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(54) Title: SMALL MOLECULE LXR INVERSE AGONISTS

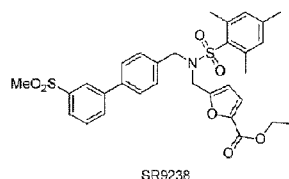
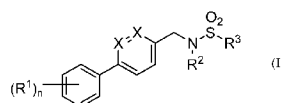


Fig. 2A



(57) **Abstract:** The invention is directed to small molecule inverse agonists of the liver X receptor, LXR. These compounds have potential use in the treatment of the following disorders: non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, obesity, insulin resistance, and metabolic syndrome. The invention is directed, in various embodiments, to small molecule inverse agonists of the liver X receptor, LXR. Administration of an effective amount of a compound of the invention, such as compound of formula (I), can be used to suppress hepatic lipogenesis, inflammation, or hepatic lipid accumulation in a mammal.

SMALL MOLECULE LXR INVERSE AGONISTS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the priority of U.S. provisional application Serial No. 61/731,206, filed Nov. 29, 2012, the disclosure of which is incorporated by reference herein in its entirety.

BACKGROUND

Fatty liver, which often accompanies obesity and type 2 diabetes, frequently leads to a much more debilitating hepatic disease including non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma.¹ Current pharmacological therapies lack conclusive efficacy and thus treatment options are limited.² Novel therapeutics that either suppress hepatic lipogenesis and/or hepatic inflammation may be useful.

Nonalcoholic fatty liver disease (NAFLD) accompanies metabolic syndrome and is comprised of a wide spectrum of disorders from a fatty liver (nonalcoholic hepatosteatosis) to the more aggressive nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinomas (HCC), and affects millions of people worldwide. NAFLD affects between ~14-30% of the general population.^{3,4} Current treatment options lifestyle changes focusing on alteration of diet and weight loss, but these treatments are inadequate for a large number of patients. Pharmacological therapies such as insulin sensitizers, antioxidants, and lipid lowering agents display only limited efficacy.⁵ There is a clear unmet medical need for development of new pharmacological therapies that limit hepatic steatosis and progression of the disease into NASH as well as even more severe hepatic disease.

NAFLD is associated with insulin resistance that promotes de novo lipogenesis and inhibits fatty acid oxidation leading to excessive accumulation of triglycerides in the liver.^{1,6} Much of the excessive fat accumulation in the liver is associated with increased lipogenesis due to increased expression of lipogenic enzymes driven by excessive sterol regulatory element binding protein 1c (SREBP-1c) and carbohydrate responsive element-binding protein (ChREBP) activity.¹

The liver X receptor (LXR), a nuclear receptor, belongs to the family of transcription factors. LXR is closely related to nuclear receptors such as the

PPARs. Liver X receptors (LXRs) act to regulate cholesterol, fatty acid, and glucose homeostasis. LXRs were earlier classified as orphan nuclear receptors, however, Endogenous oxysterols have been determined to be ligands of LXR. Two isoforms, LXR α and are given the nuclear receptor nomenclature symbols NR1H3 (LXR α) and NR1H2 (LXR β) respectively.

A series of LXR modulators including one antagonist has been described (J. Med. Chem. 2010, 53, 3412). See also a patent application from Hoffman-LaRoche (WO2009040289) for LXR α/β agonists and a patent application from Cegent Therapeutics (WO2006009876) for PTP1b inhibitors.

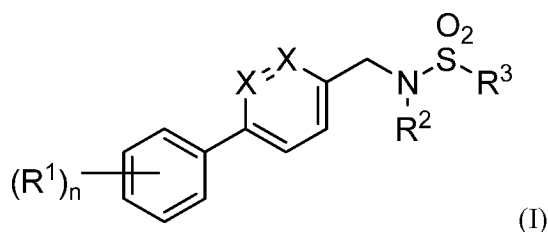
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SUMMARY

The invention is directed, in various embodiments, to small molecule inverse agonists of the liver X receptor, LXR. These compounds have potential use in the treatment of the following disorders: non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, obesity, insulin resistance, metabolic syndrome, and cancer.

15

In various embodiments, compounds of formula (I), having inverse agonist bioactivity versus isoforms of LXR are provided, wherein for a compound of formula (I):



20

R^1 is (C1-C6)alkyl, (C3-C10)cycloalkyl, (C1-C6)alkoxy, halo, halo(C1-C6)alkyl, halo(C1-C6)alkoxy, cyano, nitro, OR, $RS(O)_q$, CO_2R , $CONR_2$, $OC(O)NR_2$, $N(R)C(O)NR_2$, (C1-C6)alkyl SO_2 , (C1-C6)alkyl $IN(R)SO_2$, (C6-C10)aryl SO_2 , (C6-C10)aryl $IN(R)SO_2$, 3-10 membered heterocyclyl, 3-10 membered heterocyclyl(C1-C6)alkyl, N-bonded tetrazolyl, or C-bonded tetrazolyl; wherein the ring bearing R^1 can comprise 0, 1, or 2 nitrogen atoms, provided that the nitrogen atom is not substituted with R^1 ;

25

$n = 1, 2, \text{ or } 3$; $q = 0, 1, \text{ or } 2$;

R^2 is (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-C10)cycloalkyl, (C1-C6)alkyl $C(=O)O(C1-C6)alkyl$, (C6-C10)aryl(C1-C6)alkyl $C(=O)O(C1-C6)alkyl$, (C6-C10)aryl(C1-C6)alkyl $OC(=O)(C1-C6)alkyl$,

30

(C6-C10)aryl, (C6-C10)aryl(C1-C6)alkyl, (3- to 10-membered)heterocyclyl, (3- to 10-membered)heterocyclyl(C1-C6)alkyl, (5- to 10-membered)heteroaryl, or (5- to 10-membered)heteroaryl(C1-C6)alkyl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl moiety of any R² group is substituted with 0-3 J groups;

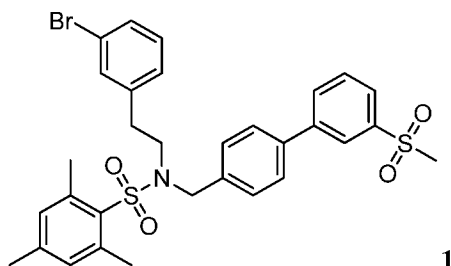
R³ is (C6-C10)aryl, (C1-C6)alkyl, (C6-C10)aryl(C1-C6)alkyl, (5- to 10-membered)heteroaryl, or (5- to 10-membered)heteroaryl(C1-C6)alkyl; wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl moiety of any R³ group is substituted with 0-3 J groups;

R is independently at each occurrence H, (C1-C6)alkyl, halo(C1-C6)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C6)alkyl, (C6-C10)aryl, (C6-C10)aryl(C1-C6)alkyl, (3- to 10-membered)heterocyclyl, (3- to 10-membered)heterocyclyl(C1-C6)alkyl, (5- to 10-membered)heteroaryl, or (5- to 10-membered)heteroaryl(C1-C6)alkyl; and,

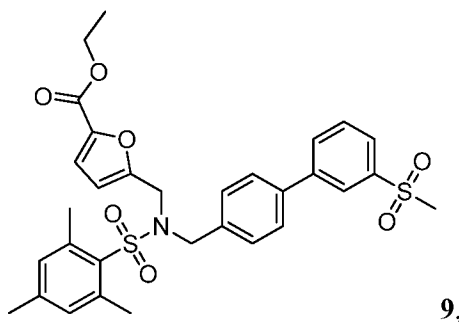
J is (C1-C6)alkyl, (C3-C10)cycloalkyl, (C6-C10)aryl, (3- to 10-membered)heterocyclyl, (5- to 10-membered)heteroaryl, halo, halo(C1-C6)alkyl, halo((C1-C6)alkoxy, nitro, cyano, OR, RS(O)_q, NR₂, C(O)OR, C(O)NR₂, OC(O)OR, OC(O)NR₂, N(R)C(O)OR, or N(R)C(O)NR₂ or a thio/thiono analog thereof;

each X is independently CH or N, provided that only one X is N; or any salt thereof.

The invention provides, in various embodiments, inverse agonists of LXR, such as any of the specific compounds 1-28 shown below, e.g., compound 1 (also known as SR9243):



or compound 9 (also known as SR9238):



and salts thereof.

The invention, in various embodiments, provides a method to suppresses hepatic lipogenesis, inflammation or hepatic lipid accumulation in a mammal, comprising administering to the mammal an effective amount of a compound of formula (I), e.g., such as any of compounds of examples 1-58.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows evidence of activity of GSK2033 in an animal model of hepatic steatosis. (A) Structure of the LXR antagonist GSK2033. (B) A cell-based cotransfection assay using a LXR responsive luciferase reporter illustrates the ability of GSK2033 to suppress basal transcriptional activity of both LXR α and LXR β in HEK293 cells. All cotransfection assays use dual glow luciferase for normalization. (C) Pharmacokinetic data illustrating the plasma and liver concentrations after a single injection of GSK2033 (30 mg/kg, i.p.). (D) Expression of lipogenic genes in the liver following 30 day treatment of diet induced obese (DIO) mice (n=8) with GSK2033 (30 mg/kg, i.p., q.d.). (E) Expression of proinflammatory genes in the liver following 30 day treatment of DIO mice (n=8) with GSK2033 (30 mg/kg, i.p., q.d.). mRNA expression was normalized to GAPDH expression. * indicates $p < 0.05$ using Student's t-test. (F) Nuclear receptor specificity panel illustrating the promiscuous nature of GSK2033. A Gal4-NR LBD cell-based cotransfection assay was utilized. Data was analyzed by ANOVA followed by Tukey's post hoc test. * indicates $p < 0.05$

Figure 2 depicts data in support of the characterization of **9**, a LXR Inverse Agonist. (A) Structure of the LXR inverse agonist **9**. (B) A cell-based cotransfection assay using a LXR responsive luciferase reporter illustrates the ability of SR9238 to suppress basal transcriptional activity of both LXR α and LXR β in HEK293 cells. IC₅₀ values were 214 nM and 43 nM for LXR α and LXR β respectively. (C) Nuclear receptor specificity panel illustrating the

specificity of SR9238. A Gal4-NR LBD cell-based cotransfection assay was utilized. Data was analyzed by ANOVA followed by Tukey's post hoc test. * indicates $p < 0.05$ (D) Full-length LXR α cotransfection assay performed in HEK293 cells demonstrates the ability of SR9238 (10 μ M) to suppress basal transcription driven by the FAS promoter. (E) Biochemical interaction assay displaying the ability of SR9238 to induce interaction of LXR α and LXR β with CoNR box peptides derived from NCoR. Concentrations of compounds used was 10 μ M. (F) Biochemical assay illustrating the SR9238 dose-responsiveness of recruitment of CoNR box peptides to LXR α and LXR β . (G) SR9238 suppresses *FASN* and *SREBP1c* mRNA expression in HepG2 cells. HepG2 cells incubated in the presence of insulin were treated with SR9238 (10 μ M) for 1 day followed by assessment of *FASN* and *SREBP1c* mRNA expression by QPCR. mRNA expression was normalized to GAPDH expression. * indicates $p < 0.05$ using Student's t-test.

Figure 3 shows data evidencing that the acid analogue of SR9238 displays no LXR activity and has significant liver exposure with no plasma exposure. (A) Schematic showing the predicted cleavage of the ester group of SR9238 to the acid analogue, SR10389. (B) SR10389 was synthesized and tested for activity in the LXR cotransfection assay. As indicated in the figure, activity was not observed in this assay. (C) Pharmacokinetic data illustrating that SR9238 displays significant liver exposure but no plasma exposure following a single injection (30 mg/kg, i.p.). Levels were assessed by mass spectroscopy 2h after treatment.

Figure 4 shows data indicating that SR9238 suppresses the expression of lipogenic enzyme and proinflammatory cytokine genes in an animal model of hepatic steatosis. (A) Gene expression analysis of the livers of DIO mice (n=8) following a 1-month treatment with SR9238. (B) Liver sections stained with Biodipy 493/503 to identify lipids and counterstained with DAPI to identify the nuclei (c) Gene expression analysis of inflammation markers from liver tissue of DIO mice following a 1-month treatment with SR9238. (C) Gene expression analysis of the brown adipose tissue of treated DIO mice. As indicated above, there was no significant change in the expression of *ABCA1* and *FAS* in the BAT. mRNA expression was normalized to GAPDH expression. * indicates $p < 0.05$ using Student's t-test.

Figure 5 depicts results of a TR-FRET assay illustrating the ability of the LXR agonist T0901317 to induce a dose-dependent interaction of LXR α (5A), and LXR β (5B), with a NR box peptide derived from the coactivator protein, TRAP220. The EC₅₀ for LXR α is 6.6 nM and for LXR β the value is 2.1 nM.

Figures 6, 7, and 8 show the effect of compound 1 (SR9243) in treatment of colorectal cancer cells, Figure 6A (HT-29) and Figure 6B (SW620); prostate cancer cell lines Figure 7A (PC3) and Figure 7B (DU145); and non-small cell lung cancer cell lines Figure 8A (NCI-H23) and Figure 8B (HOP-62), respectively.

10 DETAILED DESCRIPTION

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.

The term "about" as used herein, when referring to a numerical value or
15 range, allows for a degree of variability in the value or range, for example,
within 10%, or within 5% of a stated value or of a stated limit of a range.

All percent compositions are given as weight-percentages, unless otherwise stated.

20 All average molecular weights of polymers are weight-average molecular weights, unless otherwise specified.

As used herein, “individual” (as in the subject of the treatment) or “patient” means both mammals and non-mammals. Mammals include, for example, humans; non-human primates, e.g. apes and monkeys; and non-primates, e.g. dogs, cats, cattle, horses, sheep, and goats. Non-mammals include, for example, fish and birds.

The term "disease" or "disorder" or "malcondition" are used interchangeably, and are used to refer to diseases or conditions wherein LXR plays a role in the biochemical mechanisms involved in the disease or malcondition or symptom(s) thereof such that a therapeutically beneficial effect can be achieved by acting on LXR. "Acting on" LXR, or "modulating" LXR, can include binding to LXR and/or inhibiting the bioactivity of LXR and/or allosterically regulating the bioactivity of LXR in vivo.

A compound of the invention can act as an “inverse agonist” of the LXR, either the α or β isoform thereof, or both isoforms. An inverse agonist is an

agent that binds to a receptor but induces a pharmacological response opposite that of an agonist. The receptor must have an intrinsic or basal level of activity in the absence of any ligand for inverse agonism to be possible. An agonist increases the activity of a receptor above its basal level while an inverse agonist
5 decreases the activity below the basal level.

The expression “effective amount”, when used to describe therapy to an individual suffering from a disorder, refers to the amount of a compound of the invention that is effective to inhibit or otherwise act on LXR in the individual's tissues wherein LXR involved in the disorder is active, wherein such inhibition
10 or other action occurs to an extent sufficient to produce a beneficial therapeutic effect.

“Substantially” as the term is used herein means completely or almost completely; for example, a composition that is “substantially free” of a component either has none of the component or contains such a trace amount
15 that any relevant functional property of the composition is unaffected by the presence of the trace amount, or a compound is “substantially pure” if there are only negligible traces of impurities present.

“Treating” or “treatment” within the meaning herein refers to an alleviation of symptoms associated with a disorder or disease, or inhibition of
20 further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder, or curing the disease or disorder. Similarly, as used herein, an “effective amount” or a “therapeutically effective amount” of a compound of the invention refers to an amount of the compound that alleviates, in whole or in part, symptoms associated with the disorder or
25 condition, or halts or slows further progression or worsening of those symptoms, or prevents or provides prophylaxis for the disorder or condition. In particular, a “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount is also one in which any toxic or detrimental
30 effects of compounds of the invention are outweighed by the therapeutically beneficial effects.

Phrases such as “under conditions suitable to provide” or “under conditions sufficient to yield” or the like, in the context of methods of synthesis, as used herein refers to reaction conditions, such as time, temperature, solvent,

reactant concentrations, and the like, that are within ordinary skill for an experimenter to vary, that provide a useful quantity or yield of a reaction product. It is not necessary that the desired reaction product be the only reaction product or that the starting materials be entirely consumed, provided the desired
5 reaction product can be isolated or otherwise further used.

By "chemically feasible" is meant a bonding arrangement or a compound where the generally understood rules of organic structure are not violated; for example a structure within a definition of a claim that would contain in certain situations a pentavalent carbon atom that would not exist in nature would be
10 understood to not be within the claim. The structures disclosed herein, in all of their embodiments are intended to include only "chemically feasible" structures, and any recited structures that are not chemically feasible, for example in a structure shown with variable atoms or groups, are not intended to be disclosed or claimed herein.

15 An "analog" of a chemical structure, as the term is used herein, refers to a chemical structure that preserves substantial similarity with the parent structure, although it may not be readily derived synthetically from the parent structure. A related chemical structure that is readily derived synthetically from a parent chemical structure is referred to as a "derivative."

20 When a substituent is specified to be an atom or atoms of specified identity, "or a bond", a configuration is referred to when the substituent is "a bond" that the groups that are immediately adjacent to the specified substituent are directly connected to each other in a chemically feasible bonding configuration.

25 All chiral, diastereomeric, racemic forms of a structure are intended, unless a particular stereochemistry or isomeric form is specifically indicated. In several instances though an individual stereoisomer is described among specifically claimed compounds, the stereochemical designation does not imply that alternate isomeric forms are less preferred, undesired, or not claimed.

30 Compounds used in the present invention can include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions, at any degree of enrichment. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be isolated or synthesized

so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of the invention.

As used herein, the terms “stable compound” and “stable structure” are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Only stable compounds are contemplated herein.

A “small molecule” refers to an organic compound, including an organometallic compound, of a molecular weight less than about 2 kDa, that is not a polynucleotide, a polypeptide, a polysaccharide, or a synthetic polymer composed of a plurality of repeating units.

As to any of the groups described herein, which contain one or more substituents, it is understood that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this disclosed subject matter include all stereochemical isomers arising from the substitution of these compounds.

When a group is recited, wherein the group can be present in more than a single orientation within a structure resulting in more than single molecular structure, e.g., a carboxamide group $C(=O)NR$, it is understood that the group can be present in any possible orientation, e.g., $X-C(=O)N(R)-Y$ or $X-N(R)C(=O)-Y$, unless the context clearly limits the orientation of the group within the molecular structure. For example, the group (C1-C6)alkyl $C(=O)O$ (C1-C6)alkyl bonded to a moiety such as Ar represents either of $Ar(C1-C6)alkylC(=O)O(C1-C6)alkyl$ or $(C1-C6)alkylC(=O)O(C1-C6)alkylAr$.

Substituent groups can be categorized into a variety of sets based upon their steric and electronic properties, allowing predictions to be made about the properties of molecules or of domains of molecules incorporating these groups.

For example, steric classifications, i.e., groups that can influence the reactivity of moieties and molecules containing them, include a “sterically bulky” group, that can “sterically hinder” a region or reactive grouping of a molecule. A sterically bulky group is a group of large molecular volume that can block approach of reactants to itself or neighboring groups; an example is a *tert*-butyl group, wherein the three methyl groups bonded to the central carbon atom serve to impede approach of, e.g., an incoming nucleophile to an adjacent carbonyl group, reducing reaction rate for nucleophilic substitution at that center.

Classifications can be made on the basis of electronic properties as well, that is, where factors such as electronegativity or electropositivity, or resonance factors, enable a substituent group to influence the reactivity of neighboring atoms or groupings of atoms.

5 For example, an electron-withdrawing group, as is well-known in the art, is a substituent, such as on an aryl ring (e.g., a phenyl ring) that is electronegative and withdraws electron density from an adjacent atom or configuration of atoms. An example is a halo group, such as fluoro, chloro, etc. Another example is a alkylsulfonyl or arylsulfonyl group. These two examples
10 can function to withdraw electron density along a σ , or single, bond, reducing electron densities, e.g., of aryl rings to which they are bonded, consequently reducing the rate and/or favorable energetics of electrophilic substitution of that aryl group. Electron-withdrawing groups can operate through π , i.e., double-bonded (or triple-bonded), systems, where electron density flows via conjugated
15 π bond systems. An example is an α,β -unsaturated enone group, such as an acryloyl group. The carbon-carbon double bond of the enone can act to transmit the polarization of the carbonyl group to, e.g., an aryl ring, withdrawing electron density from the ring.

 For example, an electron donating group, as is well-known in the art, is a
20 substituent, such as on an aryl ring (e.g., a phenyl ring) that is electronpositive and donates electron density from an adjacent atom or configuration of atoms. An example is a trialkylsilyl group, where due to the electropositivity of the silicon atom, electron density is pushed onto adjacent atoms or groupings of atoms via a σ , or single, bond. Or, electron donating groups can act via π , i.e.,
25 double (or triple) bonds as well. For example, an alkoxyl group, when bonded to an aryl ring, can be electron-donating despite the electronegativity of the oxygen atom, because of electron density donation via π -conjugation into an aryl ring, thus increasing the rate and favorable energetics of electrophilic substitution of the ring.

30 Groups can also be classified on the basis of polarity (or hydrophilicity) and non-polarity (or lipophilicity, also known as hydrophobicity). These properties can influence the manner in which molecules can interact via non-bonding interactions with other molecules in the vicinity, such as solvent molecules (polar groups favor dissolution of the molecule in polar solvents like

water, alcohol, and the like, and non-polar groups favor dissolution of the molecule in non-polar solvents like hydrocarbons, halocarbons, and the like), and in complex binding interactions, e.g., of small molecules with proteins or other biomolecules, including receptors, enzymes, and the like. Small molecules
 5 are believed to interact in a highly specific way with biomolecules such as receptors through “lock and key” type interactions based on steric and electronic factors of the small molecule (ligand) being complementary to the biomolecule (receptor).

When a group, e.g., an “alkyl” group, is referred to without any
 10 limitation on the number of atoms in the group, it is understood that the claim is definite and limited with respect the size of the alkyl group, both by definition; i.e., the size (the number of carbon atoms) possessed by a group such as an alkyl group is a finite number, less than the total number of carbon atoms in the universe and bounded by the understanding of the person of ordinary skill as to
 15 the size of the group as being reasonable for a molecular entity; and by functionality, i.e., the size of the group such as the alkyl group is bounded by the functional properties the group bestows on a molecule containing the group such as solubility in aqueous or organic liquid media. Therefore, a claim reciting an “alkyl” or other chemical group or moiety is definite and bounded, as the
 20 number of atoms in the group cannot be infinite.

In general, “substituted” refers to an organic group as defined herein in which one or more bonds to a hydrogen atom contained therein are replaced by one or more bonds to a non-hydrogen atom such as, but not limited to, a halogen (i.e., F, Cl, Br, and I); an oxygen atom in groups such as hydroxyl groups,
 25 alkoxy groups, aryloxy groups, aralkyloxy groups, oxo(carbonyl) groups, carboxyl groups including carboxylic acids, carboxylates, and carboxylate esters; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfoxide groups, sulfone groups, sulfonyl groups, and sulfonamide groups; a nitrogen atom in groups such as amines, hydroxylamines, nitriles, nitro groups,
 30 N-oxides, hydrazides, azides, and enamines; and other heteroatoms in various other groups. Non-limiting examples of substituents J that can be bonded to a substituted carbon (or other) atom include F, Cl, Br, I, OR', OC(O)N(R')₂, CN, NO, NO₂, ONO₂, azido, CF₃, OCF₃, R', O (oxo), S (thiono), methylenedioxy, ethylenedioxy, N(R')₂, SR', SOR', SO₂R', SO₂N(R')₂, SO₃R', C(O)R',

C(O)C(O)R', C(O)CH₂C(O)R', C(S)R', C(O)OR', OC(O)R', C(O)N(R')₂,
 OC(O)N(R')₂, C(S)N(R')₂, (CH₂)₀₋₂N(R')C(O)R', (CH₂)₀₋₂N(R')N(R')₂,
 N(R')N(R')C(O)R', N(R')N(R')C(O)OR', N(R')N(R')CON(R')₂, N(R')SO₂R',
 N(R')SO₂N(R')₂, N(R')C(O)OR', N(R')C(O)R', N(R')C(S)R', N(R')C(O)N(R')₂,
 5 N(R')C(S)N(R')₂, N(COR')COR', N(OR')R', C(=NH)N(R')₂, C(O)N(OR')R', or
 C(=NOR')R' wherein R' can be hydrogen or a carbon-based moiety, and wherein
 the carbon-based moiety can itself be further substituted; for example, wherein
 R' can be hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl,
 heteroaryl, or heteroarylalkyl, wherein any alkyl, acyl, cycloalkyl, aryl, aralkyl,
 10 heterocyclyl, heteroaryl, or heteroarylalkyl or R' can be independently mono- or
 multi-substituted with J; or wherein two R' groups bonded to a nitrogen atom or
 to adjacent nitrogen atoms can together with the nitrogen atom or atoms form a
 heterocyclyl, which can be mono- or independently multi-substituted with J.

In various embodiments, J can be halo, nitro, cyano, OR, NR₂, or R, or is
 15 C(O)OR, C(O)NR₂, OC(O)OR, OC(O)NR₂, N(R)C(O)OR, N(R)C(O)NR₂ or
 thio/thiono analogs thereof. By "thio/thiono analogs thereof", with respect to a
 group containing an O, is meant that any or all O atoms in the group can be
 replaced by an S atom; e.g., for group C(O)OR, a "thio/thiono analog thereof"
 includes C(S)OR, C(O)SR, and C(S)SR; e.g., for group OC(O)NR₂, a
 20 "thio/thiono analog thereof" includes SC(O)NR₂, OC(S)NR₂, and SC(S)NR₂;
 and so forth.

In various embodiments, J is any of halo, (C1-C6)alkyl, (C3-
 C10)cycloalkyl, (C1-C6)alkoxy, (C1-C6)haloalkyl, hydroxy(C1-C6)alkyl,
 alkoxy(C1-C6)alkyl, (C1-C6)alkanoyl, (C1-C6)alkanoyloxy, cyano, nitro, azido,
 25 R₂N, R₂NC(O), R₂NC(O)O, R₂NC(O)NR, (C1-C6)alkenyl, (C1-C6)alkynyl,
 (C6-C10)aryl, (C6-C10)aryloxy, (C6-C10)aroyle, (C6-C10)aryl(C1-C6)alkyl,
 (C6-C10)aryl(C1-C6)alkoxy, (C6-C10)aryloxy(C1-C6)alkyl, (C6-
 C10)aryloxy(C1-C6)alkoxy, (3- to 10-membered)heterocyclyl, (3- to 10-
 membered)heterocyclyl(C1-C6)alkyl, (3- to 10-membered)heterocyclyl(C1-
 30 C6)alkoxy, (5- to 10-membered)heteroaryl, (5- to 10-membered)heteroaryl(C1-
 C6)alkyl, (5- to 10-membered)heteroaryl(C1-C6)alkoxy, or (5- to 10-
 membered)heteroaroyle. For example, R independently at each occurrence can be
 H, (C1-C6)alkyl, or (C6-C10)aryl.

Alkyl groups include straight chain and branched alkyl groups and cycloalkyl groups having from 1 to about 20 carbon atoms, and typically from 1 to 12 carbons or, in some embodiments, from 1 to 8 carbon atoms. Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. As used herein, the term "alkyl" encompasses n-alkyl, isoalkyl, and anteisoalkyl groups as well as other branched chain forms of alkyl.

Representative substituted alkyl groups can be substituted one or more times with any of the groups listed above, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups.

Cycloalkyl groups are cyclic alkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group can have 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 4, 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalanyl, and the like. Cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above. Representative substituted cycloalkyl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2,2-, 2,3-, 2,4- 2,5- or 2,6-disubstituted cyclohexyl groups or mono-, di- or tri-substituted norbornyl or cycloheptyl groups, which can be substituted with, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups. The term "cycloalkenyl" alone or in combination denotes a cyclic alkenyl group.

Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms in the ring. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain about 6 to about 14 carbons in the ring portions of the groups. Aryl groups can be unsubstituted or substituted, as defined above. Representative substituted aryl groups can be

mono-substituted or substituted more than once, such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or 2-8 substituted naphthyl groups, which can be substituted with carbon or non-carbon groups such as those listed above.

Aralkyl groups are alkyl groups as defined above in which a hydrogen or
5 carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above. Representative aralkyl groups include benzyl and phenylethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl. Aralkenyl group are alkenyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as
10 defined above.

Heterocyclyl groups or the term "heterocyclyl" includes aromatic and non-aromatic ring compounds containing 3 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. Thus a heterocyclyl can be a cycloheteroalkyl, or a heteroaryl, or if polycyclic, any
15 combination thereof. In some embodiments, heterocyclyl groups include 3 to about 20 ring members, whereas other such groups have 3 to about 15 ring members. A heterocyclyl group designated as a C₂-heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C₄-heterocyclyl can be a 5-ring
20 with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. A heterocyclyl ring can also include one or more double bonds. A heteroaryl ring is an embodiment of a heterocyclyl group. The phrase "heterocyclyl group" includes fused ring species including those comprising
25 fused aromatic and non-aromatic groups. For example, a dioxolanyl ring and a benzodioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclyl groups within the meaning herein. The phrase also includes polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. Heterocyclyl groups can be unsubstituted, or can be substituted as
30 discussed above. Heterocyclyl groups include, but are not limited to, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, dihydrobenzofuranyl, indolyl, dihydroindolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl,

benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups.

Representative substituted heterocyclyl groups can be mono-substituted or
5 substituted more than once, such as, but not limited to, piperidinyl or quinolinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with groups such as those listed above.

Heteroaryl groups are aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to,
10 N, O, and S; for instance, heteroaryl rings can have 5 to about 8-12 ring members. A heteroaryl group is a variety of a heterocyclyl group that possesses an aromatic electronic structure. A heteroaryl group designated as a C₂-heteroaryl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C₄-
15 heteroaryl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, thiophenyl,
20 benzothiophenyl, benzofuranyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Heteroaryl groups can be unsubstituted, or can be
25 substituted with groups as is discussed above. Representative substituted heteroaryl groups can be substituted one or more times with groups such as those listed above.

Heterocyclylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group as defined above is replaced with a
30 bond to a heterocyclyl group as defined above. Representative heterocyclyl alkyl groups include, but are not limited to, furan-2-yl methyl, furan-3-yl methyl, pyridine-3-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl.

Heteroarylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heteroaryl group as defined above.

The term "alkoxy" refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined above. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, and the like. Examples of branched alkoxy include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy, and the like. Examples of cyclic alkoxy include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like. An alkoxy group can include one to about 12-20 carbon atoms bonded to the oxygen atom, and can further include double or triple bonds, and can also include heteroatoms. For example, an allyloxy group is an alkoxy group within the meaning herein. A methoxyethoxy group is also an alkoxy group within the meaning herein, as is a methylenedioxy group in a context where two adjacent atoms of a structures are substituted therewith.

The terms "halo" or "halogen" or "halide" by themselves or as part of another substituent mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine.

A "haloalkyl" group includes mono-halo alkyl groups, poly-halo alkyl groups wherein all halo atoms can be the same or different, and per-halo alkyl groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkyl include trifluoromethyl, 1,1-dichloroethyl, 1,2-dichloroethyl, 1,3-dibromo-3,3-difluoropropyl, perfluorobutyl, and the like. For example, a halo((C1-C6)alkyl) group as the term is used herein encompasses species such as monofluoromethyl, difluoromethyl, trifluoromethyl, perfluorobutyl, 4,4,4-trifluorobutyl, and the like.

A "haloalkoxy" group includes mono-halo alkoxy groups, poly-halo alkoxy groups wherein all halo atoms can be the same or different, and per-halo alkoxy groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkoxy include trifluoromethoxy, 1,1-dichloroethoxy, 1,2-dichloroethoxy, 1,3-dibromo-3,3-difluoropropoxy, perfluorobutoxy, and the like.

The terms "aryloxy" and "arylalkoxy" refer to, respectively, an aryl group bonded to an oxygen atom and an aralkyl group bonded to the oxygen atom at the alkyl moiety. Examples include but are not limited to phenoxy, naphthyloxy, and benzyloxy.

5 An "acyl" group as the term is used herein refers to a group containing a carbonyl moiety wherein the group is bonded via the carbonyl carbon atom. The carbonyl carbon atom is also bonded to another carbon atom, which can be part of an alkyl, aryl, aralkyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl group or the like. In the special
10 case wherein the carbonyl carbon atom is bonded to a hydrogen, the group is a "formyl" group, an acyl group as the term is defined herein. An acyl group can include 0 to about 12-20 additional carbon atoms bonded to the carbonyl group.

 An acyl group can include double or triple bonds within the meaning herein. An acryloyl group is an example of an acyl group. An acyl group can
15 also include heteroatoms within the meaning here. A nicotinoyl group (pyridyl-3-carbonyl) group is an example of an acyl group within the meaning herein. Other examples include acetyl, benzoyl, phenylacetyl, pyridylacetyl, cinnamoyl, and acryloyl groups and the like. When the group containing the carbon atom that is bonded to the carbonyl carbon atom contains a halogen, the group is
20 termed a "haloacyl" group. An example is a trifluoroacetyl group.

 The term "amine" includes primary, secondary, and tertiary amines having, e.g., the formula $N(\text{group})_3$ wherein each group can independently be H or non-H, such as alkyl, aryl, and the like. Amines include but are not limited to $R-NH_2$, for example, alkylamines, arylamines, alkylarylamines; R_2NH wherein
25 each R is independently selected, such as dialkylamines, diarylamines, aralkylamines, heterocyclylamines and the like; and R_3N wherein each R is independently selected, such as trialkylamines, dialkylarylamines, alkylarylamines, triarylamines, and the like. The term "amine" also includes ammonium ions as used herein.

30 An "amino" group is a substituent of the form $-NH_2$, $-NHR$, $-NR_2$, $-NR_3^+$, wherein each R is independently selected, and protonated forms of each, except for $-NR_3^+$, which cannot be protonated. Accordingly, any compound substituted with an amino group can be viewed as an amine. An "amino group" within the meaning herein can be a primary, secondary, tertiary or quaternary amino group.

An "alkylamino" group includes a monoalkylamino, dialkylamino, and trialkylamino group.

An "ammonium" ion includes the unsubstituted ammonium ion NH_4^+ , but unless otherwise specified, it also includes any protonated or quaternarized forms of amines. Thus, trimethylammonium hydrochloride and tetramethylammonium chloride are both ammonium ions, and amines, within the meaning herein.

The term "amide" (or "amido") includes C- and N-amide groups, i.e., $-\text{C}(\text{O})\text{NR}_2$, and $-\text{NRC}(\text{O})\text{R}$ groups, respectively. Amide groups therefore include but are not limited to primary carboxamide groups ($-\text{C}(\text{O})\text{NH}_2$) and formamide groups ($-\text{NHC}(\text{O})\text{H}$). A "carboxamido" group is a group of the formula $\text{C}(\text{O})\text{NR}_2$, wherein R can be H, alkyl, aryl, etc.

The term "azido" refers to an N_3 group. An "azide" can be an organic azide or can be a salt of the azide (N_3^-) anion. The term "nitro" refers to an NO_2 group bonded to an organic moiety. The term "nitroso" refers to an NO group bonded to an organic moiety. The term nitrate refers to an ONO_2 group bonded to an organic moiety or to a salt of the nitrate (NO_3^-) anion.

The term "urethane" ("carbamoyl" or "carbamyl") includes N- and O-urethane groups, i.e., $-\text{NRC}(\text{O})\text{OR}$ and $-\text{OC}(\text{O})\text{NR}_2$ groups, respectively.

The term "sulfonamide" (or "sulfonamido") includes S- and N-sulfonamide groups, i.e., $-\text{SO}_2\text{NR}_2$ and $-\text{NRSO}_2\text{R}$ groups, respectively. Sulfonamide groups therefore include but are not limited to sulfamoyl groups ($-\text{SO}_2\text{NH}_2$). An organosulfur structure represented by the formula $-\text{S}(\text{O})(\text{NR})-$ is understood to refer to a sulfoximine, wherein both the oxygen and the nitrogen atoms are bonded to the sulfur atom, which is also bonded to two carbon atoms.

Standard abbreviations for chemical groups such as are well known in the art are used; e.g., Me = methyl, Et = ethyl, i-Pr = isopropyl, Bu = butyl, t-Bu = tert-butyl, Ph = phenyl, Bn = benzyl, Ac = acetyl, Bz = benzoyl, and the like.

A "salt" as is well known in the art includes an organic compound such as a carboxylic acid, a sulfonic acid, or an amine, in ionic form, in combination with a counterion. For example, acids in their anionic form can form salts with cations such as metal cations, for example sodium, potassium, and the like; with ammonium salts such as NH_4^+ or the cations of various amines, including tetraalkyl ammonium salts such as tetramethylammonium, or other cations such

as trimethylsulfonium, and the like. A "pharmaceutically acceptable" or "pharmacologically acceptable" salt is a salt formed from an ion that has been approved for human consumption and is generally non-toxic, such as a chloride salt or a sodium salt. A "zwitterion" is an internal salt such as can be formed in a molecule that has at least two ionizable groups, one forming an anion and the other a cation, which serve to balance each other. For example, amino acids such as glycine can exist in a zwitterionic form. A "zwitterion" is a salt within the meaning herein. The compounds of the present invention may take the form of salts. The term "salts" embraces addition salts of free acids or free bases which are compounds of the invention. Salts can be "pharmaceutically-acceptable salts." The term "pharmaceutically-acceptable salt" refers to salts which possess toxicity profiles within a range that affords utility in pharmaceutical applications. Pharmaceutically unacceptable salts may nonetheless possess properties such as high crystallinity, which have utility in the practice of the present invention, such as for example utility in process of synthesis, purification or formulation of compounds of the invention.

Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid. Examples of pharmaceutically unacceptable acid addition salts include, for example, perchlorates and tetrafluoroborates.

Suitable pharmaceutically acceptable base addition salts of compounds of the invention include, for example, metallic salts including alkali metal, alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Pharmaceutically acceptable base addition

salts also include organic salts made from basic amines such as, for example, *N,N*-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Examples of pharmaceutically unacceptable base addition salts include lithium salts and

5 cyanate salts. Although pharmaceutically unacceptable salts are not generally useful as medicaments, such salts may be useful, for example as intermediates in the synthesis of Formula (I) compounds, for example in their purification by recrystallization. All of these salts may be prepared by conventional means from

10 the appropriate acid or base with the compound according to Formula (I). The term "pharmaceutically acceptable salts" refers to nontoxic inorganic or organic acid and/or base addition salts, see, for example, Lit et al., *Salt Selection for Basic Drugs* (1986), *Int J. Pharm.*, **33**, 201-217, incorporated by reference herein.

15 A "hydrate" is a compound that exists in a composition with water molecules. The composition can include water in stoichiometric quantities, such as a monohydrate or a dihydrate, or can include water in random amounts. As the term is used herein a "hydrate" refers to a solid form, i.e., a compound in water solution, while it may be hydrated, is not a hydrate as the term is used

20 herein.

In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as

25 selected from the group consisting of bromine, chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described. Moreover, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any combination of individual members or

30 subgroups of members of Markush groups. Thus, for example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, and Y is described as selected from the group consisting of methyl, ethyl, and propyl, claims for X being bromine and Y being methyl are fully described.

If a value of a variable that is necessarily an integer, e.g., the number of carbon atoms in an alkyl group or the number of substituents on a ring, is described as a range, e.g., 0-4, what is meant is that the value can be any integer between 0 and 4 inclusive, i.e., 0, 1, 2, 3, or 4.

5 In various embodiments, the compound or set of compounds, such as are used in the inventive methods, can be any one of any of the combinations and/or sub-combinations of the above-listed embodiments.

 In various embodiments, a compound as shown in any of the Examples, or among the exemplary compounds, is provided. Provisos may apply to any
10 of the disclosed categories or embodiments wherein any one or more of the other above disclosed embodiments or species may be excluded from such categories or embodiments.

 The present invention further embraces isolated compounds of the invention. The expression "isolated compound" refers to a preparation of a
15 compound of the invention, or a mixture of compounds the invention, wherein the isolated compound has been separated from the reagents used, and/or byproducts formed, in the synthesis of the compound or compounds. "Isolated" does not mean that the preparation is technically pure (homogeneous), but it is sufficiently pure to compound in a form in which it can be used therapeutically.
20 Preferably an "isolated compound" refers to a preparation of a compound of the invention or a mixture of compounds of the invention, which contains the named compound or mixture of compounds of the invention in an amount of at least 10 percent by weight of the total weight. Preferably the preparation contains the
25 named compound or mixture of compounds in an amount of at least 50 percent by weight of the total weight; more preferably at least 80 percent by weight of the total weight; and most preferably at least 90 percent, at least 95 percent or at least 98 percent by weight of the total weight of the preparation.

 The compounds of the invention and intermediates may be isolated from their reaction mixtures and purified by standard techniques such as filtration,
30 liquid-liquid extraction, solid phase extraction, distillation, recrystallization or chromatography, including flash column chromatography, or HPLC.

Overview

 We hypothesized that either blocking activation of lipogenic enzyme expression or active suppression of these genes in the liver would be one method

to treat NAFLD. In order to accomplish this, we focused on the nuclear receptors, liver X receptor α and β (LXR α and LXR β) that are well-characterized regulators of the expression of an array of lipogenic enzyme genes⁷. LXR agonists induce lipogenesis by increasing transcription of lipogenic enzyme gene expression including *Srebf1*, *fatty acid synthase (Fasn)*, *stearoyl-CoA desaturase (Scd1)*, and *Chrebp*⁸⁻¹¹. In fact, LXR α expression as well as lipogenic LXR α target genes are overexpressed in patients with NAFLD¹². A number of synthetic LXR agonists have been designed¹³, but there are limited examples of antagonists.

Using the recently described synthetic LXR antagonist, GSK2033¹⁴ (Fig. 1A), we assessed the ability of this compound to alter lipogenic enzyme gene expression in the livers of mice subject to a high fat diet. GSK2033 displays high affinity in an LXR β radioligand binding assay (IC₅₀=32nM)¹⁴ and we observed a similar level of potency in LXR α and LXR β cell-based cotransfection assays (IC₅₀s ranging from 9 to 17 nM) (Fig. 1B). We assessed the plasma and liver exposure of GSK2033 after i.p. injection (30 mg/kg) and observed significant levels of the compound. (Fig.1C). Plasma concentrations of GSK2033 remained above the IC₅₀ for a duration of 8h and liver concentrations of the drug were in the 8 to 18 μ M range indicating sufficient levels of the compound for *in vivo* studies.

In a mouse model of nonalcoholic hepatosteatosis, **9** displays high potency for both LXR α and LXR β (40-200 nM IC₅₀) and stabilized the interaction of the receptors with transcriptional corepressor protein fragments. Compound **9** was designed to display liver specificity so as to avoid potential side effects due to suppression of LXR in the periphery and we detected no effect of **9** treatment on LXR target genes in extrahepatic tissue. These data indicate that liver selective LXR inverse agonists can hold utility in the treatment of liver disease.

In order to determine the potential of GSK2033 to treat fatty liver disease, we induced hepatic steatosis in mice by maintaining them on a high fat diet for 14 weeks prior to initiating treatment with GSK2033 (30mg/kg/day, i.p., q.d.) for 30 days. We assessed the expression of genes involved in lipogenesis in the liver after completion of the study and noted that GSK2033 displayed

unexpected activity where *Fasn* and *Srebp1c* expression was significantly elevated but *Scd1* expression was suppressed (Fig. 1D). Tumor necrosis factor α (TNF α) and interleukin-1 β (IL-1 β) have been shown to be key proinflammatory markers elevated in patients with NAFLD¹² and we observed that the expression of these genes in the livers of GSK2033-treated mice was either elevated (*Tnfa*) or suppressed (*Il1b*) (Fig. 1E).

Clearly, this profile was not consistent with the hypothesis that LXR antagonists should decrease lipogenic gene expression and when we assessed the specificity of GSK2033 across a range of nuclear receptors (NRs) we observed that GSK2033 was quite promiscuous altering the activity of a number of NRs that may be responsible for the unexpected effects on hepatic gene expression (Fig. 1F). GSK2033 does not provide the pharmacological profile for a compound to be used to reduce lipogenesis so we sought to develop more selective LXR ligands with either antagonist or inverse agonist activity for this use. We synthesized a number of analogues of GSK2033, and one compound in particular, SR9238 (Fig. 2A, compound 9), displayed very potent inverse agonist activity in cell-based cotransfection assays using either full-length LXR α or LXR β and a reporter containing 3 copies of an LXRE within the promoter (Fig. 2F). SR9238 displayed a degree of LXR β selectivity with an IC₅₀ of 214 nM for LXR α and 43 nM for LXR β . In the identical NR specificity panel used for GSK2033, SR9238 displayed no activity at any of the NRs tested (Fig. 2C) SR9238 also effectively suppressed transcription from a *Fasn* promoter driven luciferase reporter (Fig. 2D). Based on this activity, we hypothesized that SR9238 must be inducing a conformation within the receptor allowing for effective recruitment of corepressor. This was indeed the case as we found that SR9238 induced increased interaction of CoRNR box peptides derived from NCoR (NCoR ID1 and NCoR ID2) with both LXR α and LXR β while causing decreased interaction with a coactivator NR box peptide derived from TRAP220 (Fig. 2E). As a control, the LXR agonist T0901317 was used to illustrate the ability of an agonist induce interaction of LXR α and LXR β with a NR box peptide but not with a CoRNR box peptide (Fig. 2F). SR9238 induced recruitment of CoRNR box peptides was dose-dependent for both LXR α and LXR β (Fig. 2E). There was a clear preference for NCoR ID1 for both LXR α

and LXR β with EC₅₀s of 33 nM and 13 nM for NCoR ID1 with LXR α and LXR β , respectively and >10 μ M and 93 nM for NCoR ID2 with LXR α and LXR β , respectively. Furthermore, when we treated HepG2 cells with SR9238 we found that *Fasn* and *Srebp1c* mRNA expression was substantially suppressed (Fig. 2G).

One significant concern with development of LXR inverse agonists for the treatment of fatty liver disease is that suppression of LXR target genes outside the liver may have adverse effects on reverse cholesterol transport via suppression of ATP-binding cassette transporter subfamily A1 (Abca1) expression for example. We utilized an approach where the LXR inverse agonist would be rapidly metabolized in the liver so as to provide extensive liver exposure, but not peripheral plasma exposure. As illustrated in Fig. 3A, SR9238 contains an ester group that would be expected to be rapidly metabolized to the acid analogue (SR10389) by plasma lipases. SR10389 displays no LXR α or LXR β activity in the cell-based cotransfection assay (Fig. 3V). In order to confirm that there would be liver exposure but no plasma exposure, we injected SR9238 (30 mg/kg, i.p.) into mice and assessed the concentration of SR9238. Approximately 6 μ M SR9238 was detected in the liver 2h after the injection, but no compound was detected in the plasma (Fig. 3C). Thus, SR9238 displays liver specific exposure and would not be expected to alter LXR target gene expression outside of the liver.

In order to determine the potential of SR9238 to treat fatty liver disease, we induced hepatic steatosis in mice by maintaining them on a high fat diet for 14 weeks prior to initiating treatment with SR9238 (30mg/kg/day, i.p.) for 30 days. Consistent with our cell-based data, we found that SR9238 treatment resulted in the substantial repression of lipogenic gene expression. Hepatic *Fasn* and *Srebp1c* expression was suppressed by 60% and 80%, respectively (Fig. 4A). Additionally, *Scd1* was reduced almost 90% following the treatment (Fig. 4A). Hepatic steatosis was assessed by visualization of lipid content in liver sections stained with with Bodipy 493/503. Clearly, SR9238 treated mice displayed greatly reduced lipid content in the liver (Fig. 3B).

Several studies suggest that the increased expression of *Srebp1c* together with other lipogenic genes and the induction of inflammation in hepatocytes is crucial for the development and progression of fatty liver diseases^{12,15,16}. To

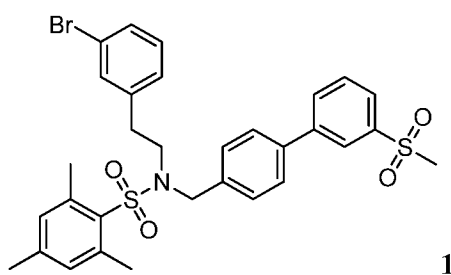
assess whether SR9238 also impacted inflammation due to the hepatic steatosis, the expression of *Tnfa* and *Il1b* was examined. As illustrated in Fig. 4B, both *Tnfa* and *Il1b* expression were substantially reduced (~80% and >95%, respectively) in the SR9238 treated mice when compared to the vehicle-treated mice. Based on the pharmacokinetic data showing that SR9238 exposure was limited in the liver (Fig. 3C), we expected that there would be no alterations in LXR target genes in other tissues. We assessed *Fasn* and *Abca1* expression in brown adipose tissue (a well-characterized LXR target tissue¹⁷⁻¹⁹) of the DIO mice and observed no significant changes in expression levels following 30-day treatment with SR9238 (Fig. 4D).

In summary, we have developed a high affinity, liver selective LXR inverse agonist that displays the ability to reduce the expression of lipogenic genes in the liver as well as reduce hepatic steatosis in obese mice. In addition, SR9238 reduces the expression of proinflammatory cytokines in the hepatic steatosis model, which indicates that this class of compound may be effective in limiting the progression of NAFLD to liver failure and cancer.

In 2012, it is estimated that there will be 1.6 million people newly diagnosed with cancer and nearly 600,000 people will die of the disease in the United States (ACS 2012 Cancer Facts and Figures). Although there has been considerable progress in diagnosis and treatment of various cancers, there is a considerable unmet medical need to improve treatments to prolong the lives of people with cancer and potentially provide cures. One method for treatment of cancer is to determine what biochemical pathways may be “over-utilized” by cancer cells vs. normal cells that provide them with a survival advantage and suppress these pathways.²⁰ Interestingly, it has been known for some time that cancer cells display unique metabolic profiles relative to normal cells that provide them with a growth advantage.²¹ One of these alterations is known as the Warburg effect whereby cancerous cells increase the rate of glycolysis even in the presence of sufficient oxygen where normal cells would utilize oxidative metabolism.²² Another metabolic pathway that is upregulated in most cancer cells is *de novo* lipogenesis where cells synthesize fatty acids from acetyl CoA that are thought to be used as critical building blocks required for production of additional cells during proliferation.²³ In fact, the rate limiting enzyme in the lipogenesis pathway, fatty acid synthase (FASN), is upregulated in many cancer

cells.²³ Inhibitors of FASN have demonstrated anti-cancer activity.²³⁻²⁵

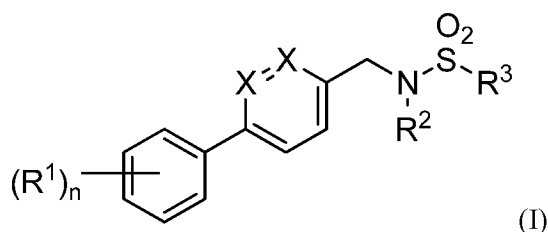
Inhibitors of other enzymes in the lipogenesis pathway have also demonstrated anti-cancer activity.²⁶ The LXR inverse agonists we have developed are effective inhibitors of lipogenesis via suppression of the expression of key genes involved in the lipogenic pathway. Given that the LXR inverse agonists we have developed are effective inhibitors of lipogenesis, we tested whether they would have anti-cancer activity. In order to examine this possibility, we examined the effect of the LXR inverse agonist, SR9243 (compound 1) on the viability of several cancer cell lines.



As shown in Figs. 6a AND 6b, treatment of colorectal cancer cells (HT-29 or SW620, respectively) with SR9243 illustrates that this compound causes a reduction in cell viability that is dose-dependent as assessed by the MTT assay.²⁷ When we examined lipogenic gene expression in these cells in response to treatment with the LXR inverse agonist, we note a significant suppression of key genes including sterol regulatory element binding protein 1c (SREBP1c), FASN, acetyl CoA carboxylase (ACC) and steroyl coA desaturase (SCD1) in both cell lines using QPCR. We also note similar efficacy in prostate cancer cell lines (PC3 and DU145) (Figs. 7A and 7B, respectively) and non-small cell lung cancer cell lines (NCI-H23 and HOP-62) (Figs. 8A and 8B, respectively). These data indicate that LXR inverse agonists may hold utility in the treatment of a wide variety of cancers.

Detailed Description

In various embodiments, compounds of formula (I), having inverse agonist bioactivity versus isoforms of LXR are provided, wherein for a compound of formula (I):



R^1 is (C1-C6)alkyl, (C1-C6)alkoxy, halo, halo(C1-C6)alkyl, halo(C1-C6)alkoxy, cyano, nitro, OR, $RS(O)_q$, CO_2R , $CONR_2$, $OC(O)NR_2$, $N(R)C(O)NR_2$, (C1-C6)alkyl SO_2 , (C1-C6)alkyl $N(R)SO_2$, (C6-C10)aryl SO_2 , (C6-C10)aryl $N(R)SO_2$, 3-10 membered heterocyclyl, 3-10 membered heterocyclyl(C1-C6)alkyl, N-bonded tetrazolyl, or C-bonded tetrazolyl; wherein the ring bearing R^1 can comprise 0, 1, or 2 nitrogen atoms, provided that the nitrogen atom is not substituted with R^1 ;

$n = 1, 2, \text{ or } 3$; $q = 0, 1, \text{ or } 2$;

R^2 is (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-C10)cycloalkyl, (C1-C6)alkyl $C(=O)O$ (C1-C6)alkyl, (C6-C10)aryl(C1-C6)alkyl $C(=O)O$ (C1-C6)alkyl, (C6-C10)aryl(C1-C6)alkyl $OC(=O)$ (C1-C6)alkyl, (C6-C10)aryl, (C6-C10)aryl(C1-C6)alkyl, (3- to 10-membered)heterocyclyl, (3- to 10-membered)heterocyclyl(C1-C6)alkyl, (5- to 10-membered)heteroaryl, or (5- to 10-membered)heteroaryl(C1-C6)alkyl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl moiety of any R^2 group is substituted with 0-3 J groups;

R^3 is (C6-C10)aryl, (C1-C6)alkyl, (C6-C10)aryl(C1-C6)alkyl, (5- to 10-membered)heteroaryl, or (5- to 10-membered)heteroaryl(C1-C6)alkyl; wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl moiety of any R^3 group is substituted with 0-3 J groups;

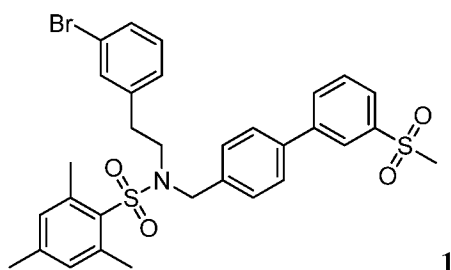
R is independently at each occurrence H, (C1-C6)alkyl, halo(C1-C6)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C6)alkyl, (C6-C10)aryl, (C6-C10)aryl(C1-C6)alkyl, (3- to 10-membered)heterocyclyl, (3- to 10-membered)heterocyclyl(C1-C6)alkyl, (5- to 10-membered)heteroaryl, or (5- to 10-membered)heteroaryl(C1-C6)alkyl; and,

J is (C1-C6)alkyl, (C3-C10)cycloalkyl, (C6-C10)aryl, (3- to 10-membered)heterocyclyl, (5- to 10-membered)heteroaryl, halo, halo(C1-C6)alkyl, halo((C1-C6)alkoxy, nitro, cyano, OR, $RS(O)_q$, NR_2 , $C(O)OR$, $C(O)NR_2$,

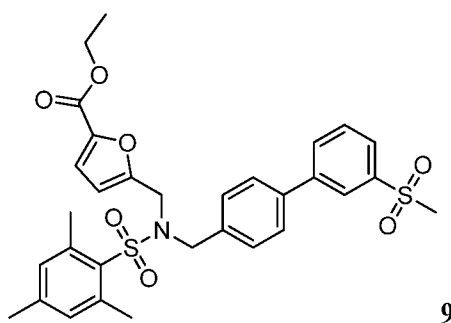
OC(O)OR, OC(O)NR₂, N(R)C(O)OR, or N(R)C(O)NR₂ or a thio/thiono analog thereof;

each X is independently CH or N, provided that only one X is N;
or any salt thereof.

- 5 The invention provides, in various embodiments, inverse agonists of LXR, e.g., compounds of formula (I), such as compound 1:



or, compound 9:



- 10 or, any of the compounds disclosed and claimed herein, e.g., examples 1-58, and salts thereof.

The invention can provide a compound of formula (I) wherein R¹ is an electron-withdrawing group. Examples of suitable electron-withdrawing groups for R¹ include halo, halo(C1-C6)alkyl, halo(C1-C6)alkoxy, cyano, nitro, CO₂R, CONR₂, OC(O)NR₂, NRC(O)NR₂, (C1-C6)alkylSO₂, (C1-C6)alkylNRSO₂, (C6-C10)arylSO₂, (C6-C10)arylNRSO₂, RS(O)_q wherein q is 0, 1, or 2, C- or N-bonded tetrazolyl, and others. Other electron-withdrawing groups, such as can also be used, and it is within ordinary skill in conjunction with the disclosure herein to make and test compounds of formula (I) containing electron-
20 withdrawing groups in the position of group R¹.

R² can be a lipophilic group, such as an alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl group, as is suitable for interaction with a lipophilic (hydrophobic) domain of a receptor or enzyme. The lipophilic group can be bonded via a linker, such as an alkylene (e.g., methylene) spacer, to

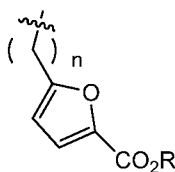
the sulfonamide nitrogen atom of formula (I). For example, R^2 can be (C1-C6)alkyl, (C6-C10)aryl, (C6-C10)aryl(C1-C6)alkyl, (3- to 10-membered)heterocyclyl, (3- to 10-membered)heterocyclyl(C1-C6)alkyl, (5- to 10-membered)heteroaryl, or (5- to 10-membered)heteroaryl(C1-C6)alkyl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl moiety of any R^2 group is substituted with 0-3 J groups. R^2 can also be a lipophilic group other than the exemplary groups listed; it is within ordinary skill in conjunction with the disclosure herein to make and test compounds of formula (I) containing electron-withdrawing groups in the position of group R^2 .

R^3 can be a lipophilic group, for example, R^3 can be a sterically hindered aryl group. Steric hinderance, such as by substitution of the aryl ring can result in lack of co-planarization of the R^3 aryl ring with the plane of bonding of the sulfonamide nitrogen atom and sulfonyl sulfur atom, such that the R^3 group lies at an angle to this plane in a preferred conformation. For example, R^3 can be (C6-C10)aryl, (C1-C6)alkyl, (C6-C10)aryl(C1-C6)alkyl, (5- to 10-membered)heteroaryl, or (5- to 10-membered)heteroaryl(C1-C6)alkyl; wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl moiety of any R^3 group is substituted with 0-3 J groups; it is within ordinary skill in conjunction with the disclosure herein to make and test compounds of formula (I) containing electron-withdrawing groups in the position of group R^3 .

The secondary substituents R and J can be selected from the gamut of organic groups typically used in pharmaceutical molecular entities. The person of ordinary skill can make and test compounds of formula (I) as defined above, bearing various R and J groups, for inverse agonist bioactivity versus LXR. For example, R can be independently at each occurrence H, (C1-C6)alkyl, (C3-C10)cycloalkyl, (C6-C10)aryl, (3- to 10-membered)heterocyclyl, (5- to 10-membered)heteroaryl, and, J can be (C1-C6)alkyl, (C3-C10)cycloalkyl, (C6-C10)aryl, (3- to 10-membered)heterocyclyl, (5- to 10-membered)heteroaryl, halo, halo(C1-C6)alkyl, halo(C1-C6)alkoxy, nitro, cyano, OR, $RS(O)_q$ wherein q is 0, 1, or 2, NR_2 , or is $C(O)OR$, $C(O)NR_2$, $OC(O)OR$, $OC(O)NR_2$, $N(R)C(O)OR$, $N(R)C(O)NR_2$ or a thio/thiono analog thereof.

For example, R^1 can be (C1-C6)alkylSO₂, (C1-C6)alkylNRSO₂, (C6-C10)arylSO₂, or (C6-C10)arylNRSO₂. More specifically, R^1 can be methanesulfonyl or ethanesulfonyl.

For example, R^2 can be (C6-C10)aryl(C1-C6)alkyl or (5- to 10-membered)heteroaryl(C1-C6)alkyl, wherein any alkyl, aryl or heteroaryl moiety of any R^2 group can be substituted with 0-3 J groups. More specifically, R^2 can be a furanylalkyl group, wherein the furanylalkyl can be substituted with 0-3 J groups; R^2 can be of formula



wherein R is as defined in claim 1, $n = 0, 1, 2, 3$, or 4, and a wavy line indicates a point of bonding.

For example, R^3 can be aryl, substituted with 0-3 J. More specifically, R^3 can be mesityl.

In various embodiments, the biphenyl group can comprise a nitrogen atom in one of the ring, as indicated by group X. Thus, a compound of formula (I) can be a biphenyl derivative or can be a phenyl-pyridyl derivative.

In various embodiments, the invention provides a pharmaceutical composition comprising a compound of the invention, and a pharmaceutically acceptable excipient.

Another aspect of an embodiment of the invention provides compositions of the compounds of the invention, alone or in combination with another medicament. As set forth herein, compounds of the invention include stereoisomers, tautomers, solvates, prodrugs, pharmaceutically acceptable salts and mixtures thereof. Compositions containing a compound of the invention can be prepared by conventional techniques, e.g. as described in Remington: *The Science and Practice of Pharmacy*, 19th Ed., 1995, or later versions thereof, incorporated by reference herein. The compositions can appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of the invention and a pharmaceutically acceptable excipient which can be a carrier or a diluent. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which can be in the form of an ampoule, capsule, sachet, paper, or other container. When the active compound is mixed

with a carrier, or when the carrier serves as a diluent, it can be solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid carrier, for example contained in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent can include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

The formulations can be mixed with auxiliary agents which do not deleteriously react with the active compounds. Such additives can include wetting agents, emulsifying and suspending agents, salt for influencing osmotic pressure, buffers and/or coloring substances preserving agents, sweetening agents or flavoring agents. The compositions can also be sterilized if desired.

The route of administration can be any route which effectively transports the active compound of the invention to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral, e.g., rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation can be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

Injectable dosage forms generally include aqueous suspensions or oil suspensions which can be prepared using a suitable dispersant or wetting agent and a suspending agent. Injectable forms can be in solution phase or in the form of a suspension, which is prepared with a solvent or diluent. Acceptable solvents or vehicles include sterilized water, Ringer's solution, or an isotonic

aqueous saline solution. Alternatively, sterile oils can be employed as solvents or suspending agents. Preferably, the oil or fatty acid is non-volatile, including natural or synthetic oils, fatty acids, mono-, di- or tri-glycerides.

For injection, the formulation can also be a powder suitable for
5 reconstitution with an appropriate solution as described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations can optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these. The
10 compounds can be formulated for parenteral administration by injection such as by bolus injection or continuous infusion. A unit dosage form for injection can be in ampoules or in multi-dose containers.

The formulations of the invention can be designed to provide quick, sustained, or delayed release of the active ingredient after administration to the
15 patient by employing procedures well known in the art. Thus, the formulations can also be formulated for controlled release or for slow release.

Compositions contemplated by the present invention can include, for example, micelles or liposomes, or some other encapsulated form, or can be administered in an extended release form to provide a prolonged storage and/or
20 delivery effect. Therefore, the formulations can be compressed into pellets or cylinders and implanted intramuscularly or subcutaneously as depot injections. Such implants can employ known inert materials such as silicones and biodegradable polymers, e.g., polylactide-polyglycolide. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides).

25 For nasal administration, the preparation can contain a compound of the invention, dissolved or suspended in a liquid carrier, preferably an aqueous carrier, for aerosol application. The carrier can contain additives such as solubilizing agents, e.g., propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as
30 parabens.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet that can be prepared by conventional tableting techniques can contain:

Core:

10	Active compound (as free compound or salt thereof)	250 mg
	Colloidal silicon dioxide (Aerosil®)	1.5 mg
	Cellulose, microcryst. (Avicel®)	70 mg
	Modified cellulose gum (Ac-Di-Sol®)	7.5 mg
	Magnesium stearate	Ad.

15 Coating:

HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

20 A typical capsule for oral administration contains compounds of the invention (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule. A typical injectable preparation is produced by aseptically placing 250 mg of compounds of the invention into a vial, aseptically freeze-drying and
 25 sealing. For use, the contents of the vial are mixed with 2 mL of sterile physiological saline, to produce an injectable preparation.

The compounds of the invention can be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of a malcondition. Such mammals include also
 30 animals, both domestic animals, e.g. household pets, farm animals, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 5000 mg, preferably from about 1 to about 2000 mg, and more preferably

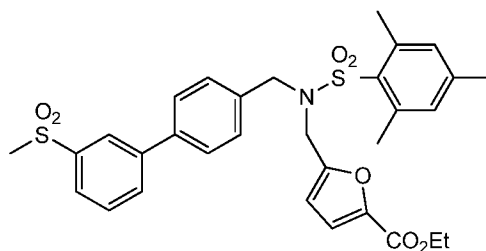
between about 2 and about 2000 mg per day can be used. A typical dosage is about 10 mg to about 1000 mg per day. In choosing a regimen for patients it can frequently be necessary to begin with a higher dosage and when the condition is under control to reduce the dosage. The exact dosage will depend upon the activity of the compound, mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the invention are dispensed in unit dosage form including from about 0.05 mg to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration include from about 125 μ g to about 1250 mg, preferably from about 250 μ g to about 500 mg, and more preferably from about 2.5 mg to about 250 mg, of the compounds admixed with a pharmaceutically acceptable carrier or diluent.

Dosage forms can be administered daily, or more than once a day, such as twice or thrice daily. Alternatively dosage forms can be administered less frequently than daily, such as every other day, or weekly, if found to be advisable by a prescribing physician.

Accordingly, the invention provides in various embodiments, a method of exerting an inverse agonistic effect on a Liver X receptor, comprising contacting the receptor with an effective amount or concentration of the compound of formula (I) of the invention, or the pharmaceutical composition of the invention. For example, the compound of formula (I) can be compound **9**, SR9238:



Accordingly, the invention provides in various embodiments, a method to suppress hepatic lipogenesis, inflammation, or hepatic lipid accumulation in a

mammal, comprising administering to the mammal an effective amount of the compound of formula (I) of the invention, or the pharmaceutical composition of the invention. For example, the compound of formula (I) for practice of an inventive method can be compound **9**, SR9238, shown above.

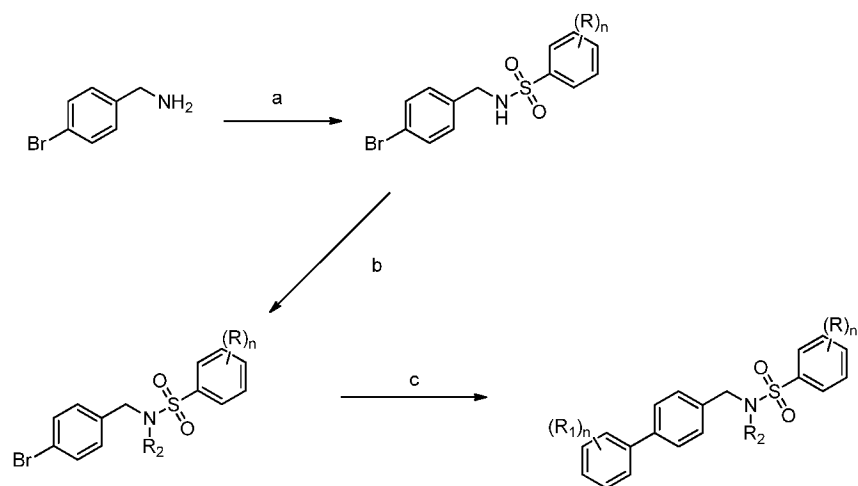
- 5 Accordingly, the invention provides in various embodiments, a method of treatment of any of the following disorders: non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, obesity, insulin resistance, and metabolic syndrome, in a patient afflicted therewith, comprising administering to the patient an effective amount of the compound of the invention, or the
10 pharmaceutical composition of the invention.

Synthetic procedures

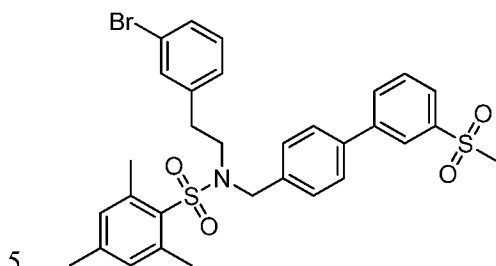
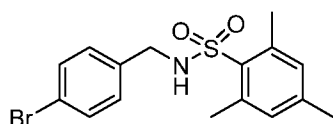
Compounds of the invention were prepared according to Scheme 1, in conjunction with ordinary skill. Specific examples are provided below.

- The substituents R, R¹, and R² of the precursors are selected to give
15 reaction products bearing the target groups desired. The assembly of the biphenyl moiety by the palladium-catalyzed Suzuki reaction allows for a high degree of versatility in preparing compounds having various substituent arrangements on the arylsulfonamides bearing the biphenyl moiety of the scaffold. In a variant of Scheme 1, the biphenyl ring system can be prepared
20 first, followed by alkylation of the nitrogen atom to provide the R² moiety.

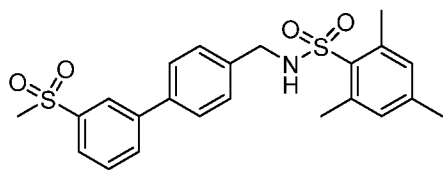
Scheme 1: Synthetic Route



Reaction Conditions: a. (R)_nArSO₂Cl, Et₃N, CH₂Cl₂; b. R₂X, Cs₂CO₃, DMF (R₂=Cl, Br, I, OMs);
c. (R₁)_nArB(OH)₂, Pd(Ph₃P)₄, K₂CO₃, dioxane

Exemplary Compounds of the InventionExample 1N-(3-Bromophenethyl)-2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamideStep 1: N-(4-Bromobenzyl)-2,4,6-trimethylbenzenesulfonamide

To a solution of (4-bromophenyl)methanamine (0.93 g, 5 mmol) and triethyl amine (1.05 mL, 7.5 mmol) in dichloromethane, was added 2,4,6-trimethylbenzene-1-sulfonyl chloride (1.09 g, 5 mmol) portion wise. The mixture was allowed to stir for 1 h at ambient temperature. The reaction mixture was washed with HCl (2N) (3 × 50 mL), water and brine. The organic layer was dried over anhydrous MgSO₄ and concentrated in *vacuo* to obtain the title compound as colorless prisms (98%); ¹H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.38 – 7.32 (m, 2H), 7.07 – 7.01 (m, 2H), 6.94 (s, 2H), 4.90 (t, *J* = 6.2 Hz, 1H), 4.03 (d, *J* = 6.2 Hz, 2H), 2.61 (s, 6H), 2.31 (s, 3H); ¹³C NMR (100 MHz, Chloroform-*d*) δ (ppm) 142.6, 139.2, 135.6, 133.7, 132.1, 131.8, 129.6, 121.9, 46.3, 23.1, 21.1; HRMS calculated for C₁₆H₁₈BrNO₂S (M+H)⁺: 368.0314, Found: 368.0319.

Step 2: 2,4,6-Trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

N-(4-bromobenzyl)-2,4,6-trimethylbenzenesulfonamide (0.736 g, 2 mmol), (3-(methylsulfonyl)phenyl)boronic acid (0.800 g, 4 mmol), palladium acetate (0.044 g, 0.2 mmol), and tri-*o*-tolylphosphine (0.121 g, 0.4 mmol) were

dissolved in 1,4-dioxane (50 mL) and the solution was degassed with argon for 10 min. K_2CO_3 (2M) was added and the solution was further degassed for additional 5 min. The reaction mixture was heated overnight at 120 °C in an oil bath. After the mixture was cooled to room temperature, it was poured into aq. NaCl (5 %) and extracted with dichloromethane (4×50 mL). The combined organics were washed with water, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The remaining crude residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes) to obtain the title compound as white sharp needles (70%); 1H NMR (400 MHz, Chloroform-*d*) δ (ppm) 8.10 (t, $J = 1.8$ Hz, 1H), 7.91 (ddd, $J = 7.8, 1.9, 1.1$ Hz, 1H), 7.82 (ddd, $J = 7.8, 1.9, 1.1$ Hz, 1H), 7.64 (t, $J = 7.8$ Hz, 1H), 7.55 – 7.48 (m, 2H), 7.33 – 7.27 (m, 2H), 6.99 – 6.94 (m, 2H), 4.81 (t, $J = 6.2$ Hz, 1H), 4.15 (d, $J = 6.2$ Hz, 2H), 3.09 (s, 3H), 2.66 (s, 6H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ (ppm) 142.5, 142.1, 141.3, 139.2, 138.6, 137.0, 133.7, 132.2, 132.1, 130.0, 128.7, 127.5, 126.2, 125.8, 46.5, 44.6, 23.1, 21.0; HRMS calculated for $C_{23}H_{25}NO_4S_2$ (M+H) $^+$: 444.1297, Found: 444.1297.

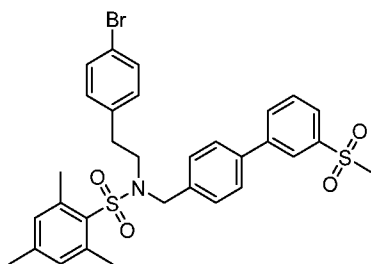
Step 3: *N*-(3-Bromophenethyl)-2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

A mixture of 2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide (0.443 g, 1 mmol), K_2CO_3 (0.276 g, 2 mmol), and 1-bromo-3-(2-bromoethyl)benzene (0.792 g, 3 mmol) in anhydrous acetonitrile (5 ml) was heated to 85 °C for 2 h under microwave irradiation. The white powder was filtered off, the solvent was evaporated and the mixture was dissolved in ethyl acetate and extracted with brine. The organic phase was separated, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The remaining crude residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes) to obtain the title compound as white sharp needles (88% based on recovery of the starting materials); 1H NMR (400 MHz, Chloroform-*d*) δ 8.14 (t, $J = 1.8$ Hz, 1H), 7.92 (ddd, $J = 7.8, 1.8, 1.1$ Hz, 1H), 7.86 (ddd, $J = 7.8, 1.9, 1.1$ Hz, 1H), 7.65 (t, $J = 7.8$ Hz, 1H), 7.61 – 7.53 (m, 2H), 7.34 – 7.27 (m, 3H), 7.10 – 7.02 (m, 2H), 6.97 (s, 2H), 6.90 (dt, $J = 7.6, 1.4$ Hz, 1H), 4.44 (s, 2H), 3.31 (dd, $J = 8.5, 6.8$ Hz, 2H), 3.10 (s, 3H), 2.71 (dd, $J = 8.7, 6.6$ Hz, 2H), 2.62 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ (ppm) 142.9, 142.2, 141.4, 141.0, 140.7, 140.3, 138.8, 136.3, 133.8, 133.0, 132.3, 131.7,

130.2, 130.1, 129.7, 129.5, 127.7, 127.5, 127.4, 126.2, 125.9, 122.6, 49.9, 46.8, 44.6, 33.6, 23.0, 21.2; HRMS calculated for $C_{31}H_{32}BrNO_4S_2$ ($M+H$)⁺: 626.10288, Found: 626.1027.

Example 2

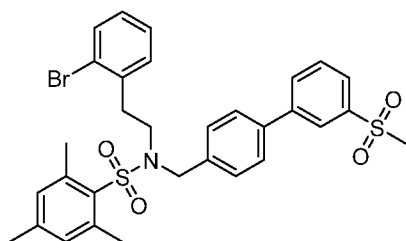
- 5 *N*-(4-bromophenethyl)-2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



- The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 1-bromo-4-(2-bromoethyl)benzene and
 10 was obtained as white solid (82 %). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.14 (t, *J* = 1.8 Hz, 1H), 7.92 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.85 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.33 – 7.26 (m, 4H), 6.95 (d, *J* = 1.1 Hz, 2H), 6.85 – 6.79 (m, 2H), 4.45 (s, 2H), 3.29 (dd, *J* = 8.4, 6.7 Hz, 2H), 3.10 (s, 3H), 2.76 – 2.66 (m, 2H), 2.59 (s, 6H), 2.34 (s, 3H). ESI-MS
 15 (m/z): 626 [$M+1$]⁺.

Example 3

- N*-(2-Bromophenethyl)-2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

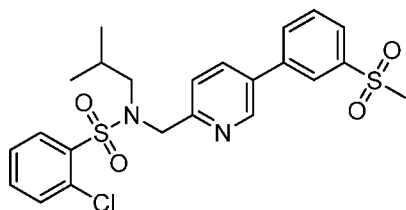


- 20 The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 1-bromo-2-(2-bromoethyl)benzene and was obtained as white solid (85 %). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.13 (t, *J* = 1.8 Hz, 1H), 7.91 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.84 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.41 (dd, *J* = 7.9, 1.3

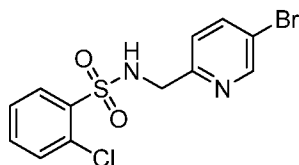
Hz, 1H), 7.37 – 7.31 (m, 2H), 7.19 – 7.13 (m, 1H), 7.07 – 7.00 (m, 2H), 6.96 (d, $J = 1.1$ Hz, 2H), 4.52 (s, 2H), 3.38 – 3.26 (m, 2H), 3.10 (s, 3H), 2.95 – 2.85 (m, 2H), 2.64 (s, 6H), 2.32 (s, 3H). ESI-MS (m/z): 626 $[M+1]^+$.

Example 4

- 5 2-Chloro-*N*-isobutyl-*N*-((5-(3-(methylsulfonyl)phenyl)pyridin-2-yl)methyl)benzenesulfonamide

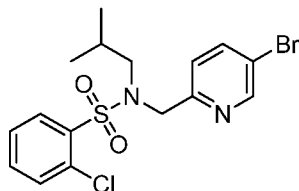


N-((5-Bromopyridin-2-yl)methyl)-2-chlorobenzenesulfonamide



- 10 The title compound was synthesized following the same general protocol as described in Example 1, Step 1 using 2-chlorobenzene-1-sulfonyl chloride and (5-bromopyridin-2-yl)methanamine.

N-((5-Bromopyridin-2-yl)methyl)-2-chloro-*N*-isobutylbenzenesulfonamide



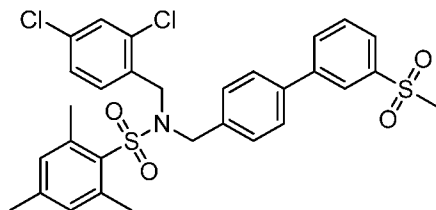
- 15 The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 1-bromo-2-methylpropane and *N*-((5-bromopyridin-2-yl)methyl)-2-chlorobenzenesulfonamide.

2-Chloro-*N*-isobutyl-*N*-((5-(3-(methylsulfonyl)phenyl)pyridin-2-yl)methyl)benzenesulfonamide

- 20 The title compound was synthesized following the same general protocol as described in Example 1, Step 2 using (3-(methylsulfonyl)phenyl)boronic acid and *N*-((5-bromopyridin-2-yl)methyl)-2-chloro-*N*-isobutylbenzenesulfonamide. ESI-MS (m/z): 493.1 $[M]^+$.

Example 5

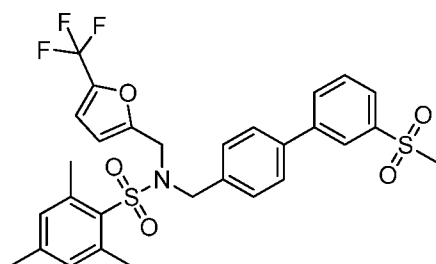
N-(2,4-Dichlorobenzyl)-2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 2,4-dichlorobenzyl bromide and 2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide. ¹H NMR (400 MHz, DMSO-*d*-6) δ 8.2 (s, 1H), 8.0 (d, 1H), 7.9 (d, 1H), 7.7 (t, 1H), 7.6 (d, 2H), 7.5 (s, 1H), 7.35 (d, 1H), 7.25 (d, 1H), 7.2 (d, 2H), 7.05 (s, 2H), 4.4 (d, 4H), 3.3 (s, 3H), 2.6 (s, 6H), 2.3 (s, 3H).

Example 6

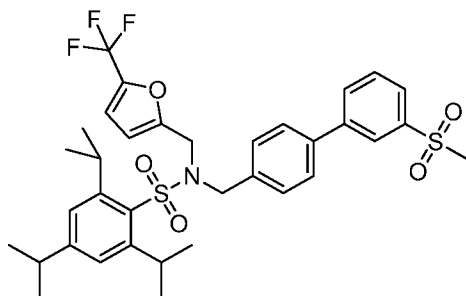
2,4,6-Trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-*N*-((5-(trifluoromethyl)furan-2-yl)methyl)benzenesulfonamide



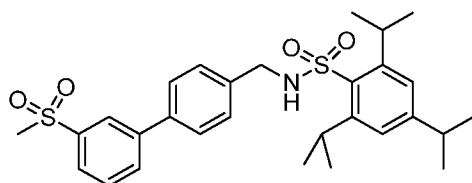
The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 2-(bromomethyl)-5-(trifluoromethyl)furan and 2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide. ¹H NMR (400 MHz, DMSO-*d*-6) δ 8.15 (s, 1H), 8.0 (d, 1H), 7.9 (d, 1H), 7.75 (t, 1H), 7.7 (d, 2H), 7.3 (d, 2H), 7.05 (s, 2H), 7.0 (d, 1H), 6.4 (d, 1H), 4.4 (s, 2H), 4.3 (s, 2H), 3.3 (s, 3H), 2.6 (s, 6H), 2.3 (s, 3H).

Example 7

2,4,6-Triisopropyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-*N*-((5-(trifluoromethyl)furan-2-yl)methyl)benzenesulfonamide



2,4,6-Triisopropyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



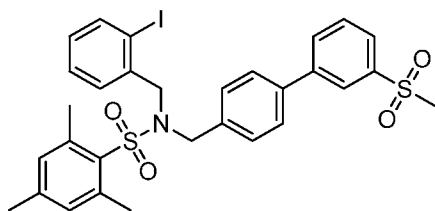
- 5 The title compound was synthesized following the same general protocol as described in Example 1, Steps 1-2 using (4-bromophenyl)methanamine, 2,4,6-triisopropylbenzene-1-sulfonyl chloride, and (3-(methylsulfonyl)phenyl)boronic acid.

2,4,6-Triisopropyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-N-((5-(trifluoromethyl)furan-2-yl)methyl)benzenesulfonamide

The title compound was synthesized following the same general protocol as described in Example 4 using 2-(bromomethyl)-5-(trifluoromethyl)furan and 2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide. ESI-MS (m/z): 676.1 [M+H]⁺.

15 Example 8

N-(2-Iodobenzyl)-2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

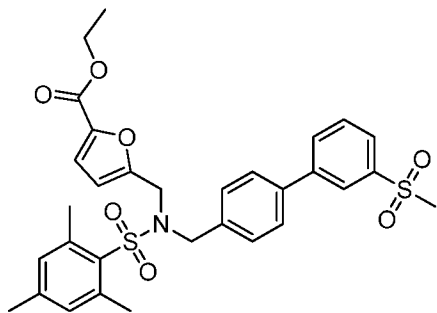


- 20 The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 2-iodobenzylbromide and 2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.11 (t, J = 1.8 Hz, 1H), 7.91 (ddd, J = 7.8,

- 1.9, 1.1 Hz, 1H), 7.83 (ddd, $J = 7.8, 1.9, 1.1$ Hz, 1H), 7.78 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.63 (t, $J = 7.8$ Hz, 1H), 7.49 – 7.44 (m, 2H), 7.41 (dd, $J = 7.7, 1.7$ Hz, 1H), 7.32 (td, $J = 7.5, 1.2$ Hz, 1H), 7.00 (d, $J = 7.8$ Hz, 4H), 6.95 (td, $J = 7.6, 1.8$ Hz, 1H), 4.46 (s, 2H), 4.35 (s, 2H), 3.10 (s, 3H), 2.68 (s, 6H), 2.34 (s, 3H). ESI-MS (m/z): 660.1 $[M+1]^+$.

Example 9

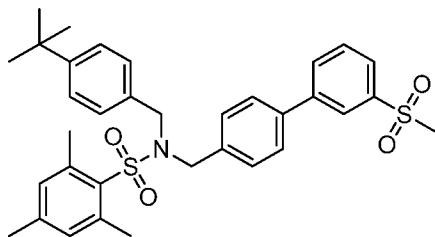
Ethyl 5-((2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)phenylsulfonamido)methyl)furan-2-carboxylate



- 10 A mixture of 2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide (0.443 g, 1 mmol), K_2CO_3 (0.276 g, 2 mmol), and ethyl 5-(chloromethyl)furan-2-carboxylate (0.566 g, 3 mmol) in anhydrous acetone (5 ml) was heated to 65 °C for 2 h under microwave irradiation. The mixture was filtered and then concentrated in vacuo. The resulting oil was
- 15 dissolved in ethyl acetate and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The remaining crude residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes) to obtain the title compound as white sharp needles; 1H NMR (400 MHz, Chloroform-*d*) δ 8.12 (t, $J = 1.8$ Hz, 1H), 7.92 (ddd, $J = 7.8, 1.9, 1.1$ Hz, 1H), 7.84 (ddd, $J = 7.8, 1.8, 1.1$ Hz, 1H), 7.64 (t, $J = 7.7$ Hz, 1H), 7.57 – 7.51 (m, 2H), 7.29 – 7.26 (m, 2H), 7.04 (d, $J = 3.4$ Hz, 1H), 7.02 – 6.98 (m, 2H), 6.28 (d, $J = 3.4$ Hz, 1H), 4.40 (s, 2H), 4.35 (q, $J = 7.1$ Hz, 2H), 4.31 (s, 2H), 3.10 (s, 3H), 2.65 (s, 6H), 2.33 (s, 3H), 1.38 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ (ppm) 158.6, 154.4, 144.6, 143.1, 142.3, 141.4, 140.6, 138.8, 135.7, 132.8, 132.3, 132.2,
- 20 130.1, 129.9, 127.6, 126.2, 125.9, 118.7, 111.4, 61.1, 50.1, 44.7, 41.6, 23.0, 21.2, 14.5

Example 10

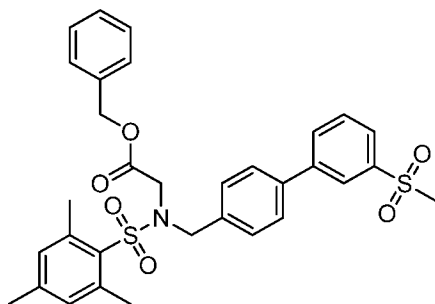
N-(4-(Tert-butyl)benzyl)-2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 4-*t*-butylbenzylbromide and 2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.15 (t, *J* = 1.8 Hz, 1H), 7.92 (ddd, *J* = 7.8, 1.9, 1.0 Hz, 1H), 7.86 (ddd, *J* = 7.9, 1.8, 1.1 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.41 – 7.36 (m, 1H), 7.34 – 7.27 (m, 3H), 7.24 – 7.17 (m, 2H), 7.02 (s, 2H), 7.00 – 6.92 (m, 2H), 4.34 (s, 2H), 4.20 (s, 2H), 3.11 (s, 3H), 2.68 (s, 6H), 2.35 (s, 3H), 1.30 (s, 9H). ESI-MS (*m/z*): 590.3 [M+H]⁺.

Example 11

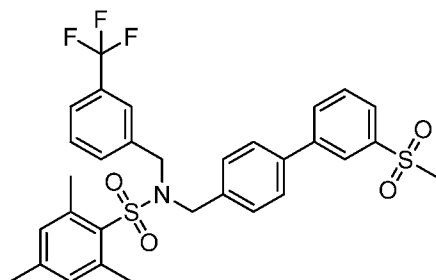
Benzyl 2-(2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)phenylsulfonamido)acetate



The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using benzyl 2-chloroacetate and 2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.11 (t, *J* = 1.8 Hz, 1H), 7.92 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.82 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.39 – 7.32 (m, 5H), 7.22 – 7.17 (m, 2H), 6.96 (s, 2H), 5.05 (s, 2H), 4.58 (s, 2H), 3.90 (s, 2H), 3.09 (s, 3H), 2.65 (s, 6H), 2.32 (s, 3H). ESI-MS (*m/z*): 592.2 [M+H]⁺.

Example 12

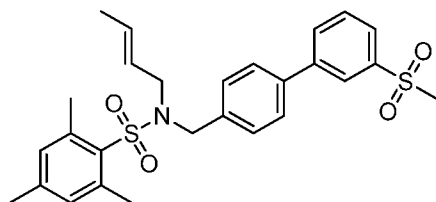
(E)-N-(but-2-en-1-yl)-2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



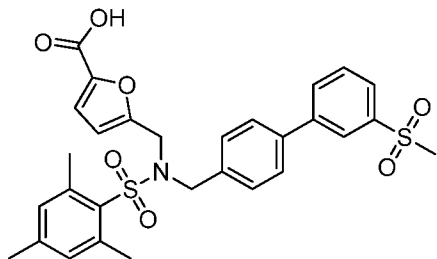
The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 3-trifluoromethylbenzylbromide and 2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.14 (t, *J* = 1.8 Hz, 1H), 7.93 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.85 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.58 – 7.49 (m, 3H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.04 (d, *J* = 10.4 Hz, 3H), 4.34 (s, 2H), 4.29 (s, 2H), 3.11 (s, 3H), 2.67 (s, 6H), 2.35 (s, 3H). ESI-MS (*m/z*): 602.2 [M+H]⁺.

Example 13

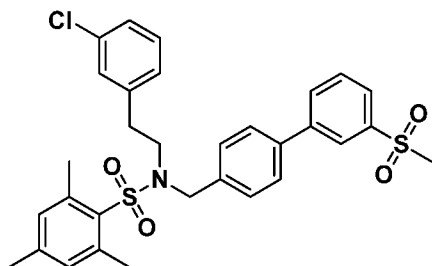
2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(3-(trifluoromethyl)benzyl)benzenesulfonamide



The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using (E)-1-chlorobut-2-ene and 2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide. ¹H NMR (400 MHz, CDCl₃): (Two rotamers) δ (ppm) 8.13 (q, *J* = 2.0 Hz, 1H), 7.91 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.84 (dtd, *J* = 7.8, 2.3, 1.8, 1.1 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.33 – 7.27 (m, 0.6H), 7.25 – 7.21 (m, 1.4H), 6.98 (s, 2H), 5.71 – 5.58 (m, 0.3H), 5.55 – 5.43 (m, 0.7H), 5.34-5.27 (m, 1H), 4.42 (s, 0.6H), 4.38 (s, 1.4H), 3.72 (d, *J* = 7.1 Hz, 0.6H), 3.63 (d, *J* = 6.8 Hz, 1.4H), 3.10 (d, *J* = 1.0 Hz, 3H), 2.66-2.65 (m, 6H), 2.32 (s, 3H), 1.66 (dq, *J* = 6.4, 1.1 Hz, 2H), 1.39 (dd, *J* = 7.0, 1.7 Hz, 1H). ESI-MS (*m/z*): 498.2 [M+H]⁺.

Example 145-((2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)phenylsulfonamido)methyl)furan-2-carboxylic acid

- 5 To a solution of Ethyl 5-((2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)phenylsulfonamido)methyl)furan-2-carboxylate (0.059 g, 0.1 mmol) in THF (5 mL) and water (2 mL) was added lithium hydroxide monohydrate (0.006 g, 0.25 mmol) and the reaction was stirred at room temperature for 12 h. The reaction mixture was acidified with HCl (2N) and
- 10 extracted with ethyl acetate. The organic phase was separated, dried over anhydrous MgSO_4 and concentrated in *vacuo* to give the title compound as white powder; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.12 (t, $J = 1.8$ Hz, 1H), 7.91 (ddd, $J = 7.8, 1.9, 1.1$ Hz, 1H), 7.83 (ddd, $J = 7.8, 1.9, 1.1$ Hz, 1H), 7.64 (t, $J = 7.8$ Hz, 1H), 7.58 – 7.51 (m, 2H), 7.25 (d, $J = 8.5$ Hz, 3H), 7.17 (d, $J = 3.5$ Hz,
- 15 1H), 7.04 – 6.97 (m, 2H), 6.35 (d, $J = 3.5$ Hz, 1H), 4.40 (s, 2H), 4.34 (s, 2H), 3.10 (s, 3H), 2.66 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ (ppm) 161.9, 155.7, 143.5, 143.3, 142.3, 141.4, 140.6, 138.9, 135.6, 132.7, 132.4, 132.3, 130.1, 129.8, 127.7, 126.2, 126.0, 120.9, 111.9, 50.4, 44.7, 41.8, 23.0, 21.2.

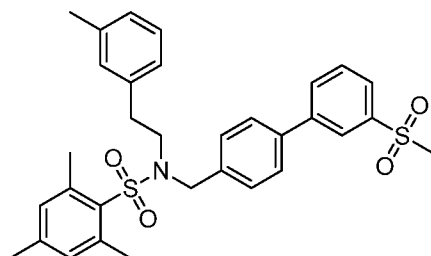
20 Example 15N-(3-Chlorophenethyl)-2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

- The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 1-(2-bromoethyl)-3-chlorobenzene and
- 25

2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.14 (d, J = 1.9 Hz, 1H), 7.92 (ddt, J = 7.9, 2.0, 1.0 Hz, 1H), 7.85 (ddt, J = 7.8, 1.9, 1.0 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.30 (d, J = 7.9 Hz, 2H), 7.17 – 7.09 (m, 2H), 6.97 (s, 2H), 6.91 – 6.83 (m, 2H), 4.44 (s, 2H), 3.31 (t, J = 7.6 Hz, 2H), 3.10 (d, J = 0.9 Hz, 3H), 2.72 (t, J = 7.6 Hz, 2H), 2.61 (s, 6H), 2.33 (s, 3H). ESI-MS (m/z): 583 $[\text{M}+\text{H}]^+$.

Example 16

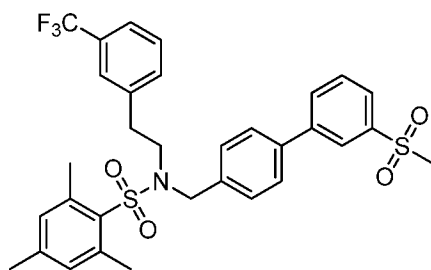
2,4,6-Trimethyl-*N*-(3-methylphenethyl)-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 1-(2-bromoethyl)-3-methylbenzene and 2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.14 (t, J = 1.8 Hz, 1H), 7.92 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.85 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.35 – 7.28 (m, 2H), 7.09 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 6.8 Hz, 3H), 6.80 – 6.73 (m, 2H), 4.46 (s, 2H), 3.37 – 3.26 (m, 2H), 3.10 (s, 3H), 2.71 (dd, J = 9.1, 6.6 Hz, 2H), 2.63 (s, 6H), 2.33 (s, 3H), 2.26 (s, 3H). ESI-MS (m/z): 562 $[\text{M}+\text{H}]^+$.

Example 17

2,4,6-Trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-*N*-(3-(trifluoromethyl)phenethyl)benzenesulfonamide



The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 1-(2-bromoethyl)-3-

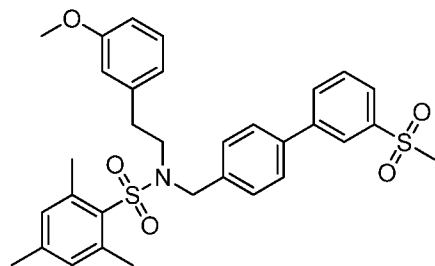
(trifluoromethyl)benzene and 2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-

biphenyl]-4-yl)methyl)benzenesulfonamide. ¹H NMR (400 MHz, CDCl₃): δ

- 5 (ppm) 8.14 (t, *J* = 1.8 Hz, 1H), 7.92 (ddd, *J* = 7.8, 1.9, 1.0 Hz, 1H), 7.85 (ddd, *J* = 7.9, 1.9, 1.1 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.46 – 7.39 (m, 1H), 7.34 – 7.27 (m, 3H), 7.16 (t, *J* = 3.4 Hz, 2H), 6.97 (s, 2H), 4.44 (s, 2H), 3.42 – 3.27 (m, 2H), 3.10 (s, 3H), 2.80 (dd, *J* = 8.7, 6.7 Hz, 2H), 2.62 (s, 6H), 2.33 (s, 3H). ESI-MS (*m/z*): 616 [M+H]⁺.

10 Example 18

N-(3-Methoxyphenethyl)-2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

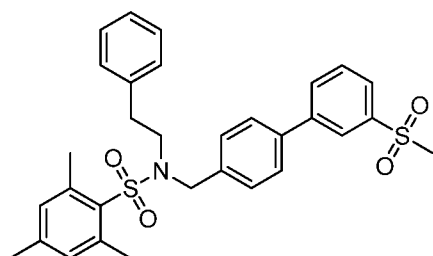


The title compound was synthesized following the same general protocol as

- 15 described in Example 1, Step 3 using 1-(2-bromoethyl)-3-methoxybenzene and 2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.13 (t, *J* = 1.8 Hz, 1H), 7.92 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.85 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.35 – 7.27 (m, 2H), 7.12 (dd, *J* = 8.3, 7.5 Hz, 1H), 6.97 (s, 2H), 6.71 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.56 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.48 (dd, *J* = 2.6, 1.6 Hz, 1H), 4.45 (s, 2H), 3.73 (s, 3H), 3.38 – 3.26 (m, 2H), 3.10 (s, 3H), 2.71 (dd, *J* = 9.0, 6.6 Hz, 2H), 2.63 (s, 6H), 2.33 (s, 3H). ESI-MS (*m/z*): 578 [M+H]⁺.

Example 19

- 25 2,4,6-Trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-*N*-phenethylbenzenesulfonamide

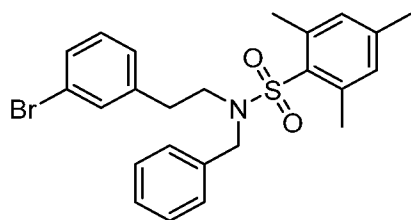


The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using (2-bromoethyl)benzene and 2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-

- 5 yl)methyl)benzenesulfonamide. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.14 (dd, $J = 2.1, 1.6$ Hz, 1H), 7.92 (ddd, $J = 7.8, 1.9, 1.1$ Hz, 1H), 7.85 (ddd, $J = 7.8, 1.9, 1.1$ Hz, 1H), 7.68 – 7.61 (m, 1H), 7.59 – 7.53 (m, 2H), 7.32 – 7.27 (m, 2H), 7.23 – 7.14 (m, 3H), 6.97 (dt, $J = 6.7, 1.6$ Hz, 4H), 4.45 (s, 2H), 3.38 – 3.28 (m, 2H), 3.10 (s, 3H), 2.80 – 2.70 (m, 2H), 2.63 (s, 6H), 2.33 (s, 3H). ESI-MS (m/z): 548
- 10 $[\text{M}+\text{H}]^+$.

Example 20

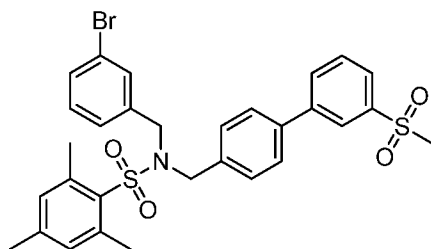
N-Benzyl-*N*-(3-bromophenethyl)-2,4,6-trimethylbenzenesulfonamide



- The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using benzyl bromide and was obtained as a
- 15 white solid (94 %). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.40 – 7.27 (m, 5H), 7.21 – 7.16 (m, 2H), 7.08 – 7.02 (m, 2H), 6.96 (s, 2H), 6.88 (dt, $J = 7.7, 1.2$ Hz, 1H), 4.37 (s, 2H), 3.28 (t, $J = 7.6$ Hz, 2H), 2.69 (t, $J = 7.6$ Hz, 2H), 2.62 (s, 6H), 2.33 (s, 3H). ESI-MS (m/z): 472.1 $[\text{M}+1]^+$.

20 Example 21

N-(3-Bromobenzyl)-2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

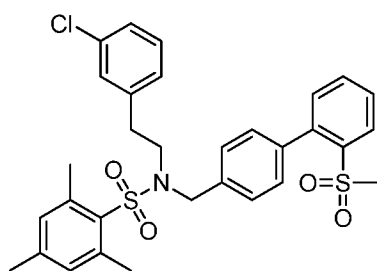


The title compound was synthesized following the same general protocol as described in Example 1, Step 3 using 1-bromo-3-(bromomethyl)benzene and 2,4,6-trimethyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-

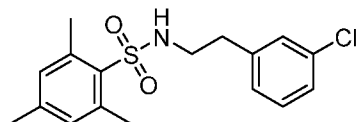
- 5 yl)methyl)benzenesulfonamide. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.15 (t, J = 1.9 Hz, 1H), 7.93 (dt, J = 7.8, 1.4 Hz, 1H), 7.86 (dt, J = 7.8, 1.4 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.39 (ddd, J = 8.0, 2.0, 1.1 Hz, 1H), 7.22 – 7.12 (m, 3H), 7.03 (s, 3H), 6.98 (d, J = 1.9 Hz, 1H), 4.35 (s, 2H), 4.21 (s, 2H), 3.10 (s, 3H), 2.66 (s, 6H), 2.36 (s, 3H). ESI-MS (m/z): 613 $[\text{M}+\text{H}]^+$.

10 Example 22

N-(3-Chlorophenethyl)-2,4,6-trimethyl-*N*-((2'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



Step1: *N*-(3-Chlorophenethyl)-2,4,6-trimethylbenzenesulfonamide

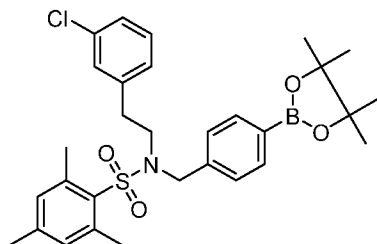


15

To a solution of 2-(3-chlorophenyl)ethanamine (0.778 g, 5 mmol) and triethyl amine (1.05 mL, 7.5 mmol) in dichloromethane, was added 2,4,6-trimethylbenzene-1-sulfonyl chloride (1.09 g, 5 mmol) portion wise. The mixture was allowed to stir for 1 h at ambient temperature. The reaction mixture was washed with HCl (2N) (3 × 50 mL), water and brine. The organic layer was dried over anhydrous MgSO_4 and concentrated in *vacuo* to obtain the title compound.

20

Step 2: *N*-(3-Bromophenethyl)-2,4,6-trimethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzenesulfonamide



A mixture of *N*-(3-chlorophenethyl)-2,4,6-trimethylbenzenesulfonamide (0.338 g, 1 mmol), K₂CO₃ (0.276 g, 2 mmol), and 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.0365 g, 1.2 mmol) in anhydrous acetonitrile (5 ml) was heated to 85 °C for 2 h under microwave irradiation. The white powder was filtered off, the solvent was evaporated and the mixture was dissolved in ethyl acetate and extracted with brine. The organic phase was separated, dried over anhydrous MgSO₄, filtered and concentrated in *vacuo*. The remaining crude residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes) to obtain the title compound.

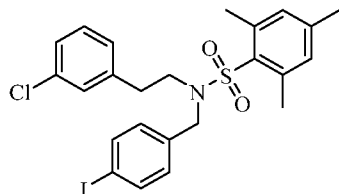
Step 3: *N*-(3-Chlorophenethyl)-2,4,6-trimethyl-*N*-((2'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

1-Bromo-2-(methylsulfonyl)benzene (0.235 g, 1 mmol), *N*-(3-bromophenethyl)-2,4,6-trimethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzenesulfonamide (0.554 g, 1 mmol), palladium acetate (0.022 g, 0.1 mmol), and tri-*o*-tolylphosphine (0.060 g, 0.2 mmol) were dissolved in 1,4-dioxane (25 mL) and the solution was degassed with argon for 10 min. K₂CO₃ (2M) was added and the solution was further degassed for additional 5 min. The reaction mixture was heated overnight at 120 °C in an oil bath. After the mixture was cooled to room temperature, it was poured into aq. NaCl (5 %) and extracted with dichloromethane (4 × 50 mL). The combined organics were washed with water, dried over anhydrous MgSO₄ and concentrated in *vacuo*. The remaining crude residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes) to obtain the title compound. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.22 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.65 (td, *J* = 7.5, 1.6 Hz, 1H), 7.57 (ddd, *J* = 7.6, 6.1, 1.8 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.36 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.17 – 7.10 (m, 2H), 6.97 (s, 2H), 6.89-6.86 (m, 2H), 4.46 (s,

2H), 3.32 (t, $J = 7.6$ Hz, 2H), 2.72 (t, $J = 7.6$ Hz, 2H), 2.62 (s, 6H), 2.61 (s, 3H), 2.33 (s, 3H). ESI-MS (m/z): 582 $[M+1]^+$.

Example 23

N-(3-Chlorophenethyl)-*N*-(4-iodobenzyl)-2,4,6-trimethylbenzenesulfonamide



5

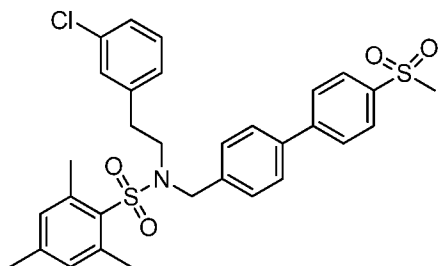
The title compound was synthesized following the same general protocol as described in Example 22, Step 2 using *N*-(3-chlorophenethyl)-2,4,6-trimethylbenzenesulfonamide and 4-iodobenzyl bromide and was obtained as a white solid (93 %). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.69 – 7.60 (m, 2H), 7.17 – 7.08 (m, 2H), 6.96 – 6.90 (m, 4H), 6.89 – 6.80 (m, 2H), 4.32 (s, 2H), 3.26 (t, $J = 7.6$ Hz, 2H), 2.67 (t, $J = 7.6$ Hz, 2H), 2.57 (s, 6H), 2.32 (s, 3H). ESI-MS (m/z): 554.07 $[M+1]^+$.

10

Example 24

N-(3-Chlorophenethyl)-2,4,6-trimethyl-*N*-((4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

15



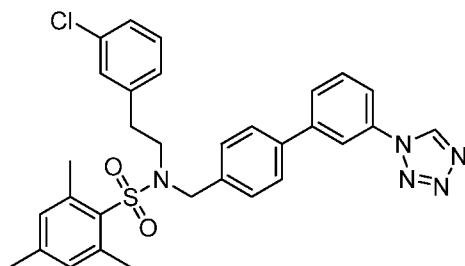
The title compound was synthesized following the same general protocol as described in Example 22, Step 3 using 1-bromo-4-(methylsulfonyl)benzene and *N*-(3-bromophenethyl)-2,4,6-trimethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzenesulfonamide. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.04 – 7.98 (m, 2H), 7.79 – 7.73 (m, 2H), 7.61 – 7.55 (m, 2H), 7.37 – 7.31 (m, 2H), 7.16 – 7.08 (m, 2H), 6.96 (d, $J = 1.1$ Hz, 2H), 6.88 – 6.82 (m, 2H), 4.46 (s, 2H), 3.31 (t, $J = 7.6$ Hz, 2H), 3.10 (s, 3H), 2.70 (t, $J = 7.6$ Hz, 2H), 2.61 (s, 6H), 2.33 (s, 3H). ESI-MS (m/z): 582 $[M+1]^+$.

20

Example 25

25

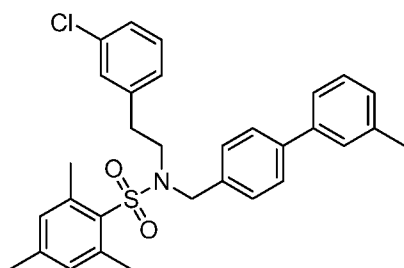
N-((3'-(1*H*-Tetrazol-1-yl)-[1,1'-biphenyl]-4-yl)methyl)-*N*-(3-chlorophenethyl)-2,4,6-trimethylbenzenesulfonamide



The title compound was synthesized following the same general protocol as described in Example 22, Step 3 using 1-(3-bromophenyl)-1*H*-tetrazole and *N*-(3-bromophenethyl)-2,4,6-trimethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzenesulfonamide. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.21 (s, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.15 – 7.04 (m, 2H), 6.95 (s, 2H), 6.87 – 6.76 (m, 2H), 4.47 (s, 2H), 3.29 (t, *J* = 7.3 Hz, 2H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.58 (s, 6H), 2.32 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 143.2, 141.8, 140.4, 140.3, 139.5, 135.6, 134.4, 132.6, 132.4, 130.1, 129.9, 129.4, 128.7, 127.6, 126.9, 126.8, 126.5, 126.2, 124.4, 76.8, 49.8, 46.5, 33.4, 23.0, 21.2. ESI-MS (*m/z*): 572 [M+1]⁺.

Example 26

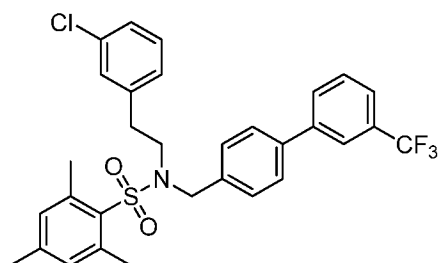
N-(3-Chlorophenethyl)-2,4,6-trimethyl-*N*-((3'-methyl-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



The title compound was synthesized following the same general protocol as described in Example 22, Step 3 using 1-bromo-3-methylbenzene and *N*-(3-bromophenethyl)-2,4,6-trimethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzenesulfonamide.

Example 27

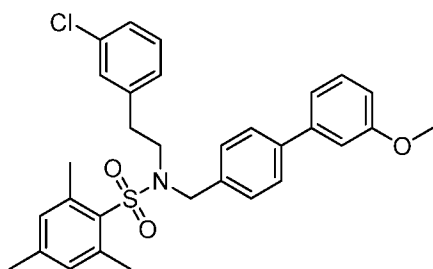
N-(3-Chlorophenethyl)-2,4,6-trimethyl-*N*-((3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



The title compound was synthesized following the same general protocol as described in Example 22, Step 3 using 1-bromo-3-(trifluoromethyl)benzene and *N*-(3-bromophenethyl)-2,4,6-trimethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzenesulfonamide.

Example 28

N-(3-Chlorophenethyl)-*N*-((3'-methoxy-[1,1'-biphenyl]-4-yl)methyl)-2,4,6-trimethylbenzenesulfonamide

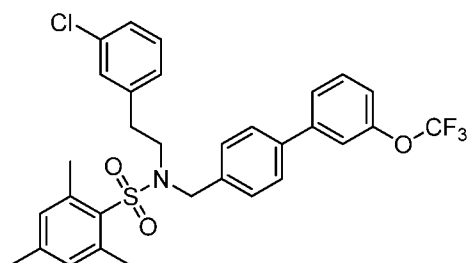


- 10 The title compound was synthesized following the same general protocol as described in Example 22, Step 3 using 1-bromo-3-methoxybenzene and *N*-(3-bromophenethyl)-2,4,6-trimethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzenesulfonamide. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.57 – 7.51 (m, 2H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.18 – 7.08 (m, 4H),
- 15 6.96 (s, 2H), 6.93 – 6.83 (m, 3H), 4.41 (s, 2H), 3.86 (s, 3H), 3.32 (t, *J* = 7.6 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.61 (s, 6H), 2.33 (s, 3H). ESI-MS (*m/z*): 534 [M+1]⁺.

Example 29

N-(3-Chlorophenethyl)-2,4,6-trimethyl-*N*-((3'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

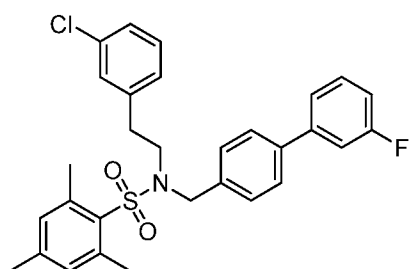
- 20



- The title compound was synthesized following the same general protocol as described in Example 22, Step 3 using 1-bromo-3-(trifluoromethoxy)benzene and *N*-(3-bromophenethyl)-2,4,6-trimethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzenesulfonamide.

Example 30

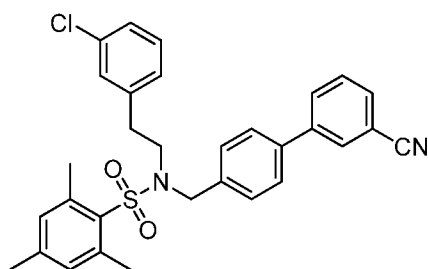
N-(3-Chlorophenethyl)-*N*-((3'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-2,4,6-trimethylbenzenesulfonamide



- The title compound was synthesized following the same general protocol as described in Example 22, Step 3 using 1-bromo-3-fluorobenzene and *N*-(3-bromophenethyl)-2,4,6-trimethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzenesulfonamide.

Example 31

- N*-(3-Chlorophenethyl)-*N*-((3'-cyano-[1,1'-biphenyl]-4-yl)methyl)-2,4,6-trimethylbenzenesulfonamide

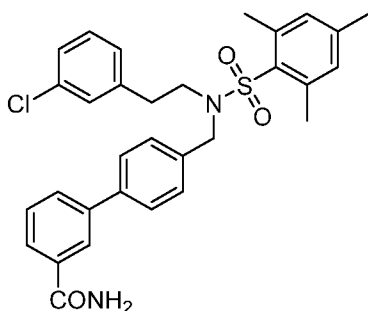


- The title compound was synthesized following the same general protocol as described in Example 22, Step 3 using 3-bromobenzonitrile and *N*-(3-bromophenethyl)-2,4,6-trimethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-

2-yl)benzyl)benzenesulfonamide. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.84 (t, J = 1.8 Hz, 1H), 7.80 (dt, J = 7.9, 1.6 Hz, 1H), 7.63 (dt, J = 7.7, 1.4 Hz, 1H), 7.58 – 7.48 (m, 3H), 7.34 – 7.29 (m, 2H), 7.16 – 7.08 (m, 2H), 6.96 (s, 2H), 6.86 (ddd, J = 8.6, 3.8, 2.0 Hz, 2H), 4.45 (s, 2H), 3.31 (t, J = 7.6 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.61 (s, 6H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 142.9, 141.9, 140.6, 140.3, 138.6, 136.3, 134.3, 132.9, 132.3, 131.5, 131.0, 130.7, 129.9, 129.8, 129.5, 128.7, 127.5, 126.9, 126.8, 118.9, 113.1, 49.9, 46.7, 33.6, 23.0, 21.2. ESI-MS (m/z): 529.17 $[\text{M}+1]^+$.

Example 32

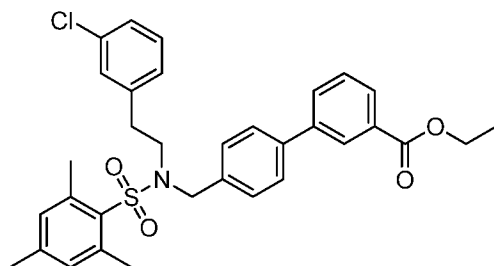
10 4'-((N-(3-Chlorophenethyl)-2,4,6-trimethylphenylsulfonamido)methyl)-[1,1'-biphenyl]-3-carboxamide



N-(3-Chlorophenethyl)-*N*-((3'-cyano-[1,1'-biphenyl]-4-yl)methyl)-2,4,6-trimethylbenzenesulfonamide (15.87 mg, 30 μmol) and KOH (6.74 mg, 120 μmol) was dissolved in isopropanol (2 mL). The mixture was heated under reflux for 18h, cooled to room temperature and saturated NH_4Cl (15 mL) was added to neutralize the solution. The reaction mixture was extracted with ethyl acetate (3×20 mL) and the organic layer was combined and dried over MgSO_4 (anhyd.). The solvent was evaporated and the residue was purified by HPLC to give the product as a white solid (55 %). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.04 (t, J = 1.8 Hz, 1H), 7.81 – 7.71 (m, 2H), 7.62 – 7.48 (m, 3H), 7.30 – 7.26 (m, 2H), 7.18 – 7.07 (m, 2H), 6.96 (br s, 2H), 6.91 – 6.82 (m, 2H), 6.34 (s, 2H), 4.43 (s, 2H), 3.31 (t, J = 7.6 Hz, 2H), 2.72 (t, J = 7.6 Hz, 2H), 2.61 (s, 6H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 170.3, 142.9, 141.4, 140.6, 140.3, 139.8, 135.7, 134.4, 133.4, 133.0, 132.3, 131.1, 129.9, 129.4, 129.4, 128.8, 127.7, 126.9, 126.8, 126.5, 126.3, 49.9, 46.7, 33.7, 29.9, 23.1, 21.2. ESI-MS (m/z): 548 $[\text{M}+1]^+$.

Example 33

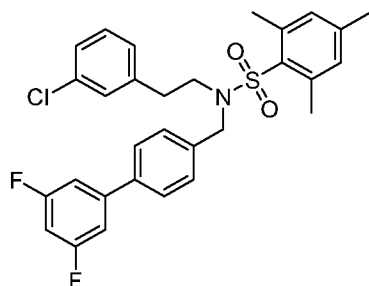
Ethyl 4'-((N-(3-chlorophenethyl)-2,4,6-trimethylphenylsulfonamido)methyl)-[1,1'-biphenyl]-3-carboxylate



The title compound was synthesized following the same general protocol as described in Example 22, Step 3 using ethyl 3-bromobenzoate and *N*-(3-bromophenethyl)-2,4,6-trimethyl-*N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzenesulfonamide.

Example 34

N-(3-Chlorophenethyl)-*N*-((3',5'-difluoro-[1,1'-biphenyl]-4-yl)methyl)-2,4,6-trimethylbenzenesulfonamide



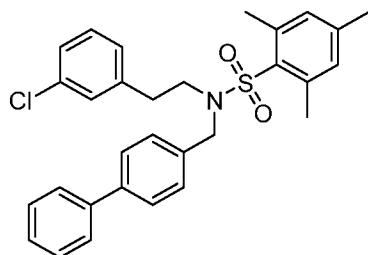
N-(3-Chlorophenethyl)-*N*-(4-iodobenzyl)-2,4,6-trimethylbenzenesulfonamide (1 equiv.), (3,5-difluorophenyl)boronic acid (1.5 equiv.), palladium acetate (0.1 equiv.), and tri-*o*-tolylphosphine (0.2 equiv.) were dissolved in 1,4-dioxane and the solution was degassed with argon for 10 min. K₂CO₃ (2M) was added and the solution was further degassed for additional 5 min. The reaction mixture was heated overnight at 90 °C in an oil bath. After the mixture was cooled to room temperature, it was poured into aq. NaCl (5 %) and extracted with dichloromethane. The combined organics were washed with water, dried over anhydrous MgSO₄ and concentrated in *vacuo*. The remaining crude residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes) to obtain the title compound in 89% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.55 – 7.47 (m, 2H), 7.31 – 7.26 (m, 2H), 7.17 – 7.04 (m, 4H), 6.96 (s, 2H), 6.91 – 6.83 (m, 2H),

6.79 (tt, $J = 8.9, 2.3$ Hz, 1H), 4.43 (s, 2H), 3.31 (t, $J = 7.6$ Hz, 2H), 2.71 (t, $J = 7.6$ Hz, 2H), 2.61 (s, 6H), 2.33 (s, 3H). ESI-MS (m/z): 540 $[M+1]^+$.

Example 35

N-([1,1'-Biphenyl]-4-ylmethyl)-*N*-(3-chlorophenethyl)-2,4,6-

5 trimethylbenzenesulfonamide

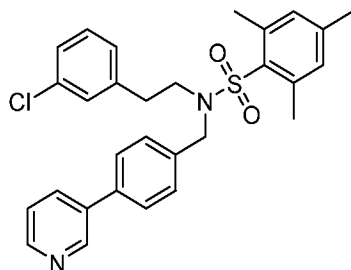


The title compound was synthesized following the same general protocol as described in example 34 using phenylboronic acid and was obtained as white solid (91 %). ^1H NMR (400 MHz, CDCl_3) δ 7.65 – 7.49 (m, 4H), 7.49 – 7.39 (m, 2H), 7.39 – 7.31 (m, 1H), 7.26 – 7.22 (m, 2H), 7.16 – 7.08 (m, 2H), 6.96 (s, 2H), 6.92 – 6.82 (m, 2H), 4.41 (s, 2H), 3.32 (t, $J = 7.6$ Hz, 2H), 2.73 (t, $J = 7.6$ Hz, 2H), 2.62 (s, 6H), 2.32 (s, 3H). ESI-MS (m/z): 504 $[M+1]^+$.

Example 36

N-(3-Chlorophenethyl)-2,4,6-trimethyl-*N*-(4-(pyridin-3-yl)benzyl)benzene-

15 sulfonamide



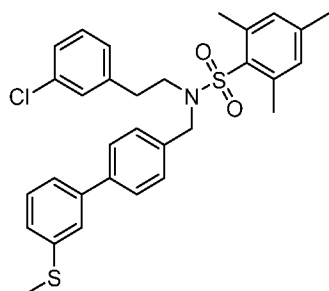
The title compound was synthesized following the same general protocol as described in example 34 using 3-pyridinylboronic acid and was obtained as white solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.83 (d, $J = 2.4$ Hz, 1H), 8.59 (dd, $J = 4.6, 1.7$ Hz, 1H), 7.86 (dt, $J = 8.1, 1.9$ Hz, 1H), 7.60 – 7.48 (m, 2H), 7.36 (dd, $J = 7.9, 4.7$ Hz, 1H), 7.33 – 7.28 (m, 2H), 7.17 – 7.06 (m, 2H), 6.95 (s, 2H), 6.91 – 6.80 (m, 2H), 4.45 (s, 2H), 3.31 (t, $J = 7.6$ Hz, 2H), 2.71 (t, $J = 7.6$ Hz, 2H), 2.61 (s, 6H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 148.68, 148.28, 142.85, 140.55, 140.26, 137.56, 136.11, 135.93, 134.40, 134.30,

132.91, 132.23, 129.82, 129.46, 128.72, 127.54, 126.86, 126.71, 123.70, 49.84, 46.61, 33.57, 23.01, 21.12. ESI-MS (m/z): 505.17 [M+1]⁺.

Example 37

N-(3-Chlorophenethyl)-2,4,6-trimethyl-N-((3'-(methylthio)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

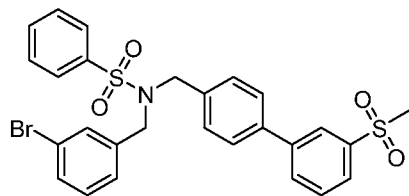
5



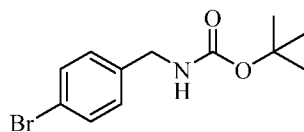
The title compound was synthesized following the same general protocol as described in example 34 using 3-(methylthio)phenylboronic acid and was obtained as white solid (79 %). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.55 – 7.50 (m, 2H), 7.44 (t, *J* = 1.7 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.26 – 7.21 (m, 3H), 7.14 – 7.09 (m, 2H), 6.96 – 6.94 (m, 2H), 6.91 – 6.83 (m, 2H), 4.41 (s, 2H), 3.31 (t, *J* = 7.6 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.61 (s, 6H), 2.53 (s, 3H), 2.33 (s, 3H). ESI-MS (m/z): 550 [M+1]⁺.

Example 38

15 N-(3-Bromobenzyl)-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzene- sulfonamide



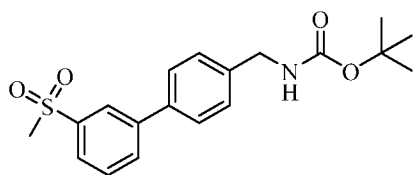
Step 1: tert-Butyl (4-bromobenzyl)carbamate



20 *p*-Bromobenzylamine (0.93 g, 5 mmol) was dissolved in 1,4-dioxane (20 mL) and was treated with 10% aq. NaOH (5 mL). To the stirred solution was added (Boc)₂O (1.1 g, 5 mmol) dissolved in dioxane (10 mL). The mixture was stirred at room temperature for 12 hours. Water was added (20 mL) and the reaction mixture was extracted with ethyl acetate (3 × 50 mL). The organic phase was

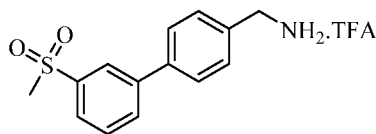
collected, washed with brine, dried over MgSO_4 , filtered, and the solvent was evaporated to give the product as a white solid (1.37 g, 96%). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.44 (d, $J = 8.1$ Hz, 2H), 7.15 (d, $J = 8.0$ Hz, 2H), 4.86 (br s, 1H), 4.26 (d, $J = 6.1$ Hz, 2H), 1.45 (s, 9H). ESI-MS (m/z): 287 $[\text{M}+2]^+$.

5 Step 2: tert-Butyl ((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)carbamate



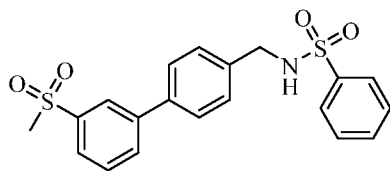
Prepared according to method B using tert-butyl (4-bromobenzyl)carbamate and (3-(methylsulfonyl)phenyl)boronic acid and was obtained as a white solid (91%). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.14 (t, $J = 1.8$ Hz, 1H), 7.91 (ddd, $J = 7.8, 1.8, 1.0$ Hz, 1H), 7.85 (ddd, $J = 7.9, 1.8, 1.1$ Hz, 1H), 7.64 (t, $J = 7.8$ Hz, 1H), 7.60 – 7.55 (m, 2H), 7.43 – 7.36 (m, 2H), 4.94 (br s, 1H), 4.38 (d, $J = 6.0$ Hz, 2H), 3.10 (s, 3H), 1.47 (s, 9H). ESI-MS (m/z): 362 $[\text{M}+1]^+$.

10 Step 3: (3'-(Methylsulfonyl)-[1,1'-biphenyl]-4-yl)methanaminium 2,2,2-trifluoroacetate



15 tert-Butyl ((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)carbamate (0.361 g, 1 mmol) was dissolved in DCM (10 mL) and trifluoroacetic acid (1.53 mL, 20 mmol) was added drop wise and the reaction was stirred for 2h at room temperature. The solvent was evaporated and the residue was triturated with diethyl ether to give the product as a yellowish solid (98 %). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.14 (t, $J = 1.8$ Hz, 1H), 7.95 – 7.82 (m, 3H), 7.67 – 7.54 (m, 4H), 7.50 – 7.37 (m, 3H), 3.93 (s, 2H), 3.08 (s, 3H). ESI-MS (m/z): 262 $[\text{M}+1]^+$.

20 Step 4: N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



25

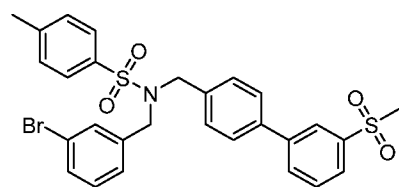
(3'-(Methylsulfonyl)-[1,1'-biphenyl]-4-yl)methanaminium 2,2,2-trifluoroacetate (0.038 g, 0.1 mmol, 1 equiv.) was dissolved in DCM (2 mL), triethyl amine (28 μ L, 0.2 mmol, 2 equiv.) was added at room temperature. The corresponding sulfonyl chloride (0.1 mmol, 1 equiv.) was dissolved in DCM (1 mL) and was added drop wise and the reaction mixture was heated under reflux for 2h. The reaction mixture was cooled, water was added (5 mL) and the mixture was extracted with DCM (4 $\times$ 5 mL). The organic phase was collected, washed with sat. Na₂CO₃ (2 $\times$ 5 mL), brine (1 $\times$ 5 mL), dried over MgSO₄, and the solvent was evaporated to give the intermediate which was used in next step without further purification.

Step 5: N-(3-Bromobenzyl)-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzene- sulfonamide

A mixture of N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide (1 equiv.), K₂CO₃ (2 equiv.), and the corresponding alkyl bromide (1 equiv.) in anhydrous acetonitrile (2 mL) was heated to 85 °C for 2 h under microwave irradiation. The white powder was filtered off, the solvent was evaporated and the mixture was dissolved in ethyl acetate and extracted with brine. The organic phase was separated, dried over anhydrous MgSO₄, filtered and concentrated in *vacuo*. The remaining crude residue was purified by flash chromatography on silica gel (0-100% ethyl acetate/hexanes gradient) to obtain the title compound as white solid (63 %). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.10 (t, *J* = 1.8 Hz, 1H), 7.95 – 7.86 (m, 3H), 7.82 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.60 – 7.52 (m, 2H), 7.49 – 7.42 (m, 2H), 7.31 (ddd, *J* = 7.7, 2.1, 1.3 Hz, 1H), 7.19 – 7.12 (m, 2H), 7.11 – 6.99 (m, 3H), 4.38 (s, 2H), 4.31 (s, 2H), 3.10 (s, 3H). ESI-MS (*m/z*): 571 [M+2]⁺.

Example 39

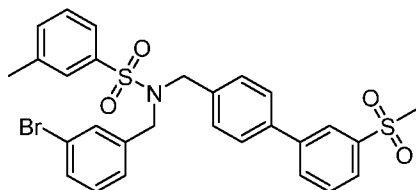
N-(3-Bromobenzyl)-4-methyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)- benzenesulfonamide



The title compound was synthesized following the same general protocol as described in example 38 using 4-methyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide and 3-bromobenzyl bromide and was obtained as white solid (96 %). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.10 (t, *J* = 1.8 Hz, 1H), 7.91 (ddd, *J* = 7.8, 2.0, 1.1 Hz, 1H), 7.82 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.80 – 7.74 (m, 2H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.39 – 7.33 (m, 2H), 7.30 (dt, *J* = 7.7, 1.7 Hz, 1H), 7.21 – 7.14 (m, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.04 – 6.97 (m, 2H), 4.36 (s, 2H), 4.28 (s, 2H), 3.10 (s, 3H), 2.48 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 143.91, 142.30, 141.33, 138.66, 138.18, 137.24, 136.02, 132.30, 131.63, 130.80, 130.08, 130.06, 130.02, 129.44, 127.39, 127.31, 127.26, 126.15, 125.93, 122.55, 51.22, 50.76, 44.69, 21.74. ESI-MS (*m/z*): 585 [M+2]⁺.

Example 40

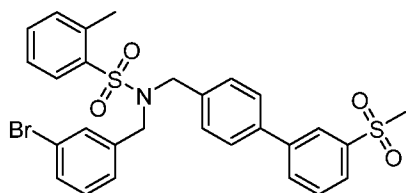
N-(3-Bromobenzyl)-3-methyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)- benzenesulfonamide



The title compound was synthesized following the same general protocol as described in example 38 using 3-methyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide and 3-bromobenzyl bromide and was obtained as white solid (94 %). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.11 (t, *J* = 1.8 Hz, 1H), 7.92 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.83 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.73 – 7.60 (m, 3H), 7.50 – 7.41 (m, 4H), 7.31 (ddd, *J* = 7.8, 2.0, 1.3 Hz, 1H), 7.21 – 7.15 (m, 2H), 7.13 – 7.00 (m, 3H), 4.38 (s, 2H), 4.30 (s, 2H), 3.10 (s, 3H), 2.45 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 142.30, 141.36, 140.12, 139.74, 138.70, 138.17, 135.98, 133.82, 132.30, 131.68, 130.86, 130.08, 130.04, 129.48, 129.32, 127.61, 127.41, 127.27, 126.19, 125.95, 124.43, 122.57, 51.21, 50.76, 44.71, 21.59. ESI-MS (*m/z*): 585 [M+2]⁺.

Example 41

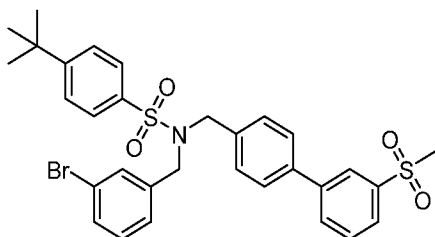
N-(3-Bromobenzyl)-2-methyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)- benzenesulfonamide



The title compound was synthesized following the same general protocol as described in example 38 using 2-methyl-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide and 3-bromobenzyl bromide and was obtained as white solid (75 %). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.13 (t, *J* = 1.7 Hz, 1H), 8.04 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.93 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.85 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.43 – 7.32 (m, 3H), 7.20 – 7.10 (m, 3H), 7.08 – 6.98 (m, 2H), 4.41 (s, 2H), 4.31 (s, 2H), 3.11 (s, 3H), 2.64 (s, 3H). ESI-MS (*m/z*): 585 [M+2]⁺.

10 Example 42

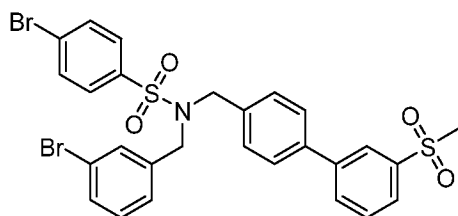
N-(3-Bromobenzyl)-4-(*tert*-butyl)-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



The title compound was synthesized following the same general protocol as described in example 38 using 4-(*tert*-butyl)-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide and 3-bromobenzyl bromide and was obtained as white solid (96 %). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.10 (t, *J* = 1.8 Hz, 1H), 7.91 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.86 – 7.77 (m, 3H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.48 – 7.41 (m, 2H), 7.29 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.09 – 6.98 (m, 3H), 4.38 (s, 2H), 4.30 (s, 2H), 3.10 (s, 3H), 1.37 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 156.9, 142.3, 141.3, 138.6, 138.2, 137.2, 136.1, 132.3, 131.6, 130.8, 130.0, 129.5, 127.4, 127.3, 127.1, 126.4, 126.2, 125.9, 122.5, 51.3, 50.8, 44.7, 35.4, 31.3. ESI-MS (*m/z*): 627 [M+2]⁺.

25 Example 43

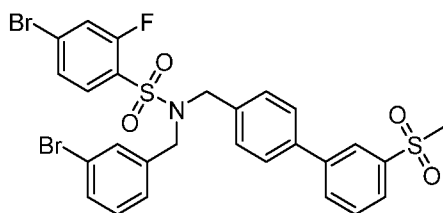
4-Bromo-*N*-(3-bromobenzyl)-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



The title compound was synthesized following the same general protocol as described in example 38 using 4-bromo-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide and 3-bromobenzyl bromide and was obtained as white solid (65 %). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.11 (t, J = 1.7 Hz, 1H), 7.93 (ddd, J = 7.9, 1.9, 1.1 Hz, 1H), 7.83 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.75 – 7.62 (m, 5H), 7.50 – 7.45 (m, 2H), 7.33 (dt, J = 7.8, 1.6 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 7.10 (t, J = 8.0 Hz, 1H), 7.06 – 7.01 (m, 2H), 4.39 (s, 2H), 4.31 (s, 2H), 3.11 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 142.2, 141.4, 139.3, 138.9, 137.8, 135.6, 132.7, 132.3, 131.6, 131.0, 130.7, 130.2, 130.2, 130.1, 130.0, 129.4, 128.7, 128.0, 127.5, 127.2, 126.2, 125.9, 125.4, 122.7, 51.3, 50.8, 44.7. ESI-MS (m/z): 648.94 [M+2]⁺.

Example 44

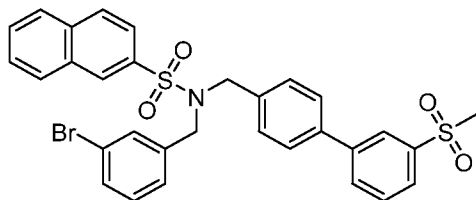
4-Bromo-*N*-(3-bromobenzyl)-2-fluoro-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



The title compound was synthesized following the same general protocol as described in example 38 using 4-bromo-2-fluoro-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide and 3-bromobenzyl bromide and was obtained as white solid (81 %). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.12 (t, J = 1.8 Hz, 1H), 7.93 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.83 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.79 (dd, J = 8.5, 7.5 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.45 – 7.38 (m, 2H), 7.37 – 7.32 (m, 1H), 7.25 – 7.18 (m, 2H), 7.15 – 7.08 (m, 1H), 7.08 – 7.03 (m, 2H), 4.49 (s, 2H), 4.40 (s, 2H), 3.11 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 159.8, 142.2, 141.4, 138.9, 137.7, 135.6, 132.3, 131.8, 131.6, 131.1, 130.2, 130.1, 129.4, 128.2, 128.1, 127.5, 127.2, 126.3, 125.9, 122.7, 121.1, 120.8, 50.7, 50.7, 44.69. ESI-MS (m/z): 666.93 [M+2]⁺.

Example 45

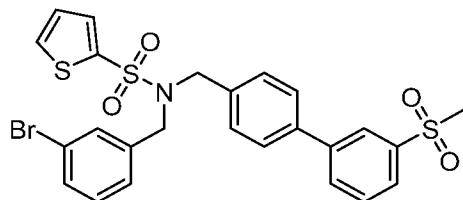
N-(3-Bromobenzyl)-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-naphthalene-2-sulfonamide



- 5 The title compound was synthesized following the same general protocol as described in example 38 using *N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)naphthalene-2-sulfonamide and 3-bromobenzyl bromide and was obtained as white solid (97 %). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.43 (d, *J* = 1.8 Hz, 1H), 8.08 (t, *J* = 1.8 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.96 (dt, *J* = 8.3, 1.5 Hz, 2H), 7.91 (ddd, *J* = 7.7, 1.9, 1.1 Hz, 1H), 7.84 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.79 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.68 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.46 – 7.39 (m, 2H), 7.28 (tt, *J* = 4.2, 2.1 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.07 (ddt, *J* = 9.6, 4.3, 0.9 Hz, 3H), 4.44 (s, 2H), 4.37 (s, 2H), 3.10 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 142.3, 141.4, 138.7, 138.1, 137.0, 135.9, 135.0, 132.4, 132.3, 131.7, 130.9, 130.1, 130.0, 129.8, 129.5, 129.4, 129.1, 128.8, 128.1, 127.9, 127.4, 127.3, 126.2, 125.9, 122.6, 122.5, 100.1, 51.3, 50.9, 44.7. ESI-MS (*m/z*): 621 [M+2]⁺.
- 10
- 15

Example 46

N-(3-Bromobenzyl)-*N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)thiophene-2-sulfonamide



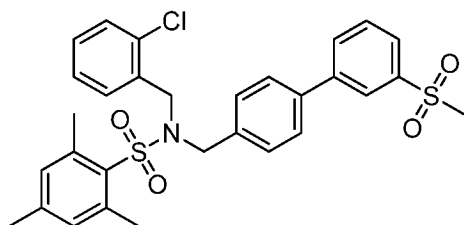
- The title compound was synthesized following the same general protocol as described in example 38 using *N*-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)thiophene-2-sulfonamide and 3-bromobenzyl bromide and was obtained as white solid (73 %). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.11 (t, *J* = 1.8 Hz, 1H), 7.92 (ddd, *J* = 7.7, 1.9, 1.1 Hz, 1H), 7.82 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.68 – 7.61 (m, 3H), 7.50 – 7.43 (m, 2H), 7.32 (dt, *J* = 7.1, 2.0 Hz, 1H),
- 20
- 25

- 7.21 – 7.17 (m, 2H), 7.15 (dd, $J = 5.0, 3.7$ Hz, 1H), 7.12 – 7.10 (m, 1H), 7.10 – 7.03 (m, 2H), 4.39 (s, 2H), 4.32 (s, 2H), 3.10 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 142.2, 141.3, 140.6, 138.8, 137.9, 135.6, 132.3, 132.3, 132.2, 131.7, 130.9, 130.1, 130.0, 129.50, 127.7, 127.4, 127.3, 126.2, 125.9, 122.6, 100.1, 51.6, 51.2, 44.7. ESI-MS (m/z): 576.99 $[\text{M}+2]^+$.

Examples 47-58 are prophetic examples. These exemplary compounds can be synthesized according to procedures described herein in conjunction with ordinary knowledge and skill.

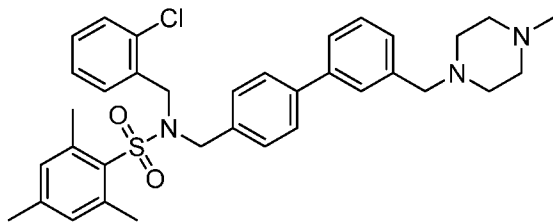
Example 47

- 10 N-(2-chlorobenzyl)-2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



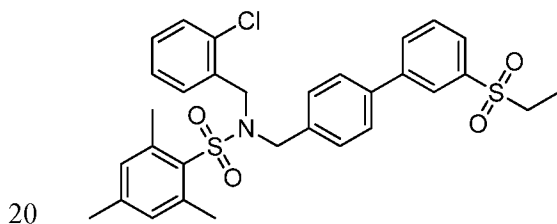
Example 48

- 15 N-(2-chlorobenzyl)-2,4,6-trimethyl-N-((3'-((4-methylpiperazin-1-yl)methyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide



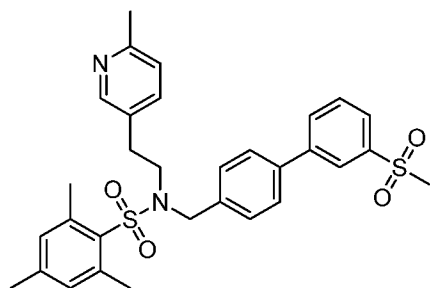
Example 49

- N-(2-chlorobenzyl)-N-((3'-(ethylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-2,4,6-trimethylbenzenesulfonamide

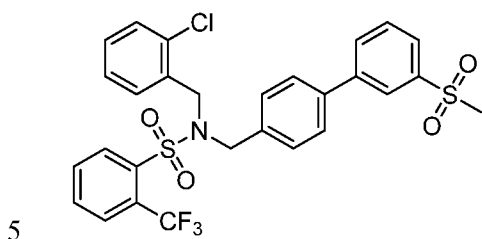


Example 50

- 2,4,6-trimethyl-N-(2-(6-methylpyridin-3-yl)ethyl)-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

Example 51

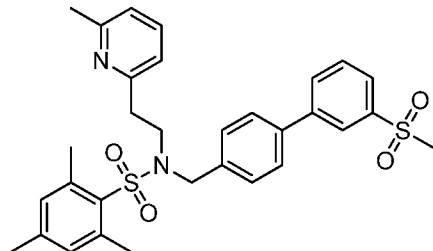
N-(2-chlorobenzyl)-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-2-(trifluoromethyl)benzenesulfonamide



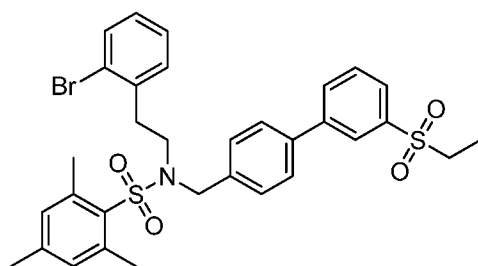
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Example 52

2,4,6-trimethyl-N-(2-(6-methylpyridin-2-yl)ethyl)-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

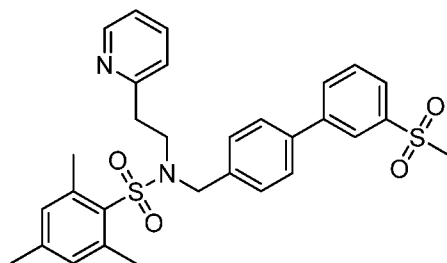


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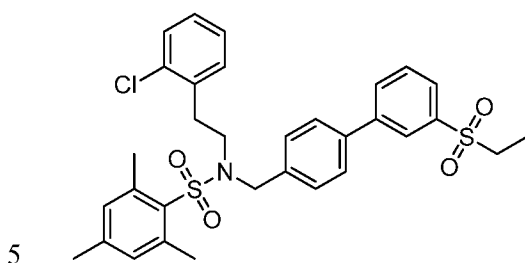
Example 53Example 54

2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(2-(pyridin-2-yl)ethyl)benzenesulfonamide

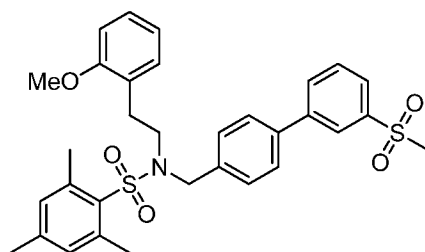
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Example 55

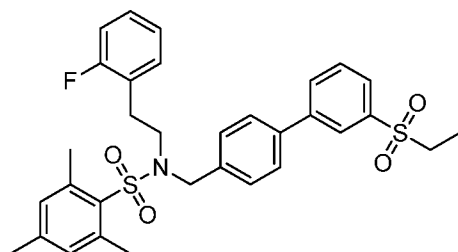
N-(2-chlorophenethyl)-N-((3'-(ethylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-2,4,6-trimethylbenzenesulfonamide

Example 56

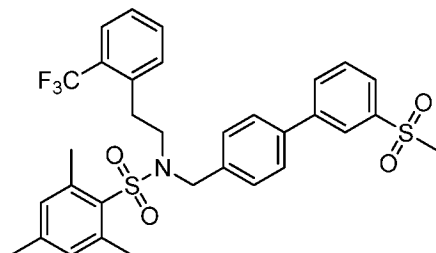
N-(2-methoxyphenethyl)-2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)benzenesulfonamide

10 Example 57

N-((3'-(ethylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(2-fluorophenethyl)-2,4,6-trimethylbenzenesulfonamide

Example 58

2,4,6-trimethyl-N-((3'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)methyl)-N-(2-(trifluoromethyl)phenethyl)benzenesulfonamide



5 Biological Methods

Cell Lines:

HEK293 cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% FBS and antibiotics (penicillin and streptomycin; Invitrogen). HepG2 cells were maintained in minimal essential medium supplemented with 10% FBS and antibiotics.

Transfection Assays:

Twenty-four hours prior to transfection, HEK293 cells were seeded in 96-well plates at density of 15×10^3 cells per well (Day 1). Transfections were performed using Lipofectamine 2000 (Invitrogen; Day 2). Twenty-four hours after the transfection, the cells were treated with vehicle or compound and incubated at 37°C for another twenty-four hours (Day 3). Luciferase activity was measured using the Dual-Glo luciferase assay system (Promega) and analyzed using GraphPad Prism software (Day 4).

Inducing lipogenesis in cultured HepG2 cells:

Cells were seeded at 6×10^4 cells per well in polylysine coated 6-well dishes and allowed to grow to 80% confluency. Once confluency was determined, new media containing 10µg/ml insulin was added to the cells. Cells were grown in the insulin containing media for 8 days, with a media change every two days.

25 *Animals and Preparation of Tissue Samples:*

21-week old male C57BL6 DIO mice were purchased from Jackson Labs. All procedures were approved and conducted in accordance to the Scripps Florida Institutional Animal Use Committee. Animals were individually housed and fed a high fat diet (60% kcal/fat diet, 20% carbohydrate) for the duration of

the experiment that included SR9238 administration for 28 days (30 mg/kg, q.d, i.p.). Prior to initiation of the experiment, animals were provided the high fat diet for 10-weeks. Animals were acclimated to the environment for one week and sham dosed with vehicle for 3 days prior to SR9238 administration. Body weight and food intake was monitored daily. Pre- and post-experiment body composition analysis was performed on all the mice by DEXA. Blood was collected by cardiac puncture and used for plasma cholesterol and triglyceride measurements. Livers were weighed and immediately flash-frozen in liquid nitrogen for gene expression analysis or put in formalin on ice for histology.

10 *Quantitative Real Time PCR:*

RNA was isolated from HepG2 cells using the Qiagen RNeasy kit or from mouse tissues by Trizol preparation (Invitrogen). Total RNA was reverse transcribed using the iScript cDNA kit (BioRad). qRT-PCR analysis was performed using the SYBR green kit (Roche) with a 7900HT Fast Real Time PCR System (Applied Biosystems). Each sample was run in duplicate and the results were analyzed according to the ddCt method. For HepG2 cells, *cyclophilin B* was used as the reference gene. For mouse tissue, *Gapdh* was used as the reference gene.

Primers:

Human

hABCA1 F (SEQ ID NO:1)	5'-AGACGACCACCATGTCAATC-3'
hABCA1 R (SEQ ID NO:2)	5'-CGAATGTCTTTTCCCAGGATG-3'
hcyclophilin F (SEQ ID NO:3)	5'-GCAAATTCCATCGTGTAATCAAG-3'
hcyclophilin R (SEQ ID NO:4)	5'-CGTAGATGCTCTTTCCTCCTG-3'
hFAS F (SEQ ID NO:5)	5'-ACAGGGACAACCTGGAGTTCT-3'
hFAS R (SEQ ID NO:6)	5'-CTGTGGTCCCACTTGATGAGT-3'
hLXRa F (SEQ ID NO:7)	5'-GGAGGTACAACCCTGGGAGT-3'
hLXRa R (SEQ ID NO:8)	5'-AGCAATGAGCAAGGCAAAC-3'
hLXRb F (SEQ ID NO:9)	5'-ATCAAGAGGCCGAGGACCA-3'
hLXRb R (SEQ ID NO:10)	5'-AGGCGAAGACCTGCTCCGAG-3'

hSREBP-1C F (SEQ ID NO:11) 5'-GGAGGGGTAGGGCCAACGGCCT-3'
hSREBP-1C R (SEQ ID NO:12) 5'-CATGTCTTCGAAAGTGCAATCC-3'

Mouse

mABCA1 F (SEQ ID NO:13) 5'-GGACATGCACAAGGTCCTGA-3'
mABCA1 R (SEQ ID NO:14) 5'-CAGAAAATCCTGGAGCTTCAAA-3'

mFASN F (SEQ ID NO:15) 5'-GCACAGCTCTGCACTGTCTACTAC-3'
5'-ATCCCAGAGGAAGTCAGATGATAG-
mFASN R (SEQ ID NO:16) 3'

mGAPDH F (SEQ ID NO:17) 5'-GCCAAGGCTGTGGGCAAGGT-3'
mGAPDH R (SEQ ID NO:18) 5'-TCTCCAGGCGGCACGTCAGA-3'

mIL-1b F (SEQ ID NO:19) 5'-GCAACTGTTCCCTGAACTCA-3'
mIL-1b R (SEQ ID NO:20) 5'-CTCGGAGCCTGTAGTGCAG-3'

mLXRa F (SEQ ID NO:21) 5'-TGCCATCAGCATCTTCTCTG-3'
mLXRa R (SEQ ID NO:22) 5'-GGCTCACCAGCTTCATTAGC-3'

mLXRb F (SEQ ID NO:23) 5'-CGCTACAACCACGAGACAGA-3'
mLXRb R (SEQ ID NO:24) 5'-TGTTGATGGCGATAAGCAAG-3'

mSCD1 F (SEQ ID NO:25) 5'-GGAGACCCCTTAGATCGAGTG-3'
mSCD1 R (SEQ ID NO:26) 5'-CACTCGAATTACTTCCCACCA-3'

mSREBP1c F (SEQ ID NO:27) 5'-TGCTCCTGTGTGATCTACTTCTTG-3'
mSREBP1c R (SEQ ID NO:28) 5'-TGTAGGAATACCCTCCTCATAGCA-3'

mTNFa F (SEQ ID NO:29) 5'-TCAGCCGATTTGCTATCTCAT-3'
mTNFa R (SEQ ID NO:30) 5'-TGGAAGACTCCTCCCAGGTAT-3'

Histology:

Liver from DIO mice was allowed to fix overnight at 4°C in formalin, and then stored in 20% sucrose in PBS solution at 4°C until cryoprotected. The tissues were then embedded in OCT compound and snap frozen on 100% ethanol with dry ice prior to sectioning. Ten µm sections were stained with
5 2µg/ml Bodipy 493/503 (Molecular Probes) in 1X PBS and counterstained with 1.5µg/ml DAPI in mounting media (Vector Laboratories).

Biochemical NR – Cofactor Peptide Interaction Assay (TR-FRET) Assay:

Purified human LXRα-LBD (GST), LXRβ-LBD (GST), fluorescein (FL)-labeled peptides, terbium (TB)-labeled anti-GST tag antibody, and all
10 buffers were purchased from Invitrogen. All LXR assays were conducted in 384-well black medium-binding polystyrene assay plates (Greiner Bio-One). Test compound stock solutions and subsequent serial dilutions were prepared at 100X the final concentration in DMSO, and then were diluted to the final assay concentration of 2X in assay buffer and dispensed into assay plates. LXR-LBDs
15 were added to assay plates and then a mixture of FL-peptide/TB-anti-GST was added to each well containing either a test compound or DMSO control for final concentrations of 2.5nM LXRα-LBD, 5nM LXRβ-LBD, 10nM TB-anti-GST, and 250nM FL-peptide. Assay plates were protected from light and incubated with gentle shaking for 3.5 hours at room temperature. The TR-FRET ratio
20 (520nm/492nm) of each assay well was measured using the Perkin Elmer EnVision plate reader. An excitation filter at 340nm was used to excite the TB-anti-GST and emission filters 492nm and 520nm were used to detect terbium and fluorescein emission signals respectively. A delay of 100µs followed by a 200µs integration time was used to collect the time-resolved emission signals.

25

Table 1: Biodata for Compounds of the Invention

Table 1. Structure Activity Relationships

Example	¹ Max Inh LXR α	² IC ₅₀ (μ M) LXR α	² IC ₅₀ (μ M) LXR β	Example	¹ Max Inh LXR α	² IC ₅₀ (μ M) LXR α	² IC ₅₀ (μ M) LXR β
1	0.7	0.32	0.13	24		0.94	0.55
2		1.9	1.2	25		5.6	5.3
3		0.12	0.02	31		>3	1.2
7	0.9			32		3.5	>5
8	1.2			34		-	0.28
9	0.37	0.21	0.044	35		3.0	
10	0.8			36		1.6	1.4
11	0.8			39		0.008	-
12	0.6			45		1.0	0.39
13	0.8						
14	1.0						
15	0.5	0.29	0.10				
16	0.6	0.11	0.099				
17	0.5	0.34	0.24				
19	0.7	0.025	0.078				
21	0.6	0.06	0.07				
22		0.50	0.48				
23		8.6	4.2				

¹Results are the average of two or more experiments. Value = fold change relative to DMSO control at 1 μ M compound (DMSO normalized to 1); ² Full length LXR receptor and luciferase reporter driven by LXRE promoter.

Evaluations

It is within ordinary skill to evaluate any compound disclosed and
 5 claimed herein for effectiveness in inhibition of LXR and in the various cellular
 assays using the procedures described above or found in the scientific literature.
 Accordingly, the person of ordinary skill can prepare and evaluate any of the
 claimed compounds without undue experimentation.

Any compound found to be an effective inhibitor of LXR can likewise be
 10 tested in animal models and in human clinical studies using the skill and
 experience of the investigator to guide the selection of dosages and treatment
 regimens.

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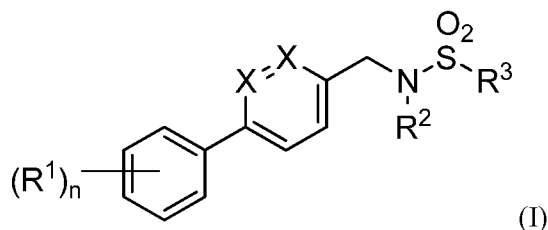
5 All patents and publications referred to herein are incorporated by reference herein to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

10 The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the
15 concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

CLAIMS

What is claimed is:

1. A compound of formula (I):



R^1 is (C1-C6)alkyl, (C3-C10)cycloalkyl, (C1-C6)alkoxy, halo, halo(C1-C6)alkyl, halo(C1-C6)alkoxy, cyano, nitro, OR, $RS(O)_q$, CO_2R , $CONR_2$, $OC(O)NR_2$, $N(R)C(O)NR_2$, (C1-C6)alkyl SO_2 , (C1-C6)alkyl $N(R)SO_2$, (C6-C10)aryl SO_2 , (C6-C10)aryl $N(R)SO_2$, 3-10 membered heterocyclyl, 3-10 membered heterocyclyl(C1-C6)alkyl, N-bonded tetrazolyl, or C-bonded tetrazolyl; wherein the ring bearing R^1 can comprise 0, 1, or 2 nitrogen atoms, provided that the nitrogen atom is not substituted with R^1 ;

$n = 1, 2, \text{ or } 3$; $q = 0, 1, \text{ or } 2$;

R^2 is (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-C10)cycloalkyl, (C1-C6)alkyl $C(=O)O$ (C1-C6)alkyl, (C6-C10)aryl(C1-C6)alkyl $C(=O)O$ (C1-C6)alkyl, (C6-C10)aryl(C1-C6)alkyl $OC(=O)$ (C1-C6)alkyl, (C6-C10)aryl, (C6-C10)aryl(C1-C6)alkyl, (3- to 10-membered)heterocyclyl, (3- to 10-membered)heterocyclyl(C1-C6)alkyl, (5- to 10-membered)heteroaryl, or (5- to 10-membered)heteroaryl(C1-C6)alkyl, wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl moiety of any R^2 group is substituted with 0-3 J groups;

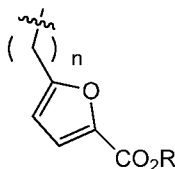
R^3 is (C6-C10)aryl, (C1-C6)alkyl, (C6-C10)aryl(C1-C6)alkyl, (5- to 10-membered)heteroaryl, or (5- to 10-membered)heteroaryl(C1-C6)alkyl; wherein any alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl moiety of any R^3 group is substituted with 0-3 J groups;

R is independently at each occurrence H, (C1-C6)alkyl, halo(C1-C6)alkyl, (C3-C10)cycloalkyl, (C3-C10)cycloalkyl(C1-C6)alkyl, (C6-C10)aryl, (C6-C10)aryl(C1-C6)alkyl, (3- to 10-membered)heterocyclyl, (3- to 10-membered)heterocyclyl(C1-C6)alkyl, (5- to 10-membered)heteroaryl, or (5- to 10-membered)heteroaryl(C1-C6)alkyl; and,

J is (C1-C6)alkyl, (C3-C10)cycloalkyl, (C6-C10)aryl, (3- to 10-membered)heterocyclyl, (5- to 10-membered)heteroaryl, halo, halo(C1-C6)alkyl, halo((C1-C6)alkoxy, nitro, cyano, OR, RS(O)_q, NR₂, C(O)OR, C(O)NR₂, OC(O)OR, OC(O)NR₂, N(R)C(O)OR, or N(R)C(O)NR₂ or a thio/thiono analog thereof;

each X is independently CH or N, provided that only one X is N;
or any salt thereof.

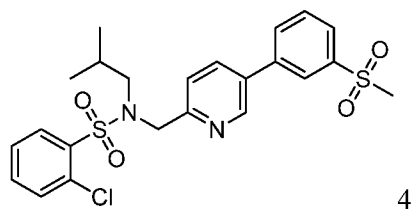
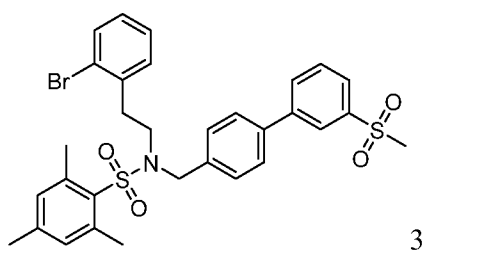
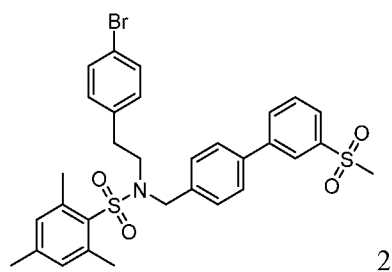
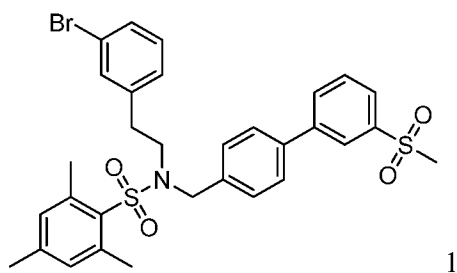
2. The compound of claim 1 wherein R¹ is (C1-C6)alkylSO₂, (C1-C6)alkylNRSO₂, (C6-C10)arylSO₂, or (C6-C10)arylNRSO₂.
3. The compound of claim 2 wherein R¹ is methanesulfonyl.
4. The compound of claim 1 wherein n=1 and the R¹ is disposed *meta* to the biphenyl bond.
5. The compound of claim 1, wherein R² is (C6-C10)aryl(C1-C6)alkyl or (5- to 10-membered)heteroaryl(C1-C6)alkyl, wherein any alkyl, aryl or heteroaryl moiety of any R² group is substituted with 0-3 J groups.
6. The compound of claim 5, wherein R² is a furanylalkyl group, wherein the furanylalkyl is substituted with 0-3 J groups.
7. The compound of claim 6, wherein R² is of formula

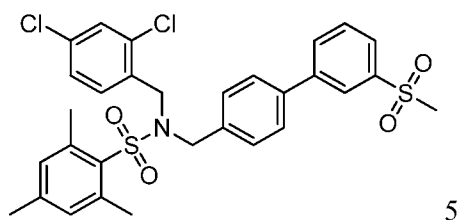


wherein R is alkyl, n = 0, 1, 2, 3, or 4, and a wavy line indicates a point of bonding.

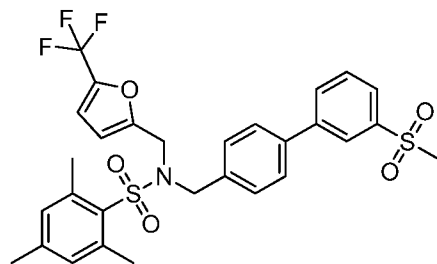
8. The compound of claim 1 wherein R³ is aryl, substituted with 0-3 J.
9. The compound of claim 1 wherein R³ is mesityl.

10. The compound of claim 1, wherein the compound is any one of:

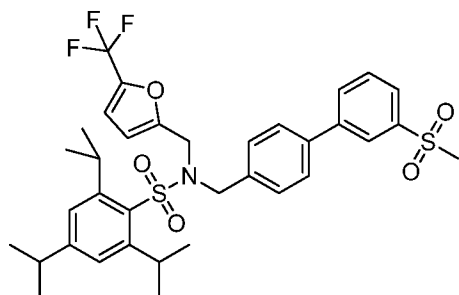




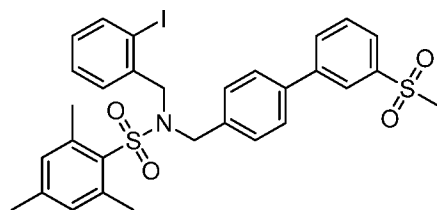
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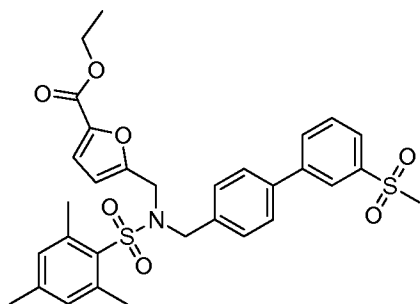
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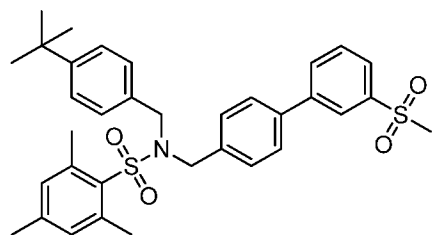
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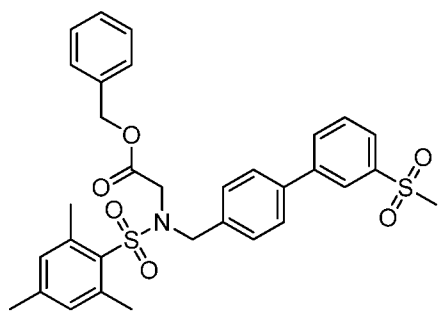
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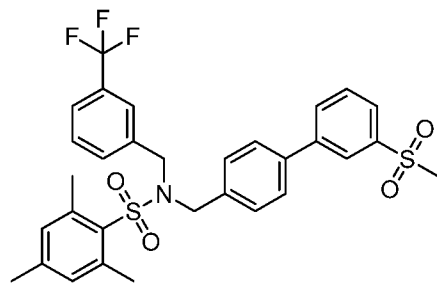
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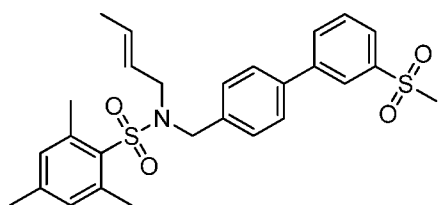
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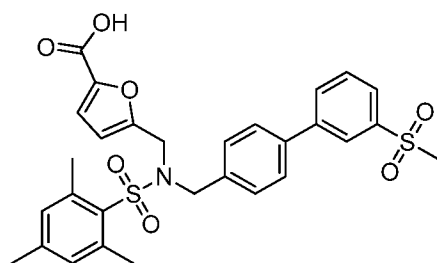
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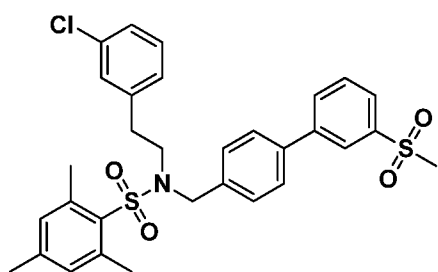
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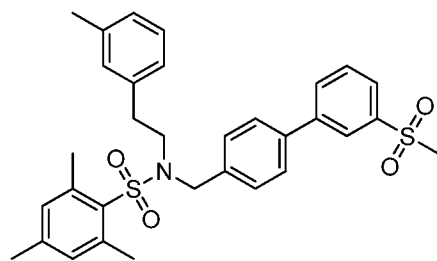
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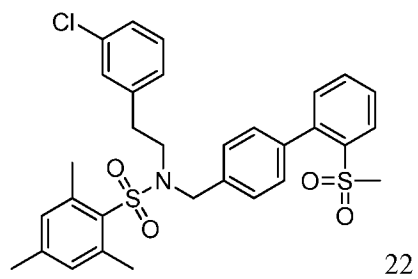
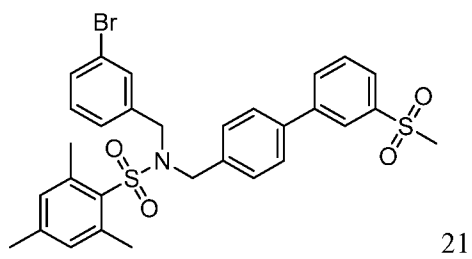
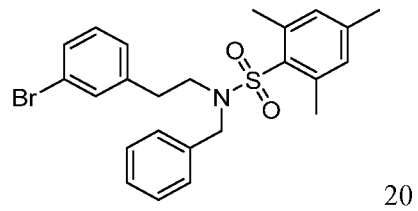
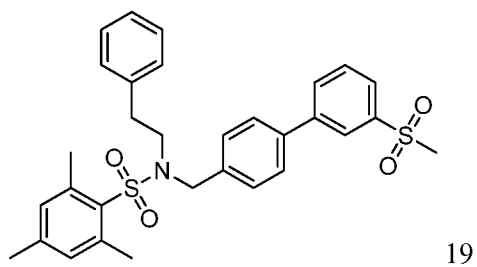
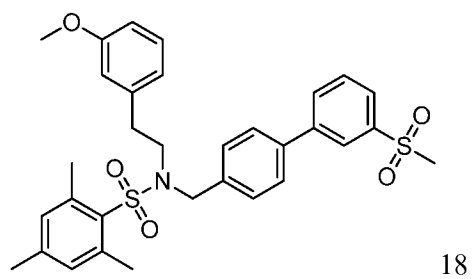
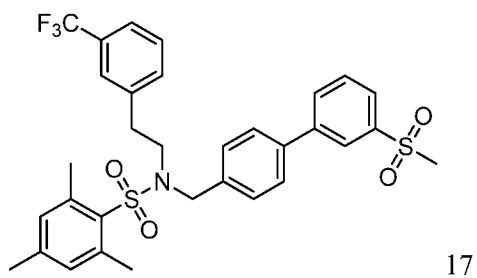
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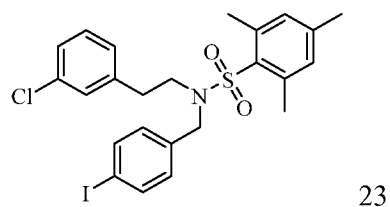


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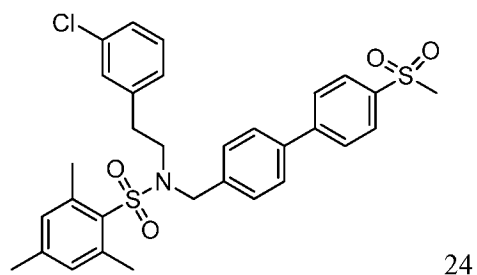


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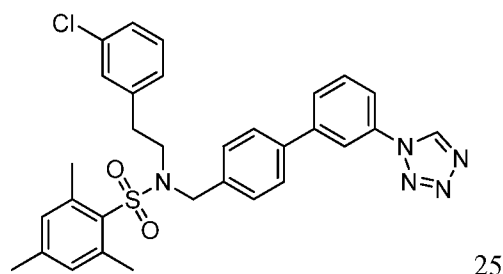




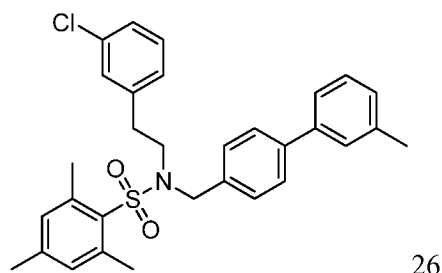
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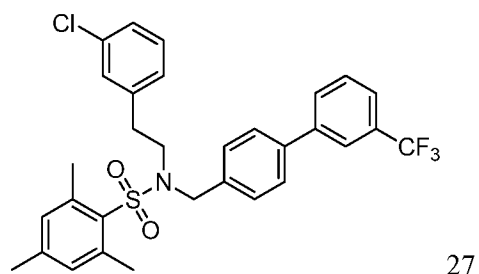
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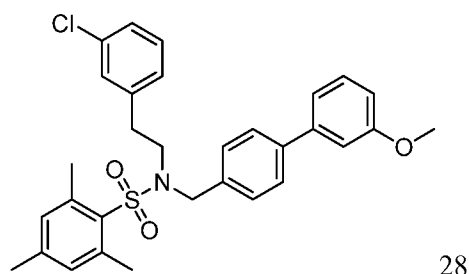
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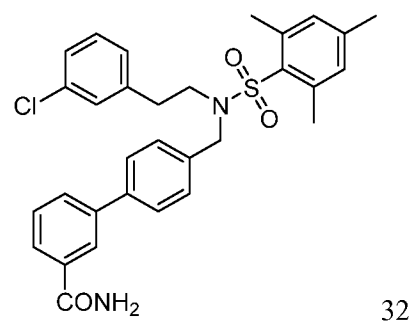
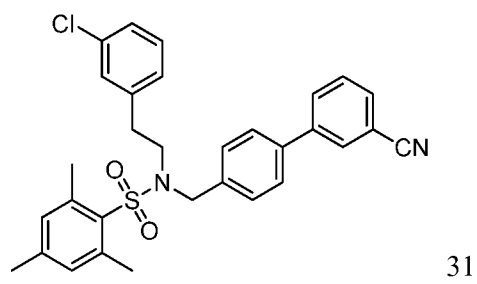
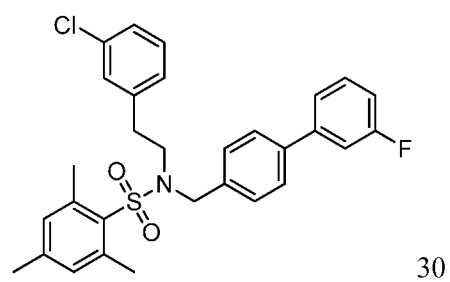
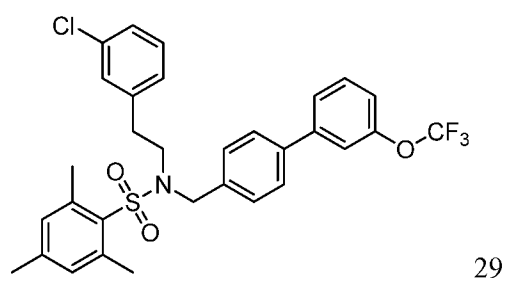
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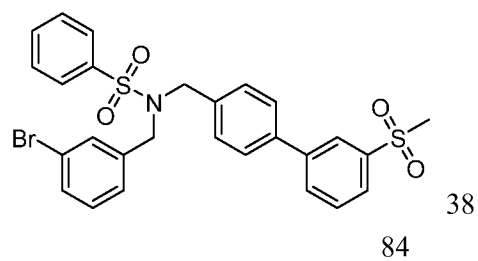
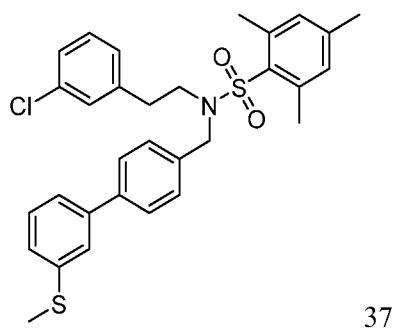
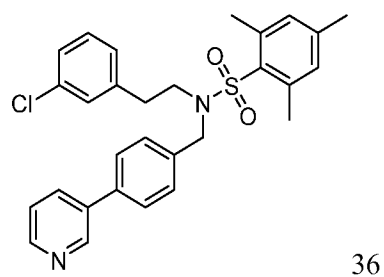
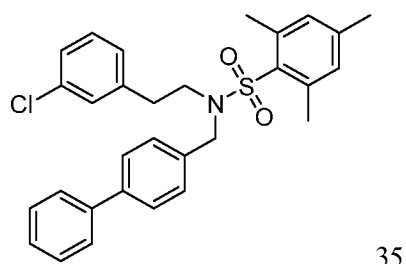
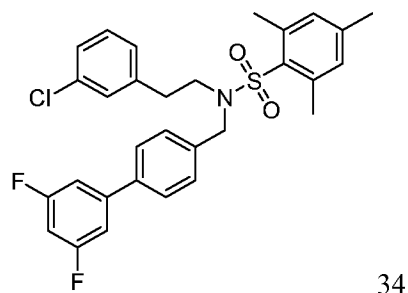
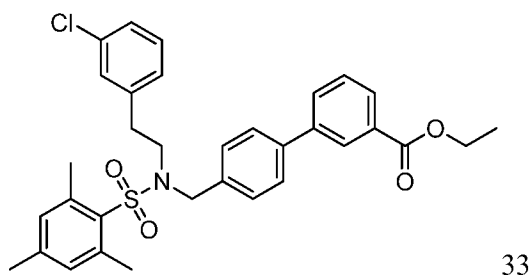


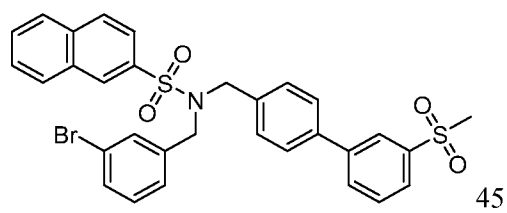
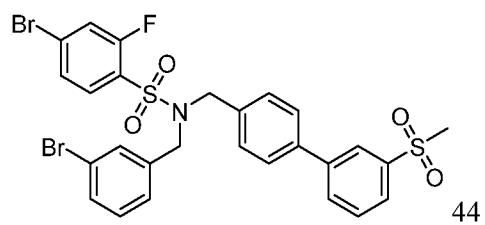
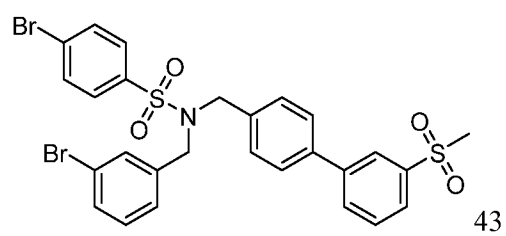
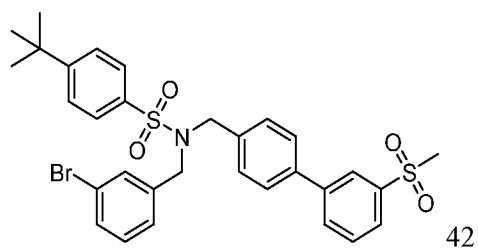
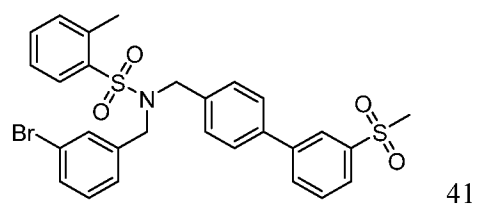
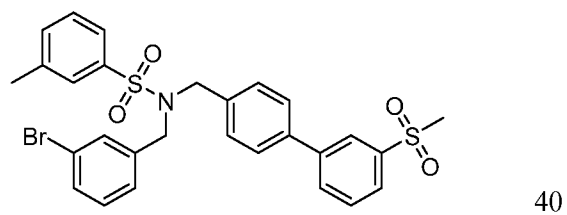
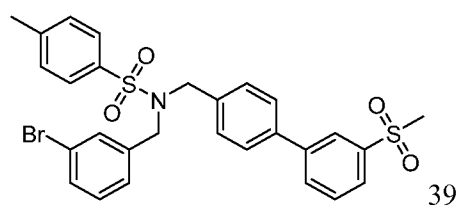
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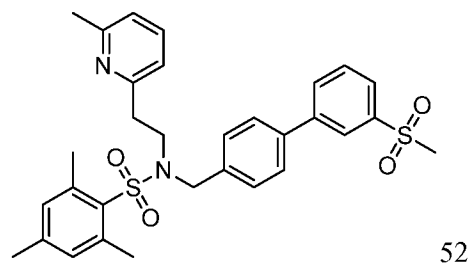
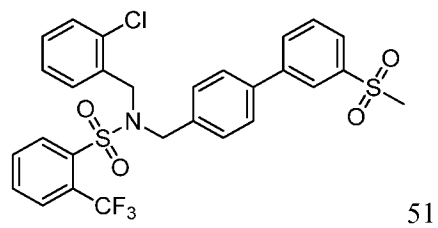
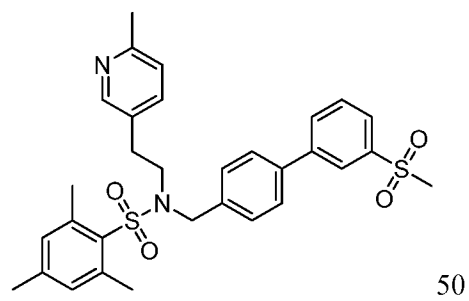
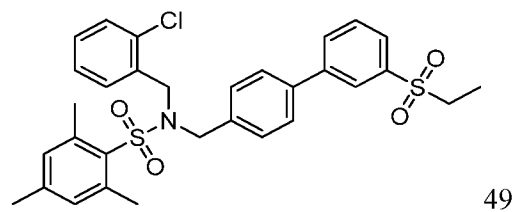
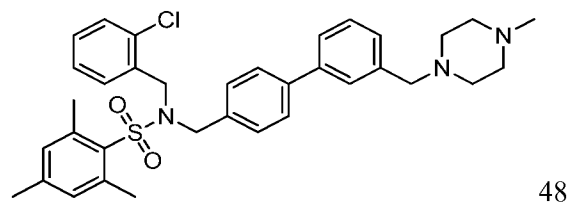
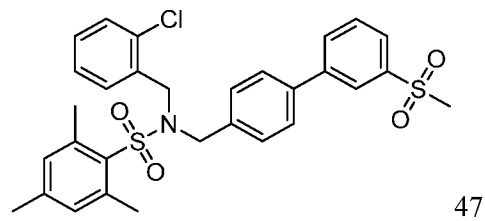
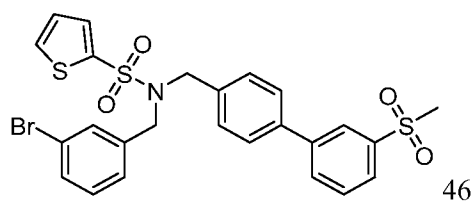


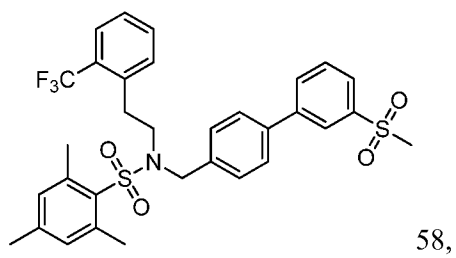
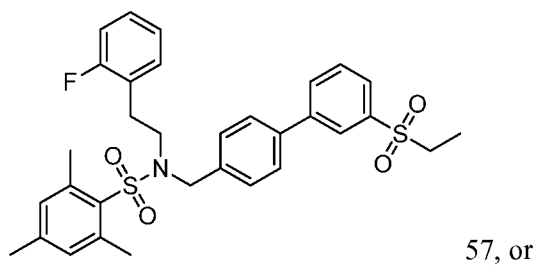
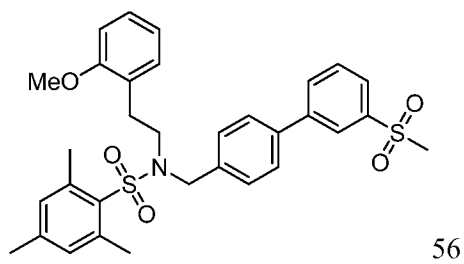
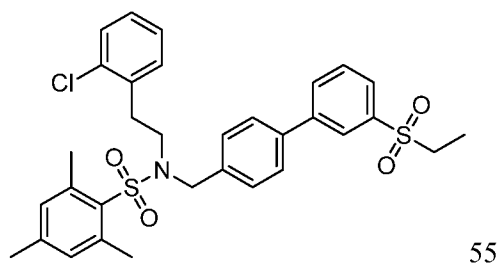
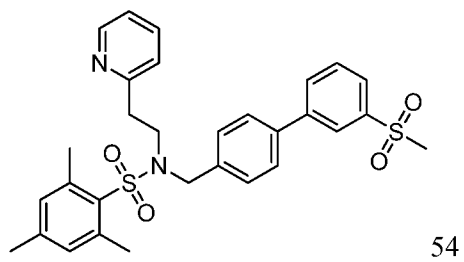
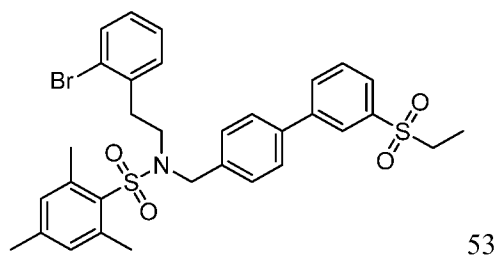
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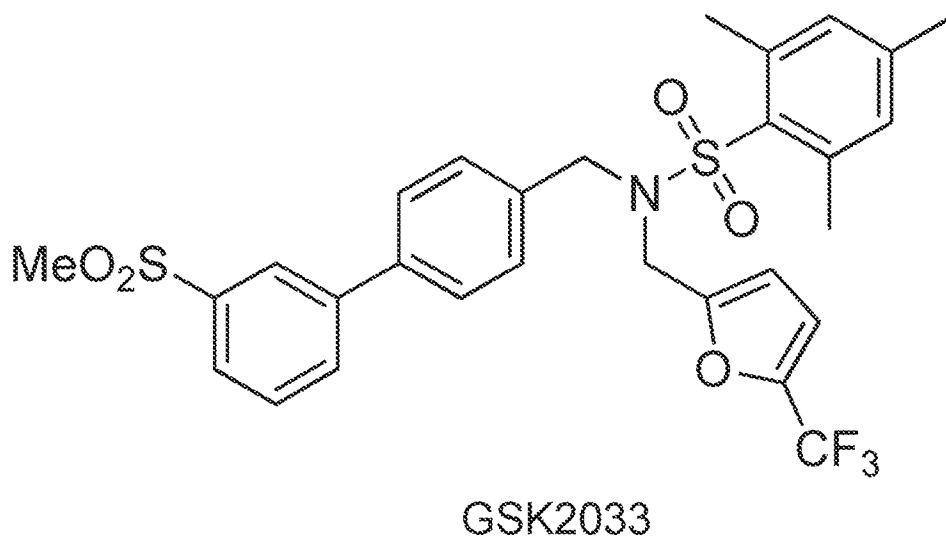
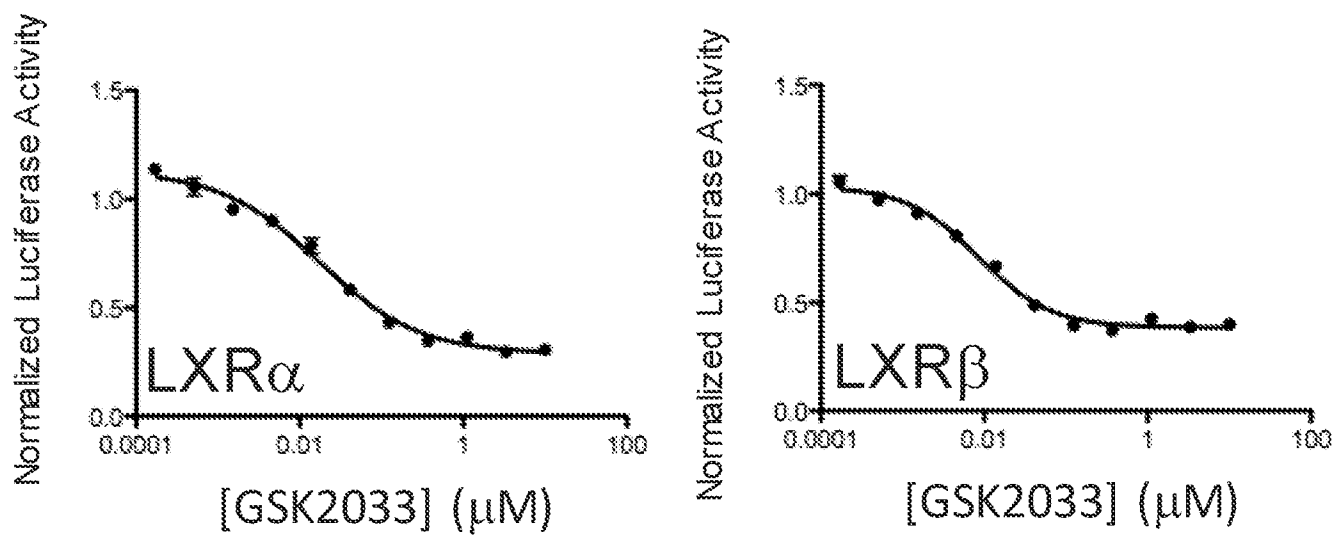




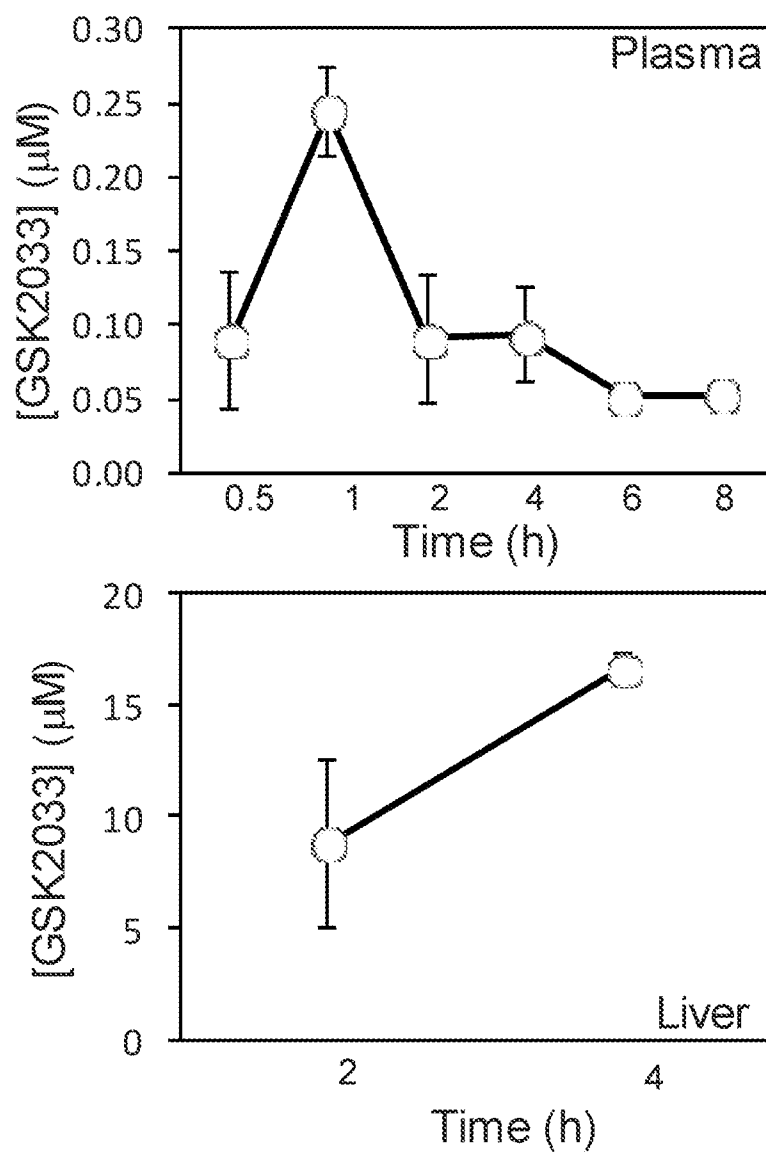
or any salt thereof.

11. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient.
12. A method of exerting an inverse agonistic effect on a Liver X receptor, comprising contacting the receptor with an effective amount or concentration of the compound of formula (I) of claim 1.
13. A method to suppress hepatic lipogenesis, inflammation, or hepatic lipid accumulation in a mammal, comprising administering to the mammal an effective amount of the compound of formula (I) of claim 1.
14. A method of treatment of any of the following disorders: non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, obesity, insulin resistance, and metabolic syndrome, in a patient afflicted therewith, comprising administering to the patient an effective amount of the compound of formula (I) of claim 1.
15. A method of treatment of cancer in a patient afflicted therewith, comprising administering to the patient an effective amount of the compound of formula (I) of claim 1.

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*Fig. 1A**Fig. 1B*

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*Fig. 1C*

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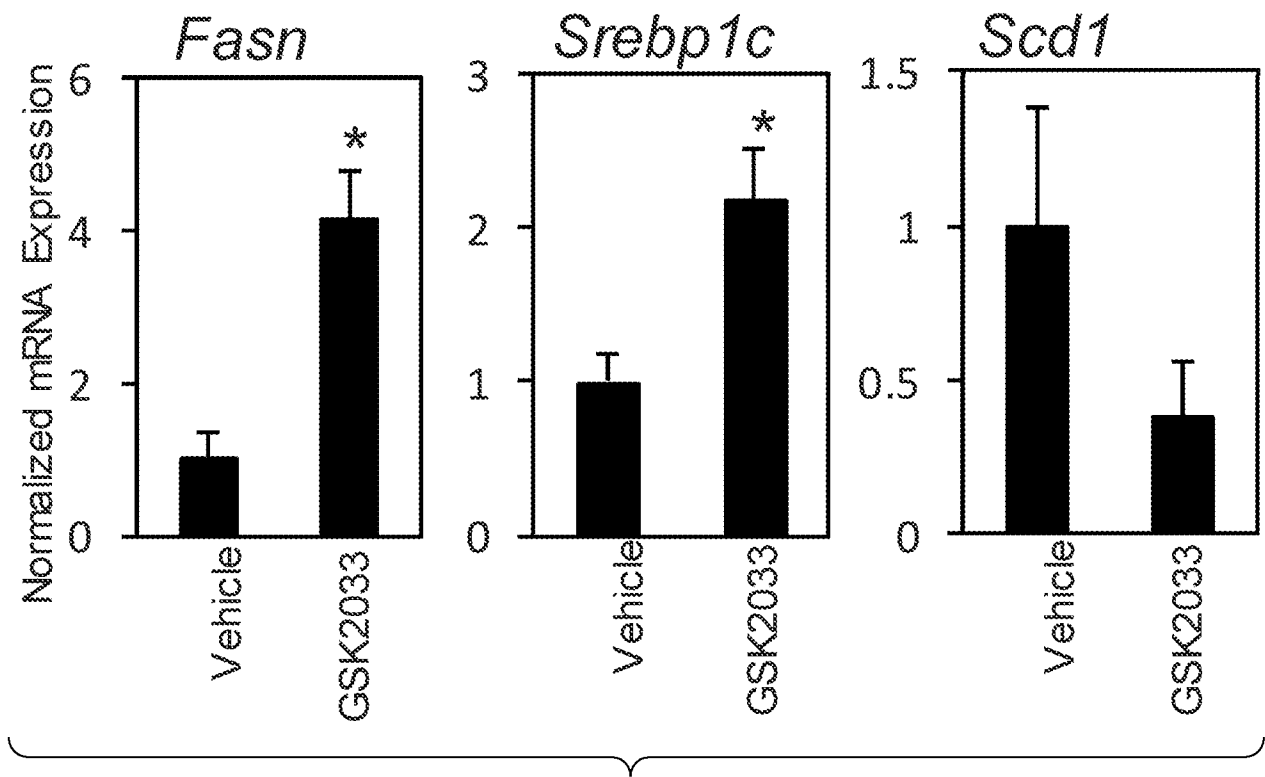


Fig. 1D

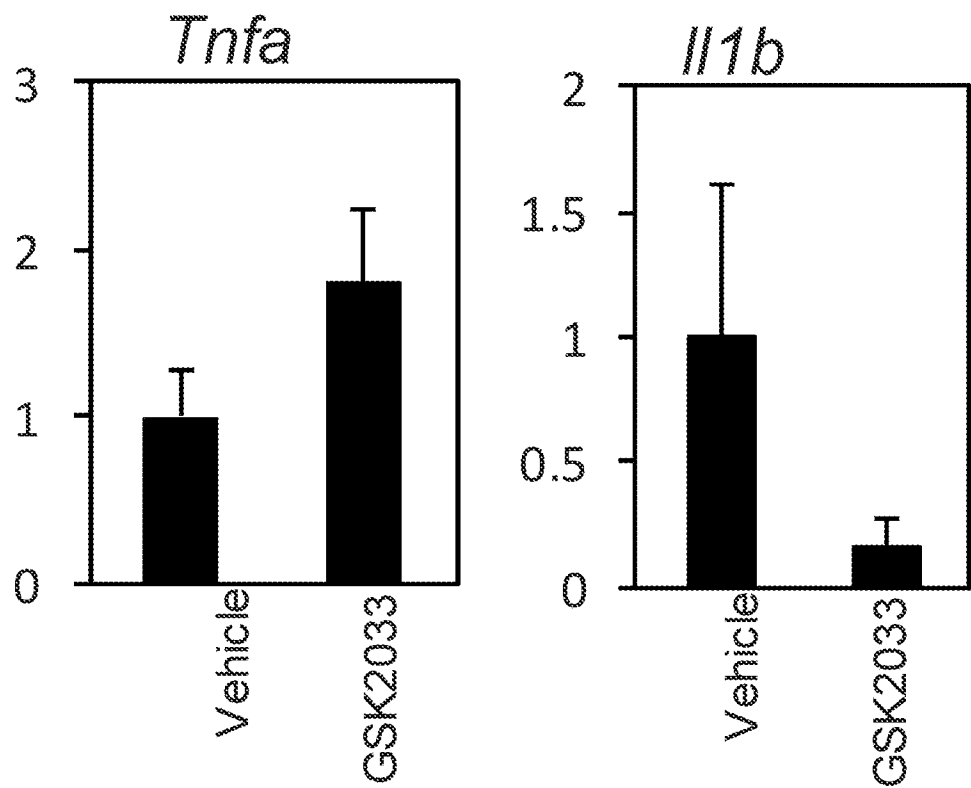


Fig. 1E

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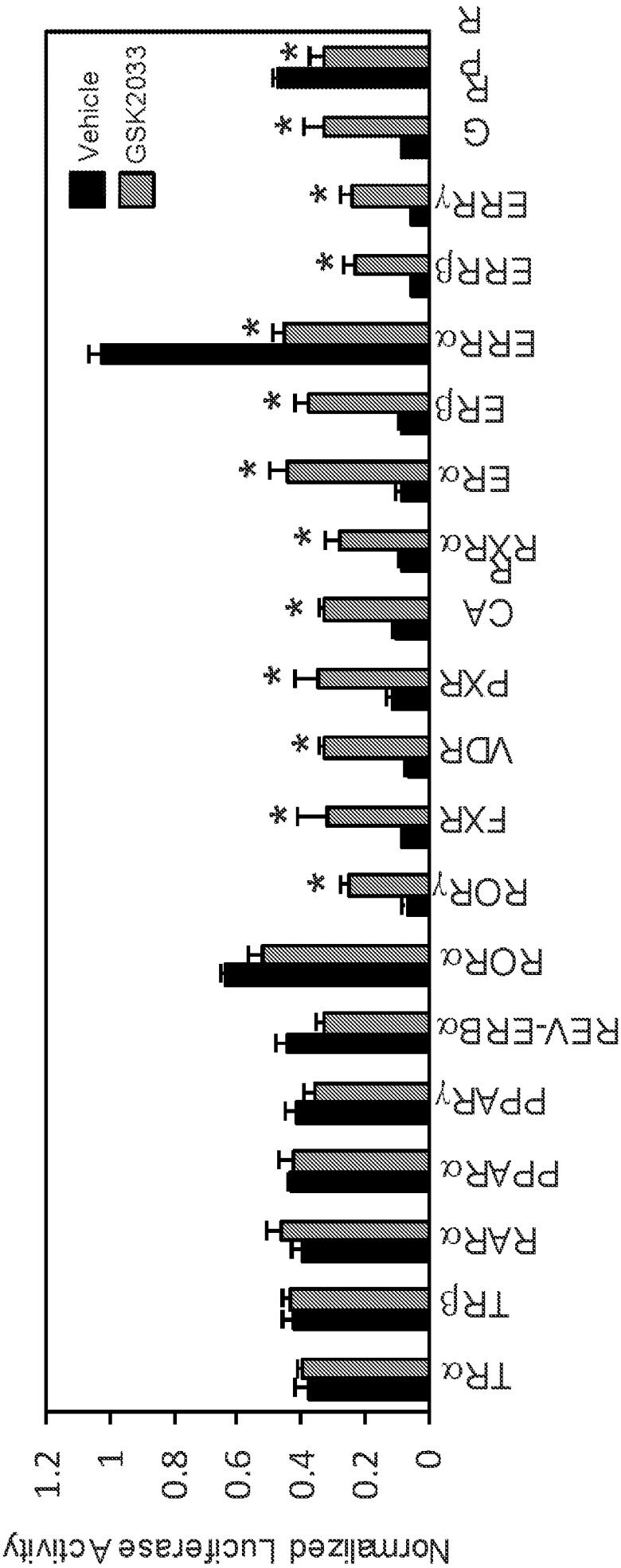
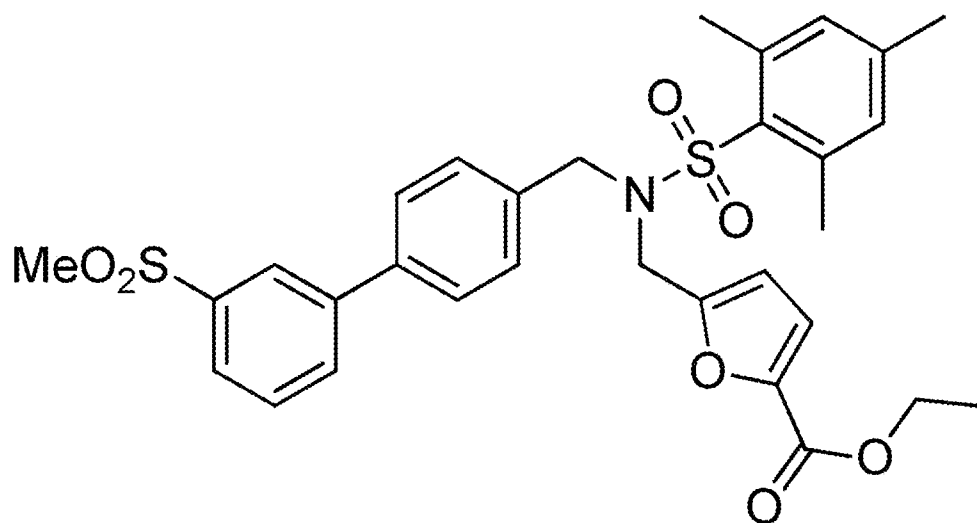
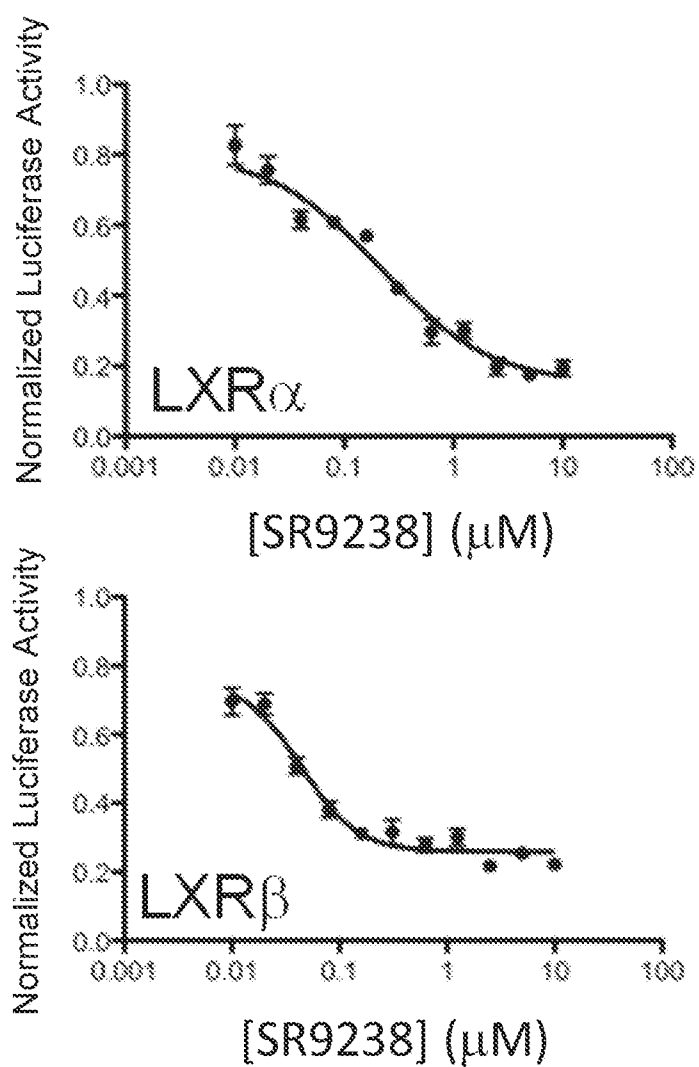


Fig. 1F

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*Fig. 2A**Fig. 2B*

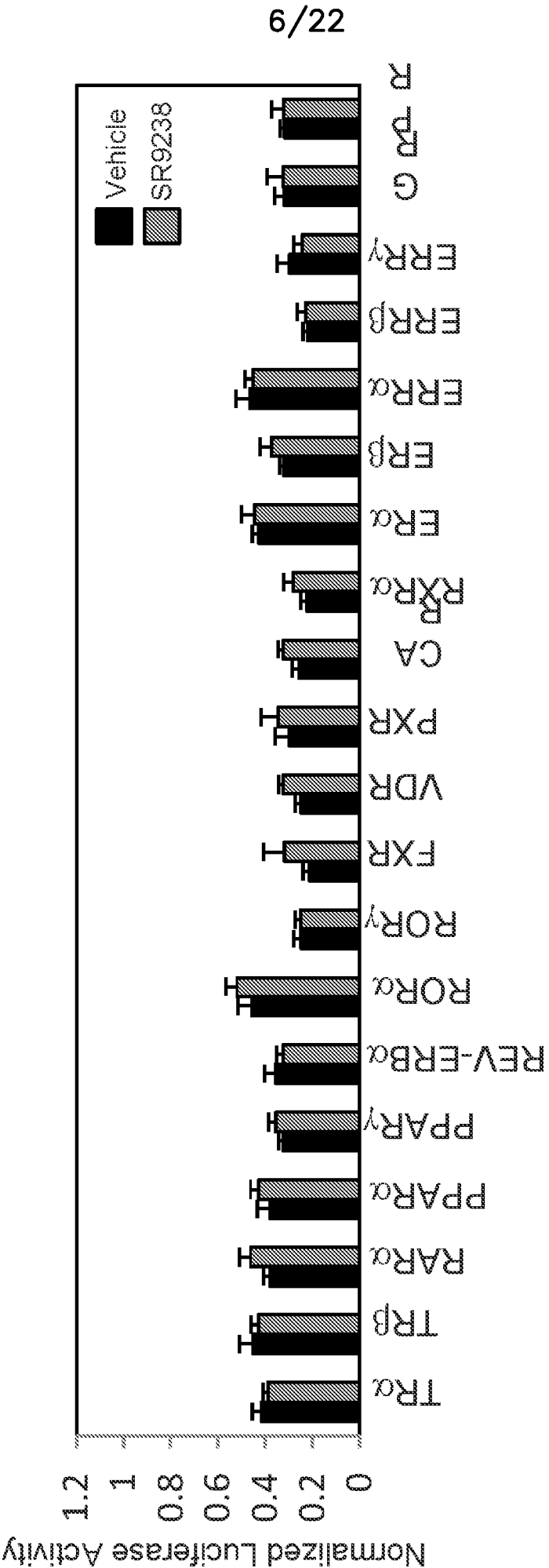
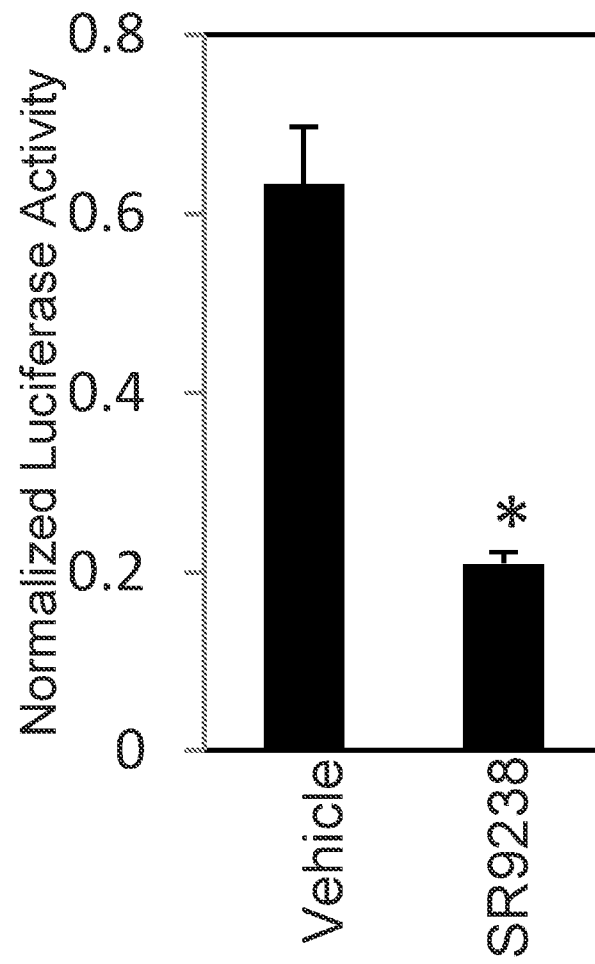


Fig. 2C

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*Fig. 2D*

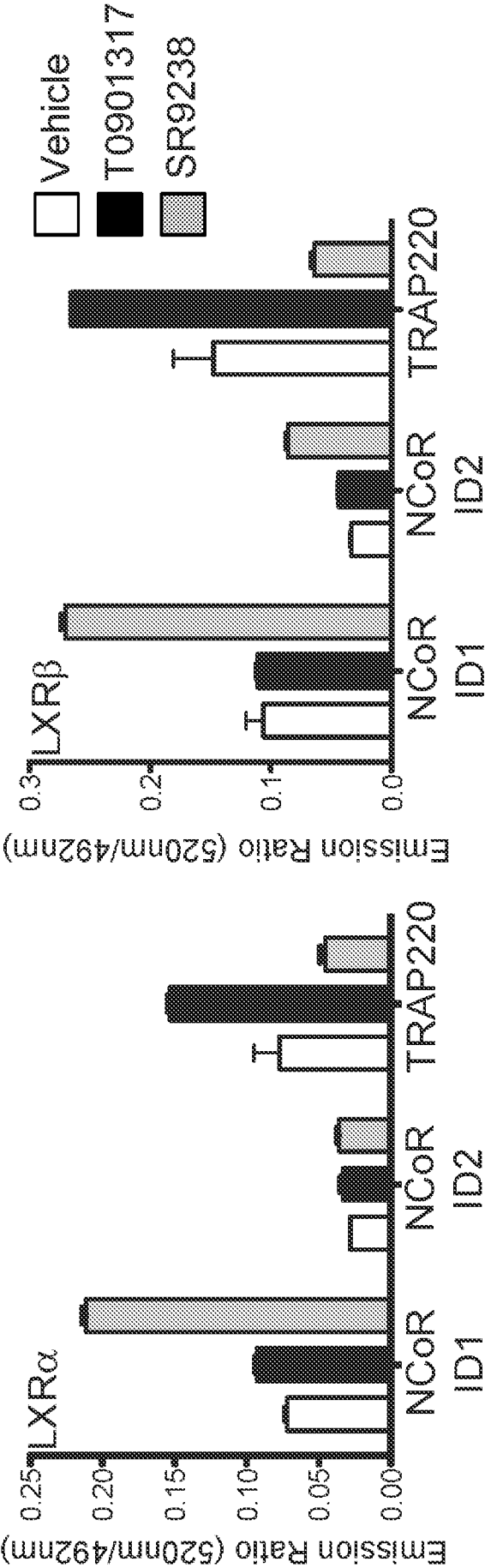


Fig. 2E

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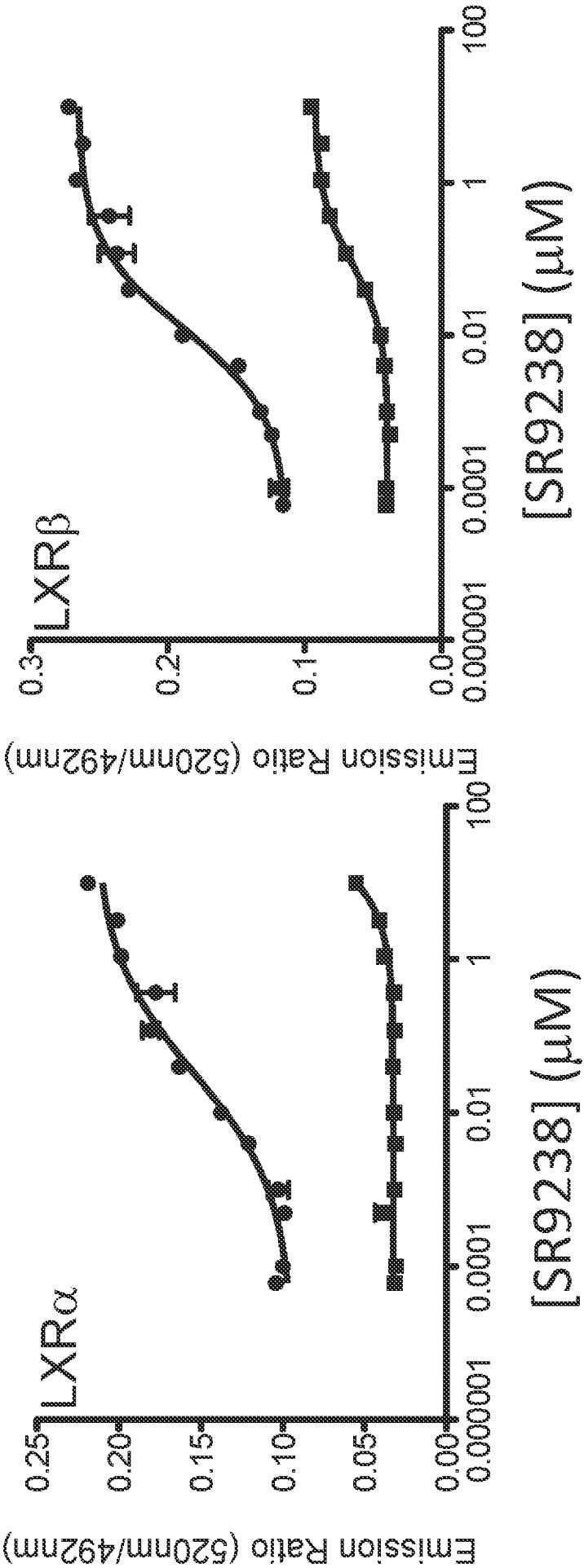
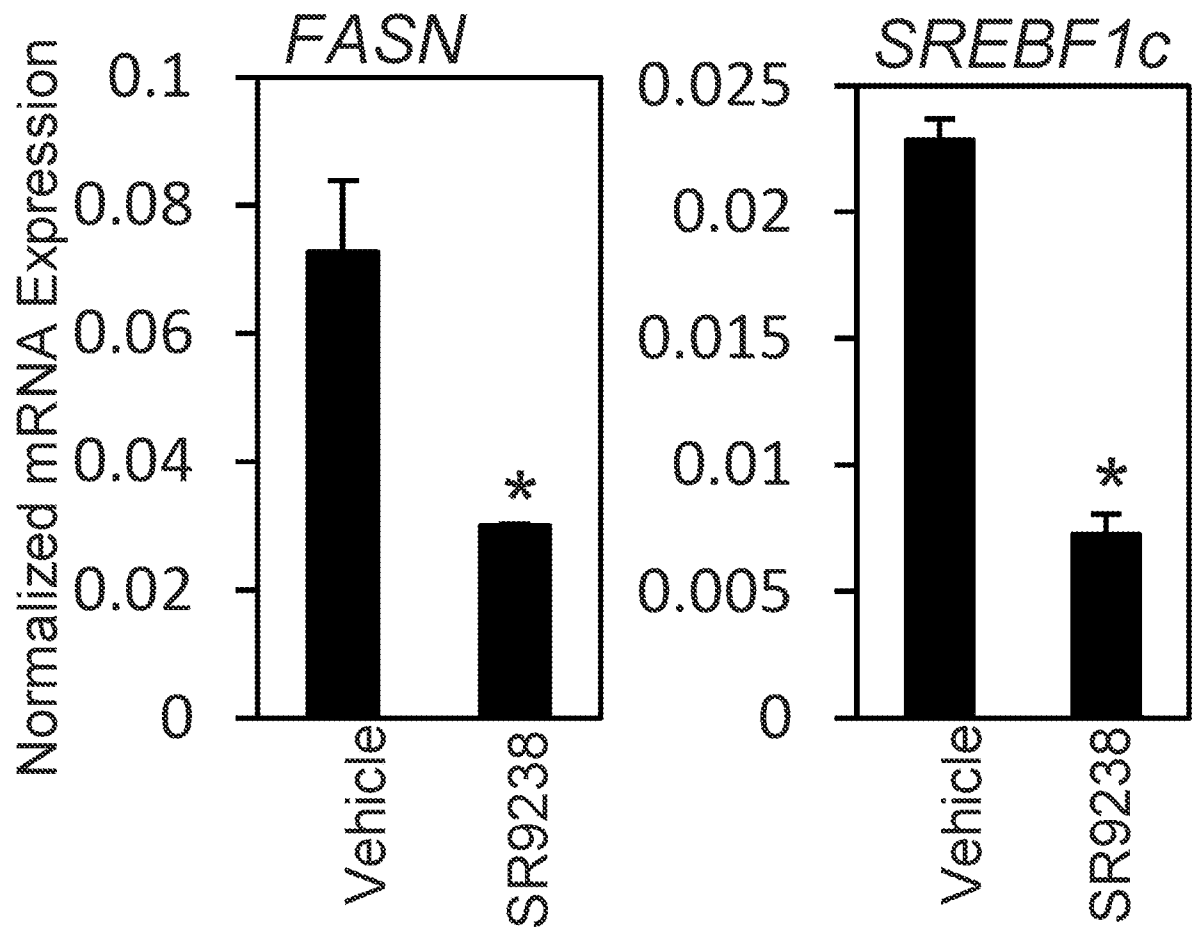
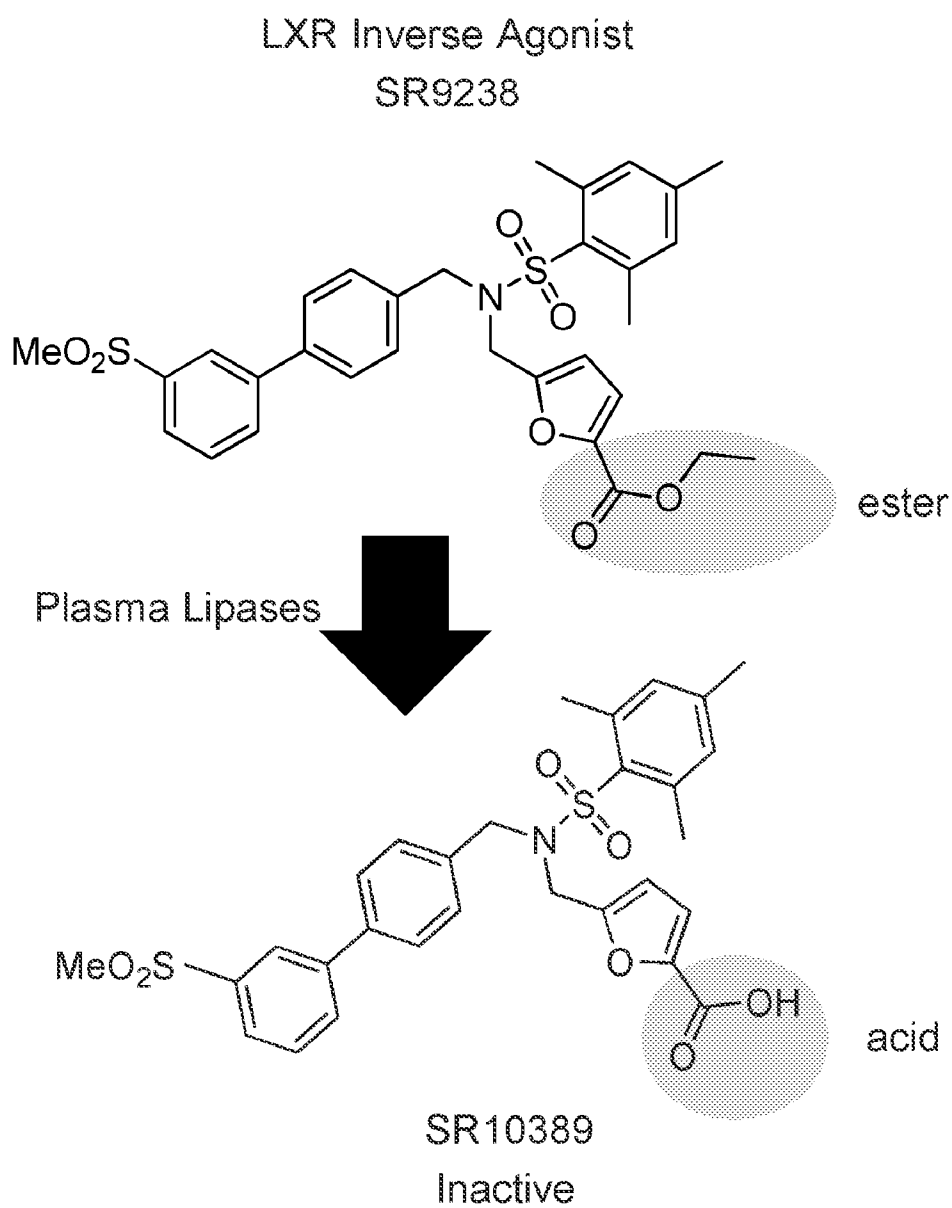


Fig. 2F

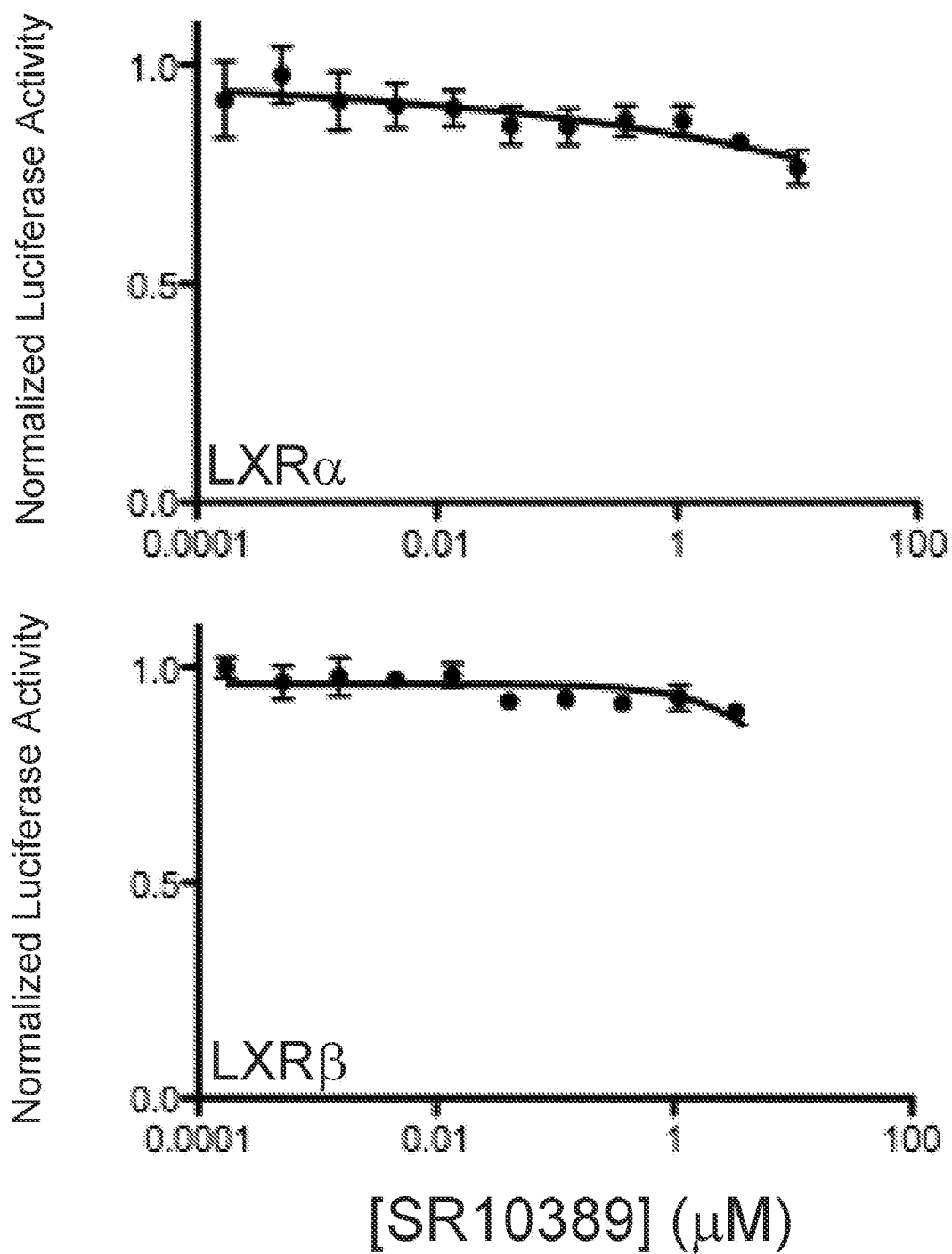
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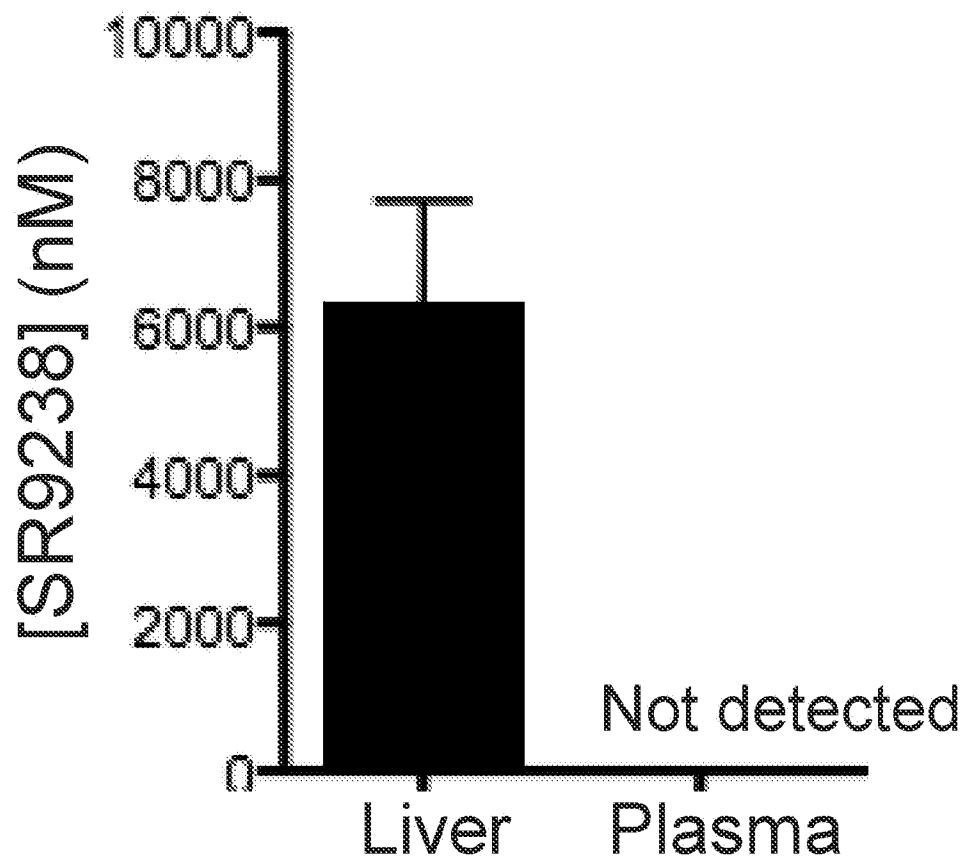
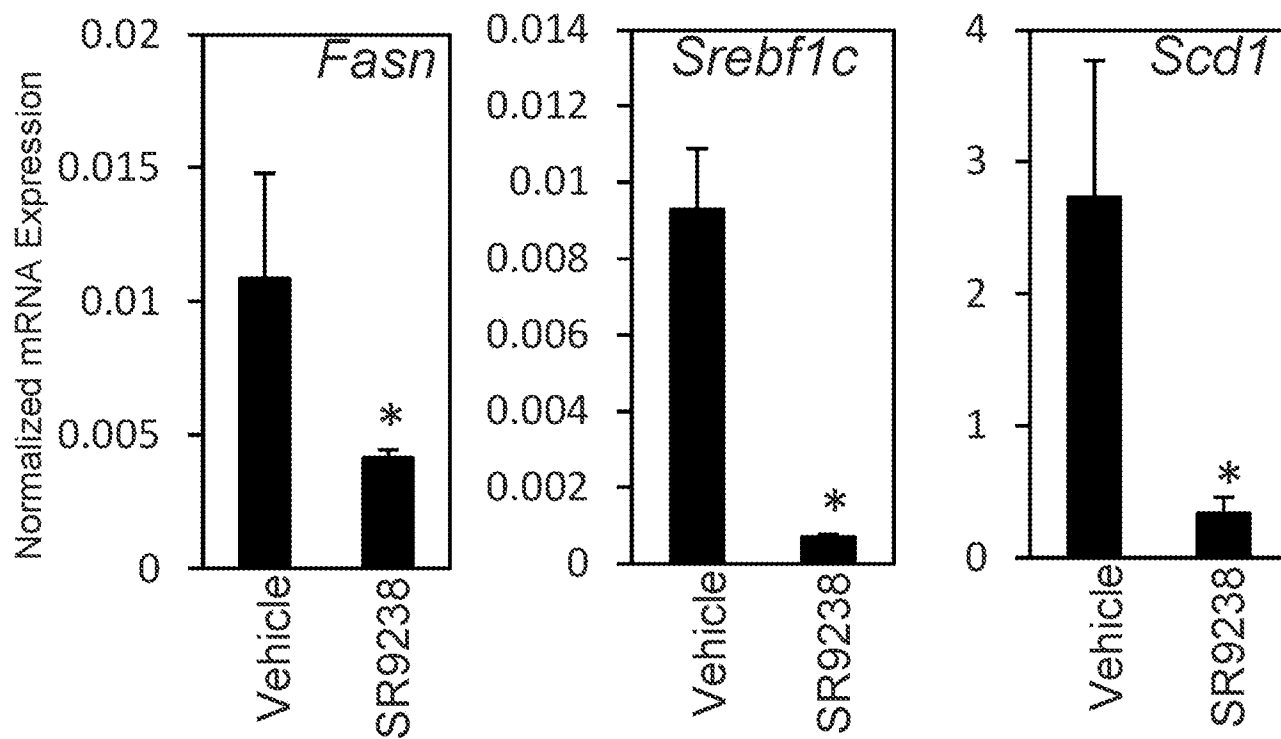
*Fig. 2G*

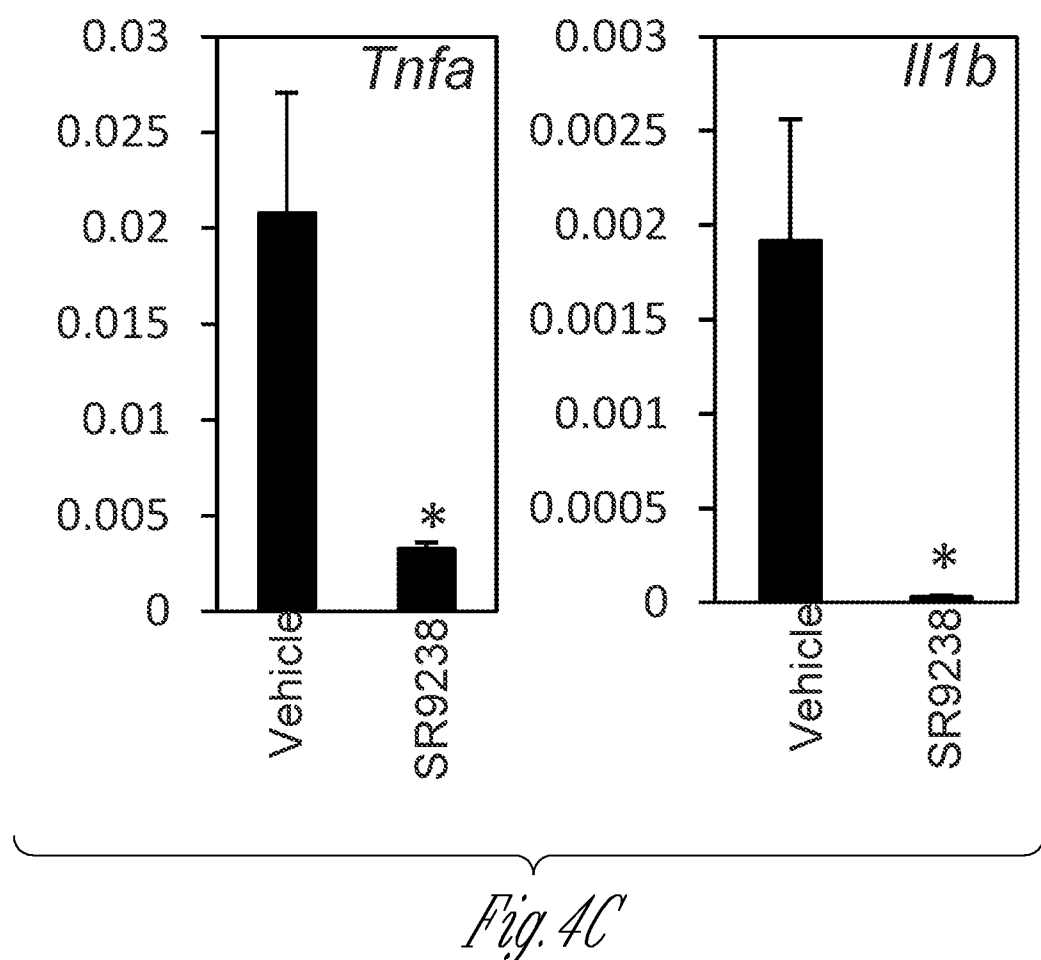
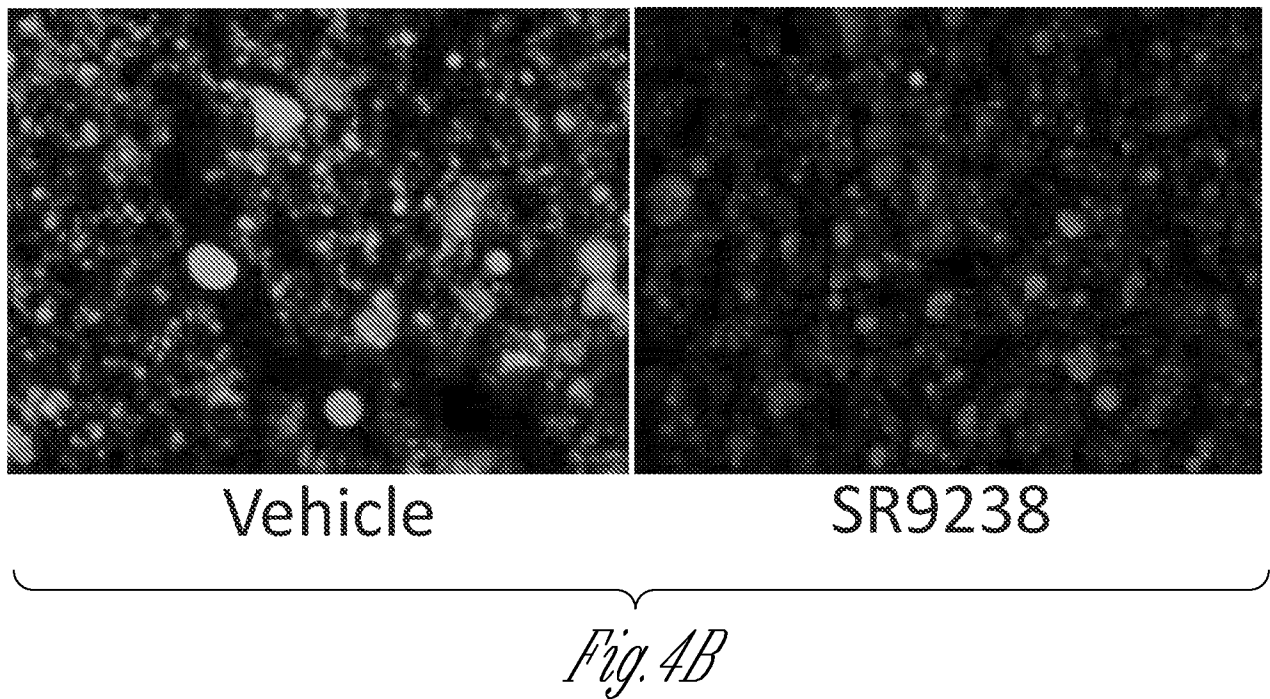
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*Fig. 3A*

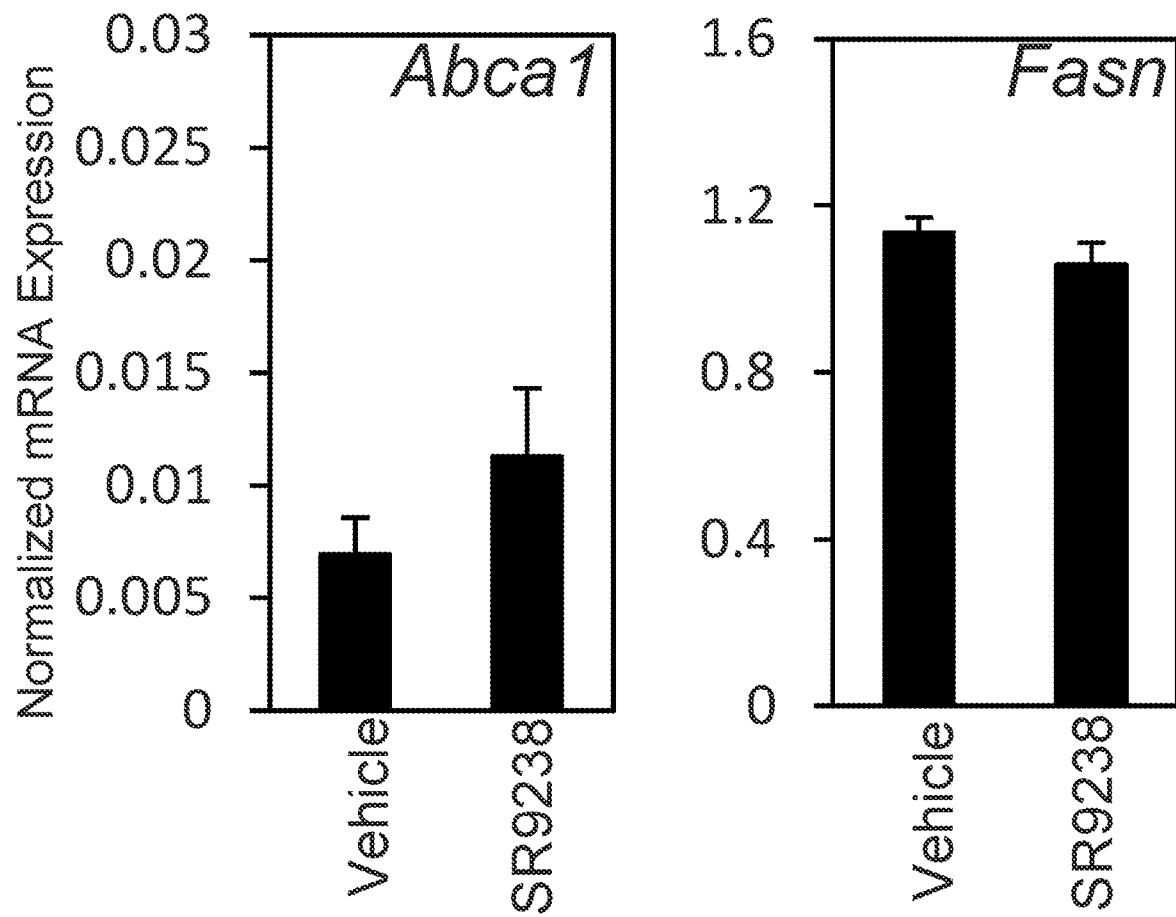
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*Fig. 3B*

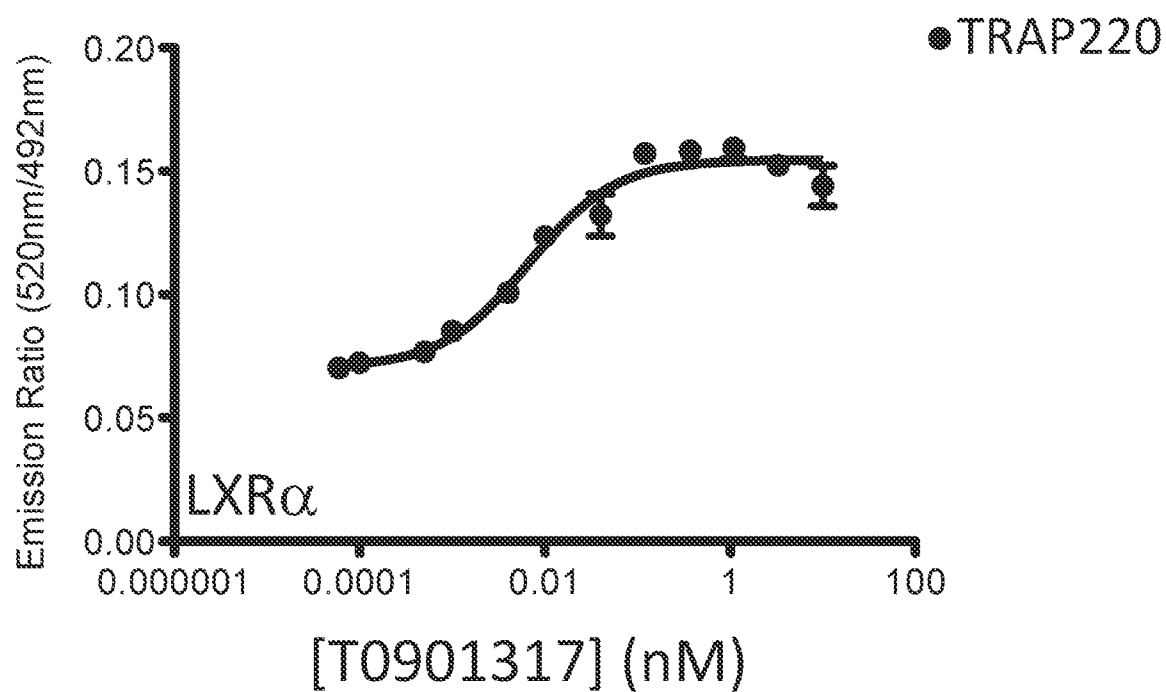
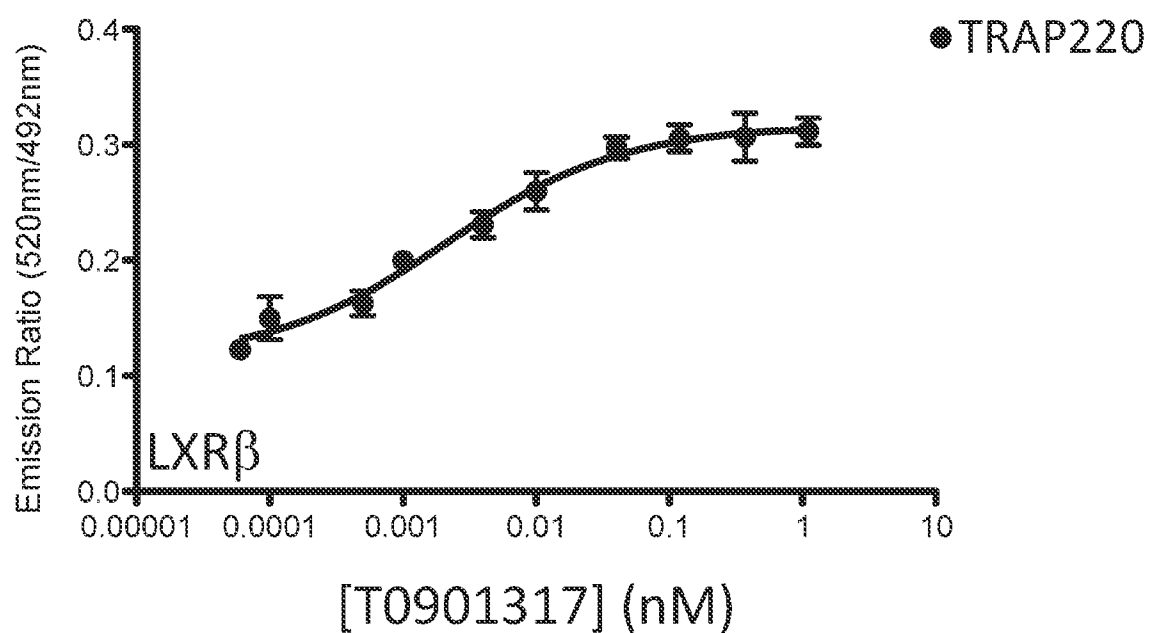
*Fig. 3C**Fig. 4A*



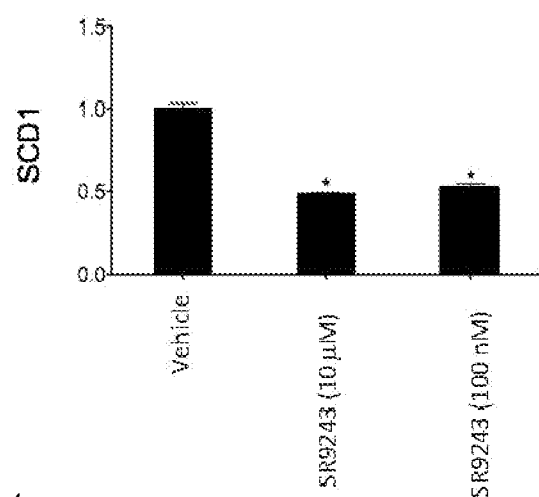
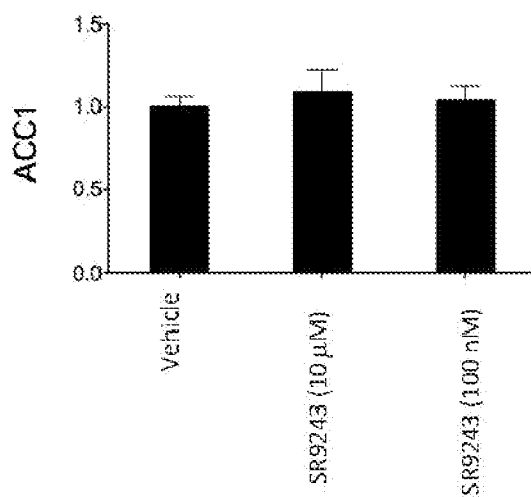
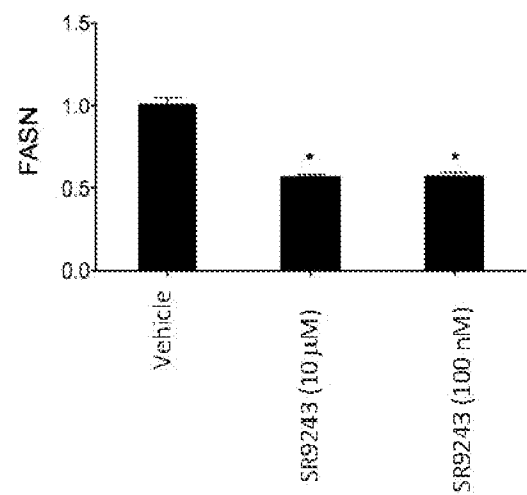
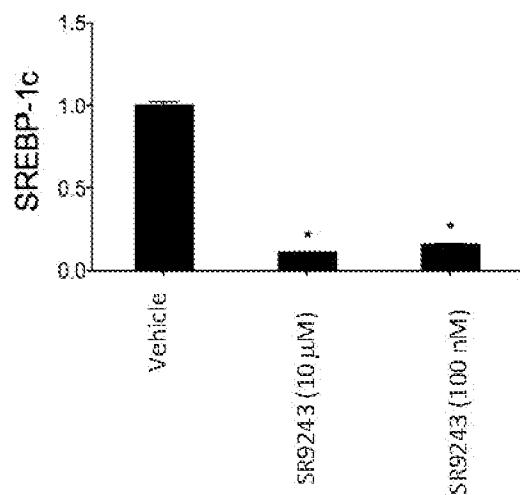
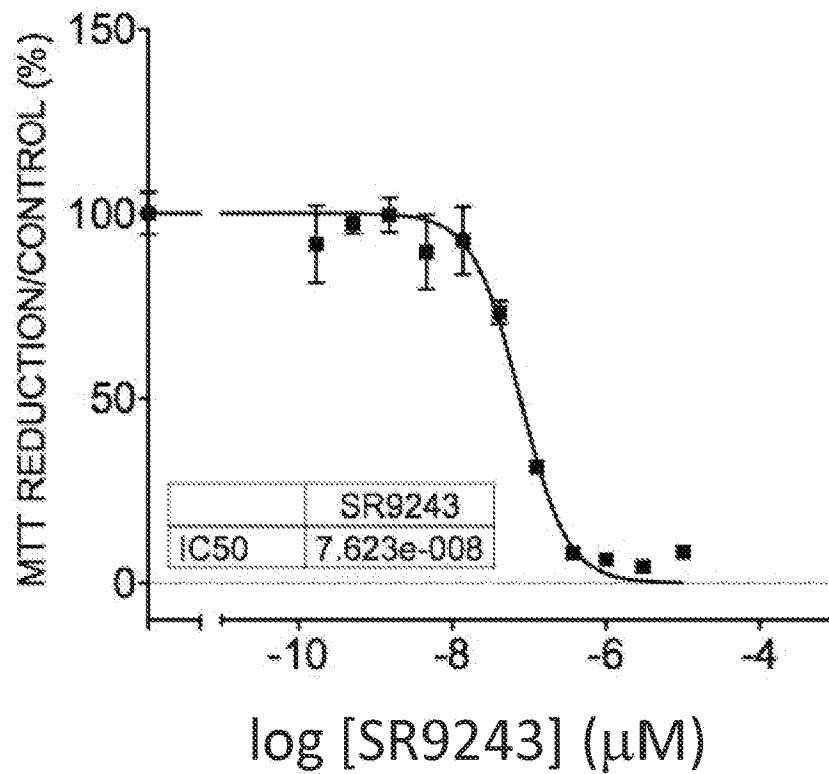
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*Fig. 4D*

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*Fig. 5A**Fig. 5B*

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*Fig. 6A*

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SW620

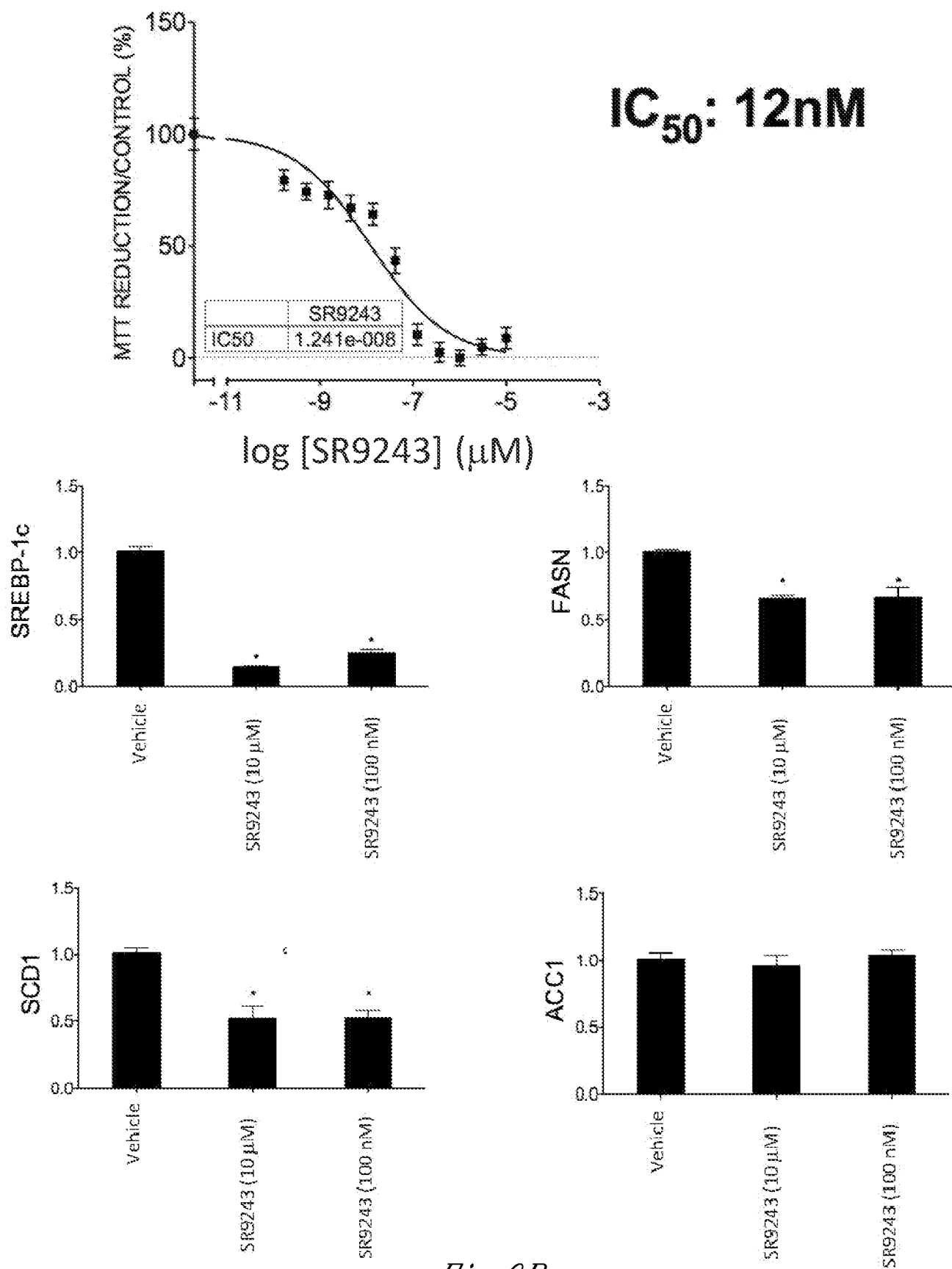


Fig. 6B

PC3

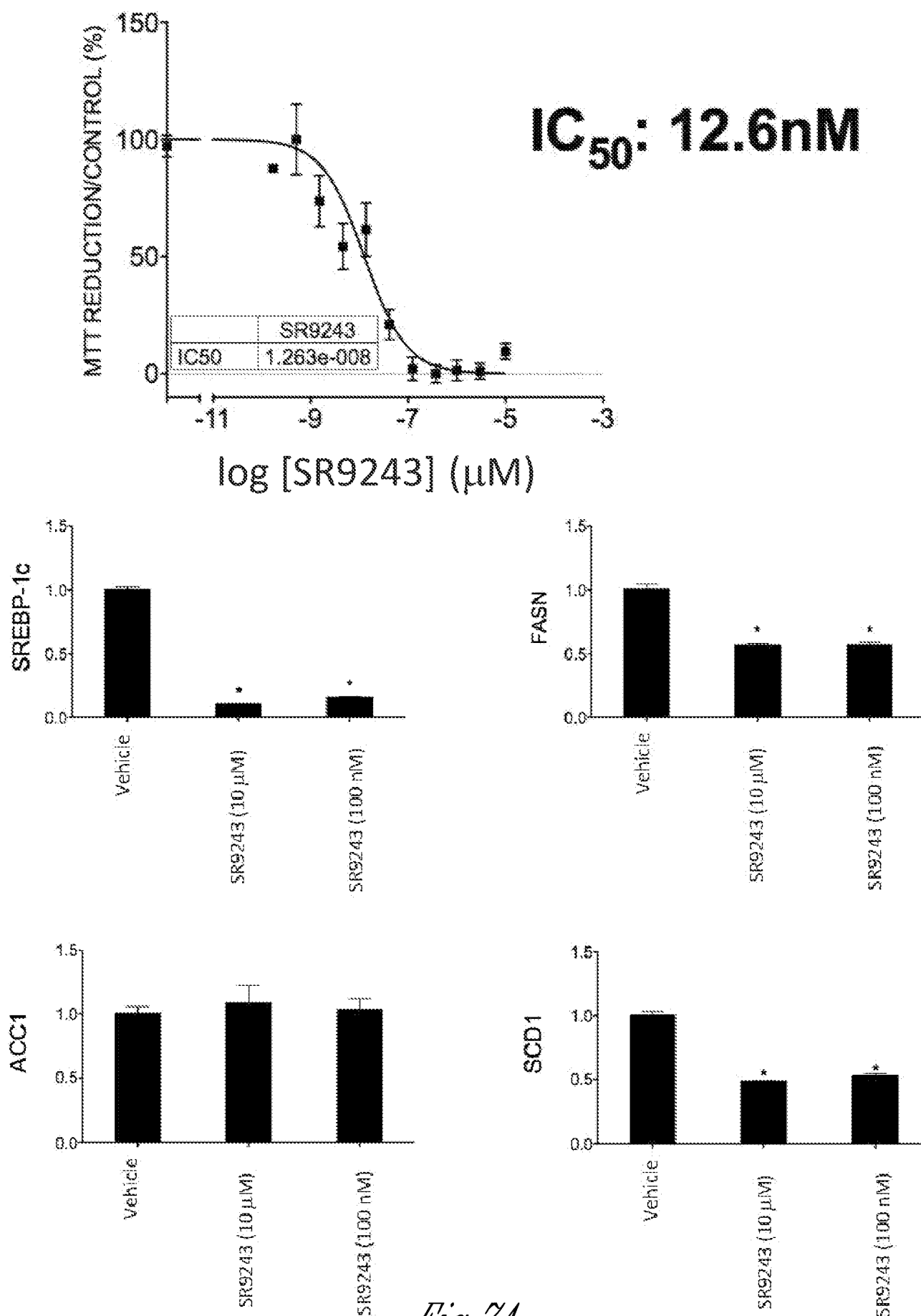


Fig. 7A

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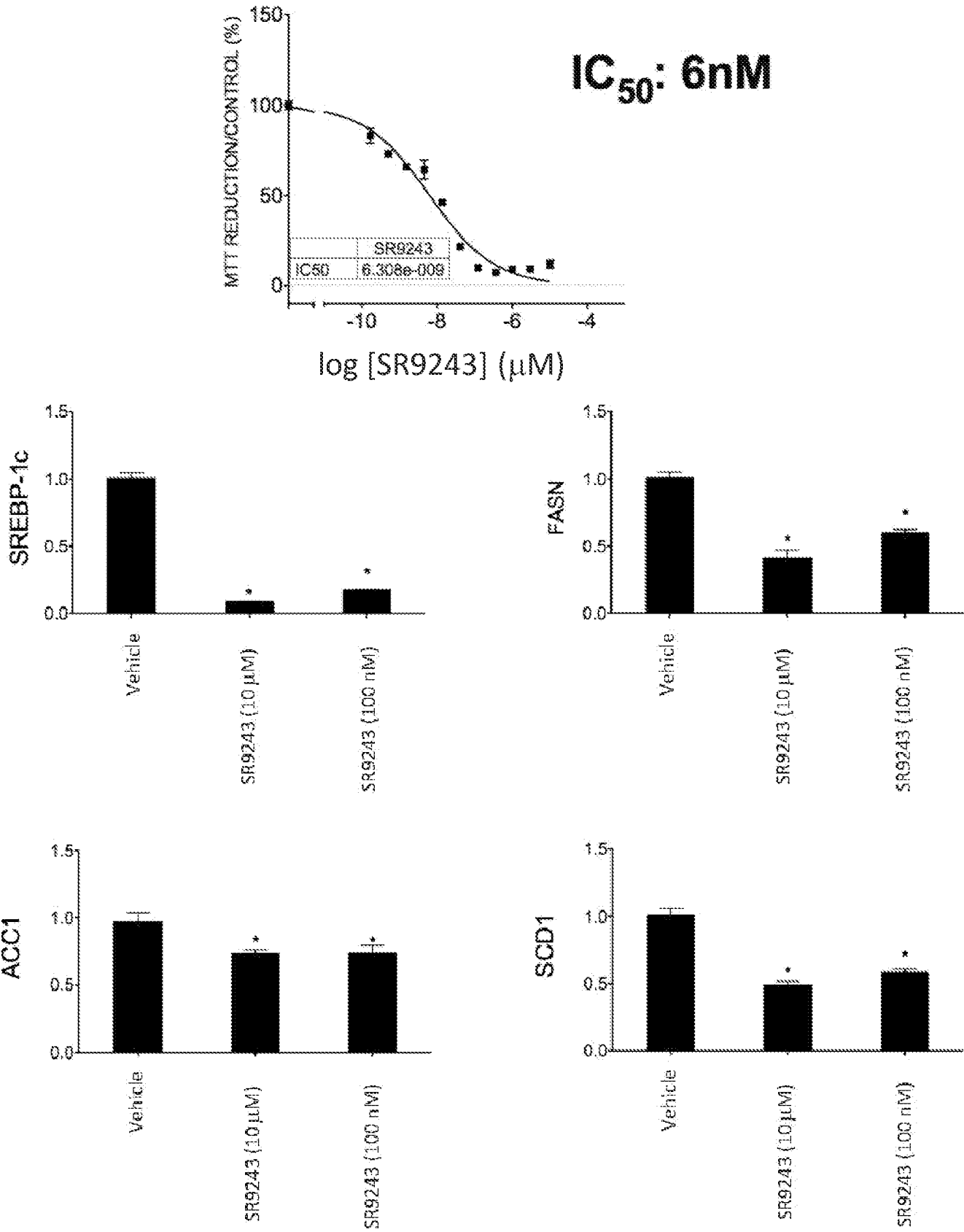


Fig. 7B

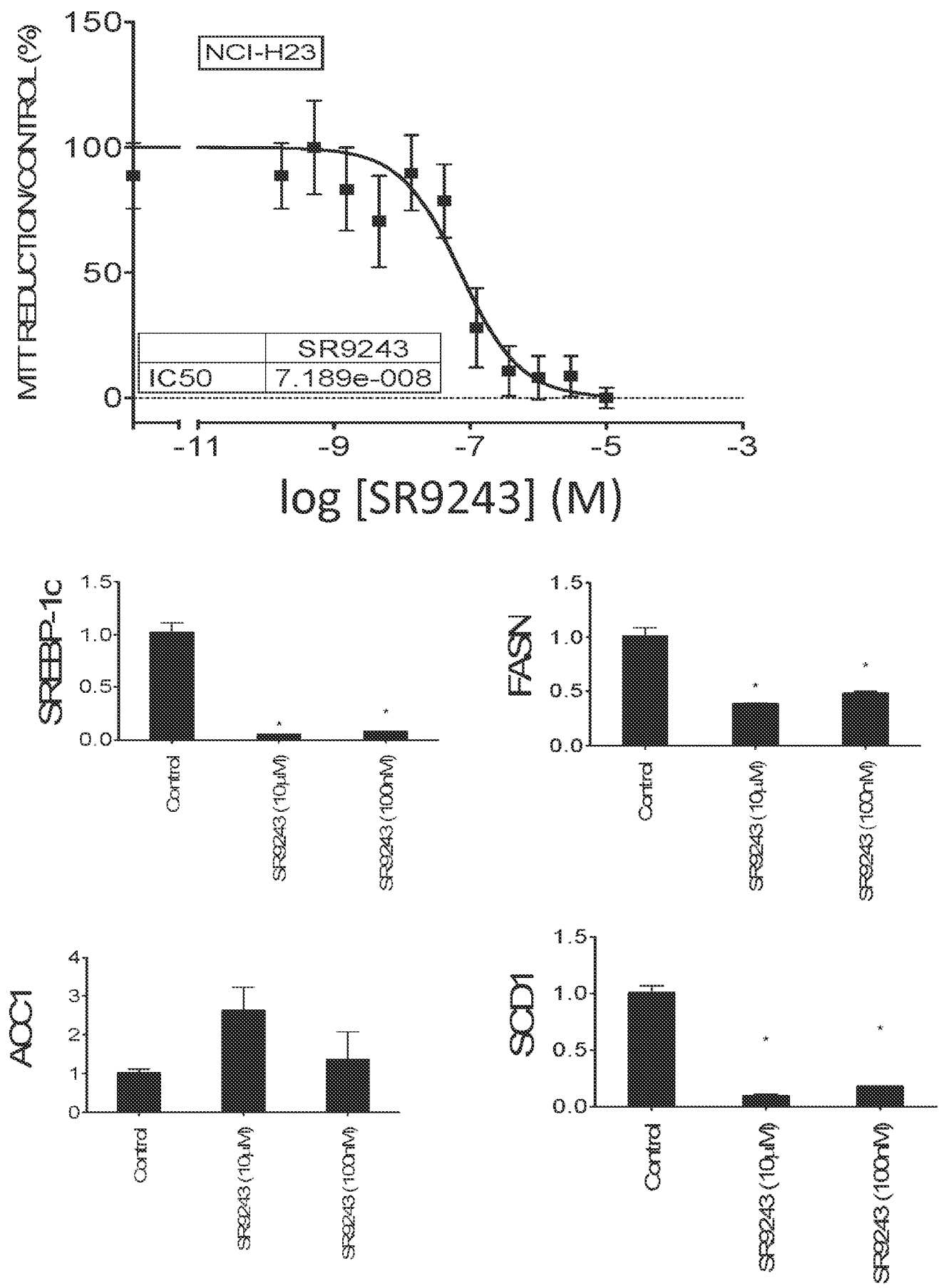


Fig. 8A

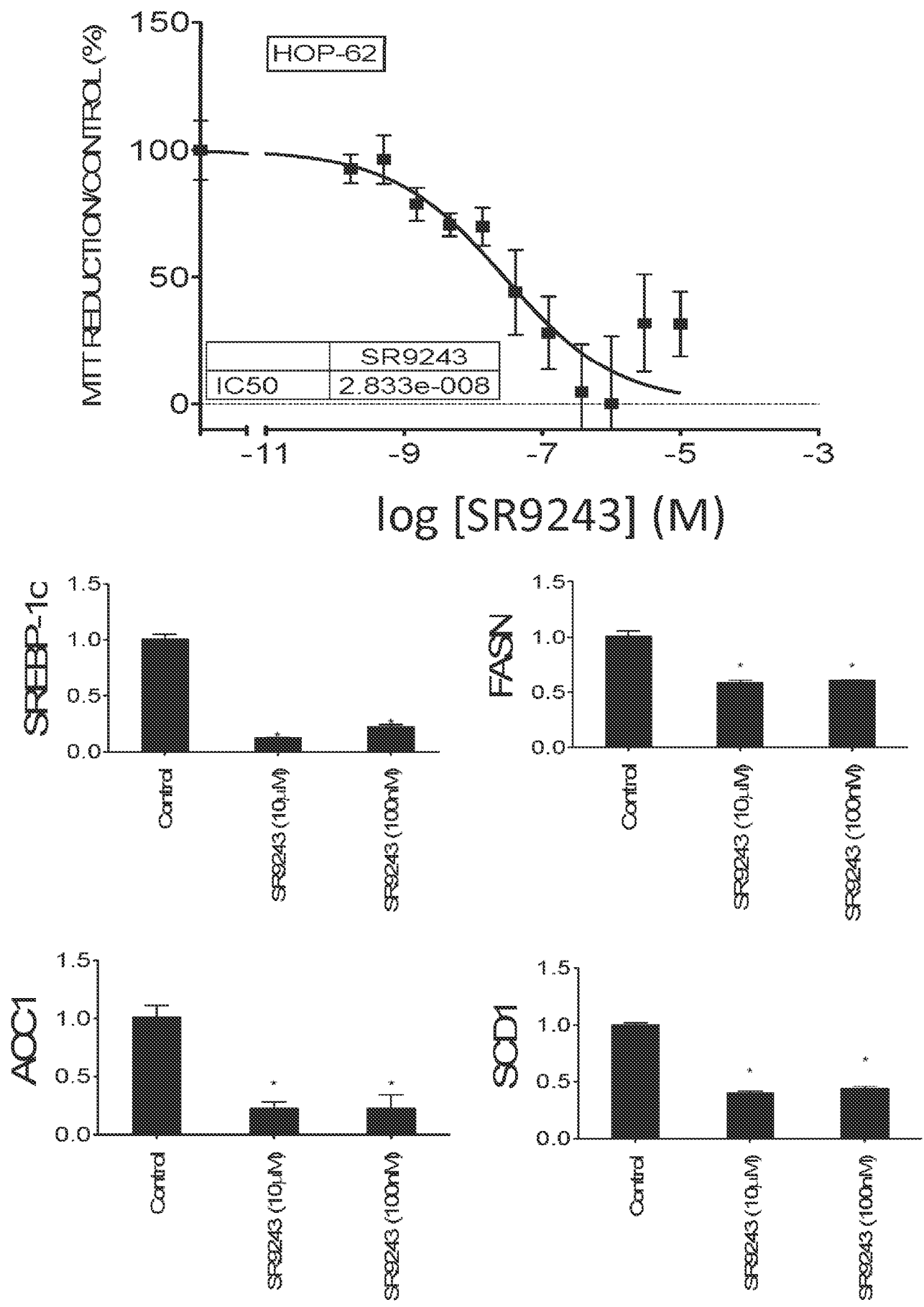


Fig. 8B