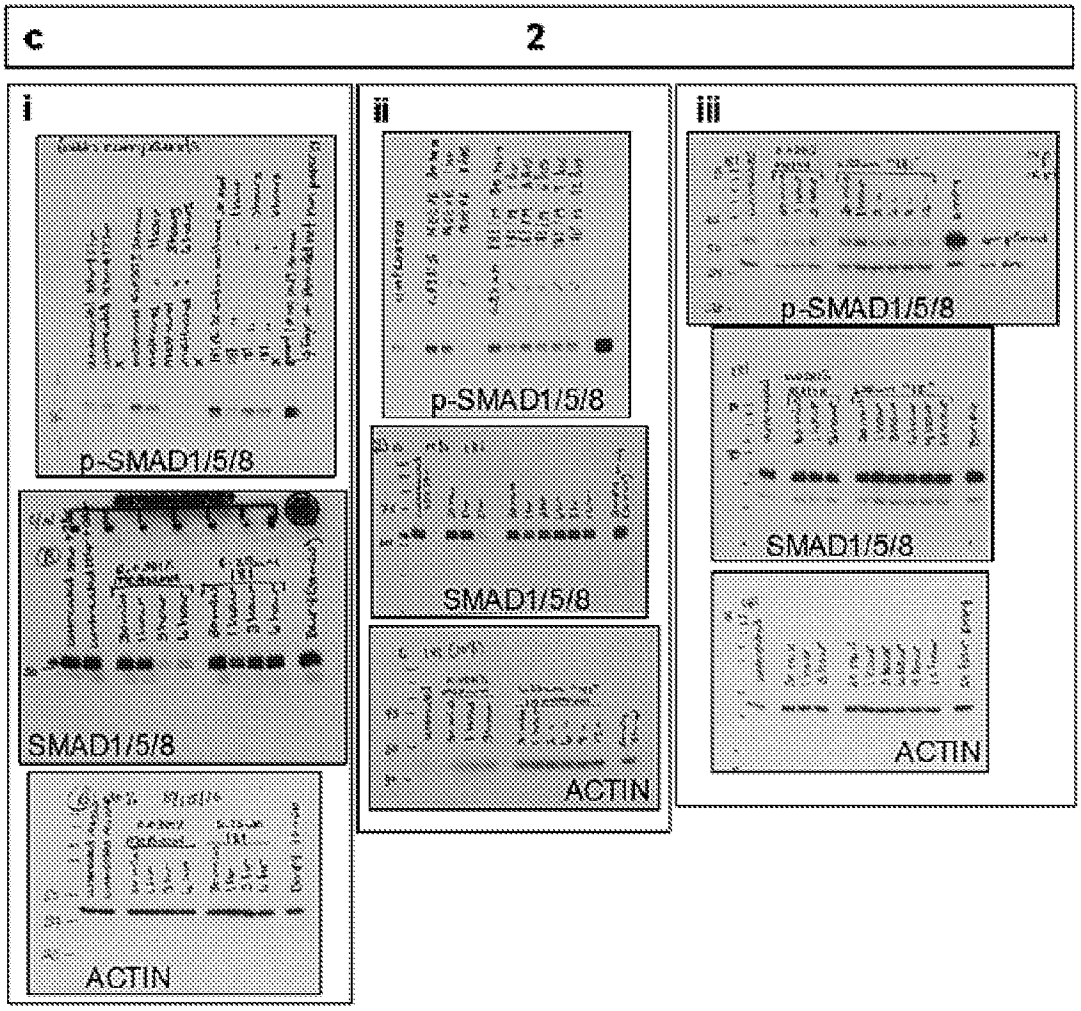

c
2
i
p-SMAD1/5/8
SMAD1/5/8
ACTIN
ii
p-SMAD1/5/8
SMAD1/5/8
ACTIN
iii
p-SMAD1/5/8
SMAD1/5/8
ACTIN

FIG. 9C

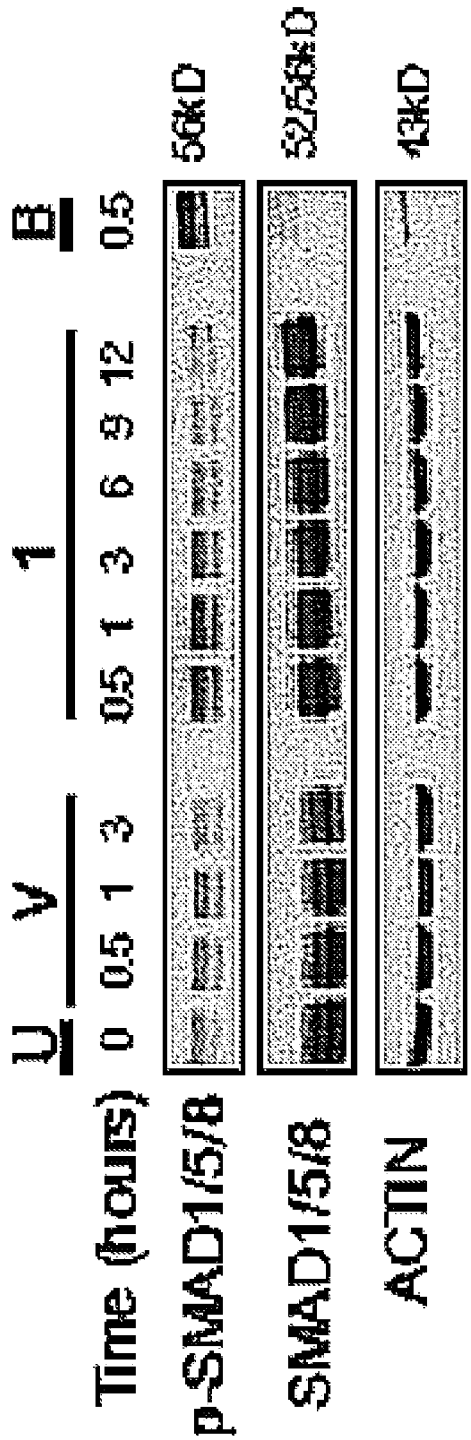

U
V
1
B
Time (hours)
0 0.5 1 3 0.5 1 3 6 9 12 0.5
p-SMAD1/5/8
SMAD1/5/8
ACTIN
56kD
52/53kD
43kD

FIG. 10A

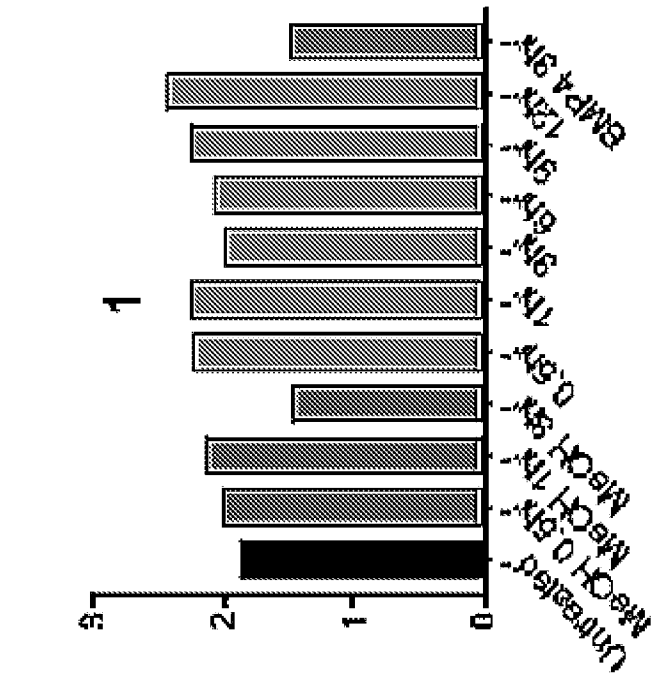


FIG. 10C

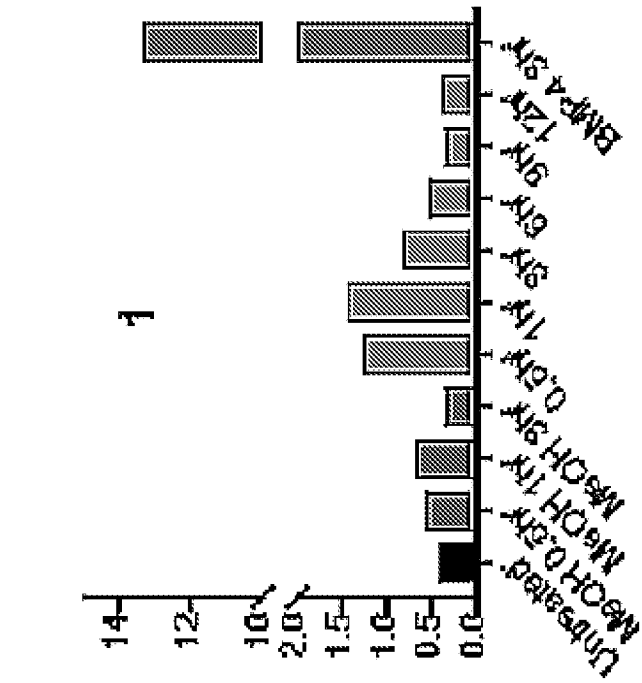


FIG. 10B

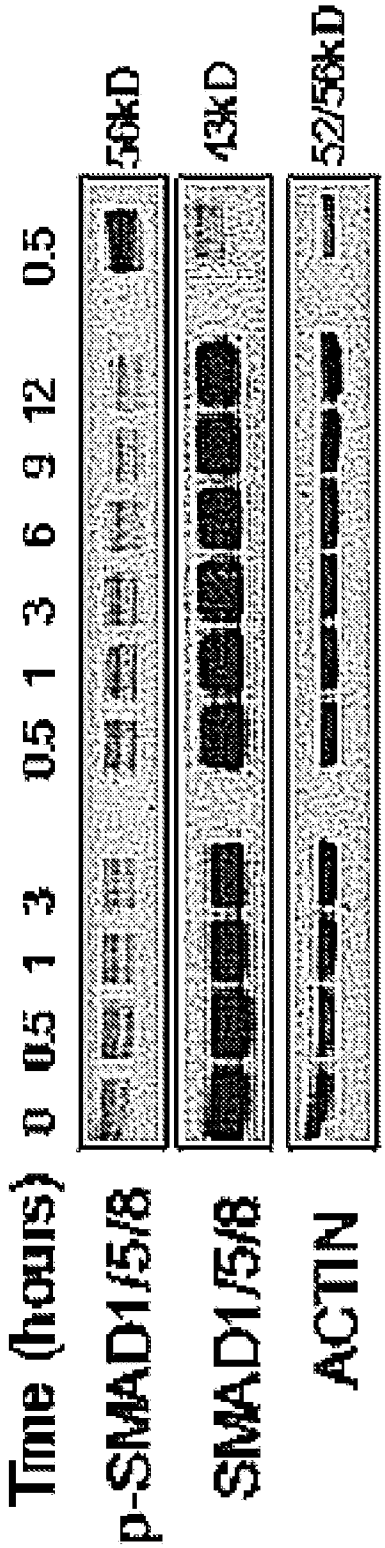

U
V
2
B
Time (hours)
0 0.5 1 3 0.5 1 3 6 9 12 0.5
p-SMAD1/5/8
SMAD1/5/8
ACTIN
50kD
43kD
52/56kD

FIG. 10D

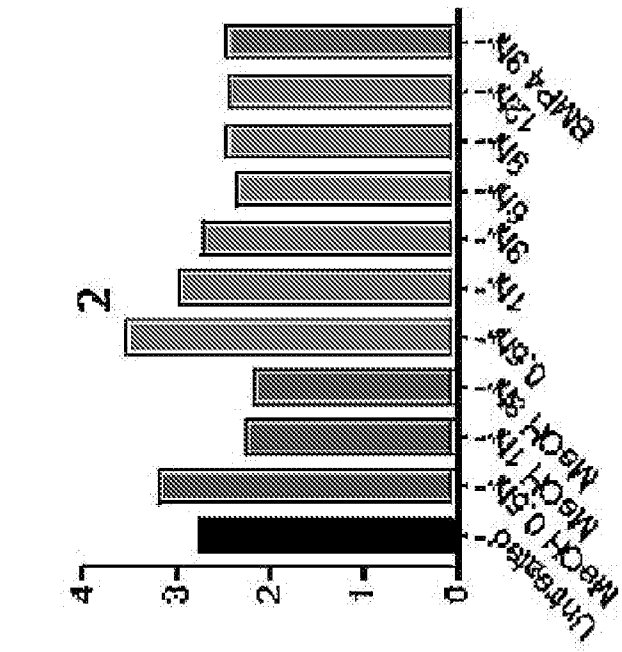


FIG. 10F

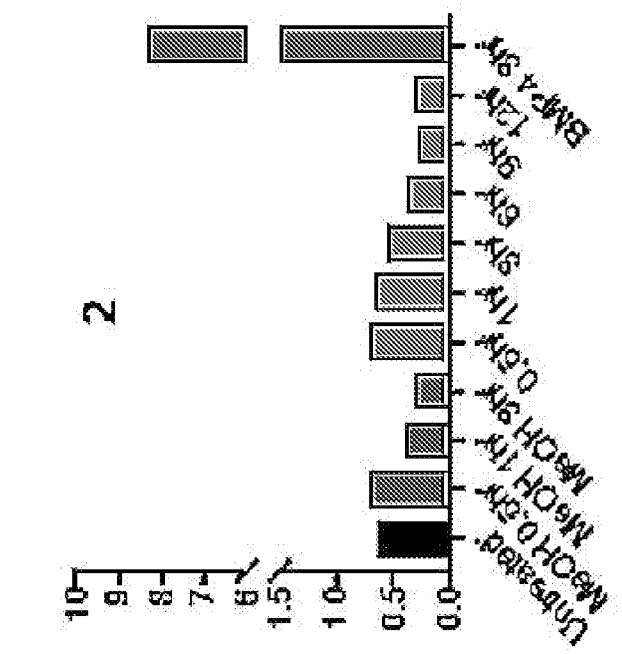


FIG. 10E

Ratio p-SMAD/ACTIN

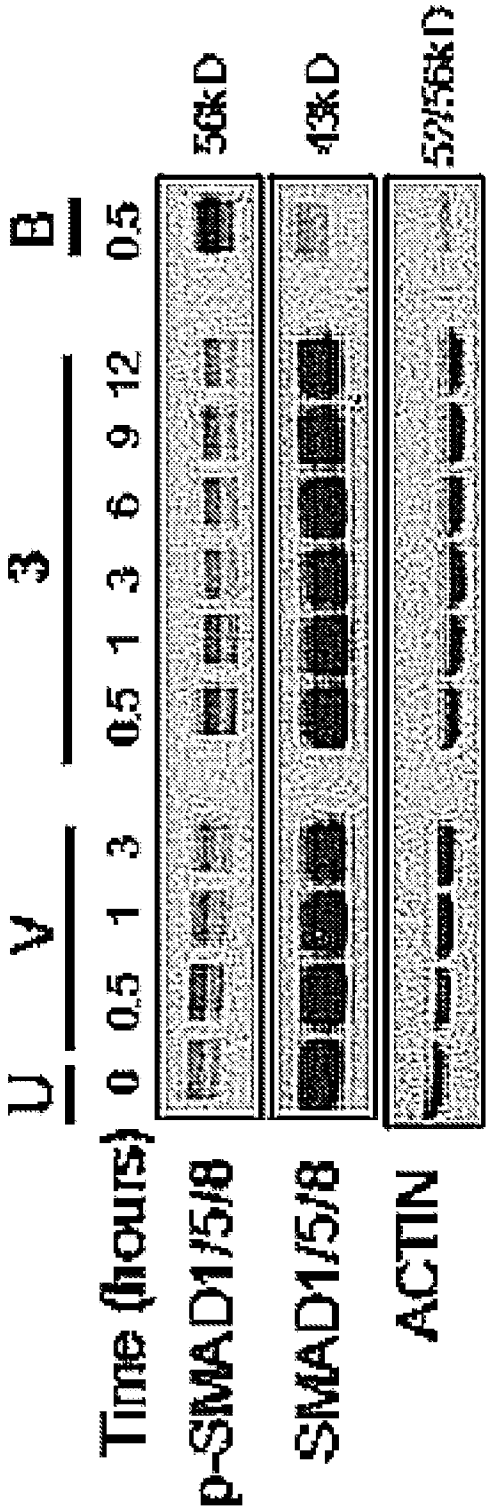

U
V
3
B
Time (hours)
0
0.5
1
3
0.5
1
3
6
9
12
0.5
p-SMAD1/5/8
SMAD1/5/8
ACTIN
56kD
43kD
52/56kD

FIG. 10G

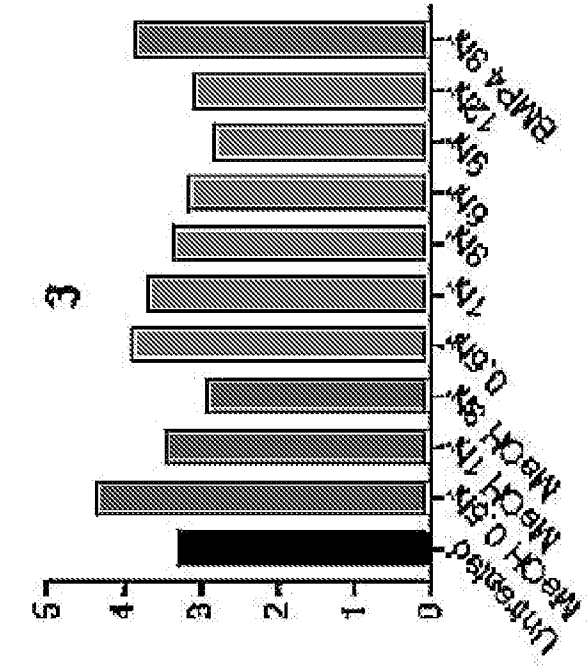


FIG. 10I

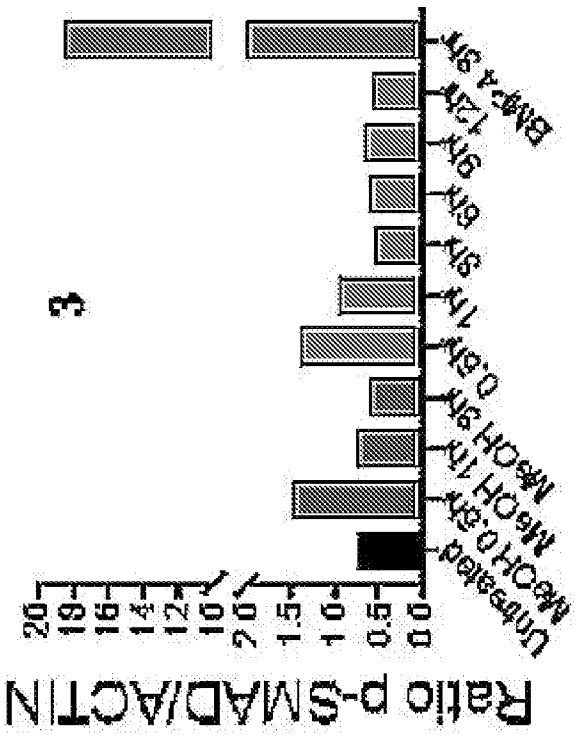


FIG. 10H

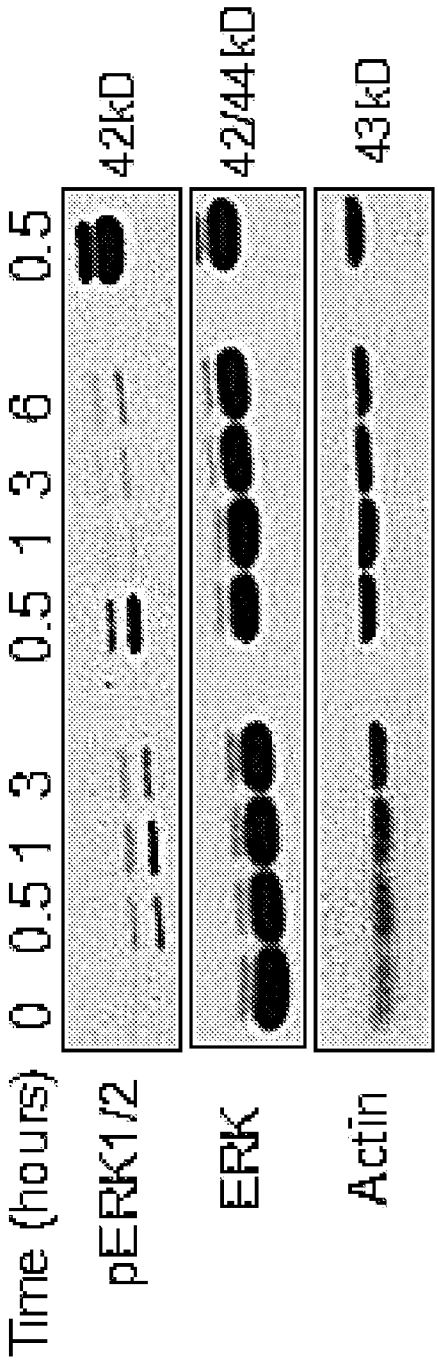

U
V
1
B
0
0.5
1
3
0.5
1
3
6
0.5
Time (hours)
pERK1/2
ERK
Actin
42kD
42/44kD
43kD

FIG. 11A

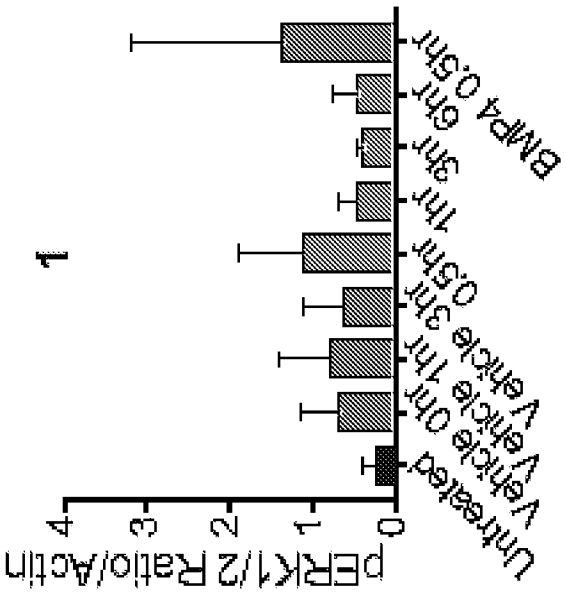


FIG. 11B

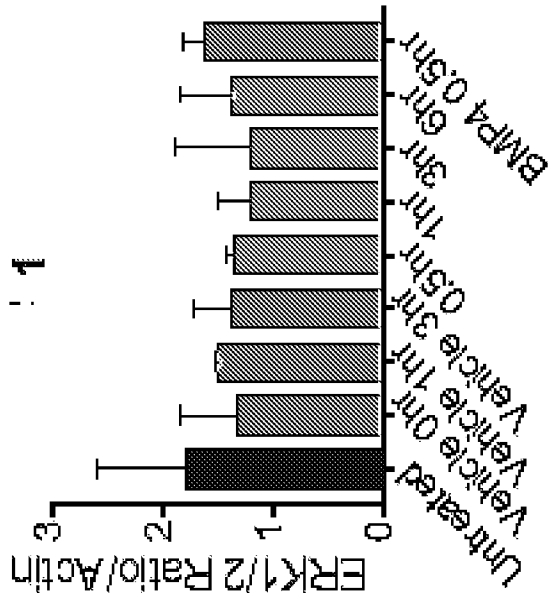


FIG. 11C

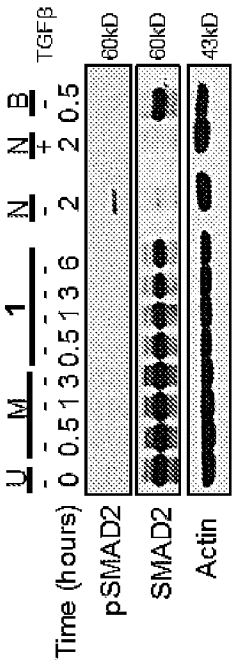


FIG. 12A

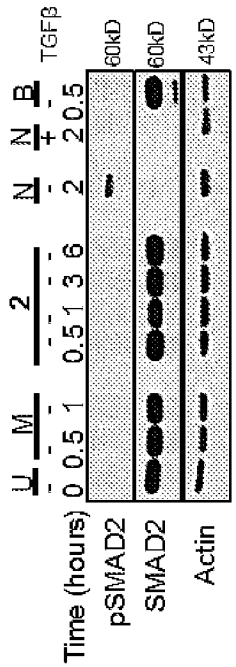


FIG. 12B

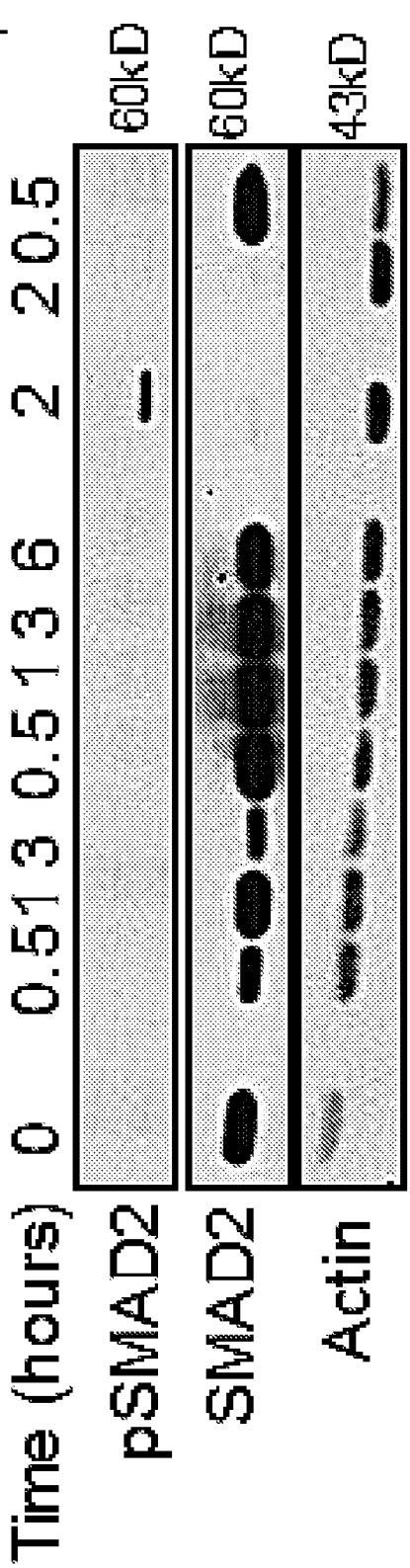

U
M
3
N
N
B
TGFβ
0
0.5
1
3
0.5
1
3
6
2
2
0.5
60kD
60kD
43kD
Time (hours)
pSMAD2
SMAD2
Actin

FIG. 12C

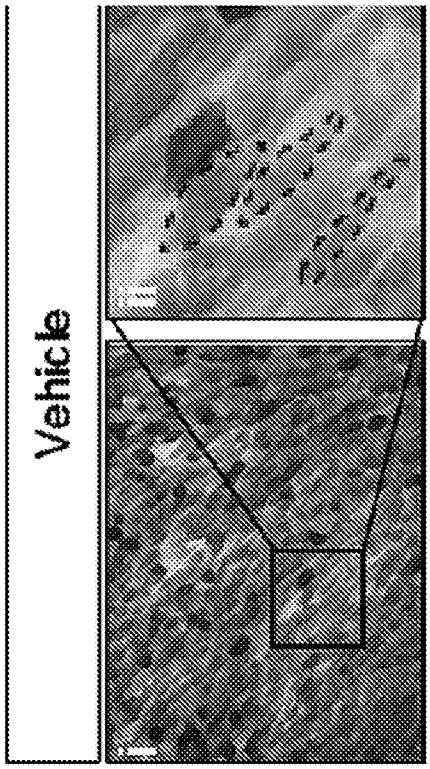


FIG. 13B

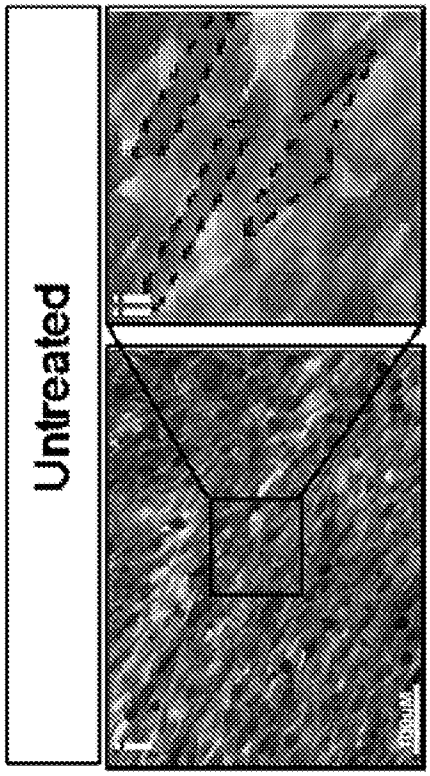


FIG. 13A

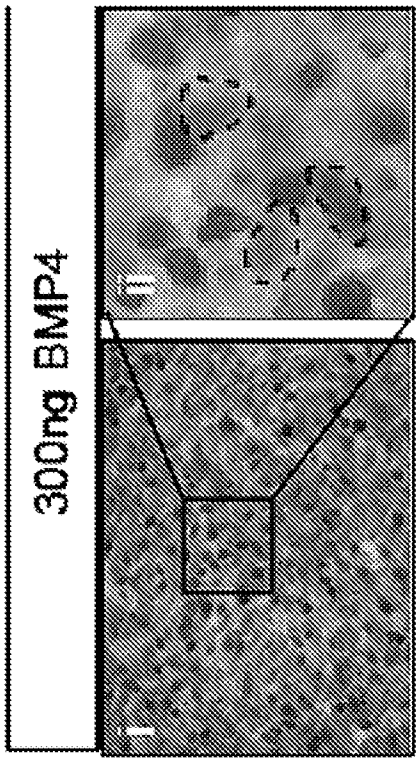


FIG. 13D

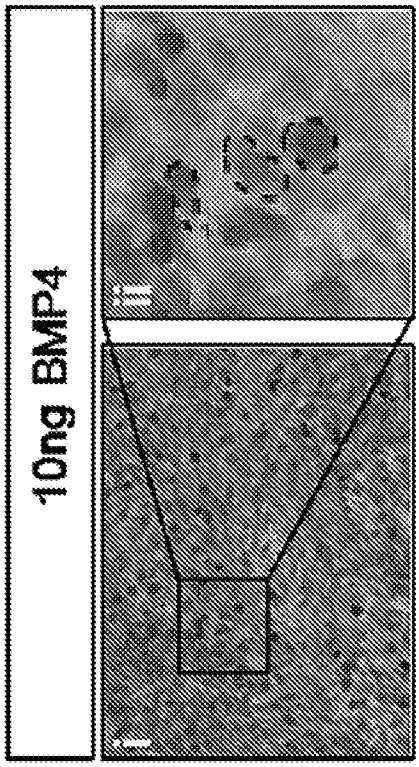


FIG. 13C

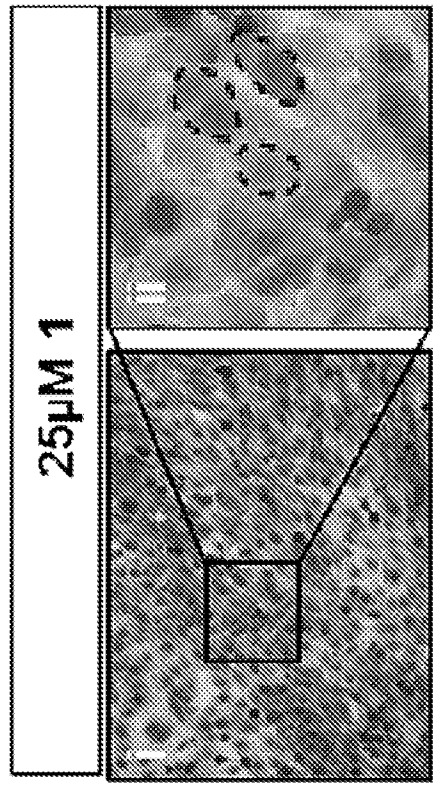


FIG. 13F

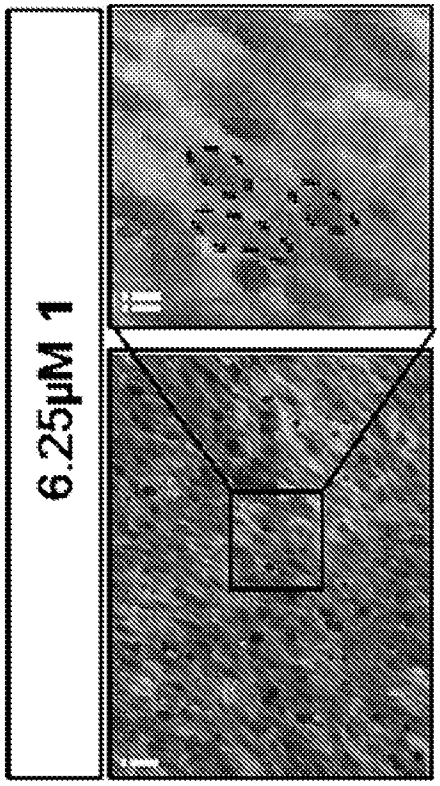


FIG. 13E

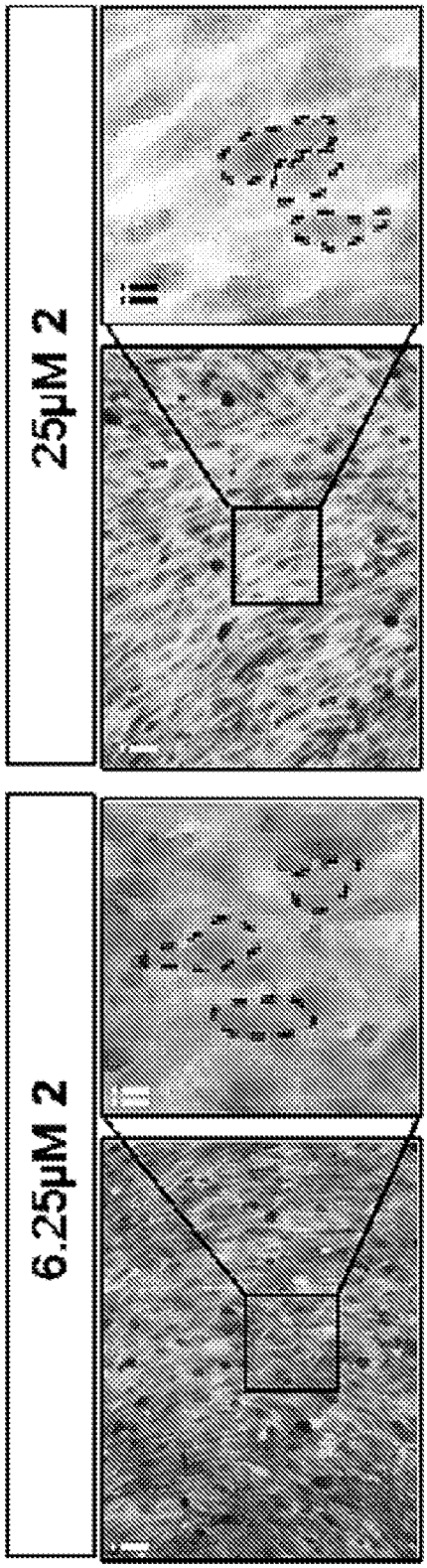


FIG. 13H

FIG. 13G

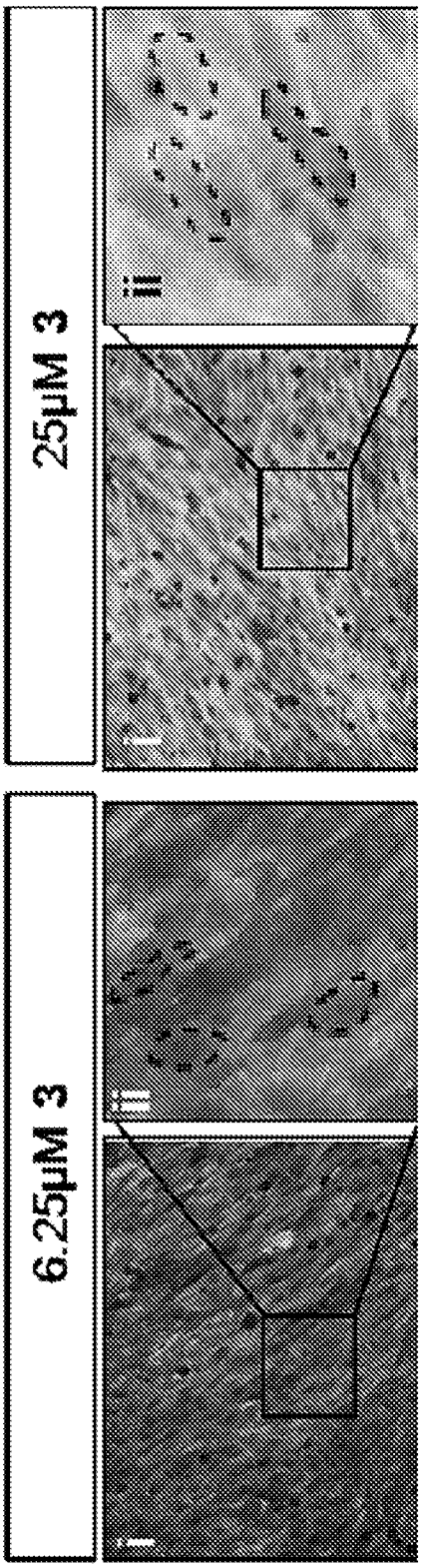


FIG. 13J

FIG. 13I

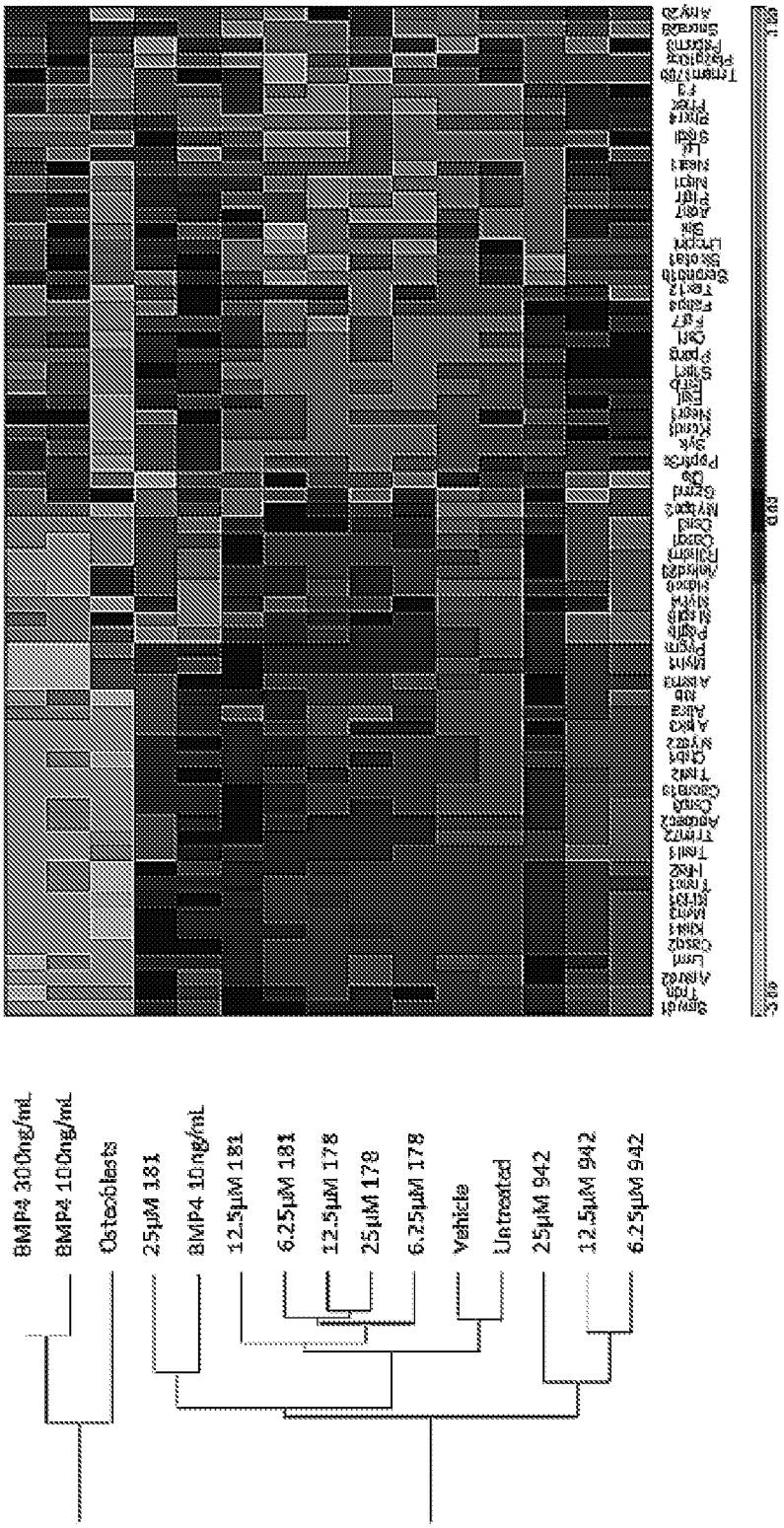

BMP4 300ng/mL
BMP4 100ng/mL
Osteoblasts
25μM 181
BMP4 10ng/mL
12.5μM 181
6.25μM 181
12.5μM 178
25μM 178
6.25μM 178
Vehicle
Untreated
25μM 942
12.5μM 942
6.25μM 942

FIG. 14A

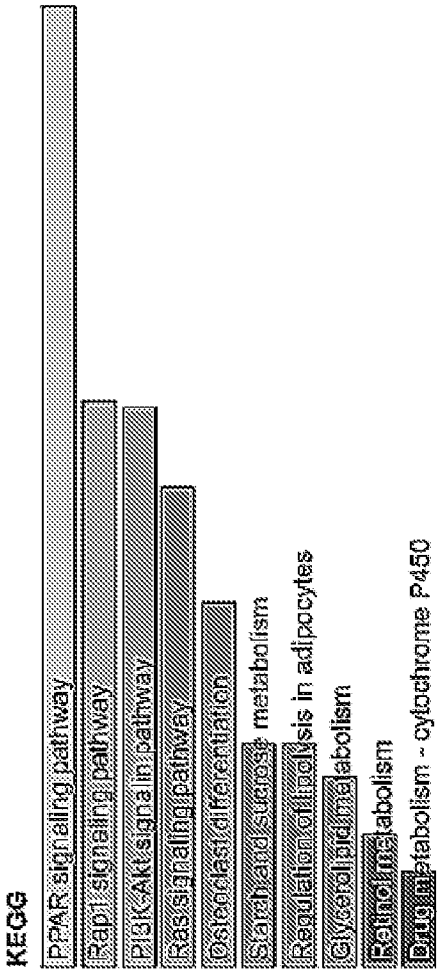


FIG. 14B

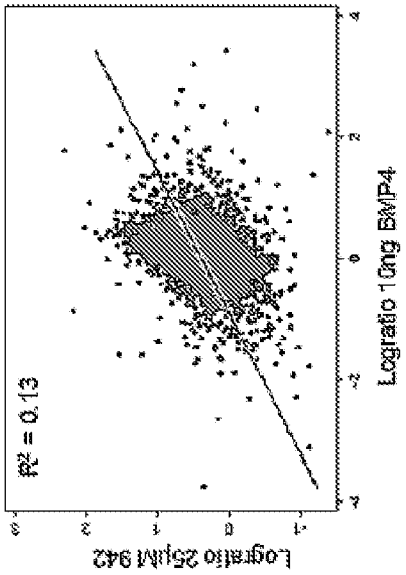


FIG. 14C

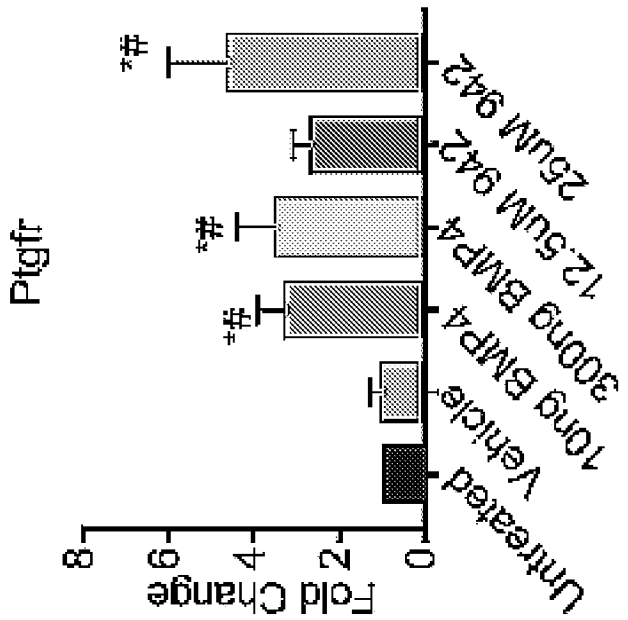


FIG. 14E

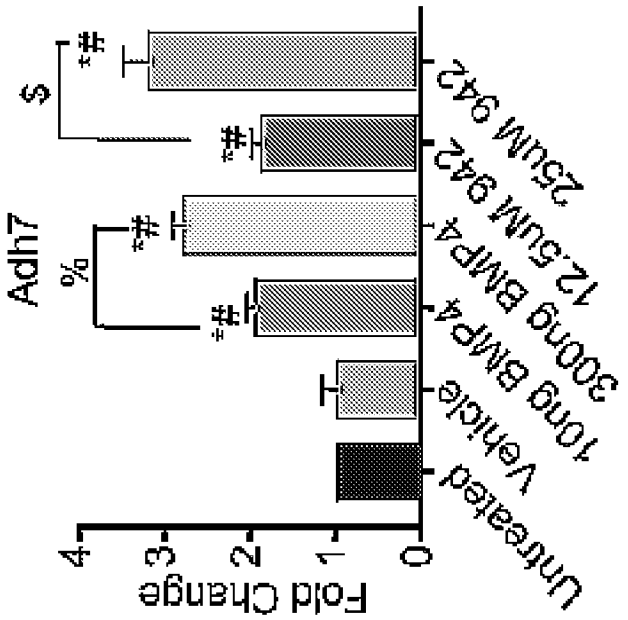


FIG. 14D

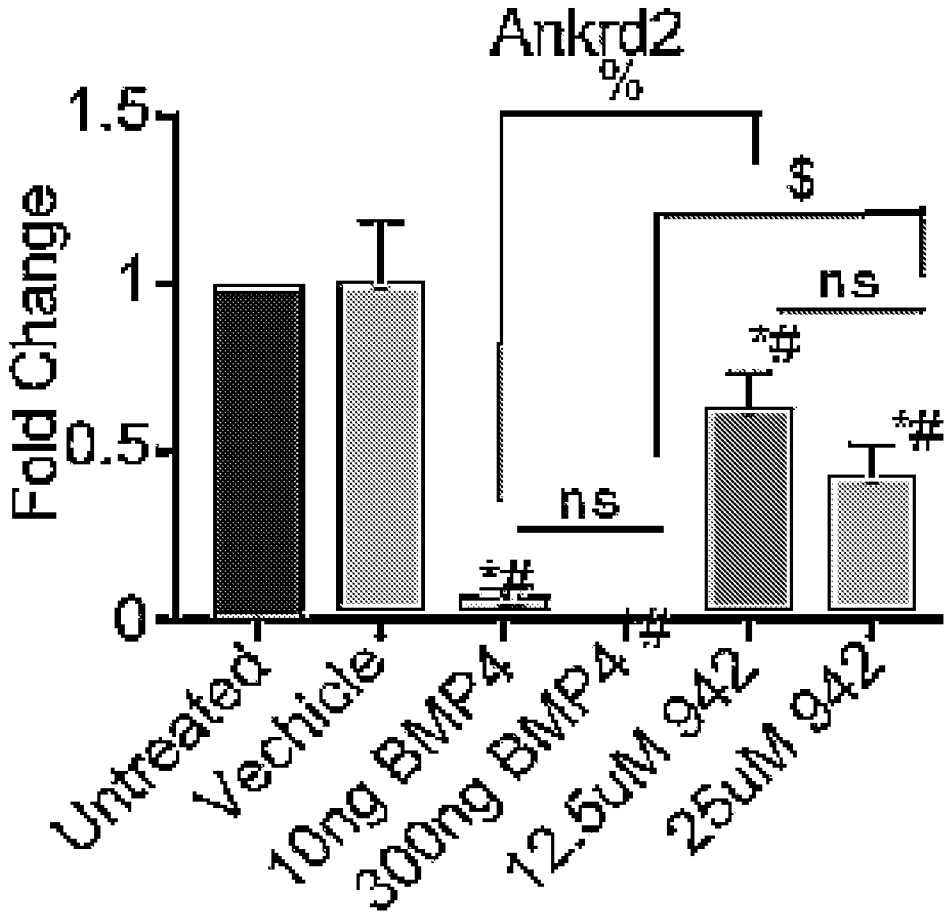

Ankrd2
Fold Change
1.5
1
0.5
0
%
$
ns
ns
*#
*#
*#
Untreated
Vechicle
10ng BMP4
300ng BMP4
12.5uM 942
25uM 942

FIG. 14F

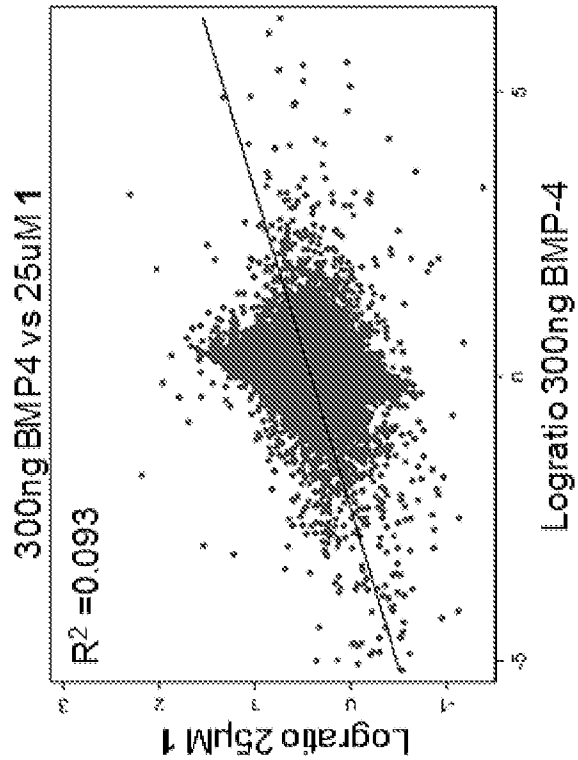


FIG. 15B

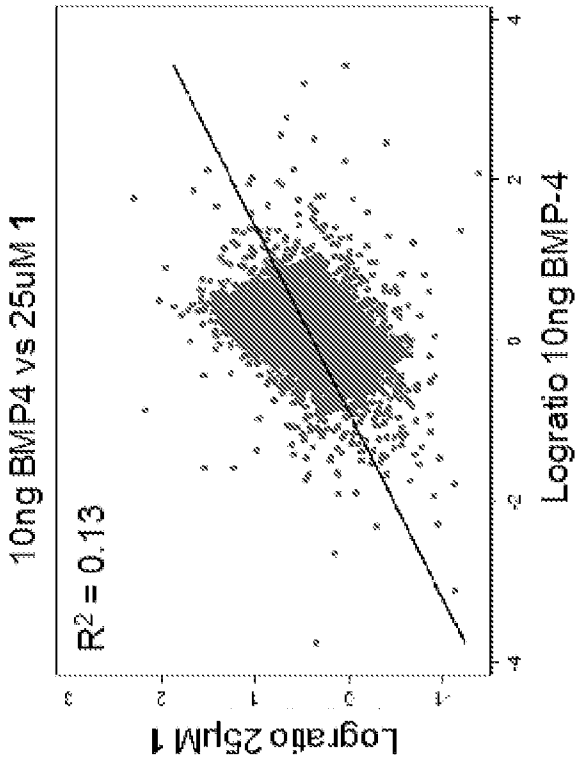


FIG. 15A

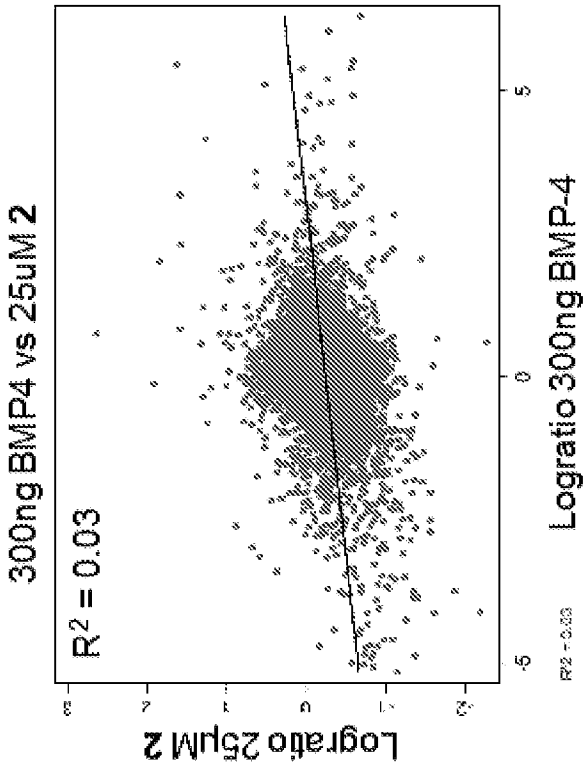


FIG. 15D

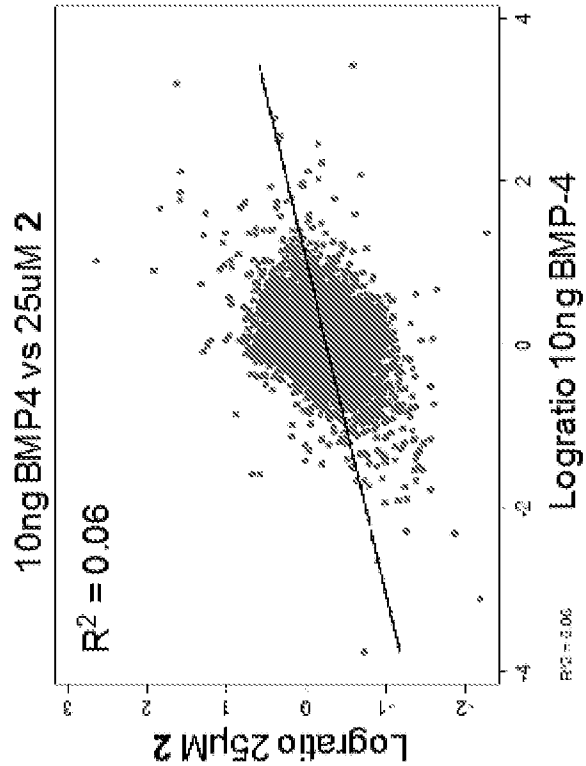


FIG. 15C

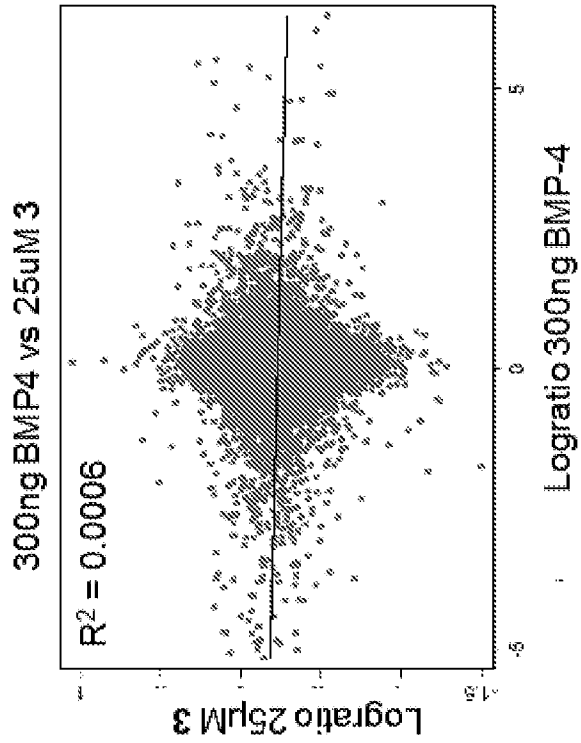


FIG. 15F

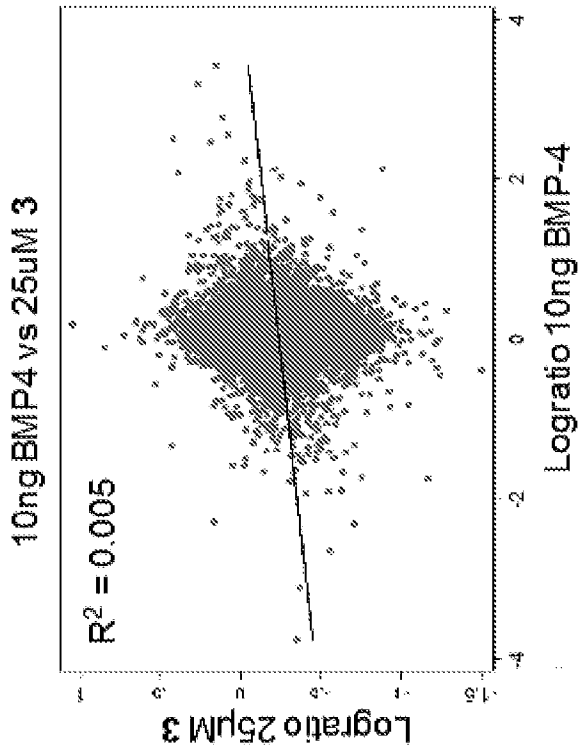


FIG. 15E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/38600

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/395, C07K 16/24 (2018.01)
CPC - A61K 2039/505, A61K 2039/507, A61K 31/519

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)
See Search History Document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,919,808 A (Petrie et al.) 06 July 1999 (06.07.1999); Claim 4, p61, col3, col4, col5, col12	1-3, 9-10
A	US 6,534,268 B1 (Kawai et al.) 18 March 2003 (18.03.2003); entire document	1-3, 9-10
A	US 2013/0089560 A1 (Chartier-Courtaud et al.) 11 April 2013 (11.04.2013); entire document	1-3, 9-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2018	19 OCT 2018

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/38600

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.:
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:

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:

See Supplemental Box

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.:
1-3, 9-10

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 18/38600

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-10, 19-20(in part) directed to a method for treating a disorder associated with diminished BMP signaling in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula in claim 1, or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with diminished BMP signaling. The compound having a structure represented by a formula in claim 1 will be searched to the extent that it encompasses the compound having a structure represented by a formula in claim 1, wherein n is 0; wherein Z is O; wherein R1 is hydrogen; wherein Ar1 is aryl and substituted with 0 group; wherein Ar2 is aryl and substituted with 0 group; or a pharmaceutically acceptable salt thereof. It is believed that claims 1-3(in part), 9-10 read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be the compound having a structure represented by a formula in claim 1, wherein n is 0; wherein Z is O; wherein R1 is hydrogen; wherein Ar1 is aryl and substituted with 0 group; wherein Ar2 is aryl and substituted with 1 group of halogen; or a pharmaceutically acceptable salt thereof (i.e., claims 1-4(in part), 9-10, 19-20(in part)).

Group II: claims 11-18, 19-20(in part) directed to a method for treating a disorder associated with diminished BMP signaling in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula in claim 11; or a pharmaceutically acceptable salt thereof, thereby treating the disorder associated with diminished BMP signaling.

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound having a structure represented by a formula in claim 1 containing the same, which is not required by any other invention of Group I+.

Group II includes the technical feature of a compound having a structure represented by a formula in claim 11, not required by Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of a method for treating a disorder associated with diminished BMP signaling in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula in claim 1, containing the same. These shared technical features, however, do not provide a contribution over the prior art, as being obvious over US 5,919,808 A to Petrie et al. (hereinafter 'Petrie'). Petrie teaches a method for treating a disorder associated with diminished BMP signaling in a subject (col4, ln26-29 "The active compounds ("BMP promoter-active compounds" or "active compounds") are useful in promoting bone or cartilage growth, and thus in the treatment of vertebrates in need of bone or cartilage growth"), the method comprising the step of administering to the subject an effective amount of at least one compound (col5, ln19-21 "Bone or cartilage deficit or defect can be treated in vertebrate subjects by administering compounds of the invention", col9, ln23 -25 "Generally, they can be administered to a typical human on a daily basis on an oral dose of about 0.1 mg/kg-1000 mg/kg") having an analogous structure represented by a formula: wherein n is 0; wherein Z is O; wherein R1 is hydrogen; wherein Ar1 is aryl and substituted with 1 group of C1 alkyl; wherein Ar2 is aryl and substituted with 1 group (p61, FIG. 3GGG "Compound 59-8011"), but does not teach wherein the substituent of Ar2 is -CO2(C1-C4)alkyl. However, Petrie further teaches Ar2 can be substituted with -CO2(C1-C4)alkyl (col12, ln24-27 "Among substituents that do not interfere with the beneficial effect of the compounds of the invention on bone in treated subjects are included", col12, ln32 "COOR", col12, ln34 "wherein R is alkyl (1-6C) or is H") in the general formula (col3, ln14-16 "Therefore, the compounds useful in the invention can be described as having the formula Ar1-linker-Ar2, wherein each of Ar1 and Ar2 is independently an aromatic system", col3, ln19-21 "Ar1, Ar2 and the linker may optionally be substituted with non interfering substituents"). Thus, it would have been obvious to one of ordinary skill in the art to be motivated to formulate the compound by routine experimentation, in order to find the most effective compound treating a disorder associated with diminished BMP signaling.

Groups I+ and II share the technical feature of a method for treating a disorder associated with diminished BMP signaling in a subject, the method comprising the step of administering to the subject an effective amount of at least one compound having a structure represented by a formula in claim 11. These shared technical features, however, do not provide a contribution over the prior art, as being obvious over Petrie. Petrie teaches a method for treating a disorder associated with diminished BMP signaling in a subject (col4, ln26-29 "The active compounds ("BMP promoter-active compounds" or "active compounds") are useful in promoting bone or cartilage growth, and thus in the treatment of vertebrates in need of bone or cartilage growth"), the method comprising the step of administering to the subject an effective amount of at least one compound (col5, ln19-21 "Bone or cartilage deficit or defect can be treated in vertebrate subjects by administering compounds of the invention", col9, ln23-25 "Generally, they can be administered to a typical human on a daily basis on an oral dose of about 0.1 mg/kg-1000 mg/kg") having an analogous structure represented by a formula in claim 11: wherein R1 is hydrogen; wherein Ar2 is aryl, and substituted with 1 group; and wherein Ar3 is 6-membered heteroaryl of the moiety in the 2nd column and the 3rd row; wherein R21a is C1 alkyl; R21b, R21c, and R21d are hydrogen (p71, FIG. 4H "Compound 850-8278"), but does not teach wherein the substituent of Ar2 is C1-C4 alkyl. However, Petrie further teaches Ar2 can be C1-C4 alkyl (col12, ln39-40 "Preferred non-interfering substituents include hydrocarbyl groups of 1-6C") in the general formula (col3, ln14-16 "Therefore, the compounds useful in the invention can be described as having the formula Ar1-linker-Ar2, wherein each of Ar1 and Ar2 is independently an aromatic system", col3, ln19-21 "Ar1, Ar2 and the linker may optionally be substituted with non interfering substituents"). Thus, it would have been obvious to one of ordinary skill in the art to be motivated to formulate the compound by routine experimentation, in order to find the most effective compound treating a disorder associated with diminished BMP signaling.

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ and II. The inventions of Group I+ and II thus lack unity under PCT Rule 13.