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(54) Titre : BLOQUEURS DES SREBP DESTINES A L'UTILISATION DANS LE TRAITEMENT DE LA FIBROSE
HEPATIQUE, LE CHOLESTEROL ELEVE ET LA RESISTANCE A L'INSULINE
(54) Title: SREBP BLOCKERS FOR USE IN TREATING LIVER FIBROSIS, ELEVATED CHOLESTEROL AND INSULIN
RESISTANCE

(57) **Abrégé/Abstract:**

This disclosure provides compounds and methods of using those compounds to treat liver fibrosis, including liver fibrosis which is a precursor to, is concurrent with, is associated with, or is secondary to nonalcoholic steatohepatitis (NASH); elevated cholesterol levels, and insulin resistance.



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- (54) Title: SREBP BLOCKERS FOR USE IN TREATING LIVER FIBROSIS, ELEVATED CHOLESTEROL AND INSULIN RESISTANCE
- (57) Abstract: This disclosure provides compounds and methods of using those compounds to treat liver fibrosis, including liver fibrosis which is a precursor to, is concurrent with, is associated with, or is secondary to nonalcoholic steatohepatitis (NASH); elevated cholesterol levels, and insulin resistance.

SREBP BLOCKERS FOR USE IN TREATING LIVER FIBROSIS, ELEVATED
CHOLESTEROL AND INSULIN RESISTANCE

[001] This application claims priority to Serial No. 62/128,251 filed on March 5, 2015. Serial No. 62/128,251 as well as each reference cited in this disclosure is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[002] This disclosure relates generally to therapeutics for treatment of liver fibrosis, elevated cholesterol levels, and insulin resistance.

BACKGROUND

[003] Sterol regulatory element-binding proteins (SREBPs) are major transcription factors regulating the biosynthesis of cholesterol, fatty acid, and triglyceride. They control the expression of crucial genes involved in lipogenesis and uptake. Inhibition of the SREBP pathway can reduce lipid biosynthesis and thus can be a strategy to treat metabolic diseases, such as type II diabetes, insulin resistance, fatty liver and atherosclerosis [Xiao, et al. *Acta Biochim. Biophys. Sin* (2013) 45:1, pp 2-10]. In mammals, three SREBP isoforms are known, designated SREBP-1a, SREBP-1c, and SREBP-2. SREBP-1a controls a broad range of SREBP targets including production of fatty acids, triglycerides, phospholipids and cholesterol. SREBP-1c preferentially activates genes of fatty acid and triglyceride metabolism, whereas SREBP-2 preferentially activates genes of cholesterol metabolism, both of which have been studied in human and mice models [Horton, et al. *J. Clin. Invest.* (2002) 109:9, pp 1125-1131], as well as *Drosophila* [Rawson. *Nature Rev. Mol. Cell Biol.* (2003) 4:8, pp 631-640].

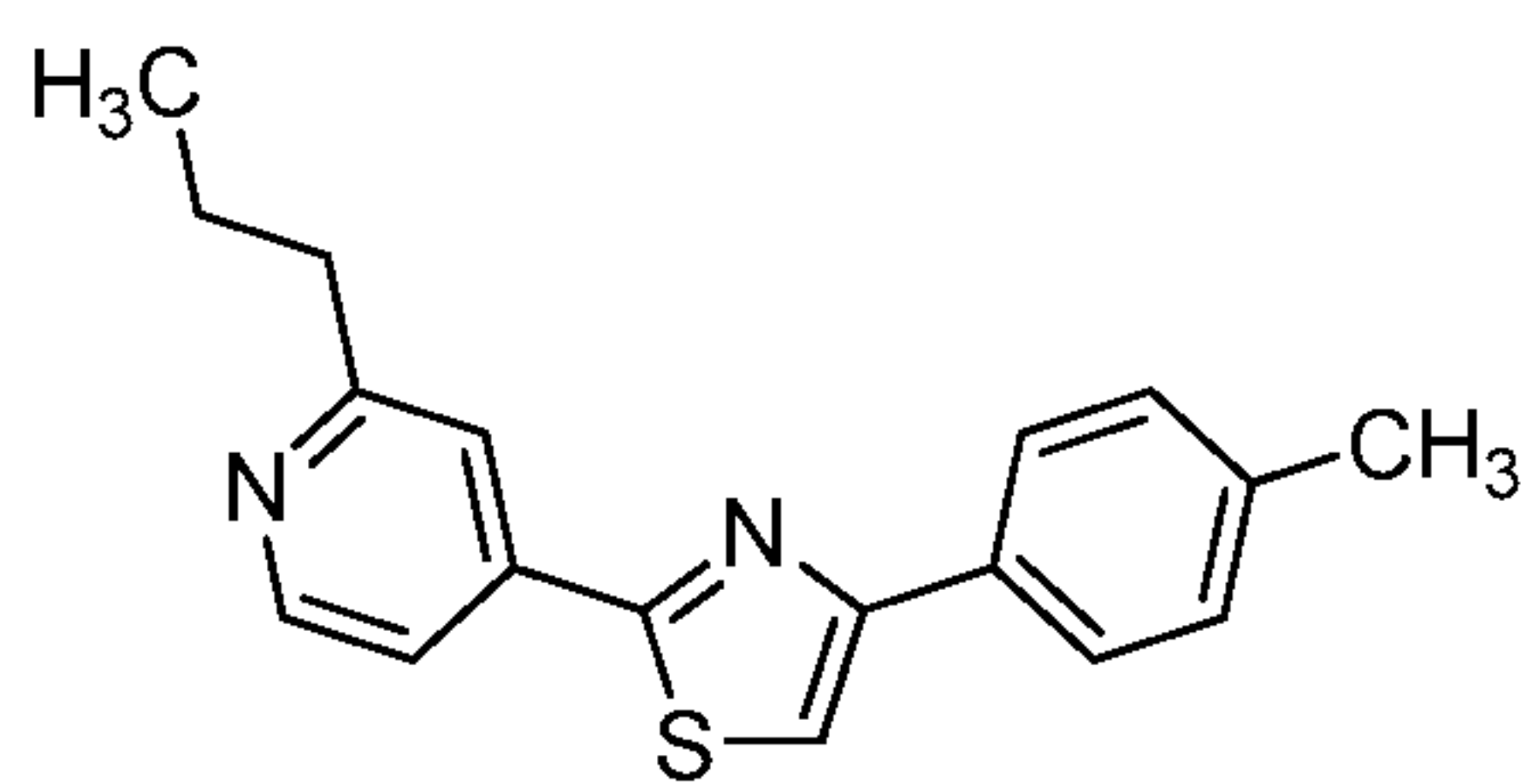
[004] Recent studies have also presented a link between upregulation of lipid synthesis and prostate cancer [Suburu, et al. *Prostaglandins Other Lipid Mediat.* (2012) 98:0, pp 1-10]. The metabolic shift from catabolic to anabolic metabolism is a hallmark of cancer cells. Many cancers require synthesis of fatty acids, and other lipids such as cholesterol and androgens are implicated in prostate cancer. SREBP-1c is the major transcriptional regulator of enzymes in the fatty acid synthesis pathway, and its expression can be stimulated by androgens and epidermal growth factor (EGF) in prostate cancer cells. Overexpression of SREBP-1c is sufficient to cause tumorigenicity and invasion of prostate cancer cells. SREBP-1 can also increase expression of NOX5, a prominent producer of reactive oxygen species (ROS) and regulator of prostate cancer cell growth [Brar, et al. *Am. J. Physiol. Cell Physiol.* (2003)

285:2, pp C353-369; Huang, et al. Mol. Cancer Res. (2012) 10:1, pp 133-142; Huang, et al. Cancer Research (2012) 72:8, SUPPL. 1; Huang, et al. Mol. Cancer Res. (2014) 13:4, pp 855-866].

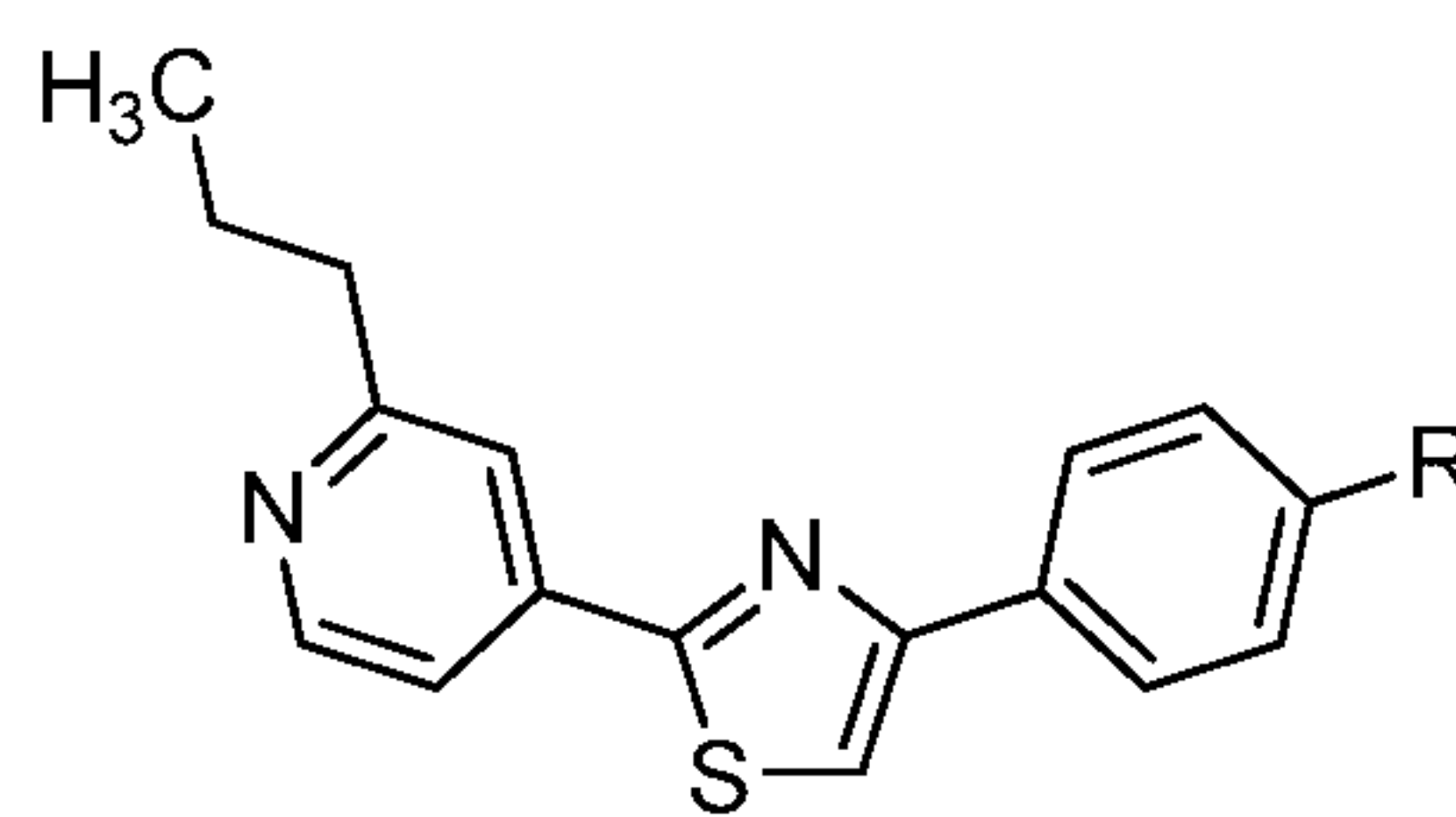
[005] SREBP-2, a regulator of androgen synthesis, is also itself regulated by androgens, demonstrating a direct feedback circuit for regulation of androgen production. SREBP-2 expression increases during disease progression and is significantly higher after castration. This transcription factor also lacks its feedback inhibition in prostate cancer cells, implicating a role for cholesterol and androgen synthesis in prostate cancer [Eberle, et al. Biochimie (2004) 86:11, pp 839-848; Ettinger, et al. Cancer Res. (2004), 64:6, pp2212-2221; Chen, et al. Int. J. Cancer (2001), 91:1, pp 41-45].

[006] Blocking SREBP functions linked to disease states therefore represents an important therapeutic approach for limiting lipid/cholesterol synthesis in membrane production which occurs in metabolic diseases and in cancer progression, as well as in viral pathogenesis [Naar, et al. Clin. Lipidol. (2012) 7:1, pp 27-36]. Small molecule therapeutics affecting metabolic regulators such as mTOR, AMPK or SIRT1, including Rapamycin, Metformin, or Resveratrol, respectively, may impinge on the transcriptional activity of SREBPs. Recently, two non-sterol small molecules, fatostatin and betulin have been found to inhibit SREBP processing [Kamisuki, et al. Chem. Biol. (2009) 16:8, pp 882-892; Tang, et al. Cell. Metab. (2011) 13:1, pp 44-56]. Methods for the treatment of cancers having a p53 mutation, such as breast cancer cells, using SREBP inhibitors have been presented [Freed-Pastor, et al. PCT. Publication WO2013-110007A1].

[007] Fatostatin analogs have recently been described as potential therapeutics for the treatment of metabolic disorders [Uesugi, et al. U.S. Patent No. 8,207,196]. Key compounds presented therein are based around Formula X:



Fatostatin



Formula X

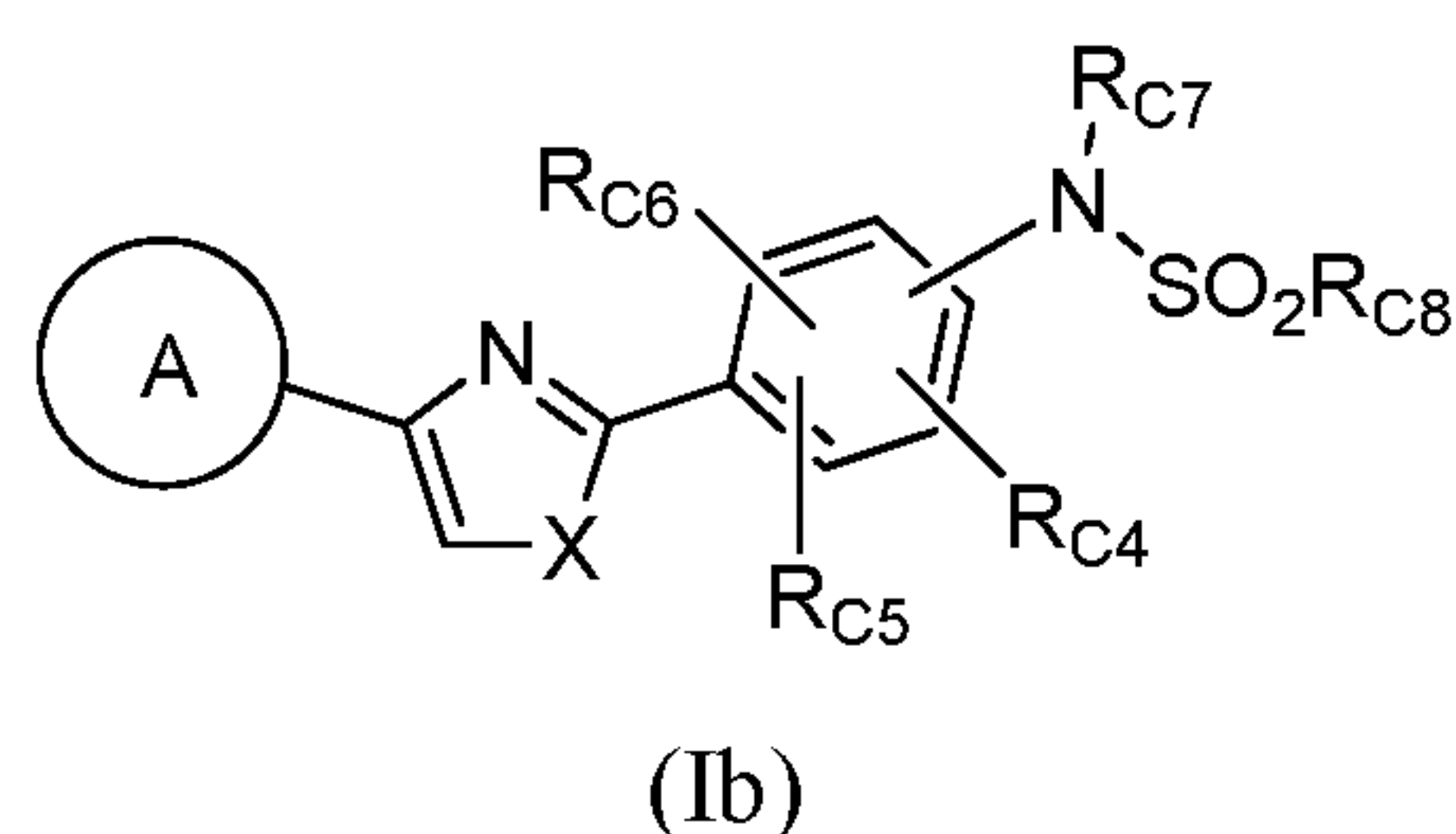
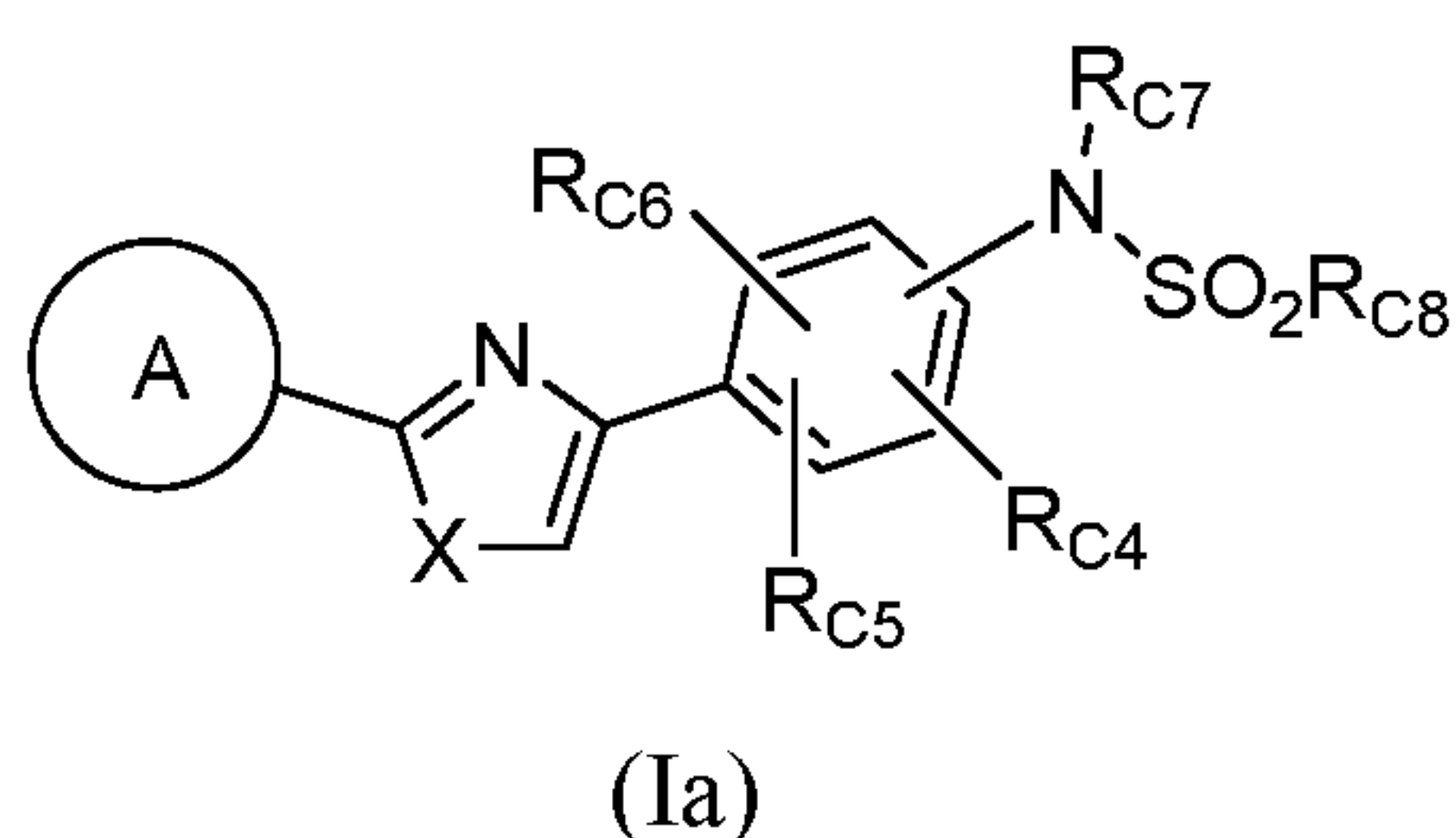
wherein R is H, F, Cl, Br, OBz, OH, OCH₃, OCH₂CO₂Me, OCH₂CO₂H, NH₂, NHiPr, NHCOCH₃, NHSO₂Me, NH[benzyl], NH[cyclopropyl], NH[tertbutyloxycarbonyl], NH[cyclohexyl], NH[tosyl], NH[quinolin-8-yl], and NH[thiophen-2-yl]. In particular, one

compound (FGH10019), the methanesulfonamide derivative of fatostatin above wherein R is $\text{NH}\text{SO}_2\text{Me}$, has been described as a lead candidate [Kamisuki, et al. J. Med. Chem. (2011) 54:13, pp 4923-4927].

BRIEF SUMMARY

[008] This disclosure provides compounds and methods of using those compounds to treat liver fibrosis, elevated cholesterol levels, and insulin resistance.

[009] In some embodiments, compounds disclosed herein fall within formulae (Ia) or (Ib):



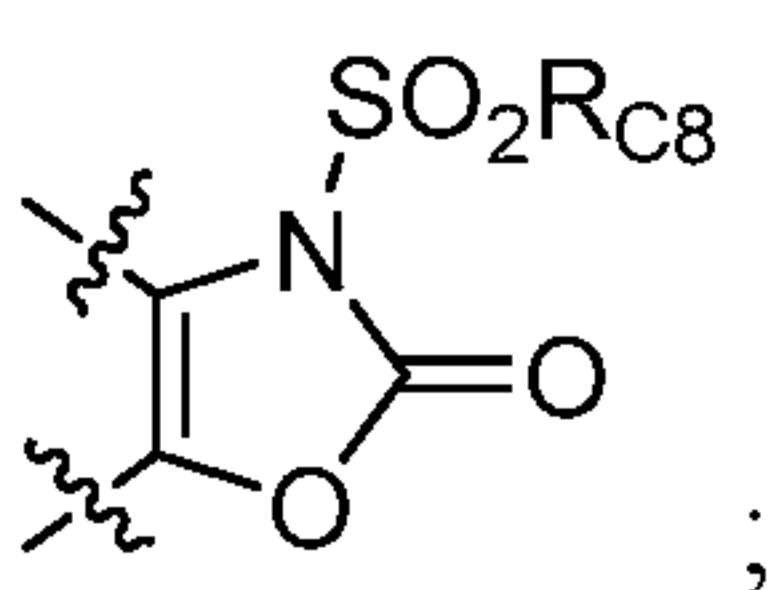
or a pharmaceutically acceptable salt thereof, wherein:

A is either:

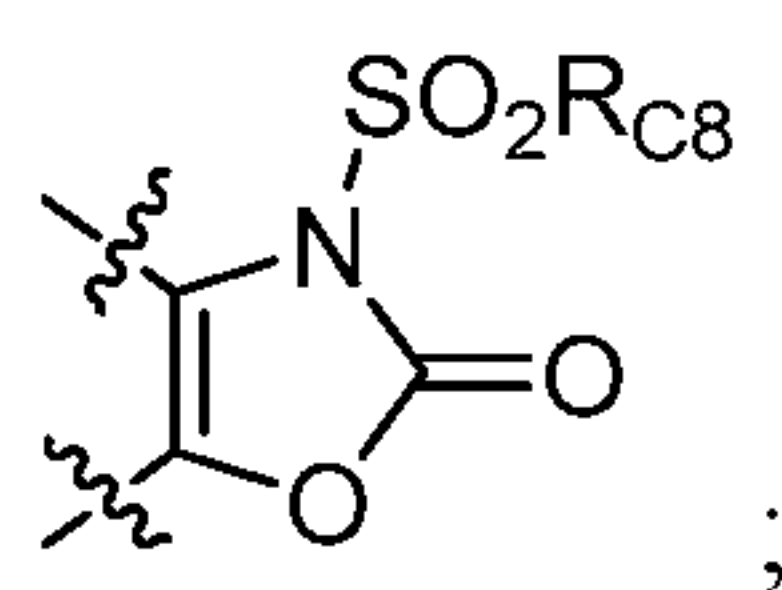
- i. an aryl or heteroaryl, each having only one ring, substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF_3 , OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, $-(\text{CH}_2)_m\text{CF}_3$, $=\text{O}$, $-\text{CH}_2\text{OCH}_3$, $-\text{OBn}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{-Alkyl}$, $-\text{NR}_{10}\text{R}_{11}$, and $-\text{CONR}_{10}\text{R}_{11}$; or
- ii. an aryl or heteroaryl, each having more than one ring, optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF_3 , OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, $-(\text{CH}_2)_m\text{CF}_3$, $=\text{O}$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OH}$, $-\text{OBn}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{-Alkyl}$, $-\text{NR}_{10}\text{R}_{11}$, and $-\text{CONR}_{10}\text{R}_{11}$;

Each $\text{R}_{\text{C}4}$, $\text{R}_{\text{C}5}$, and $\text{R}_{\text{C}6}$, is independently hydrogen, halogen, CN, CF_3 , OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl,

C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, -CO₂H, -CONR¹⁰R¹¹,

or -NHCONH₂; or is taken with R_{C7} to form the moiety  ;

R_{C7} is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -(CR_{9a}R_{9b})_mNR¹⁰R¹¹, -CO₂-Alkyl, -(CR_{9a}R_{9b})_mO-Alkyl, -(CR_{9a}R_{9b})_mOPO₃Na₂, -(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO-Alkyl, -(CR_{9a}R_{9b})_mO(C=O)-Alkyl, -(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)-Alkyl, -(C=O)CH=CH₂, -SO₂R_{C8'};

or is taken with one of R_{C4}, R_{C5} or R_{C6} to form the moiety  ;

R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

R_{C8'} is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

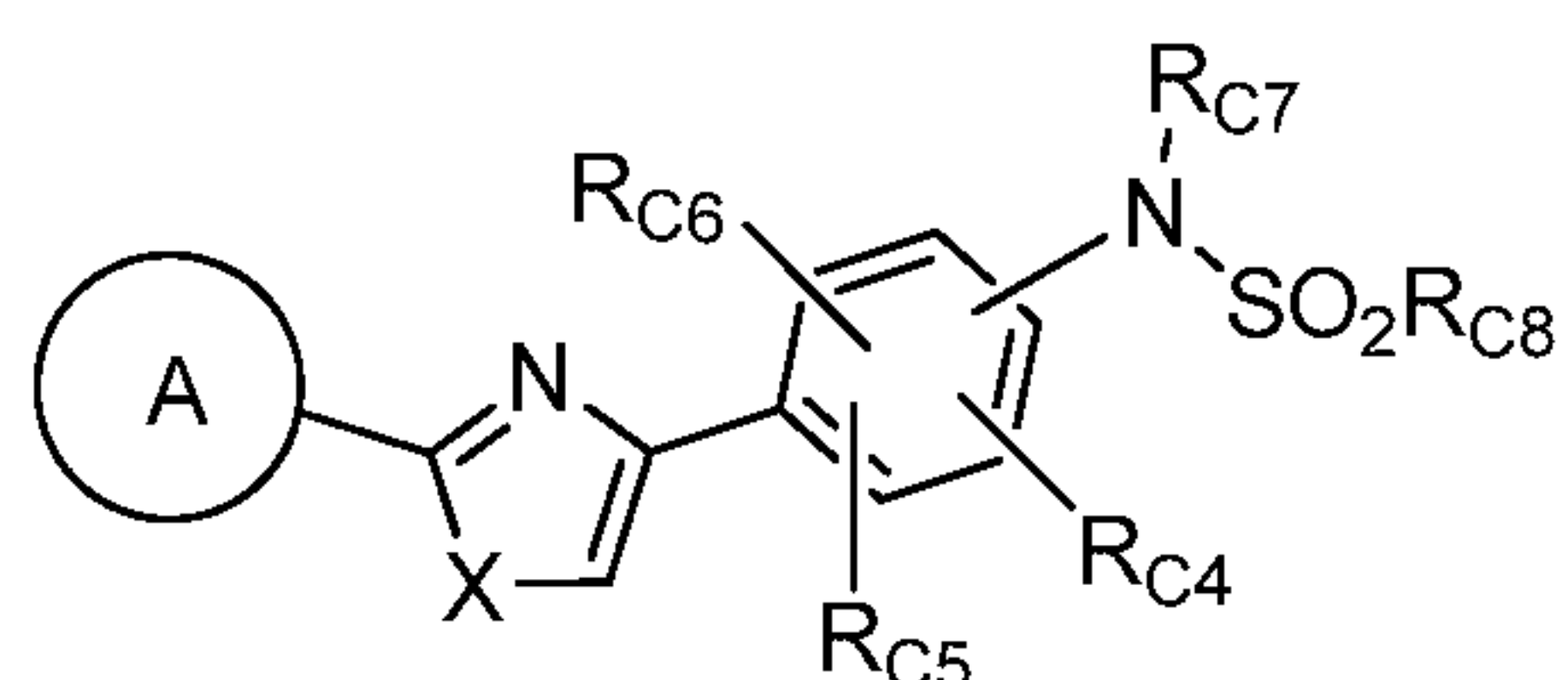
Each R_{9a} and R_{9b}, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R¹⁰ and R¹¹ are independently hydrogen, -SO₂R_{C8'}, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a 1λ⁶,2-thiazolidine-1,1-dione, a 1,2λ⁶,3-oxathiazolidine-2,2-dione, or a 1λ⁶,2,5-thiadiazolidine-1,1-dione;

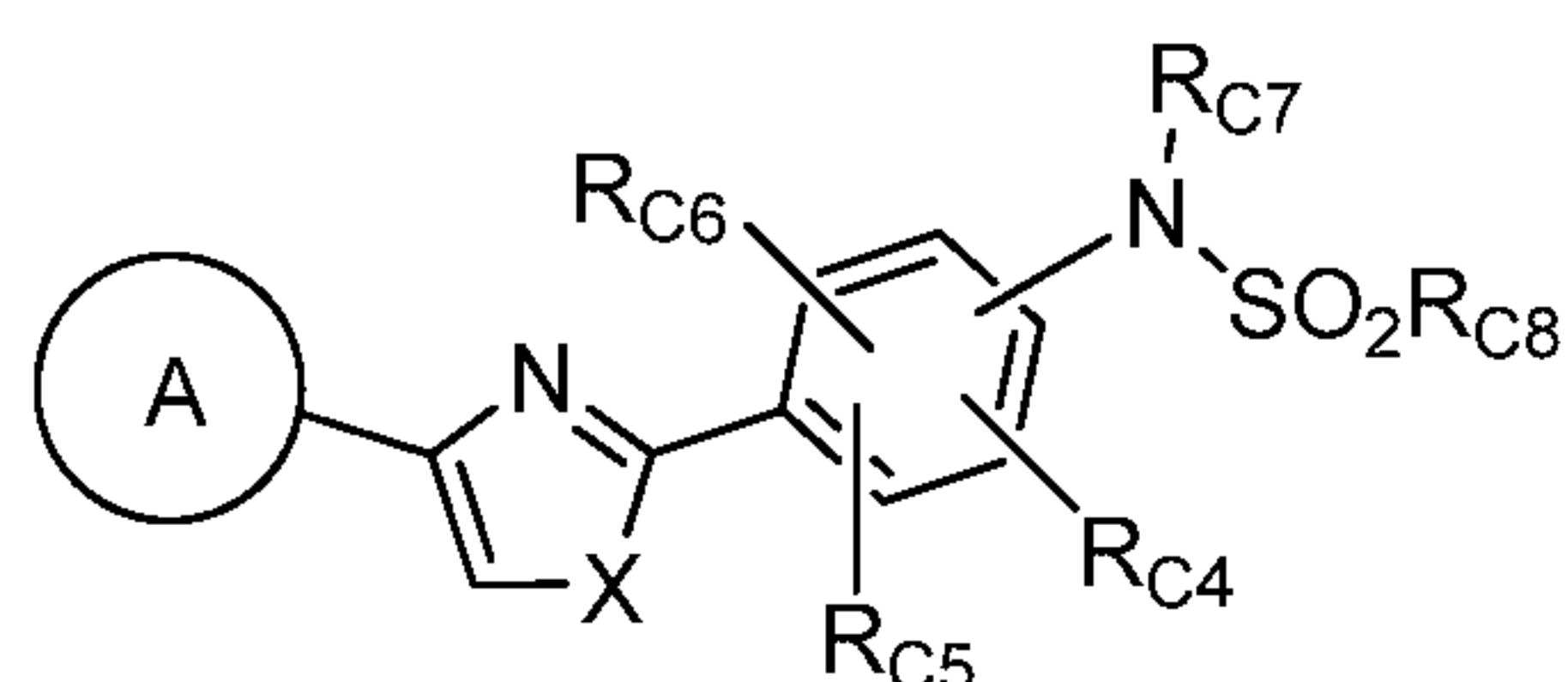
X is a heteroatom selected from S, O; or NR_B wherein R_B is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

Each *m* and *n* is 1, 2 or 3.

[010] In some embodiments, compounds disclosed herein fall within formulae (IIa) or (IIb):



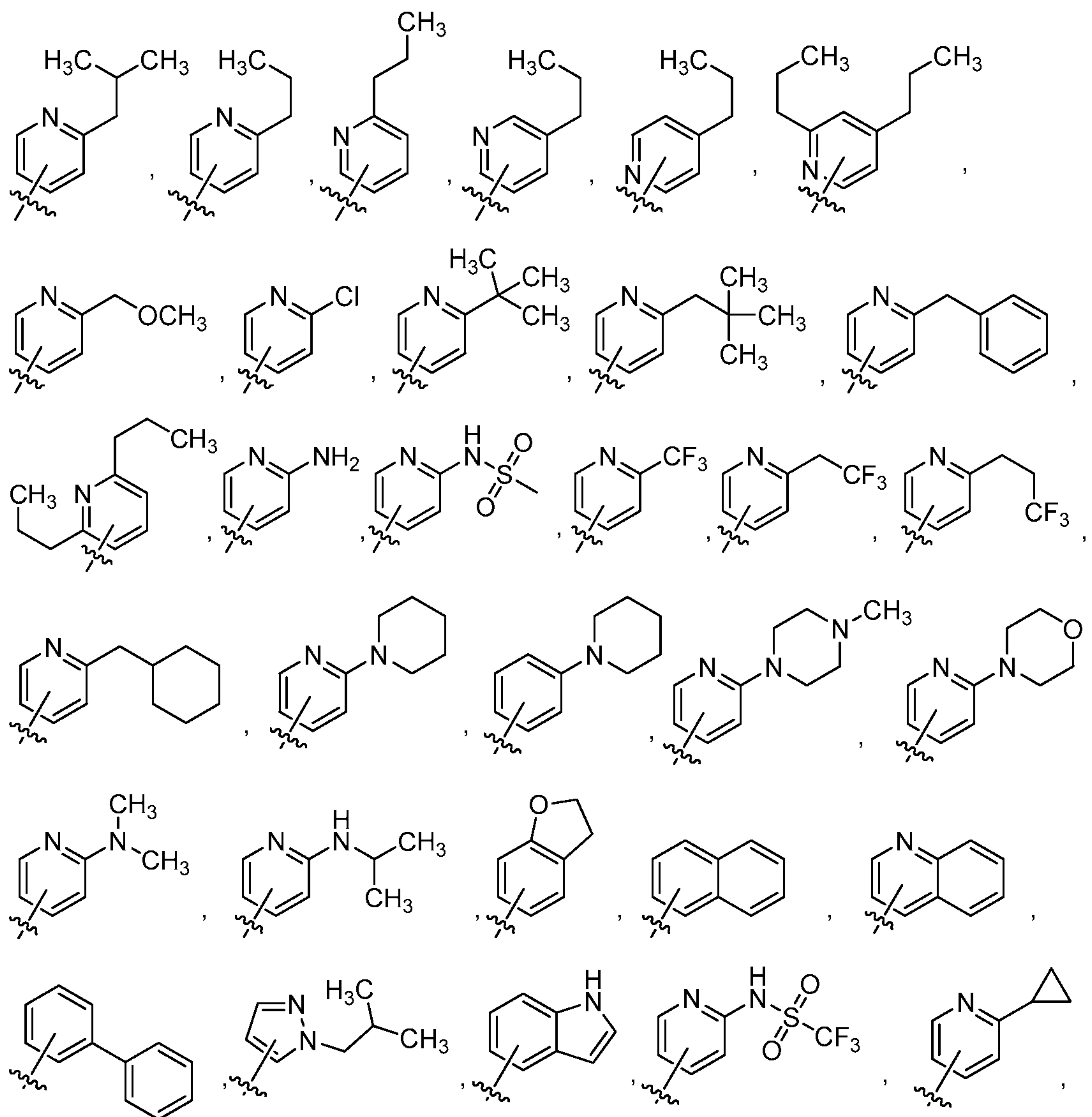
(IIa)

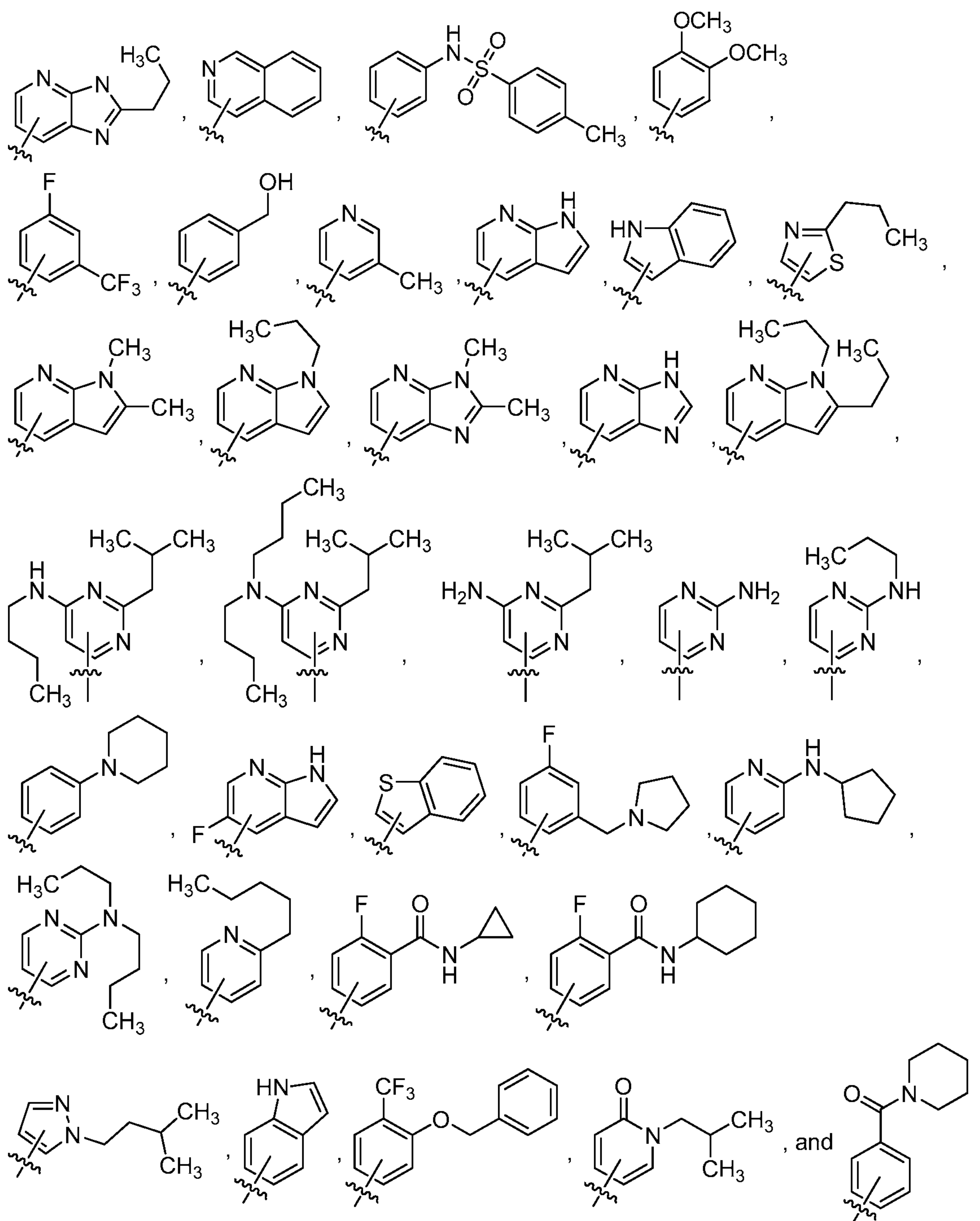


(IIb)

or a pharmaceutically acceptable salt thereof, wherein:

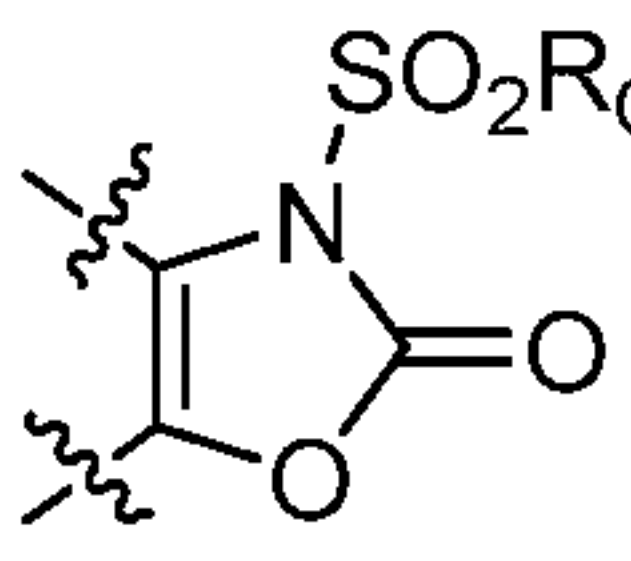
A is a moiety selected from the group consisting of:



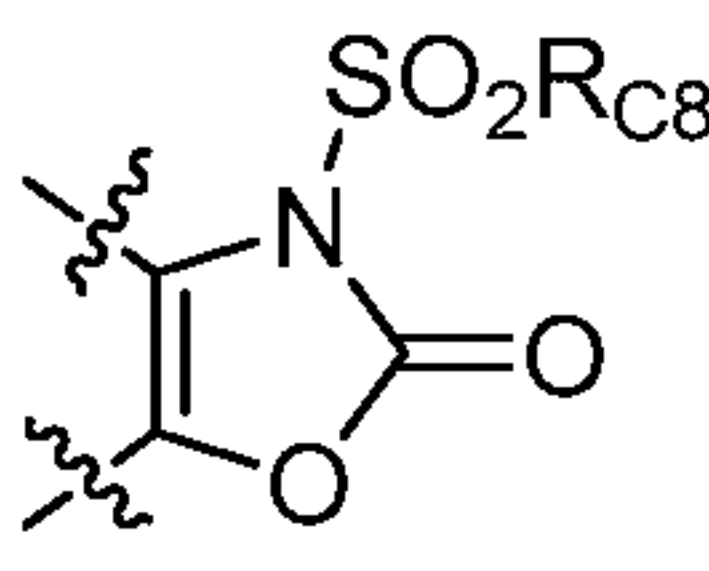


wherein the ring containing X is linked to ring A at any available position on ring A;

Each **R_{C4}**, **R_{C5}**, and **R_{C6}**, is independently hydrogen, halogen, CN, CF₃, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, -CO₂H, -CONR¹⁰R¹¹,

or -NHCONH₂; or is taken with **R_{C7}** to form the moiety  ;

R_{C7} is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{NR}_{10}\text{R}_{11}$, $-\text{CO}_2\text{-Alkyl}$, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{O-Alkyl}$, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{OPO}_3\text{Na}_2$, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{O}(\text{CR}_{9a}\text{R}_{9b})_n\text{O-Alkyl}$, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{O}(\text{C}=\text{O})\text{-Alkyl}$, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{O}(\text{CR}_{9a}\text{R}_{9b})_n\text{O}(\text{C}=\text{O})\text{-Alkyl}$, $-(\text{C}=\text{O})\text{CH}=\text{CH}_2$, $-\text{SO}_2\text{R}_{C8'}$;

or is taken with one of **R_{C4}**, **R_{C5}** or **R_{C6}** to form the moiety  ;

R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

R_{C8'} is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

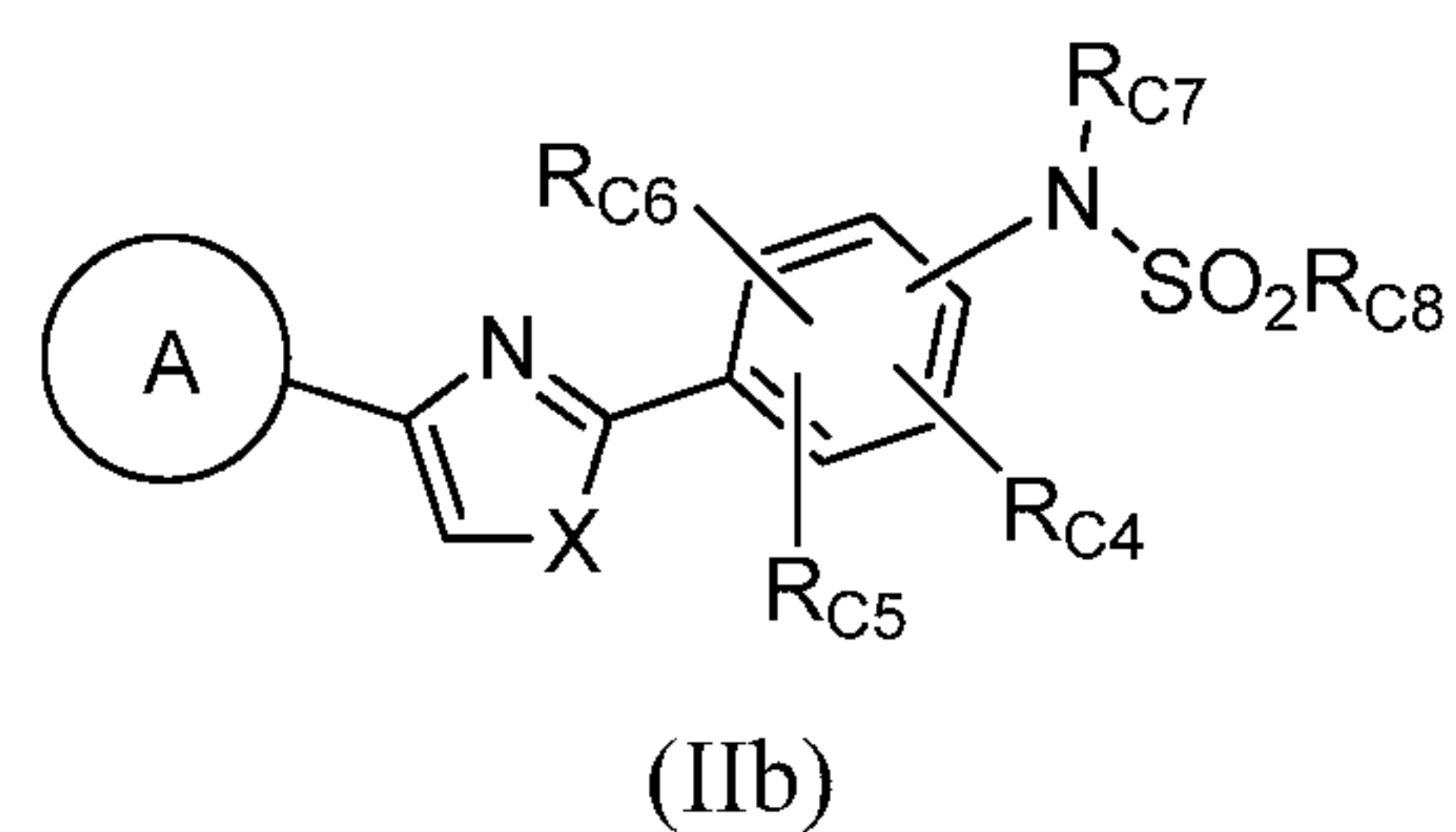
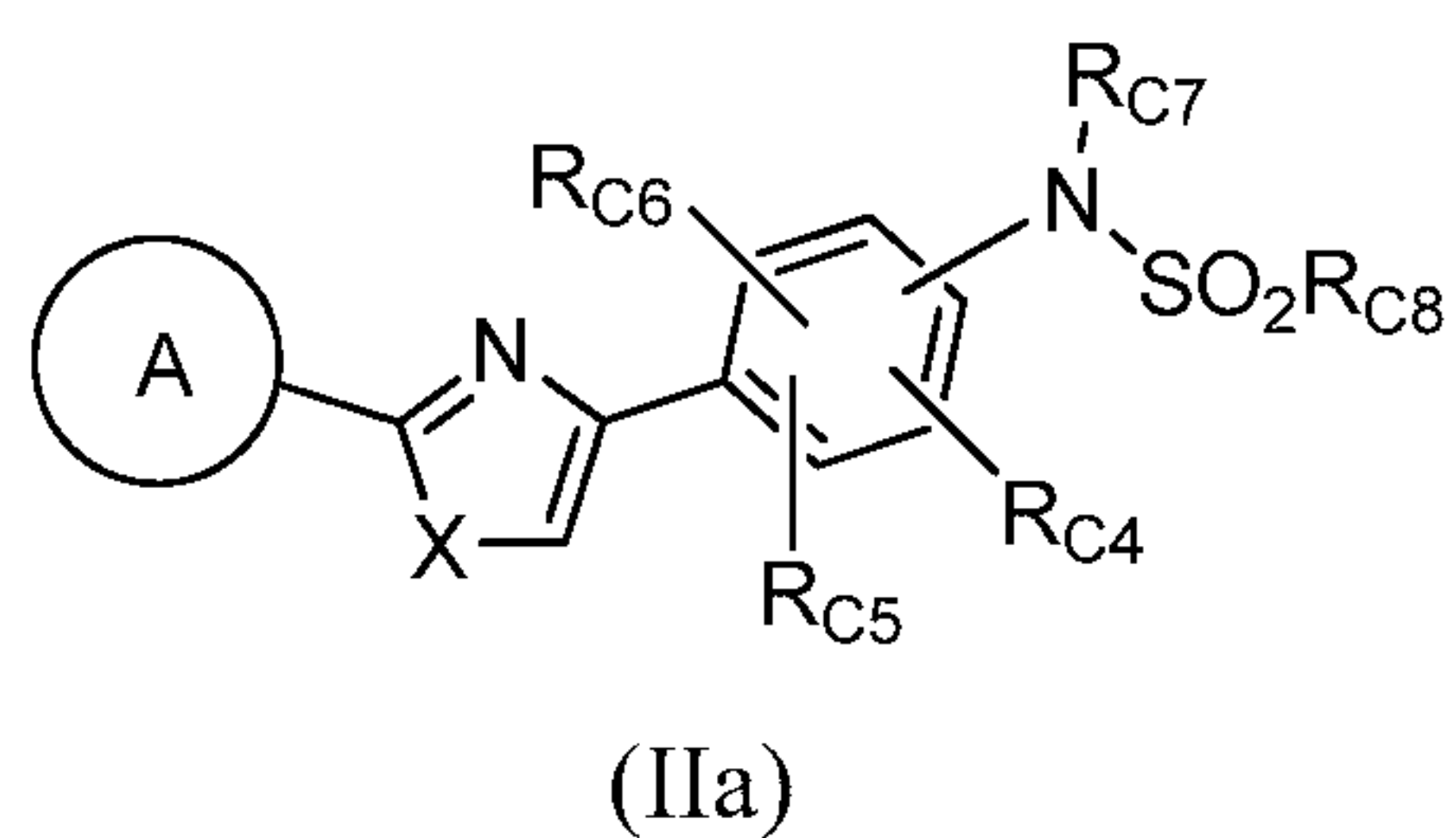
Each **R_{9a}** and **R_{9b}**, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R₁₀ and **R₁₁** are independently hydrogen, $-\text{SO}_2\text{R}_{C8'}$, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6,2\text{-thiazolidine-1,1-dione}$, a $1,2\lambda^6,3\text{-oxathiazolidine-2,2-dione}$, or a $1\lambda^6,2,5\text{-thiadiazolidine-1,1-dione}$;

X is a heteroatom selected from S, O; or **NR_B** wherein **R_B** is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

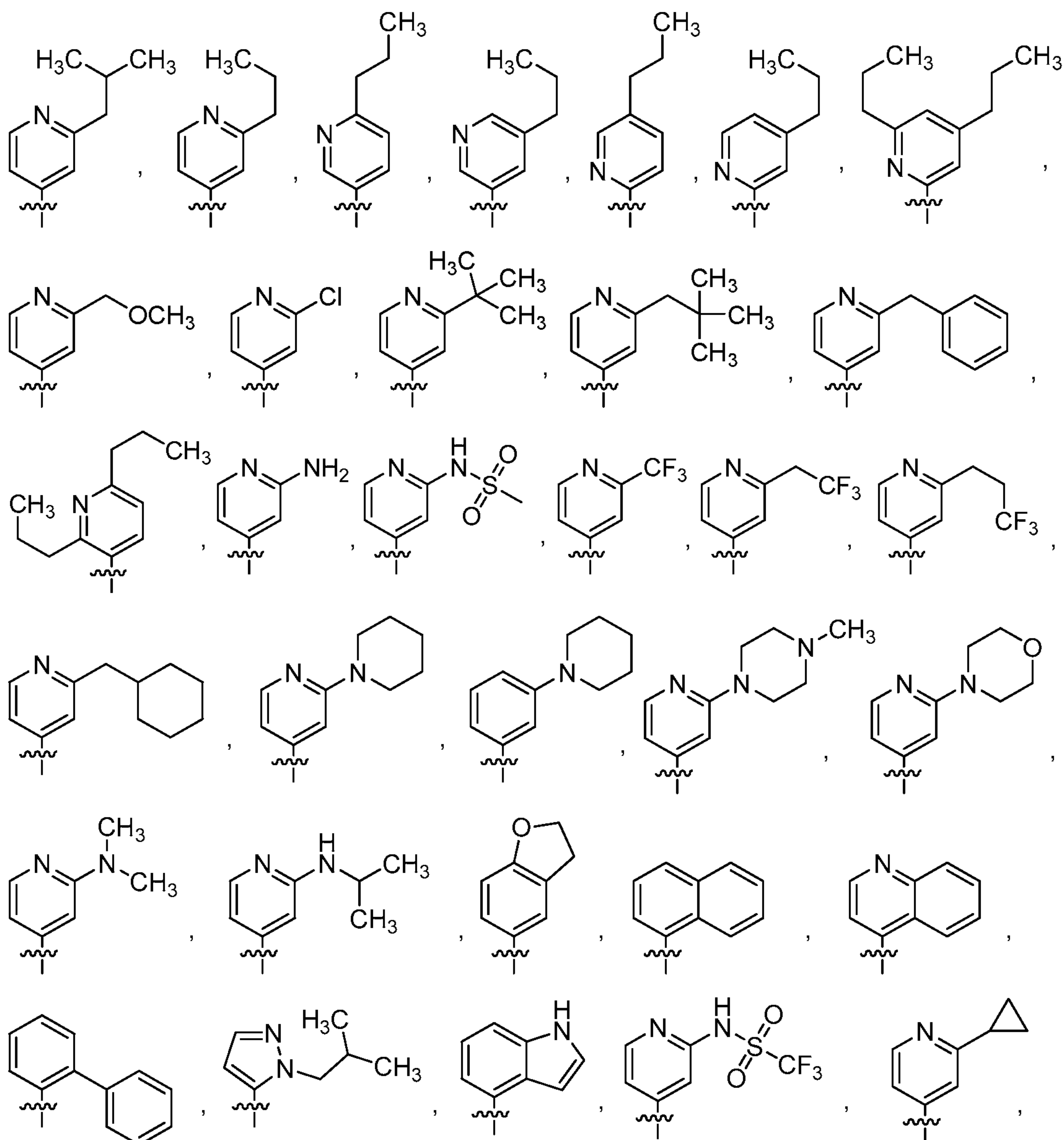
Each **m** and **n** is 1, 2 or 3.

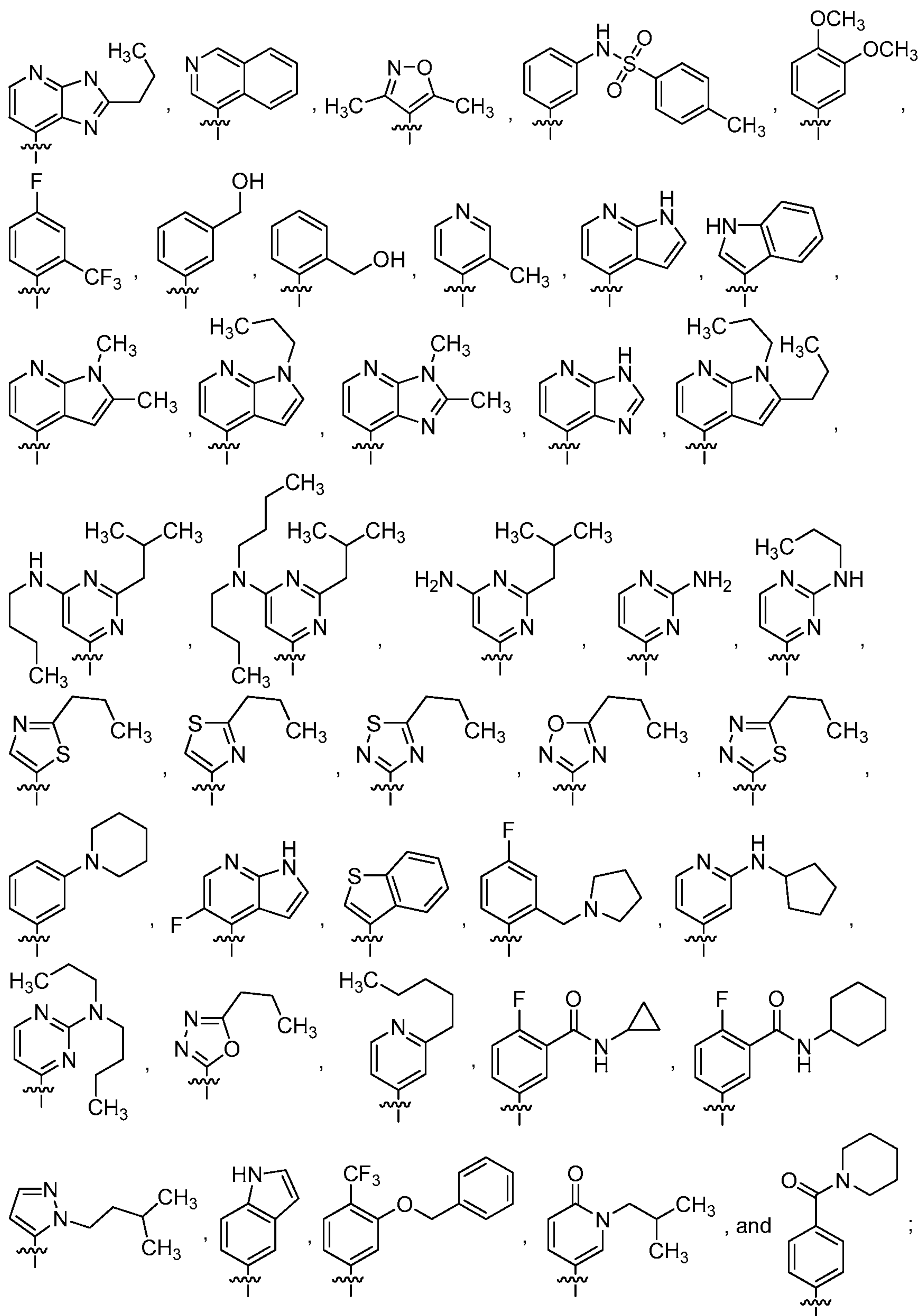
[011] In some embodiments, compounds disclosed herein fall within formulae (IIa) or (IIb):



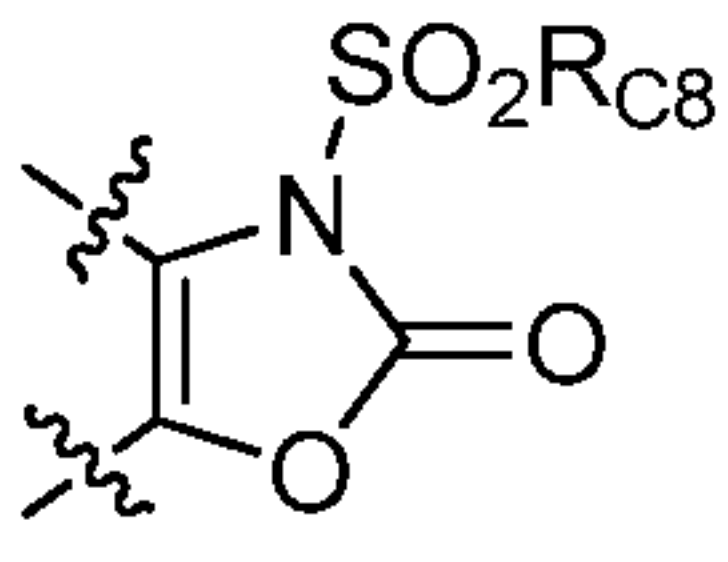
or a pharmaceutically acceptable salt thereof, wherein:

A is a moiety selected from the group consisting of:

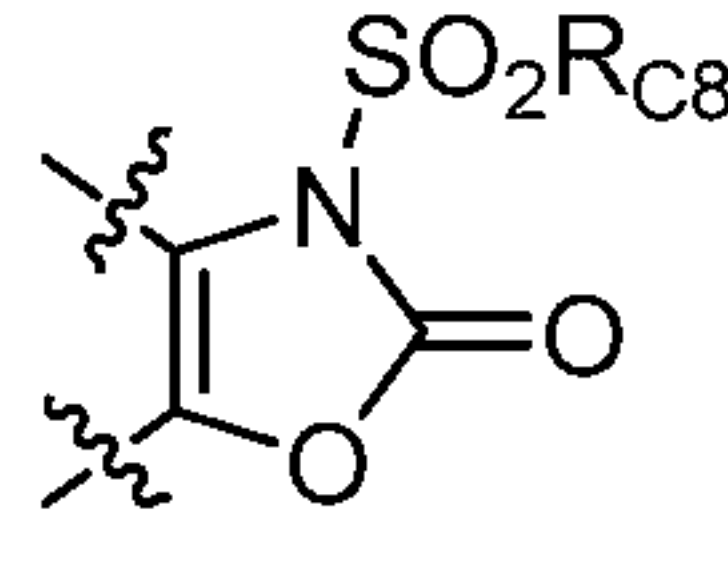




Each **R_{C4}**, **R_{C5}**, and **R_{C6}**, is independently hydrogen, halogen, CN, CF₃, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, -CO₂H, -CONR¹⁰R¹¹,

or -NHCONH₂; or is taken with **R**_{C7} to form the moiety  ;

R_{C7} is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -(**CR**_{9a}**R**_{9b})_m**NR**₁₀**R**₁₁, -CO₂-Alkyl, -(**CR**_{9a}**R**_{9b})_mO-Alkyl, -(**CR**_{9a}**R**_{9b})_mOPO₃Na₂, -(**CR**_{9a}**R**_{9b})_mO(**CR**_{9a}**R**_{9b})_nO-Alkyl, -(**CR**_{9a}**R**_{9b})_mO(C=O)-Alkyl, -(**CR**_{9a}**R**_{9b})_mO(**CR**_{9a}**R**_{9b})_nO(C=O)-Alkyl, -(C=O)CH=CH₂, -SO₂**R**_{C8'};

or is taken with one of **R**_{C4}, **R**_{C5} or **R**_{C6} to form the moiety  ;

R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

R_{C8'} is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

Each **R**_{9a} and **R**_{9b}, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R₁₀ and **R**₁₁ are independently hydrogen, -SO₂**R**_{C8'}, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a 1λ⁶,2-thiazolidine-1,1-dione, a 1,2λ⁶,3-oxathiazolidine-2,2-dione, or a 1λ⁶,2,5-thiadiazolidine-1,1-dione;

X is a heteroatom selected from S, O; or **NR**_B wherein **R**_B is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

Each *m* and *n* is 1, 2 or 3.

[012] Examples of compounds falling within one or more of the formulae described above are provided in Table 1, such as a compound selected from the group consisting of Compound Nos. 1 to 152; or a pharmaceutically acceptable salt, solvate, prodrug, or N-oxide thereof.

[013] Further provided is a pharmaceutical composition, comprising a compound of Formulae (Ia), (Ib), (IIa), or (IIb), or any variations described herein, or a salt thereof, and a pharmaceutically acceptable carrier or excipient.

[014] Further provided is a kit, comprising a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variations described herein, or a salt thereof, and instructions for use.

[015] Further provided are methods of treating liver fibrosis, elevated cholesterol levels, and insulin resistance in individuals in need thereof, such as humans, comprising administering to an individual in need thereof a therapeutically effective amount of a compound of Formulae (Ia), (Ib), (IIa), or (IIb), or any variations described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the individuals are diagnosed with or are suspected of having non-alcoholic steatohepatitis (NASH).

BRIEF DESCRIPTION OF THE DRAWINGS

[016] **FIG. 1A.** Western blot demonstrating inhibition of SREBP cleavage by Compound #37 in HepG2 Cells.

[017] **FIG. 1B.** Dose-response curves for IC₅₀ of Compound #37 for SREBP cleavage in HepG2 cells determined by Western blot and IC₅₀ of Compound #37 for effect on HepG2 cell viability. Error bars are $\pm$ SEM.

[018] **FIG. 1C.** Dose-response curve for IC₅₀ of Compound #37 for SREBP cleavage in HepG2 cells determined by luciferase expression. Error bars are $\pm$ SEM.

[019] **FIG. 2A.** Pharmacokinetic parameters for Compound #37 (mouse).

[020] **FIGS. 2-B.** Pharmacokinetic parameters for Compound #37 (dog).

[021] **FIG. 3.** Summary of lipid and cholesterol pathways downregulated by Compound #37 based on total transcriptome mRNA levels determined by microarray. Degree of pathway down-regulation is indicated by the shading, with darker shading indicating greater inhibition.

- [022] **FIG. 4.** Graph showing the effect of Compound #37 on collagen deposition in a diet-induced chronic NASH mouse model. Error bars indicate $\pm$ SEM. *, $p < 0.001$ by Mann-Whitney test. NASH, nonalcoholic steatohepatitis.
- [023] **FIGS. 5A-C.** HOMA-IR scores and blood glucose and plasma insulin concentrations in a diet-induced chronic NASH mouse model. **FIG. 5A**, plasma glucose. **FIG. 5B**, insulin. **FIG. 5C**, calculated HOMA-IR scores. Error bars indicate $\pm$ SEM.
- [024] **FIG. 6.** Photomicrographs showing the effect of Compound #37 on liver Oil red O staining in healthy female rats after 28 days of treatment. Left panel, control; right panel, 100/75 mg/g/day Compound #37.
- [025] **FIG. 7.** Graph showing the effect of Compound #37 on leptin concentration staining in healthy female rats. D4, day 4; D28, day 28; D56, day 56. *, $p < 0.05$.
- [026] **FIGS. 8A-B.** Graphs showing the effect of Compound #37 on circulating triglyceride concentration in male and female dogs on days. **FIG. 8A**, male dogs. **FIG. 8B**, female dogs. D-5, day 5 (pre-dose); D14, day 14; D27, day 27 (end of dosing, $N = 3$); D57, day 57 (end of recovery, $N = 2$). *, $p < 0.01$; * *, $p < 0.05$.
- [027] **FIGS. 9A-B.** Graphs showing the effect of Compound #37 on circulating total cholesterol concentration in male and female dogs on days. **FIG. 9A**, male dogs. **FIG. 9B**, female dogs. D-5, day 5 (pre-dose); D14, day 14; D28, day 28 (end of dosing, $N = 3$); D58, day 58 (end of recovery, $N = 2$).

DETAILED DESCRIPTION

Definitions

[028] For use herein, unless clearly indicated otherwise, use of the terms “a,” “an,” and the like refers to one or more.

[029] As used herein, reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X.”

[030] “Alkyl” refers to and includes saturated linear or branched univalent hydrocarbon structures and combinations thereof. Particular alkyl groups are those having 1 to 6 carbon atoms (a “C1-C6 alkyl”). When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, “butyl” is meant to include *n*-butyl, *sec*-butyl, *iso*-butyl, and

tert-butyl; “propyl” includes *n*-propyl and *iso*-propyl. This term is exemplified by groups such as methyl, *t*-butyl, *n*-heptyl, octyl, and the like.

[031] “Alkenyl” refers to an unsaturated hydrocarbon group having at least one site of olefinic unsaturation (*i.e.*, having at least one moiety of the formula C=C) and preferably having from 2 to 10 carbon atoms and more preferably 2 to 8 carbon atoms. Examples of alkenyl include but are not limited to ethenyl, $-\text{CH}=\text{CH}_2$, $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_3$ and $-\text{CH}=\text{CH}-\text{CH}=\text{CH}_2$.

[032] “Alkynyl” refers to an unsaturated hydrocarbon group having at least one site of acetylenic unsaturation (*i.e.*, having at least one moiety of the formula C≡C) and preferably having from 2 to 10 carbon atoms and more preferably 2 to 8 carbon atoms and the like. Examples of alkynyl include but are not limited to ethynyl, “ $-\text{C}\equiv\text{CH}$,” $-\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_3$ and $-\text{C}\equiv\text{C}-\text{C}\equiv\text{CH}$.

[033] “Cycloalkyl” refers to and includes cyclic univalent hydrocarbon structures. Cycloalkyl can consist of one ring, such as cyclohexyl, or multiple rings, such as adamantyl. A cycloalkyl comprising more than one ring may be fused, spiro or bridged, or combinations thereof. A preferred cycloalkyl is a saturated cyclic hydrocarbon having from 3 to 13 annular carbon atoms. A more preferred cycloalkyl is a saturated cyclic hydrocarbon having from 3 to 6 annular carbon atoms (a “C3-C6 cycloalkyl”). Examples of cycloalkyl groups include adamantyl, decahydronaphthalenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

[034] “Cycloalkenyl” refers to an unsaturated hydrocarbon group within a cycloalkyl having at least one site of olefinic unsaturation (*i.e.*, having at least one moiety of the formula C=C). Cycloalkenyl can consist of one ring, such as cyclohexyl, or multiple rings, such as norbornenyl. A more preferred cycloalkenyl is an unsaturated cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a “C₃-C₈ cycloalkenyl”). Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and the like.

[035] “Heterocycle,” “heterocyclic,” or “heterocyclyl” refers to a saturated or an unsaturated non-aromatic group having a single ring or multiple condensed rings, and having from 1 to 10 annular carbon atoms and from 1 to 4 annular heteroatoms, such as nitrogen, sulfur or oxygen, and the like. A heterocycle comprising more than one ring may be fused, spiro or bridged, or any combination thereof. In fused ring systems, one or more of the rings can be aryl or heteroaryl. A heterocycle having more than one ring where at least one ring is

aromatic may be connected to the parent structure at either a non-aromatic ring position or at an aromatic ring position. In one variation, a heterocycle having more than one ring where at least one ring is aromatic is connected to the parent structure at a non-aromatic ring position.

[036] “Aryl” as used herein refers to an unsaturated aromatic carbocyclic group having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl) which condensed rings may or may not be aromatic. The aryl group may be optionally substituted independently with one or more substituents described herein. Particular aryl groups are those having from 6 to 14 annular (*i.e.*, ring) carbon atoms (a “C6-C14 aryl”). An aryl group having more than one ring where at least one ring is non-aromatic may be connected to the parent structure at either an aromatic ring position or at a non-aromatic ring position. In one variation, an aryl group having more than one ring where at least one ring is non-aromatic is connected to the parent structure at an aromatic ring position.

[037] “Heteroaryl” as used herein refers to an unsaturated aromatic cyclic group having from 1 to 14 annular (*i.e.*, ring) carbon atoms and at least one annular heteroatom, including but not limited to heteroatoms such as nitrogen, oxygen and sulfur. A heteroaryl group may have a single ring (*e.g.*, pyridyl, furyl) or multiple condensed rings (*e.g.*, indoliziny, benzothienyl) which condensed rings may or may not be aromatic. The heteroaryl group may be optionally substituted independently with one or more substituents described herein. Particular heteroaryl groups are 5- to 14-membered rings having 1 to 12 annular (*i.e.*, ring) carbon atoms and 1 to 6 annular (*i.e.*, ring) heteroatoms independently selected from nitrogen, oxygen and sulfur; 5- to 10-membered rings having 1 to 8 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur; and 5-, 6- or 7-membered rings having 1 to 5 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. In one variation, heteroaryl includes monocyclic aromatic 5-, 6- or 7-membered rings having from 1 to 6 annular carbon atoms and 1 to 4 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. In another variation, heteroaryl includes polycyclic aromatic rings having from 1 to 12 annular carbon atoms and 1 to 6 annular heteroatoms independently selected from nitrogen, oxygen and sulfur. A heteroaryl group having more than one ring where at least one ring is non-aromatic may be connected to the parent structure at either an aromatic ring position or at a non-aromatic ring position. In one variation, a heteroaryl group having more than one ring where at least one ring is non-aromatic is connected to the parent structure at an aromatic ring position.

[038] “Alkoxy” refers to the group alkyl-O-, which includes, by way of example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.

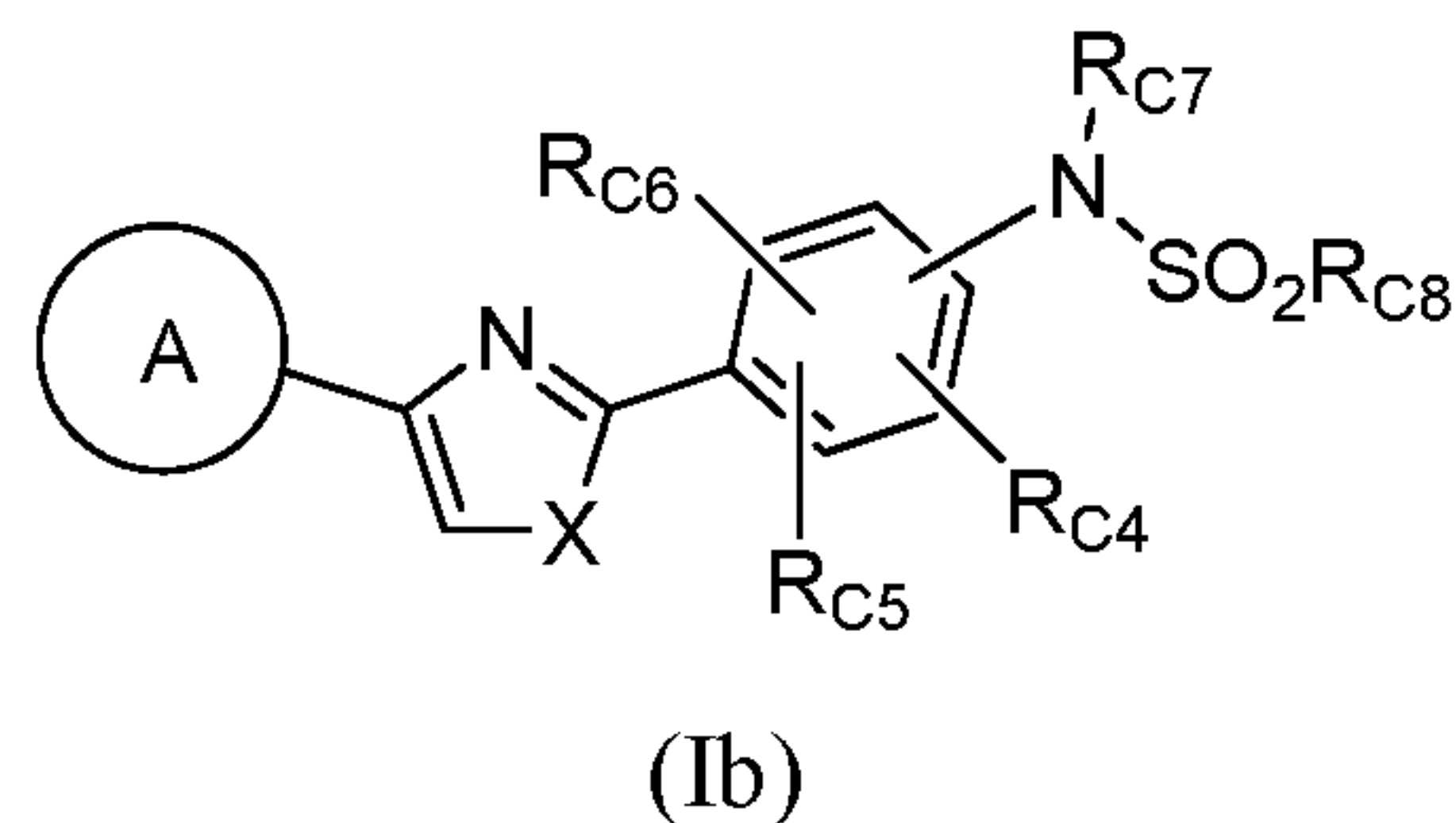
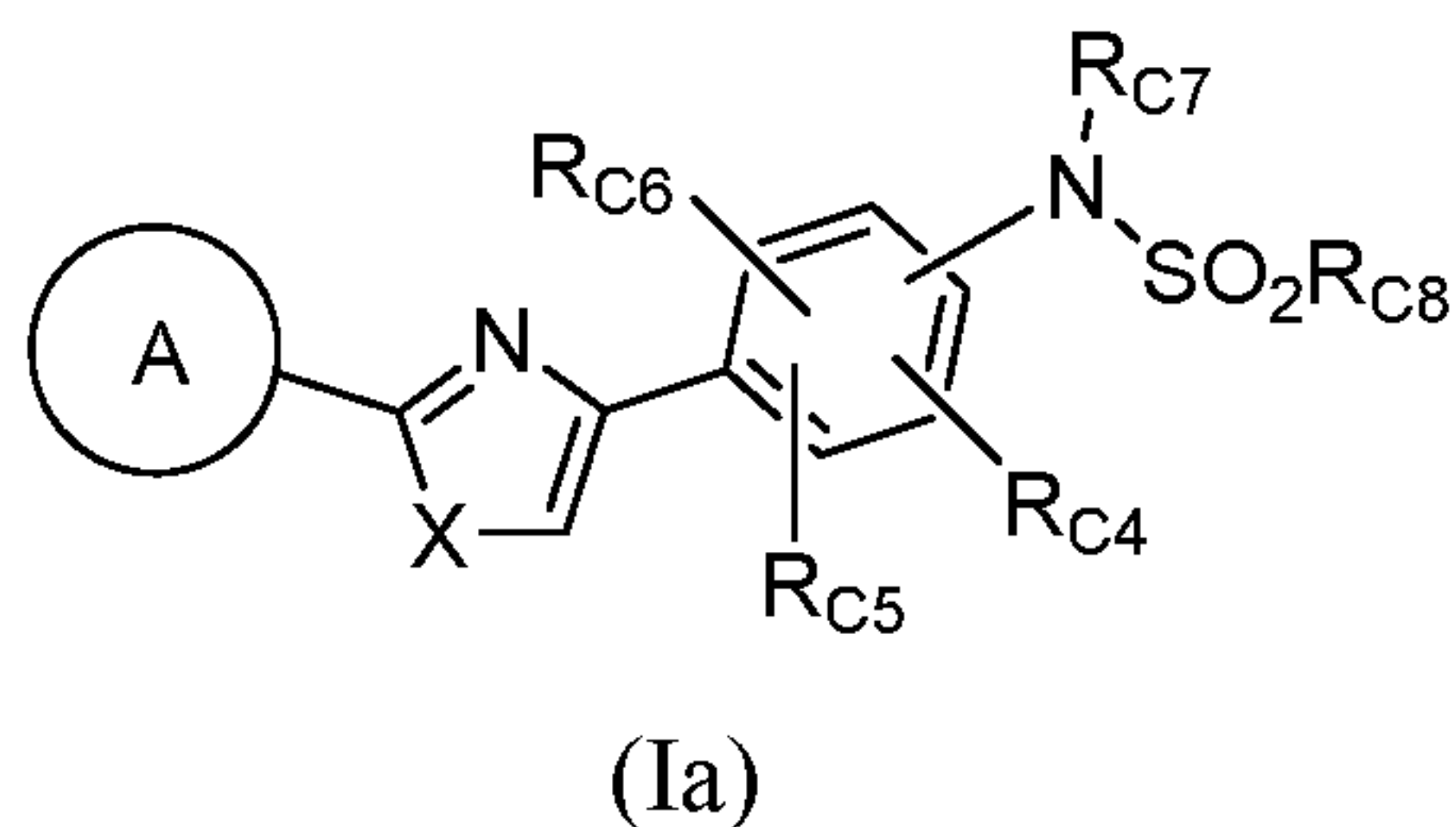
[039] “Hydroxyalkyl” refers to the group alkyl-OH, which includes, by way of example, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxyprop-1-yl, 2-hydroxyprop-2-yl, 3-hydroxypropyl, 4-hydroxybutyl, 5-hydroxypentyl, 6-hydroxyhexyl, and the like.

[040] “Halogen” refers to elements of the Group 17 series having atomic number 9 to 85. Preferred halo groups include the radicals of fluorine, chlorine, bromine and iodine. Where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached, *e.g.*, dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be but are not necessarily the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl. An alkyl group in which each H is replaced with a halo group is referred to as a “perhaloalkyl.” An alkenyl group in which each H is replaced with a halo group is referred to as a “perhaloalkenyl.” An alkynyl group in which each H is replaced with a halo group is referred to as a “perhaloalkynyl.” A preferred perhaloalkyl group is trifluoroalkyl (-CF₃). Similarly, “perhaloalkoxy” refers to an alkoxy group in which a halogen takes the place of each H in the hydrocarbon making up the alkyl moiety of the alkoxy group. An example of a perhaloalkoxy group is trifluoromethoxy (-OCF₃).

[041] Any and all stereoisomers, including geometric isomers (*cis/trans* or *E/Z* isomers), tautomers, salts, N-oxides, and solvates of the compounds described herein can be used in the disclosed methods. This disclosure also provides methods of making such compounds.

Compounds

[042] In some embodiments, compounds disclosed herein fall within formulae (Ia) or (Ib):

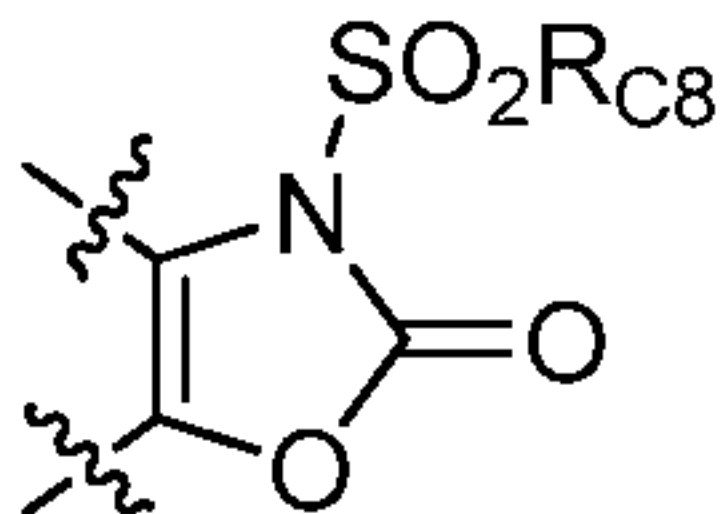


or a pharmaceutically acceptable salt thereof, wherein:

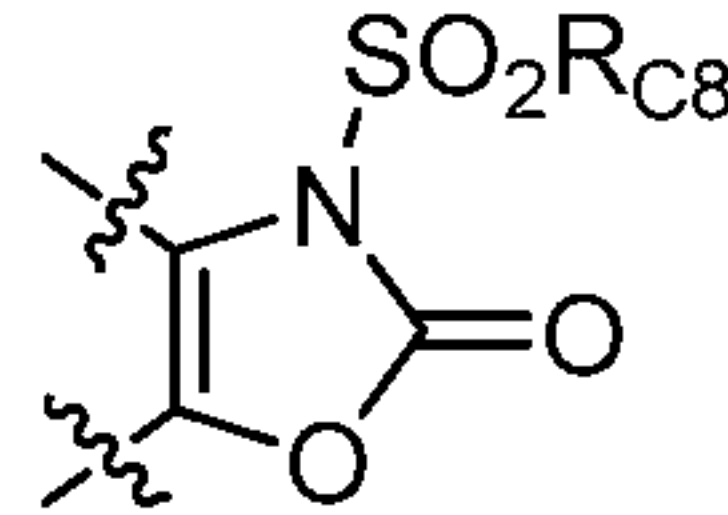
A is either:

- i. an aryl or heteroaryl, each having only one ring, substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF₃, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -(CH₂)_mCF₃, =O, -CH₂OCH₃, -OBn, -CO₂H, -CO₂-Alkyl, -NR₁₀R₁₁, and -CONR₁₀R₁₁; or
- ii. an aryl or heteroaryl, each having more than one ring, optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF₃, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -(CH₂)_mCF₃, =O, -CH₂OCH₃, -CH₂OH, -OBn, -CO₂H, -CO₂-Alkyl, -NR₁₀R₁₁, and -CONR₁₀R₁₁;

Each **R_{C4}**, **R_{C5}**, and **R_{C6}**, is independently hydrogen, halogen, CN, CF₃, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, -CO₂H, -CONR₁₀R₁₁,

or -NHCONH₂; or is taken with **R_{C7}** to form the moiety  ;

R_{C7} is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -(CR_{9a}R_{9b})_mNR₁₀R₁₁, -CO₂-Alkyl, -(CR_{9a}R_{9b})_mO-Alkyl, -(CR_{9a}R_{9b})_mOPO₃Na₂, -(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO-Alkyl, -(CR_{9a}R_{9b})_mO(C=O)-Alkyl, -(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)-Alkyl, -(C=O)CH=CH₂, -SO₂R_{C8};

or is taken with one of **R_{C4}**, **R_{C5}** or **R_{C6}** to form the moiety  ;

R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

R_{C8'} is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

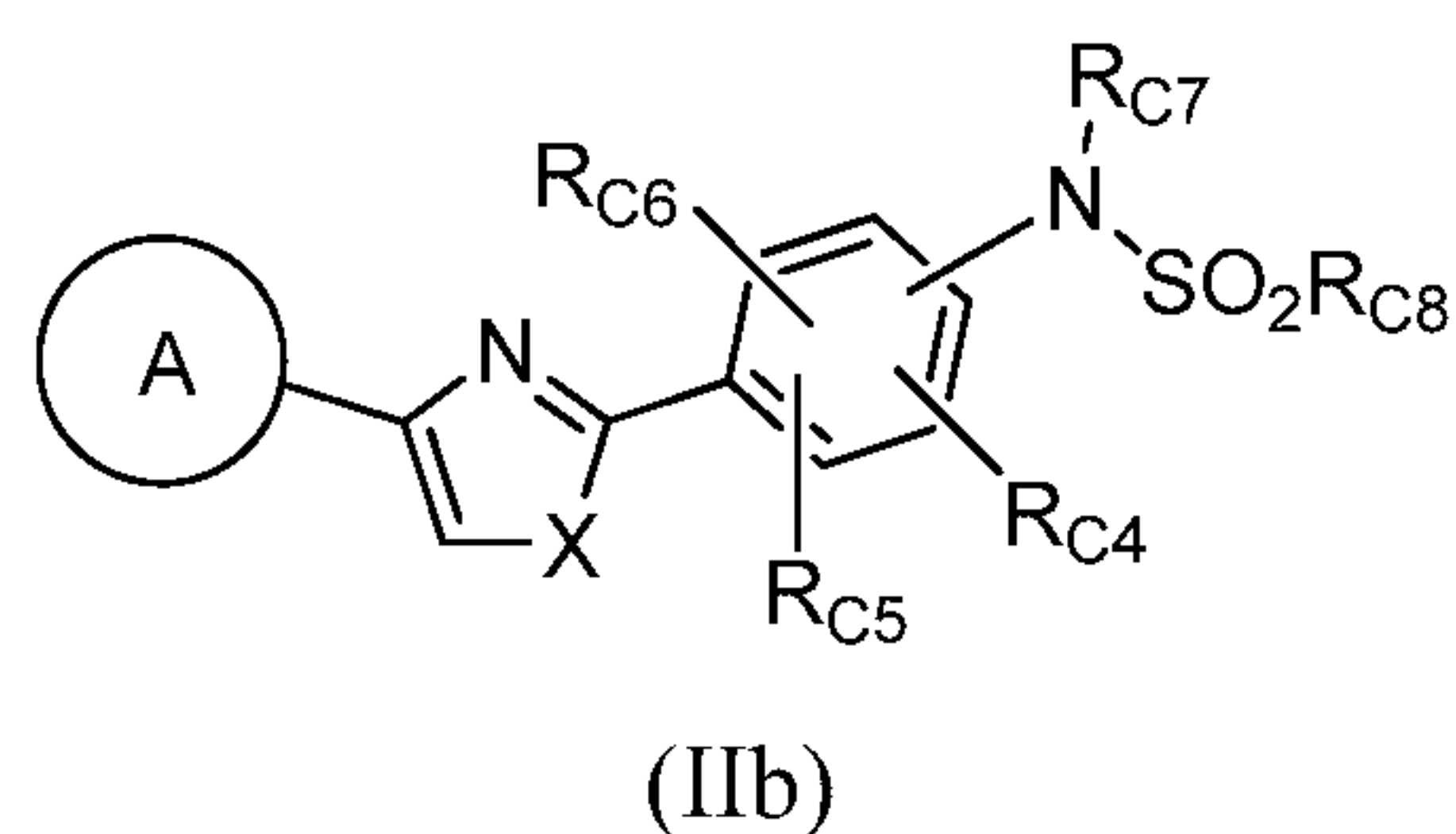
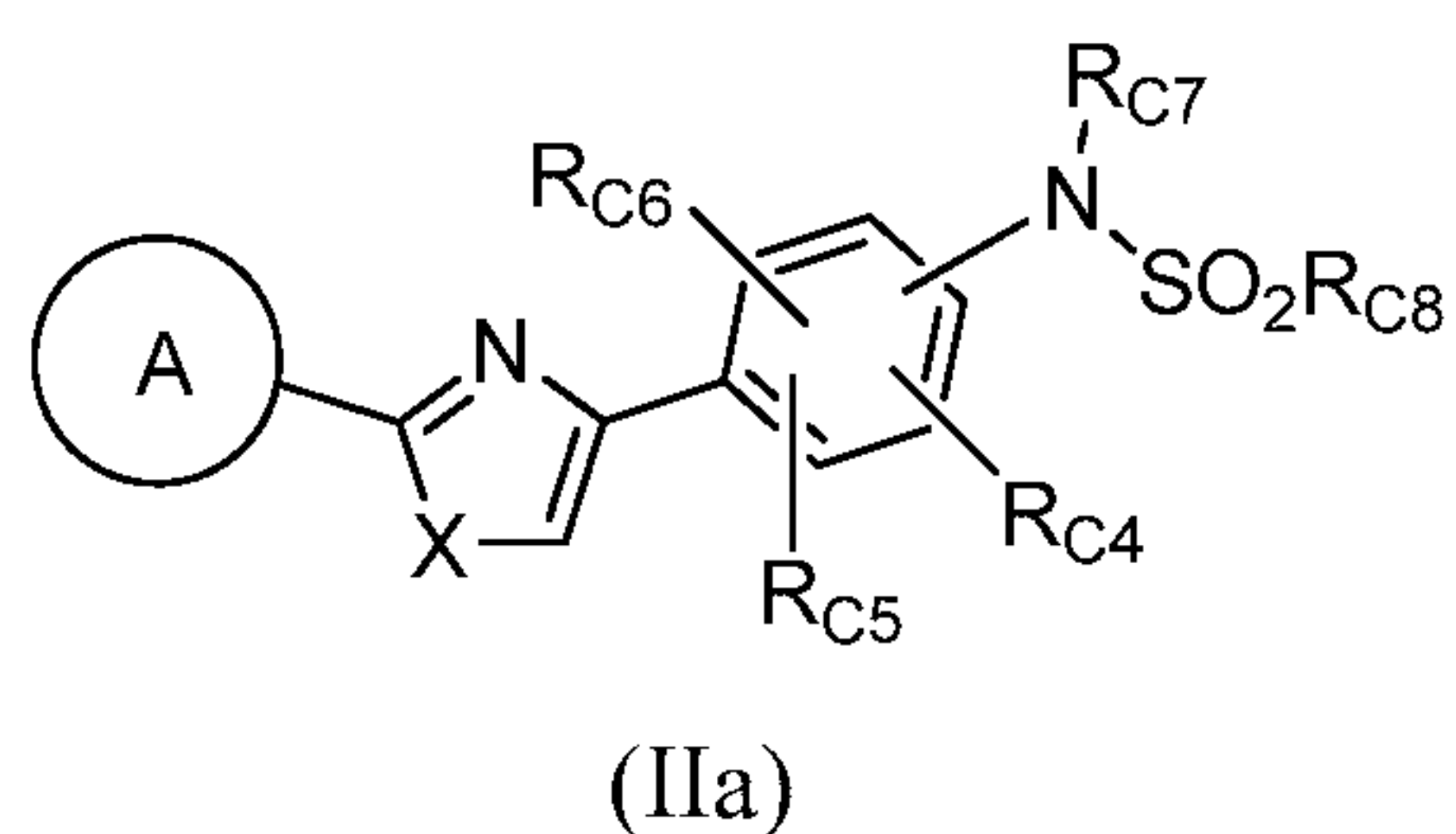
Each **R_{9a}** and **R_{9b}**, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R10 and **R11** are independently hydrogen, -SO₂**R_{C8'}**, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a 1λ⁶,2-thiazolidine-1,1-dione, a 1,2λ⁶,3-oxathiazolidine-2,2-dione, or a 1λ⁶,2,5-thiadiazolidine-1,1-dione;

X is a heteroatom selected from S, O; or **NR_B** wherein **R_B** is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

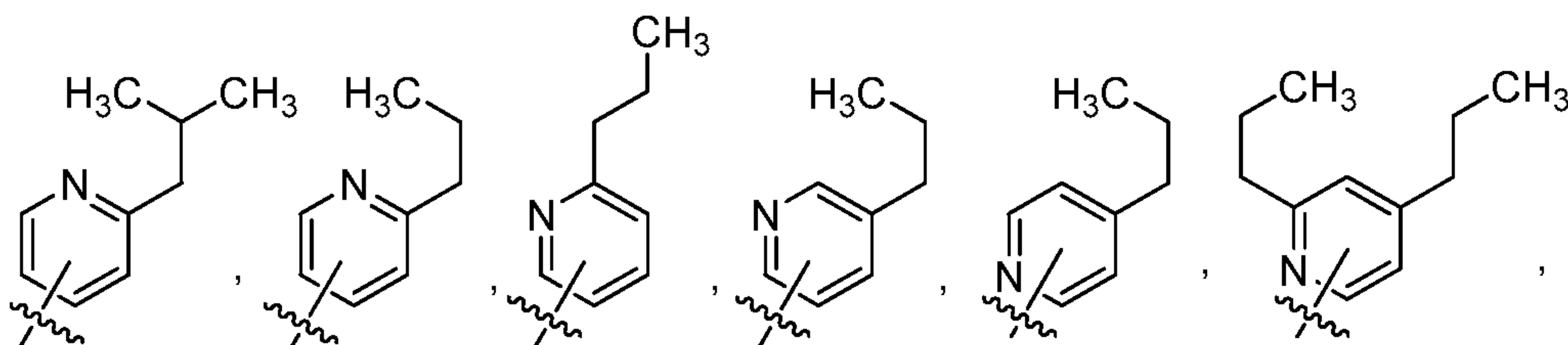
Each **m** and **n** is 1, 2 or 3.

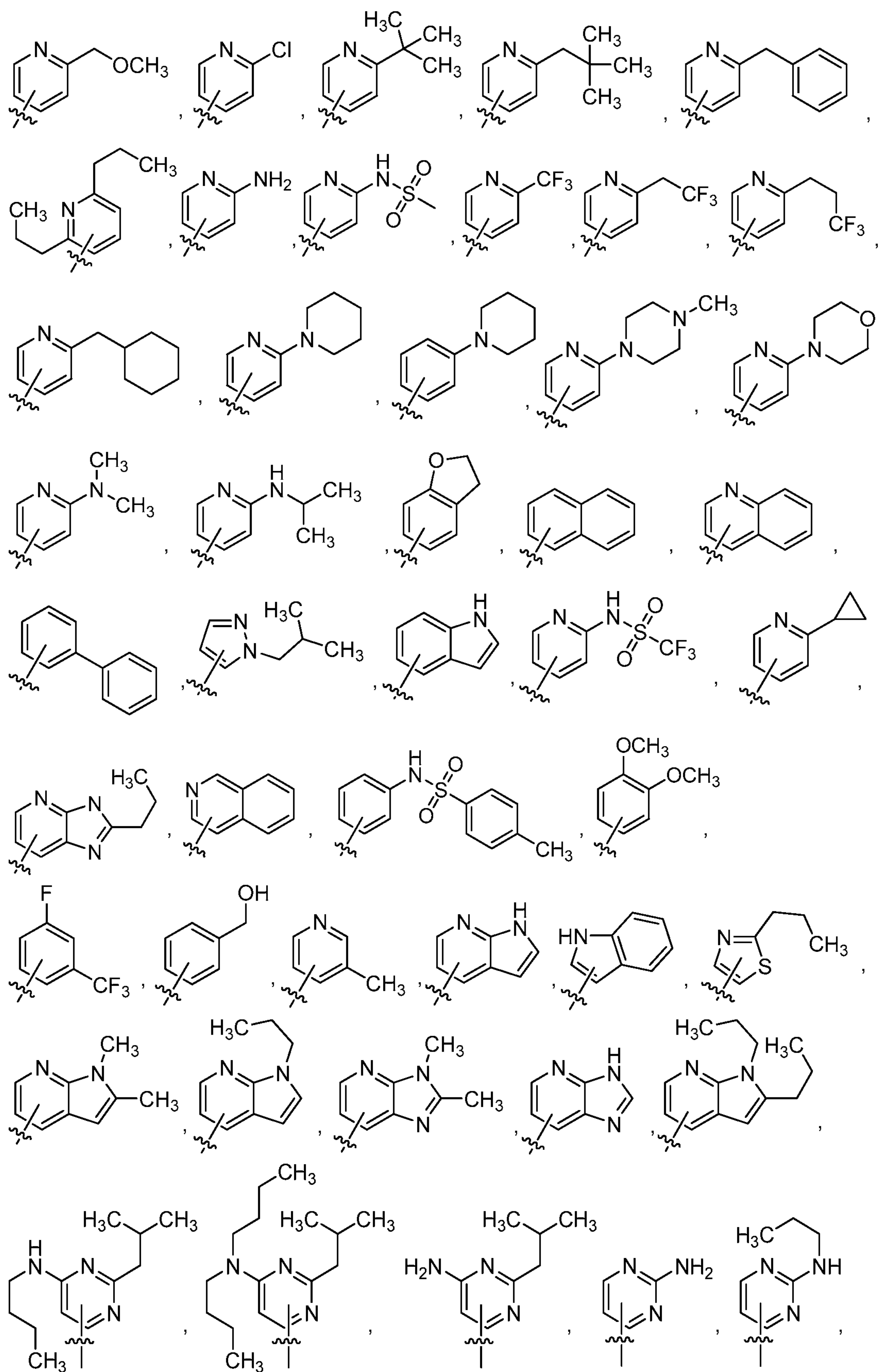
[043] In some embodiments, compounds disclosed herein fall within formulae (IIa) or (IIb):

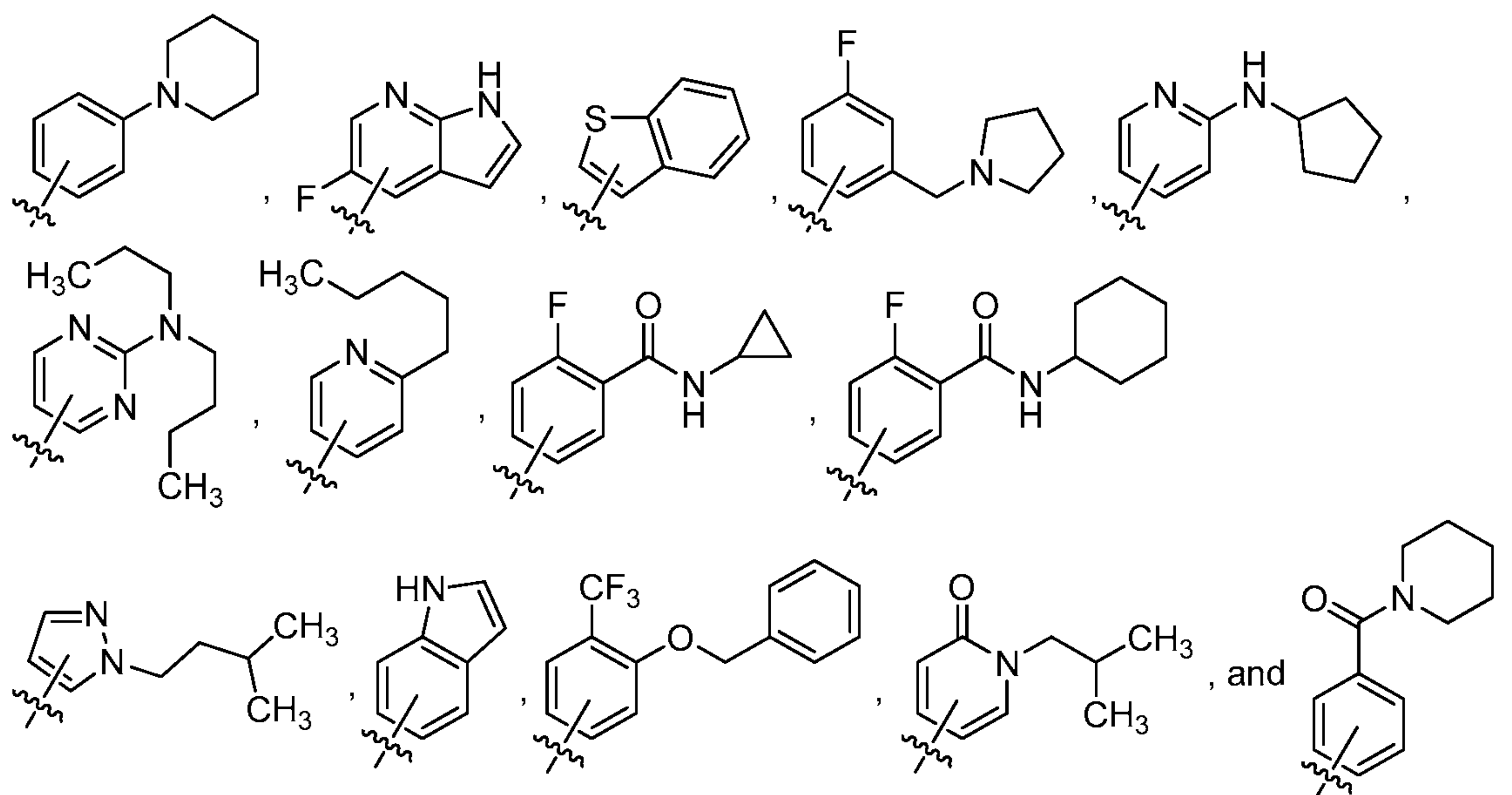


or a pharmaceutically acceptable salt thereof, wherein:

A is a moiety selected from the group consisting of:

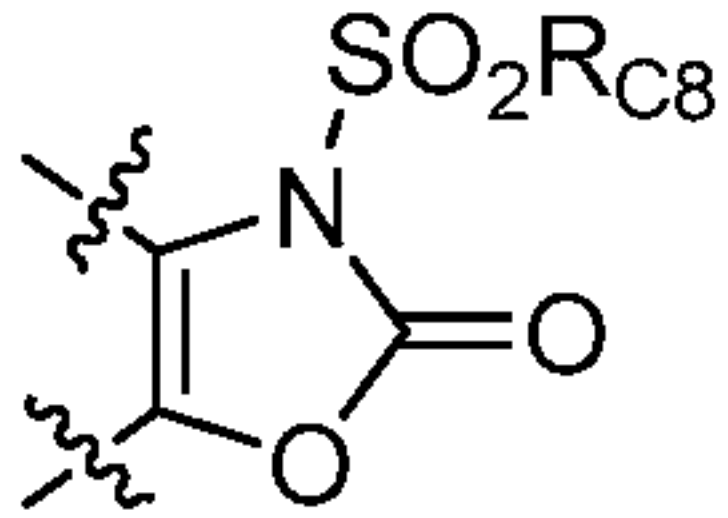




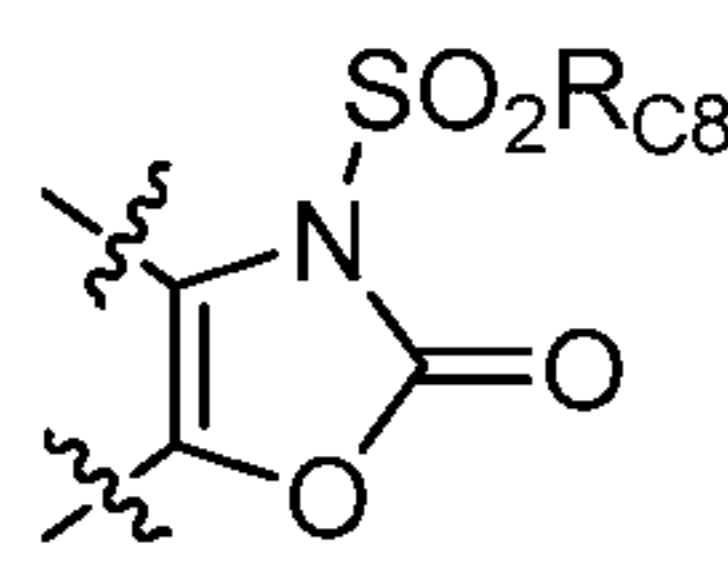


wherein the ring containing X is linked to ring A at any available position on ring A;

Each **R_{C4}**, **R_{C5}**, and **R_{C6}**, is independently hydrogen, halogen, CN, CF₃, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, -CO₂H, -CONR₁₀R₁₁,

or -NHCONH₂; or is taken with **R_{C7}** to form the moiety  ;

R_{C7} is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -(CR_{9a}R_{9b})_mNR₁₀R₁₁, -CO₂-Alkyl, -(CR_{9a}R_{9b})_mO-Alkyl, -(CR_{9a}R_{9b})_mOPO₃Na₂, -(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO-Alkyl, -(CR_{9a}R_{9b})_mO(C=O)-Alkyl, -(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)-Alkyl, -(C=O)CH=CH₂, -SO₂R_{C8};

or is taken with one of **R_{C4}**, **R_{C5}** or **R_{C6}** to form the moiety  ;

R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

R_{C8'} is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6

perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

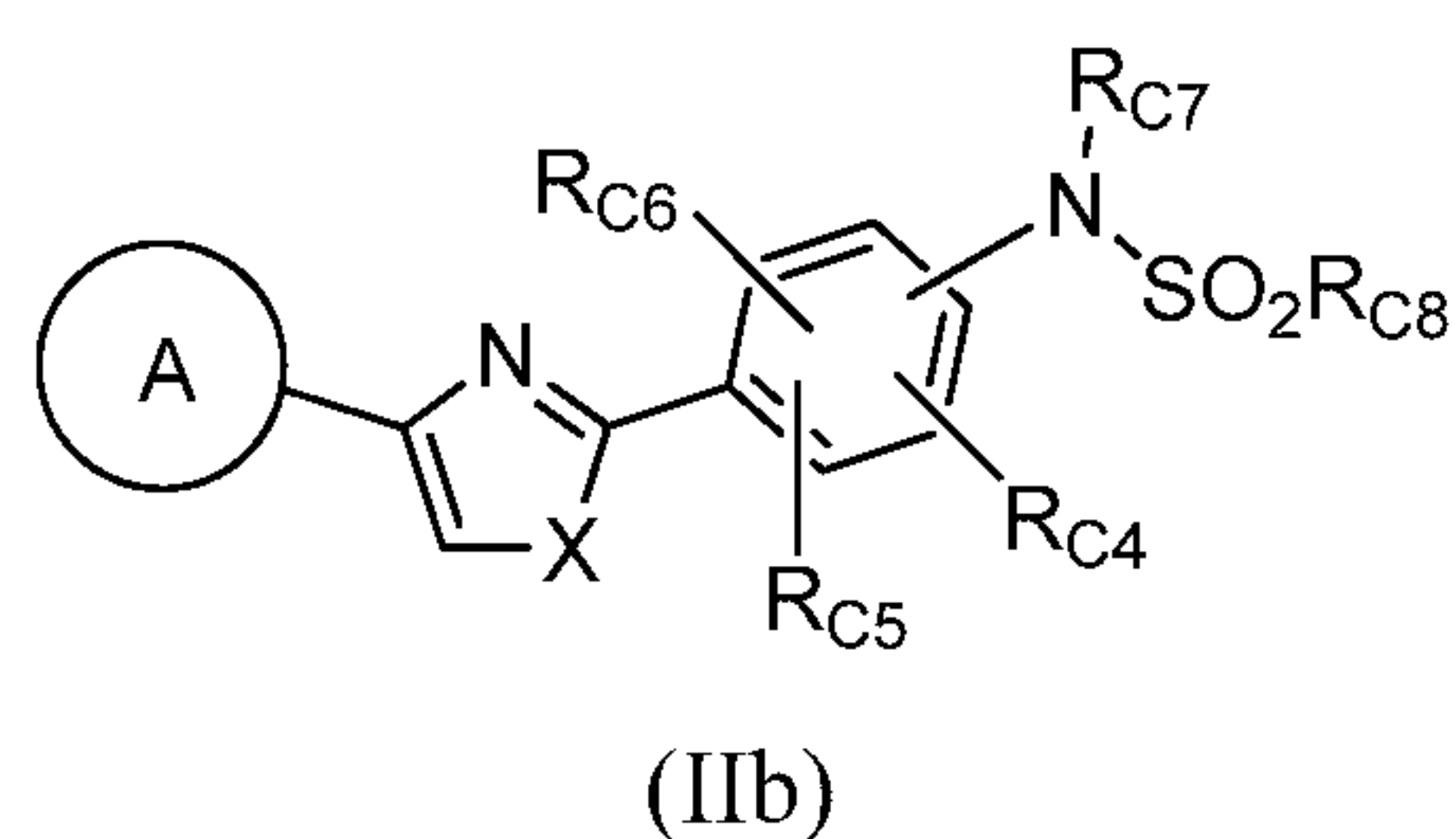
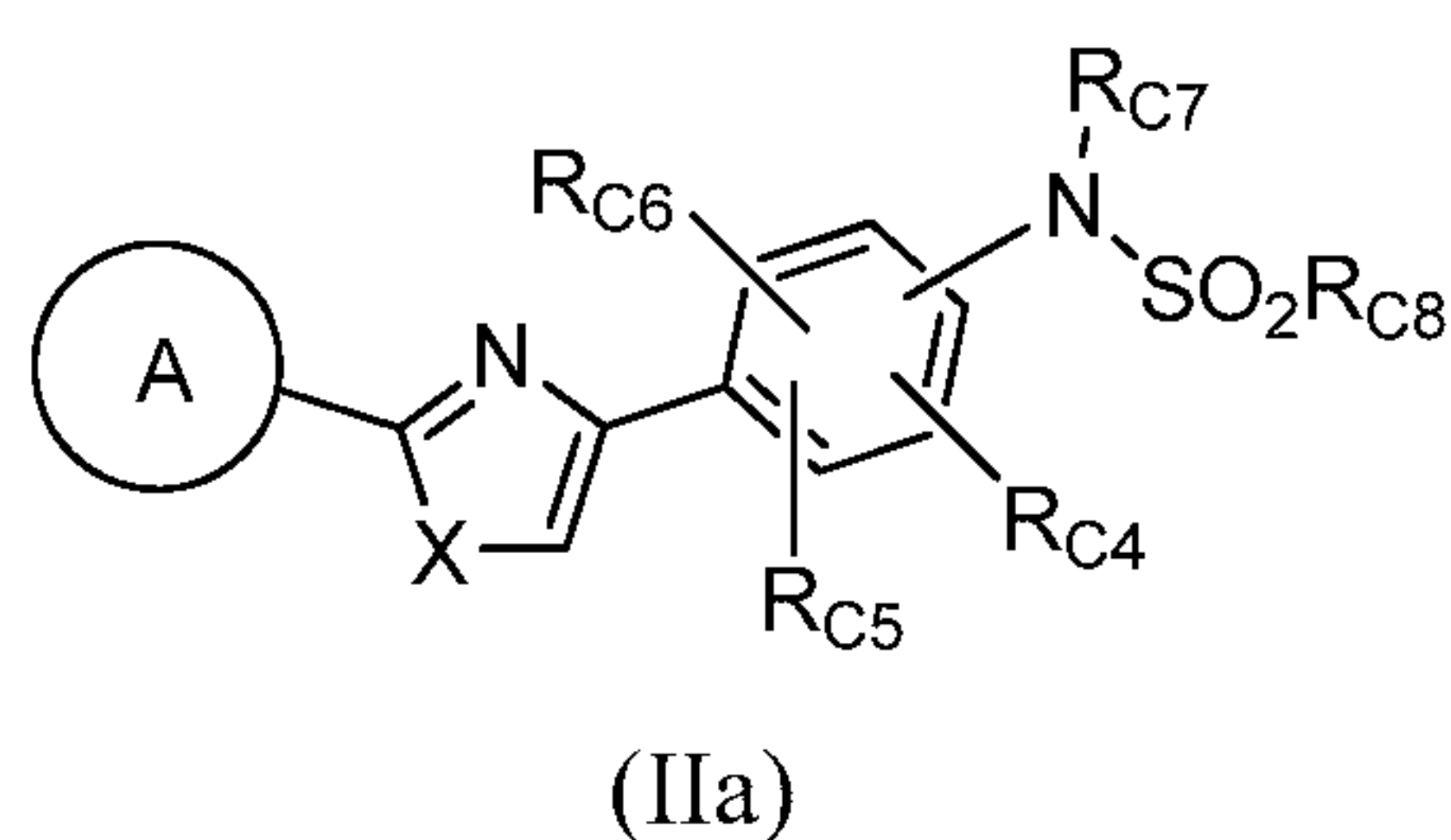
Each **R**_{9a} and **R**_{9b}, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R₁₀ and **R**₁₁ are independently hydrogen, -SO₂**R**_{C8'}, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a 1λ⁶,2-thiazolidine-1,1-dione, a 1,2λ⁶,3-oxathiazolidine-2,2-dione, or a 1λ⁶,2,5-thiadiazolidine-1,1-dione;

X is a heteroatom selected from S, O; or **NR**_B wherein **R**_B is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

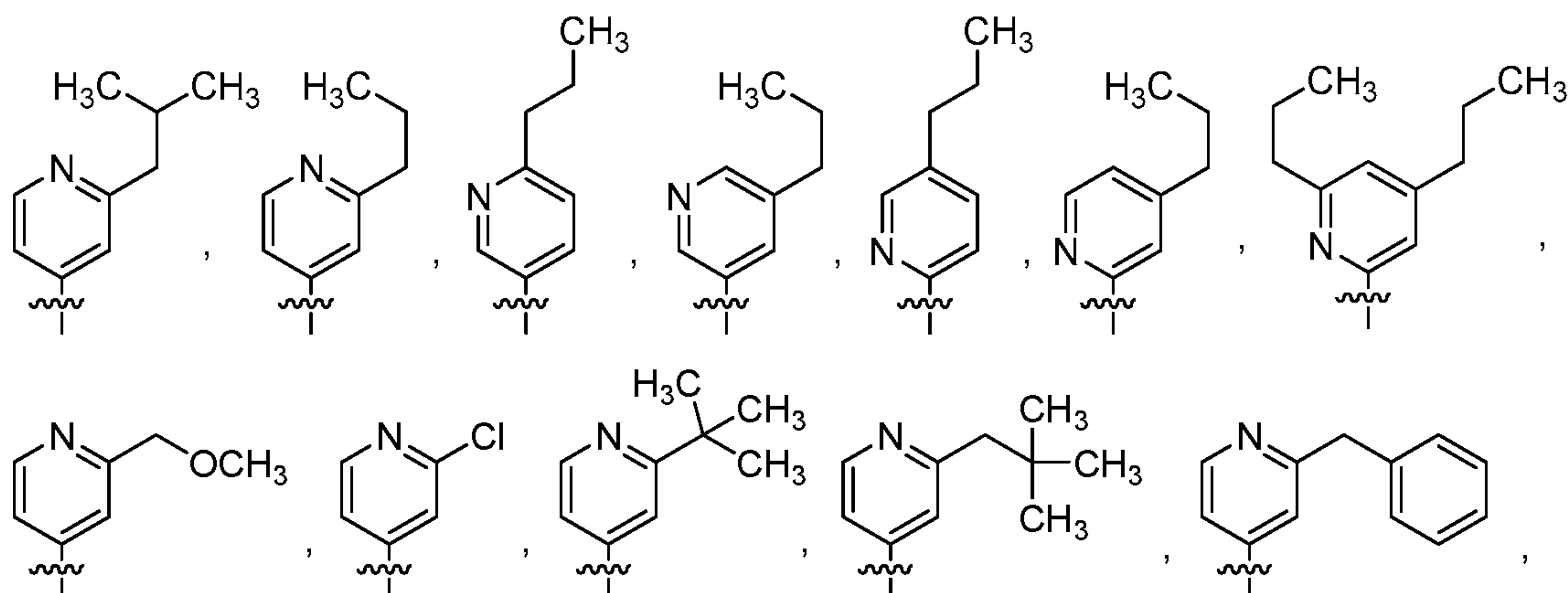
Each *m* and *n* is 1, 2 or 3.

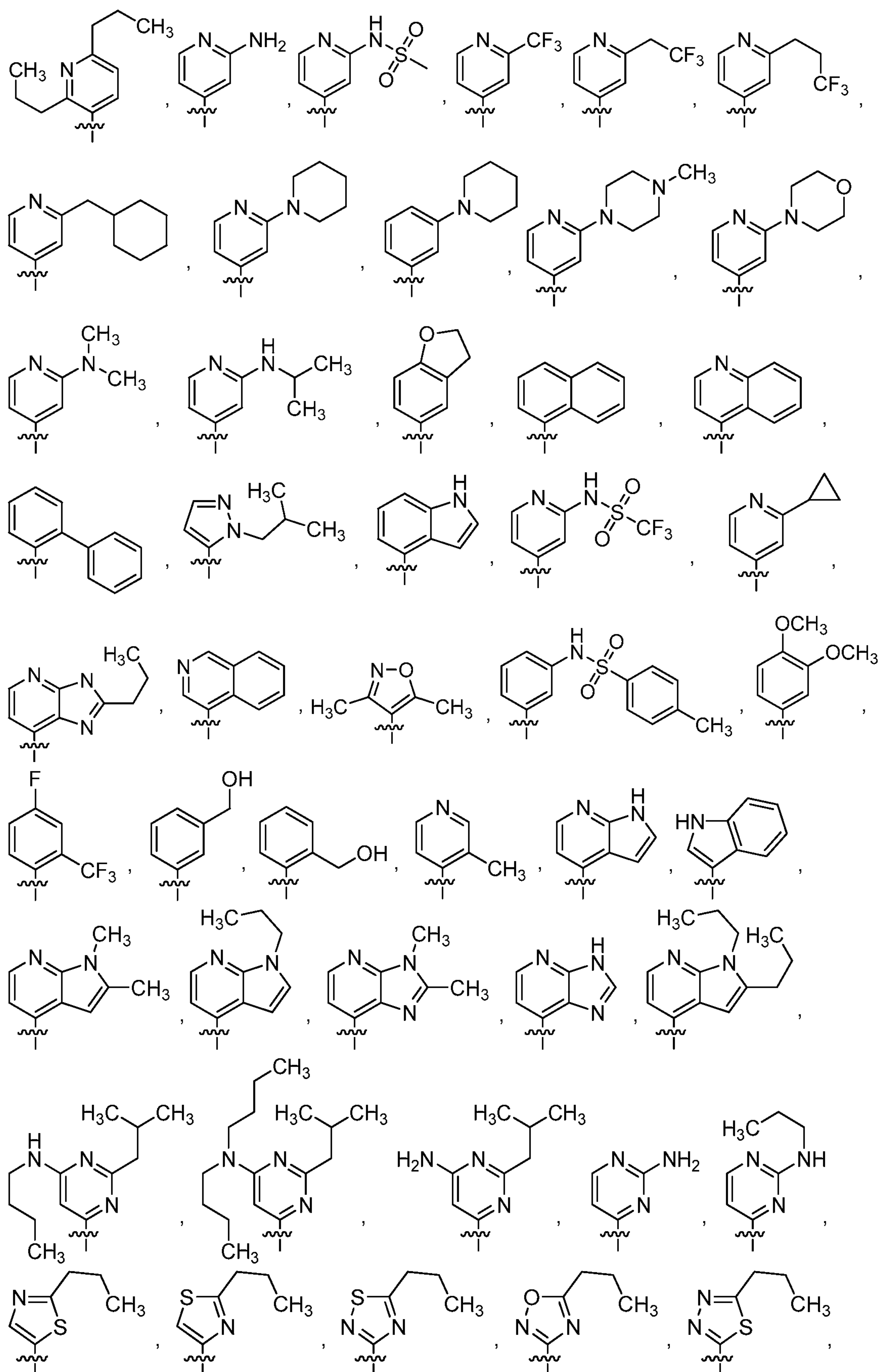
[044] In some embodiments, compounds disclosed herein fall within formulae (IIa) or (IIb):

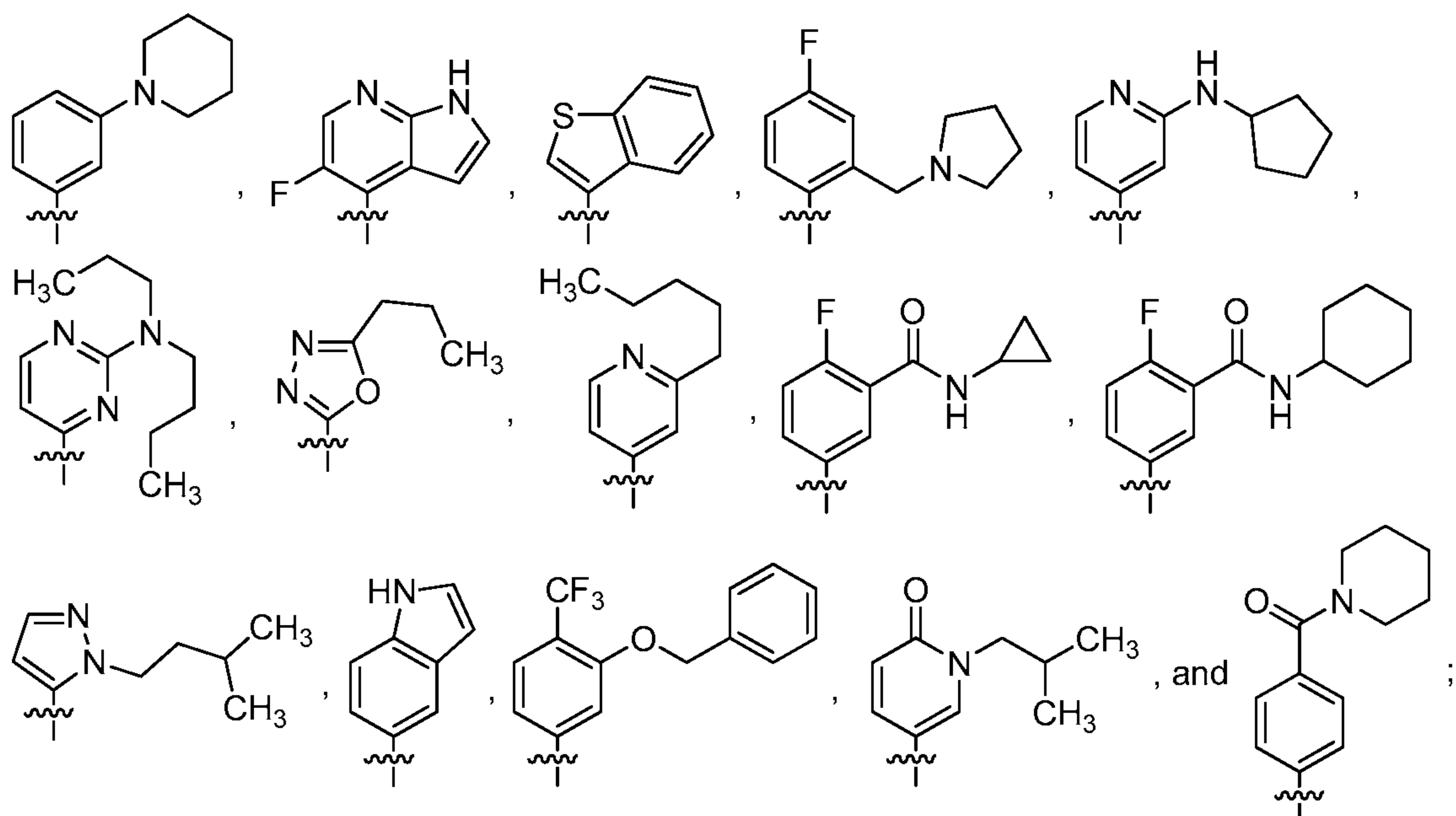


or a pharmaceutically acceptable salt thereof, wherein:

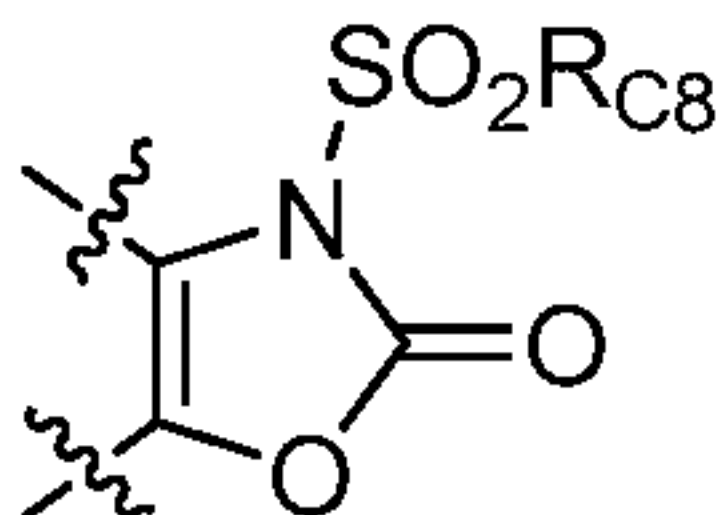
A is a moiety selected from the group consisting of:



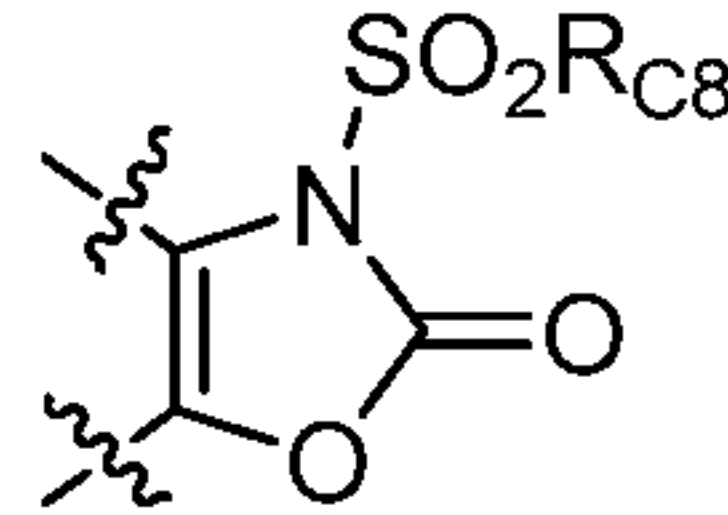




Each **R_{C4}**, **R_{C5}**, and **R_{C6}**, is independently hydrogen, halogen, CN, CF₃, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, -CO₂H, -CONR₁₀R₁₁,

or -NHCONH₂; or is taken with **R_{C7}** to form the moiety  ;

R_{C7} is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -(C**R_{9a}****R_{9b}**)_mNR₁₀R₁₁, -CO₂-Alkyl, -(C**R_{9a}****R_{9b}**)_mO-Alkyl, -(C**R_{9a}****R_{9b}**)_mOPO₃Na₂, -(C**R_{9a}****R_{9b}**)_mO(C**R_{9a}****R_{9b}**)_nO-Alkyl, -(C**R_{9a}****R_{9b}**)_mO(C=O)-Alkyl, -(C**R_{9a}****R_{9b}**)_mO(C**R_{9a}****R_{9b}**)_nO(C=O)-Alkyl, -(C=O)CH=CH₂, -SO₂**R_{C8}**;

or is taken with one of **R_{C4}**, **R_{C5}** or **R_{C6}** to form the moiety  ;

R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

R_{C8'} is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen

atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

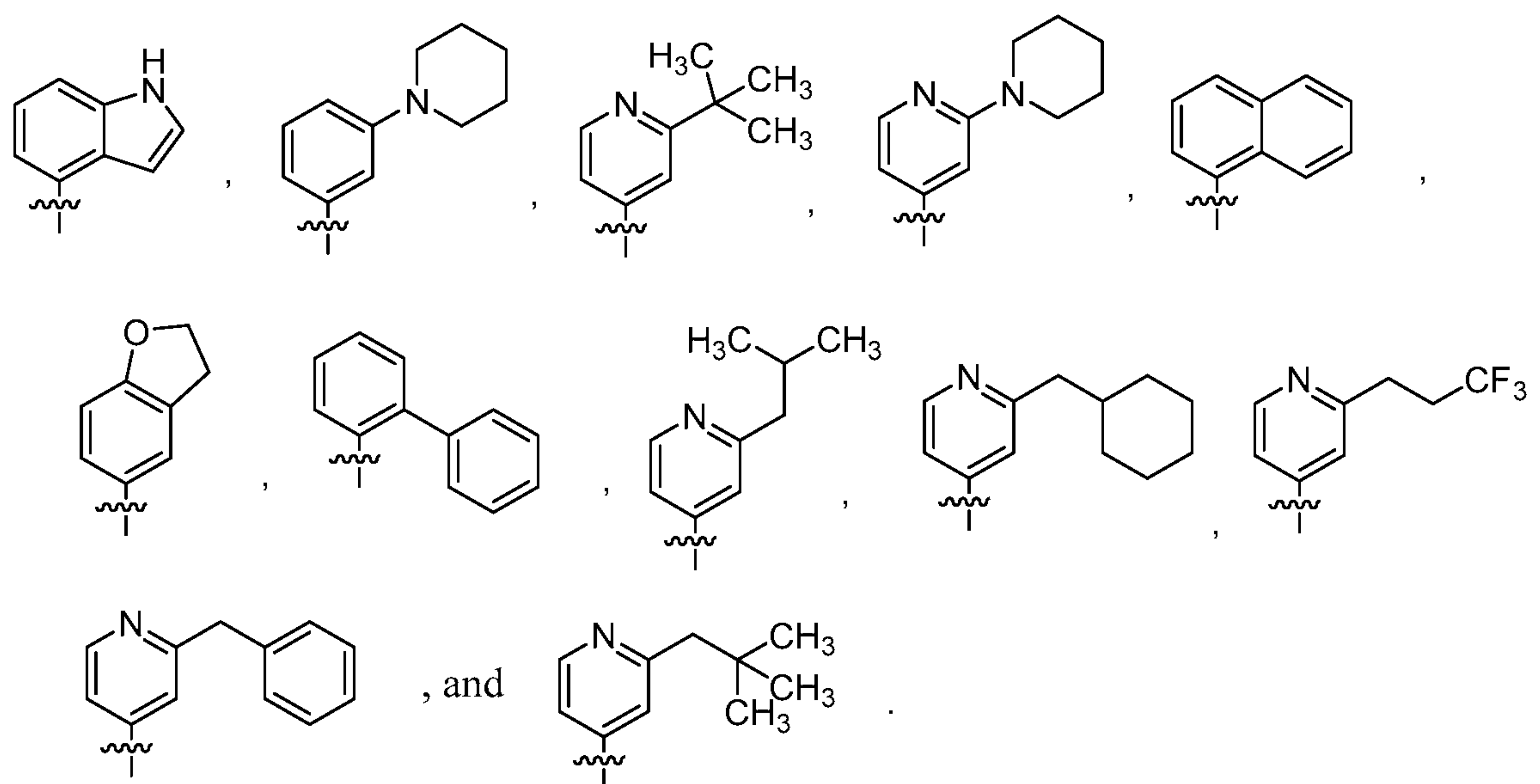
Each **R**_{9a} and **R**_{9b}, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R₁₀ and **R**₁₁ are independently hydrogen, -SO₂**R**_{C8'}, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a 1λ⁶,2-thiazolidine-1,1-dione, a 1,2λ⁶,3-oxathiazolidine-2,2-dione, or a 1λ⁶,2,5-thiadiazolidine-1,1-dione;

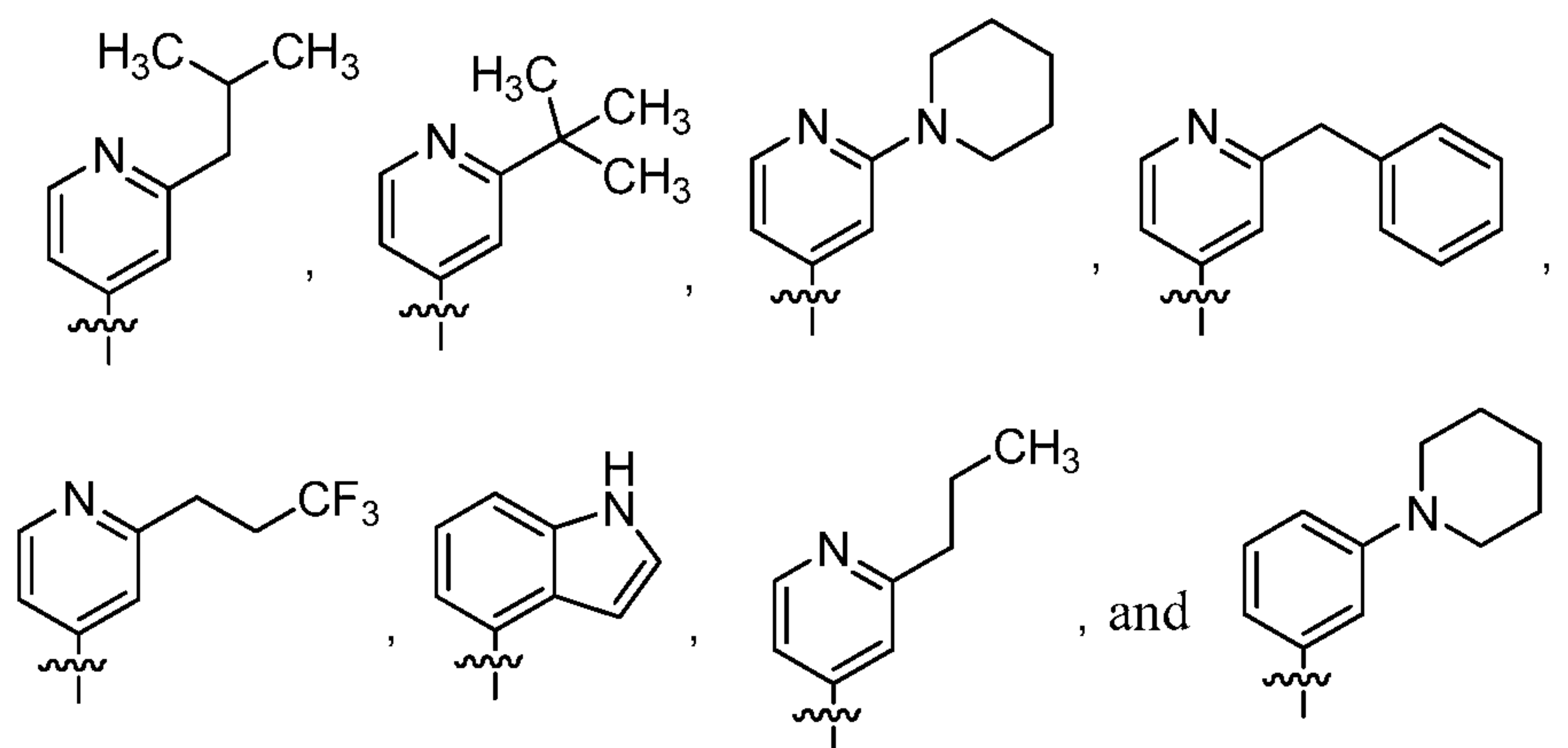
X is a heteroatom selected from S, O; or NR_B wherein **R**_B is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

Each *m* and *n* is 1, 2 or 3.

[045] In some variations of Formulae (IIa) or (IIb), A is a moiety selected from the group consisting of:

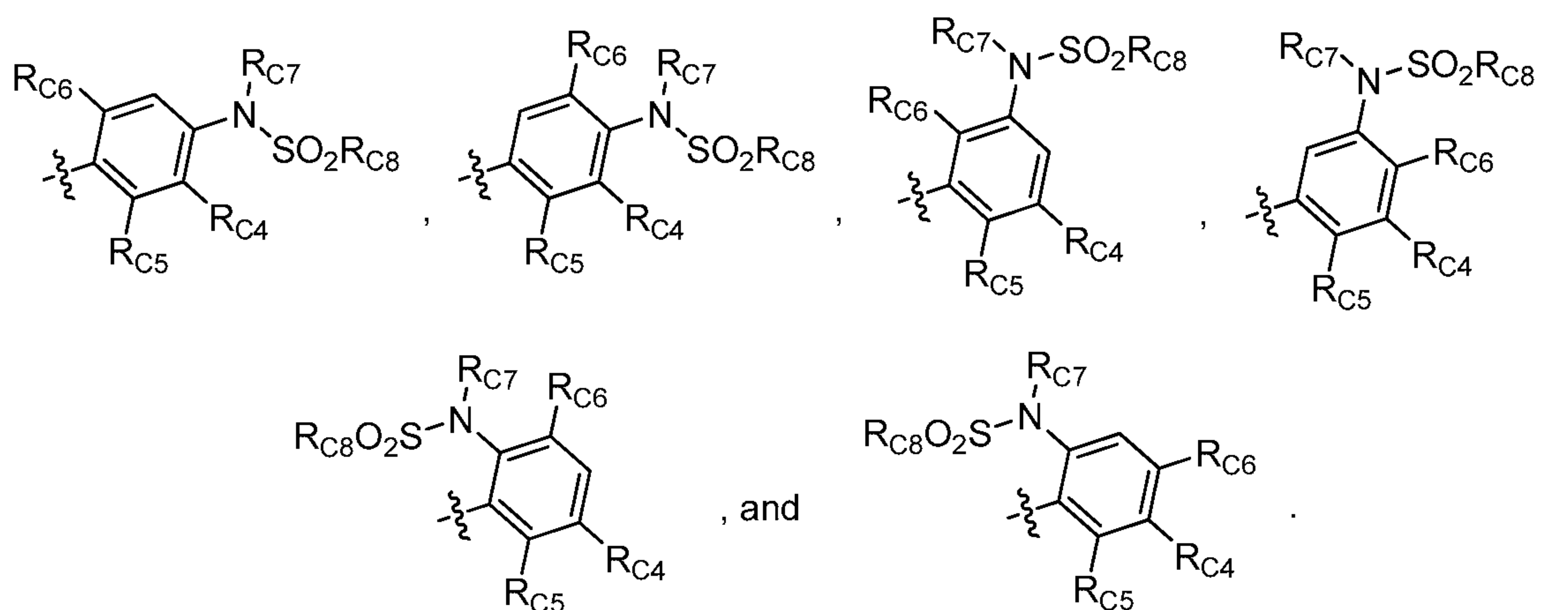


[046] In some variations of Formulae (IIa) or (IIb), A is a moiety selected from the group consisting of:

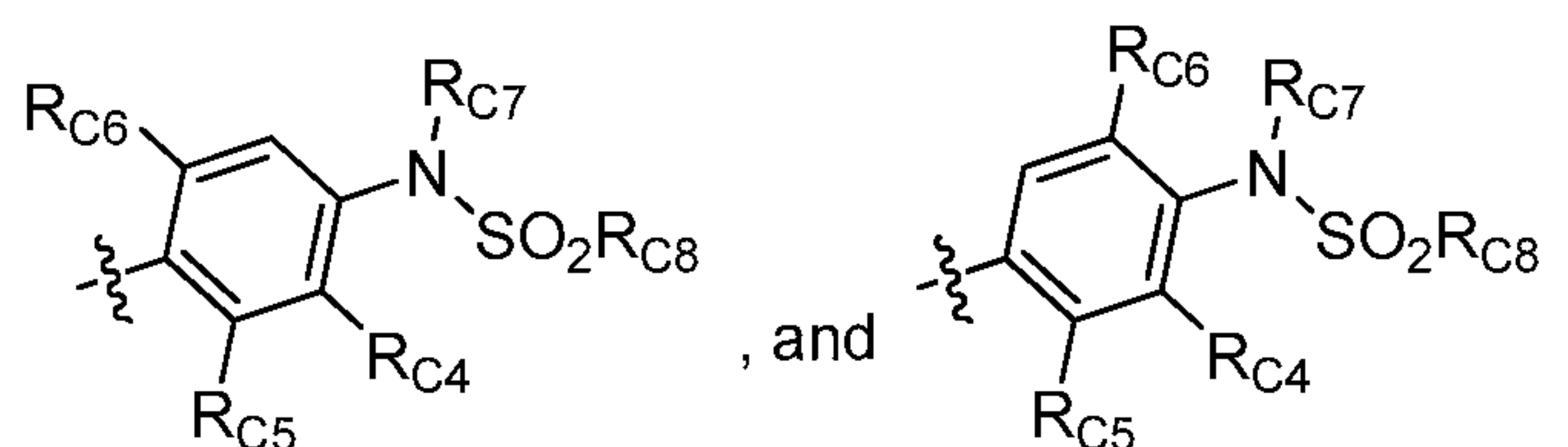


[047] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), X is S. In some variations, X is O. In some variations, X is NR_{B} , wherein R_{B} is hydrogen. In some variations, X is NR_{B} , wherein R_{B} is a linear or branched C1-C6 alkyl. In these variations, R_{B} is a linear C1-C6 alkyl selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl. In particular variations, R_{B} is methyl. In some variations, R_{B} is a branched C1-C6 alkyl selected from isopropyl, iso-pentyl, and tert-butyl.

[048] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-\text{NR}_{\text{C7}}\text{SO}_2\text{R}_{\text{C8}}$, is a moiety selected from:

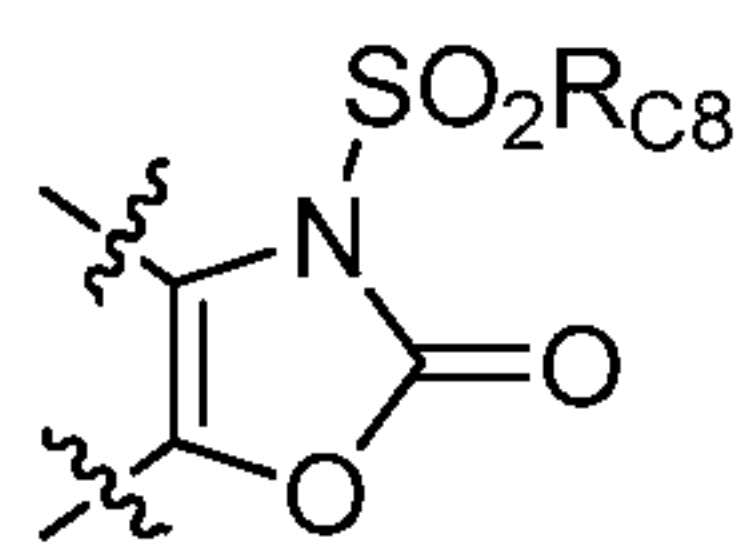


[049] In particular variations of Formulae (Ia), (Ib), (IIa) or (IIb), the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-\text{NR}_{\text{C7}}\text{SO}_2\text{R}_{\text{C8}}$, is a moiety selected from:



[050] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), one or more of R_{C4} , R_{C5} and R_{C6} , is hydrogen. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is halogen. In some

variations, one or more of R_{C4} , R_{C5} and R_{C6} , is CN. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is CF_3 . In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is OH. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is C1-C3 linear or branched alkyl. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is C2-C3 alkenyl. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is C2-C3 alkynyl. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is C3-C6 cycloalkyl. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is C3-C6 cycloalkenyl. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is C1-C3 linear or branched alkoxy. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is $-CON(CH_3)_2$. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is $-CO_2H$. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is $-CONH_2$. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is $-NHCONH_2$. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is $-CONHCH_3$. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} , is taken with R_{C7} to form the moiety

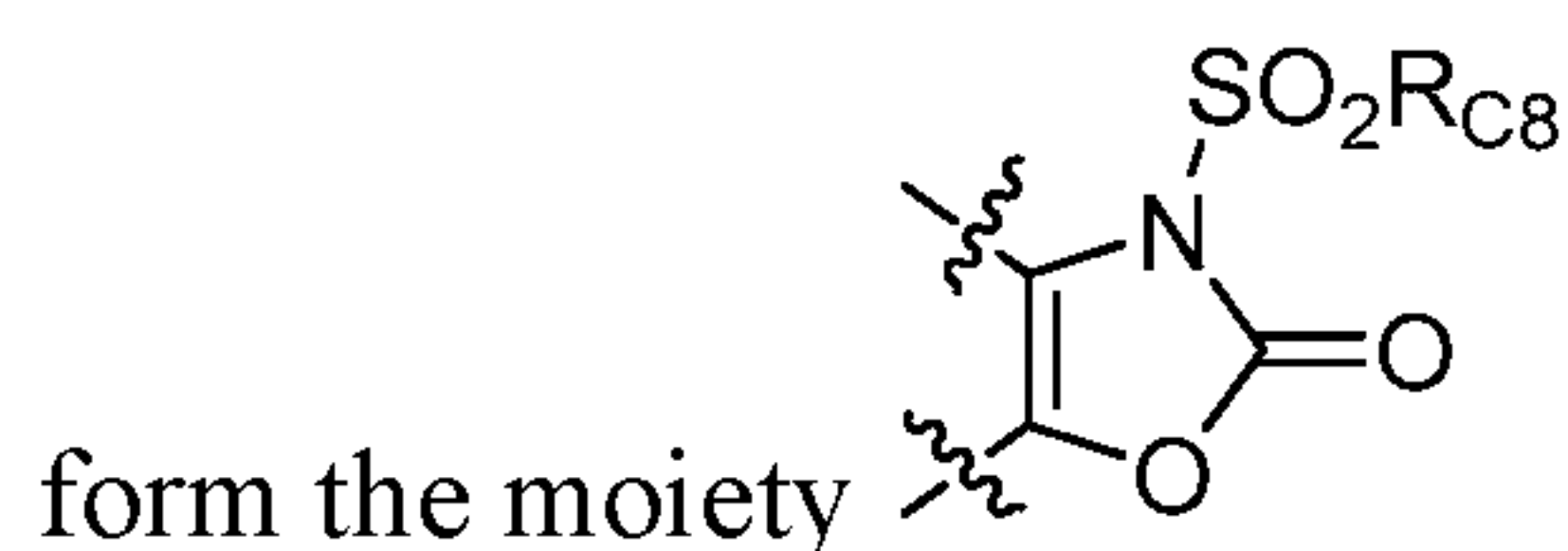


[051] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), one of R_{C4} , R_{C5} and R_{C6} is hydrogen. In some variations, two of R_{C4} , R_{C5} and R_{C6} are hydrogen. In some variations, each R_{C4} , R_{C5} and R_{C6} is hydrogen. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} is methoxy. In some variations, one or more of R_{C4} , R_{C5} and R_{C6} is OH.

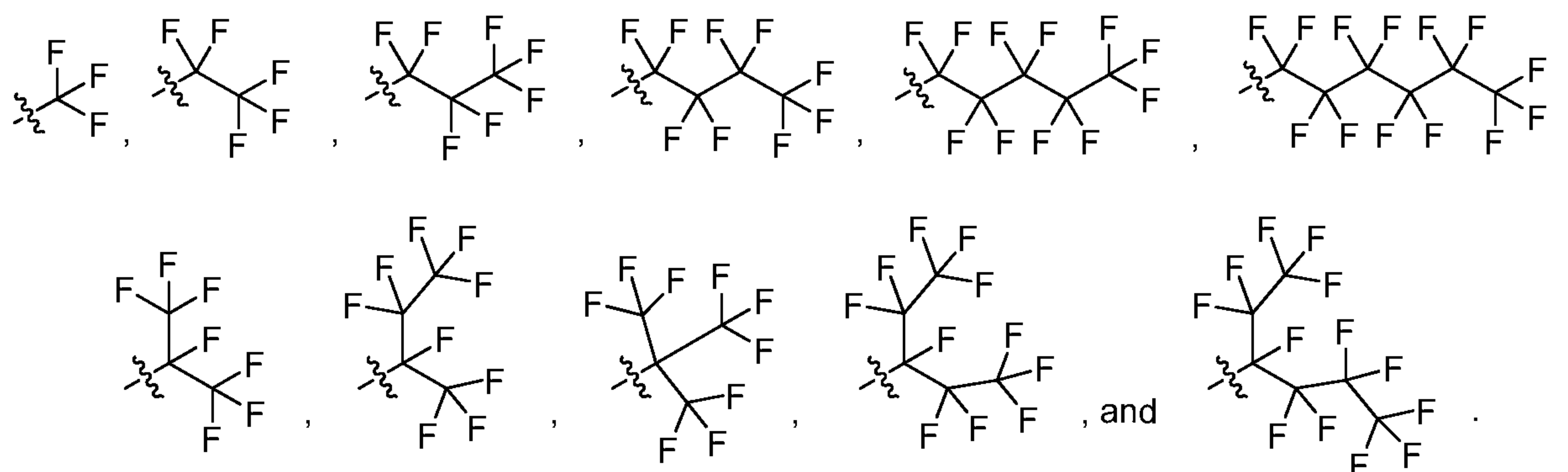
[052] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), one of R_{C4} , R_{C5} and R_{C6} is halogen. In some variations, two of R_{C4} , R_{C5} and R_{C6} are halogen. In some variations each R_{C4} , R_{C5} and R_{C6} is halogen. In some variations, one of R_{C4} , R_{C5} and R_{C6} is hydrogen, and the remaining two of R_{C4} , R_{C5} and R_{C6} are halogen. In some variations, two of R_{C4} , R_{C5} and R_{C6} are hydrogen, and the remaining one of R_{C4} , R_{C5} and R_{C6} is halogen. In some variations, R_{C4} , R_{C5} and R_{C6} are each halogen. In some embodiments, one of R_{C4} , R_{C5} and R_{C6} is fluoro, chloro or bromo. In some embodiments, two of R_{C4} , R_{C5} and R_{C6} are fluoro, chloro or bromo. In some embodiments, one of R_{C4} , R_{C5} and R_{C6} is chloro. In some embodiments, one of R_{C4} , R_{C5} and R_{C6} is chloro and one of R_{C4} , R_{C5} and R_{C6} is bromo. In some embodiments, R_{C4} is chloro. In some embodiments, R_{C5} is chloro. In some embodiments, R_{C4} is bromo. In some embodiments, R_{C5} is bromo.

[053] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), R_{C7} is hydrogen. In some variations, R_{C7} is C1-C6 linear or branched alkyl. In some variations, R_{C7} is C1-C6 linear or branched hydroxyalkyl. In some variations, R_{C7} is $-(CR_{9a}R_{9b})_mNR_{10}R_{11}$. In some variations,

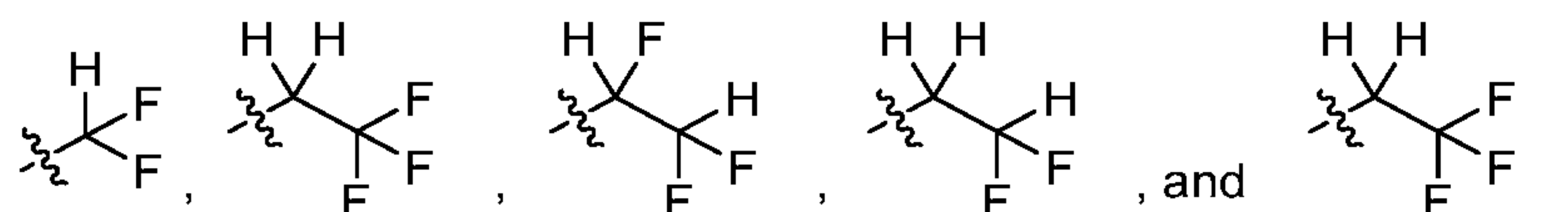
R_{C7} is $-CO_2$ -Alkyl. In some variations, R_{C7} is $-(CR_{9a}R_{9b})_mO$ -Alkyl. In some variations, R_{C7} is $-(CR_{9a}R_{9b})_mOPO_3Na_2$. In some variations, R_{C7} is $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO$ -Alkyl. In some variations, R_{C7} is $-(CR_{9a}R_{9b})_mO(C=O)$ -Alkyl. In some variations, R_{C7} is $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)$ -Alkyl. In some variations, R_{C7} is $-(C=O)CH=CH_2$. In some variations, R_{C7} is $-SO_2R_{C8}$. In some variations, R_{C7} is taken with one of R_{C4} , R_{C5} or R_{C6} to



[054] In all embodiments, R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom. In some embodiments, R_{C8} is a linear or branched C1-C6 perhaloalkyl. In some embodiments, the C1-C6 perhaloalkyl is a C1-C6 perfluoroalkyl. In some embodiments, the C1-C6 perfluoroalkyl is selected from

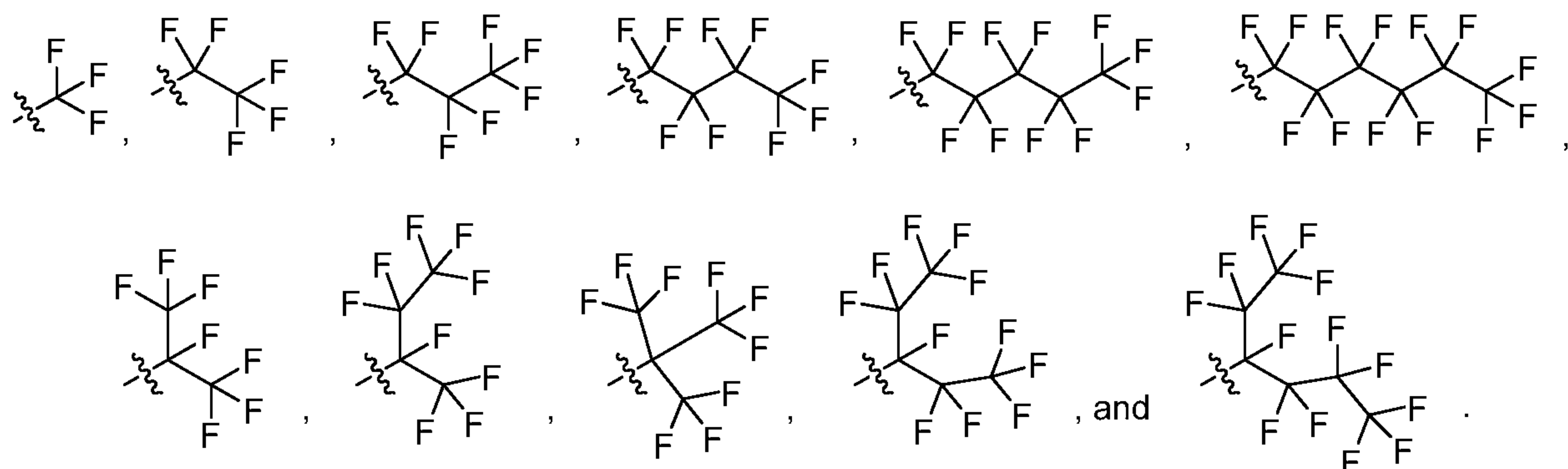


In preferred embodiments, the C1-C6 perfluoroalkyl is $-CF_3$. In some embodiments, R_{C8} is a linear or branched C1-C6 alkyl having at least two halogen atoms. In some embodiments, R_{C8} is selected from:

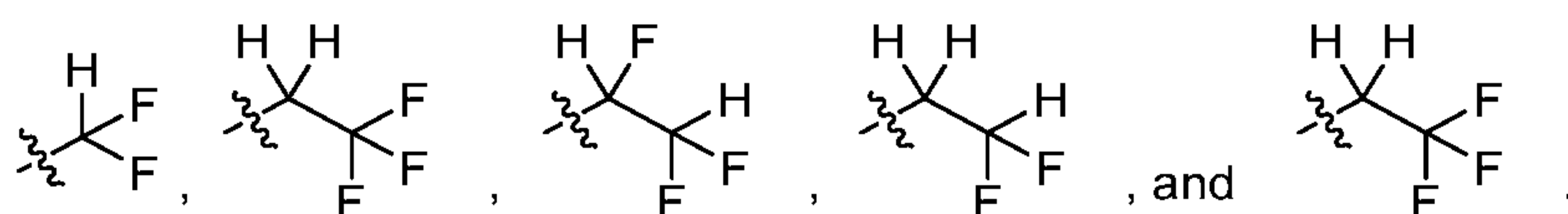


[055] In some embodiments, R_{C8} is a linear or branched C2-C6 perhaloalkenyl. In some embodiments, R_{C8} is a linear or branched C2-C6 perhaloalkynyl. In some embodiments, R_{C8} is a linear or branched C1-C6 alkyl having at least one halogen atom. In some embodiments, R_{C8} is a linear or branched C2-C6 alkenyl having at least one halogen atom. In some embodiments, R_{C8} is or a linear or branched C2-C6 alkynyl having at least one halogen atom.

[056] In some embodiments, $\mathbf{R}_{C8'}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom. In some embodiments, $\mathbf{R}_{C8'}$ is a linear or branched C1-C6 perhaloalkyl. In some embodiments, the C1-C6 perhaloalkyl is a C1-C6 perfluoroalkyl. In some embodiments, the C1-C6 perfluoroalkyl is selected from



In preferred embodiments, the C1-C6 perfluoroalkyl is $-\text{CF}_3$. In some embodiments, $\mathbf{R}_{C8'}$ is a linear or branched C1-C6 alkyl having at least two halogen atoms. In some embodiments, $\mathbf{R}_{C8'}$ is selected from:



[057] In some embodiments, $\mathbf{R}_{C8'}$ is a linear or branched C2-C6 perhaloalkenyl. In some embodiments, $\mathbf{R}_{C8'}$ is a linear or branched C2-C6 perhaloalkynyl. In some embodiments, $\mathbf{R}_{C8'}$ is a linear or branched C1-C6 alkyl having at least one halogen atom. In some embodiments, $\mathbf{R}_{C8'}$ is a linear or branched C2-C6 alkenyl having at least one halogen atom. In some embodiments, $\mathbf{R}_{C8'}$ is or a linear or branched C2-C6 alkynyl having at least one halogen atom.

[058] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), both $\mathbf{R}_{9a}$ and $\mathbf{R}_{9b}$ are hydrogen. In some embodiments, $\mathbf{R}_{9a}$ is hydrogen, and $\mathbf{R}_{9b}$ is C1-C6 linear or branched alkyl. In some embodiments, both $\mathbf{R}_{9a}$ and $\mathbf{R}_{9b}$ are C1-C6 linear or branched alkyl. In some embodiments, $\mathbf{R}_{9a}$ is hydrogen, and $\mathbf{R}_{9b}$ is methyl.

[059] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), one or both of $\mathbf{R}_{10}$ and $\mathbf{R}_{11}$ are hydrogen. In some variations, one or both of $\mathbf{R}_{10}$ and $\mathbf{R}_{11}$ are $-\text{SO}_2\mathbf{R}_{C8'}$. In some variations, one or both of $\mathbf{R}_{10}$ and $\mathbf{R}_{11}$ are C1-C6 linear or branched alkyl. In some

variations, one or both of **R10** and **R11** are C2-C6 linear or branched alkenyl. In some variations, one or both of **R10** and **R11** are C3-C6 cycloalkyl. In some variations, one or both of **R10** and **R11** are C3-C6 cycloalkenyl.

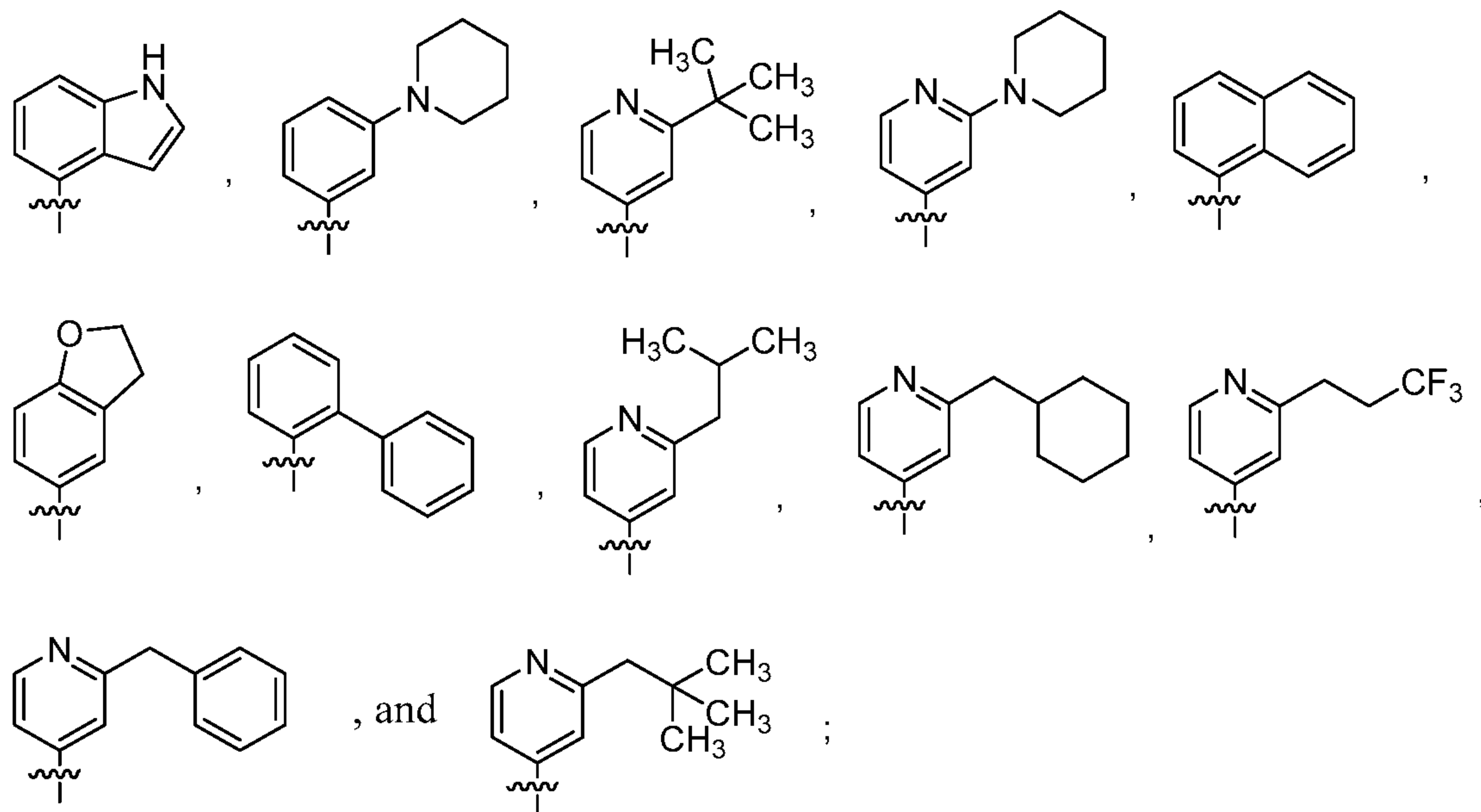
[060] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), **R10** and **R11** are taken together with the N to which they are attached to form a C3-C6 heterocycle. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a pyrrolidin-2-one or pyrrolidin-3-one. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a piperidin-2-one. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a piperidin-3-one. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a piperidin-4-one. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form an oxazolidinone. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form an oxazinanone. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form an imidazolidinone. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a tetrahydropyrimidin-2(1H)-one. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a $1\lambda^6,2$ -thiazolidine-1,1-dione. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a $1,2\lambda^6,3$ -oxathiazolidine-2,2-dione. In some variations, **R10** and **R11** are taken together with the N to which they are attached to form a $1\lambda^6,2,5$ -thiadiazolidine-1,1-dione

[061] In some variations, the compound is of formula (Ia) or (IIa), wherein **X** is a heteroatom selected from S, O; or **NR_B** wherein **R_B** is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl. In some variations, **X** is S. In some variations, **X** is O. In some variations, **X** is **NR_B** wherein **R_B** is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl. In some variations, **X** is **NR_B** wherein **R_B** is a C1-C6 linear or branched alkyl. In some variations, **X** is **NR_B** wherein **R_B** is C3-C6 cycloalkyl.

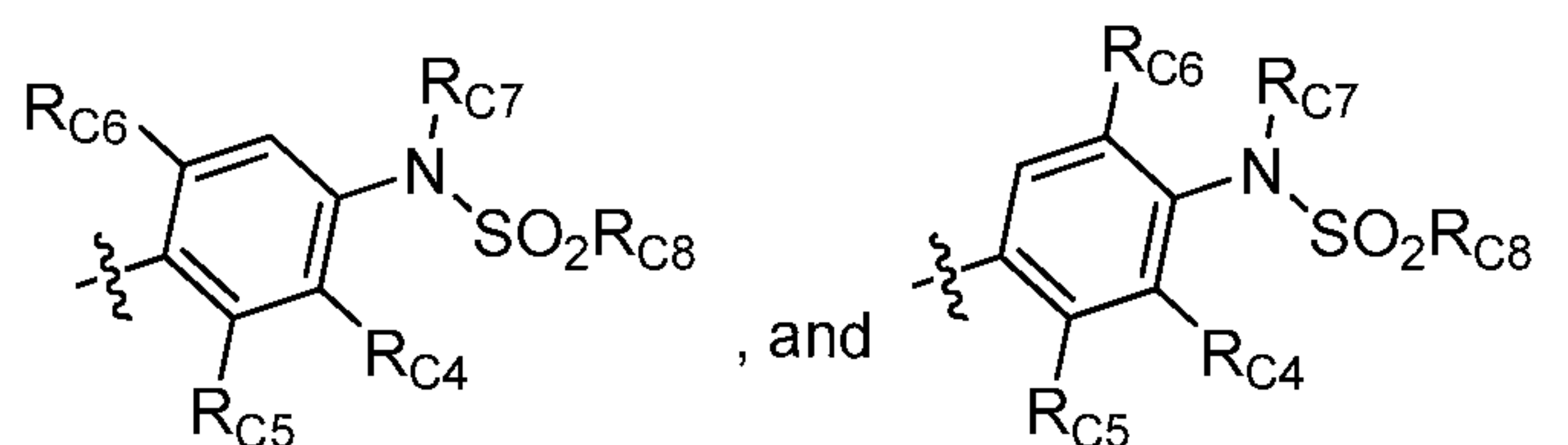
[062] In some variations, the compound is of formula (Ib) or (IIb), wherein **X** is a heteroatom selected from S, O; or **NR_B** wherein **R_B** is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl. In some variations, **X** is S. In some variations, **X** is O. In some variations, **X** is **NR_B** wherein **R_B** is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl. In some variations, **X** is **NR_B** wherein **R_B** is a C1-C6 linear or branched alkyl. In some variations, **X** is **NR_B** wherein **R_B** is C3-C6 cycloalkyl.

[063] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), both *m* and *n* are 1. In some variations, *m* is 1 and *n* is 2. In some variations, *m* is 1 and *n* is 3. In some variations, *m* is 2 and *n* is 1. In some variations, both *m* and *n* are 2. In some variations, *m* is 2 and *n* is 3. In some variations, *m* is 3 and *n* is 1. In some variations, *m* is 3 and *n* is 2. In some variations, both *m* and *n* are 3.

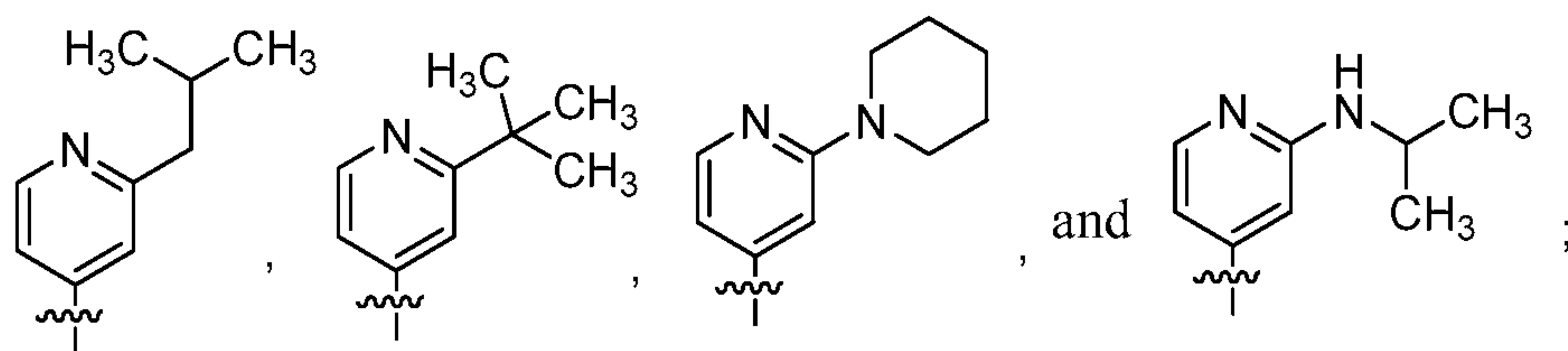
[064] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), A is a moiety selected from



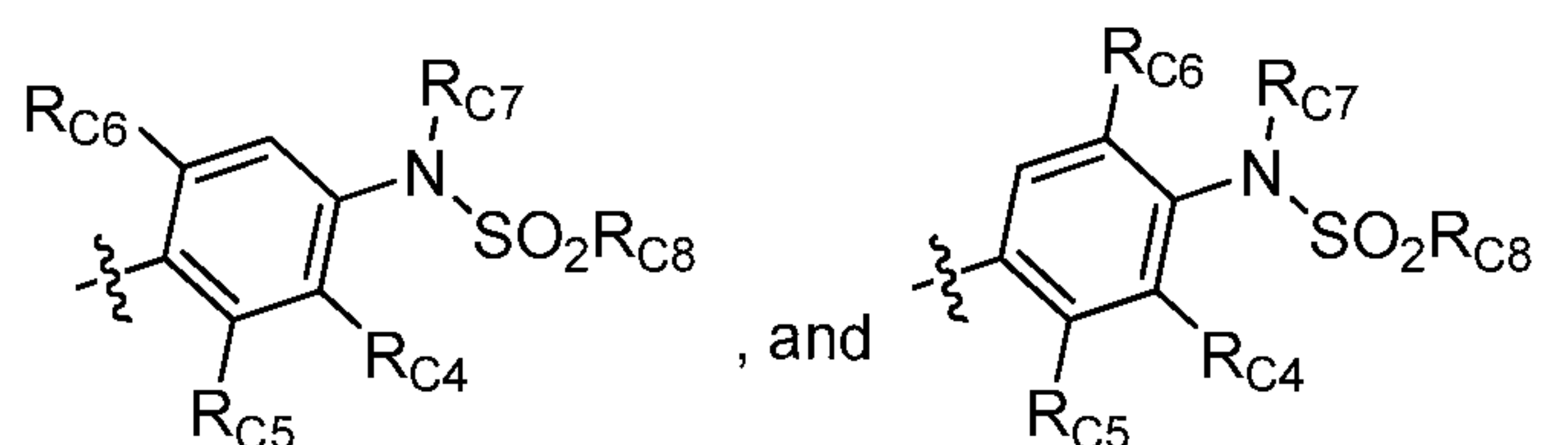
X is S, and the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is a moiety selected from:



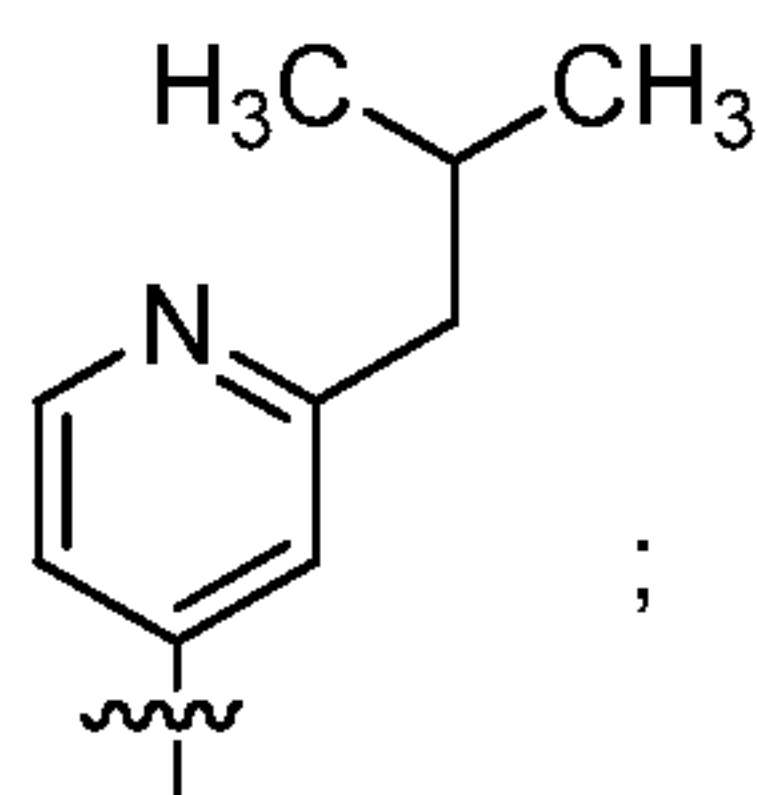
[065] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), A is a moiety selected from



X is S, and the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is a moiety selected from



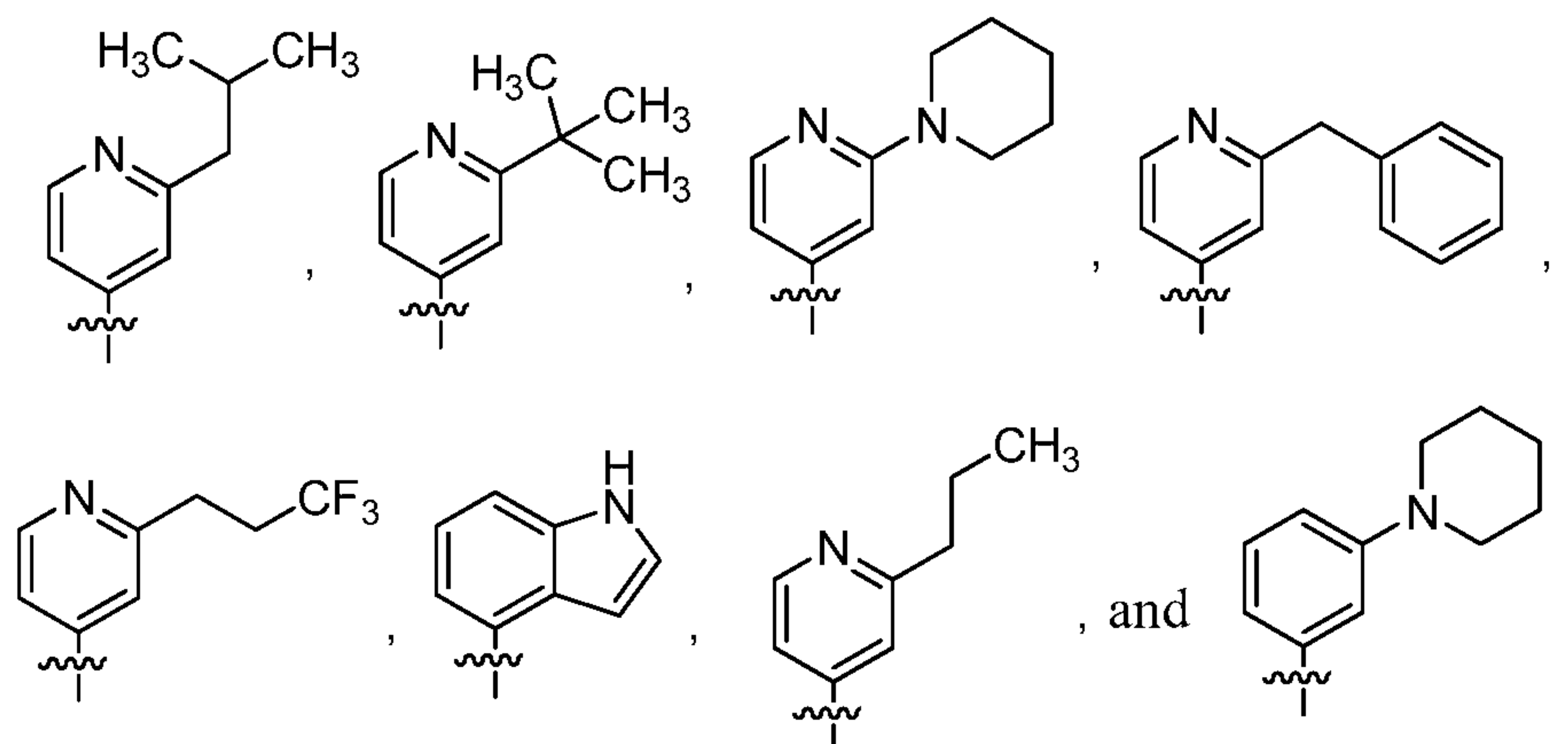
[066] In some variations of Formulae (Ia), (Ib), (IIa) or (IIb), A is



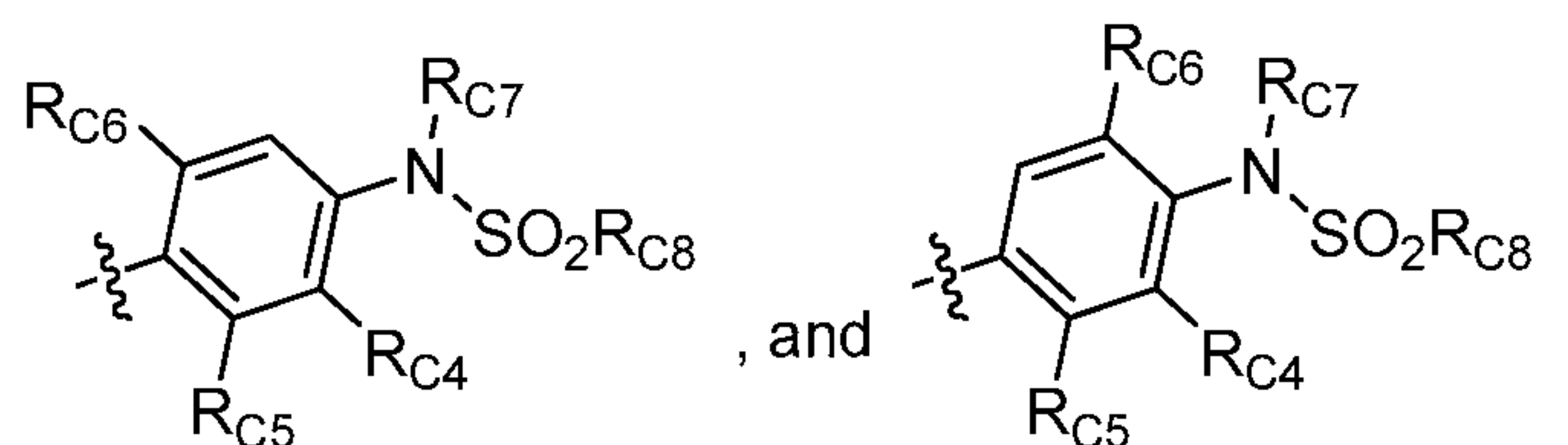
X is S; the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is selected

from and ; wherein R_{C4} , R_{C5} , and R_{C6} are hydrogen or halogen; R_{C7} is hydrogen; and R_{C8} is perfluoroalkyl. In some variations R_{C8} is $-CF_3$.

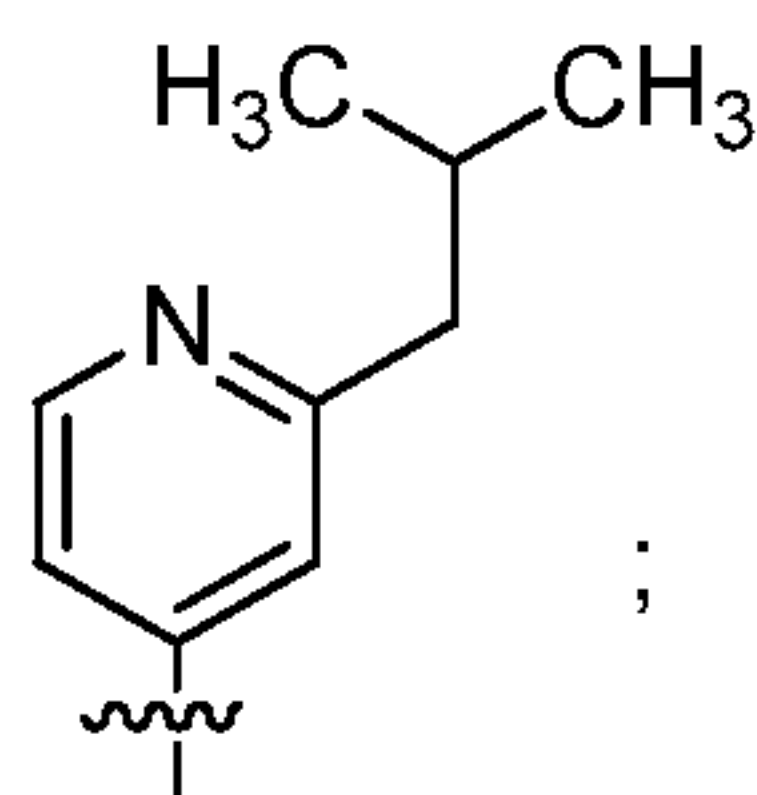
[067] In some variations, the compound is of Formula (Ia), wherein A is a moiety selected from



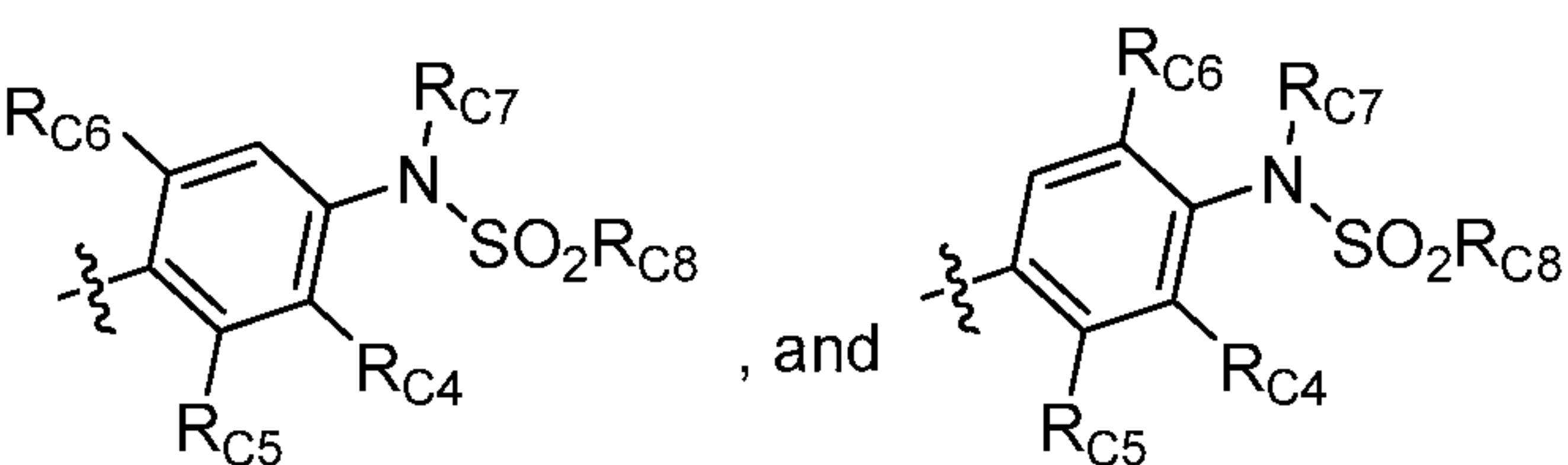
X is S, and the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is a moiety selected from



[068] In particular variations, the compound is of Formula (Ia), wherein A is



X is S; the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is selected

from  ; wherein R_{C4} , R_{C5} , and R_{C6} are hydrogen or halogen; R_{C7} is hydrogen and R_{C8} is perfluoroalkyl. In some variations, R_{C8} is $-CF_3$.

[069] It is intended and understood that each and every variation of A, R_{C4} , R_{C5} , R_{C6} , R_{C7} , R_{C8} , $R_{C8'}$, R_{9a} , R_{9b} , R_{10} , R_{11} , X, m , and n , where present, described for formulae (Ia) and (Ib), may be combined with each and every variation of A, R_{C4} , R_{C5} , R_{C6} , R_{C7} , R_{C8} , $R_{C8'}$, R_{9a} , R_{9b} , R_{10} , R_{11} , X, m , and n , as if each and every combination is individually described.

[070] In some embodiments, the compound is selected from the group consisting of:

1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(1-isobutyl-1H-pyrazol-5-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1,2-dimethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1-propyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2,3-dimethyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(3-propyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(1,2-dipropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(6-(butylamino)-2-isobutylpyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(6-(dibutylamino)-2-isobutylpyrimidin-4-yl)thiazol-4-yl)phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(6-amino-2-isobutylpyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(4-(2-(2-aminopyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-(propylamino)pyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-(dibutylamino)pyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2'-propyl-2,4'-bithiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(5-propyl-1,2,4-thiadiazol-3-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(5-propyl-1,2,4-oxadiazol-3-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2'-propyl-2,5'-bithiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(5-propyl-1,3,4-thiadiazol-2-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(5-propyl-1,3,4-oxadiazol-2-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(1-isobutyl-6-oxo-1,6-dihydropyridin-3-yl)thiazol-4-yl)phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(4-fluoro-3-isobutylphenyl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;

N-(2-bromo-3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3,5-dichloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-(trifluoromethyl)phenyl)methanesulfonamide;

N-(2-cyclopropyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methylphenyl)methanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-isopropylphenyl)methanesulfonamide;

N-(2-ethynyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-ethynyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-6-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-6-methylphenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(4-(2-tert-butylpyridin-4-yl)-1-methyl-1H-imidazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(1-methyl-2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-5-chloro-4-(1-methyl-2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(4-(2-tert-butylpyridin-4-yl)oxazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)oxazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(dimethylamino)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(trifluoromethylsulfonyl)acrylamide;
 N-(3-chloro-4-(2-(2-(methylsulfonamido)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-(3,3,3-trifluoropropyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-hydroxyphenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-(trifluoromethyl)phenyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-neopentylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 6-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-(trifluoromethylsulfonyl)benzo[d]oxazol-2(3H)-one;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,2,2,2-pentafluoroethanesulfonamide;
 1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide;
 1,1,1-trifluoro-N-{2-methoxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;
 N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-2-methoxyphenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(2-aminopyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-{2-hydroxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;
 N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(4-{2-[2-(2,2-dimethylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(4-(piperidine-1-carbonyl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-chlorophenyl}methanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-methylbenzene-1-sulfonamide;
 N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(quinolin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-chloropyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxopyrrolidin-1-yl)ethyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-yl)ethyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxoimidazolidin-1-yl)ethyl)methanesulfonamide;
 N-(2-bromo-4-(2-(2-(piperidin-1-yl)pyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 2-(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)ethyl acetate;
 (2-(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)ethoxy)methyl acetate;
 N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-N-(2-{[4-(3-chlorophenyl)-2-oxo-1,3,2λ⁵-dioxaphosphinan-2-yl]oxy}ethyl)-1,1,1-trifluoromethanesulfonamide;
 (N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)methyl acetate;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(methoxymethyl)methanesulfonamide;
 N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-N-([4-(3-chlorophenyl)-2-oxo-1,3,2λ⁵-dioxaphosphinan-2-yl]oxy)methyl)-1,1,1-trifluoromethanesulfonamide;

methyl 4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl(trifluoromethylsulfonyl)carbamate;
 sodium (N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)methyl phosphate;
 1-(N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethylsulfonamido)ethyl isobutyrate;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-yl)ethyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-(pyrrolidin-1-yl)ethyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(2-(diethylamino)ethyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(2-(dimethylamino)ethyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(3-fluoro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-methylmethanesulfonamide;
 1,1,1-trifluoro-N-(3-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 N-(2-bromo-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-methyl-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 N-(4-(2-(2-butylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide
 1,1,1-trifluoro-N-(4-(2-(2-(methoxymethyl)pyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(4,6-dipropylpyridin-2-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(4-(2-(4-propylpyridin-2-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 N-(4-(2-(2,6-dipropylpyridin-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(2-(cyclohexylmethyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-methoxyphenyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-((trifluoromethylsulfonyl)methyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-propyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 5-(4-(2-chloro-4-(trifluoromethylsulfonamido)phenyl)thiazol-2-yl)-N-cyclopropyl-2-fluorobenzamide;
 5-(4-(2-chloro-4-(trifluoromethylsulfonamido)phenyl)thiazol-2-yl)-N-cyclohexyl-2-fluorobenzamide;
 N-(4-(2-(1H-indol-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(3-(piperidin-1-yl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-(piperidin-1-yl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-5-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide; and
 N-(2-bromo-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

[071] In some embodiments, the compound is selected from the group consisting of:

- 1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
- 1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
- N-(3-chloro-4-(2-(1-isobutyl-1H-pyrazol-5-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
- N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
- N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
- N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
- 1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide;
- 1,1,1-trifluoro-N-{2-methoxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;
- N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-2-methoxyphenyl}-1,1,1-trifluoromethanesulfonamide;
- N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
- N-{4-[2-(2-aminopyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
- N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
- 1,1,1-trifluoro-N-{2-hydroxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;
- N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
- N-(4-{2-[2-(2,2-dimethylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;
- N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(4-(piperidine-1-carbonyl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-chlorophenyl}methanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-methylbenzene-1-sulfonamide;
 N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide; and
 N-(3-chloro-4-(2-(quinolin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

[072] In some embodiments, the compound is selected from the group consisting of:

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide; and

N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide.

[073] In some embodiments, the compound is compound #37: N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

[074] The compounds described below are not intended to be limiting; rather, these embodiments and variations are intended to provide examples of compounds within the scope of Formulae (Ia), (Ib), (IIa) or (IIb).

[075] Representative compounds are presented in Table 1.

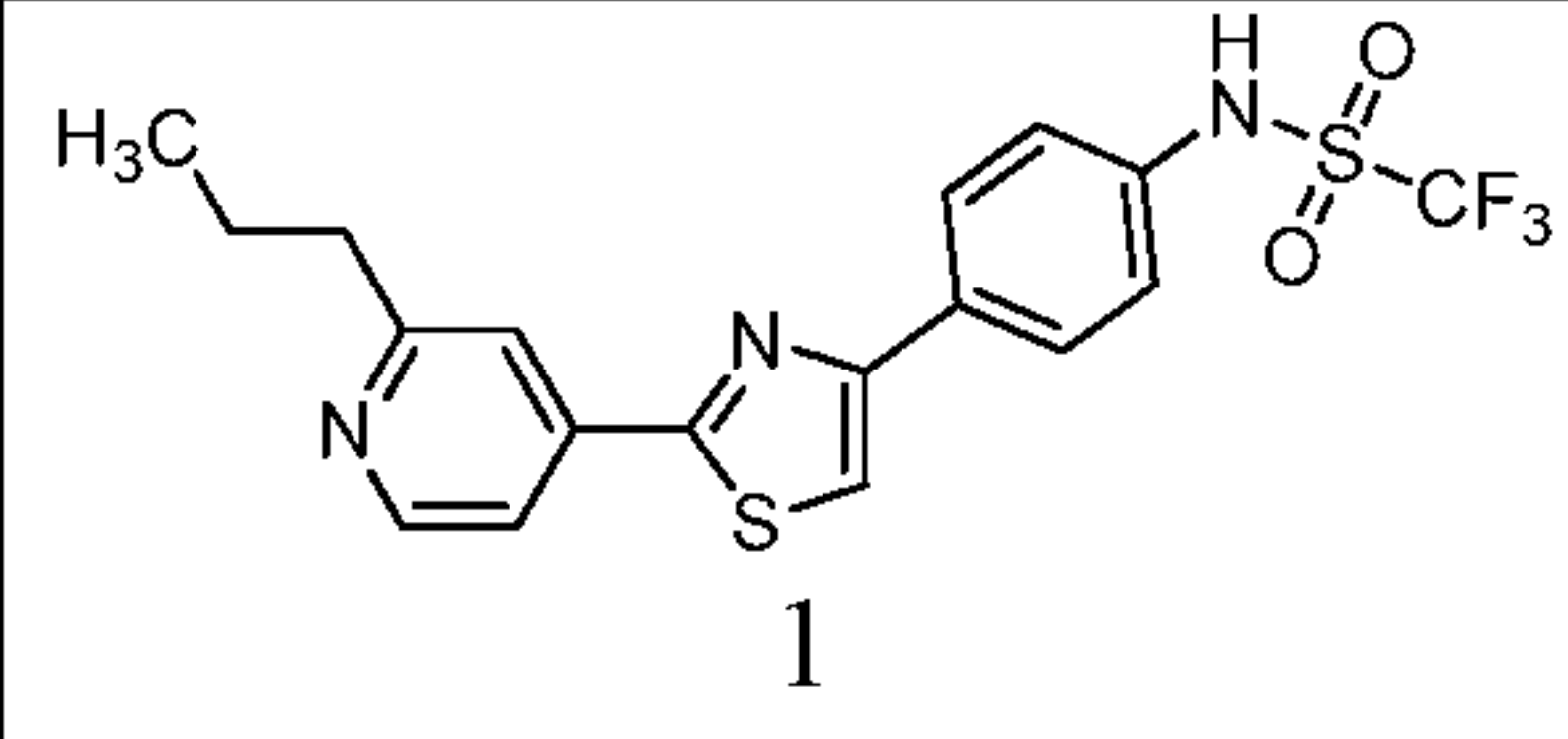
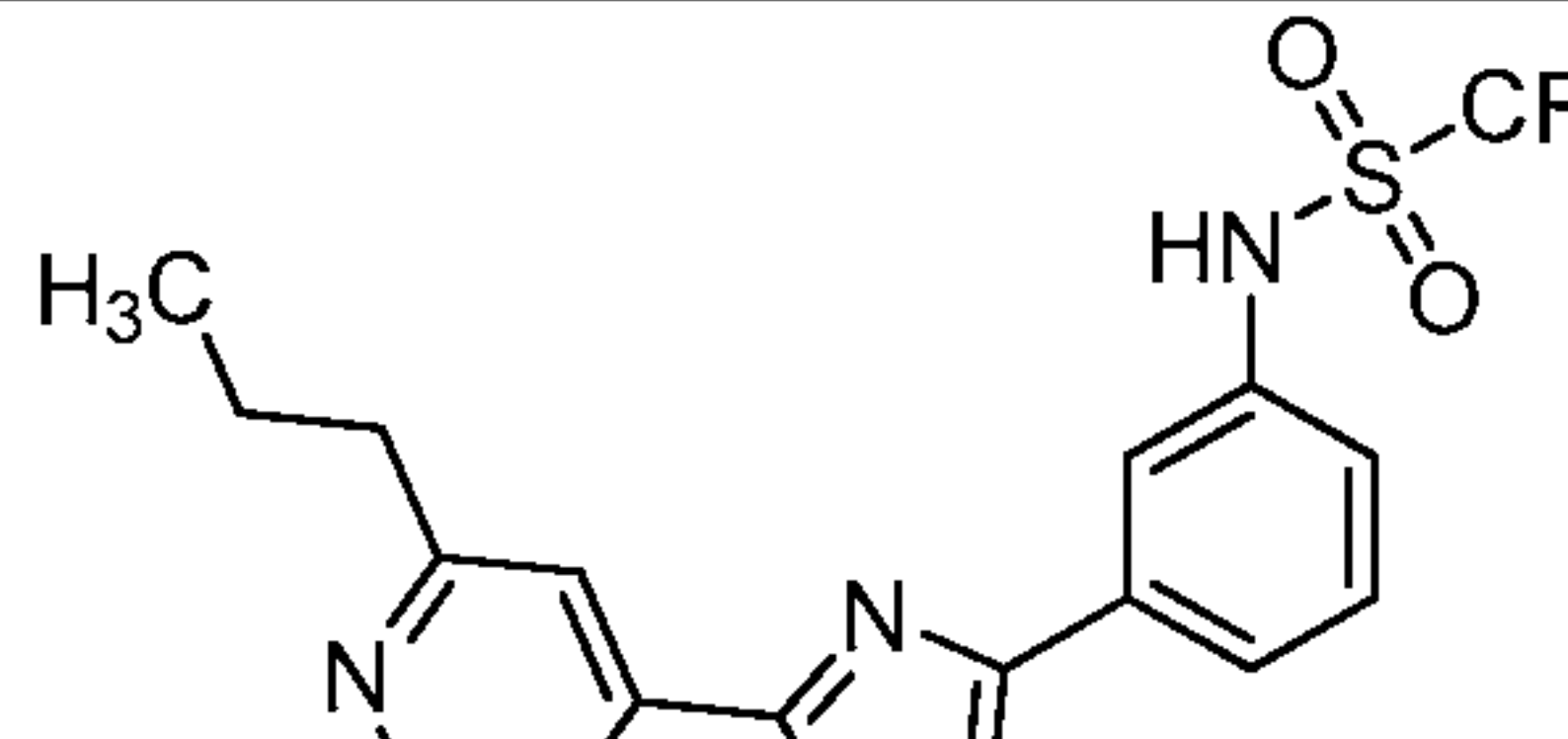
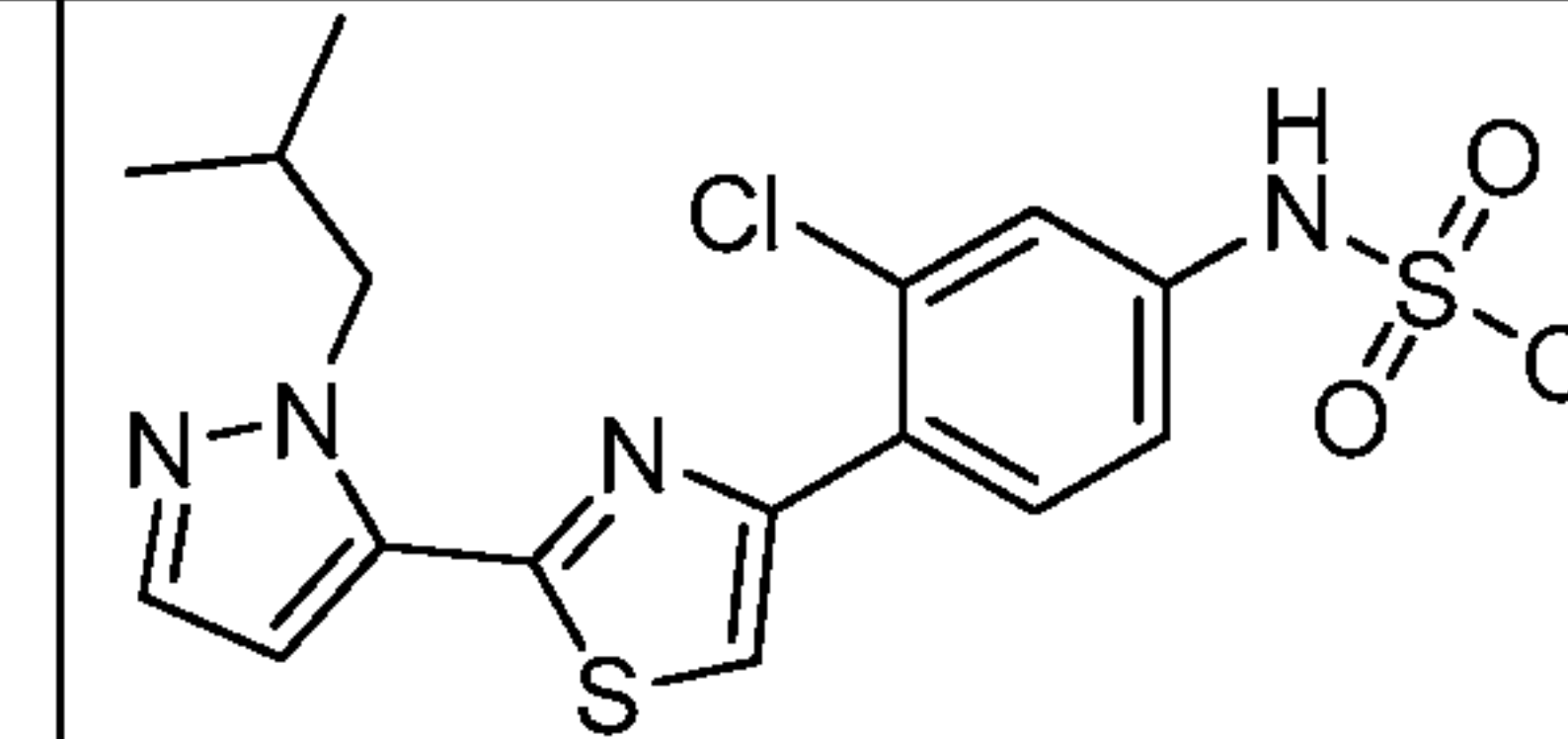
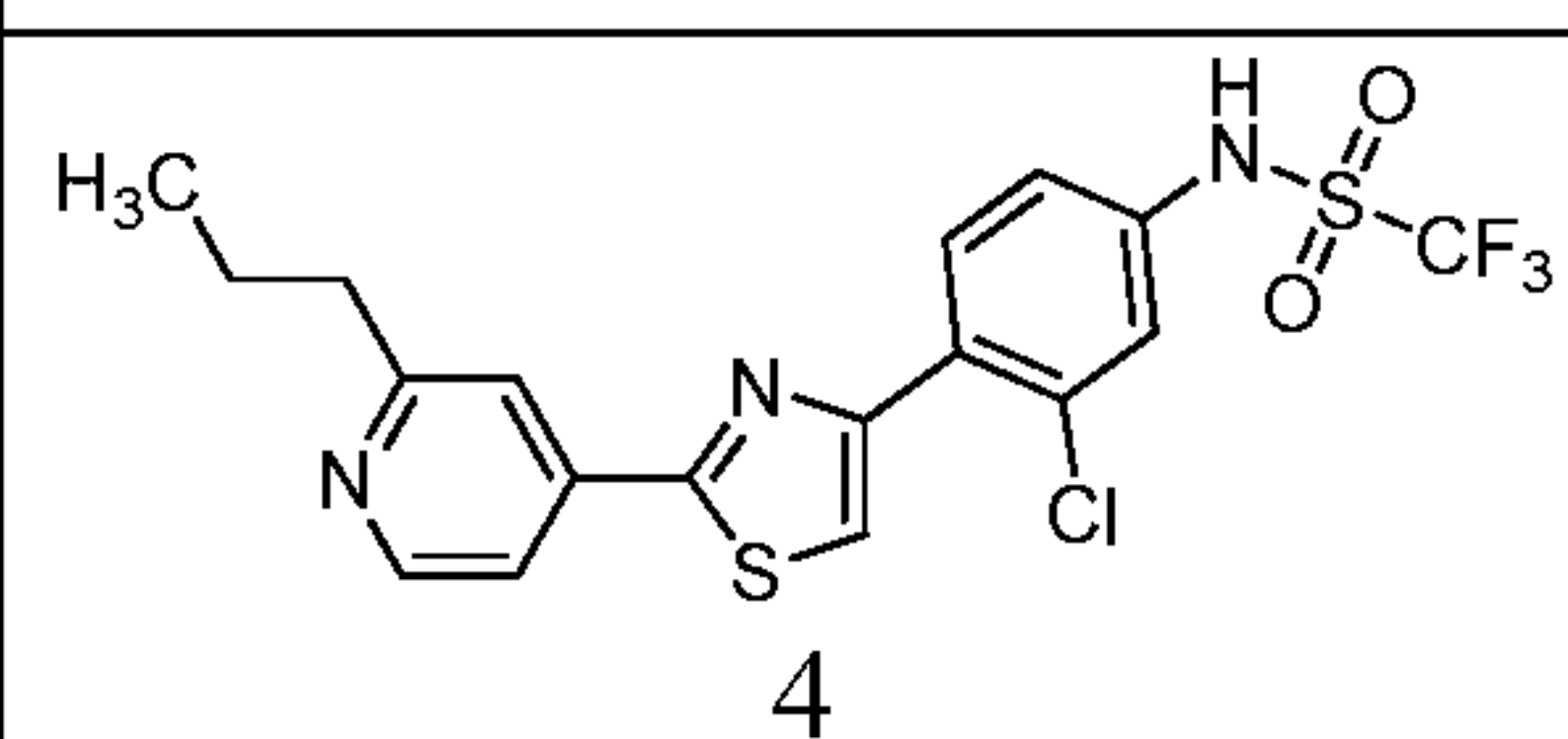
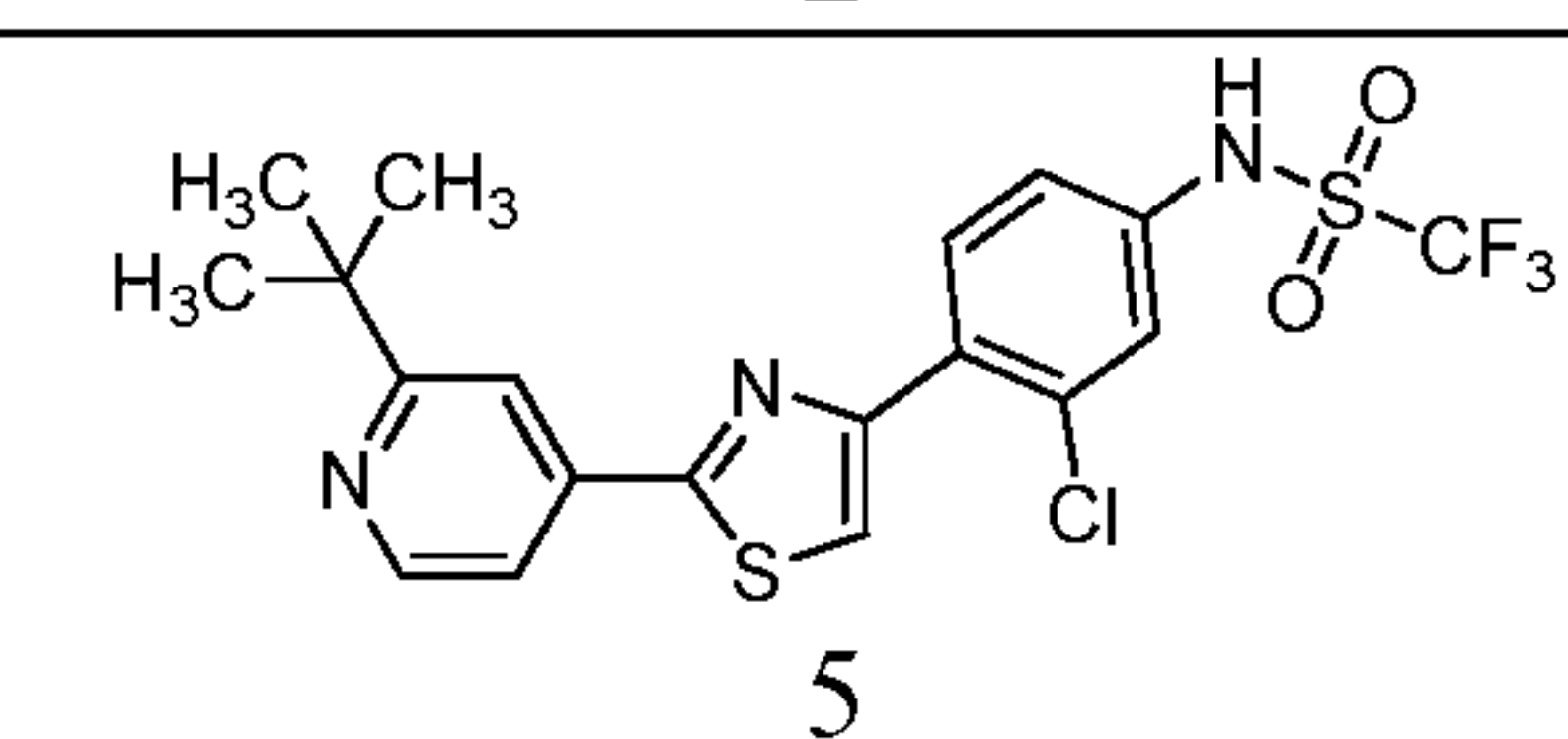
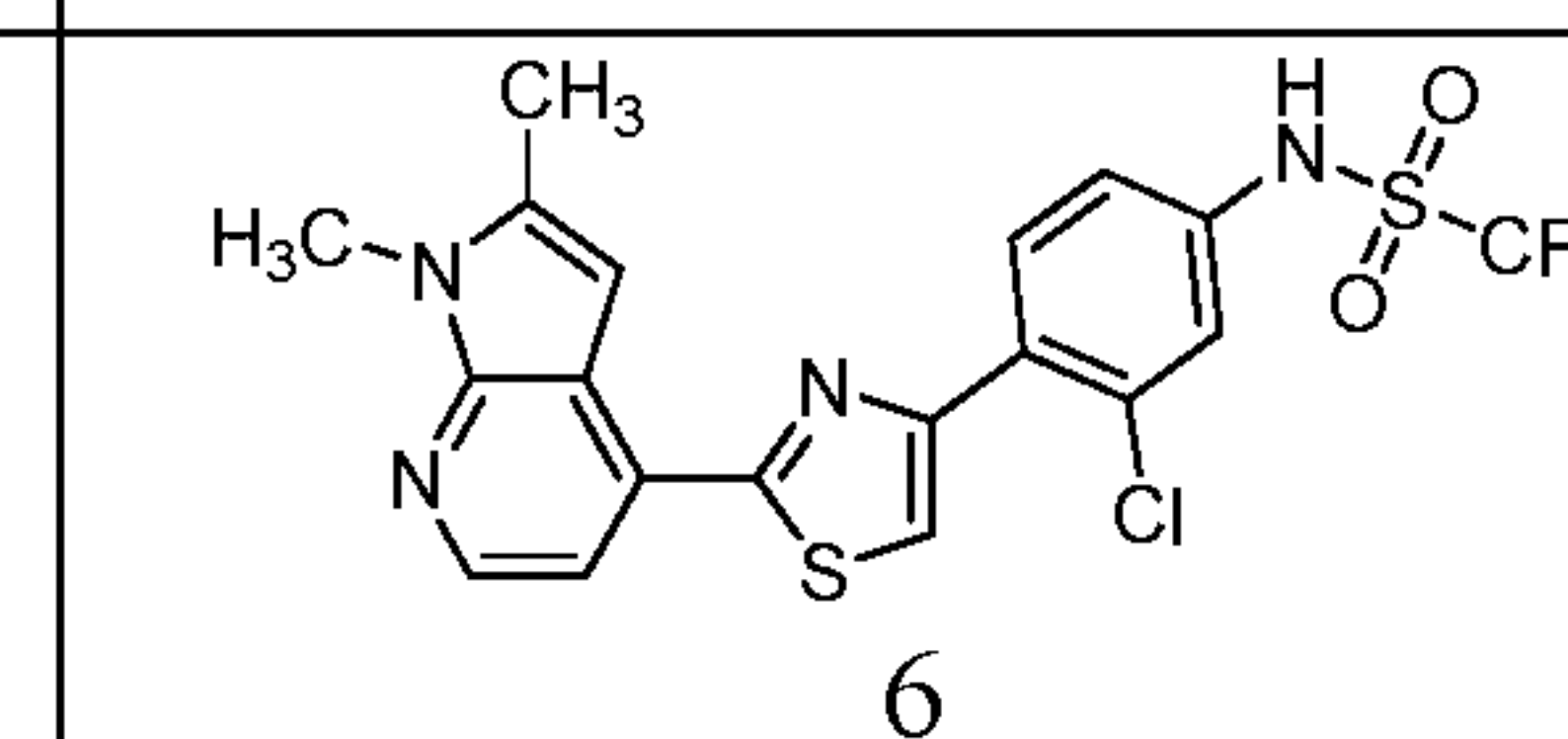
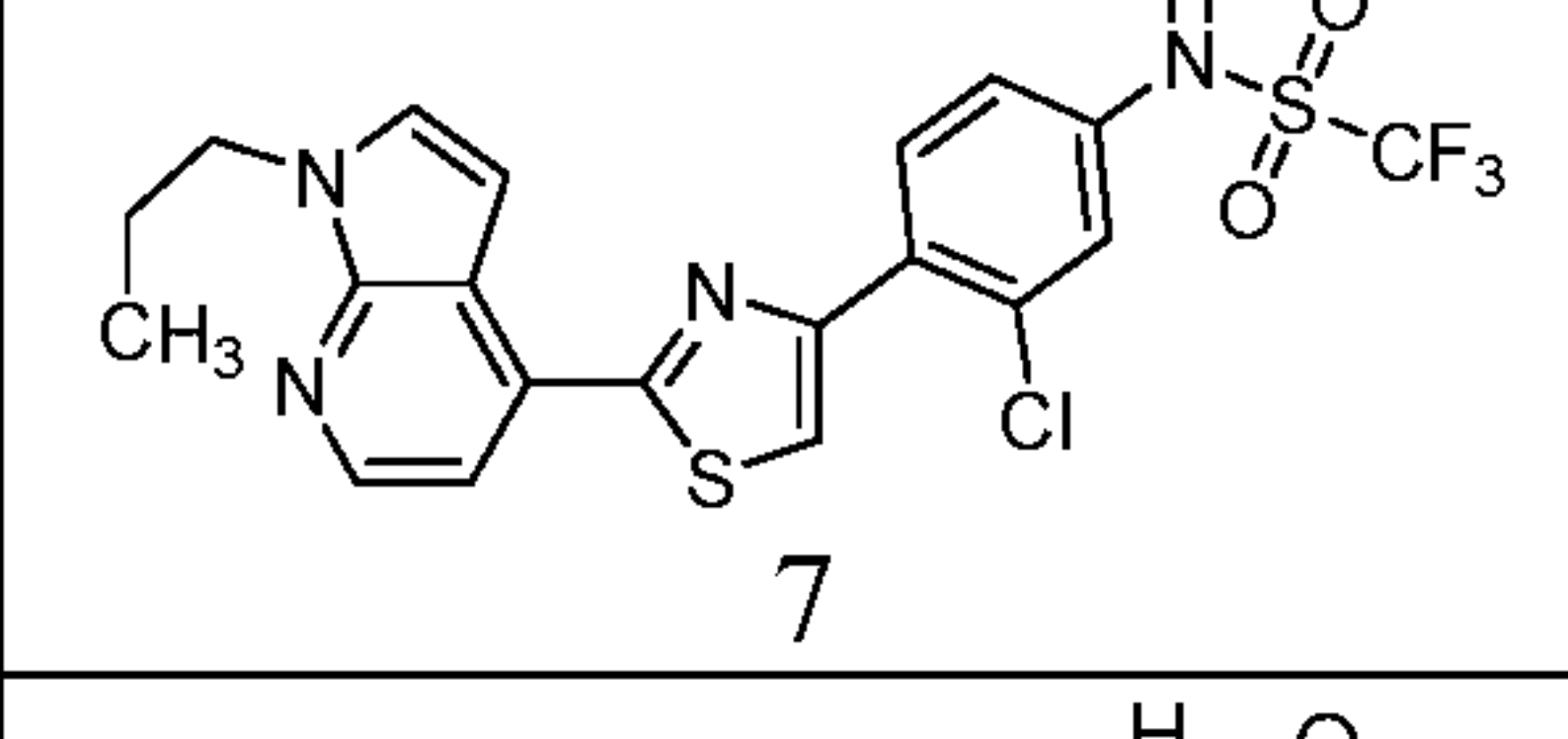
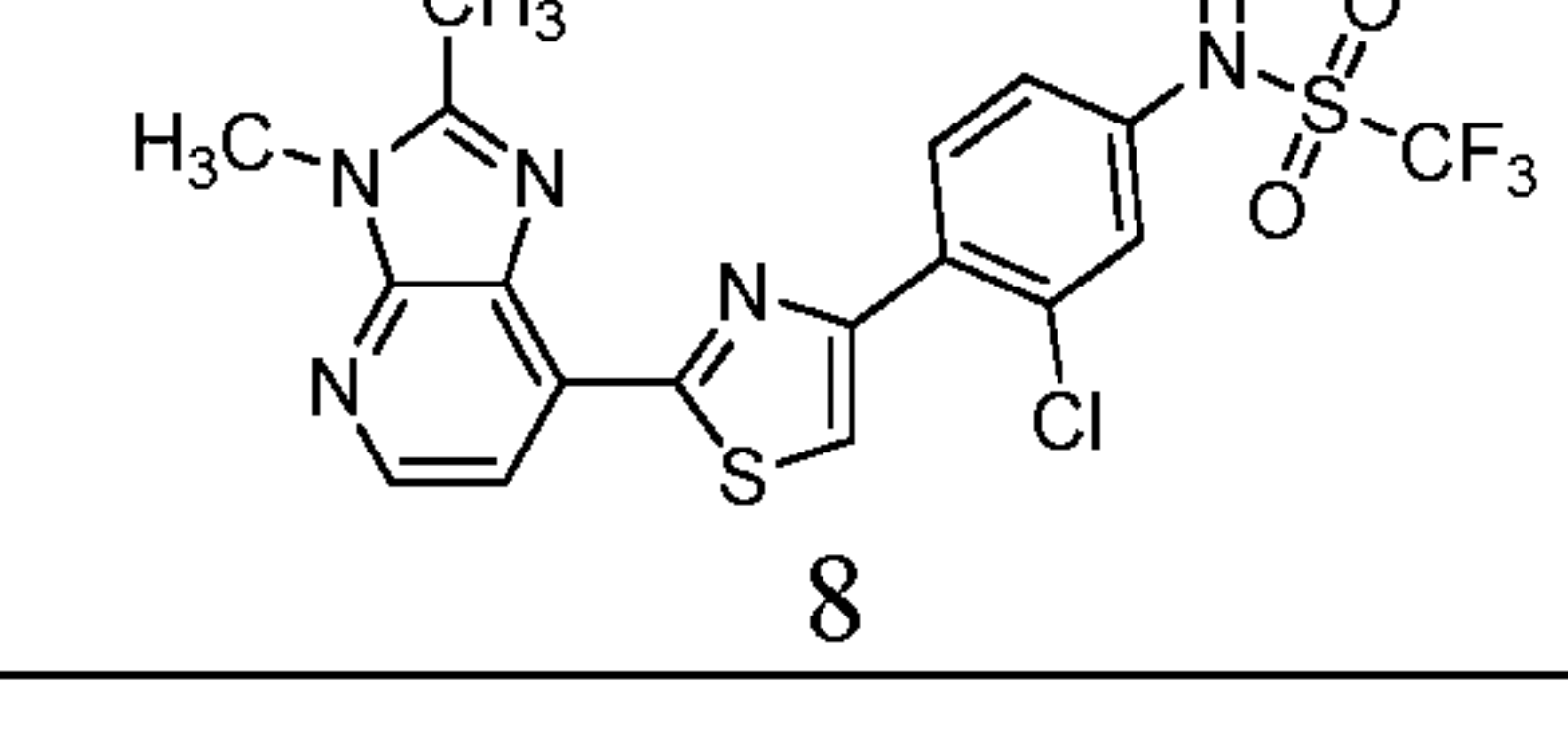
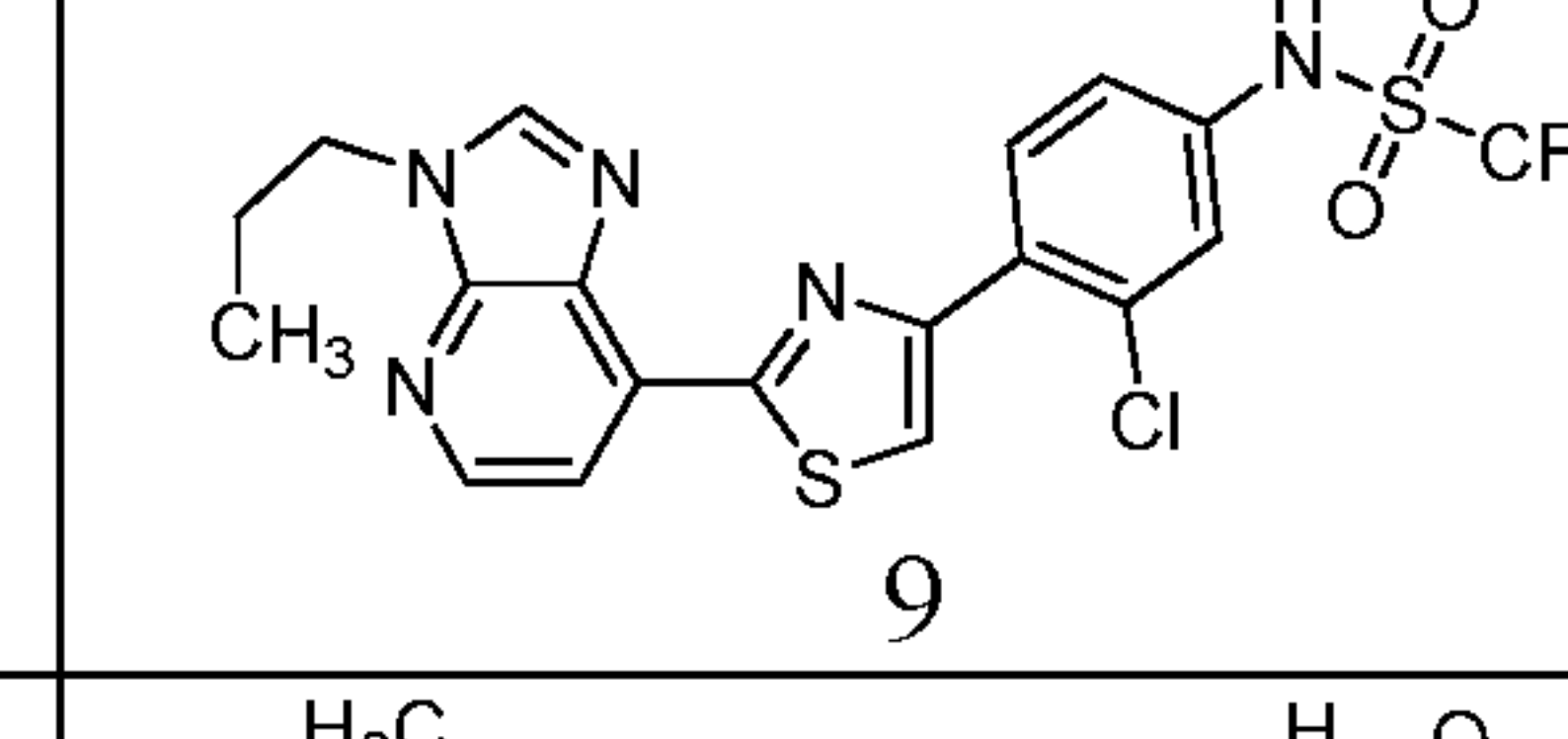
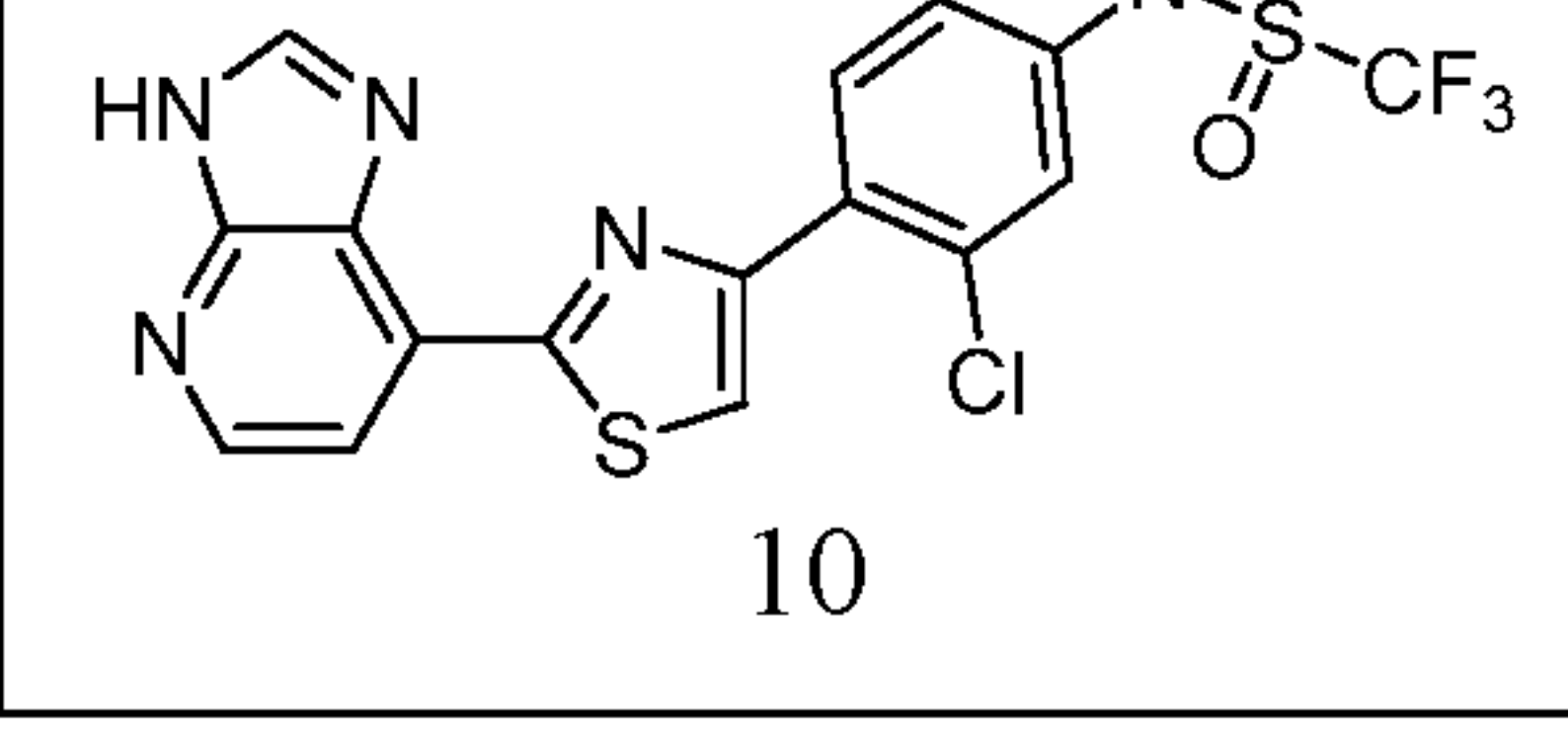
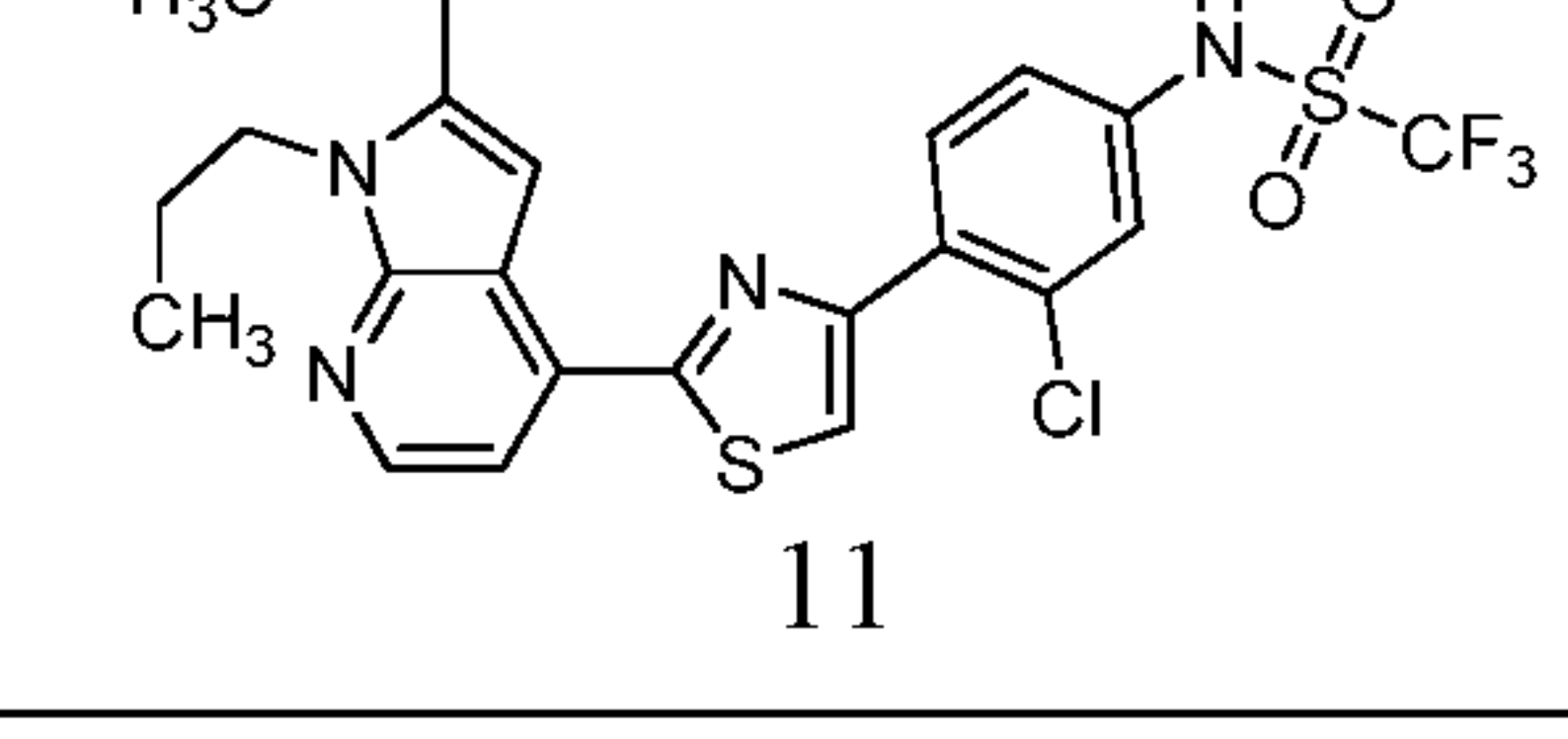
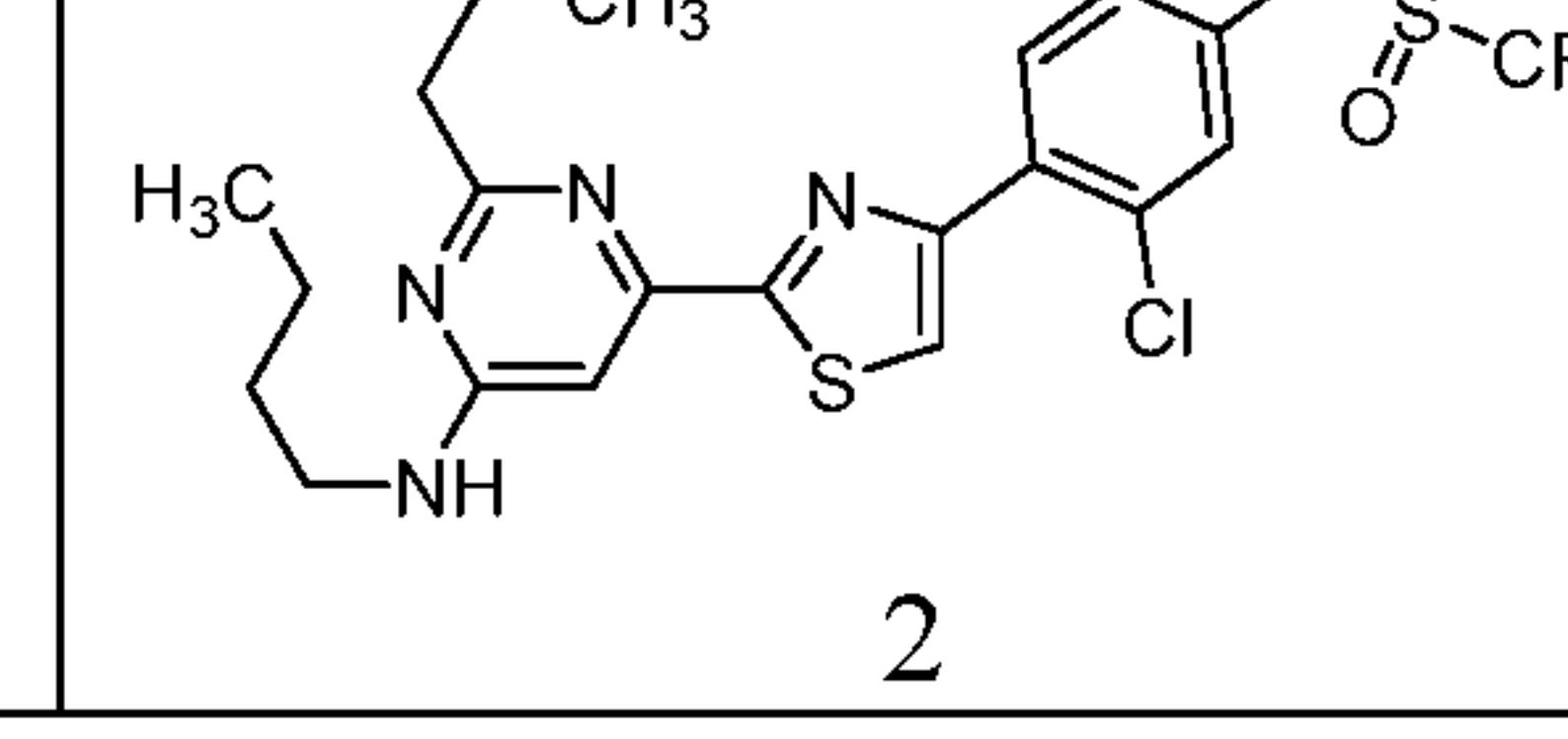
Table 1		
		
		
		
		

Table 1

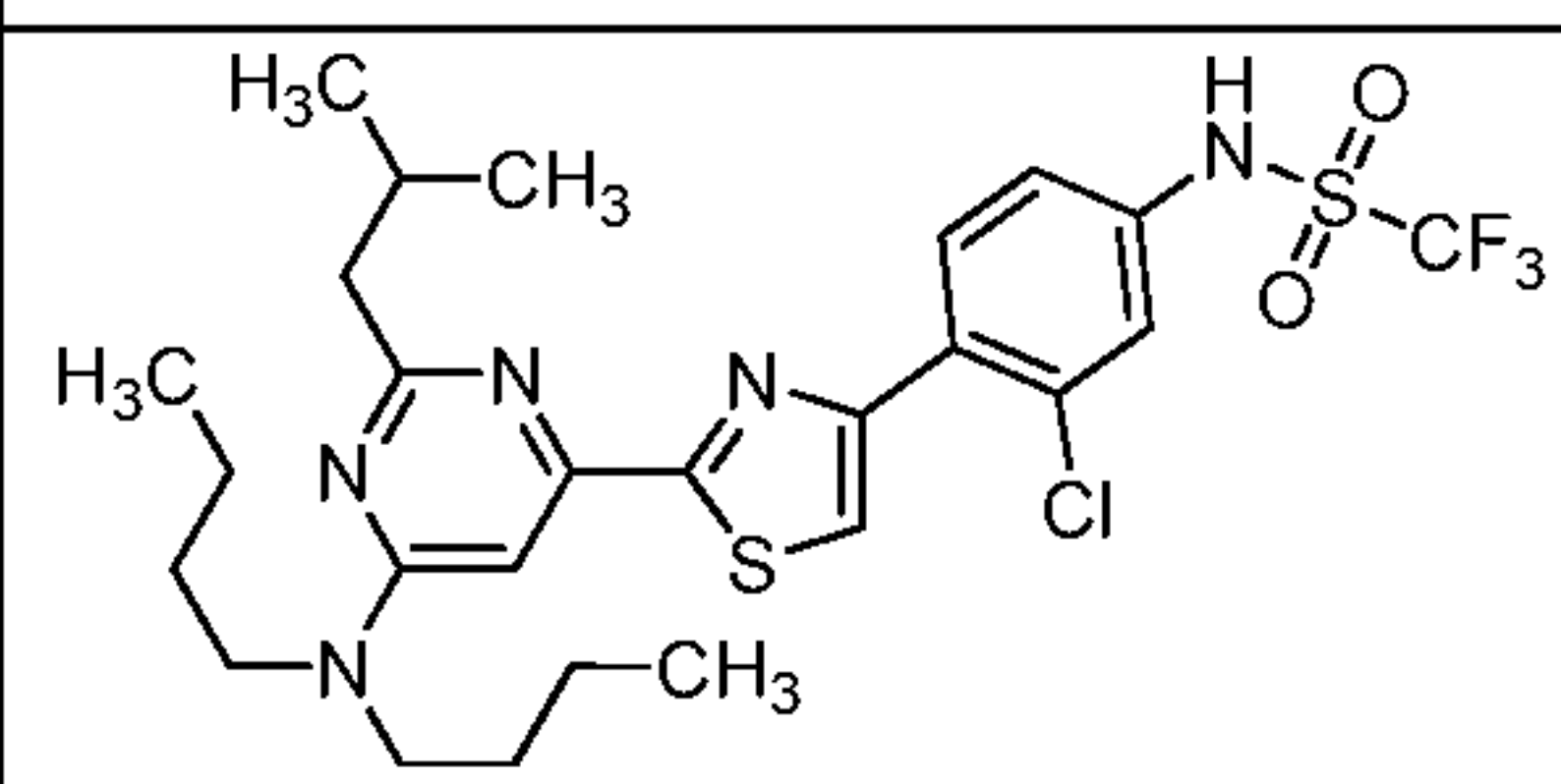
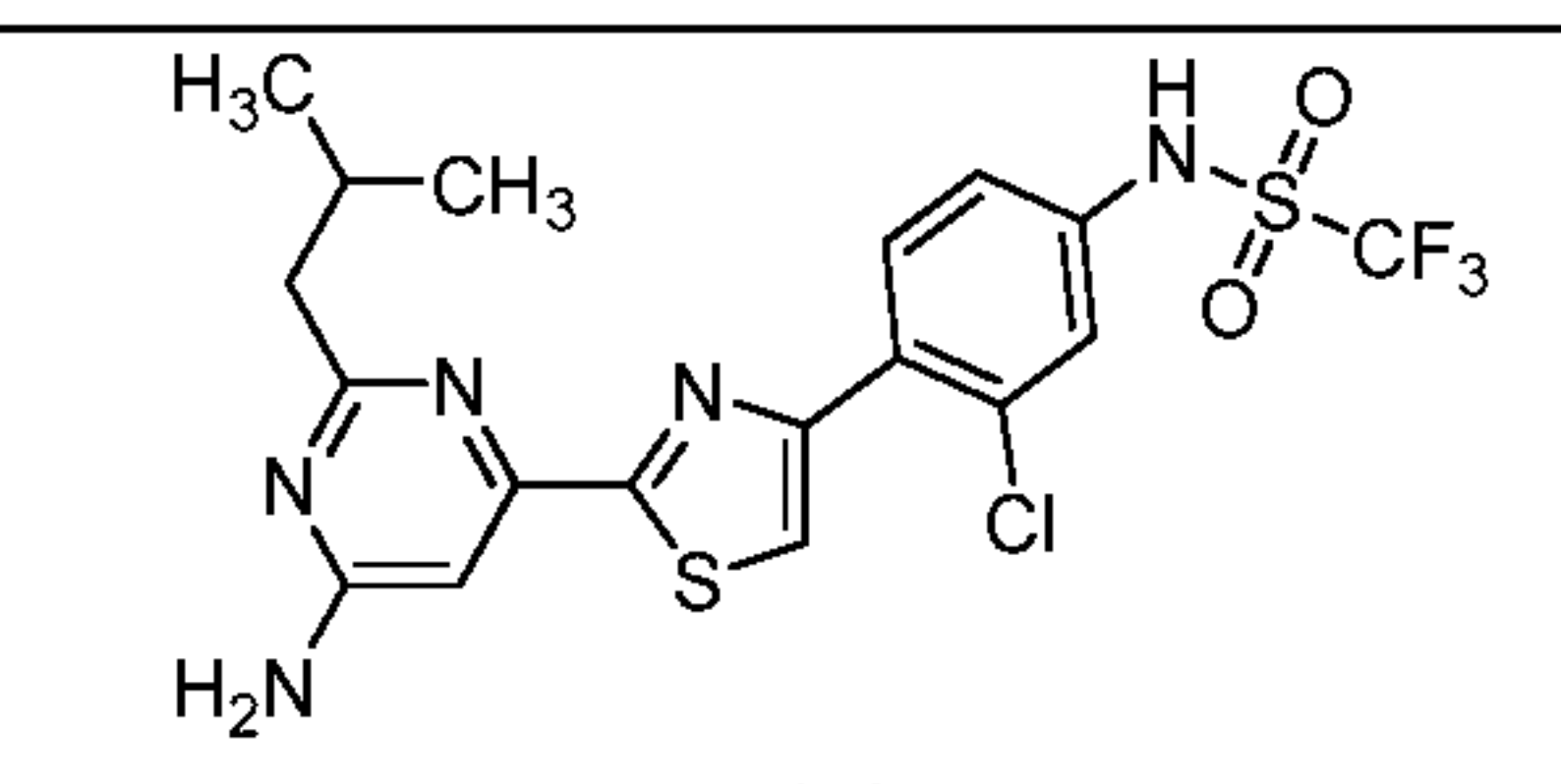
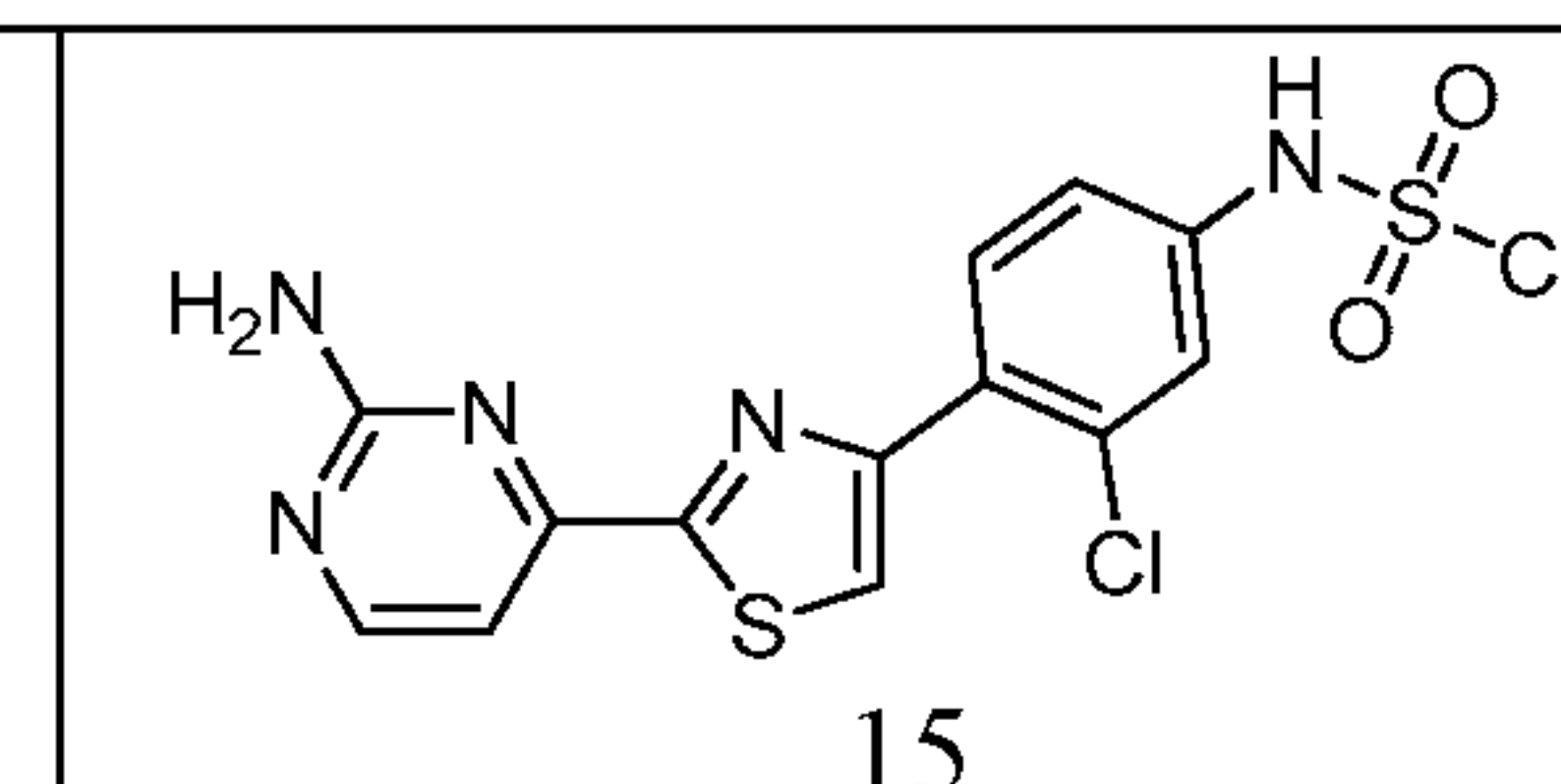
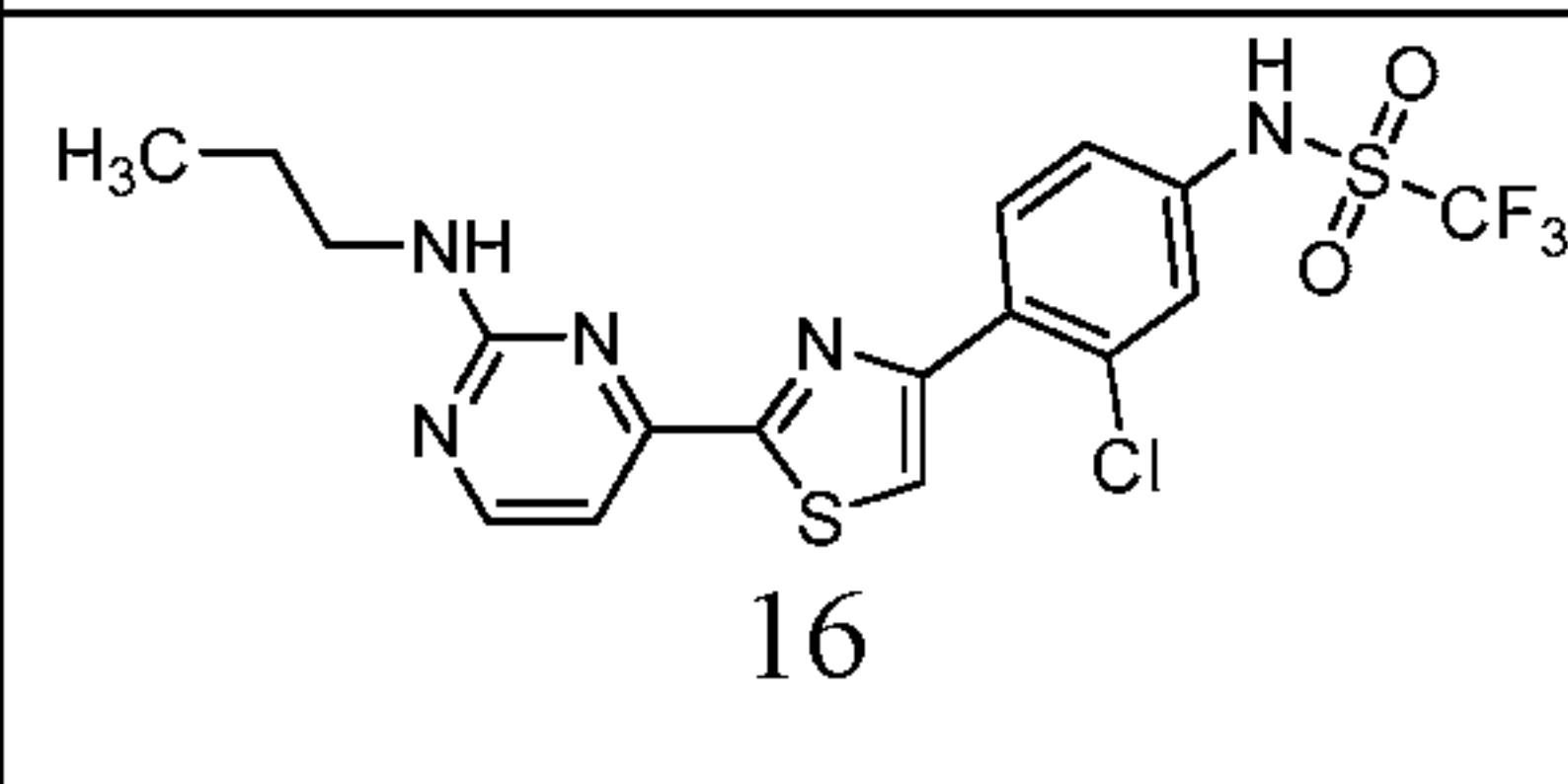
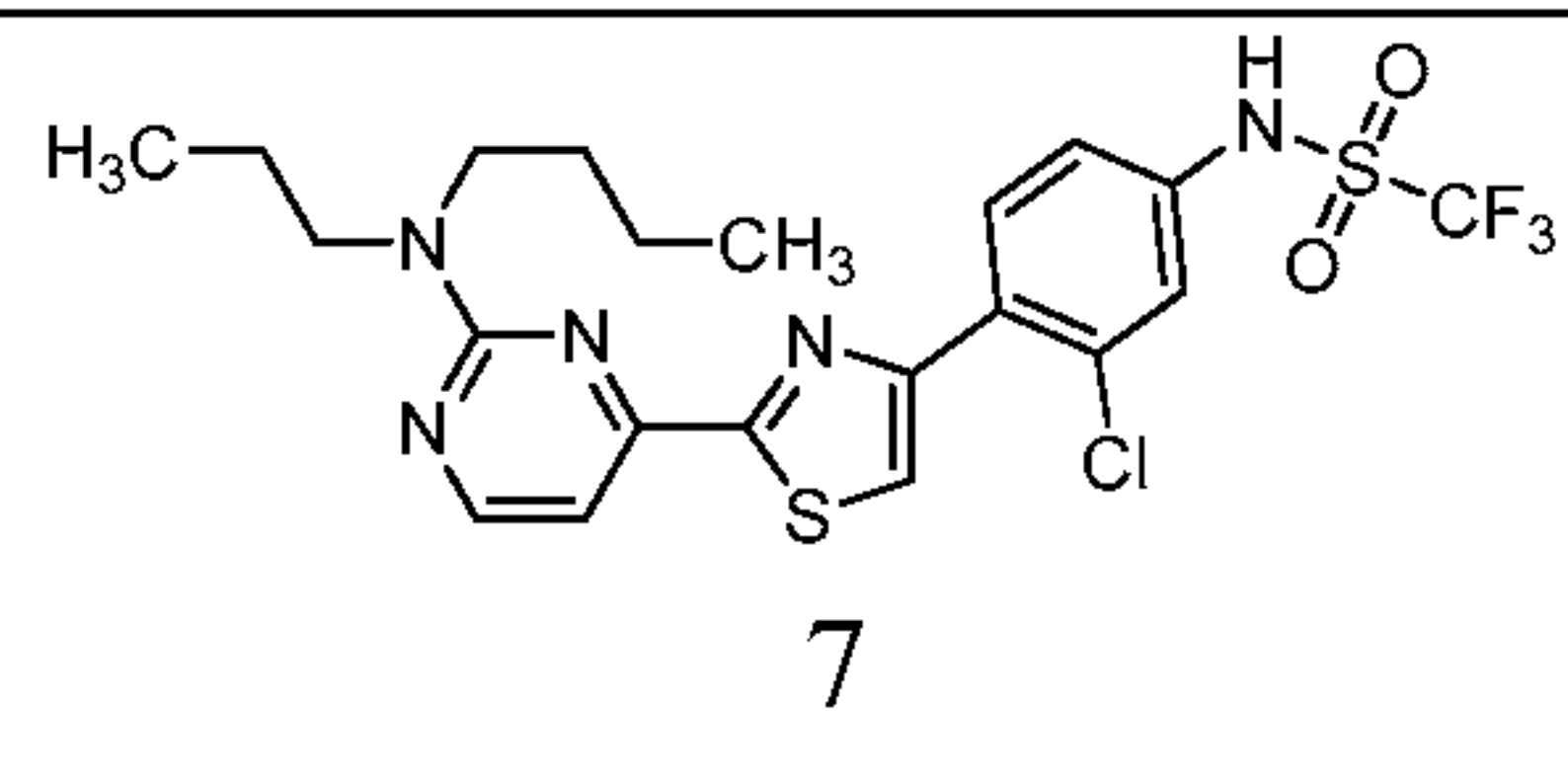
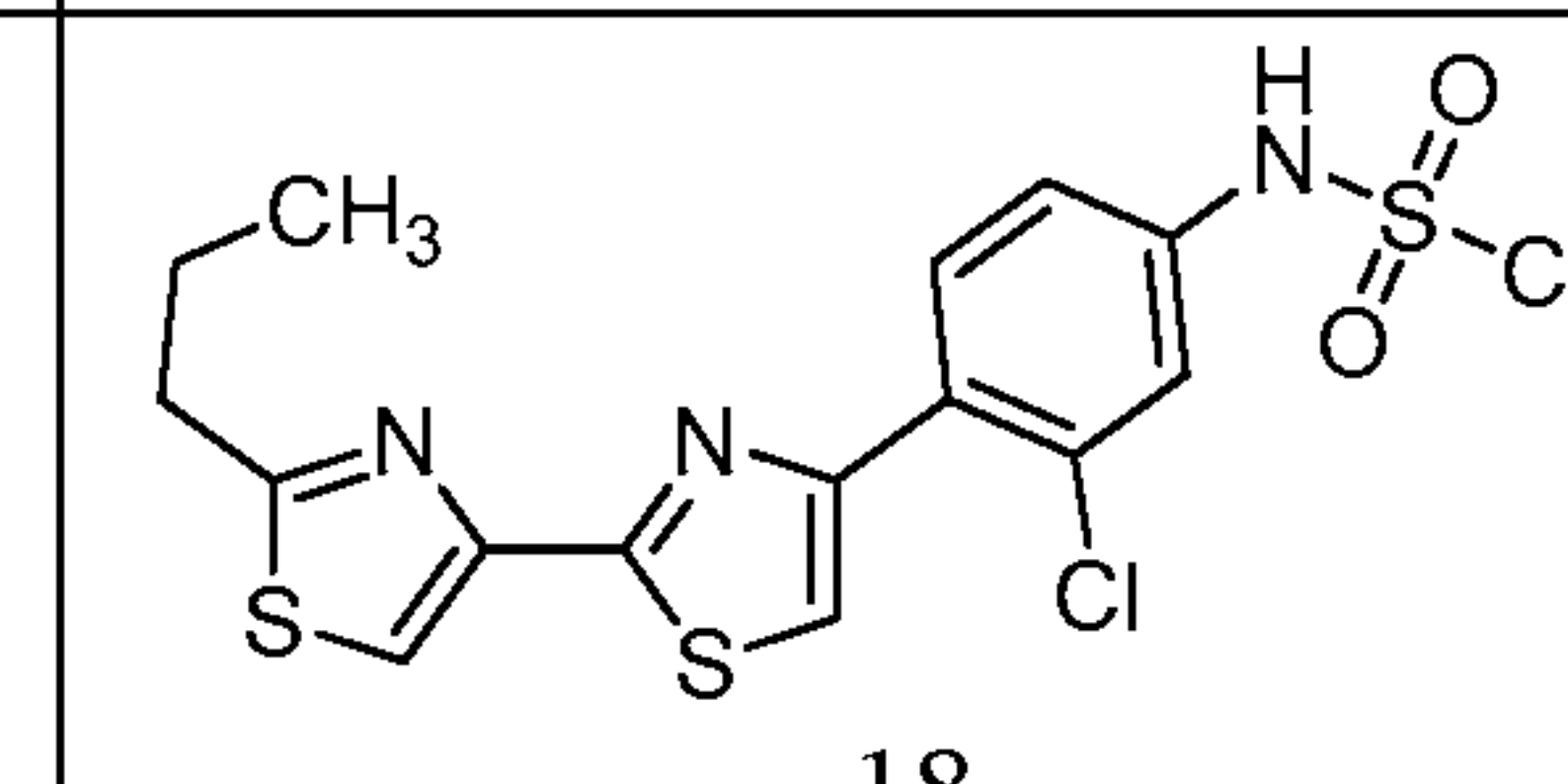
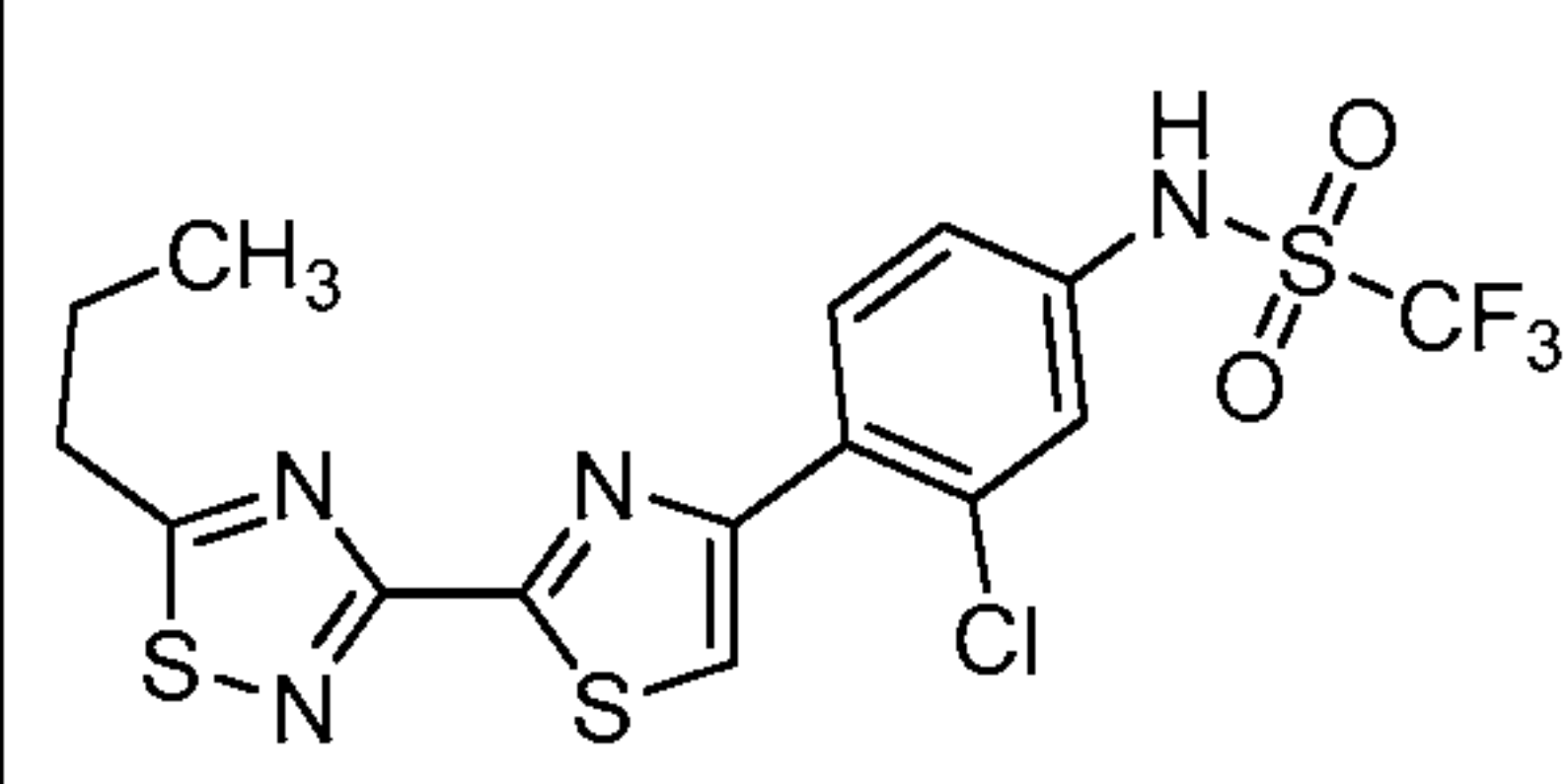
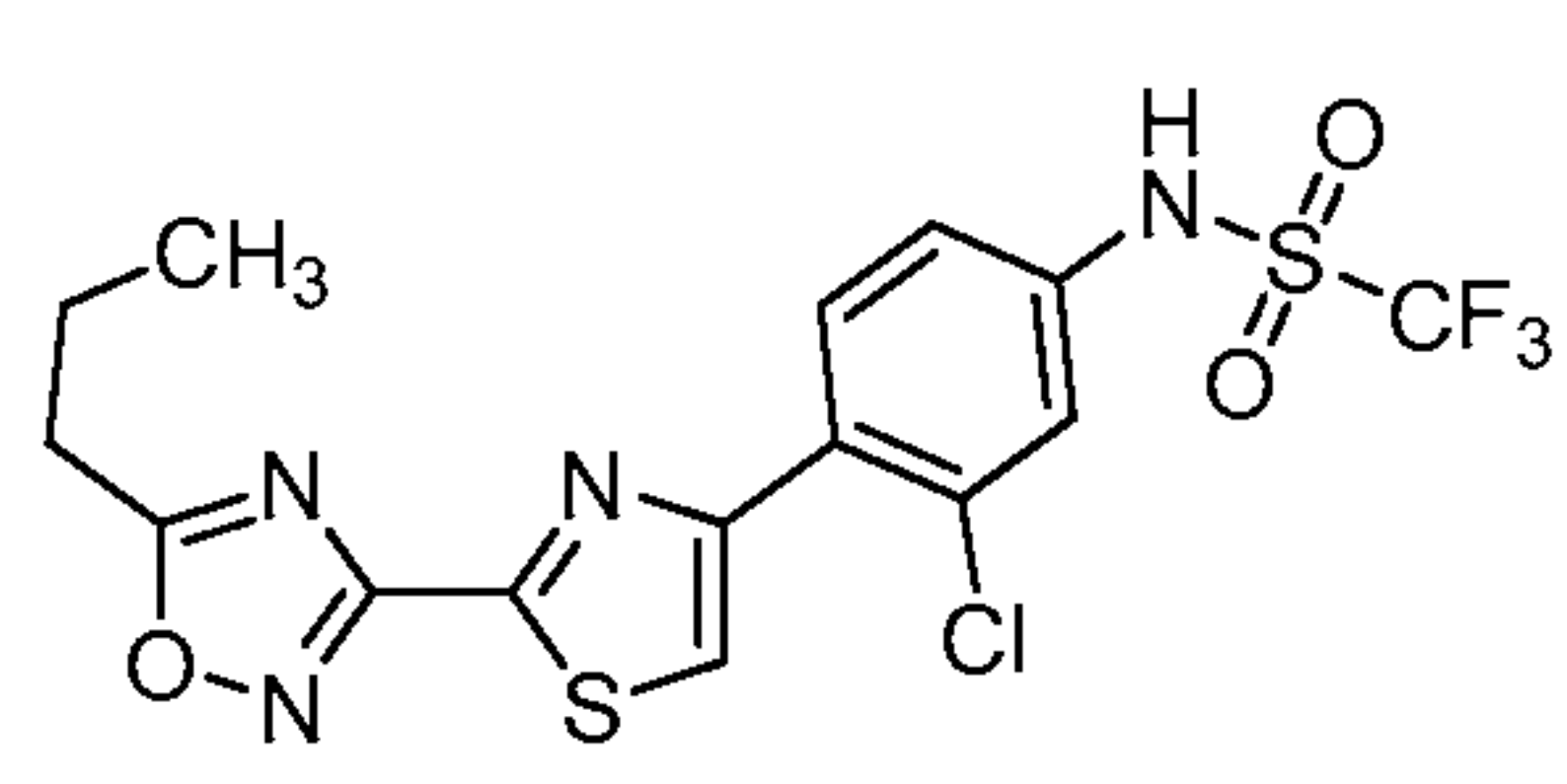
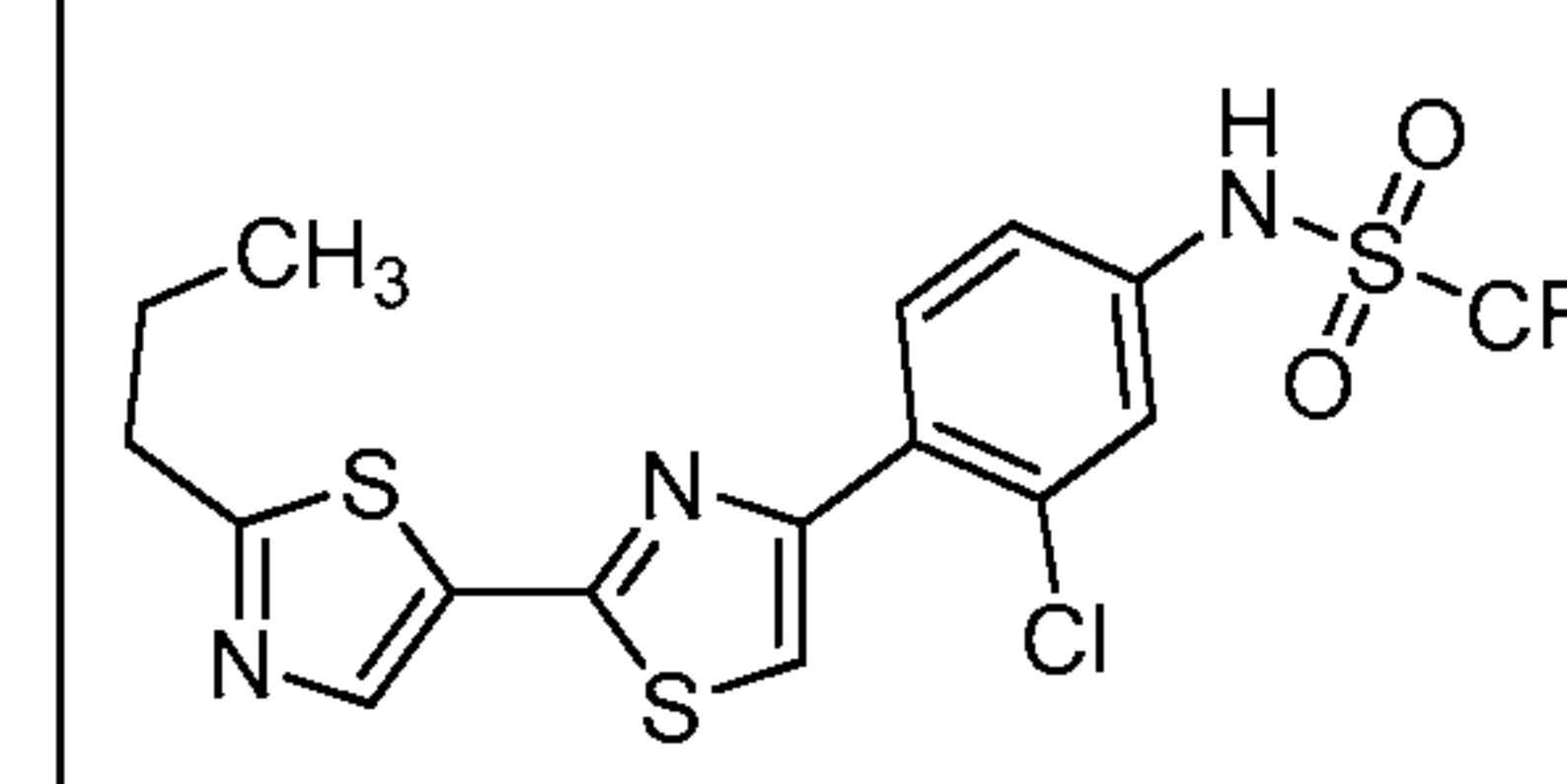
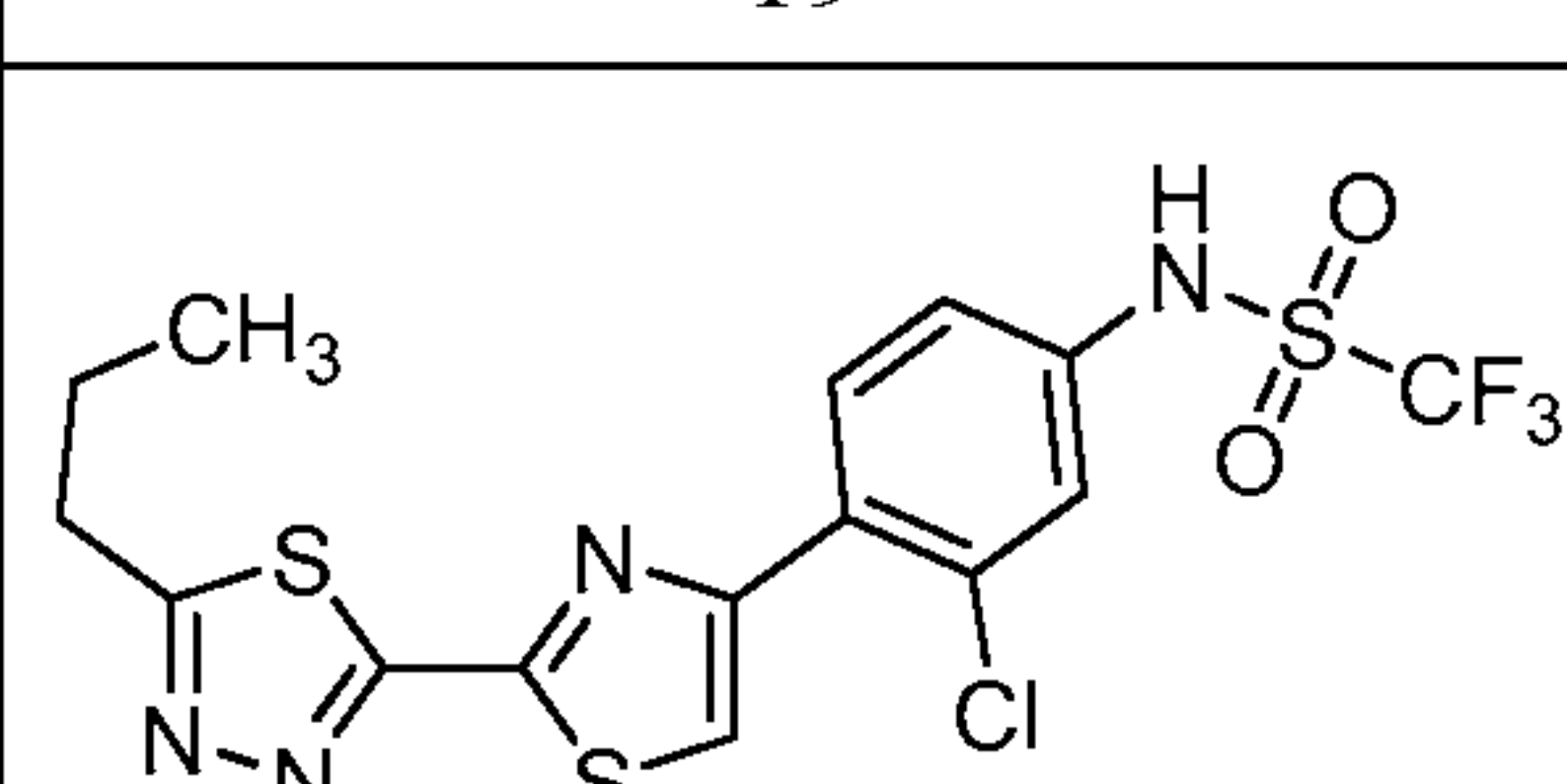
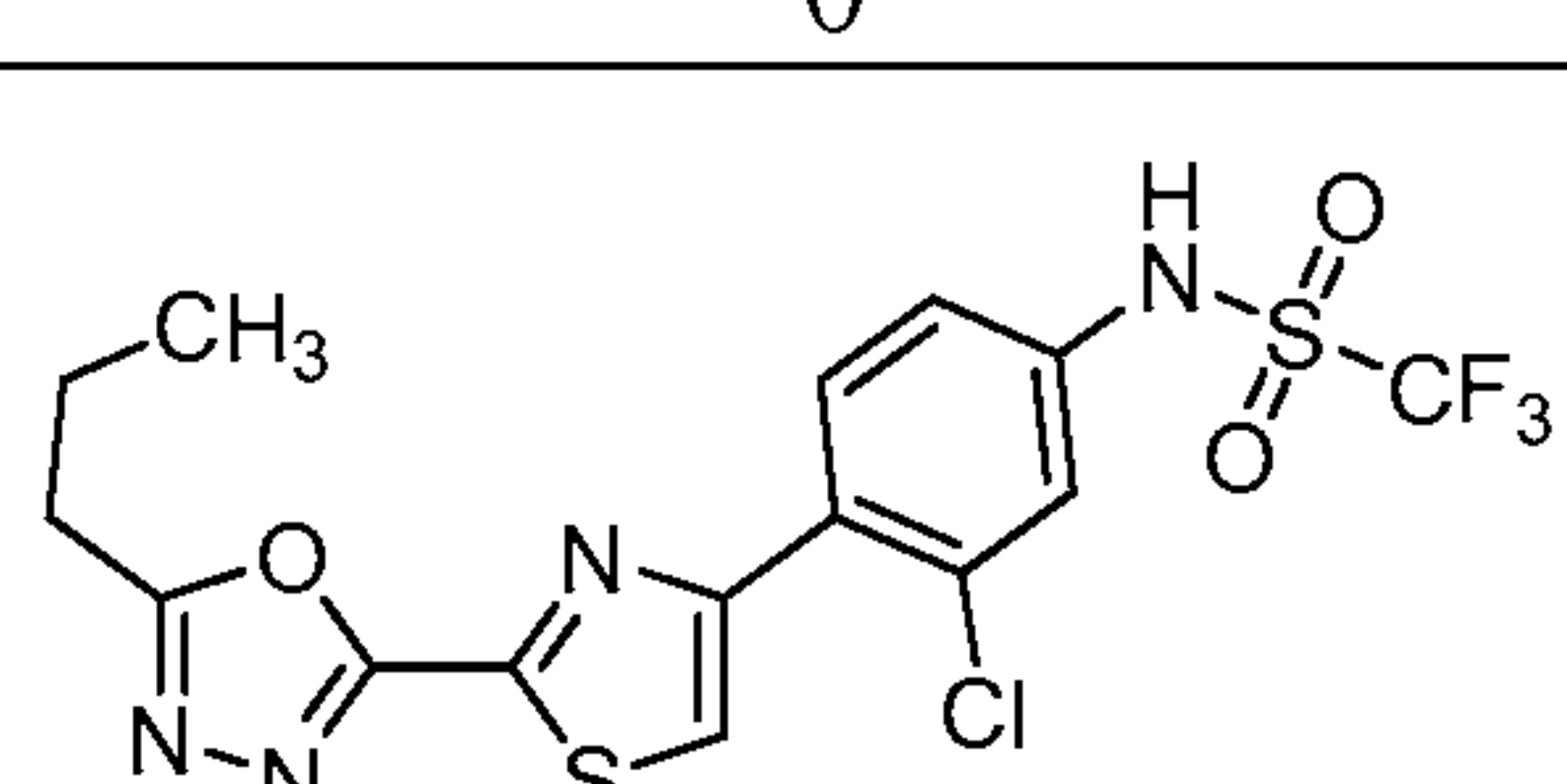
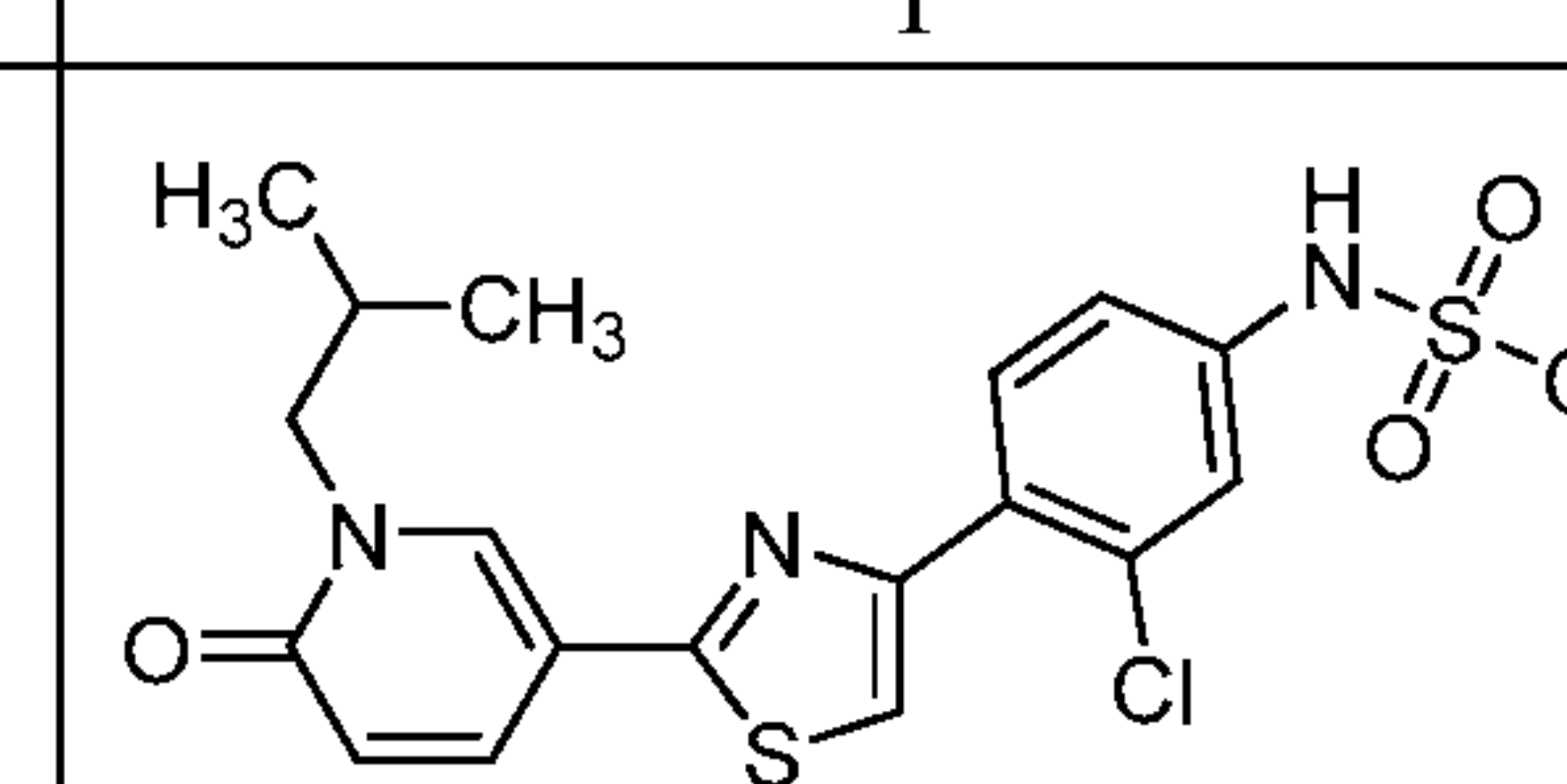
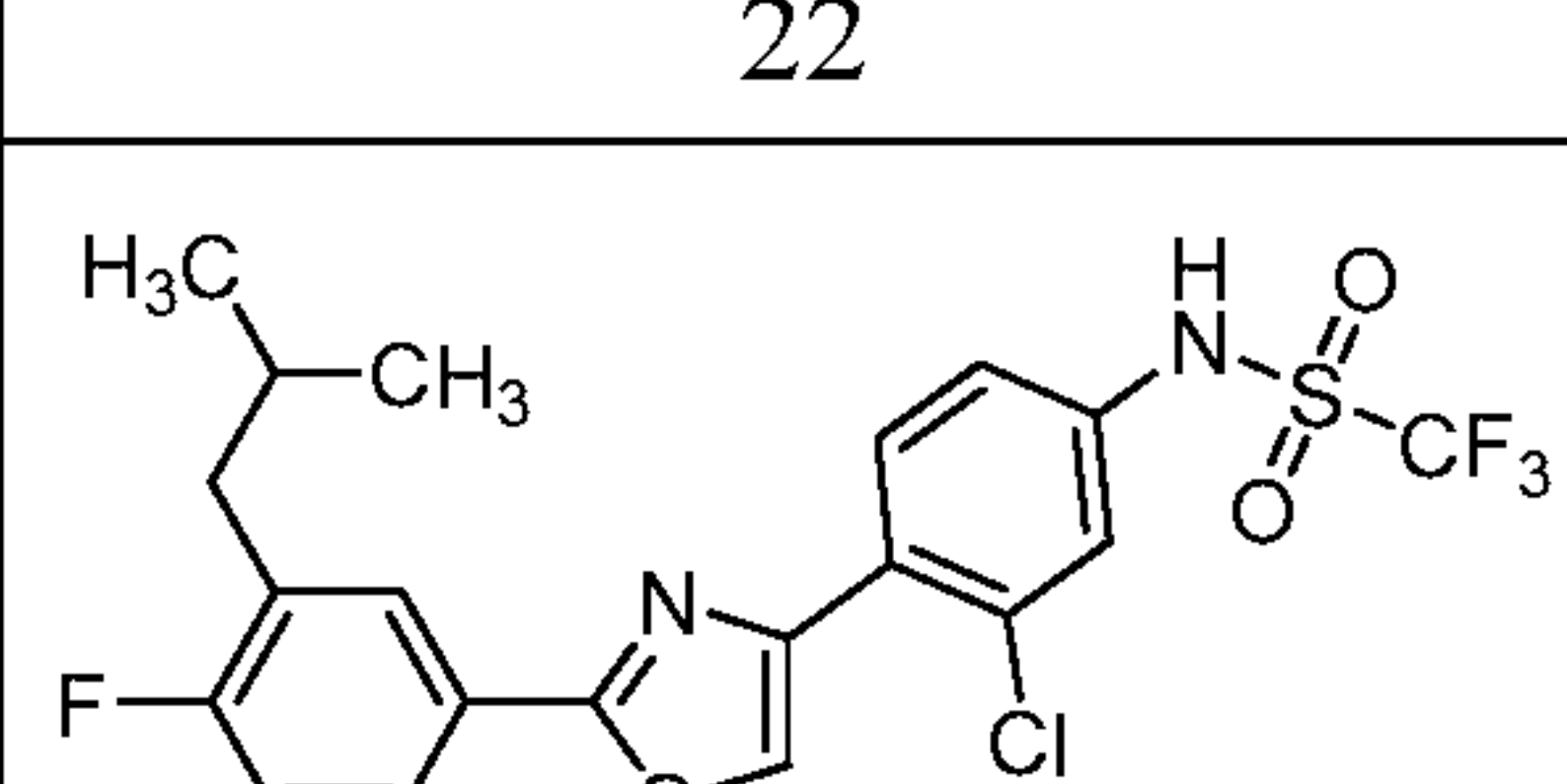
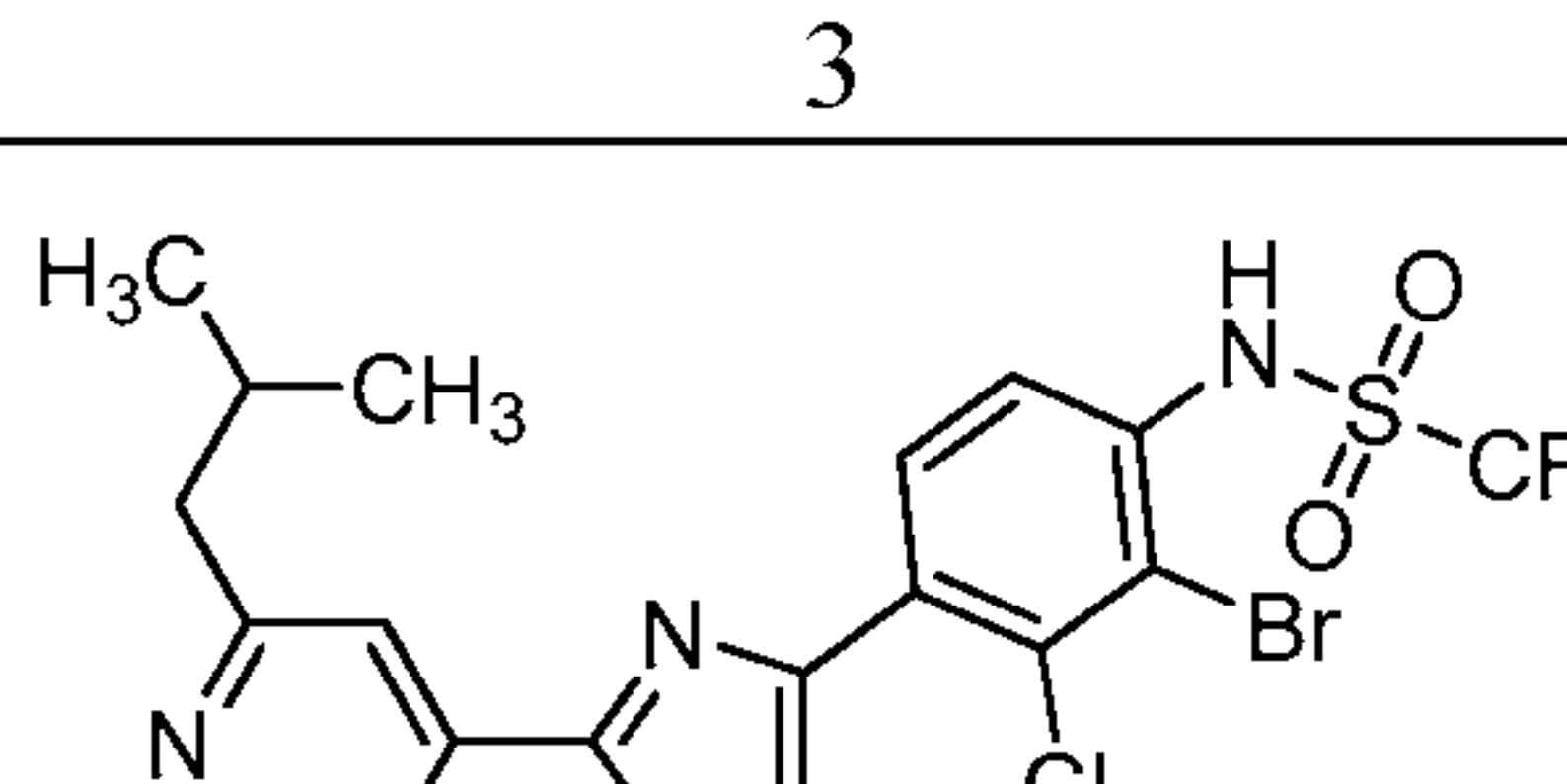
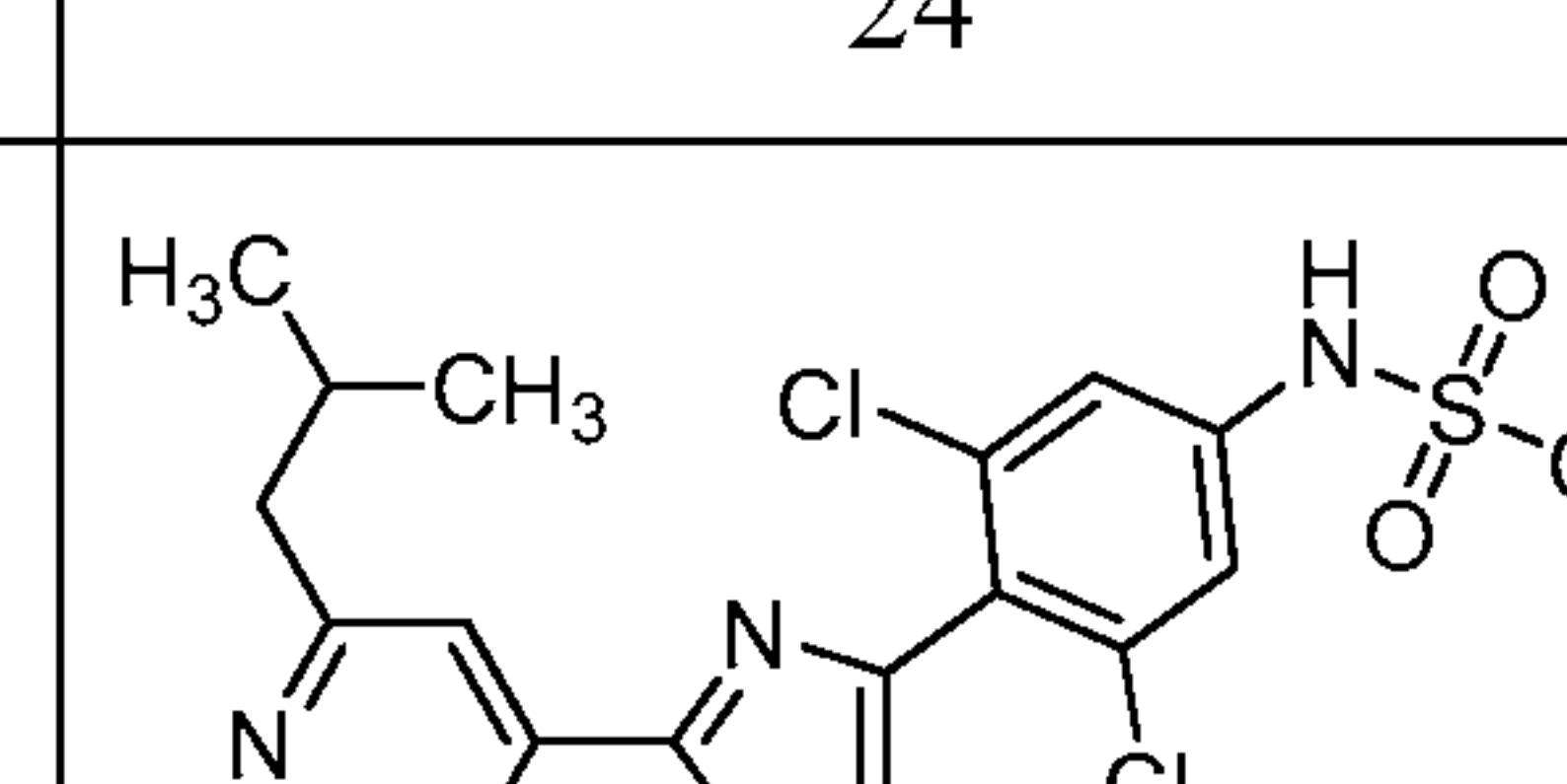
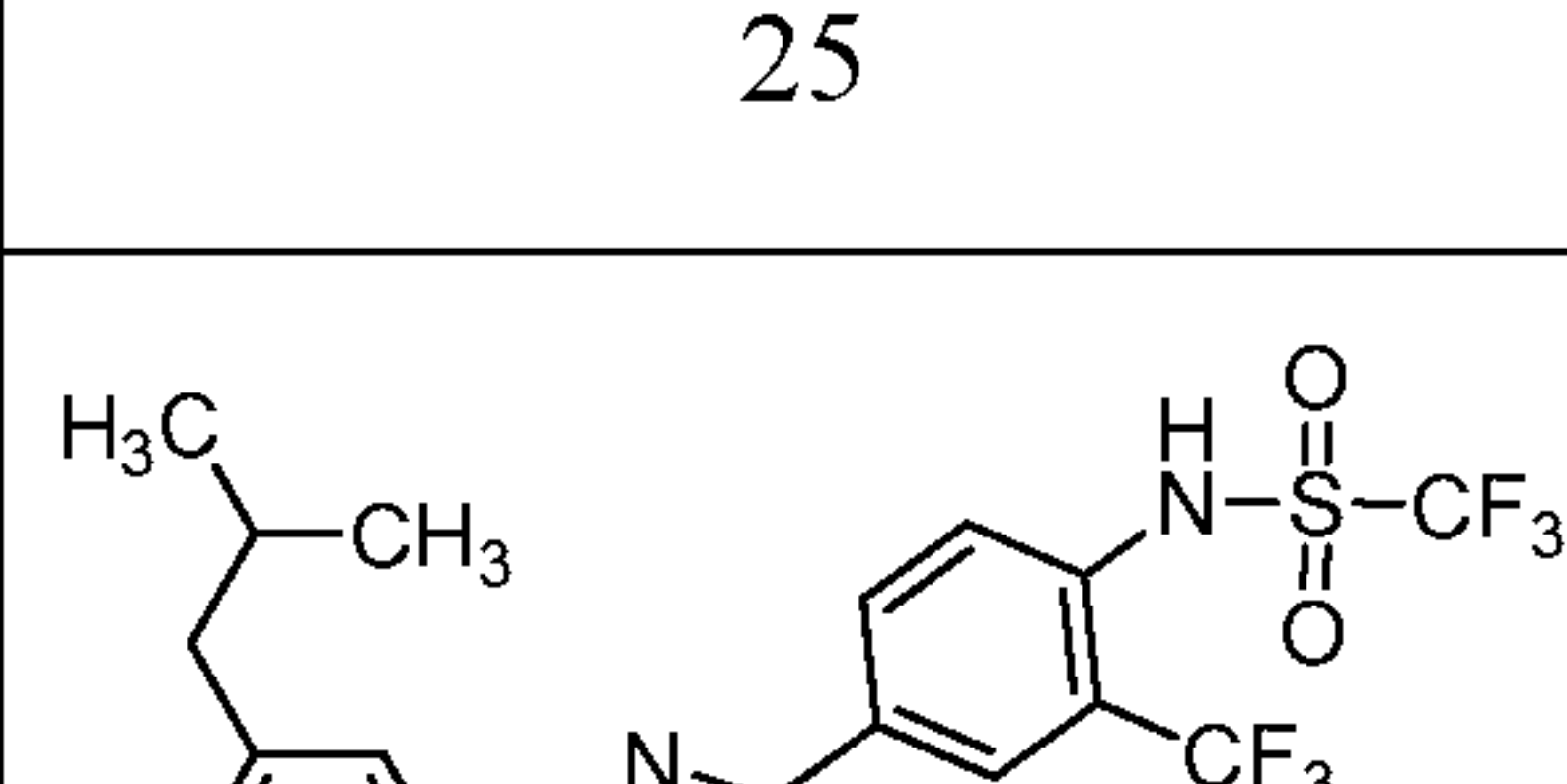
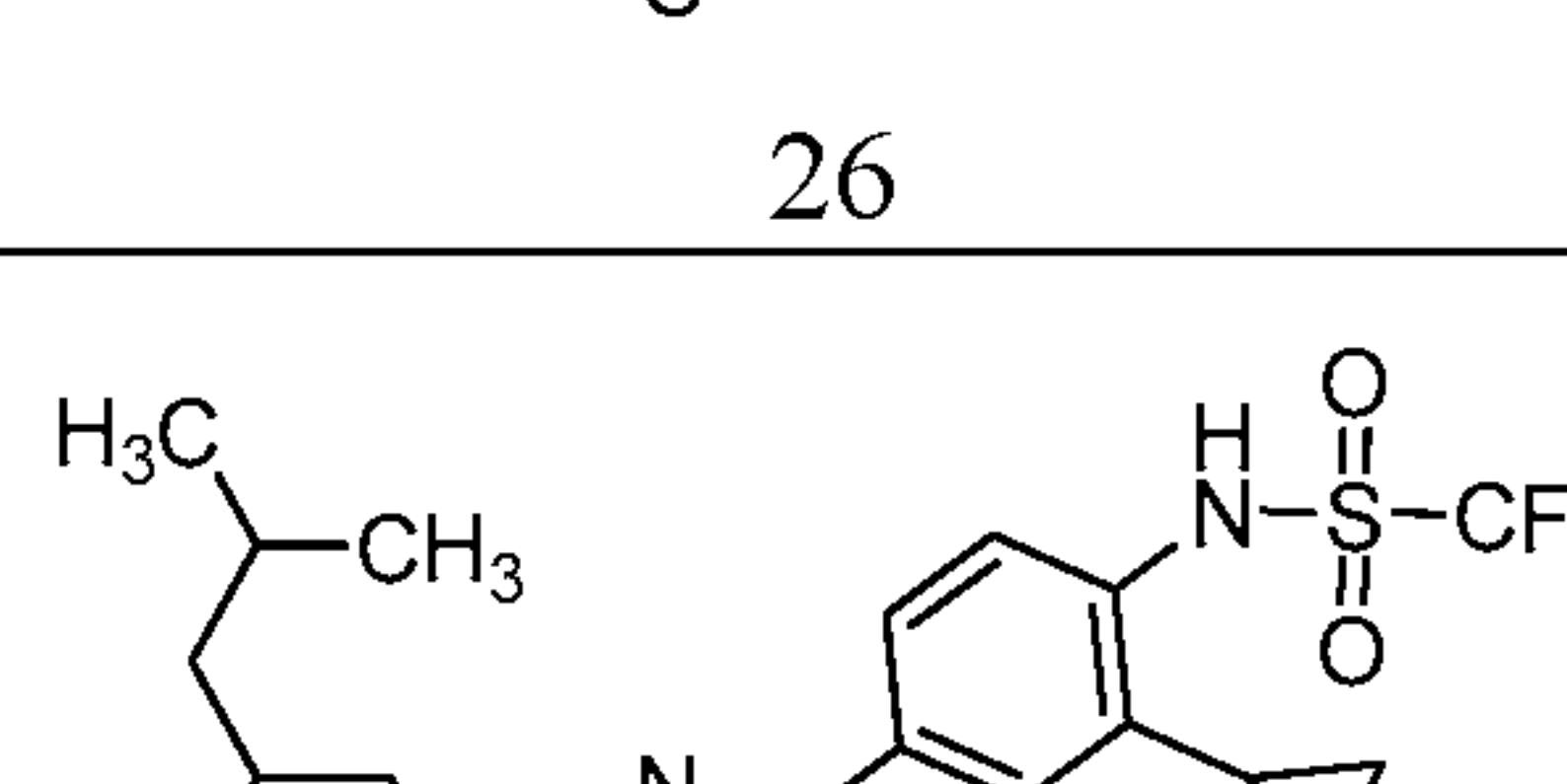
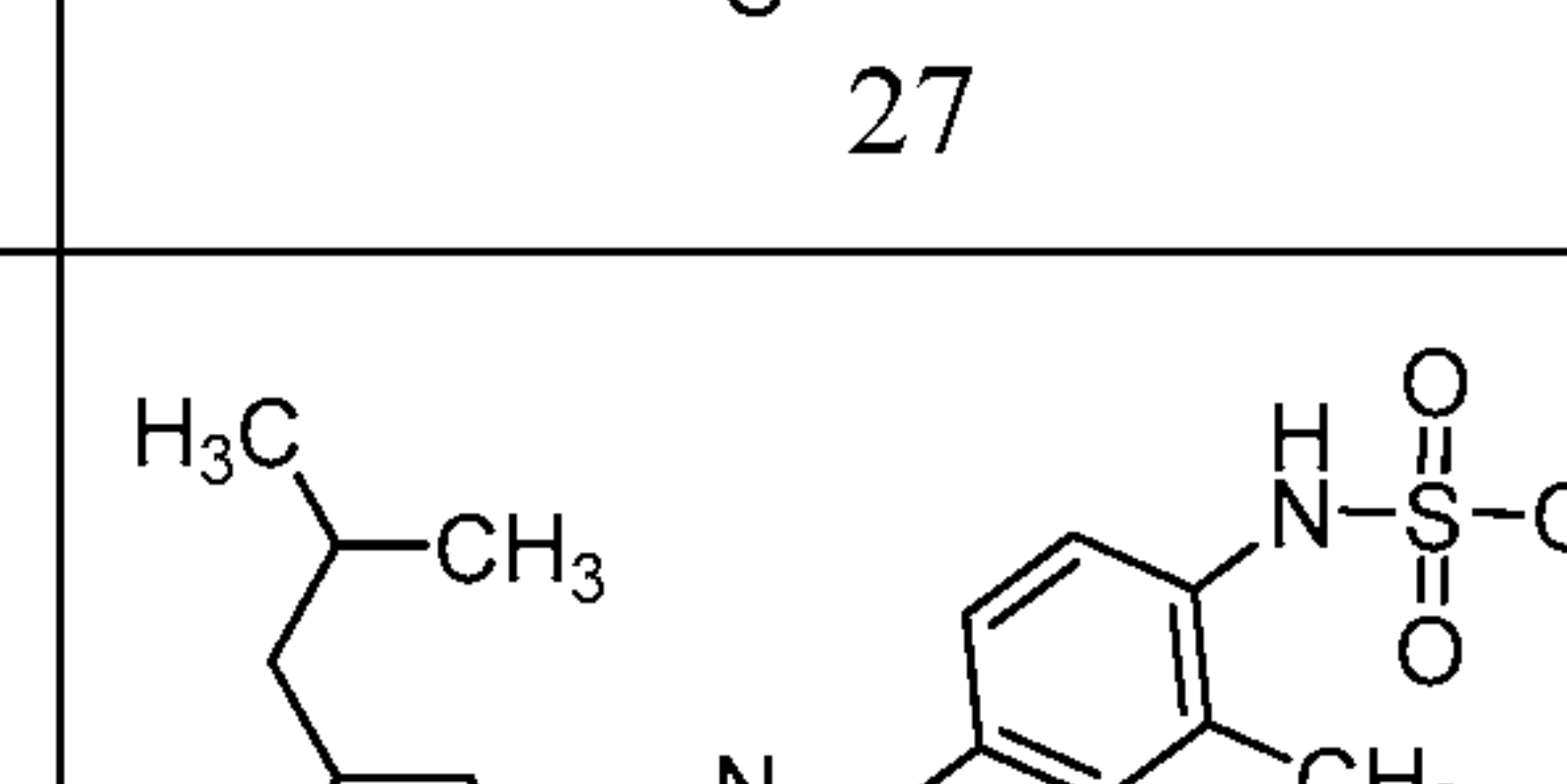
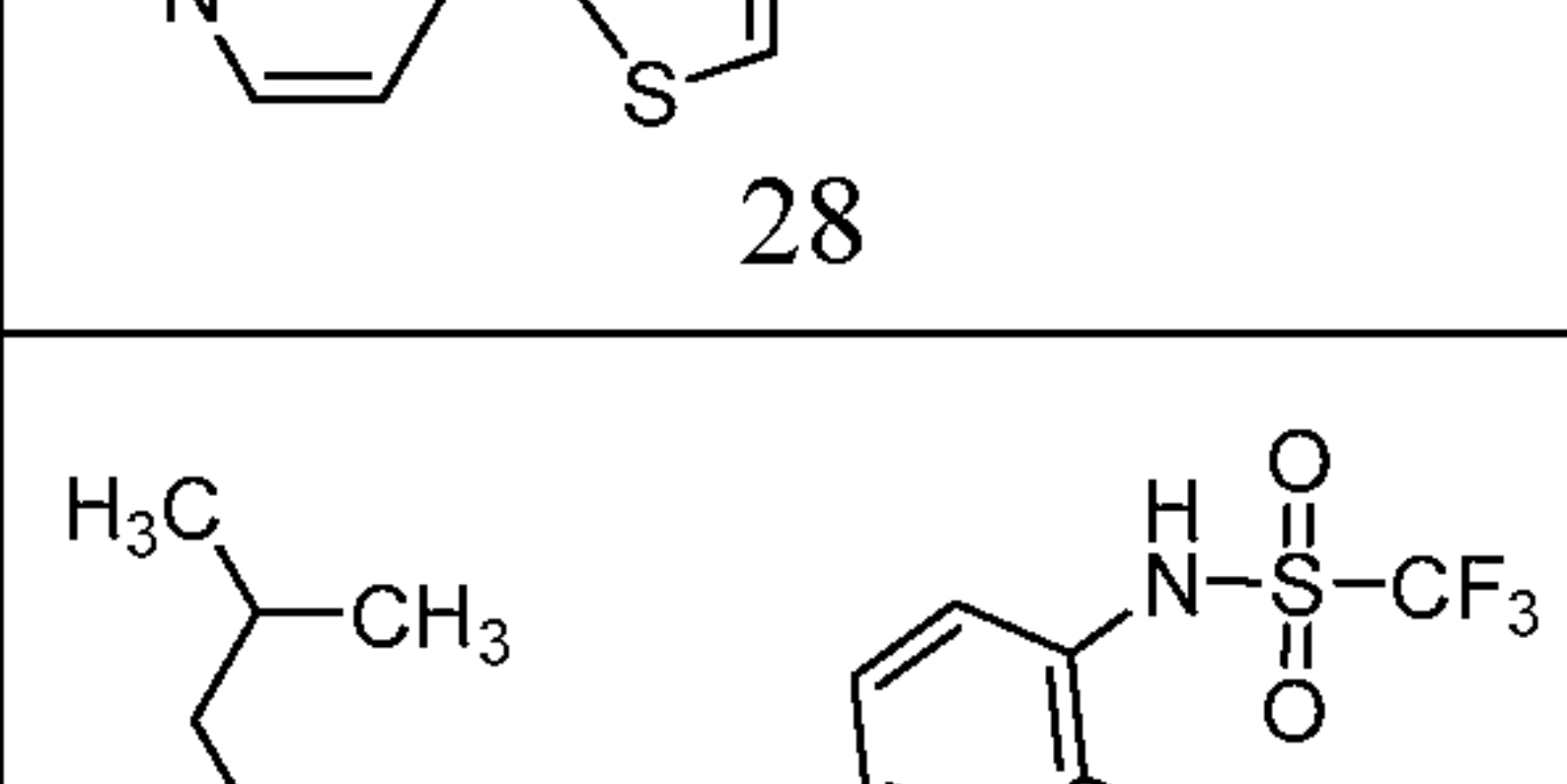
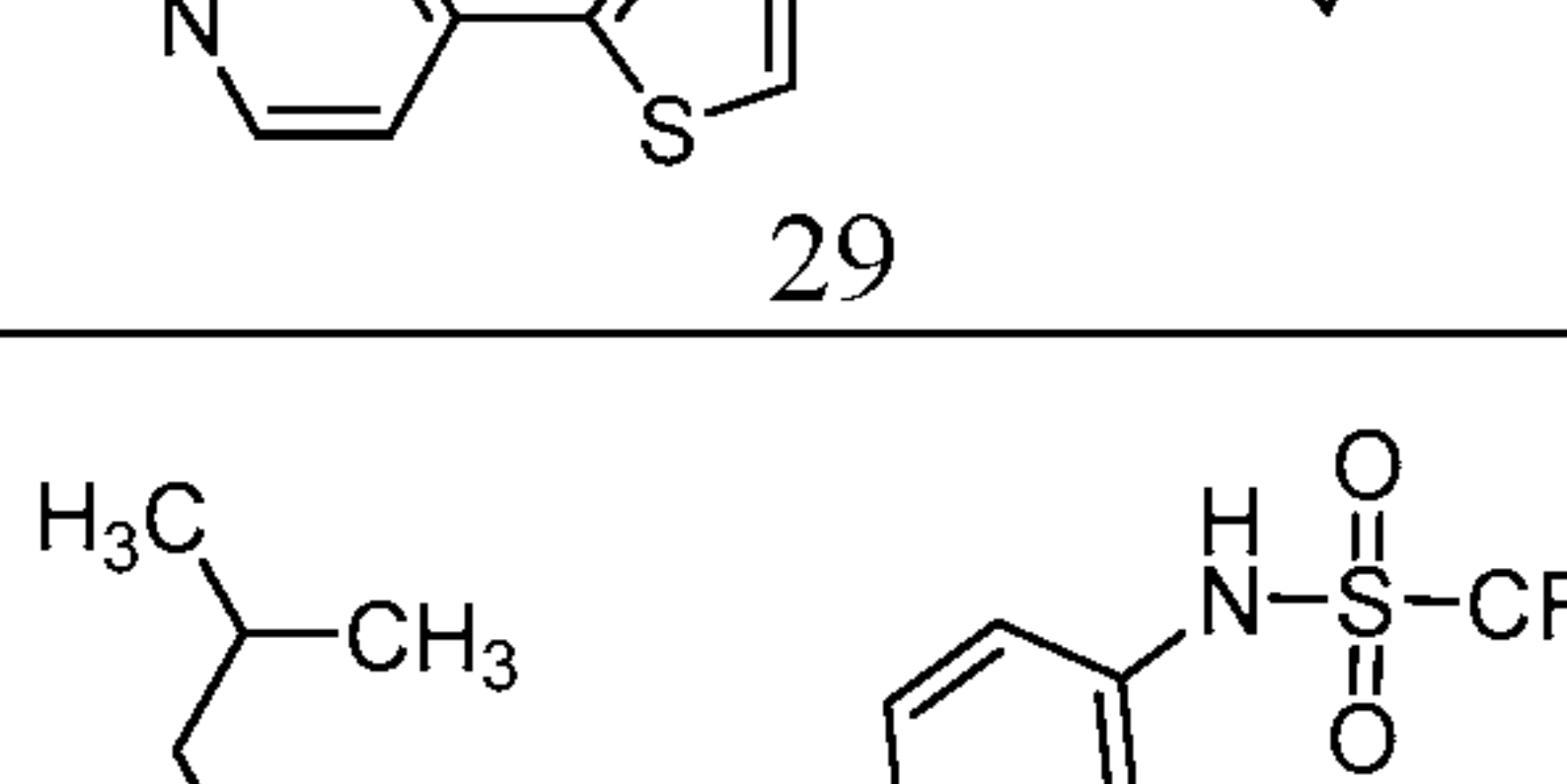
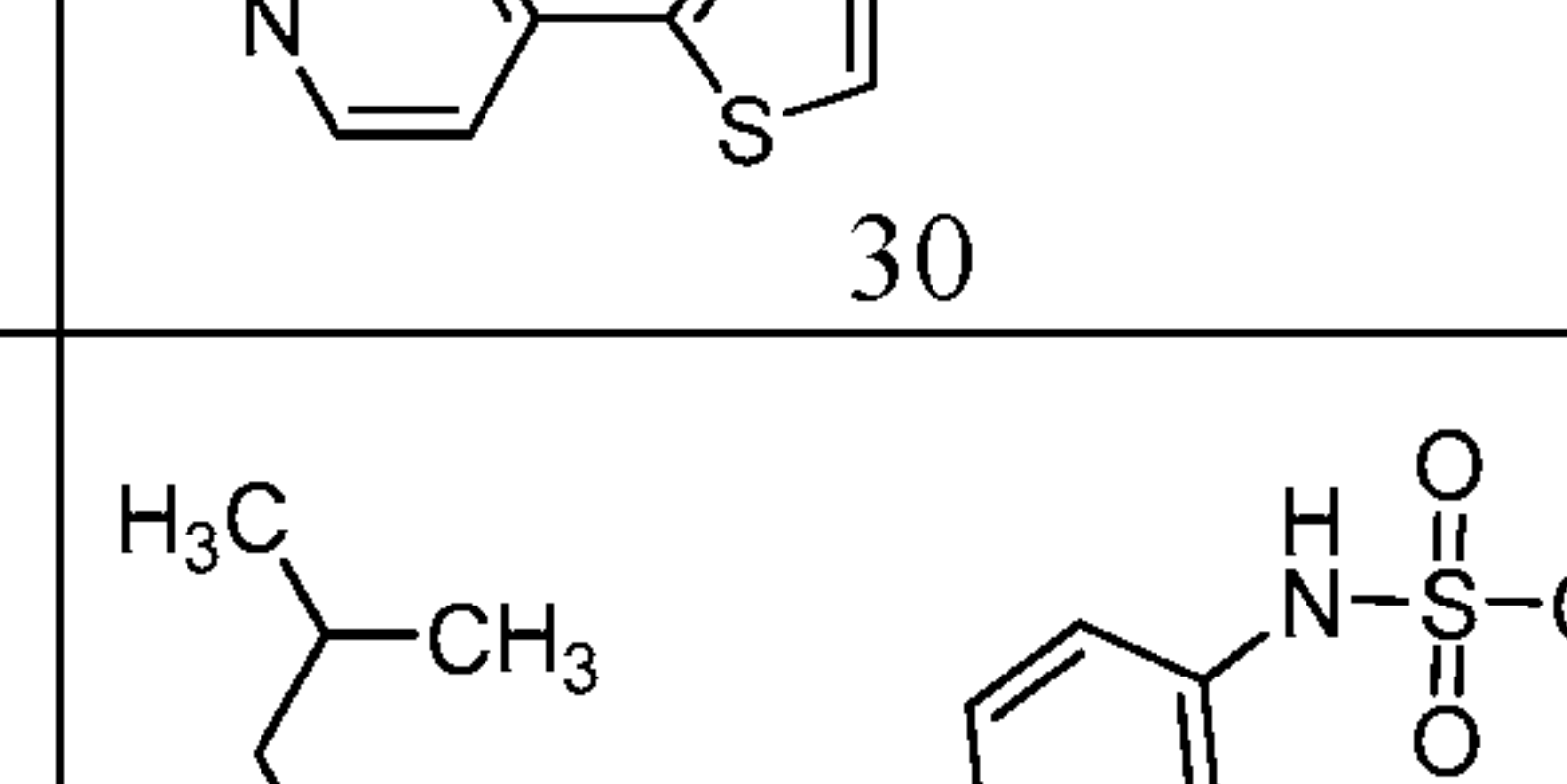
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Table 1

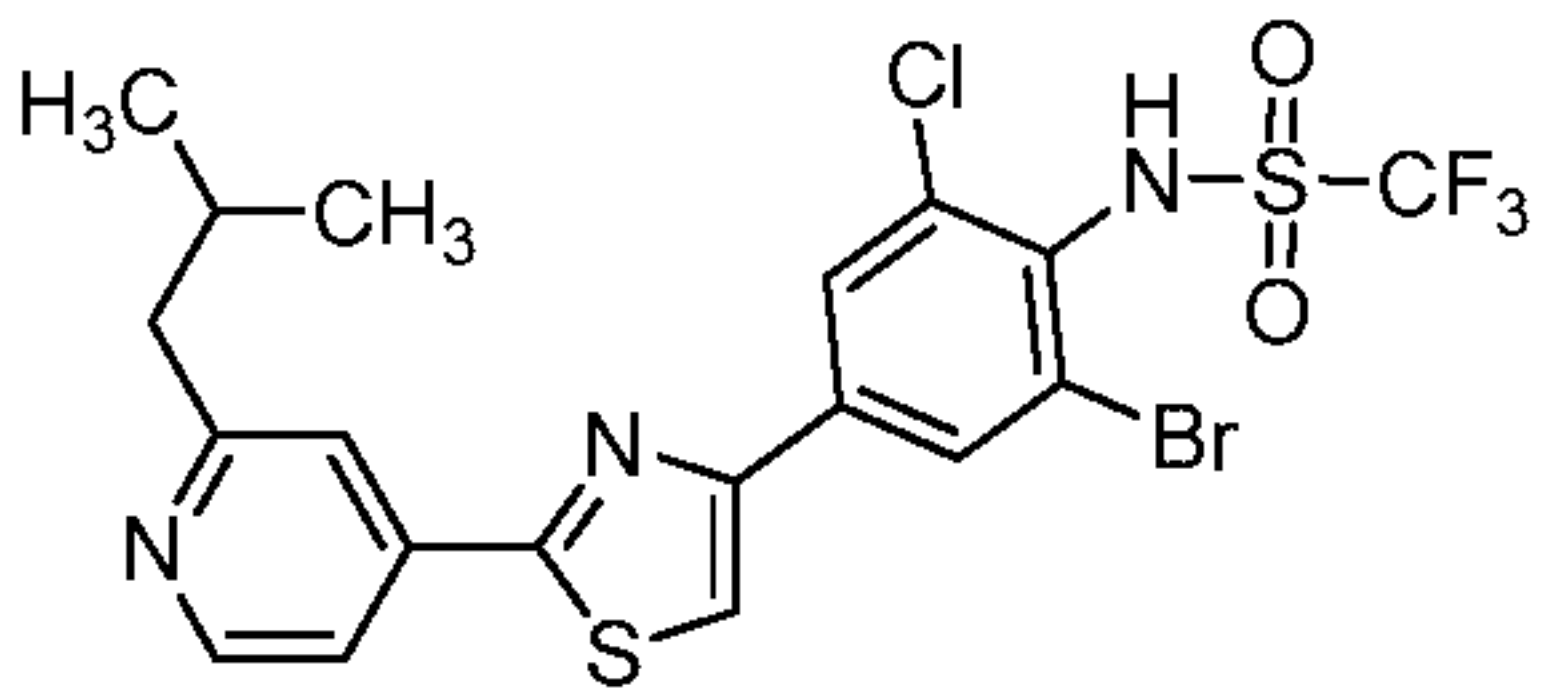
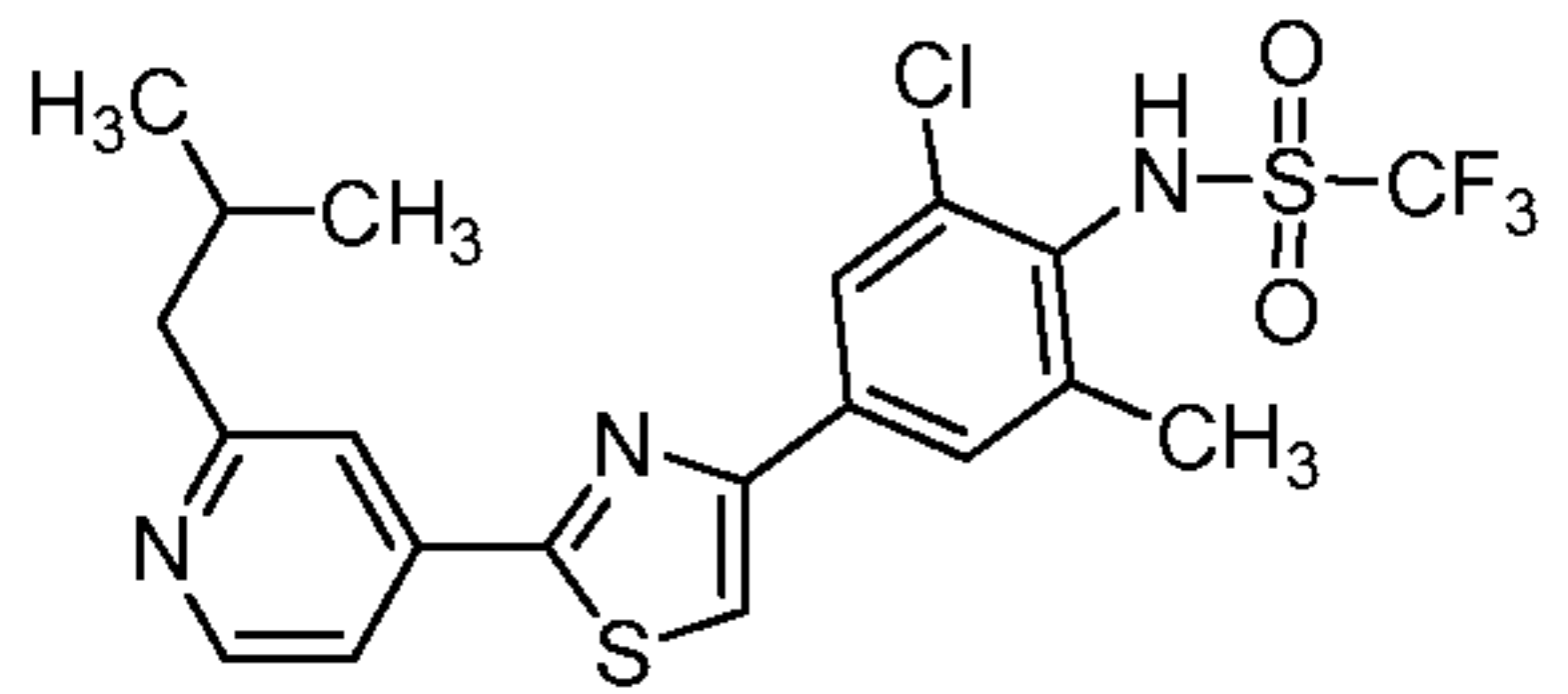
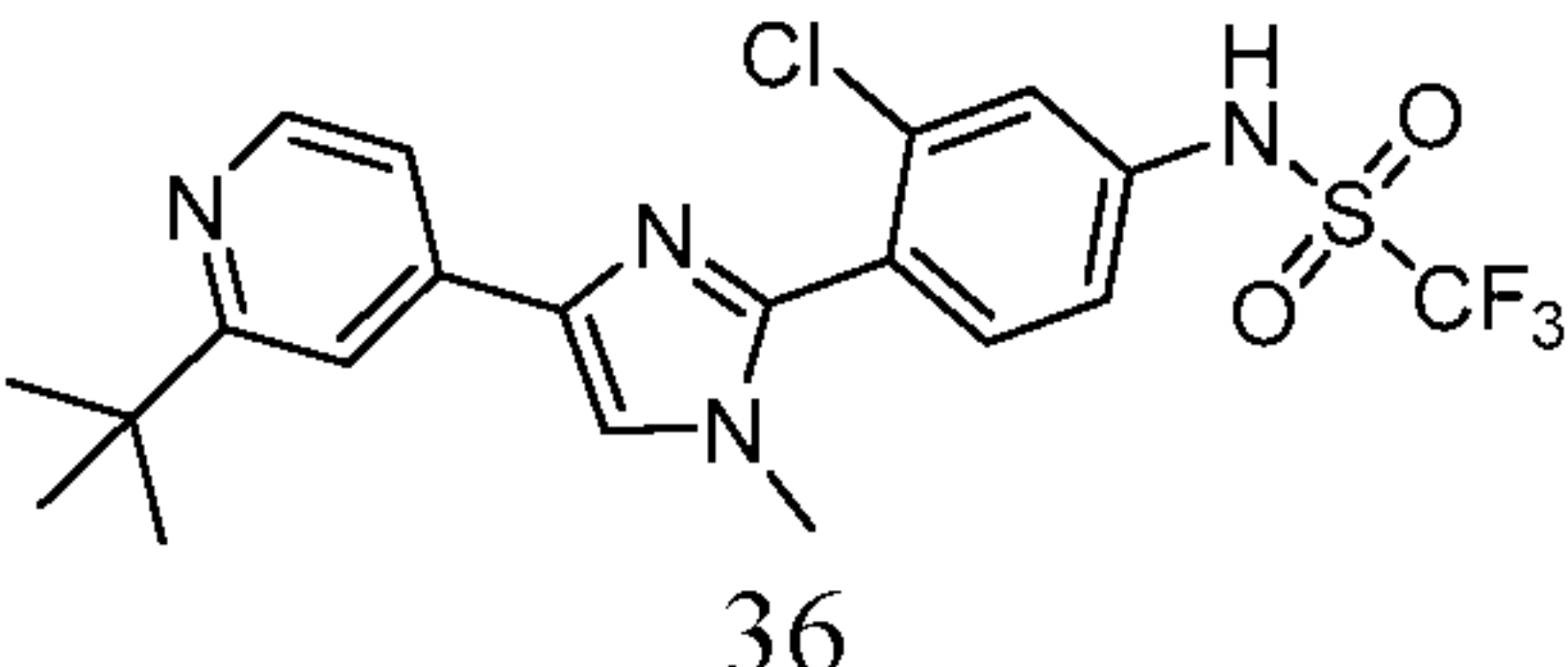
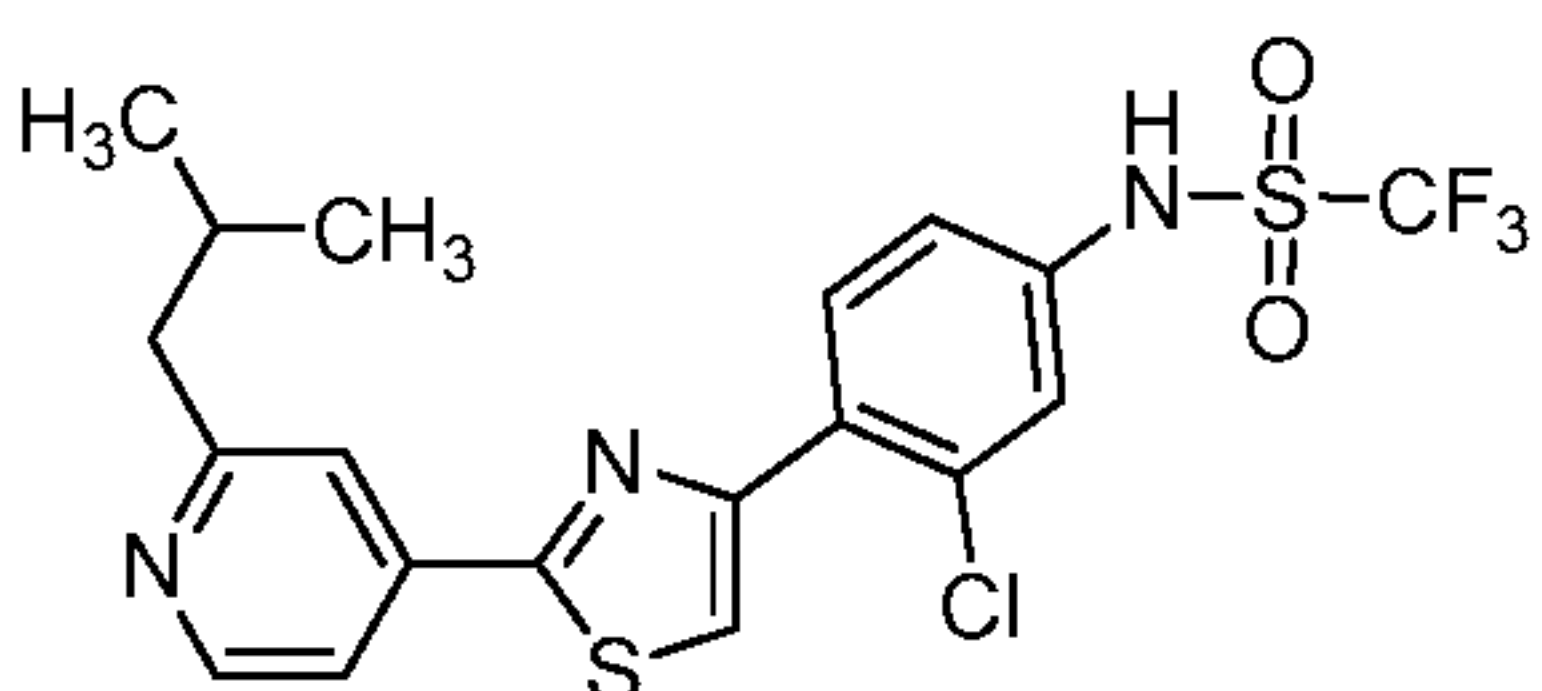
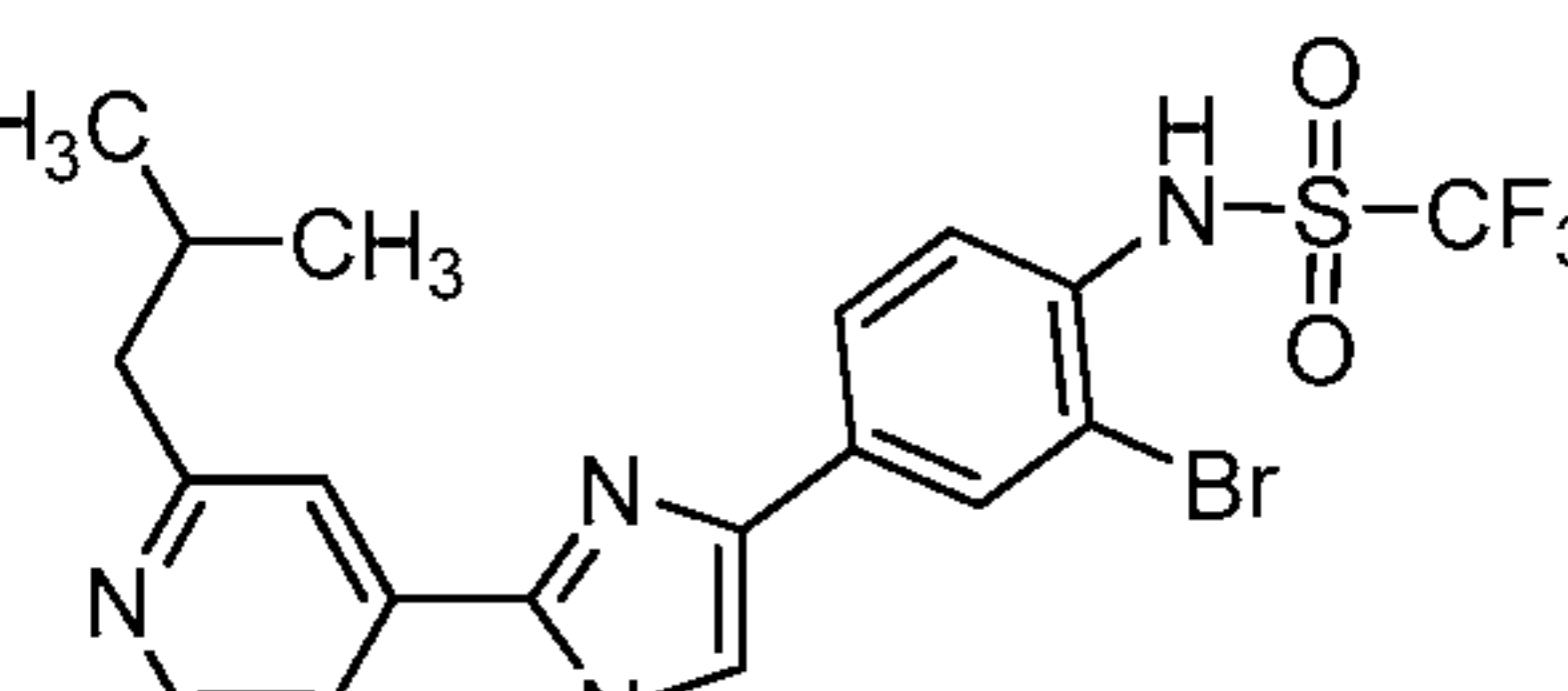
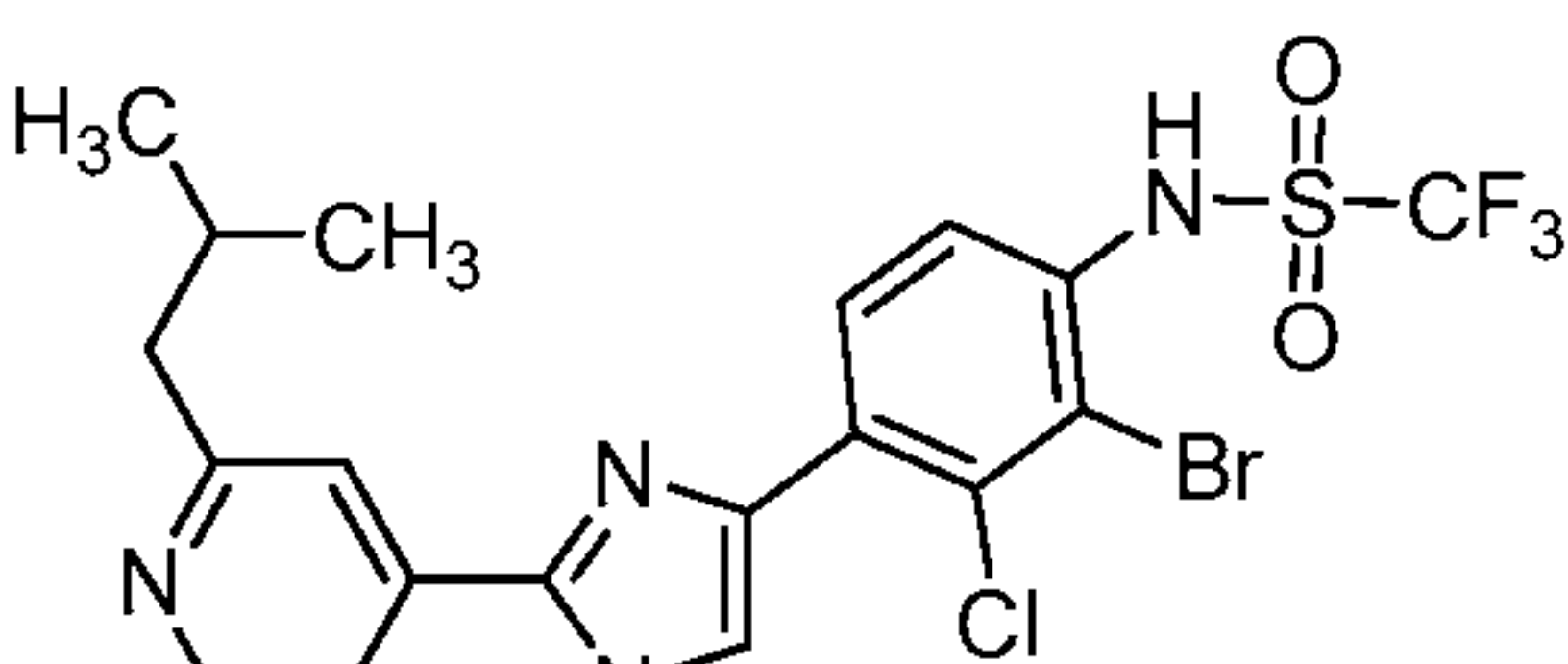
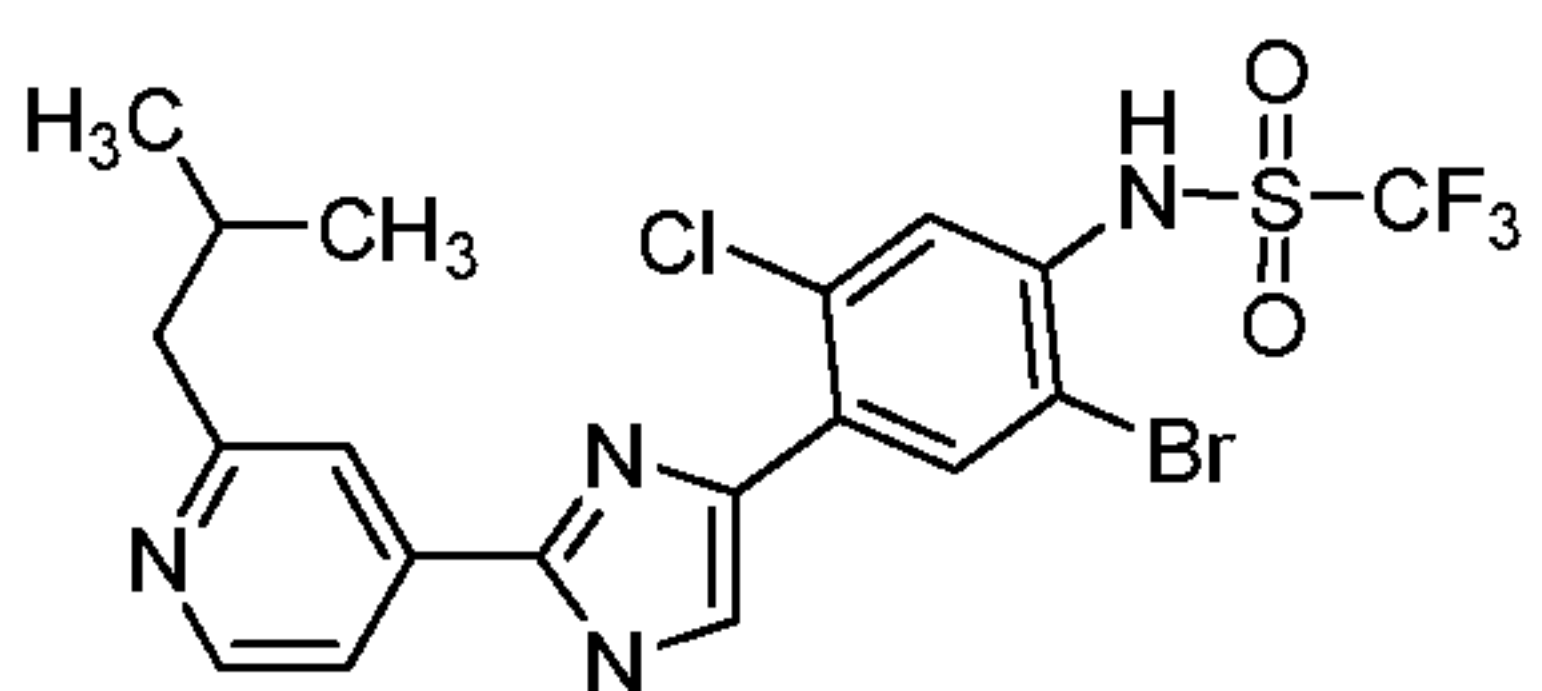
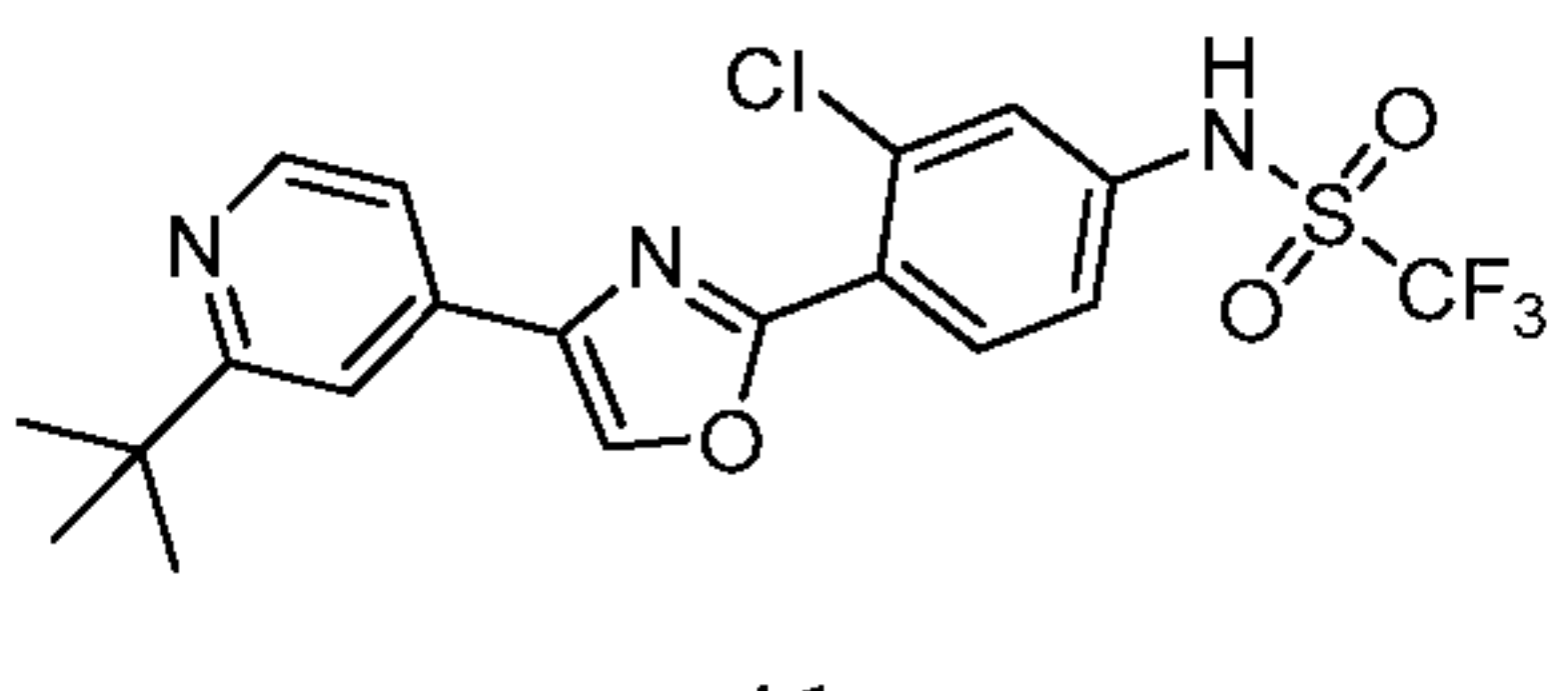
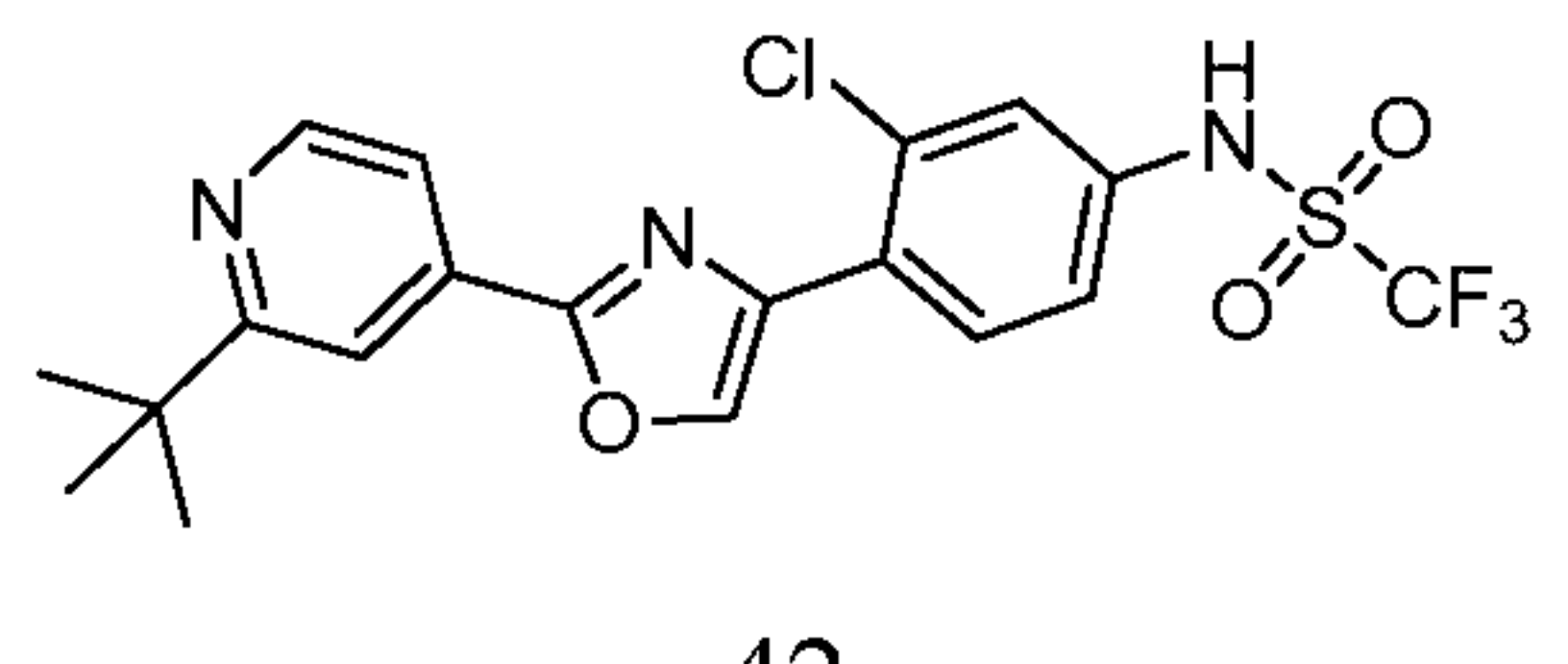
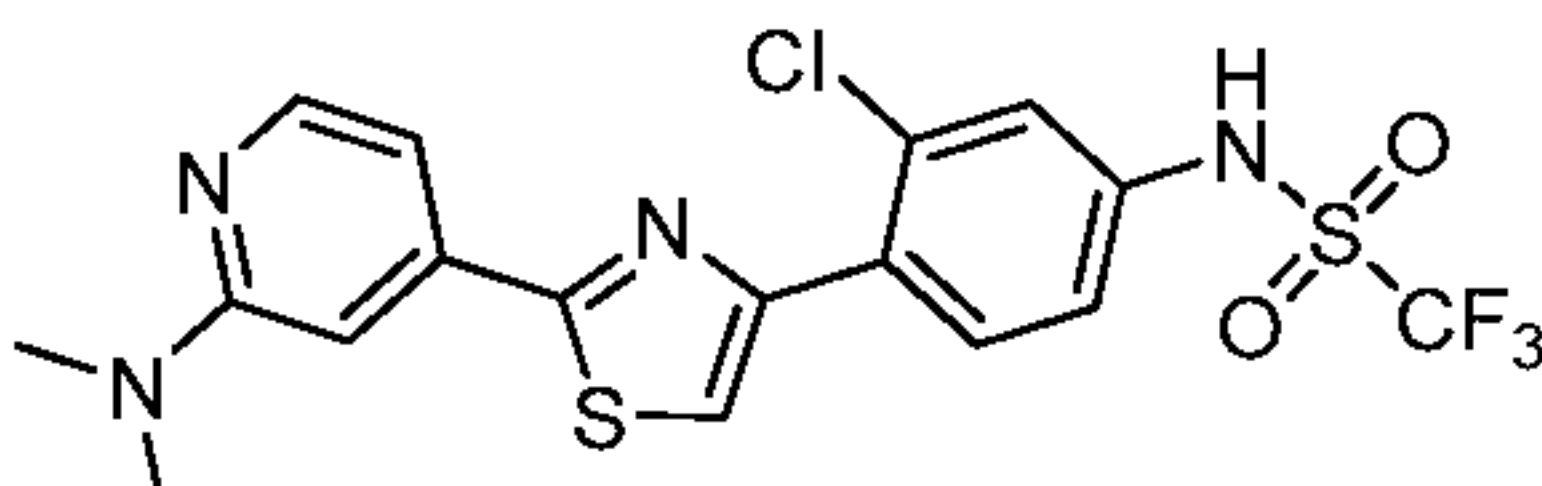
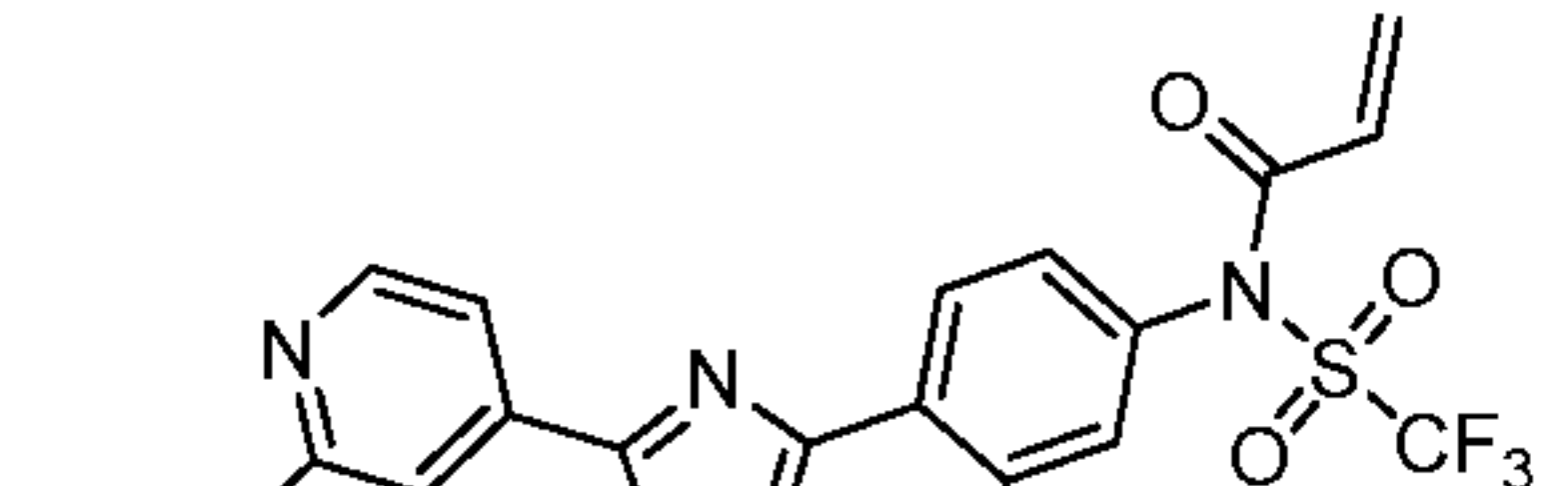
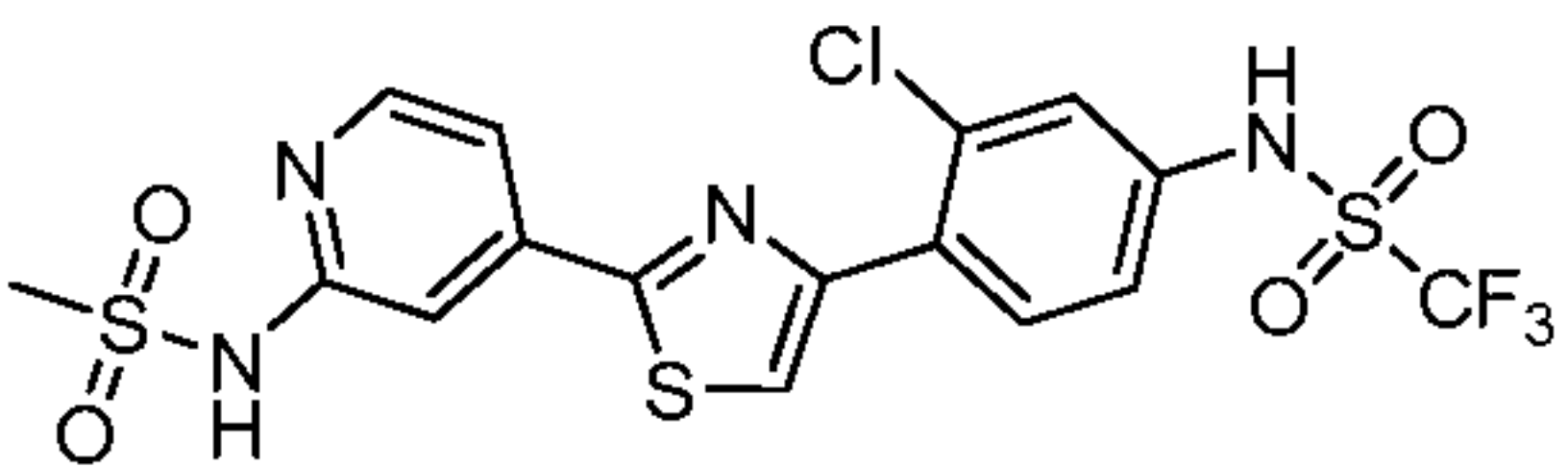
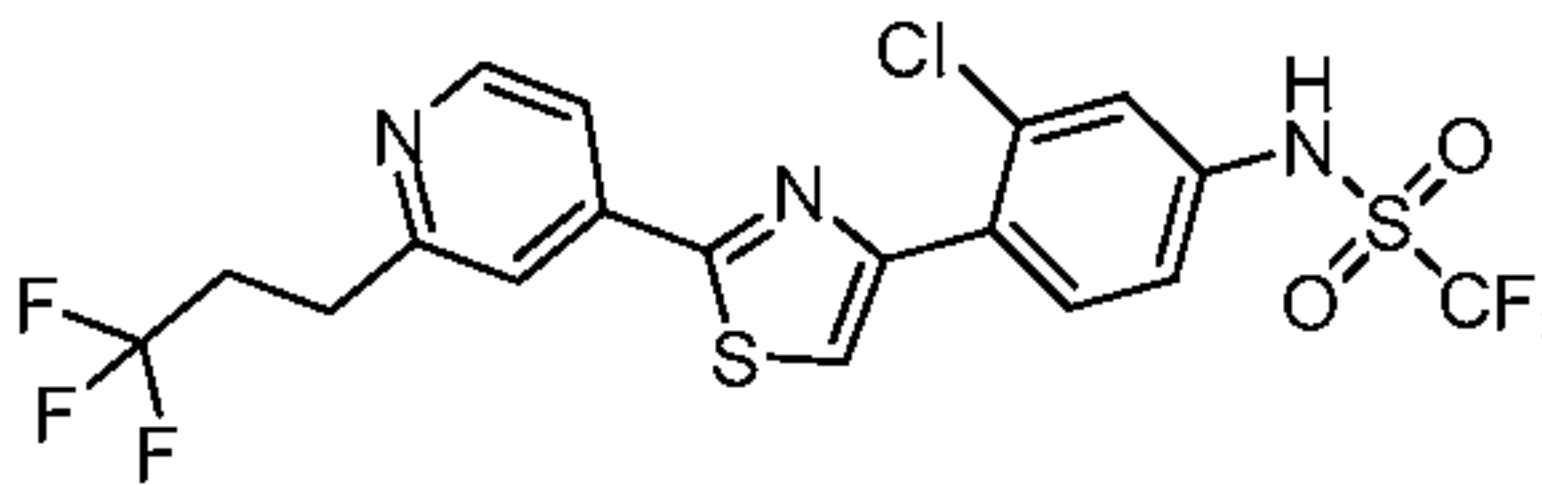
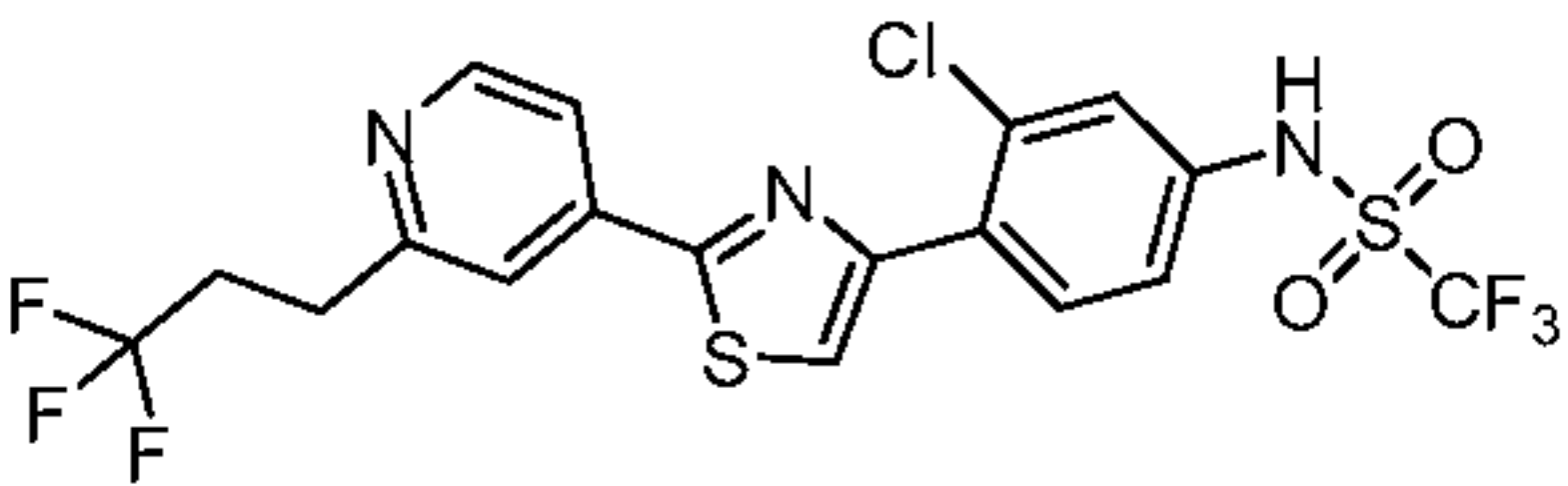
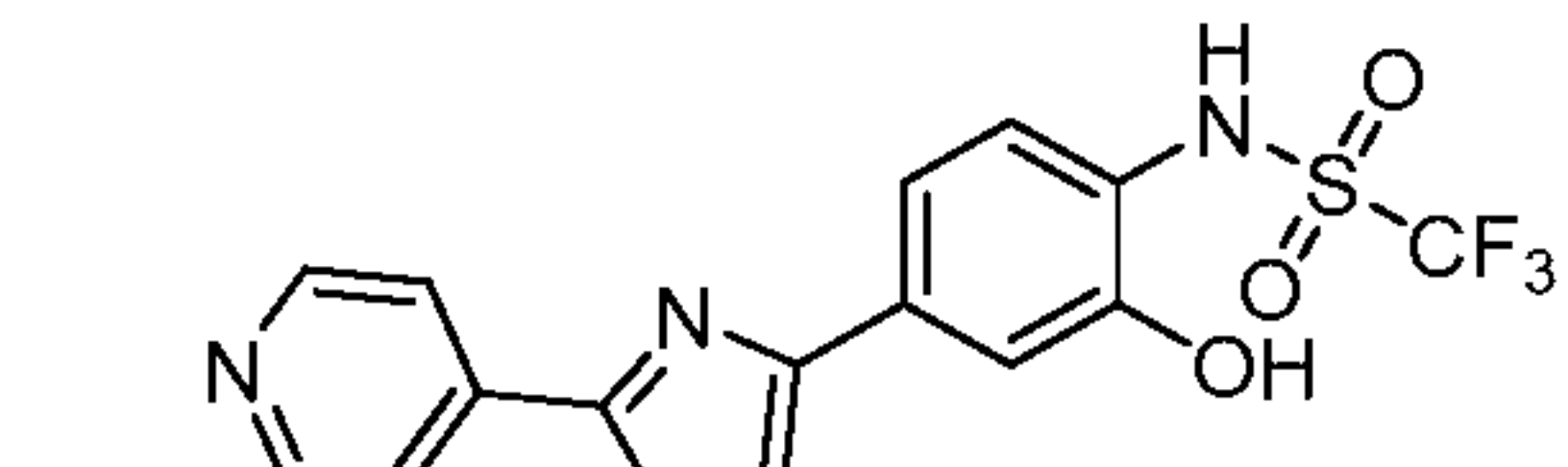
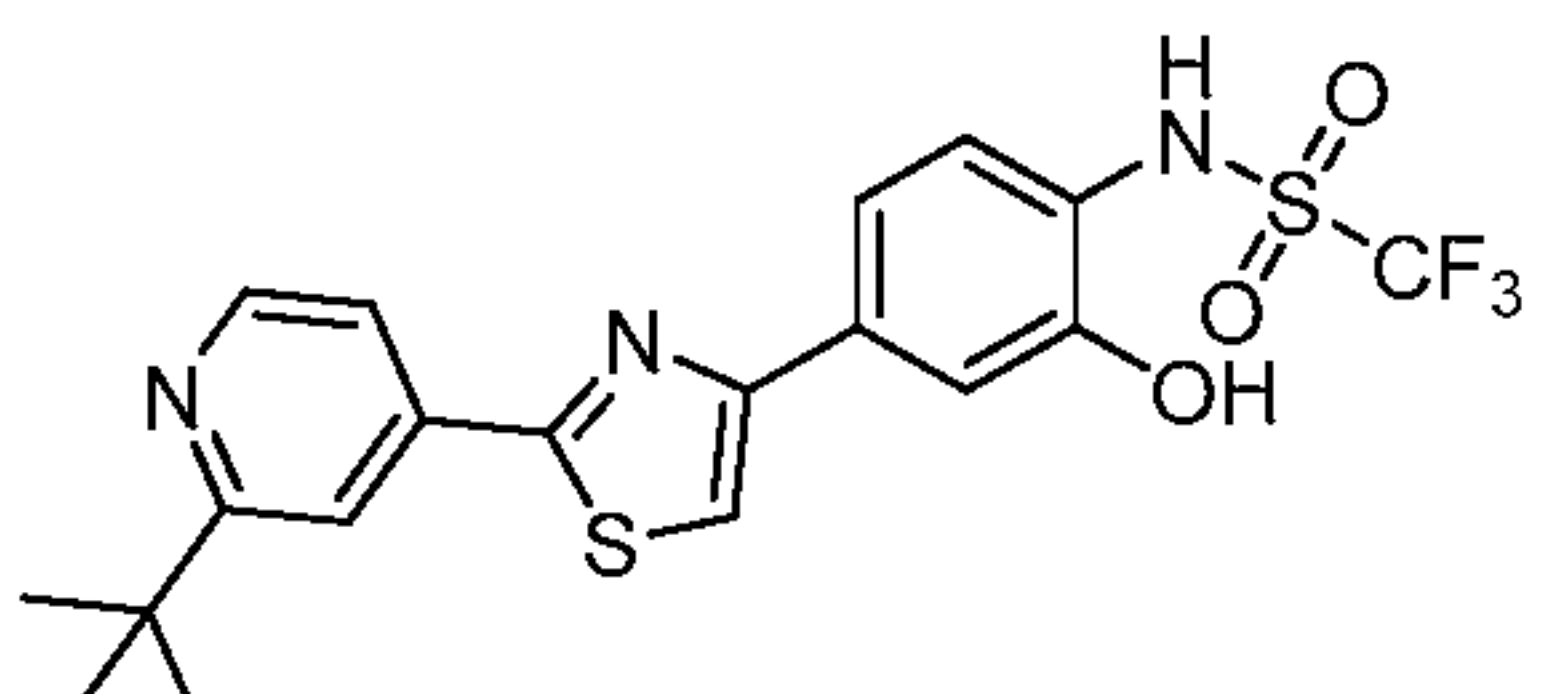
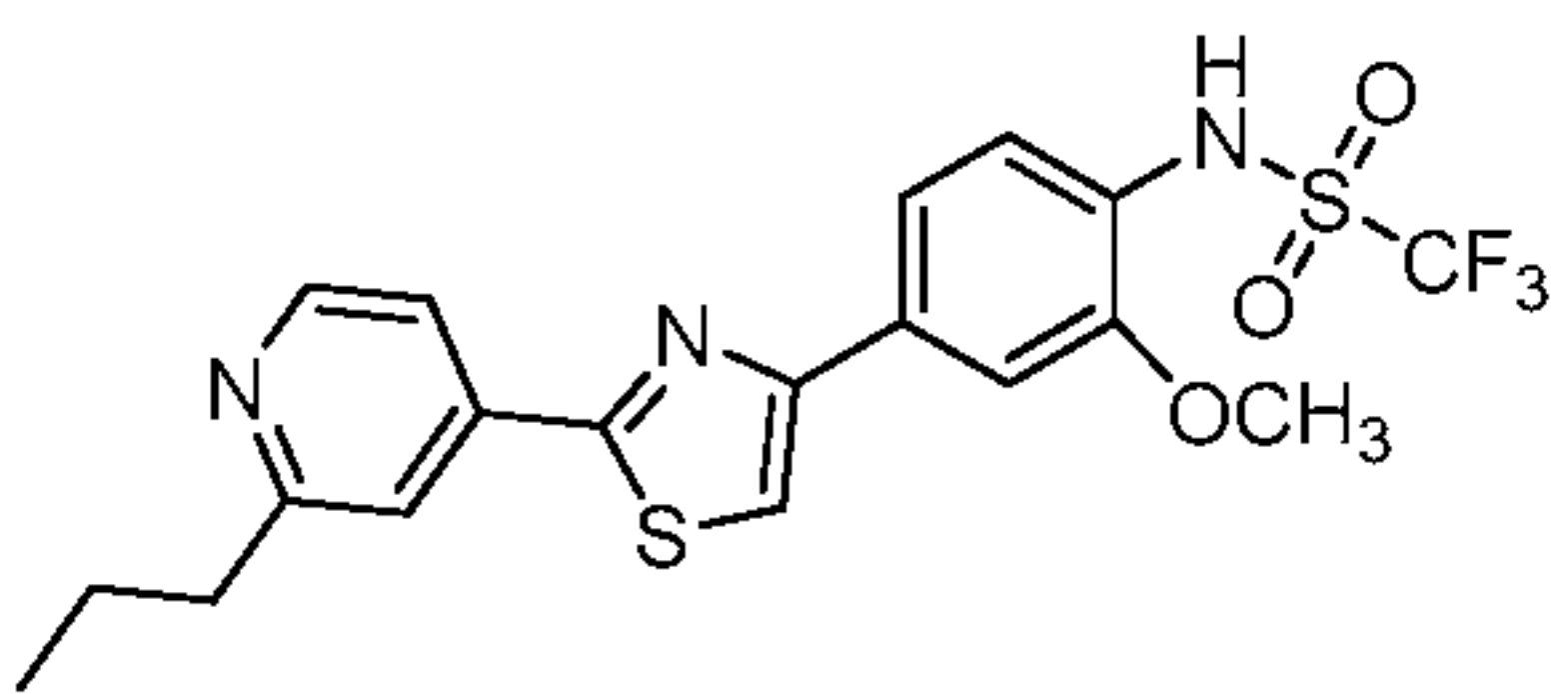
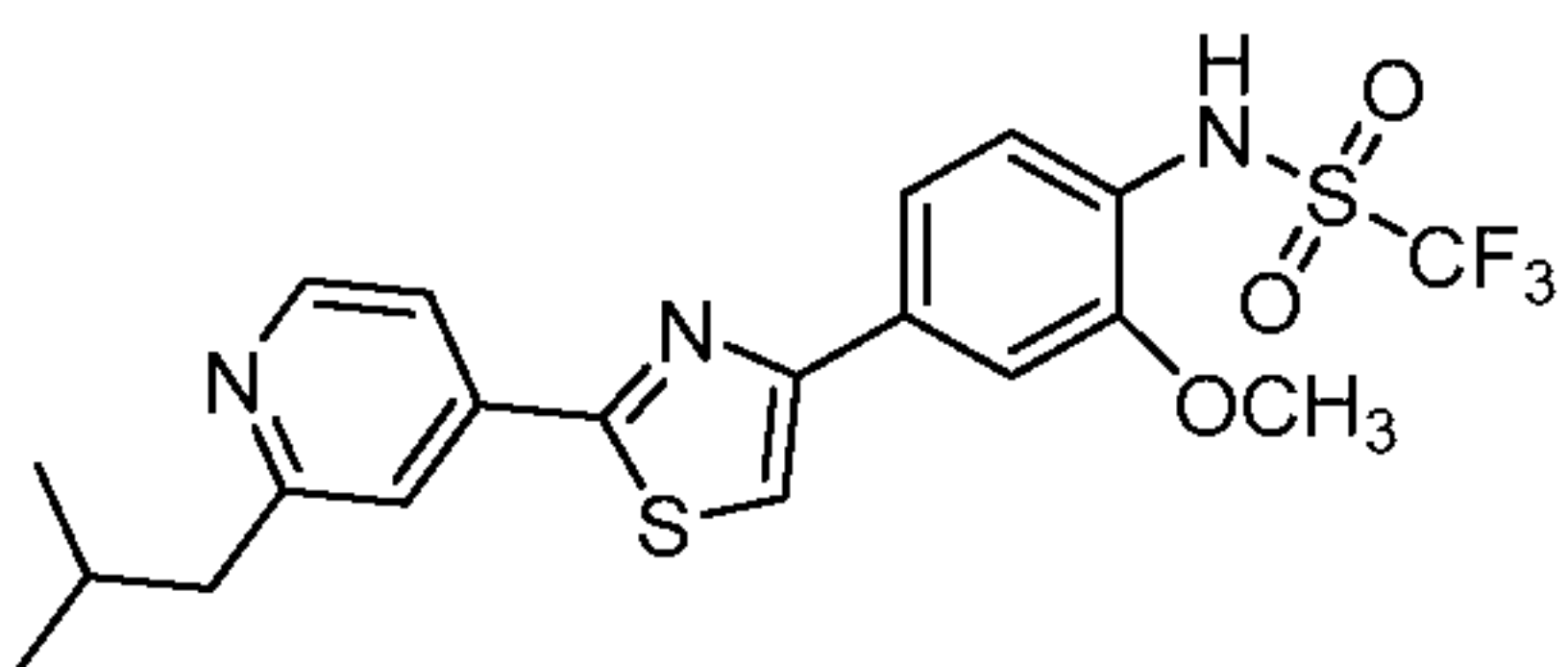
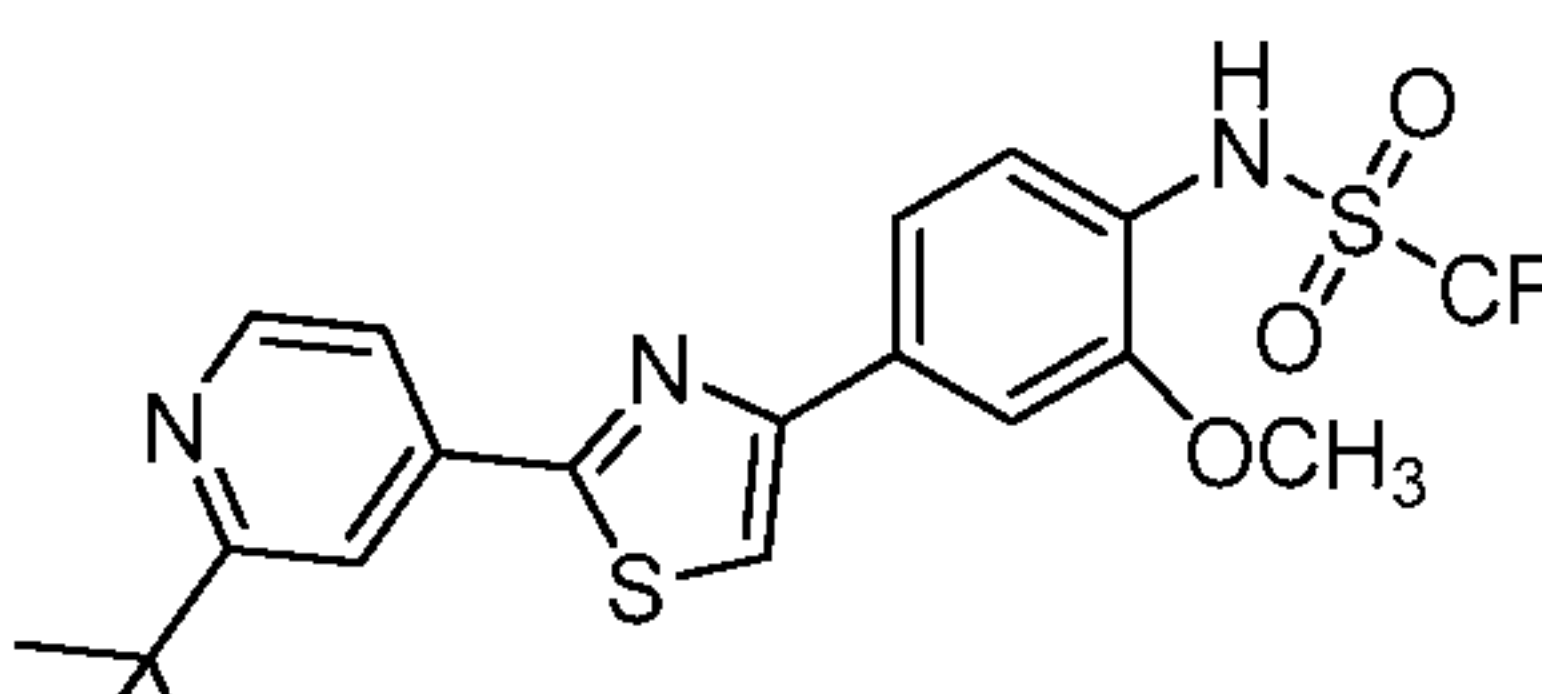
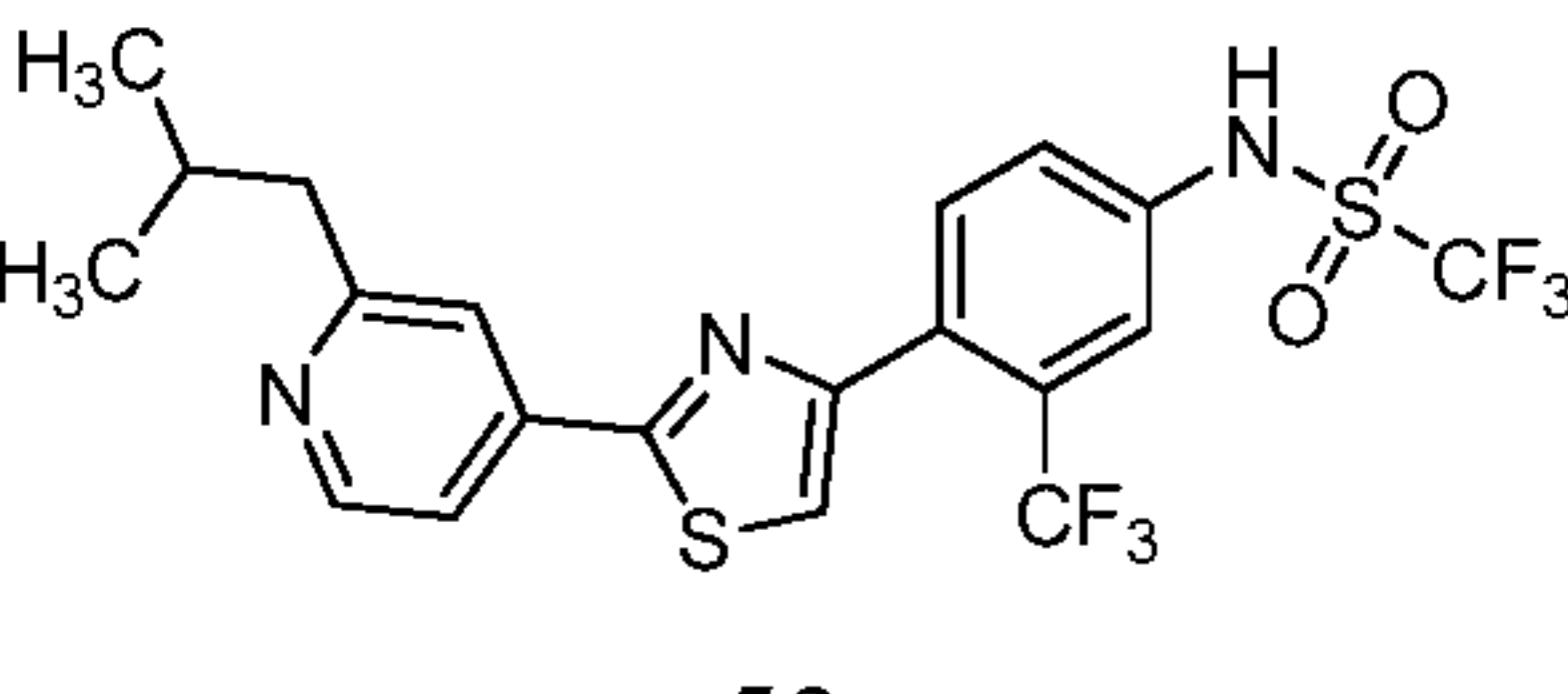
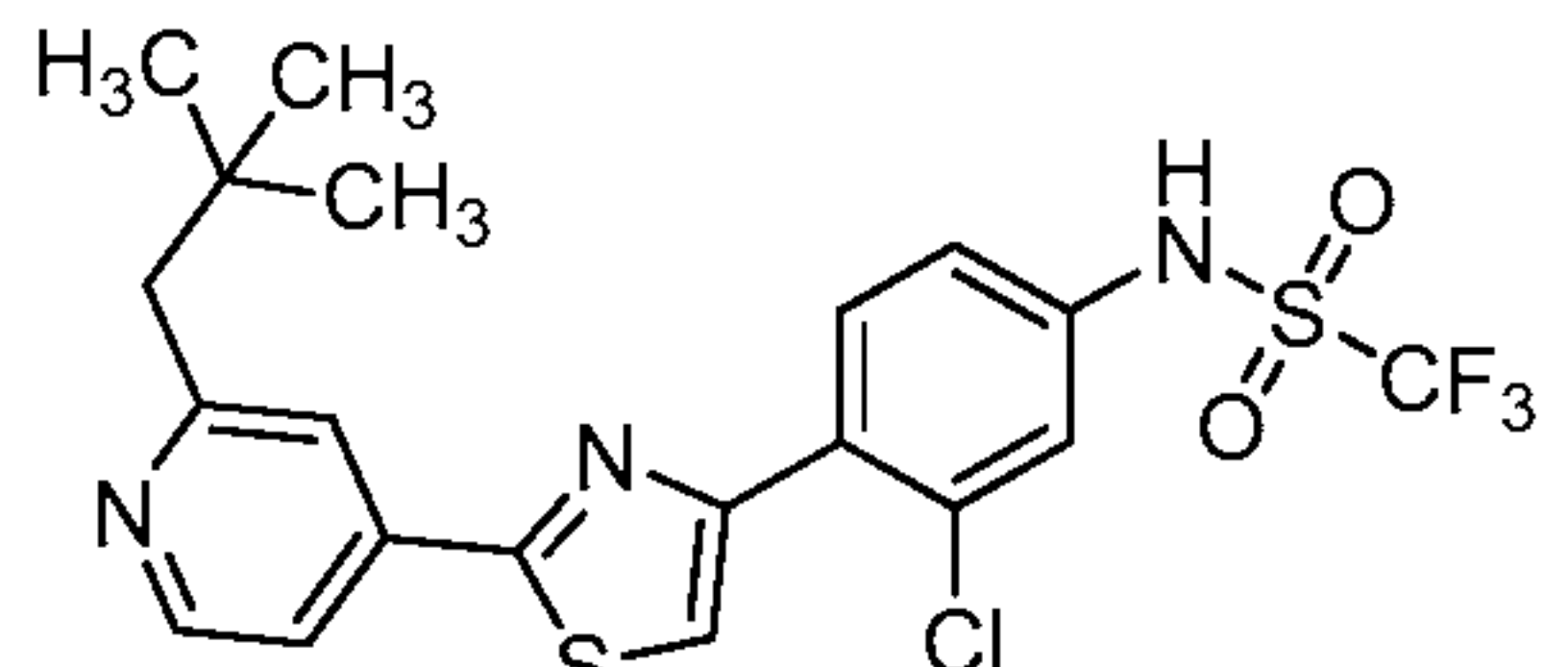
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Table 1

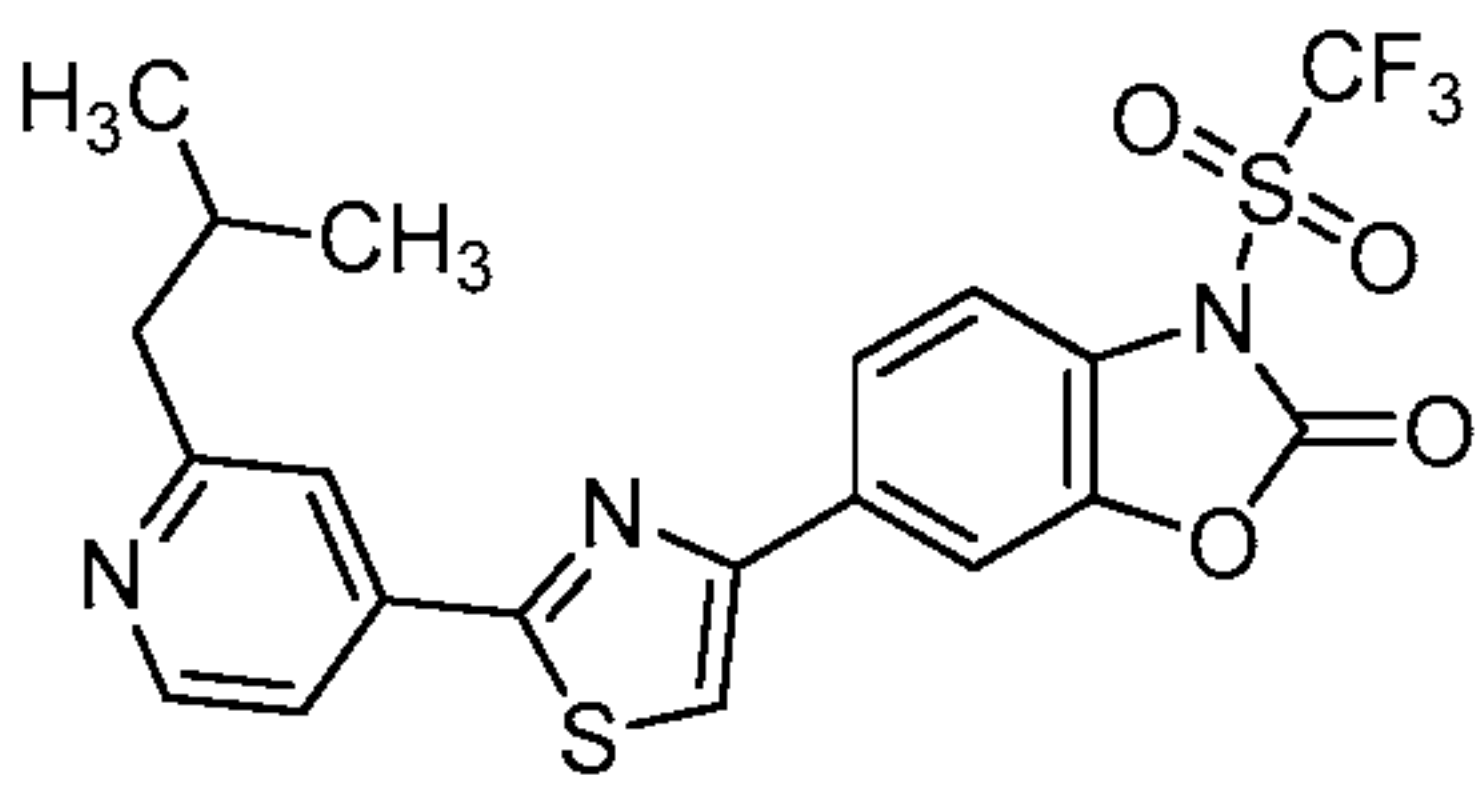
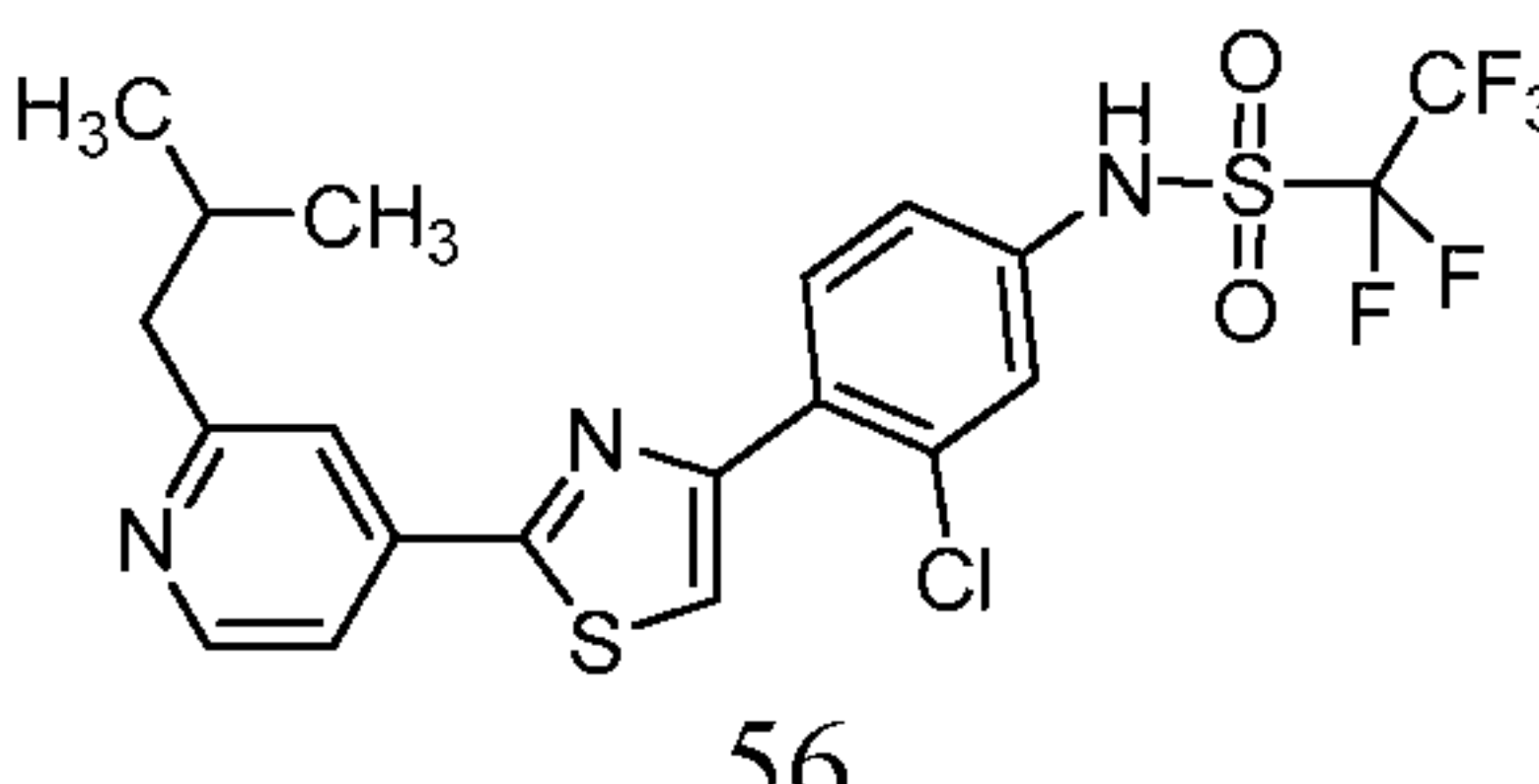
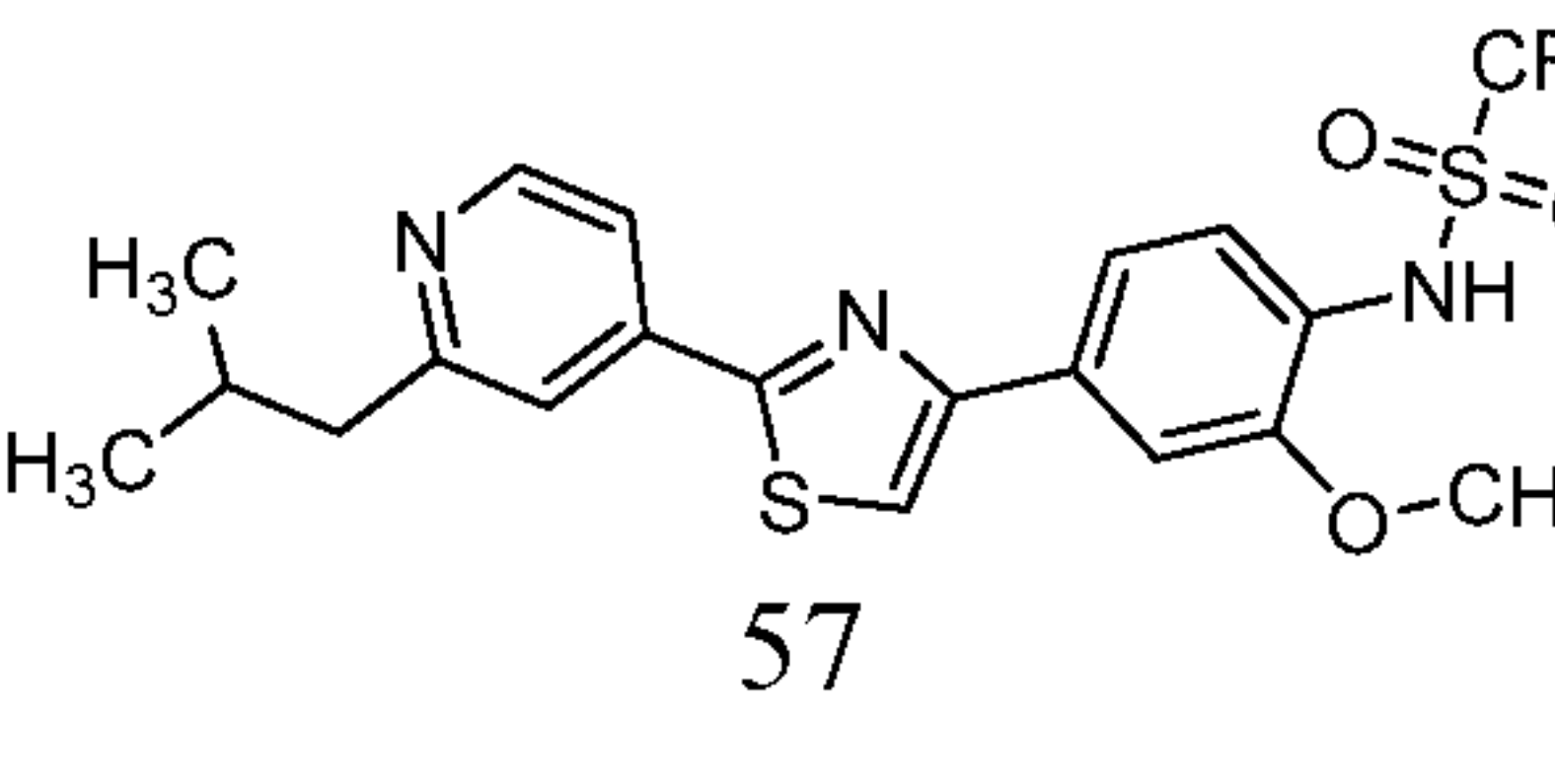
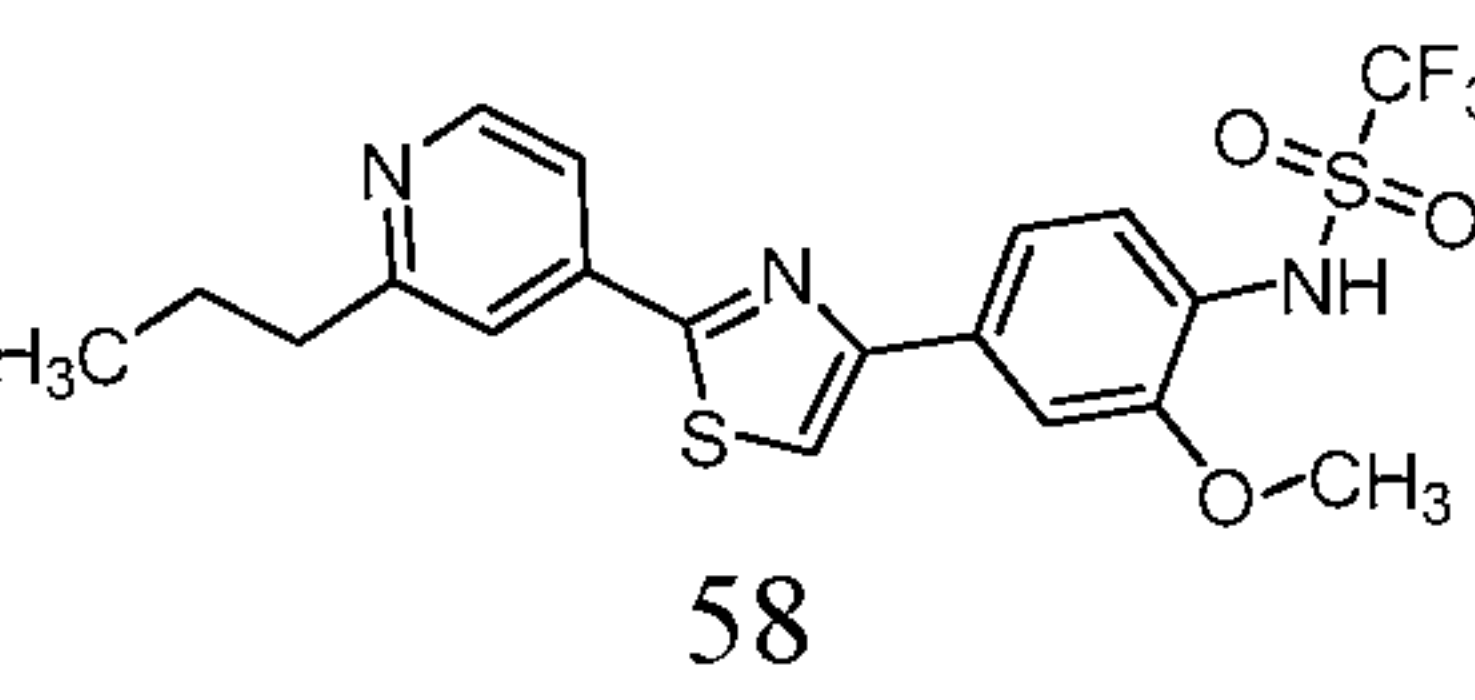
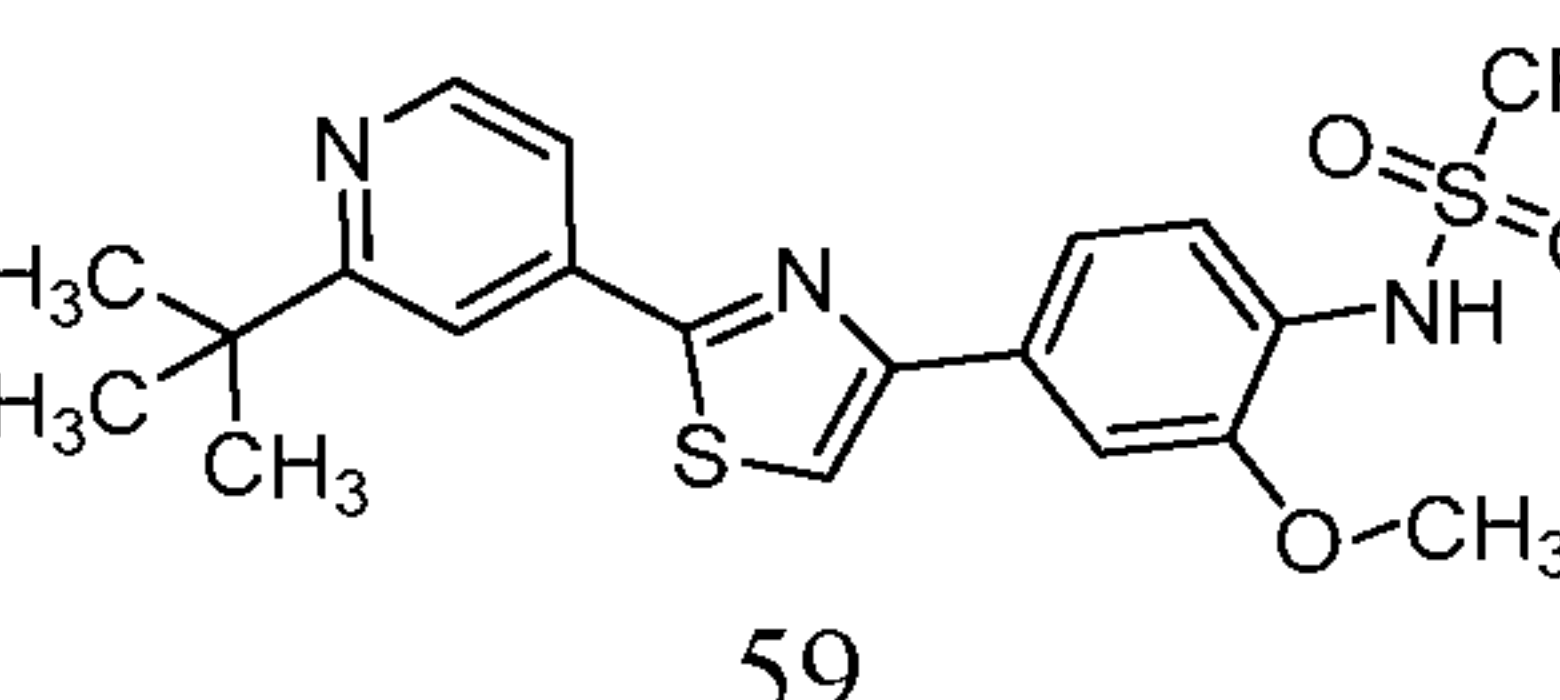
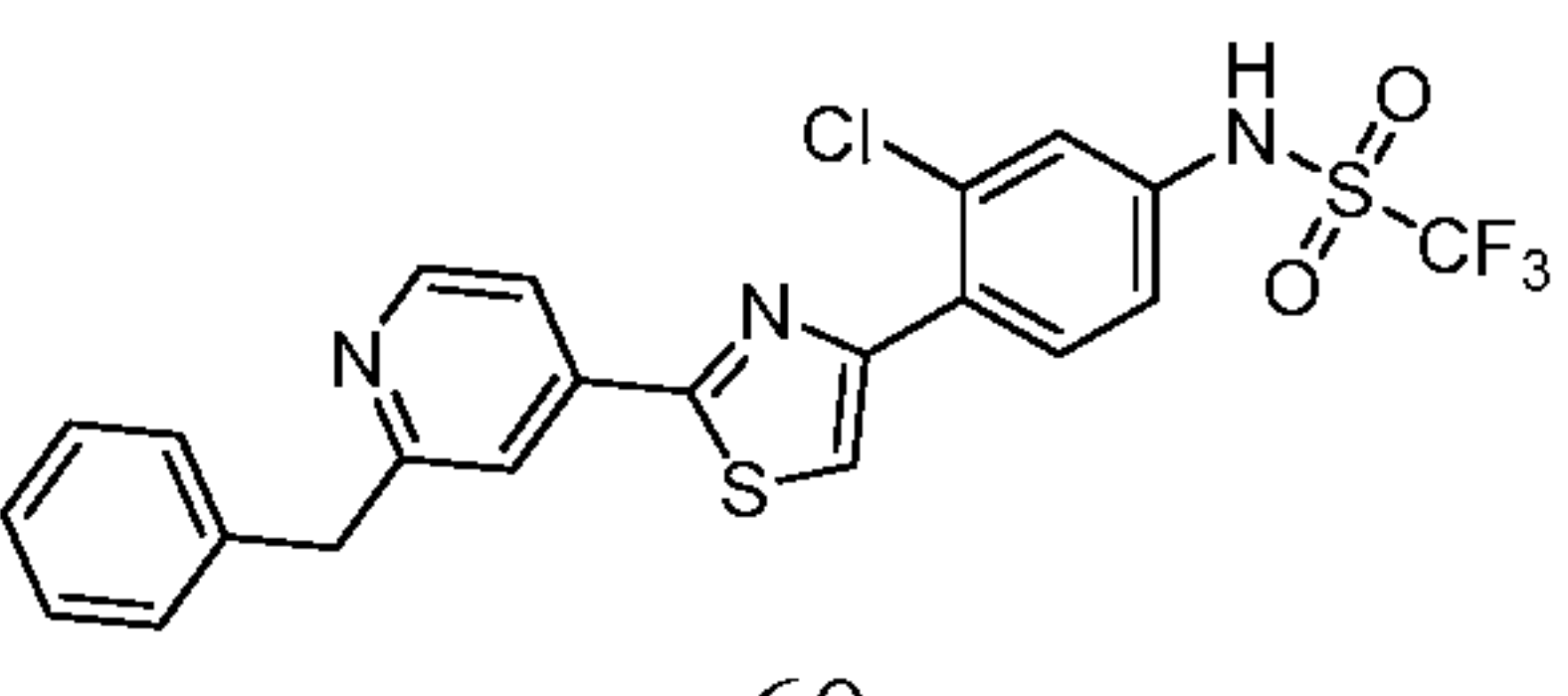
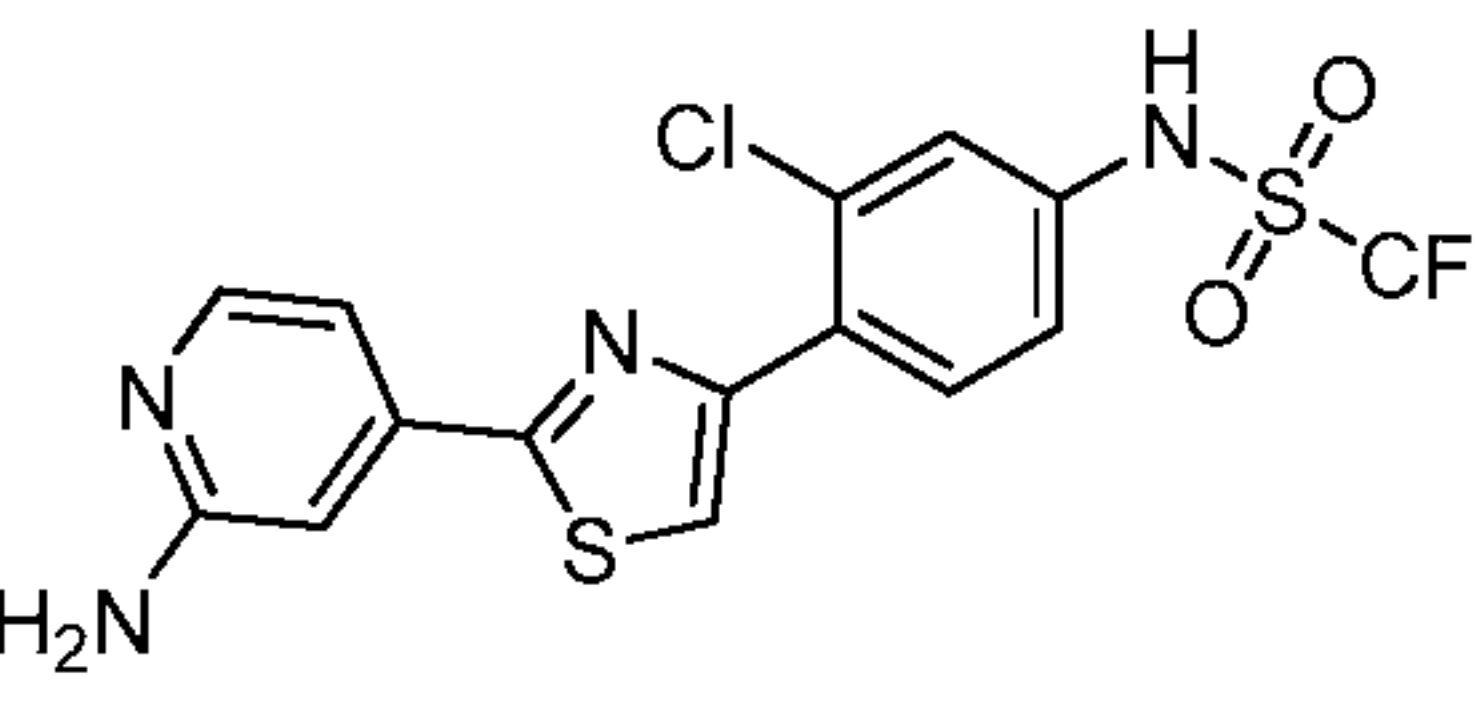
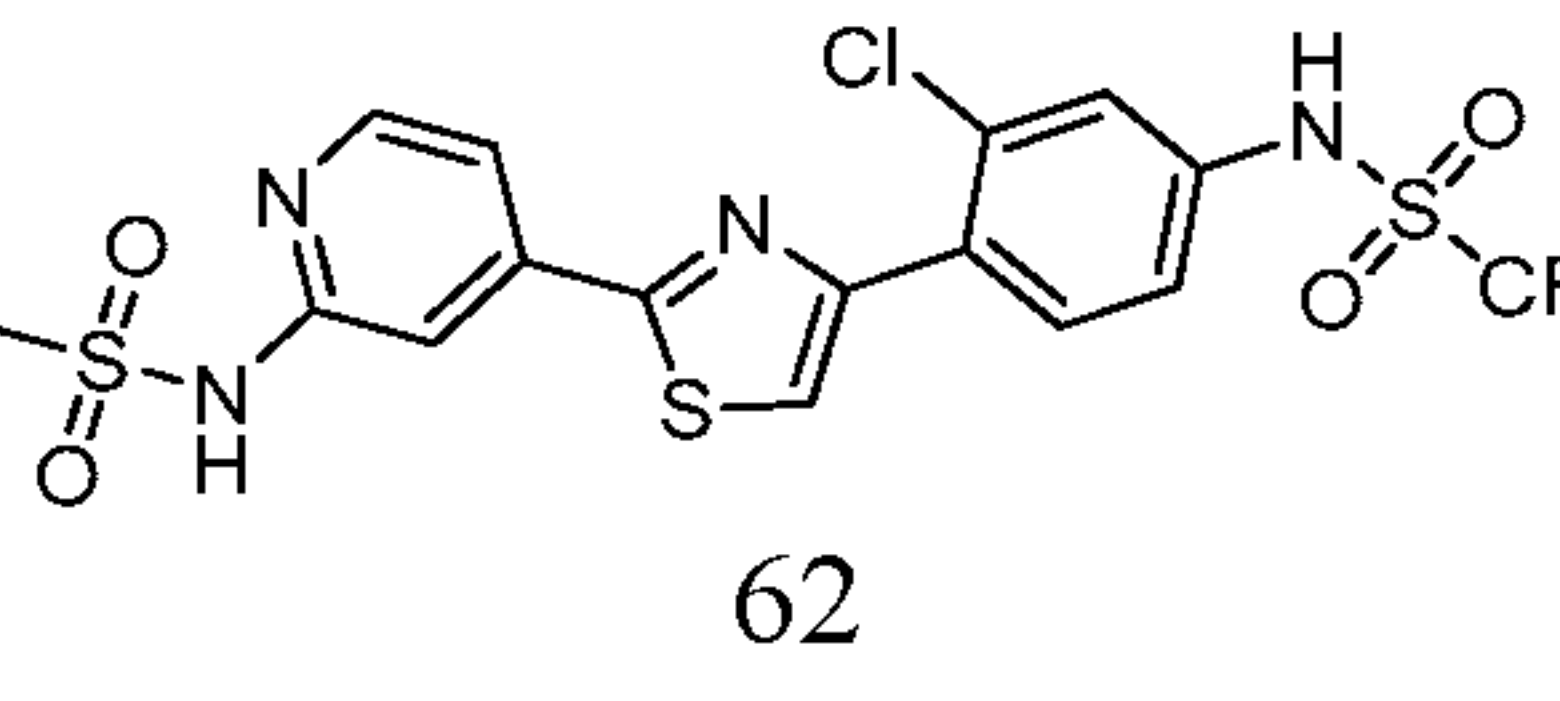
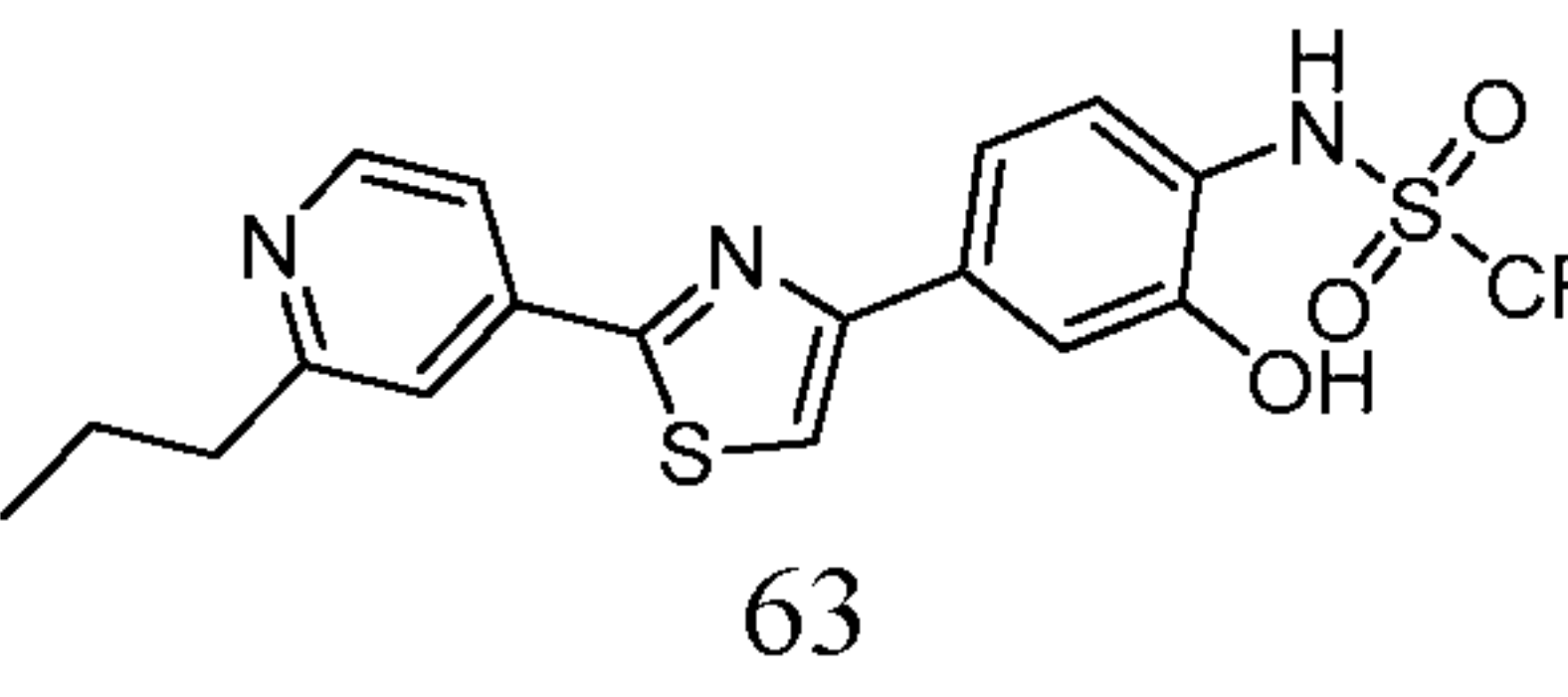
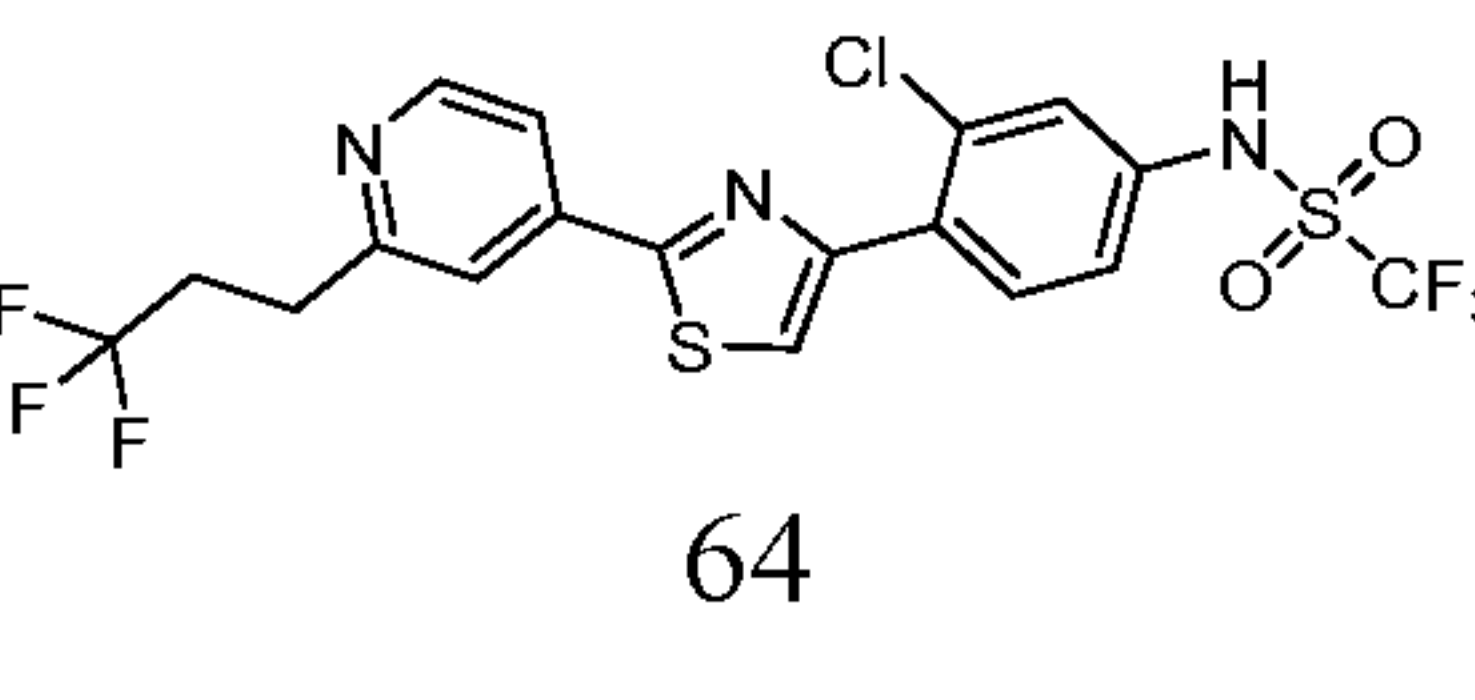
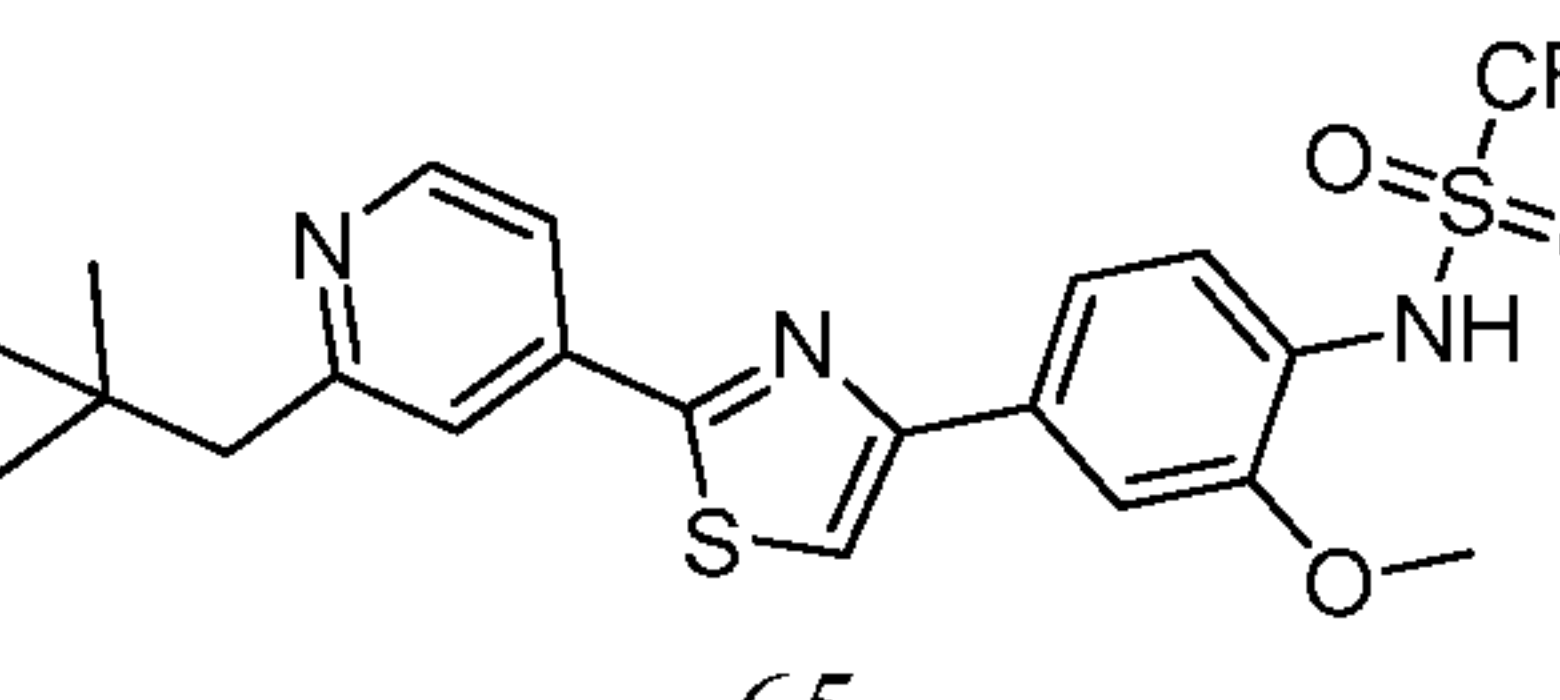
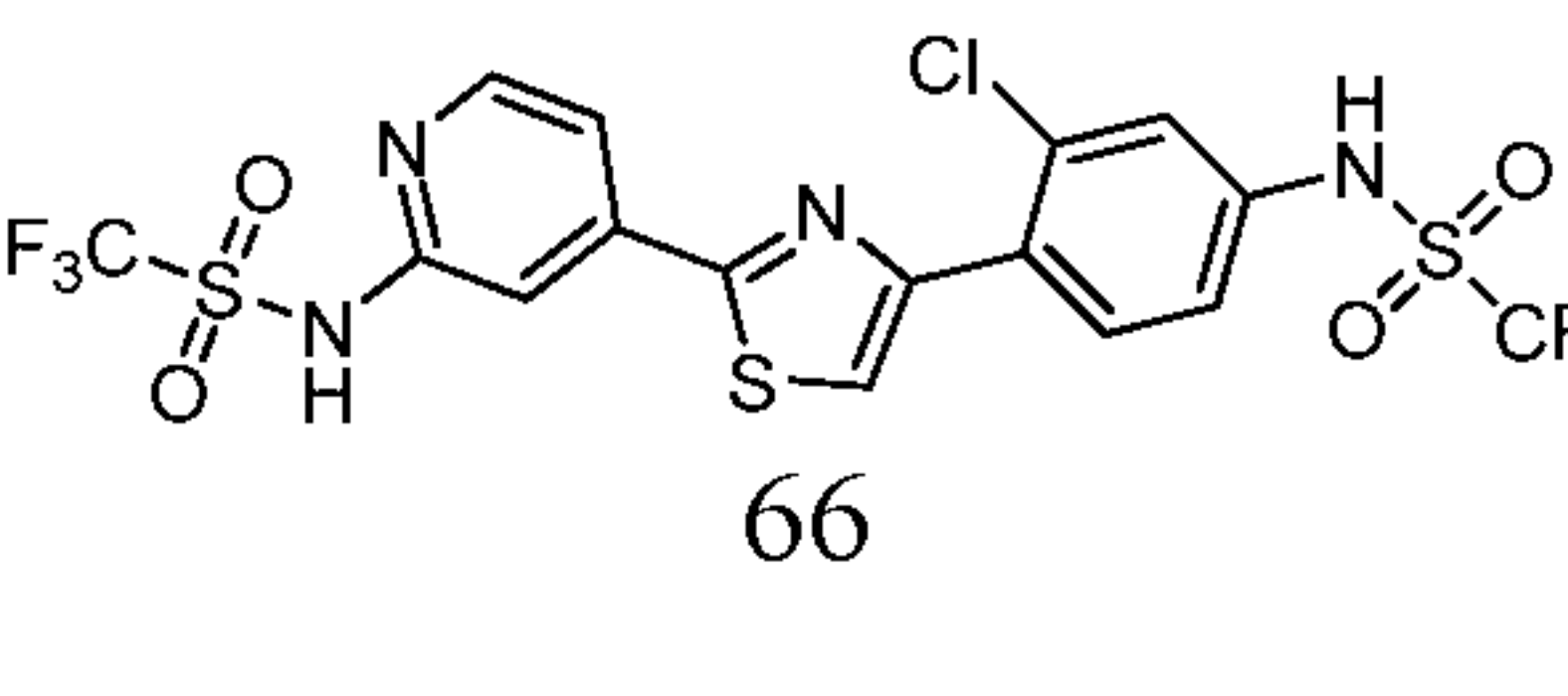
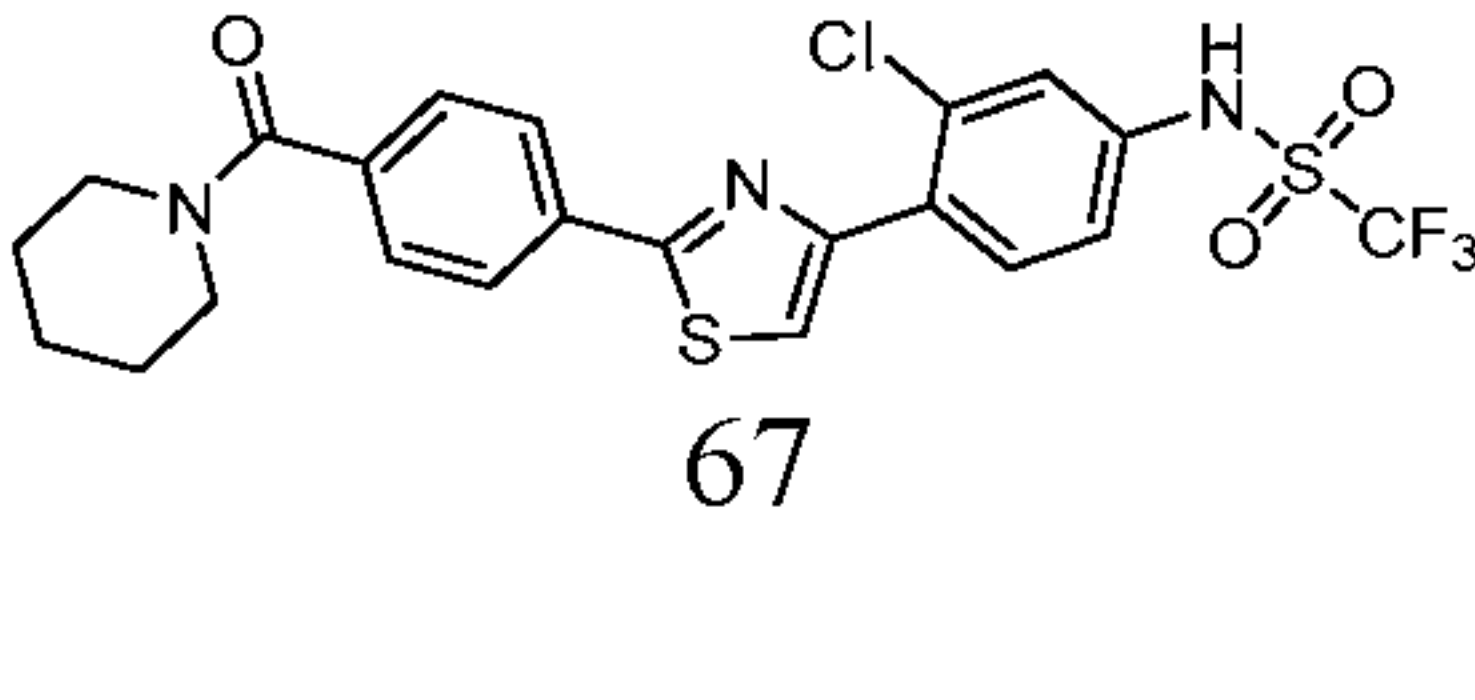
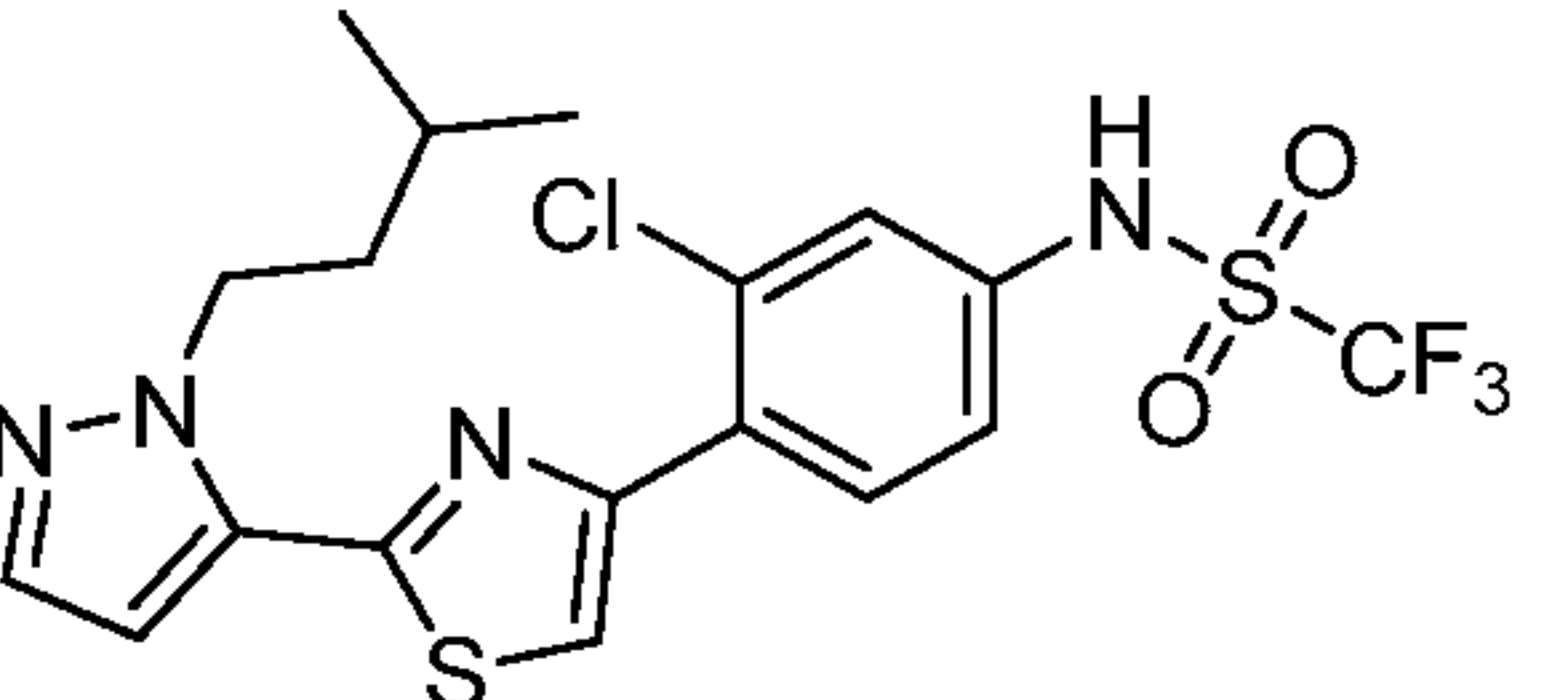
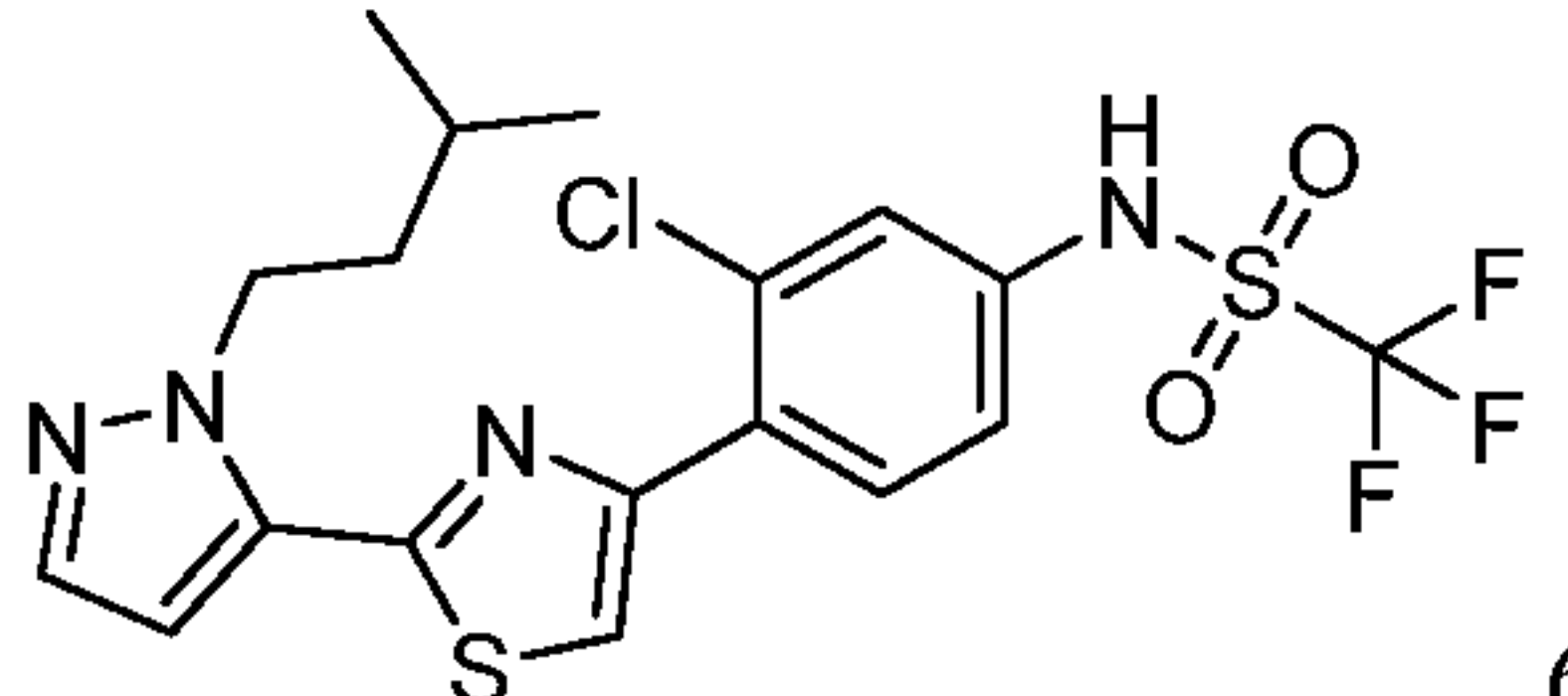
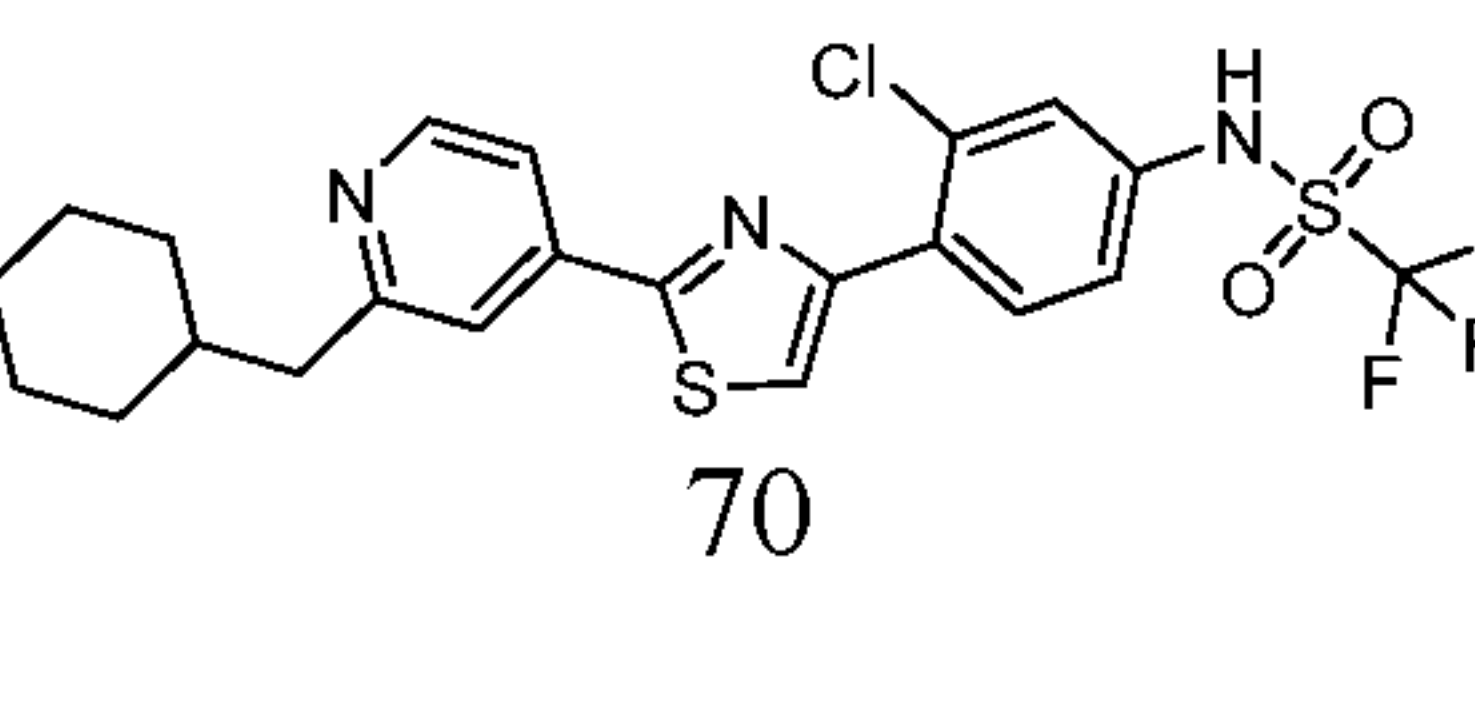
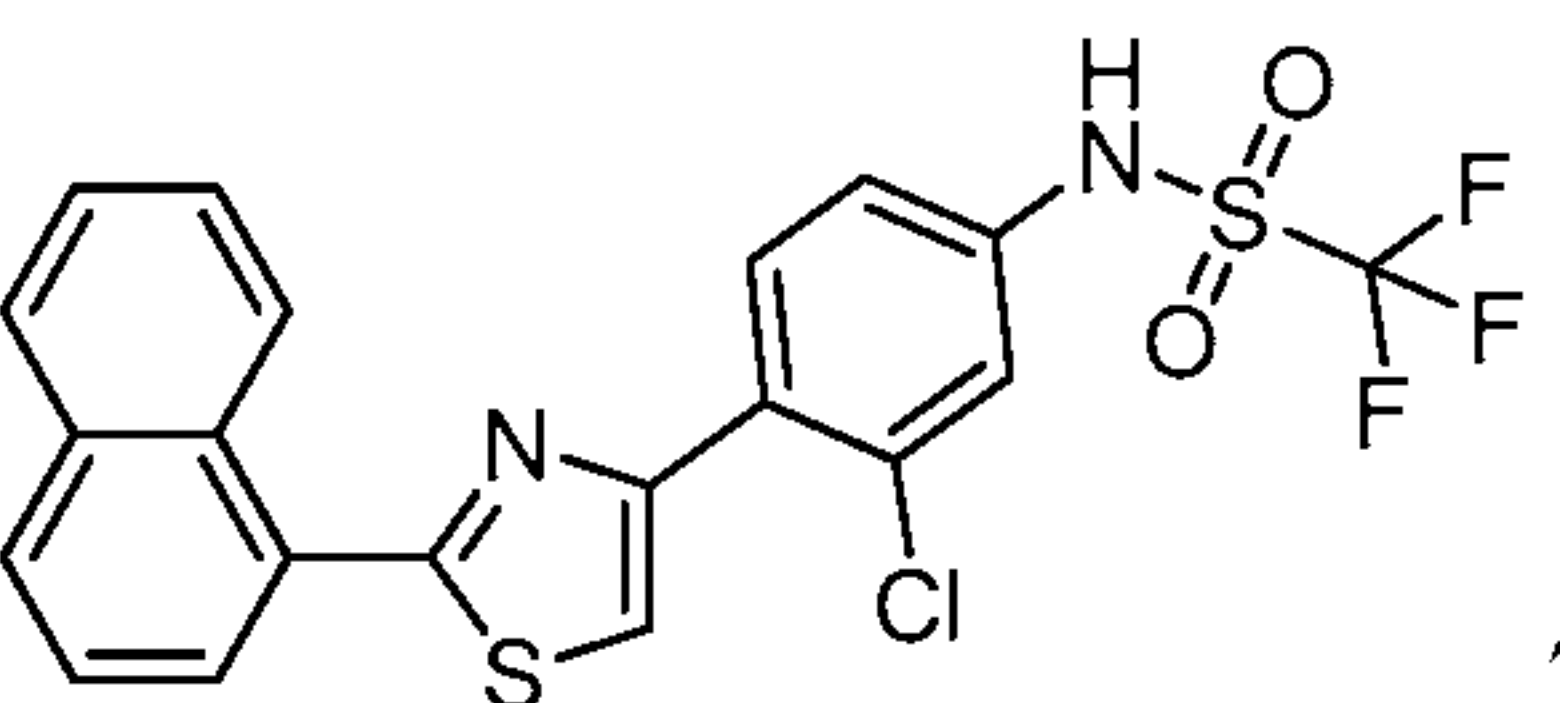
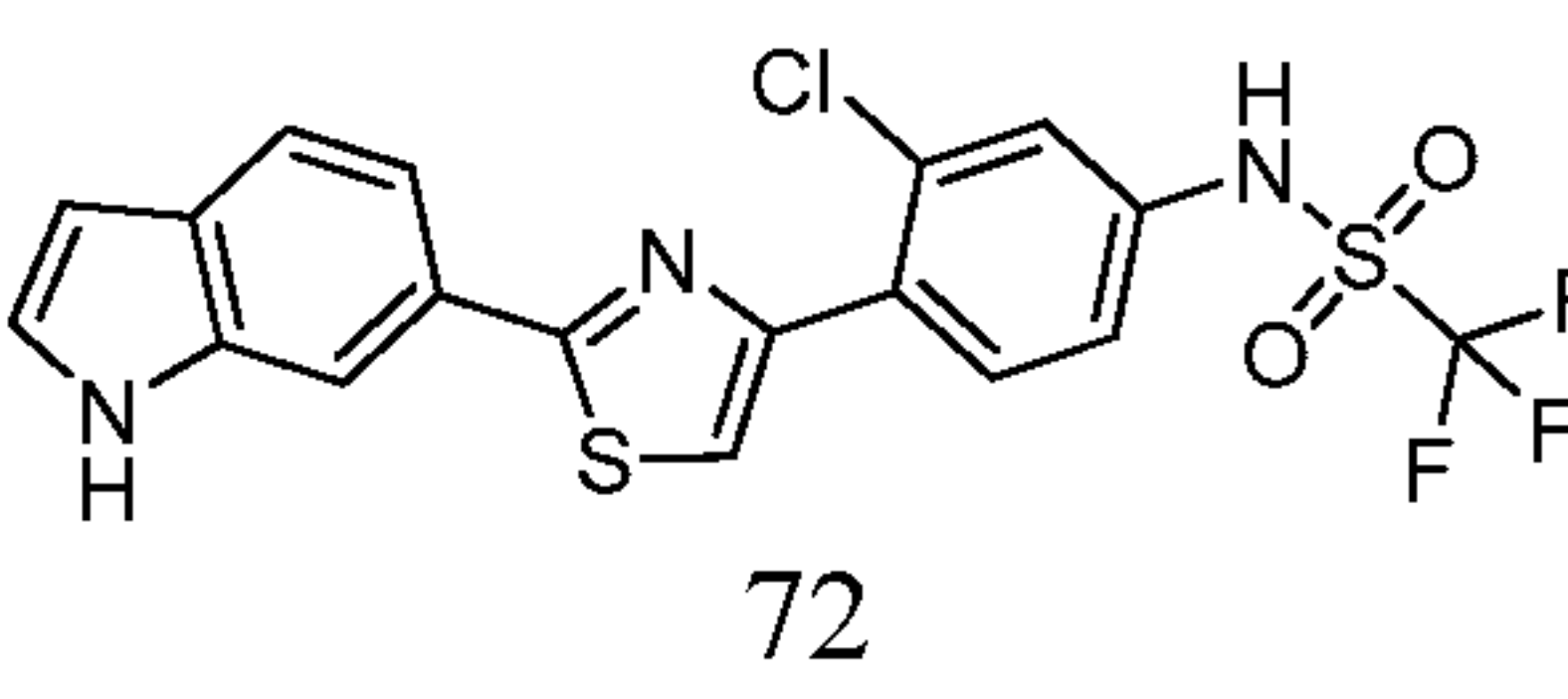
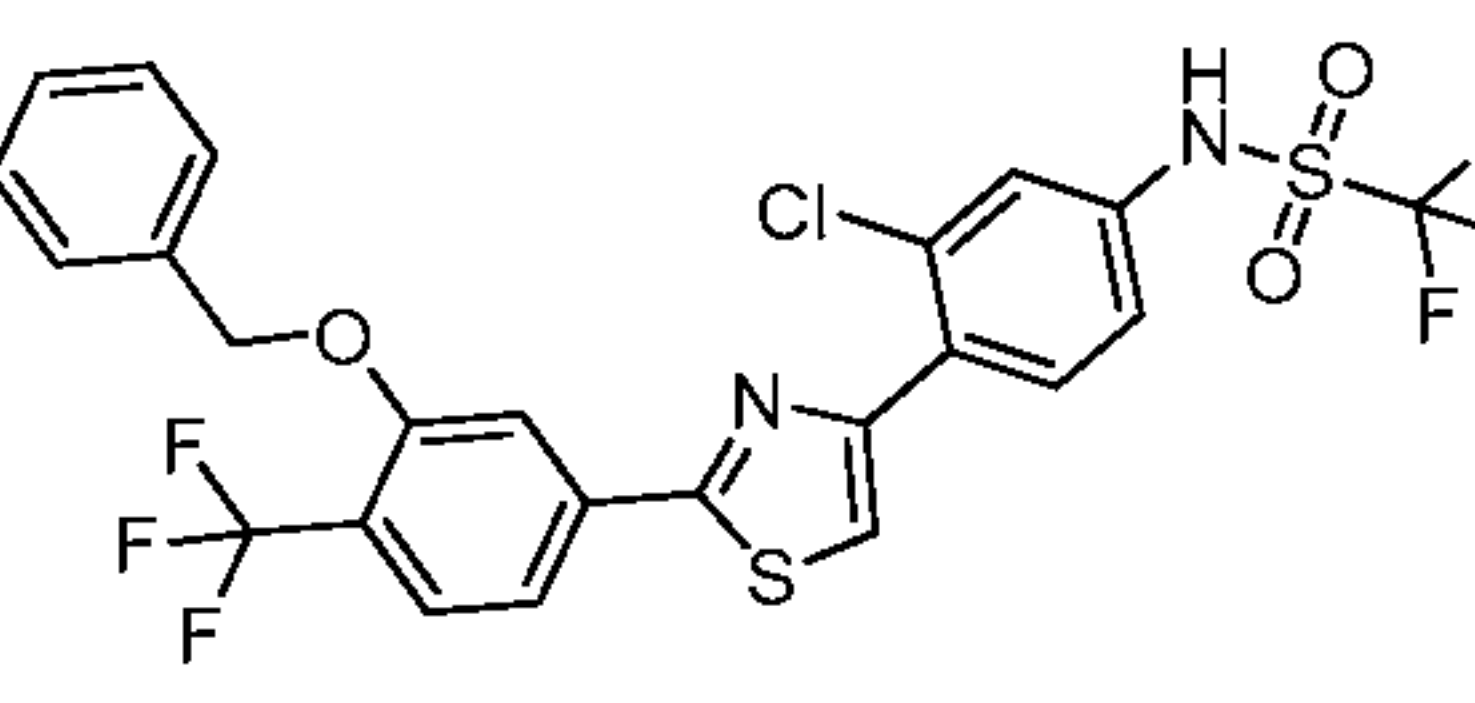
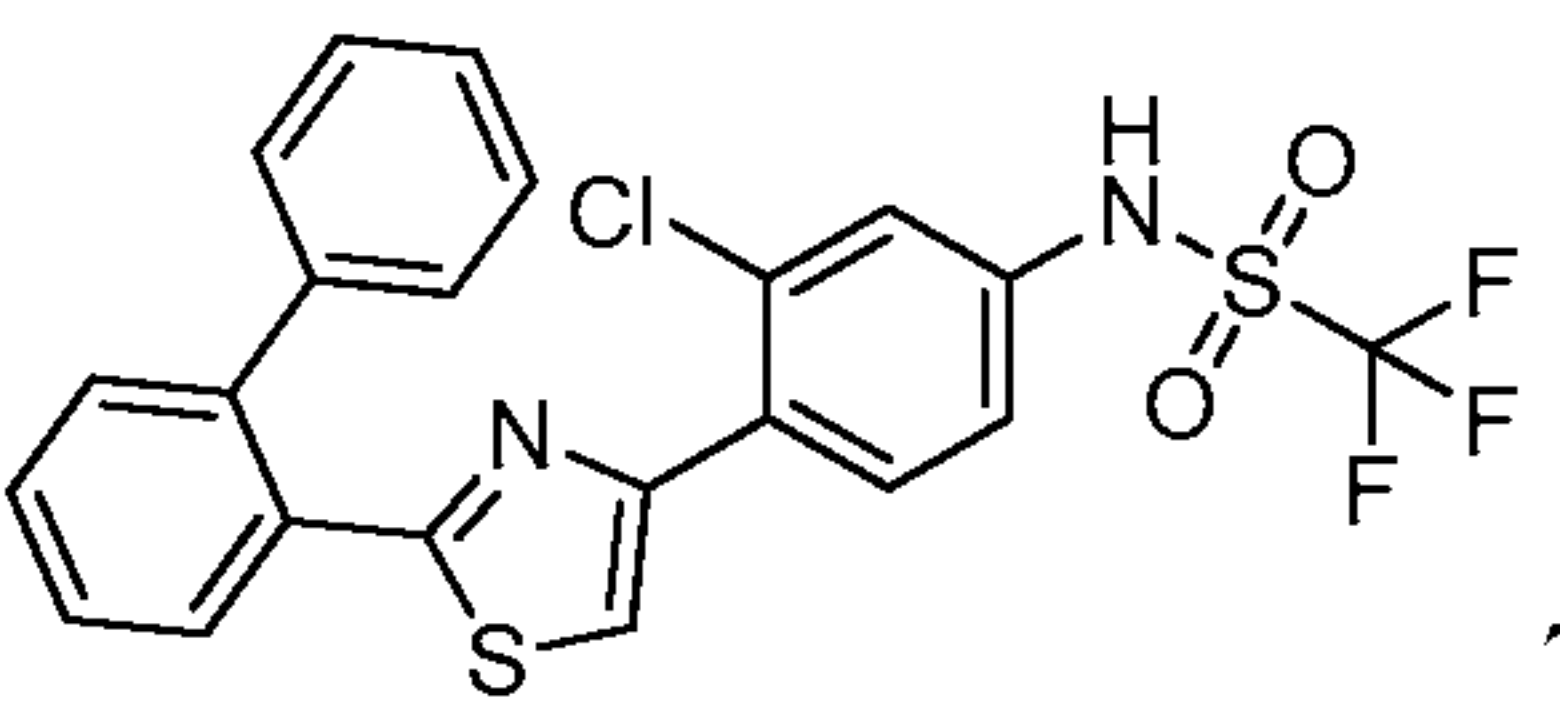
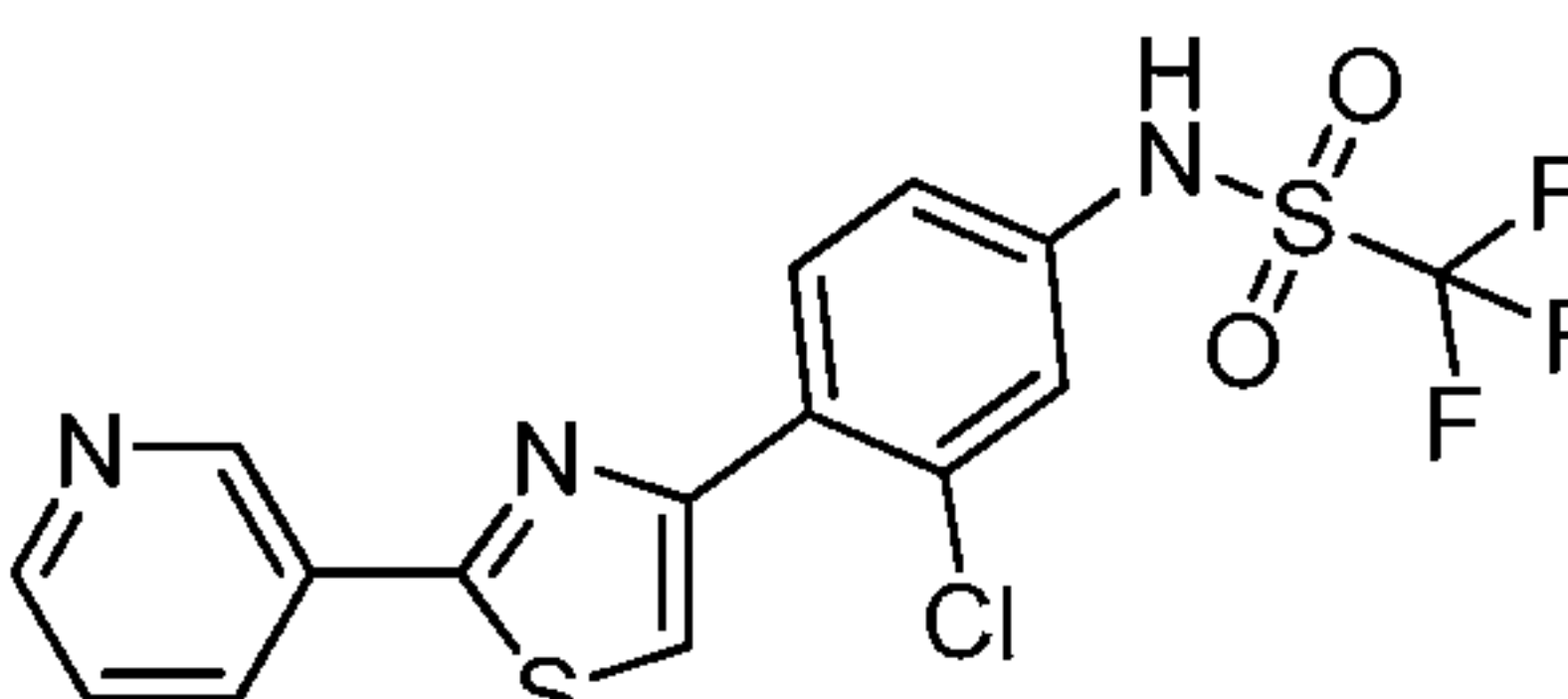
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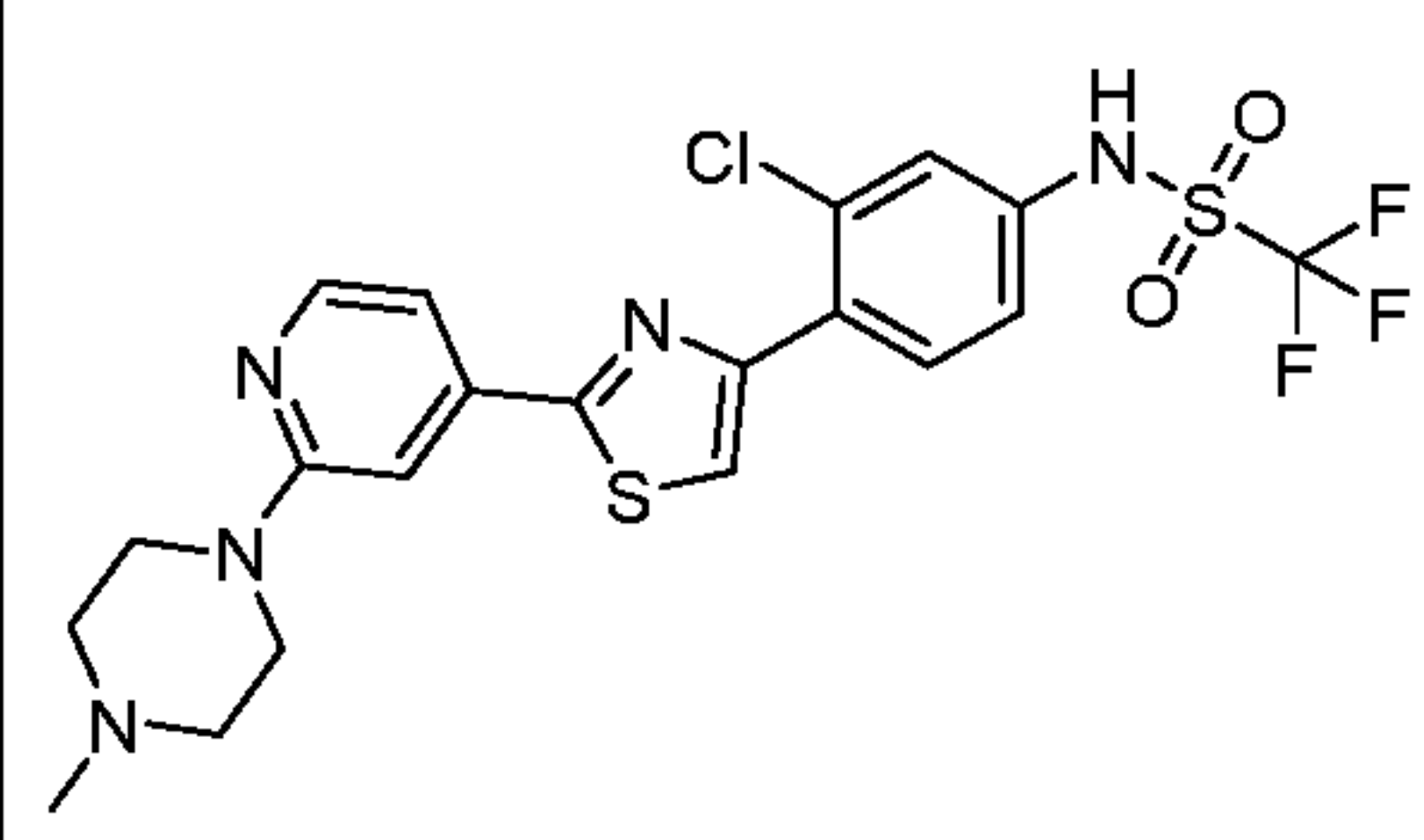
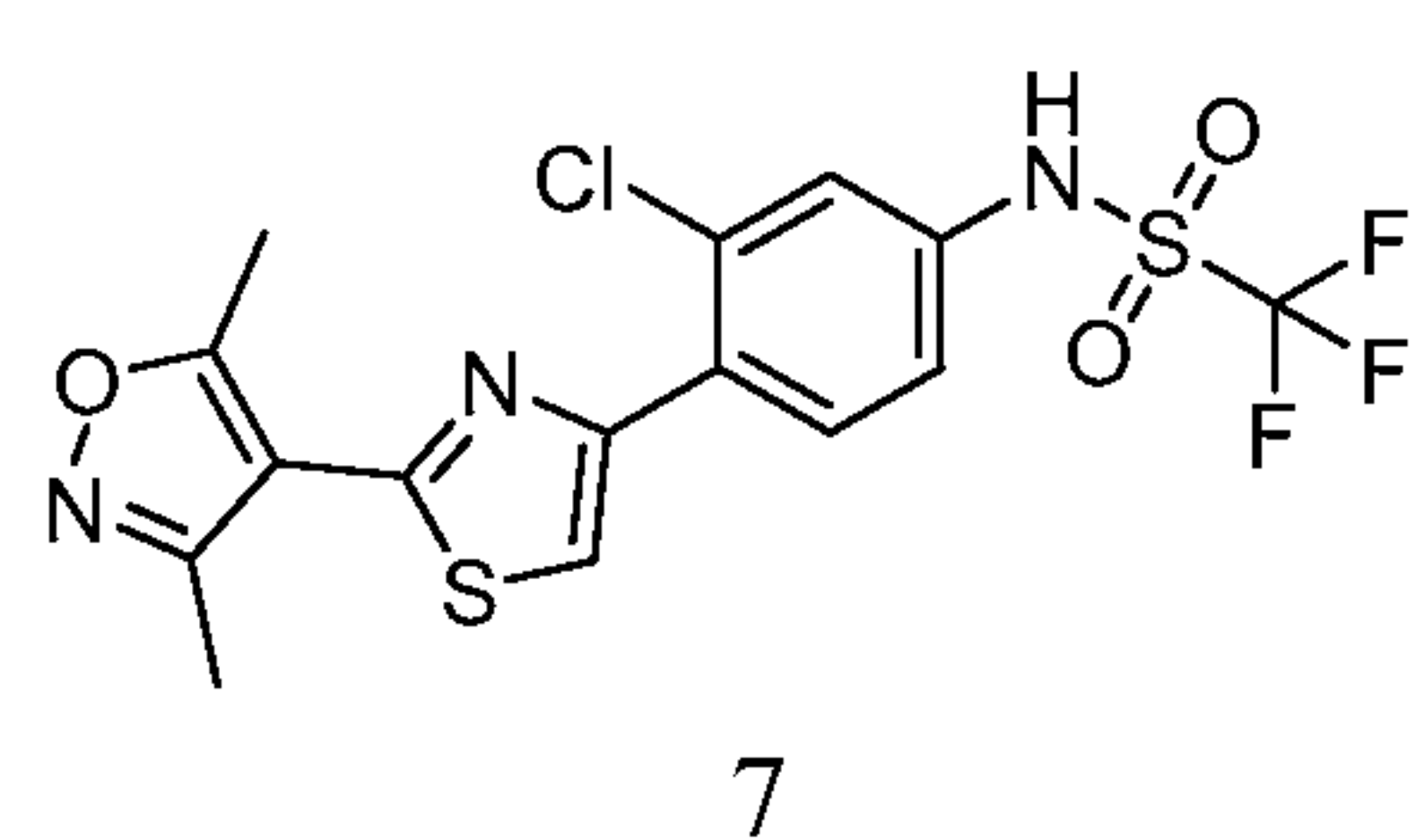
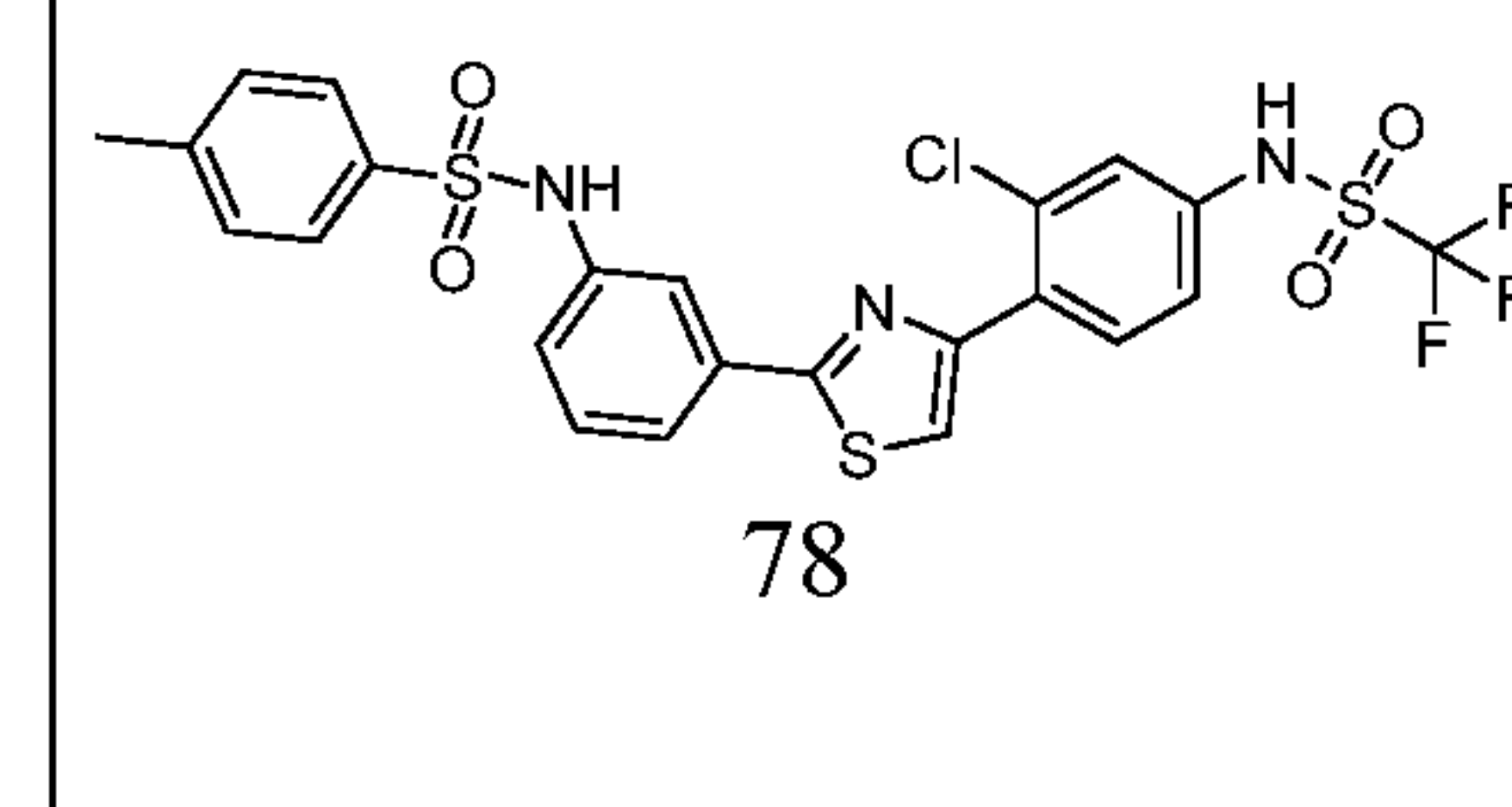
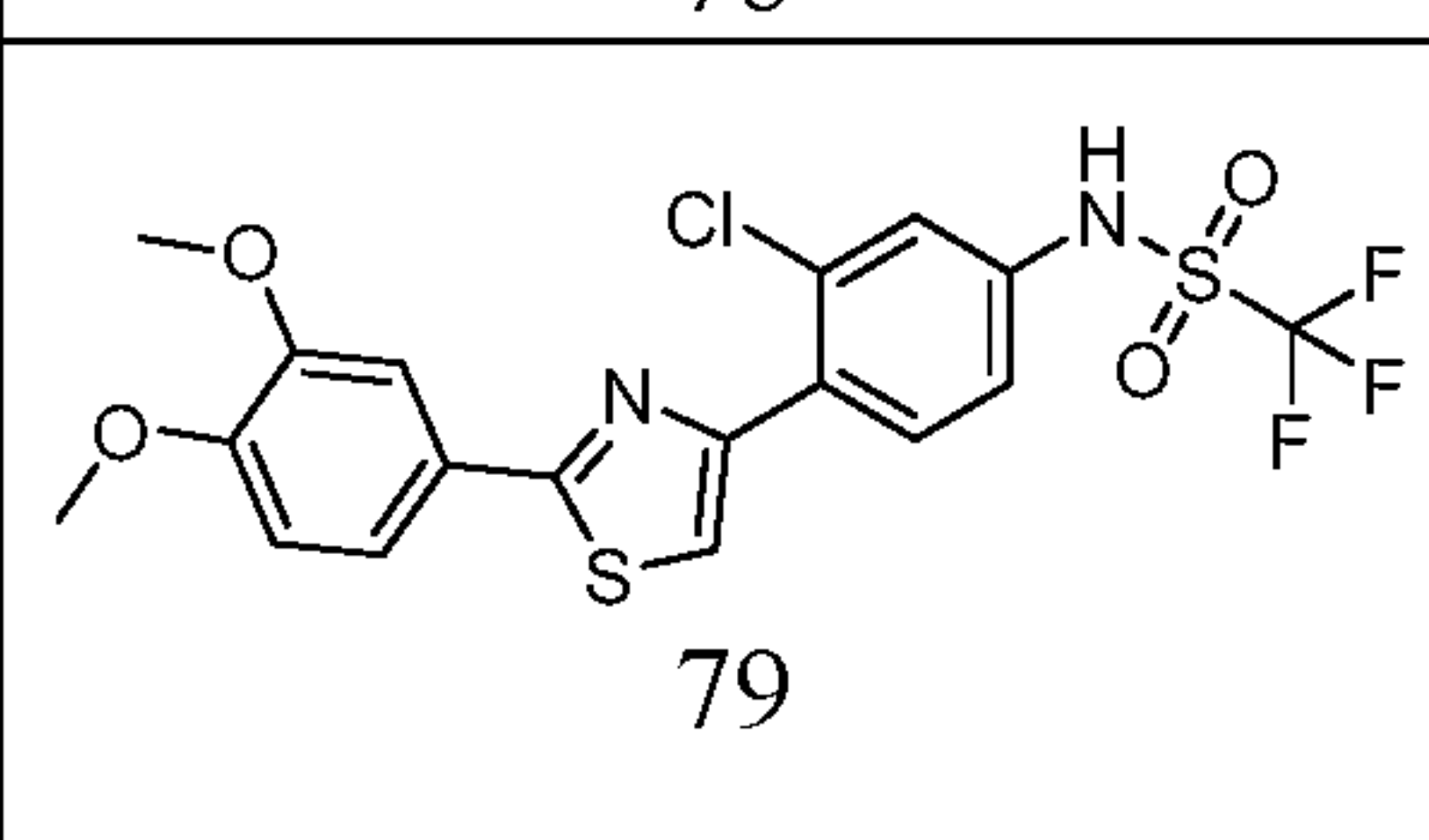
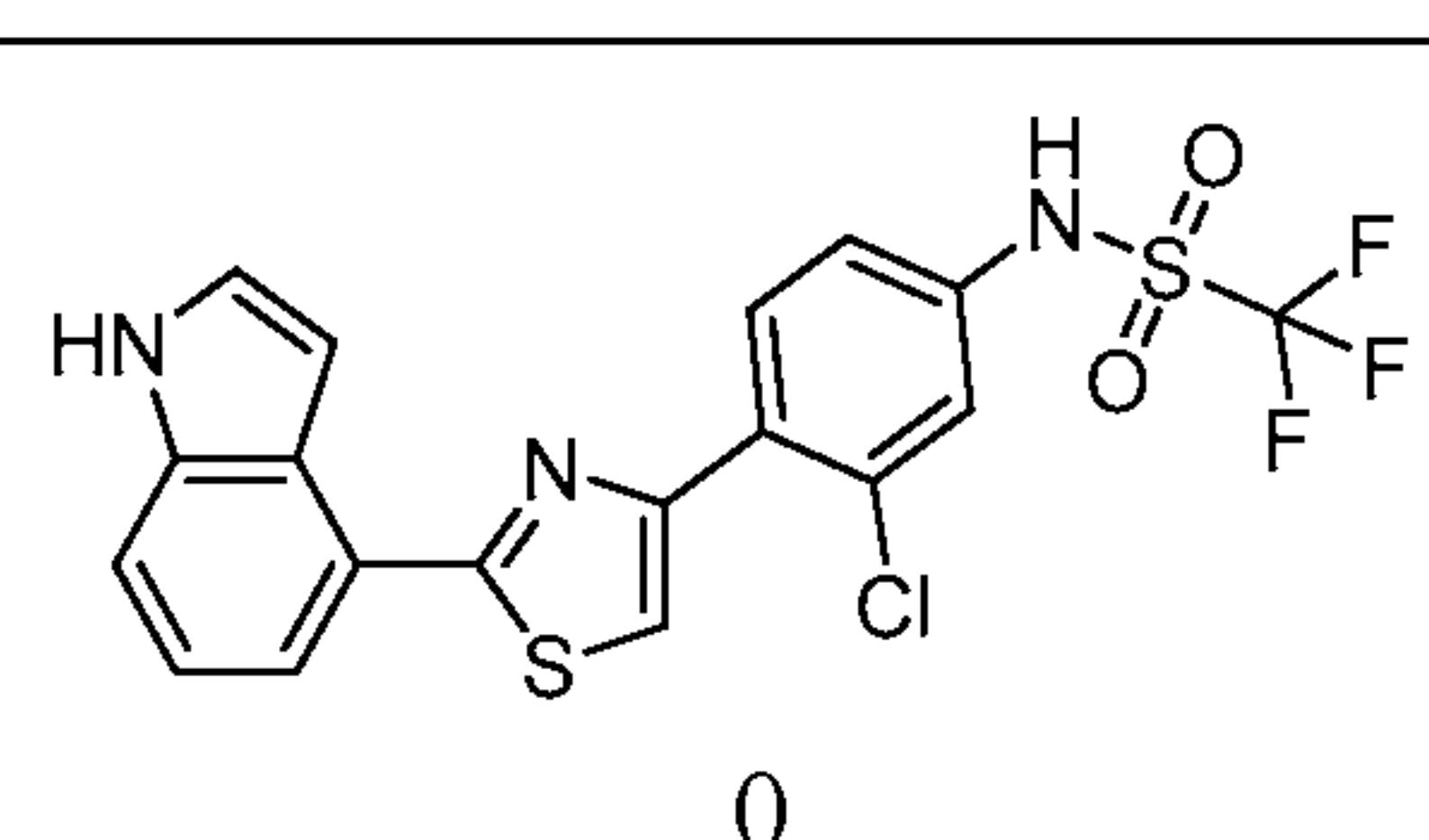
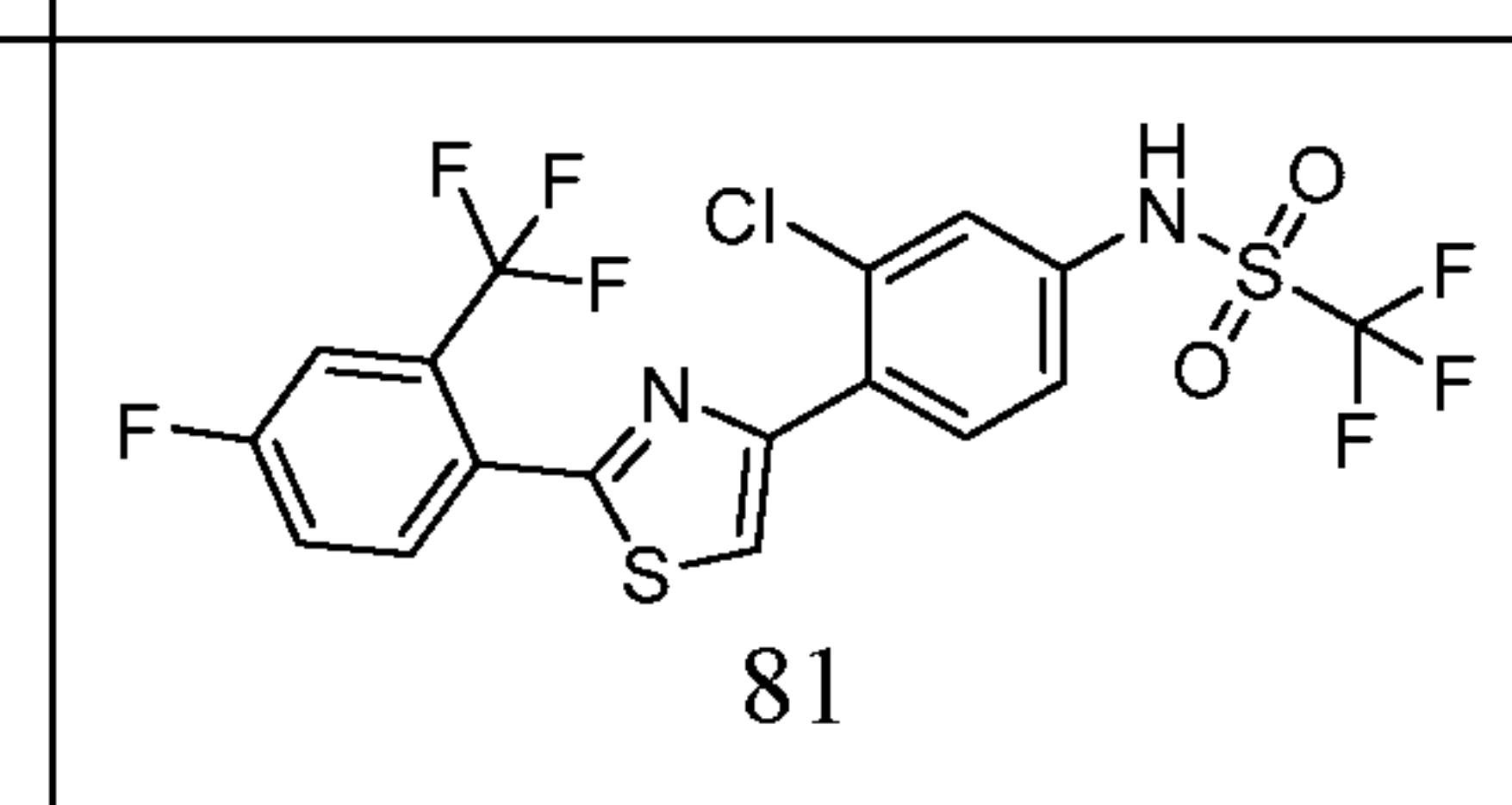
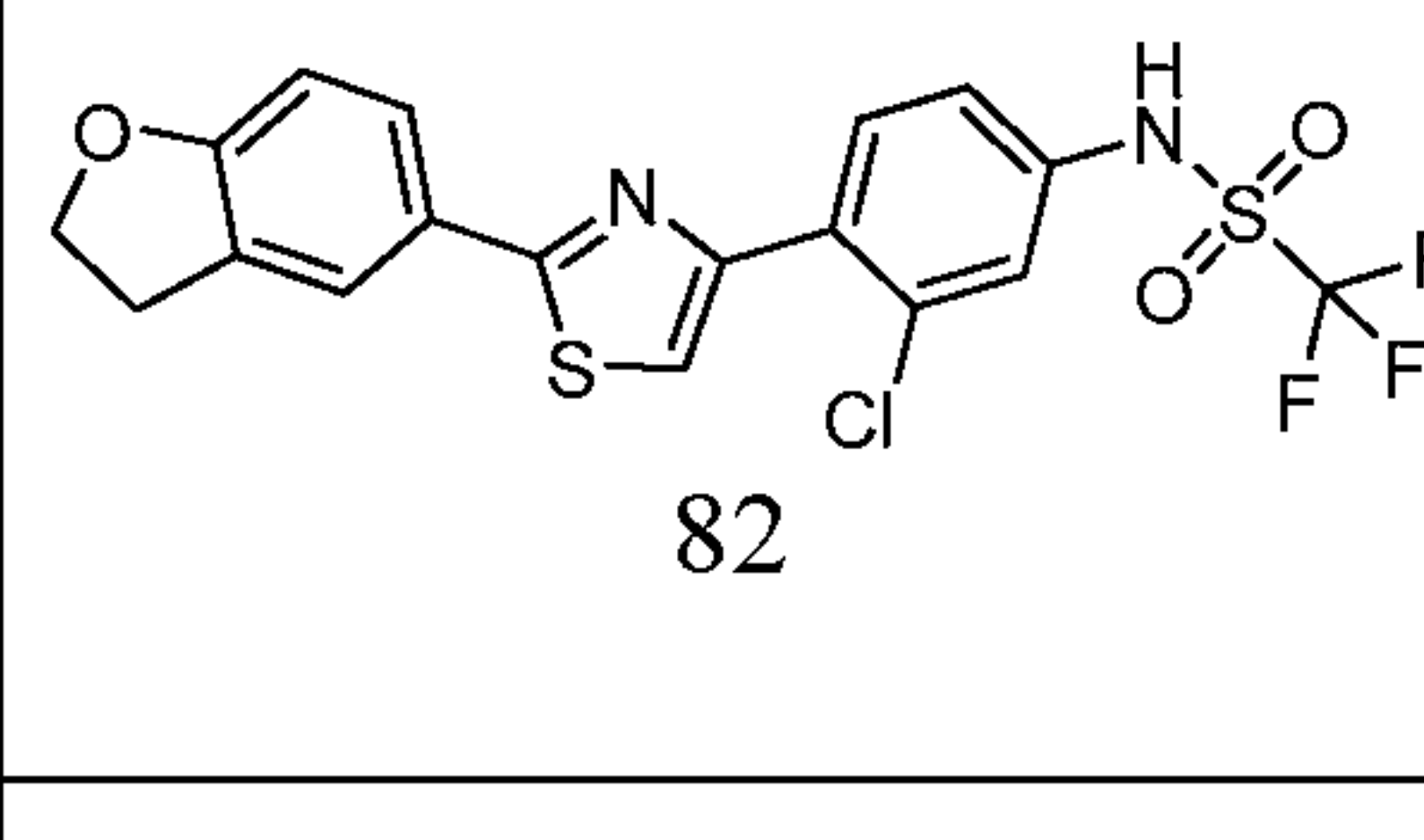
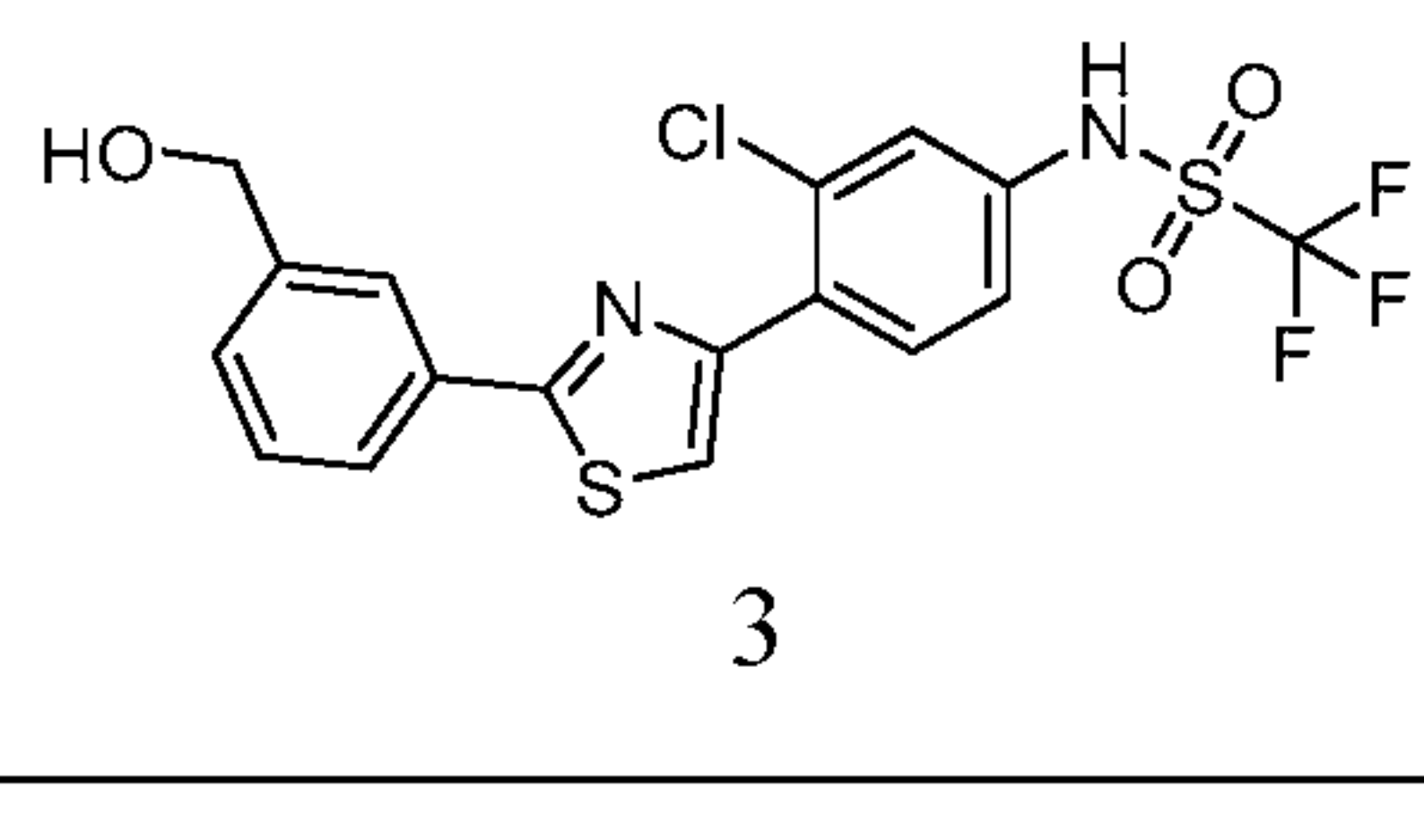
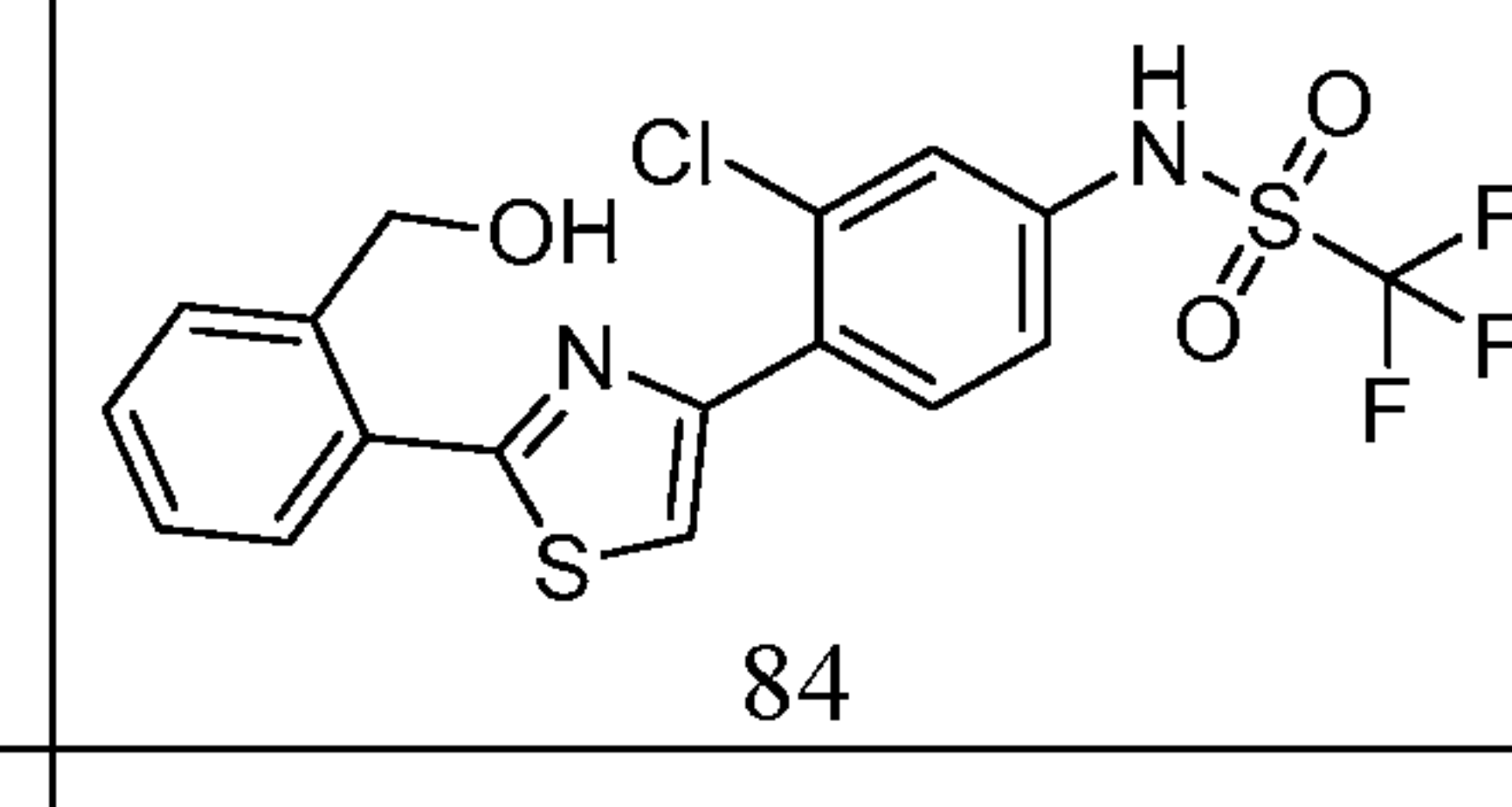
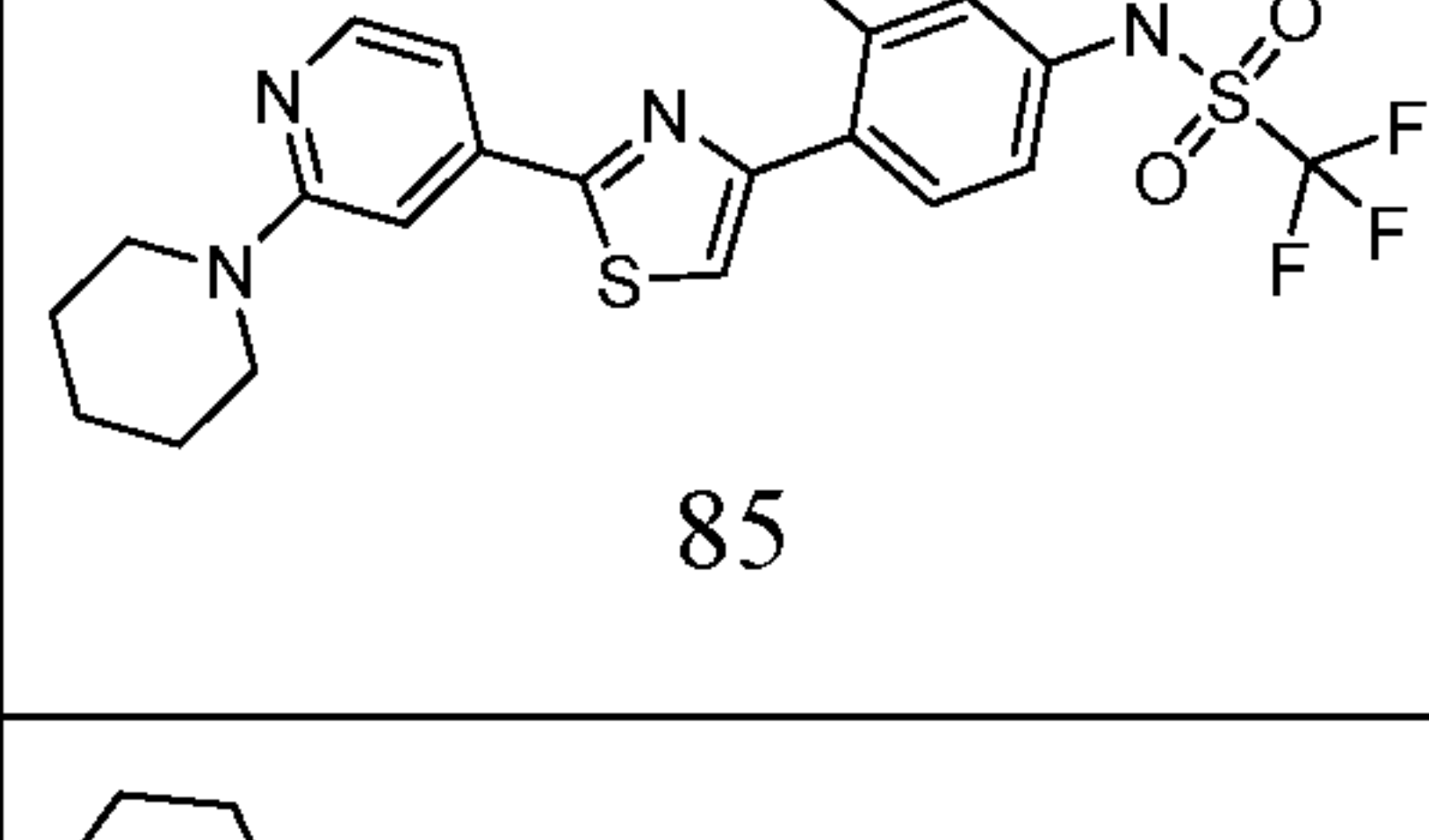
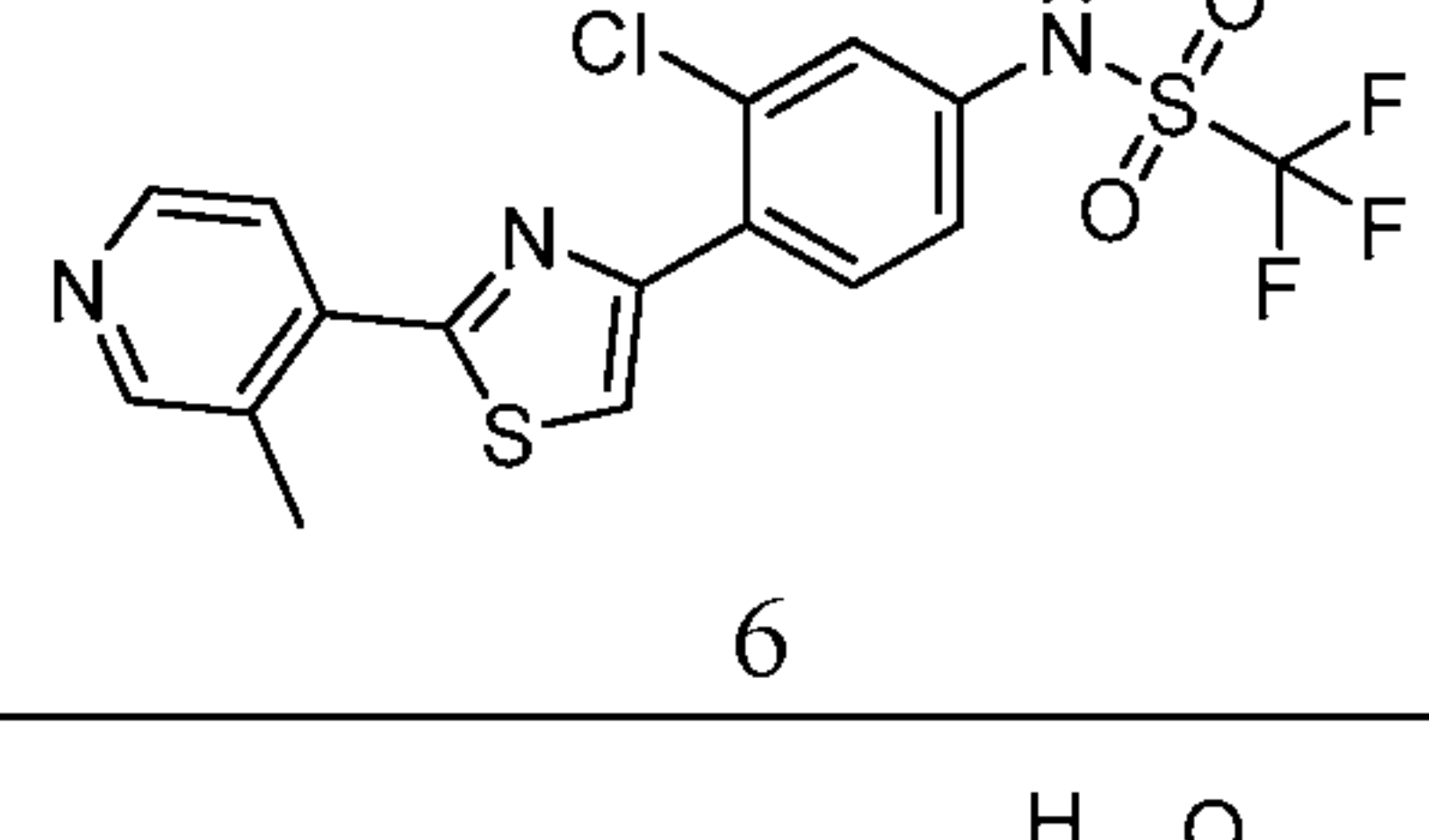
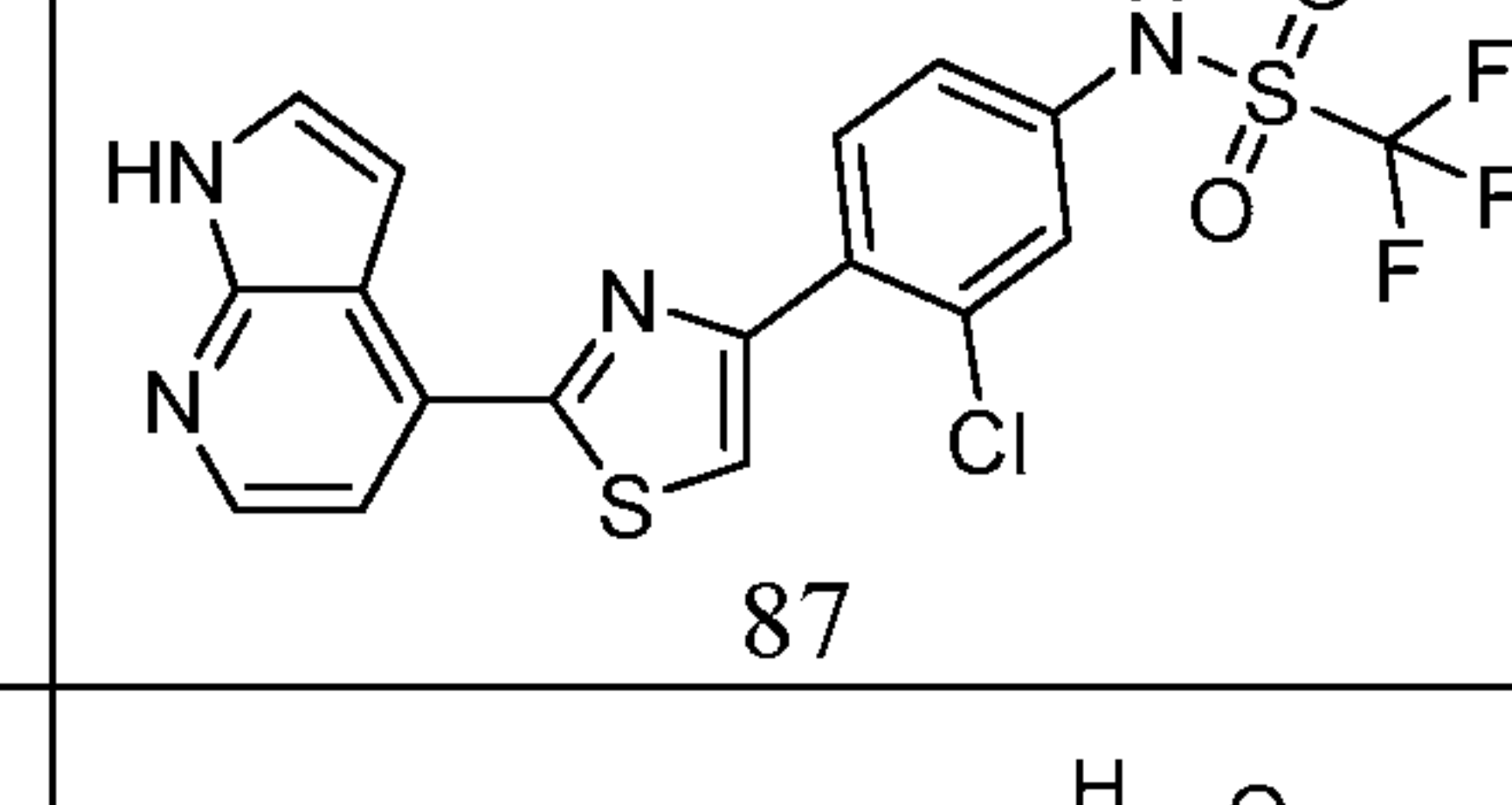
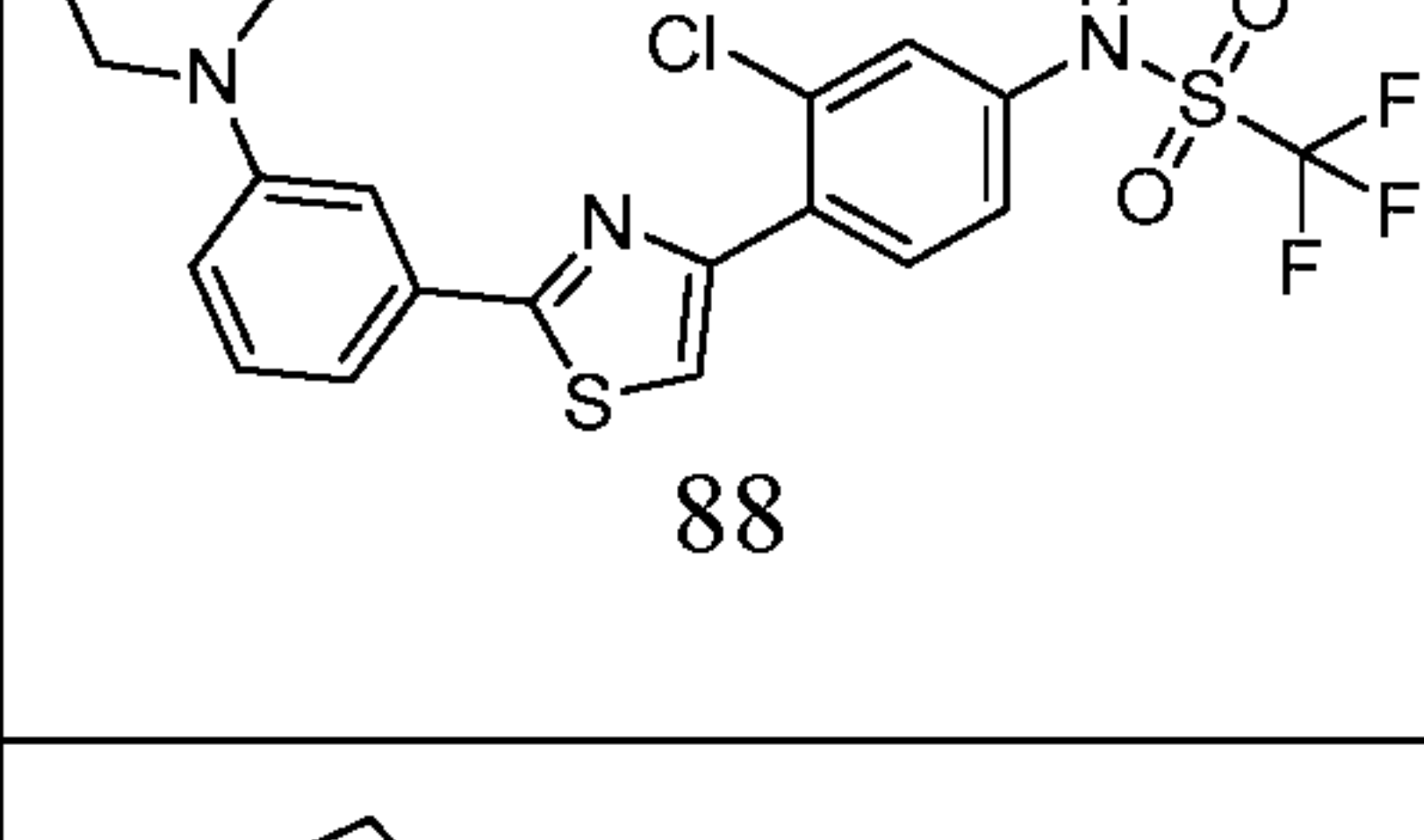
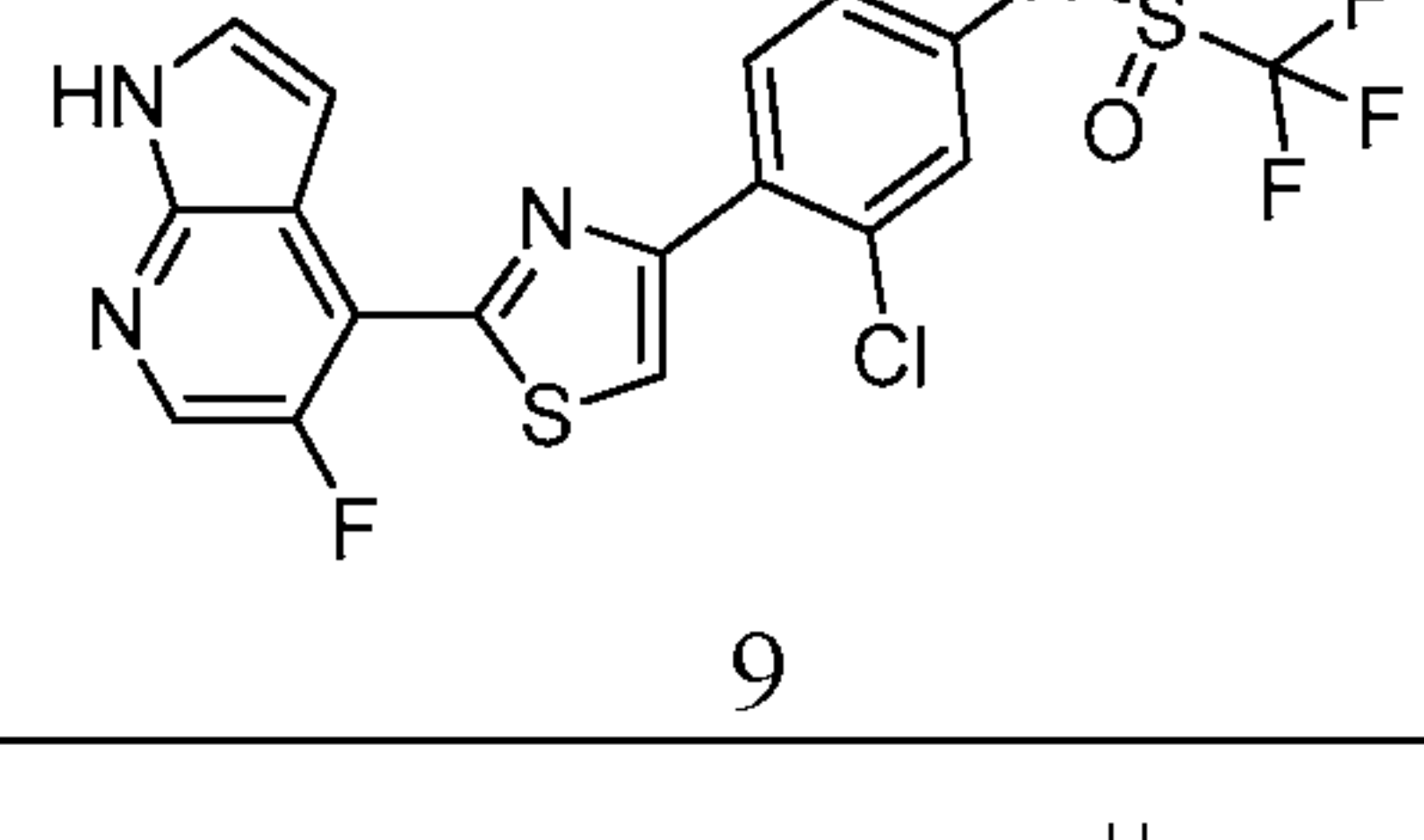
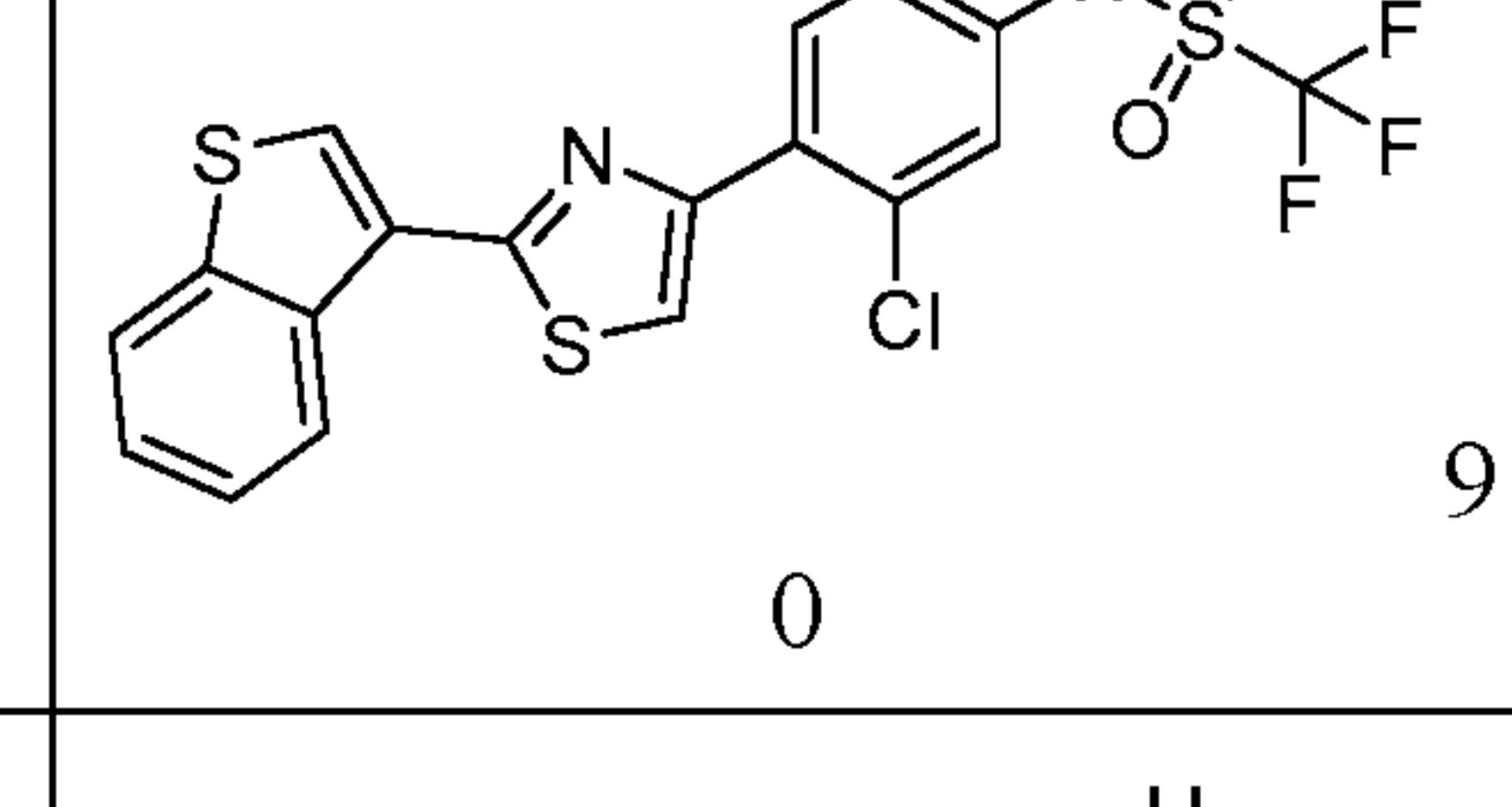
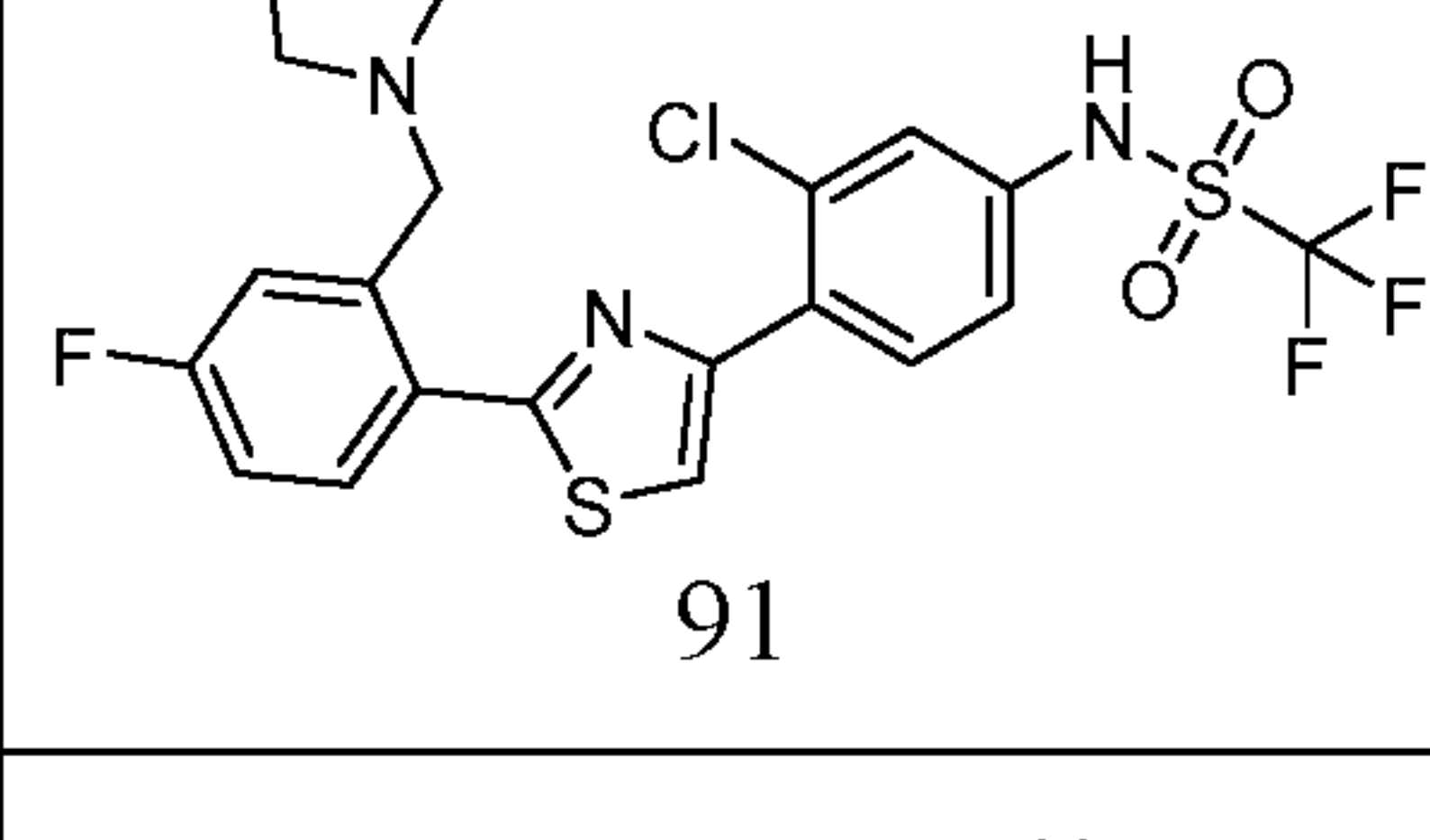
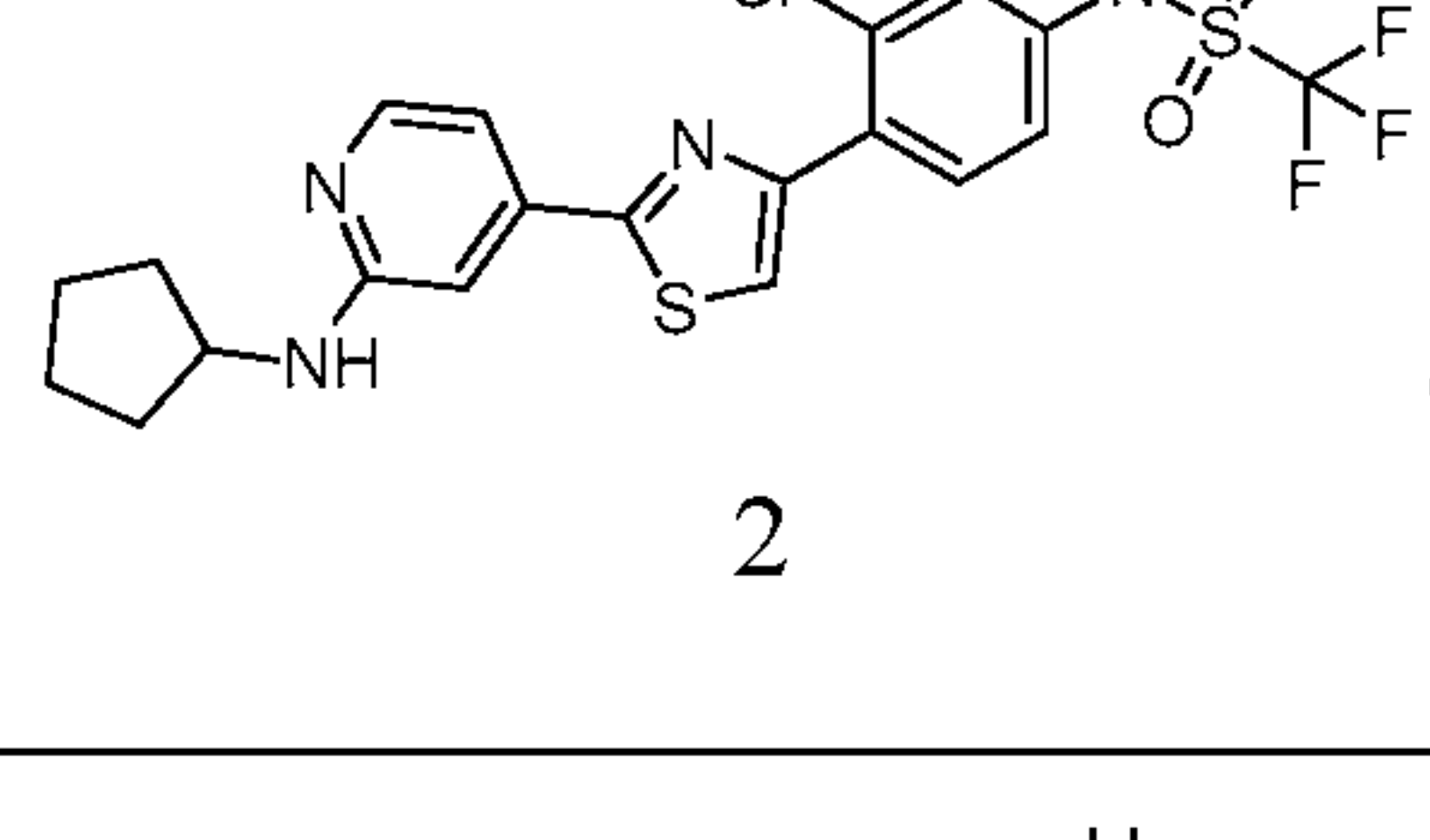
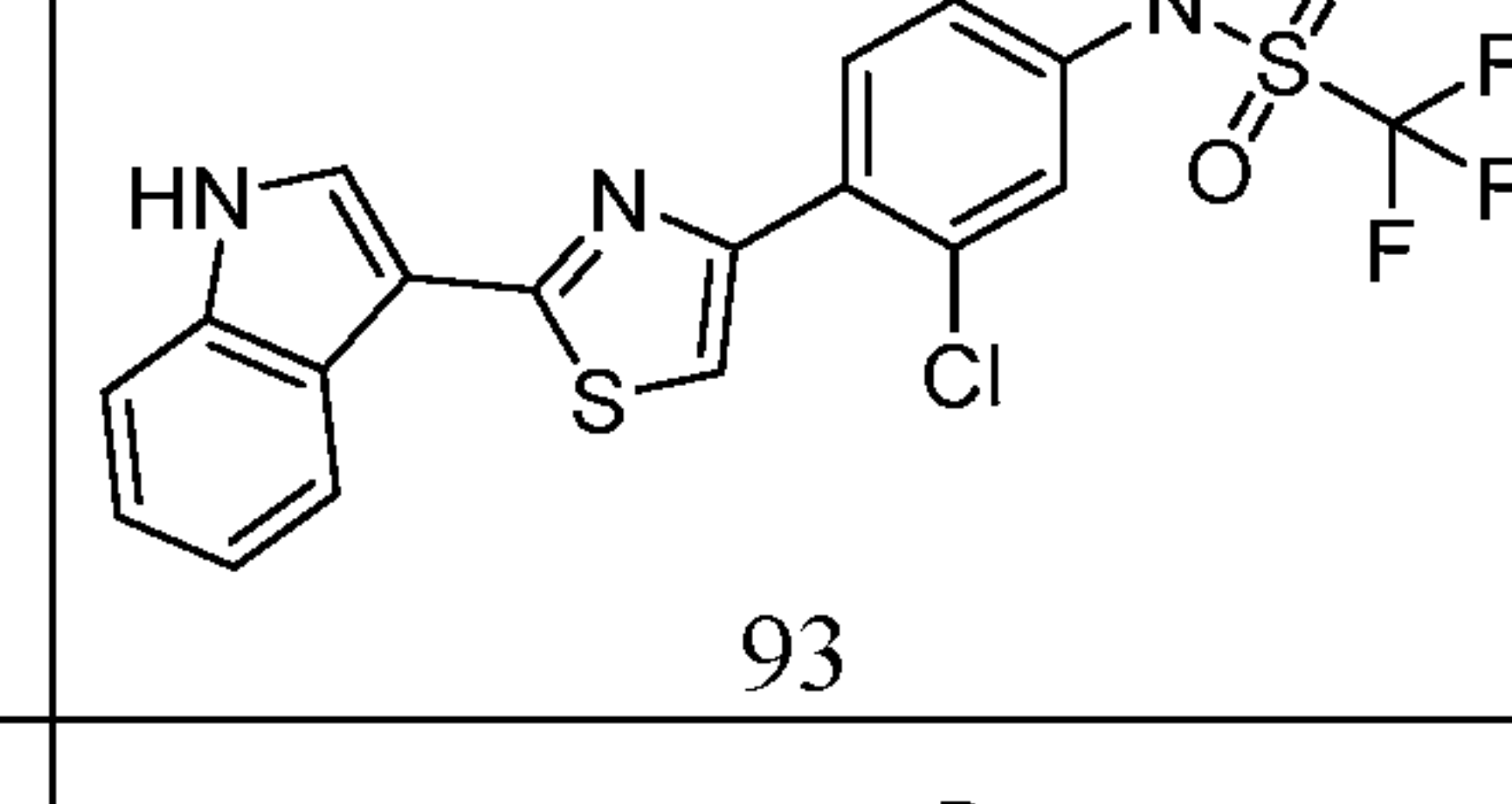
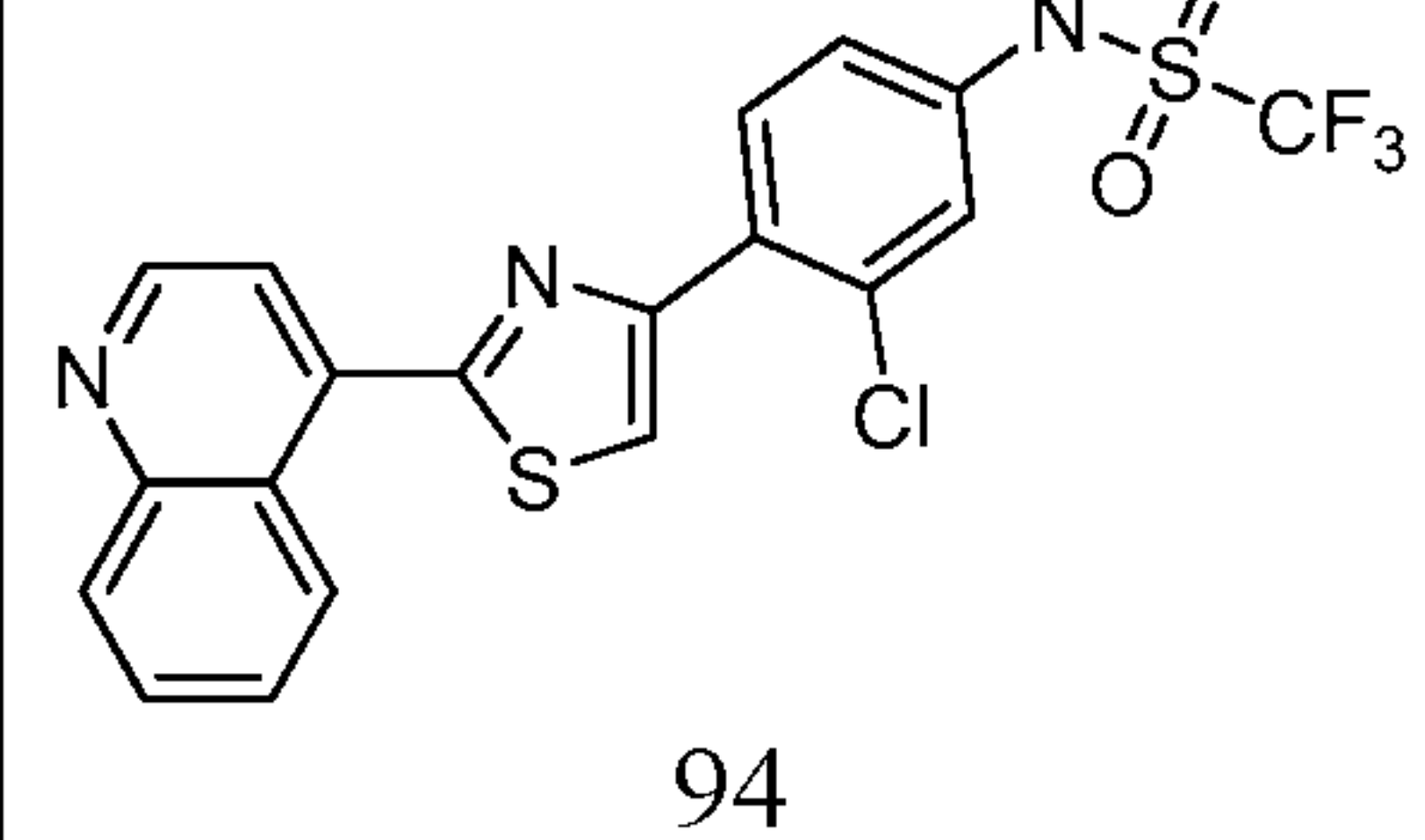
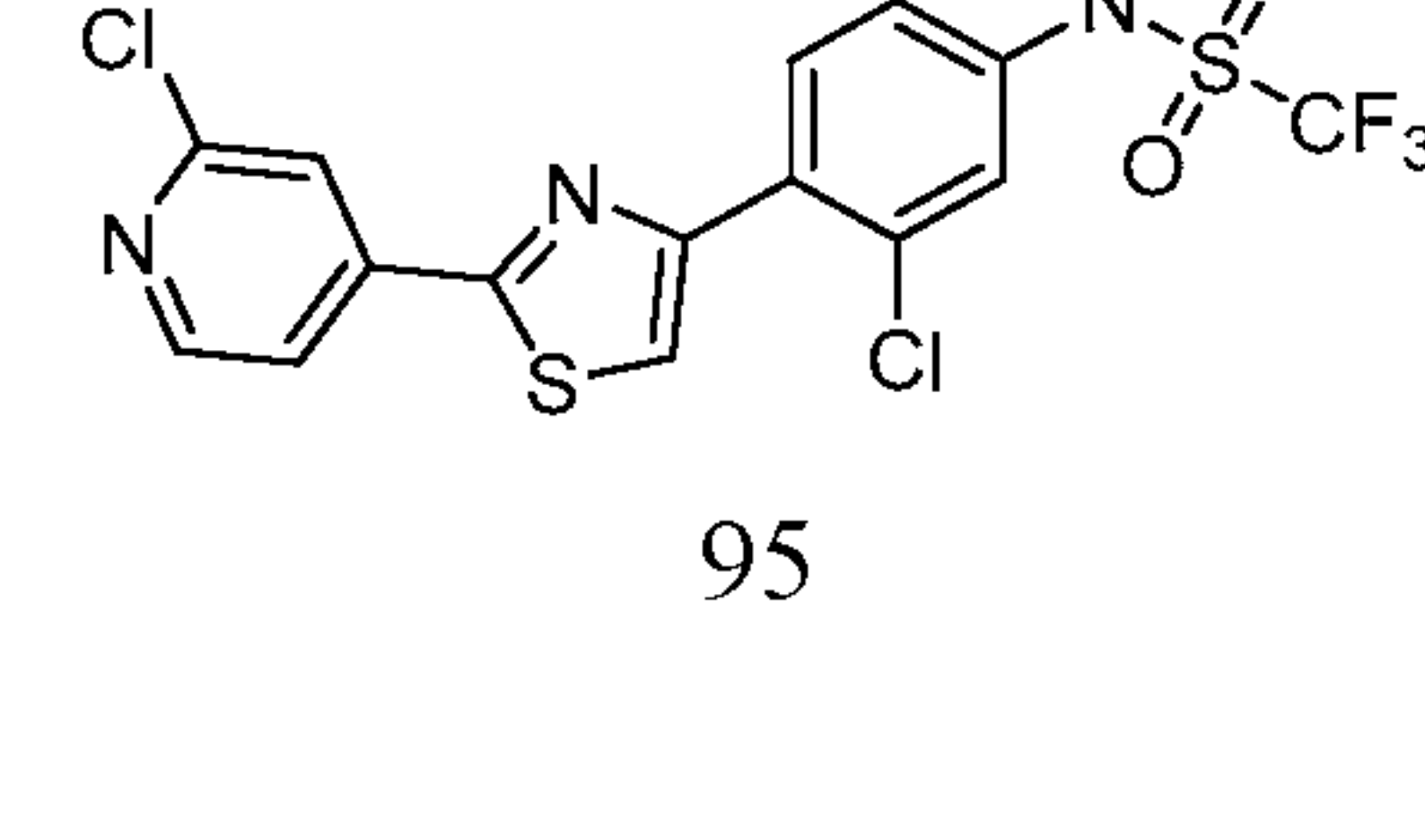
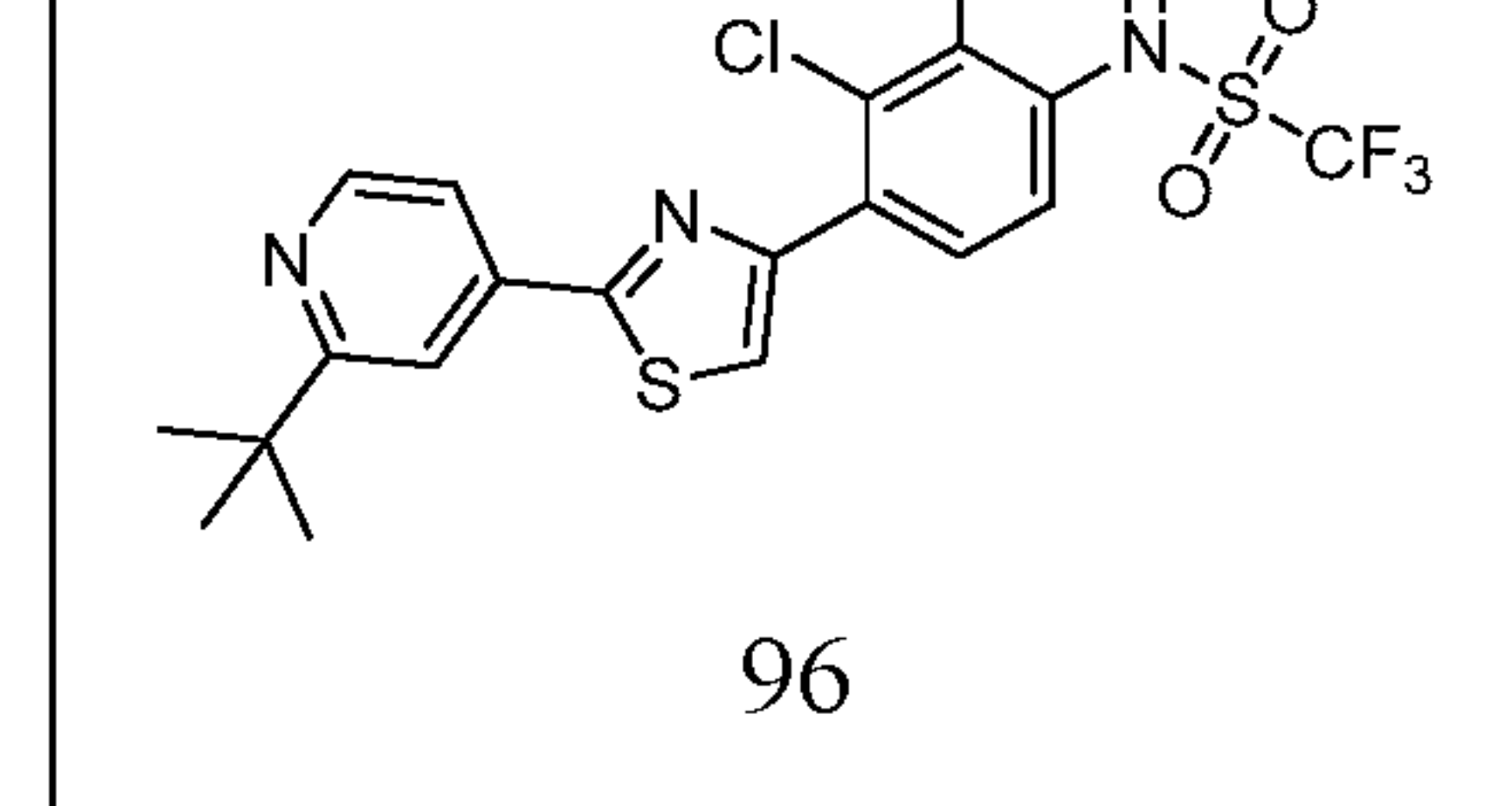
Table 1		
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 85	 6	 87
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 94	 95	 96

Table 1

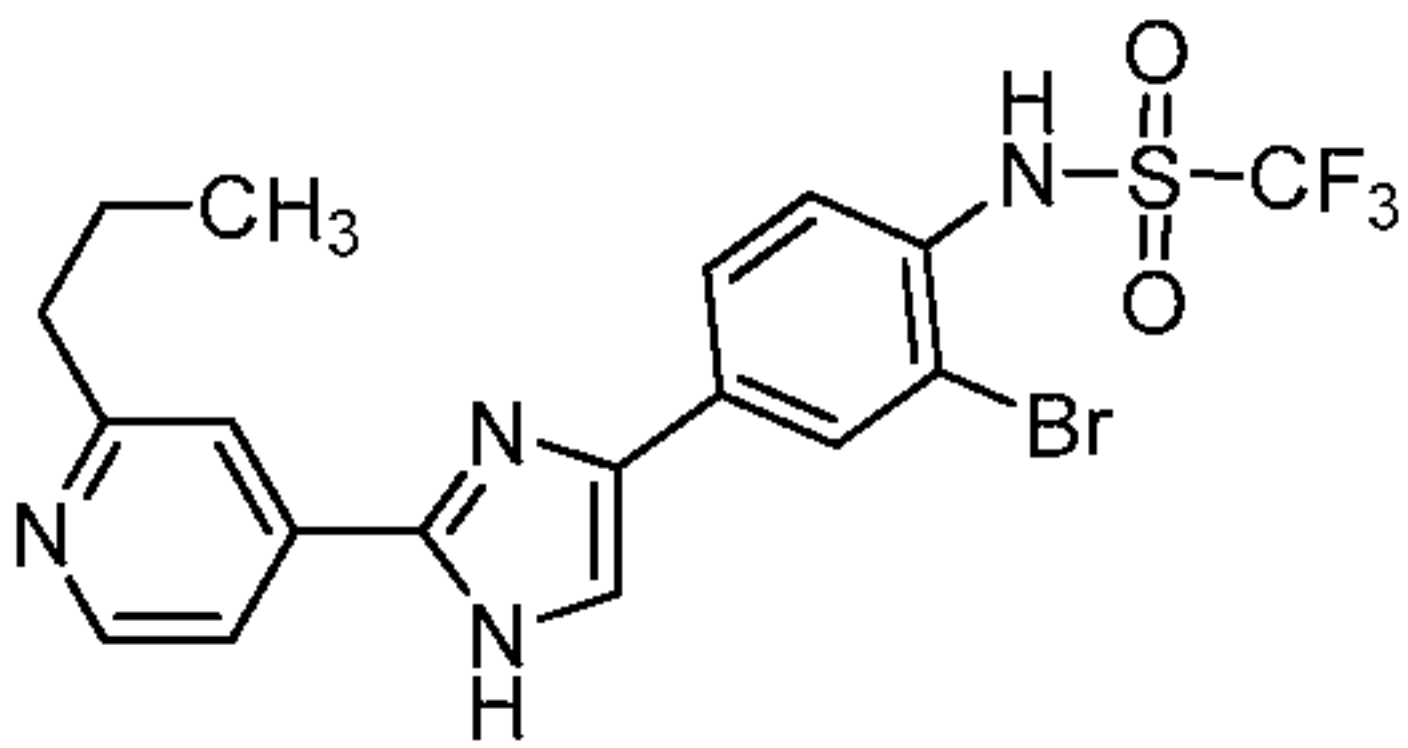
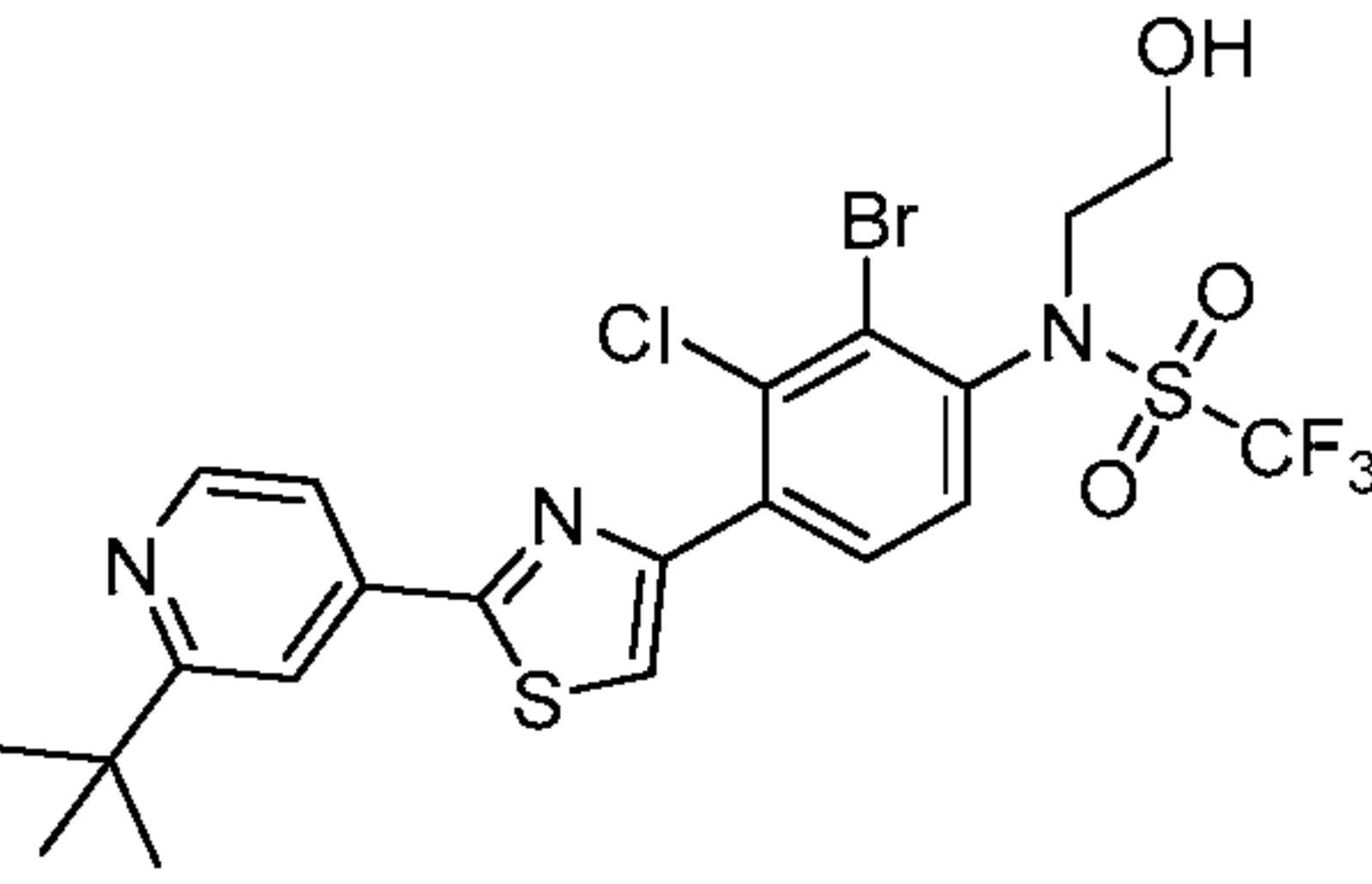
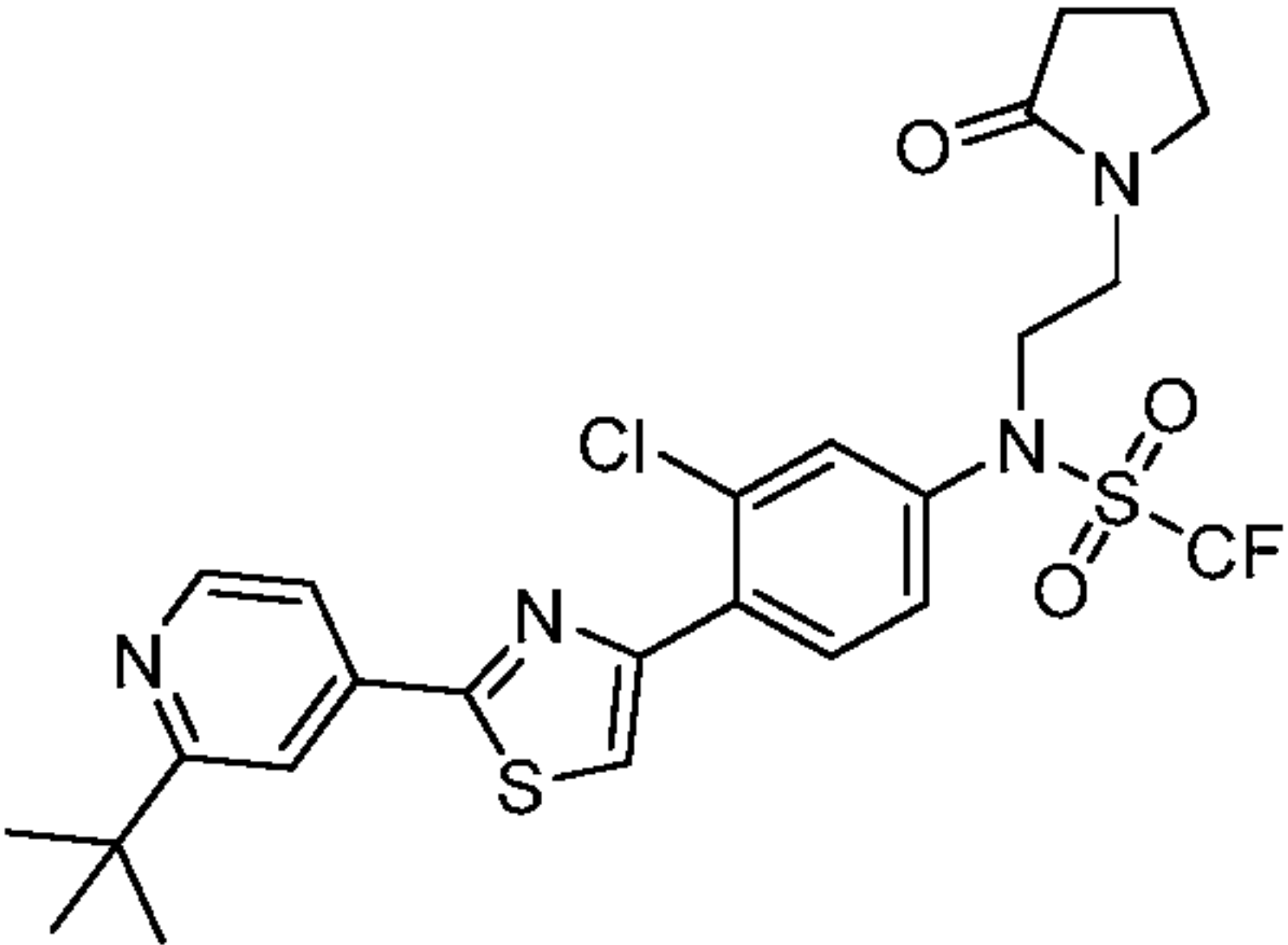
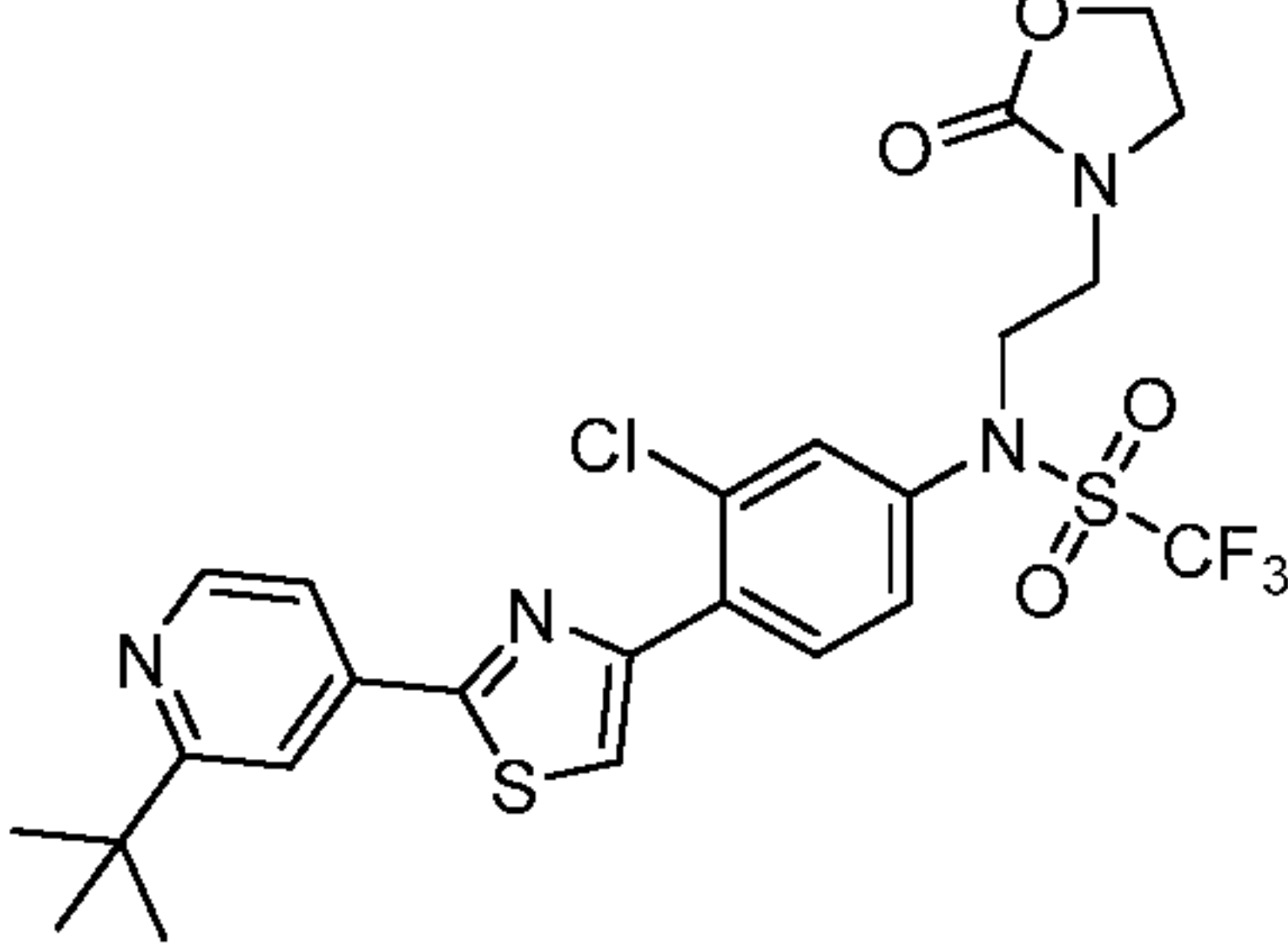
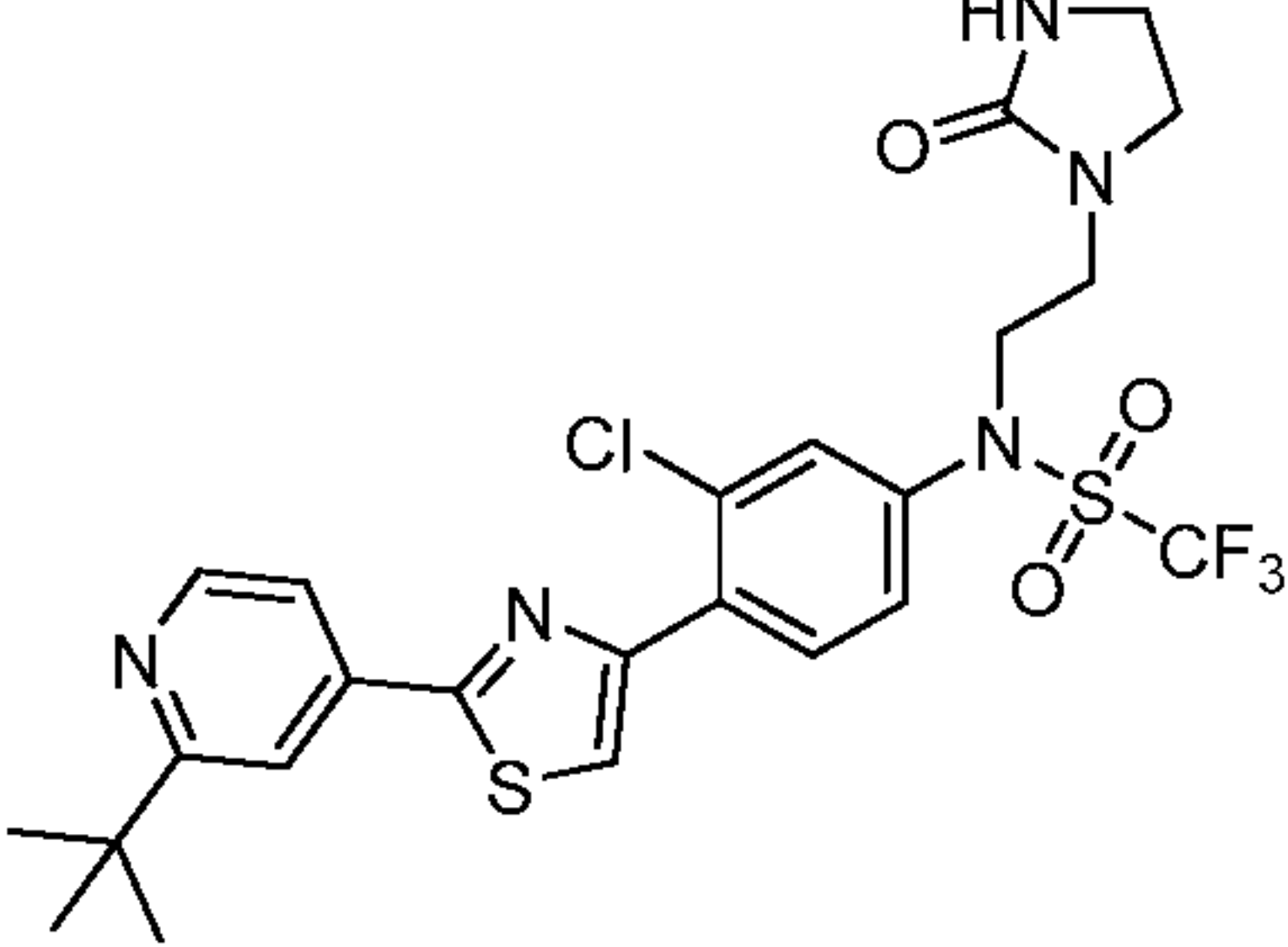
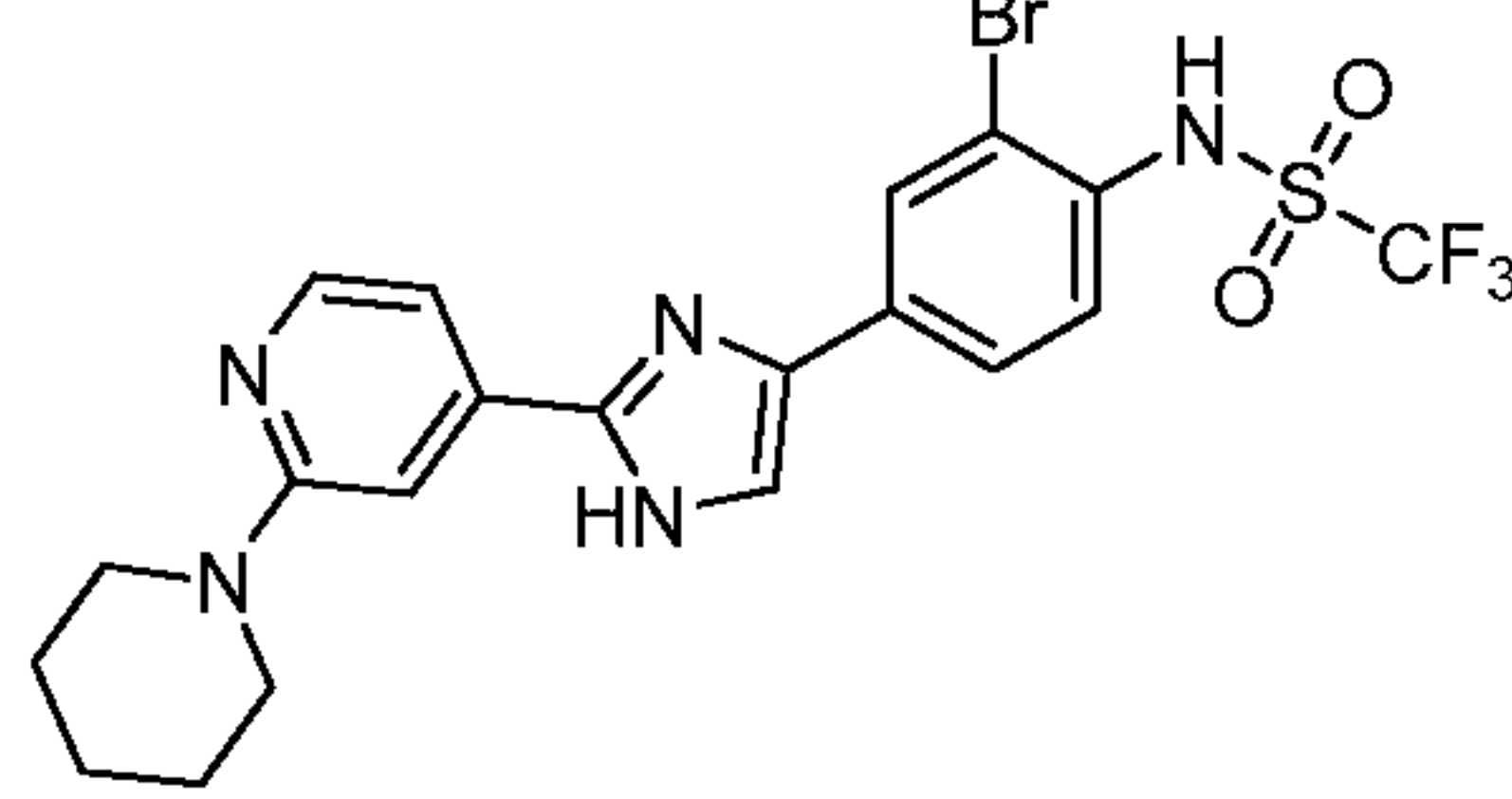
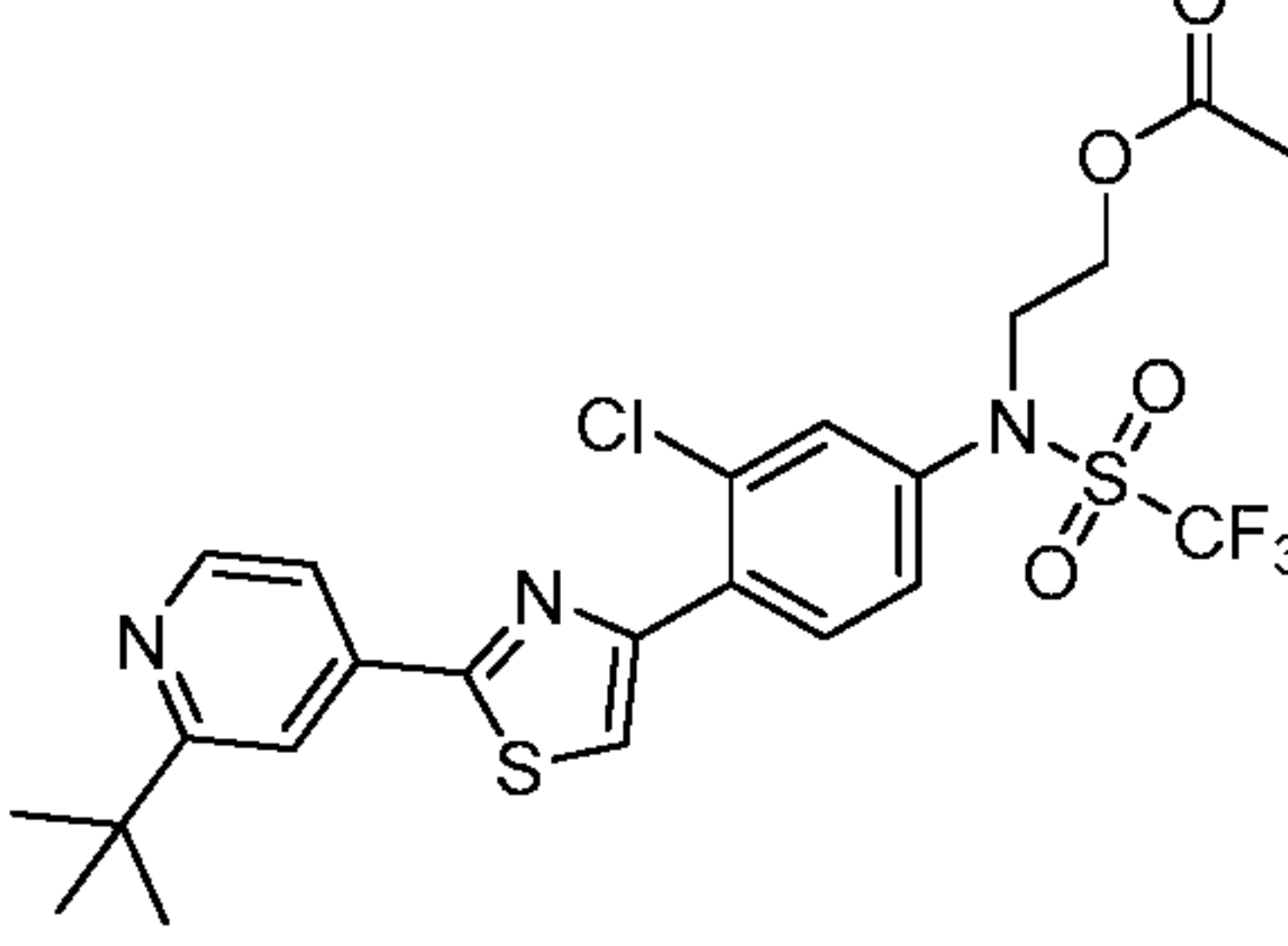
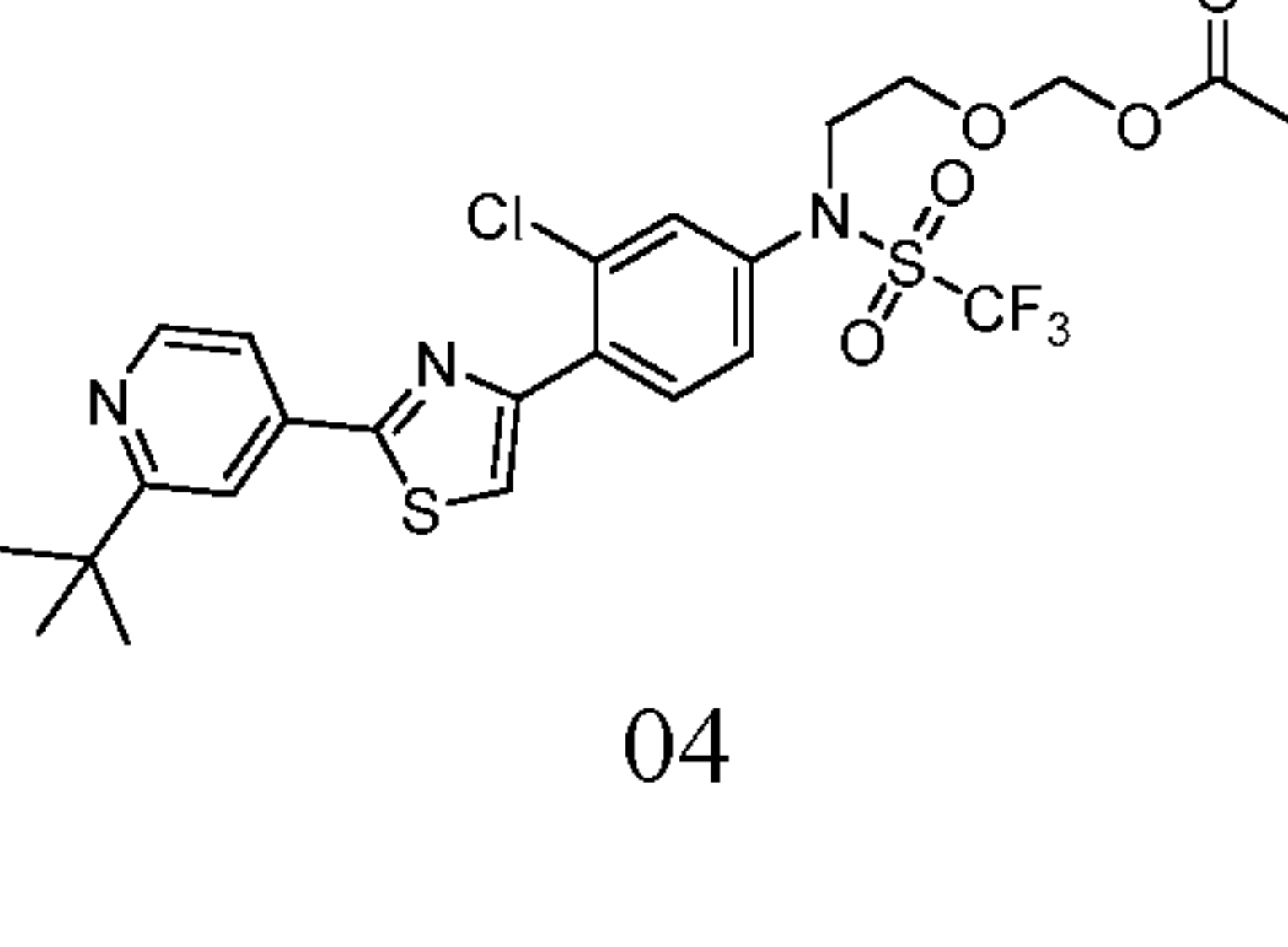
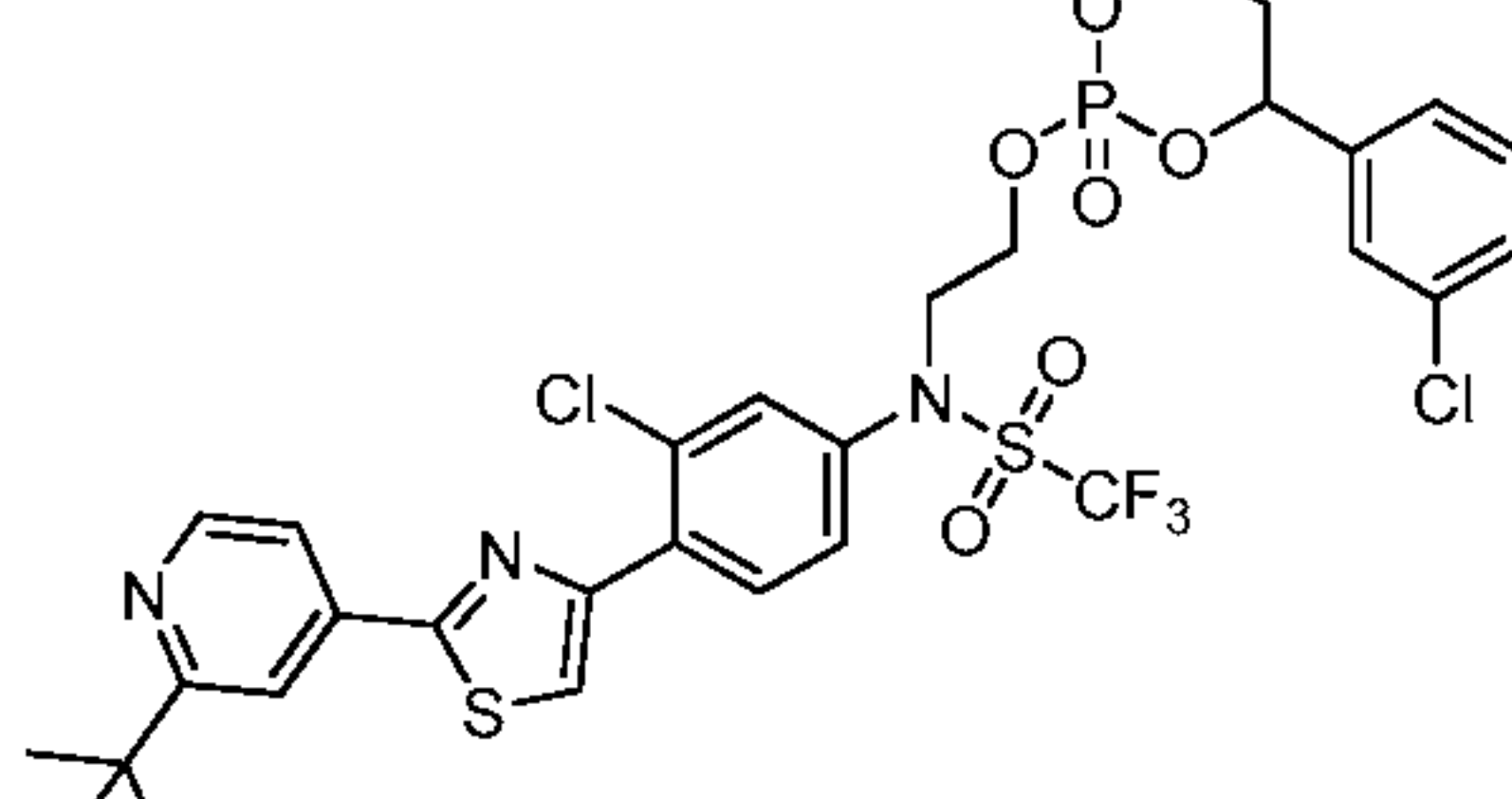
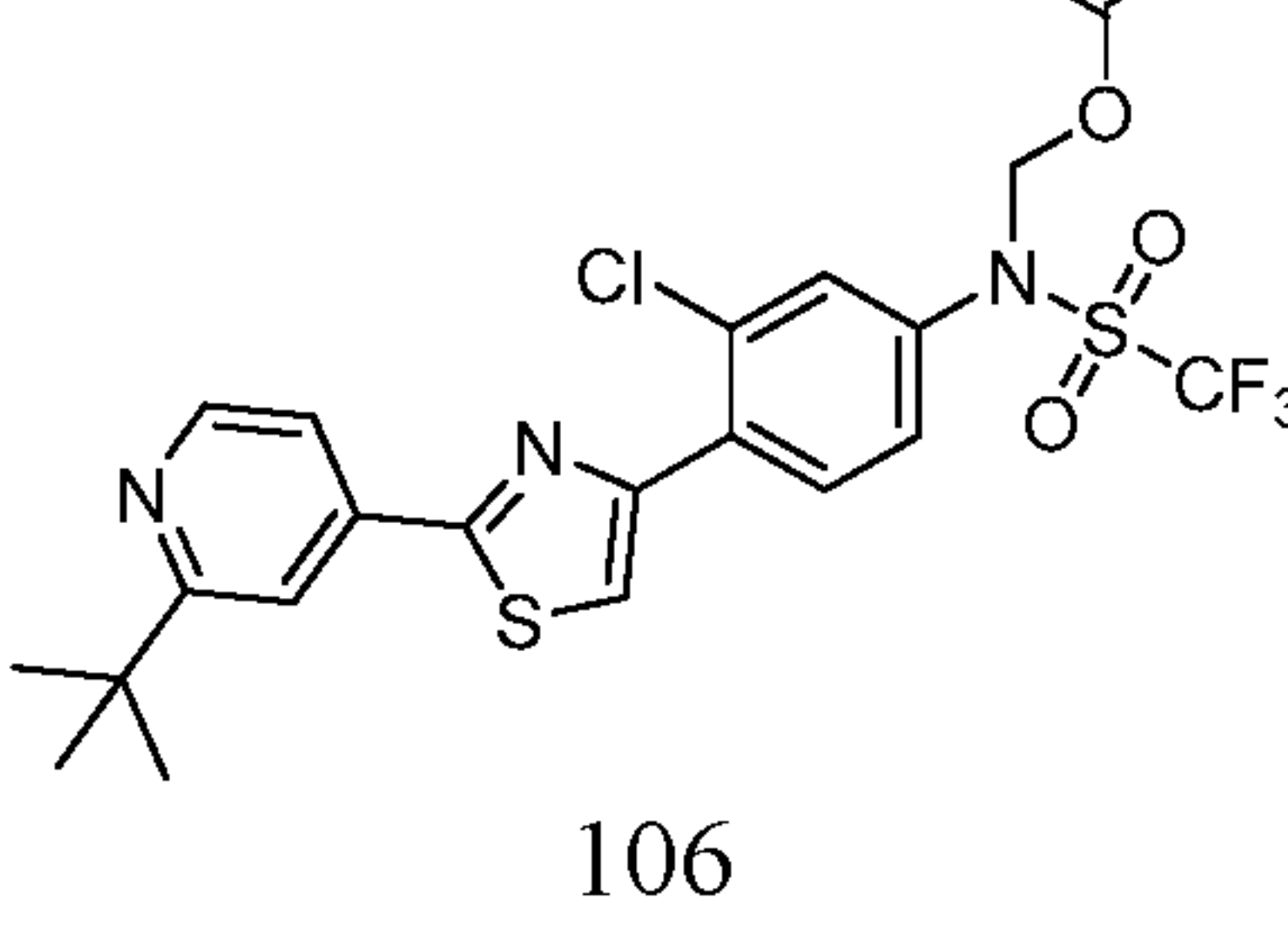
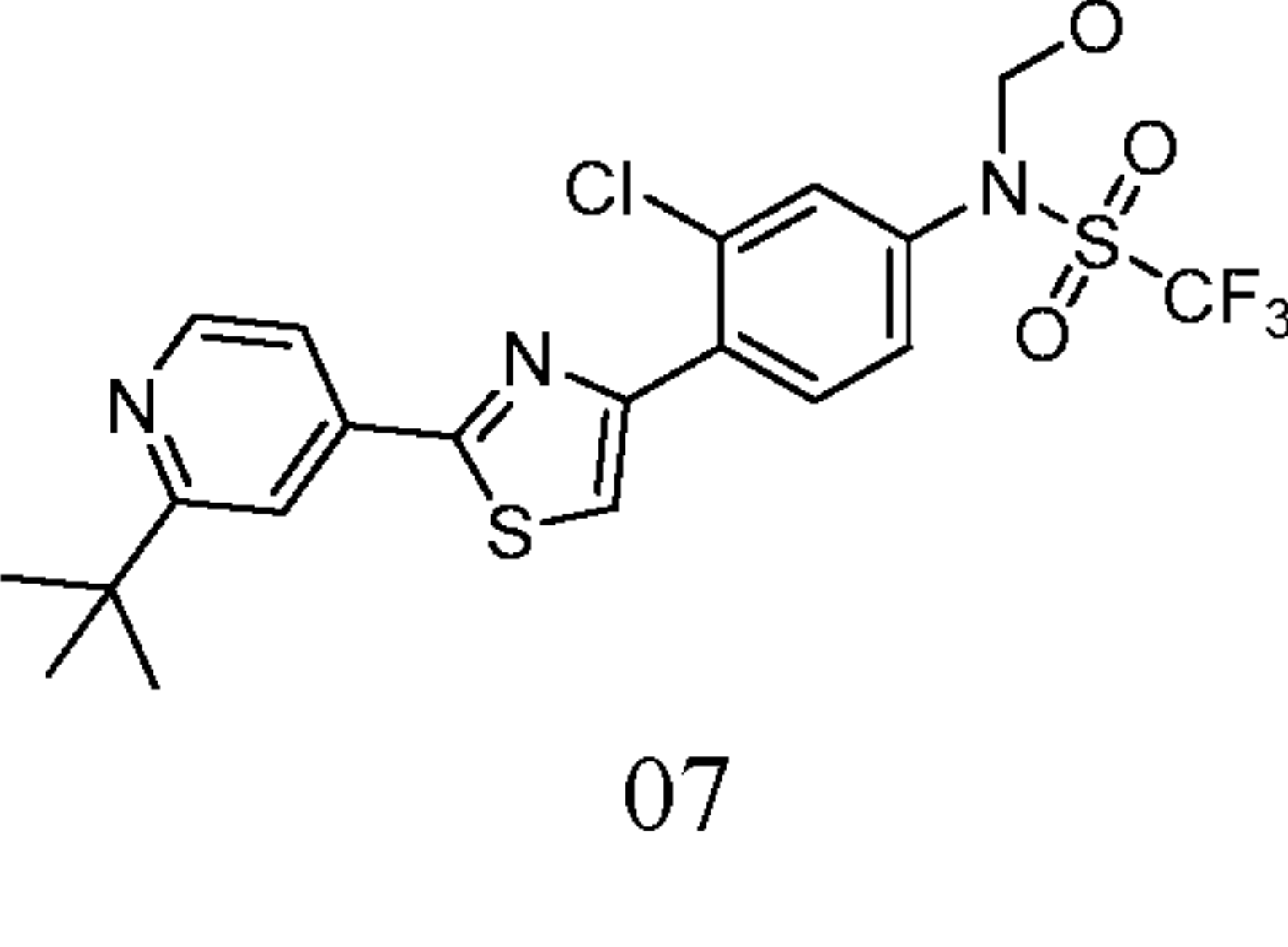
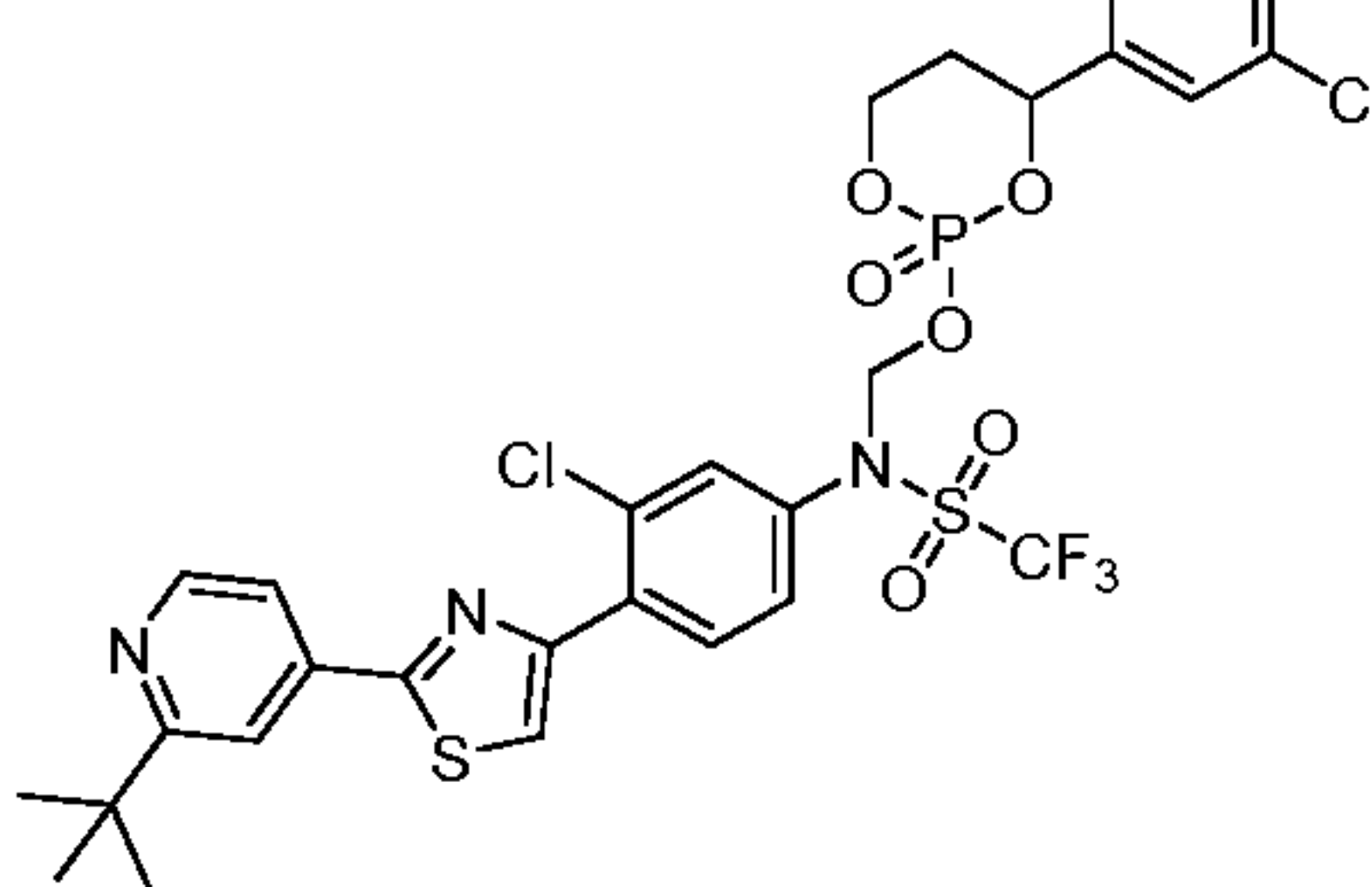
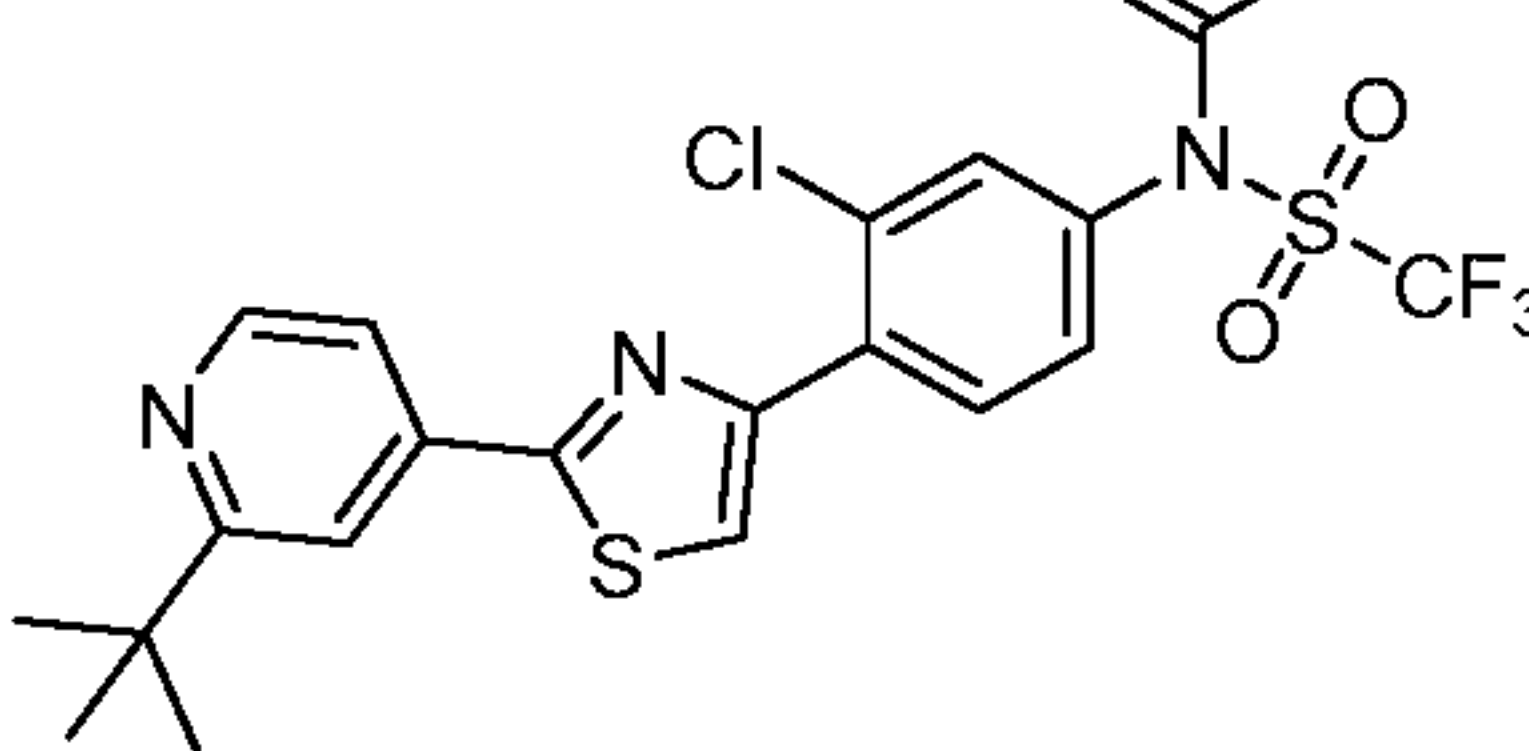
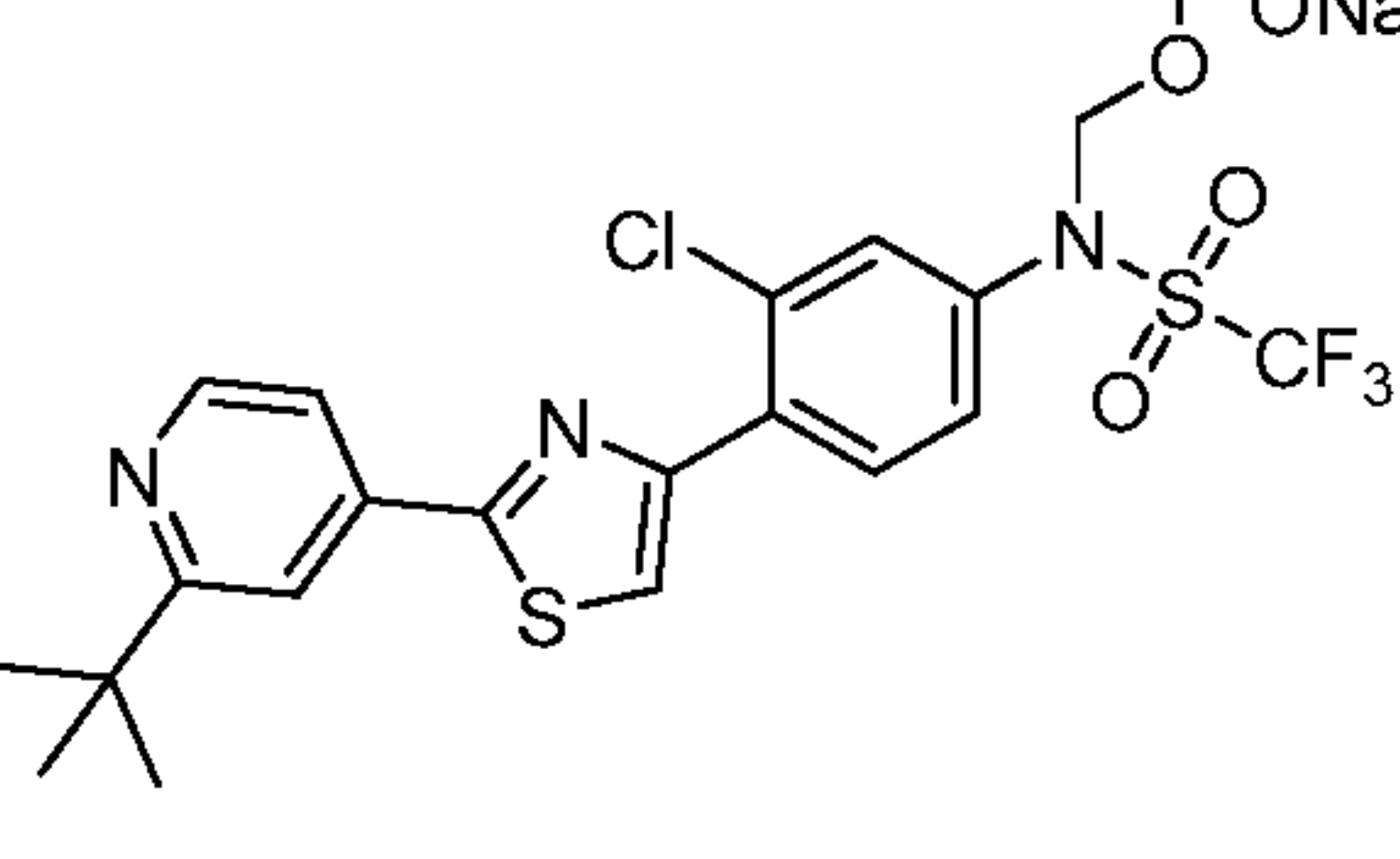
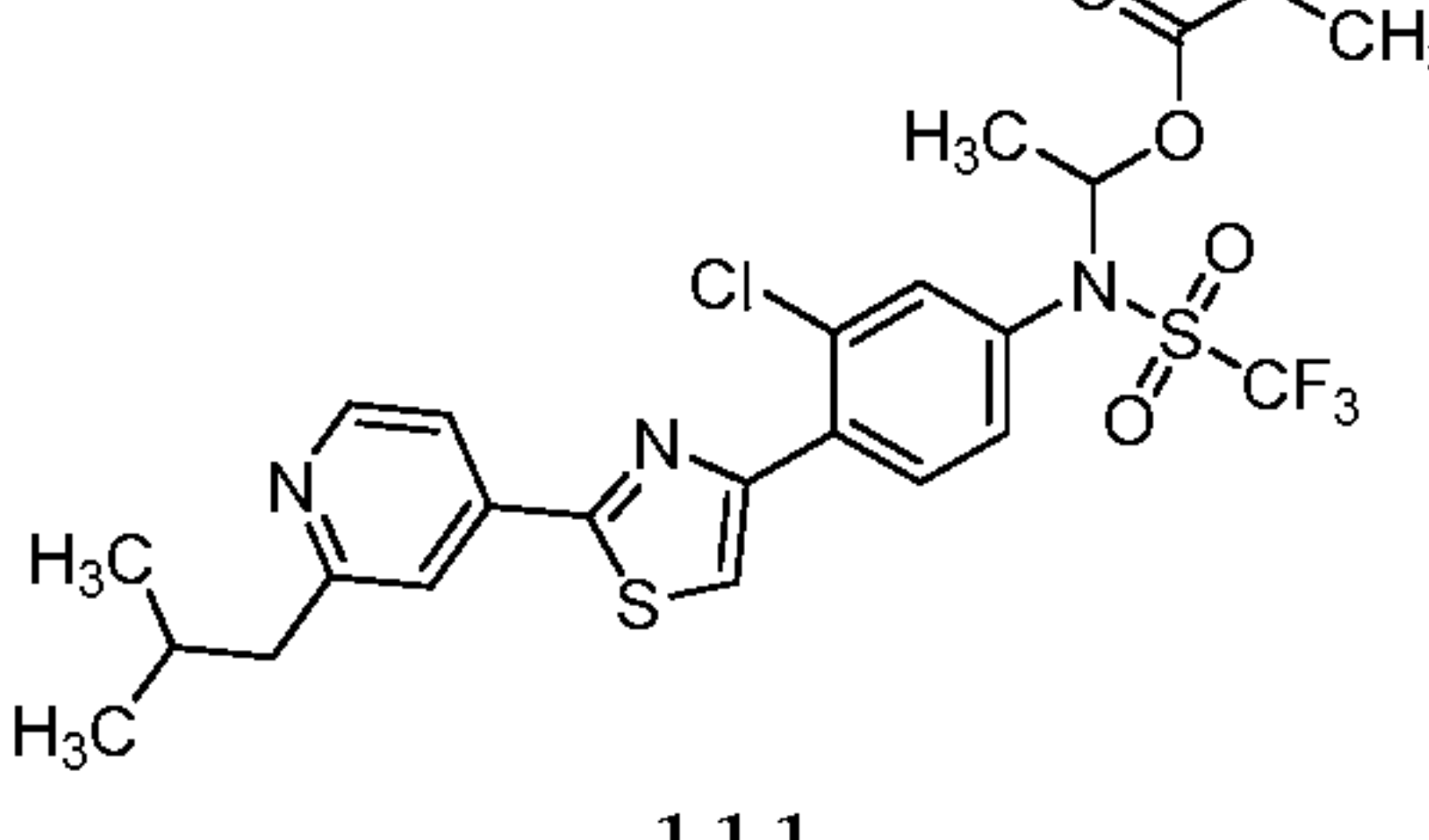
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 100	 01	 102
 103	 04	 105
 106	 07	 108
 109	 10	 111

Table 1

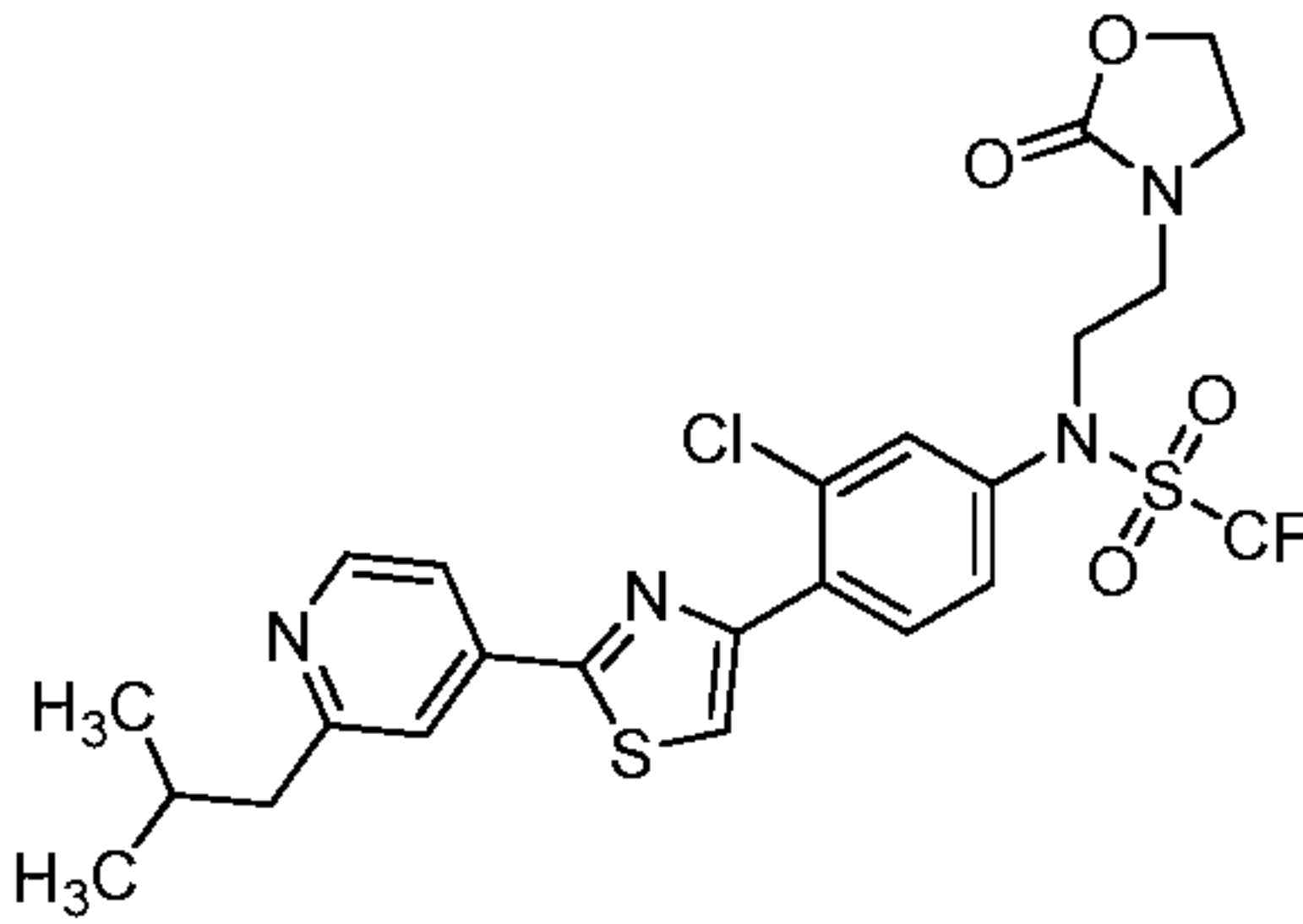
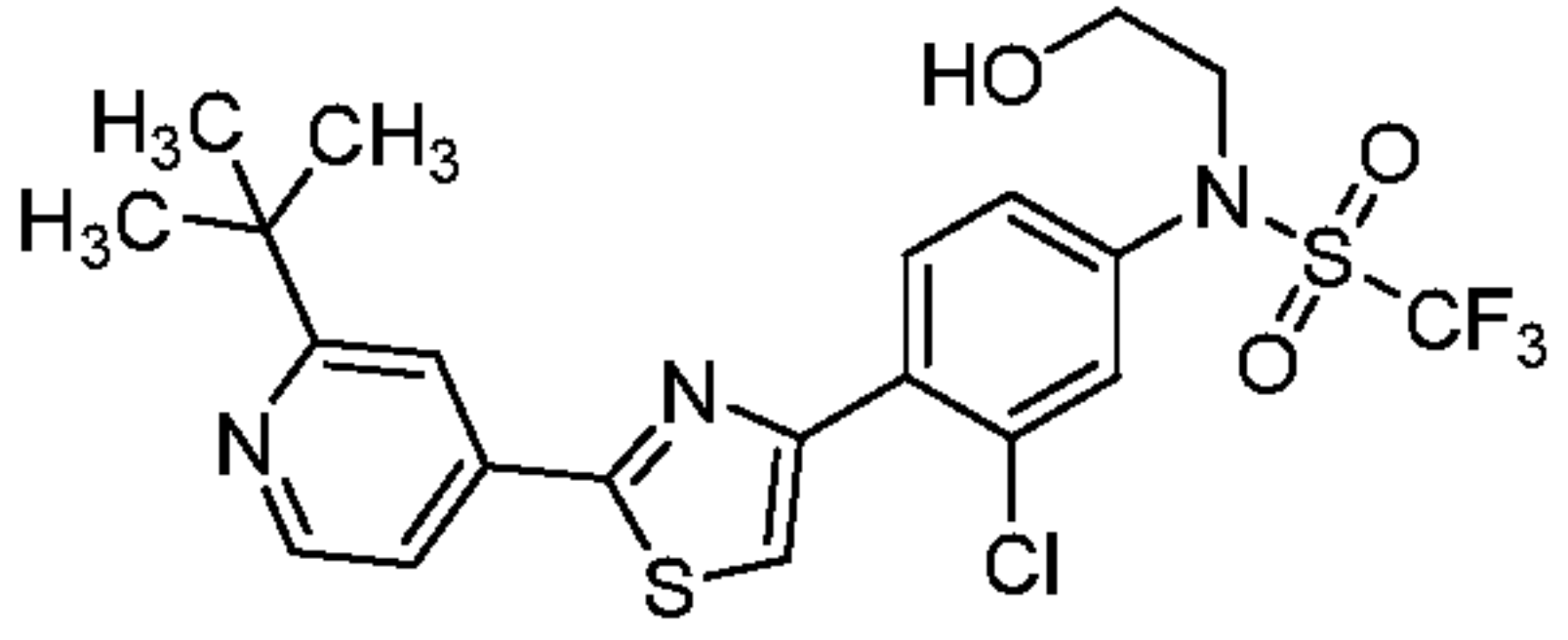
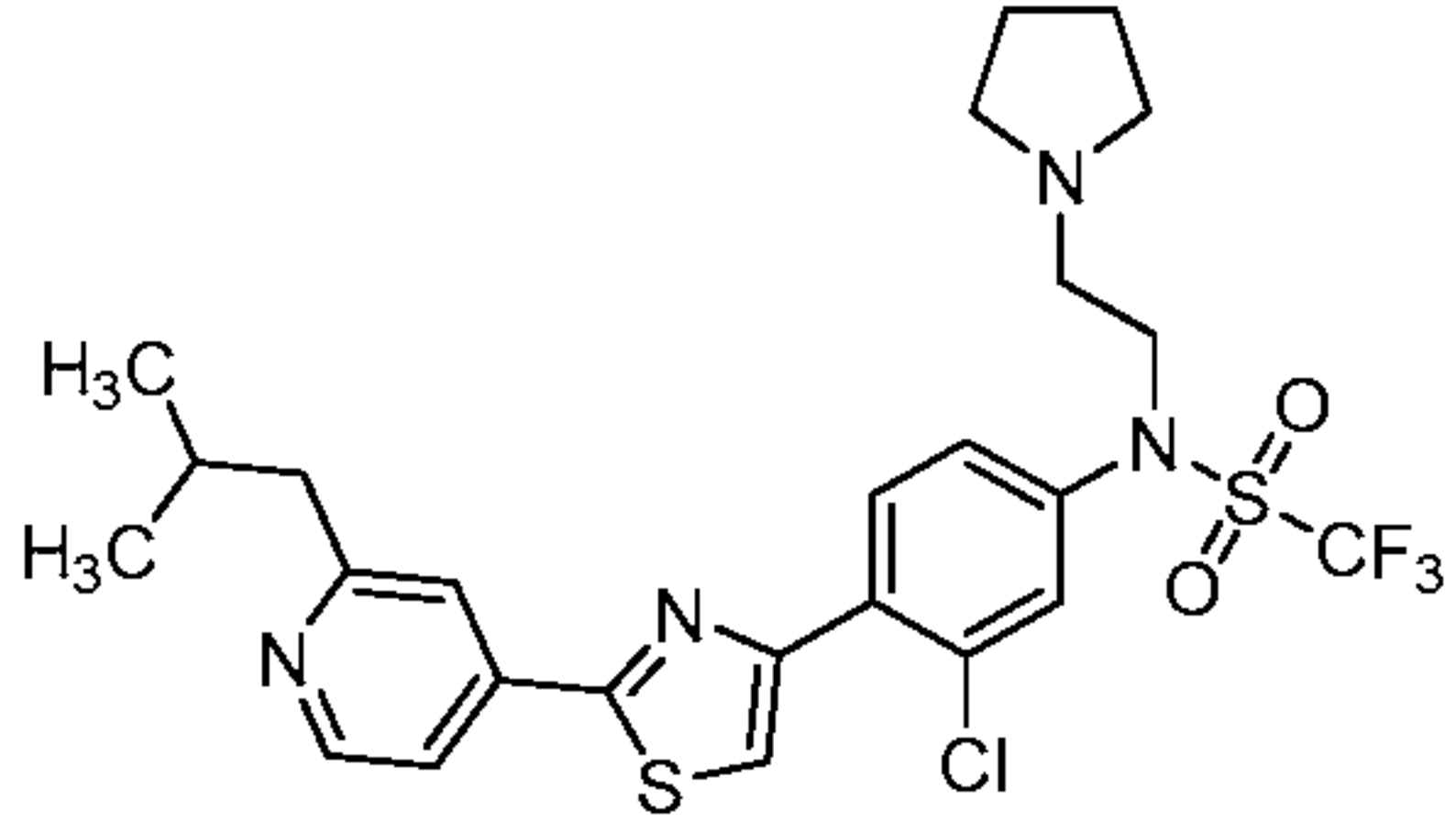
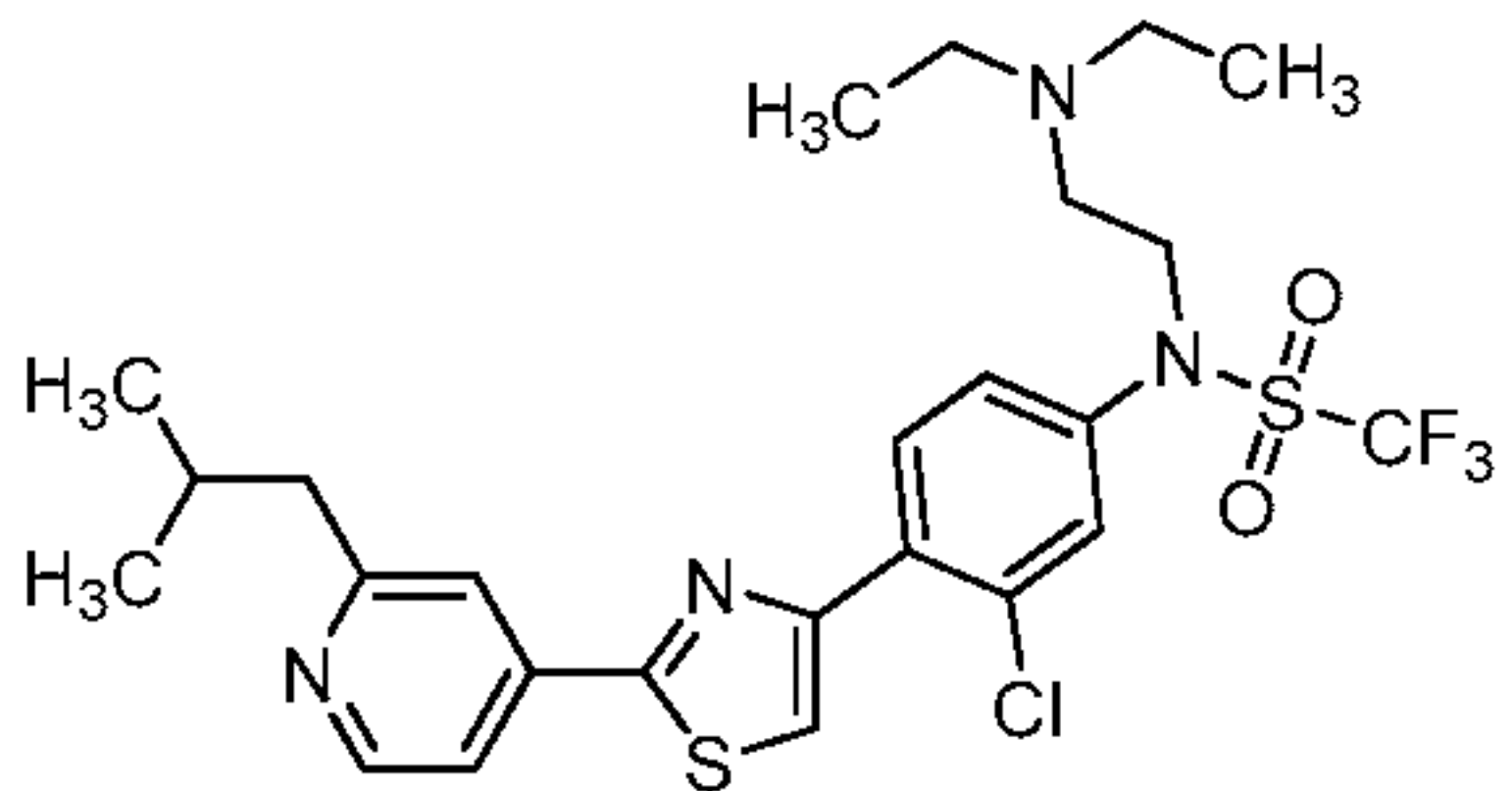
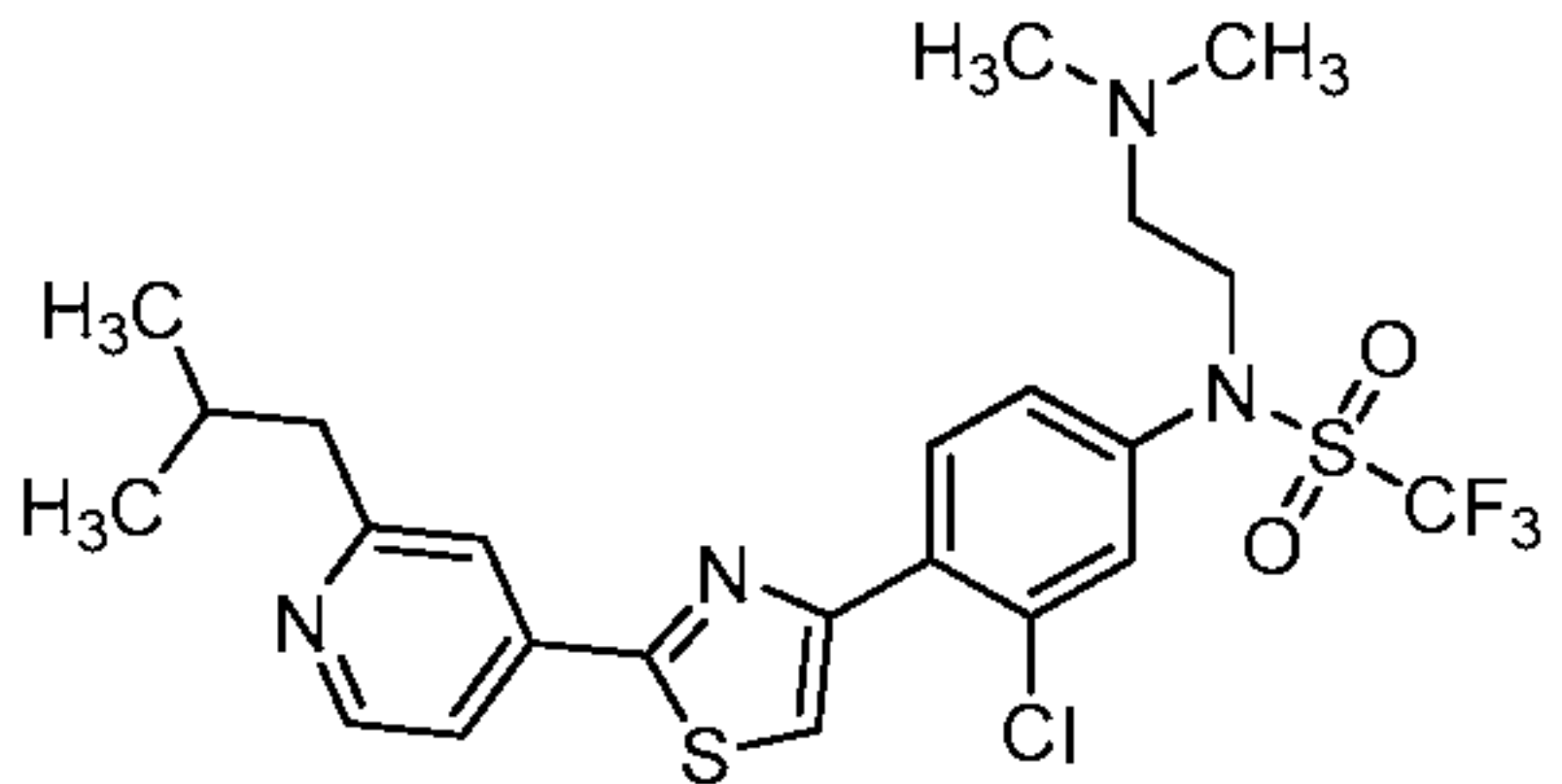
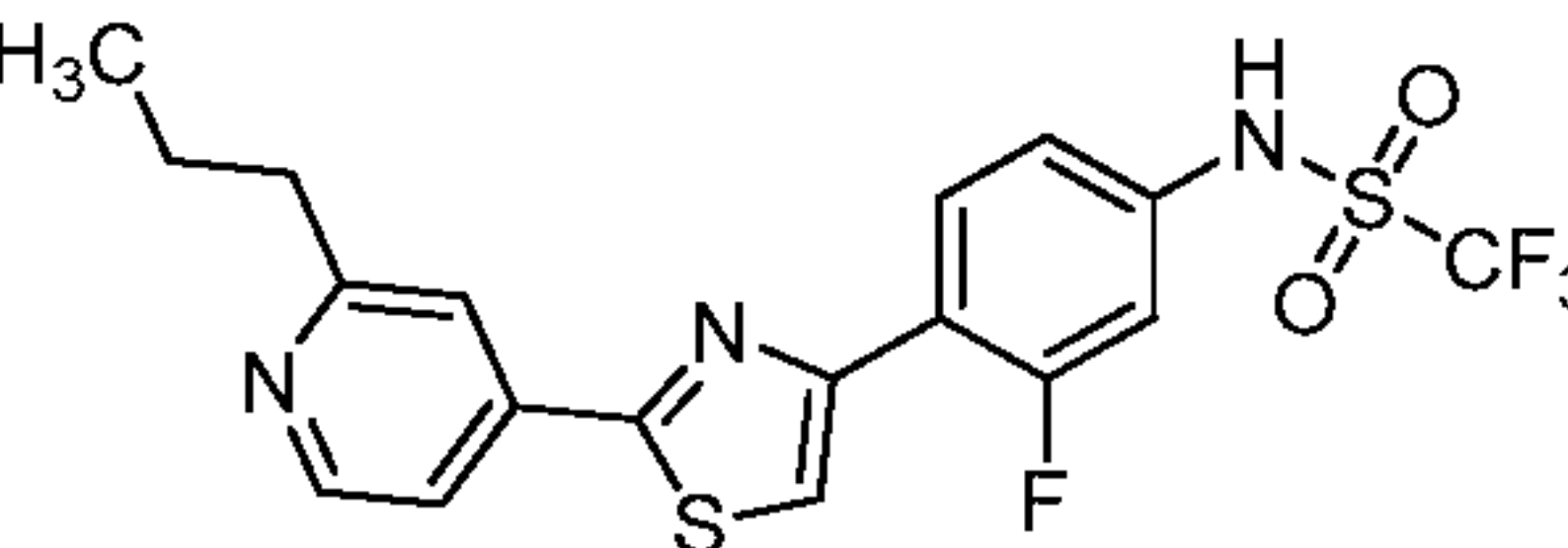
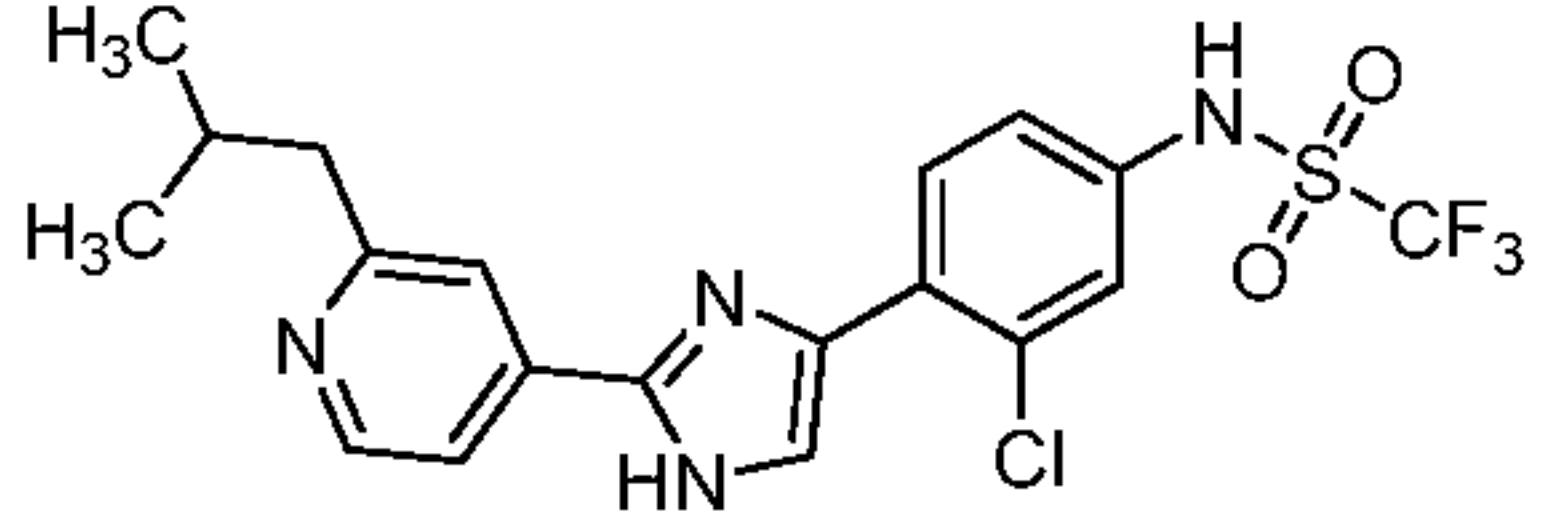
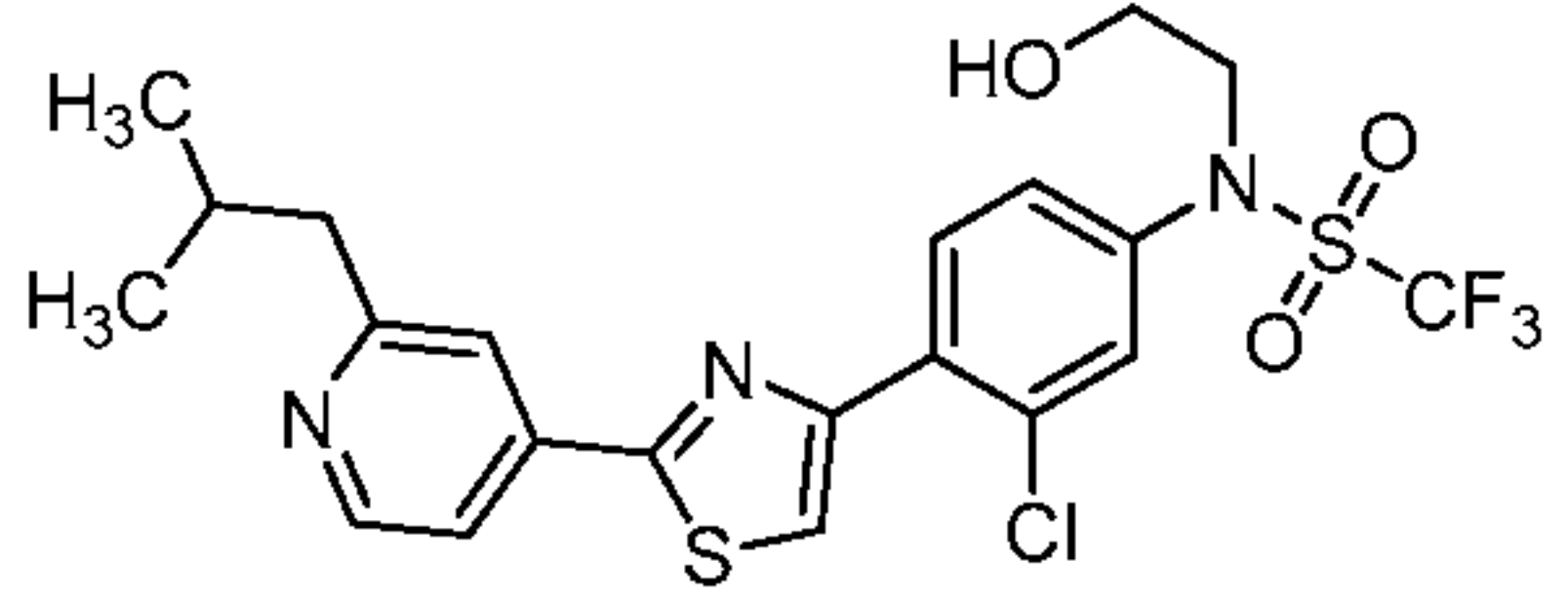
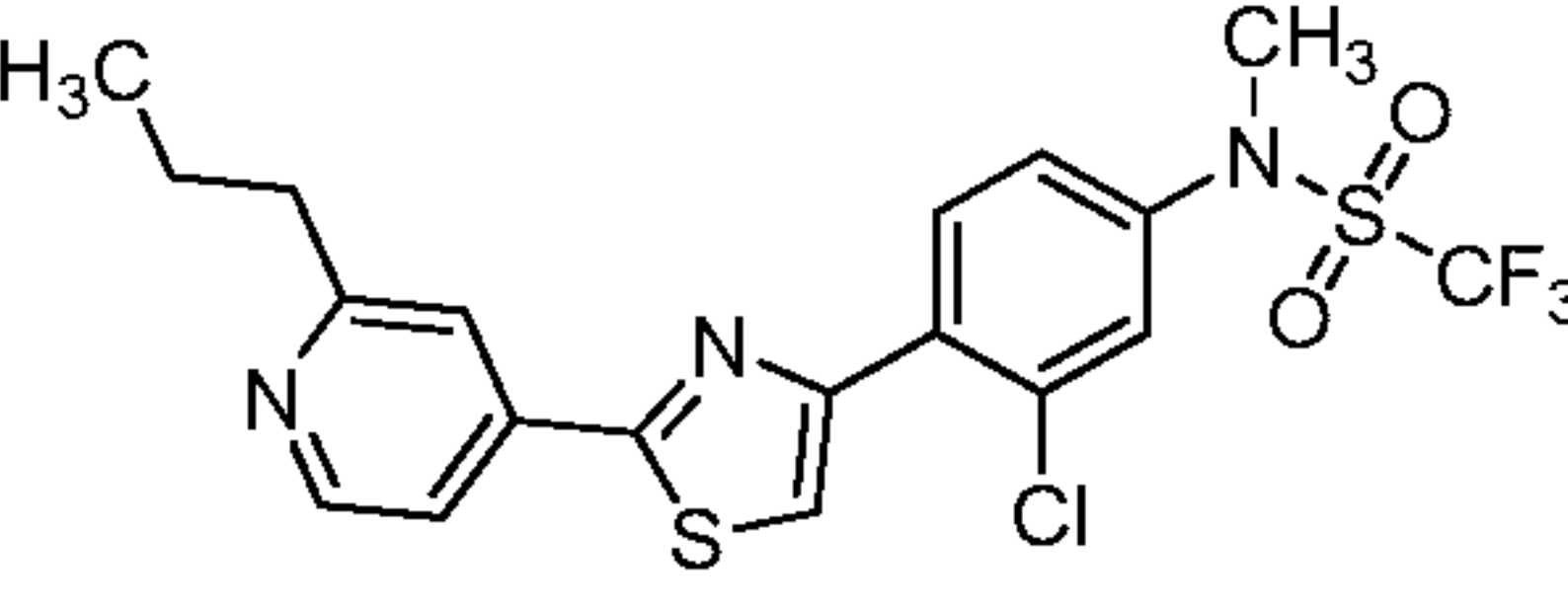
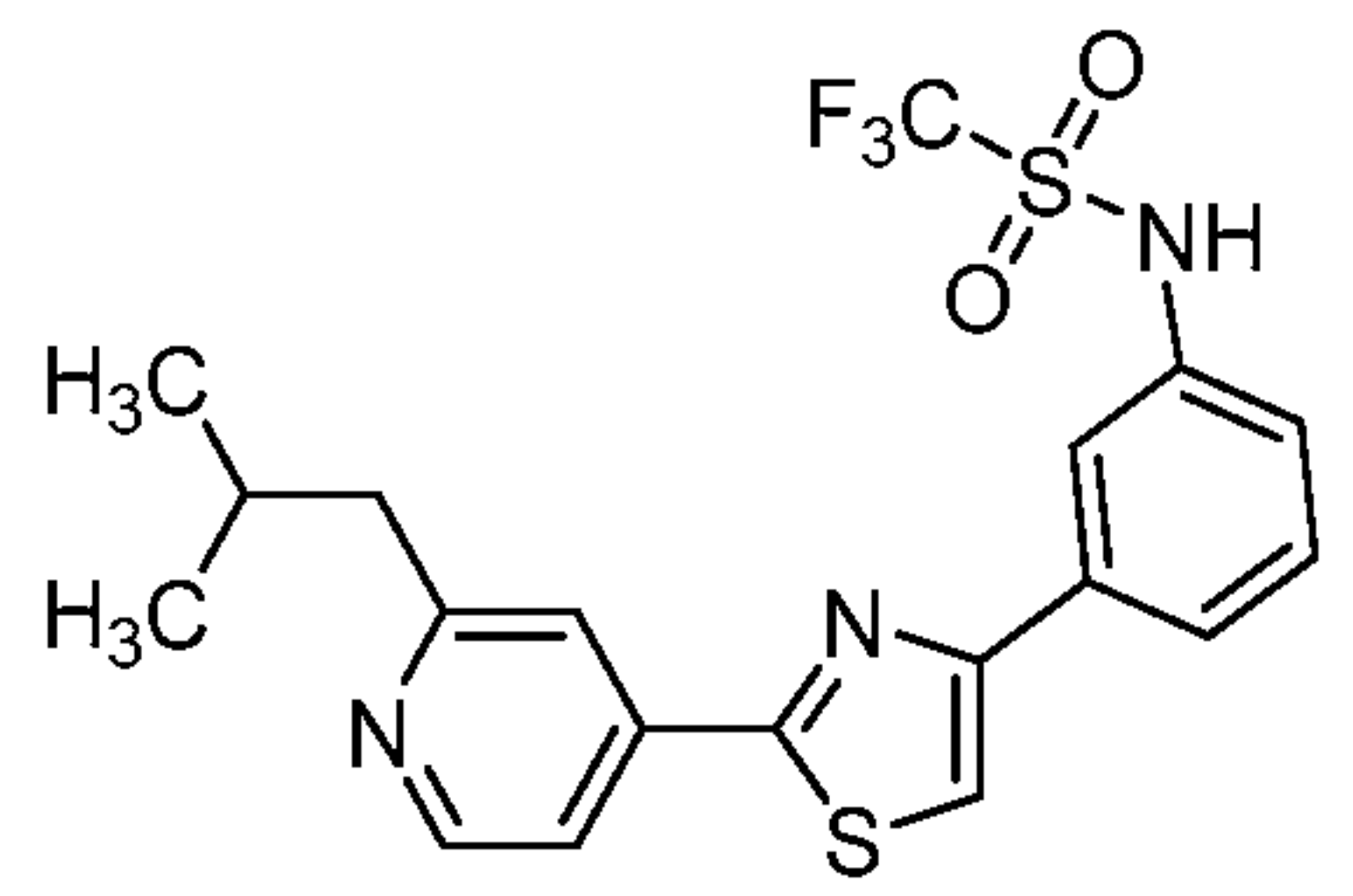
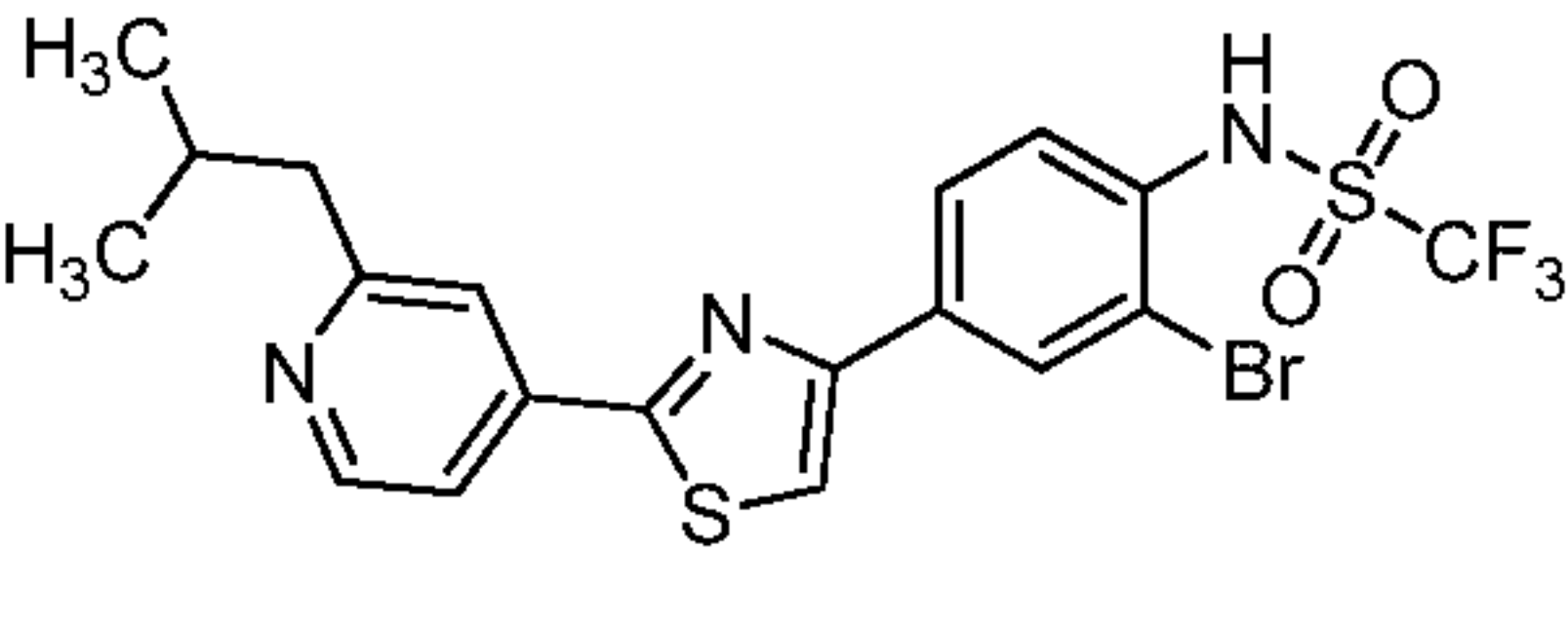
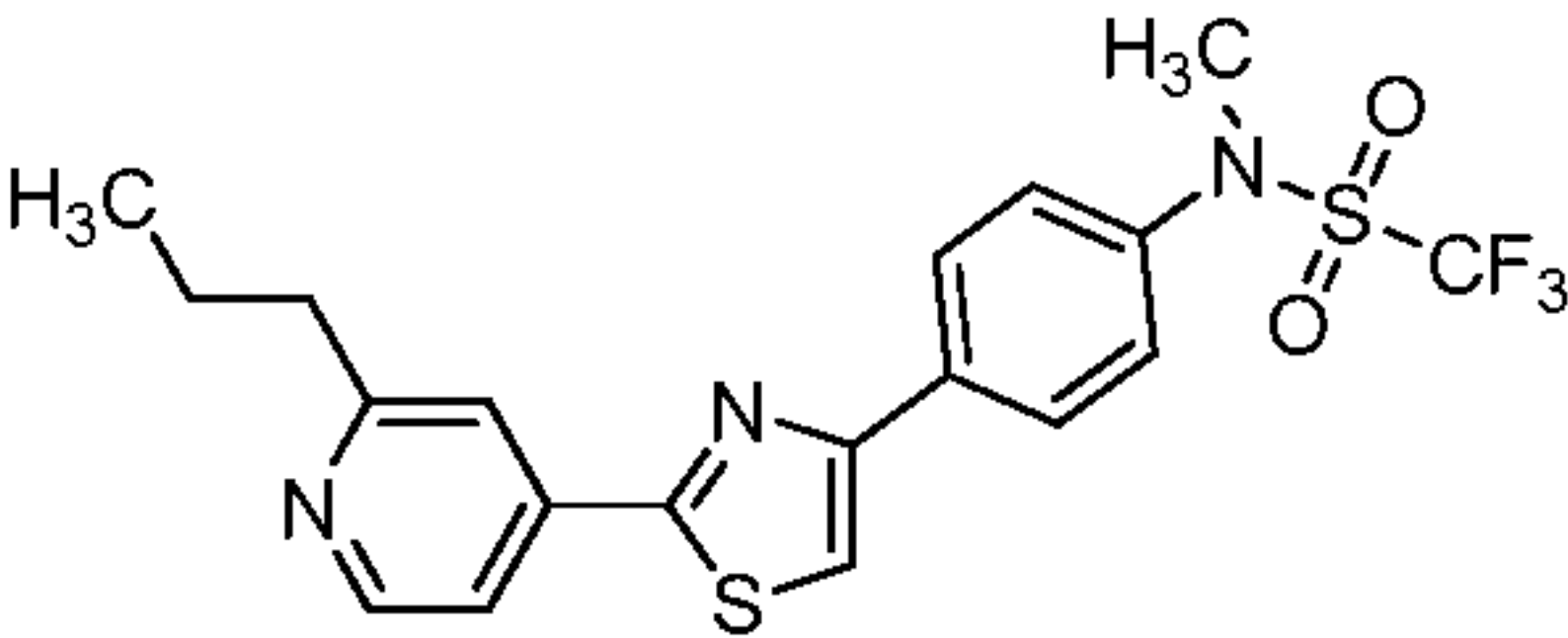
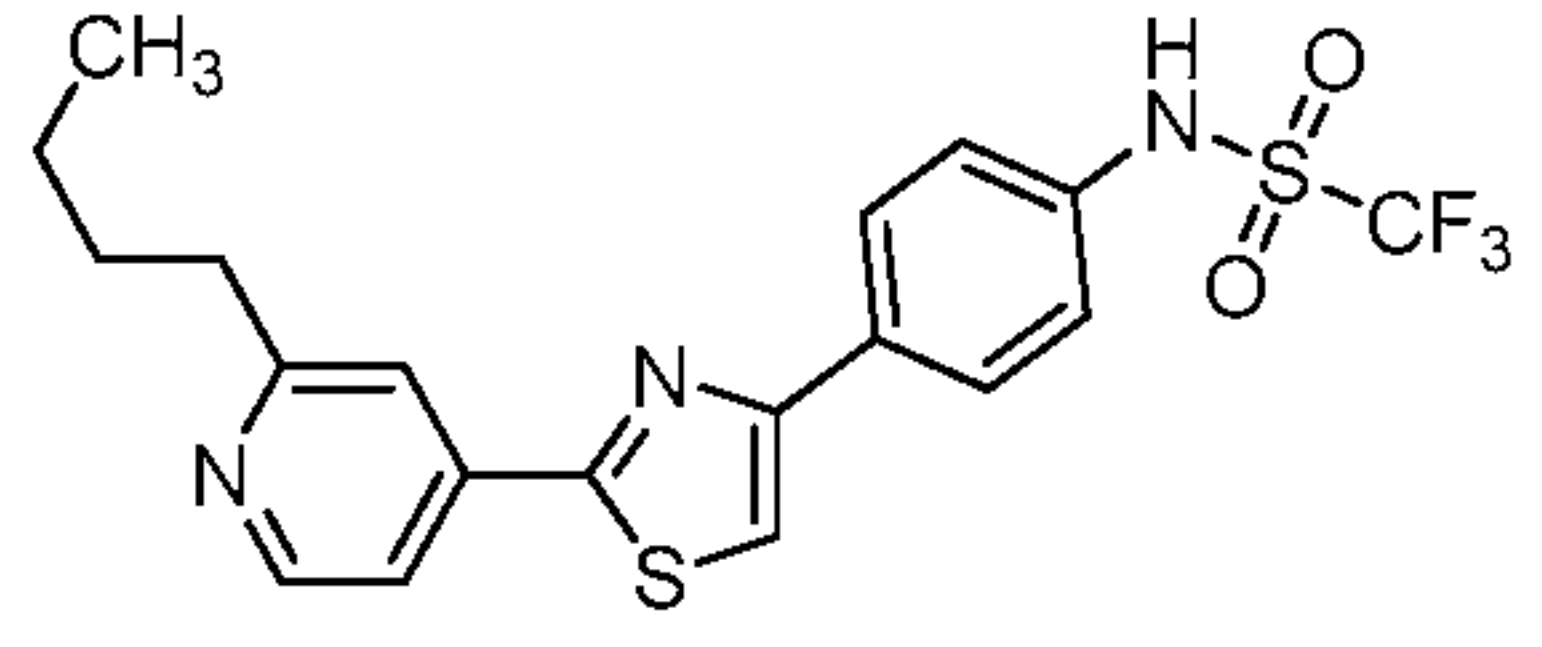
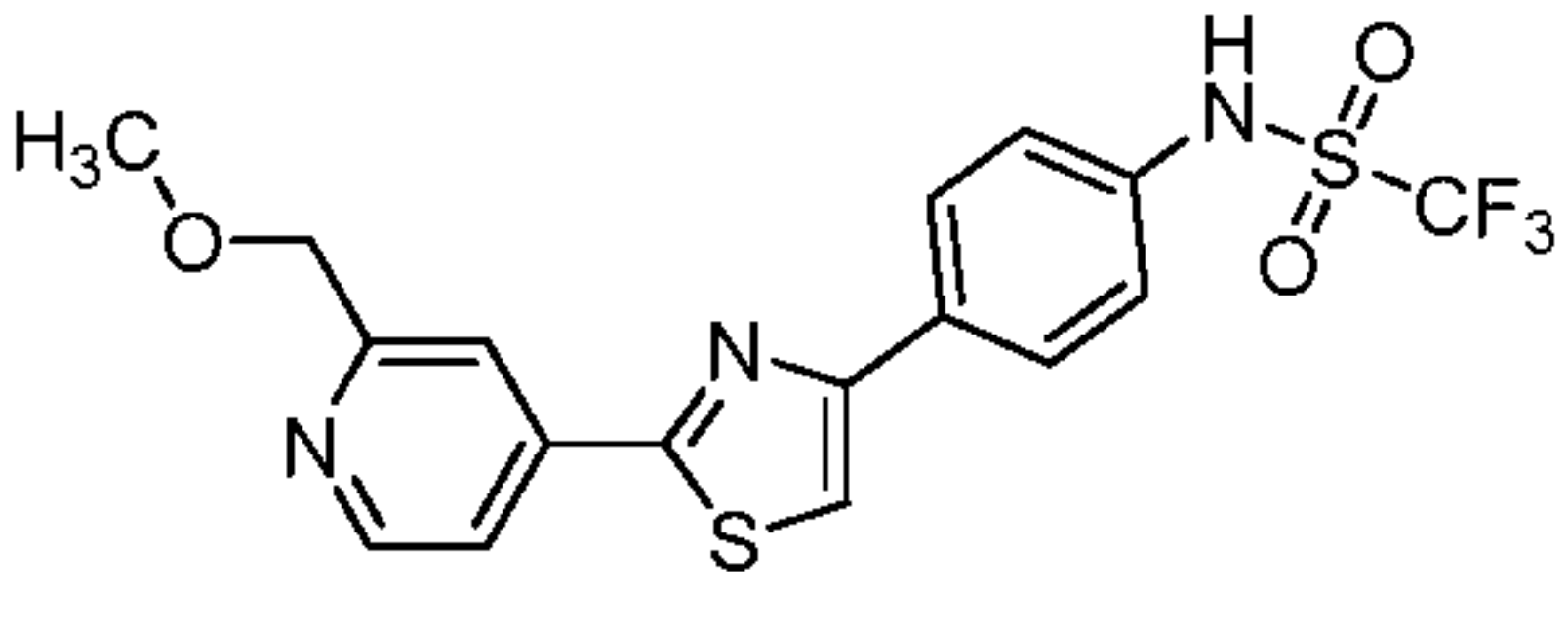
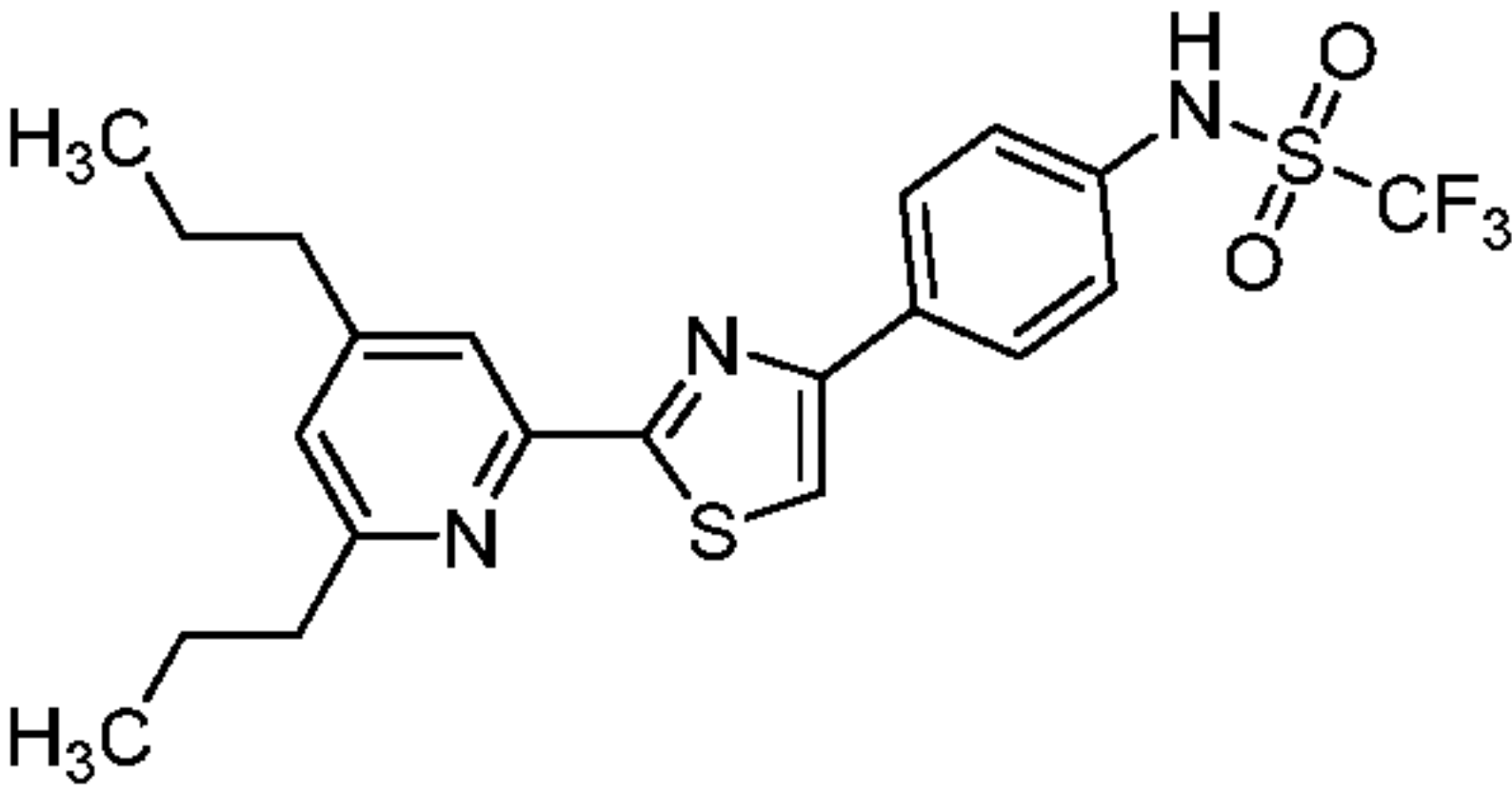
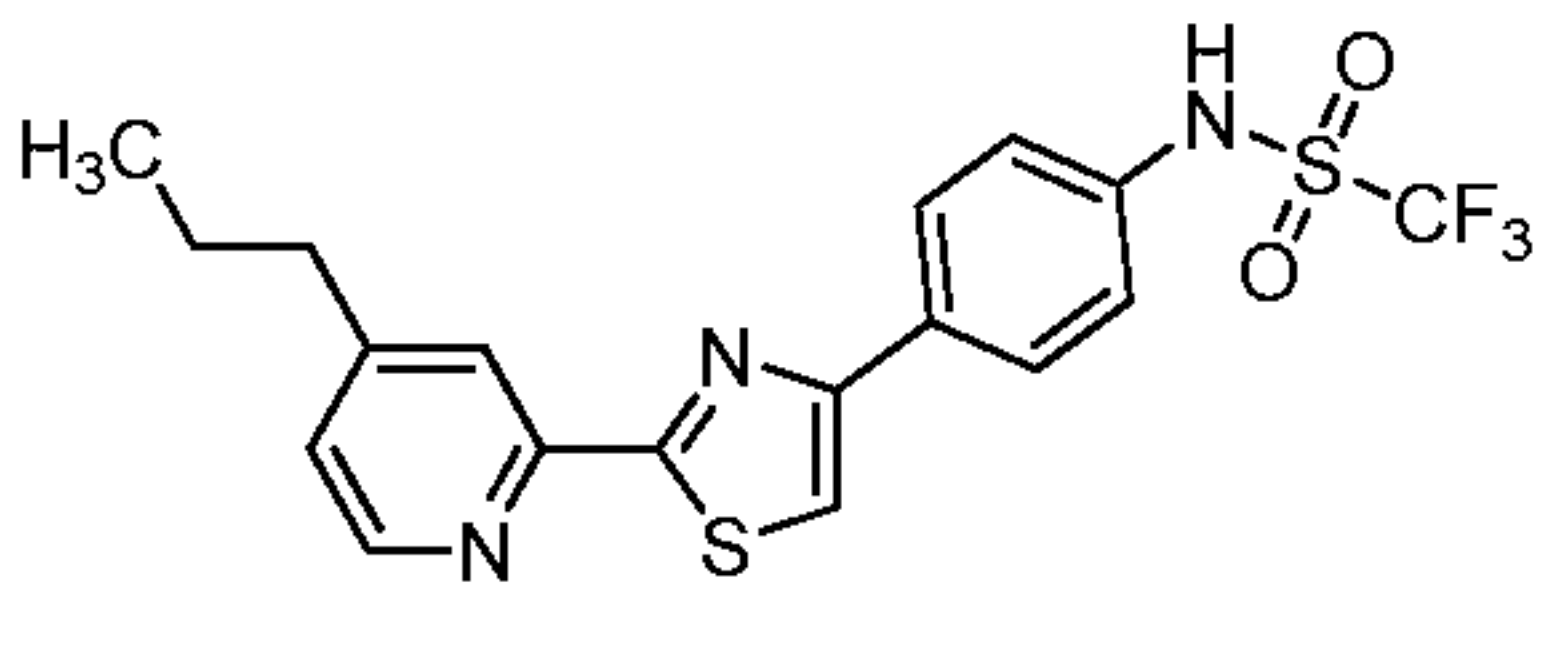
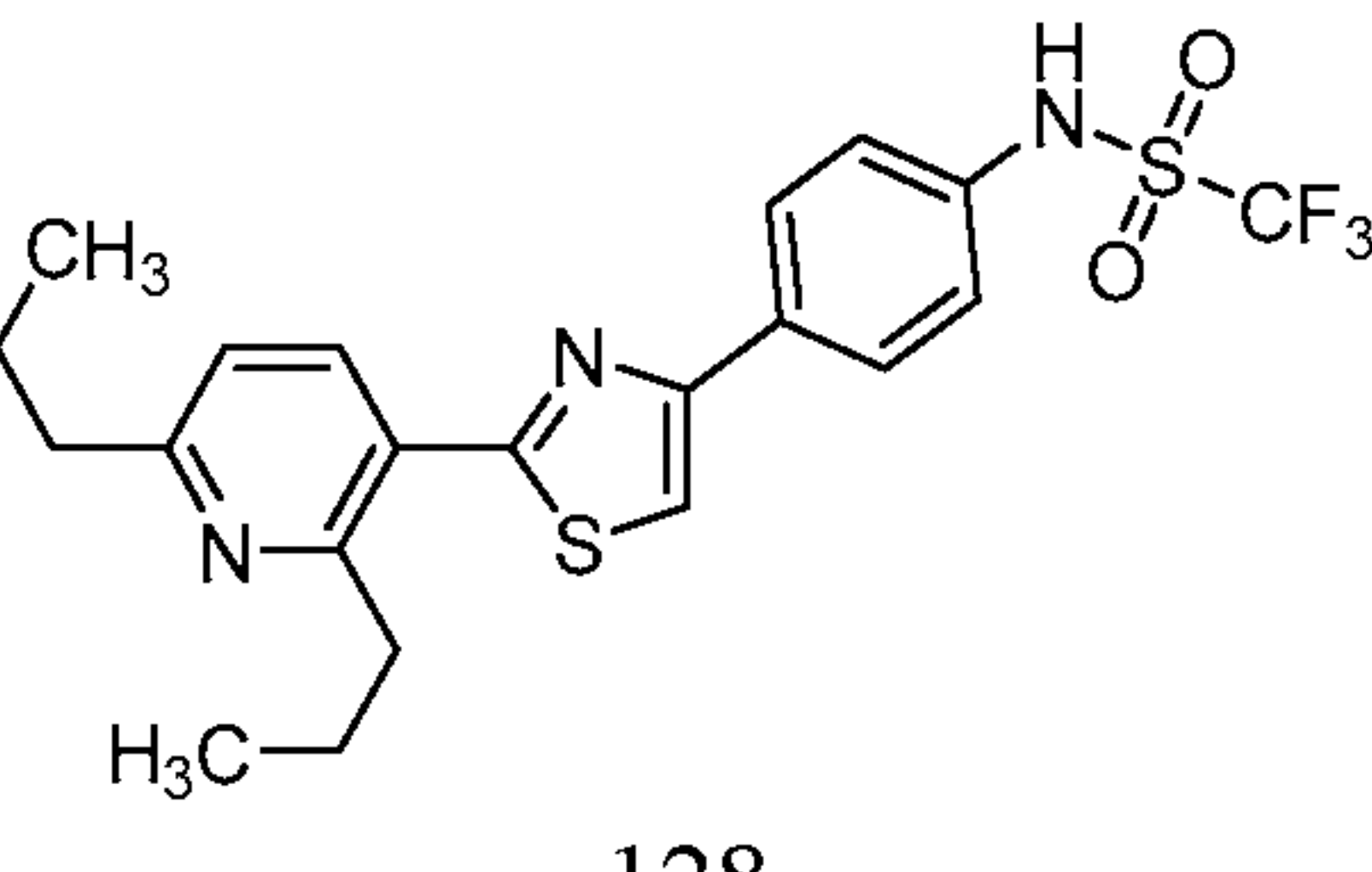
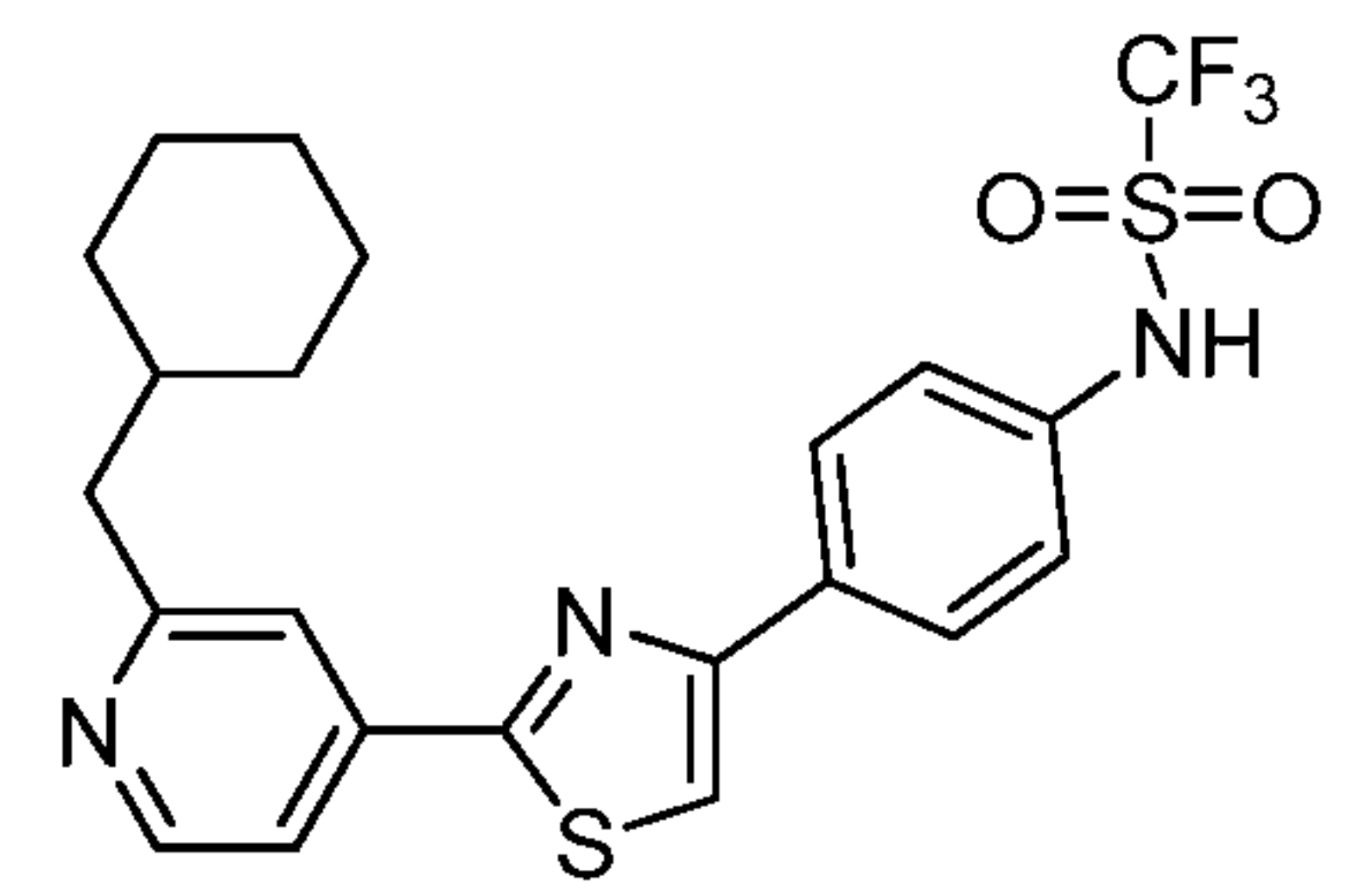
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 115	 116	 117
 118	 119	 120
 121	 122	 123
 124	 125	 126
 127	 128	 129

Table 1

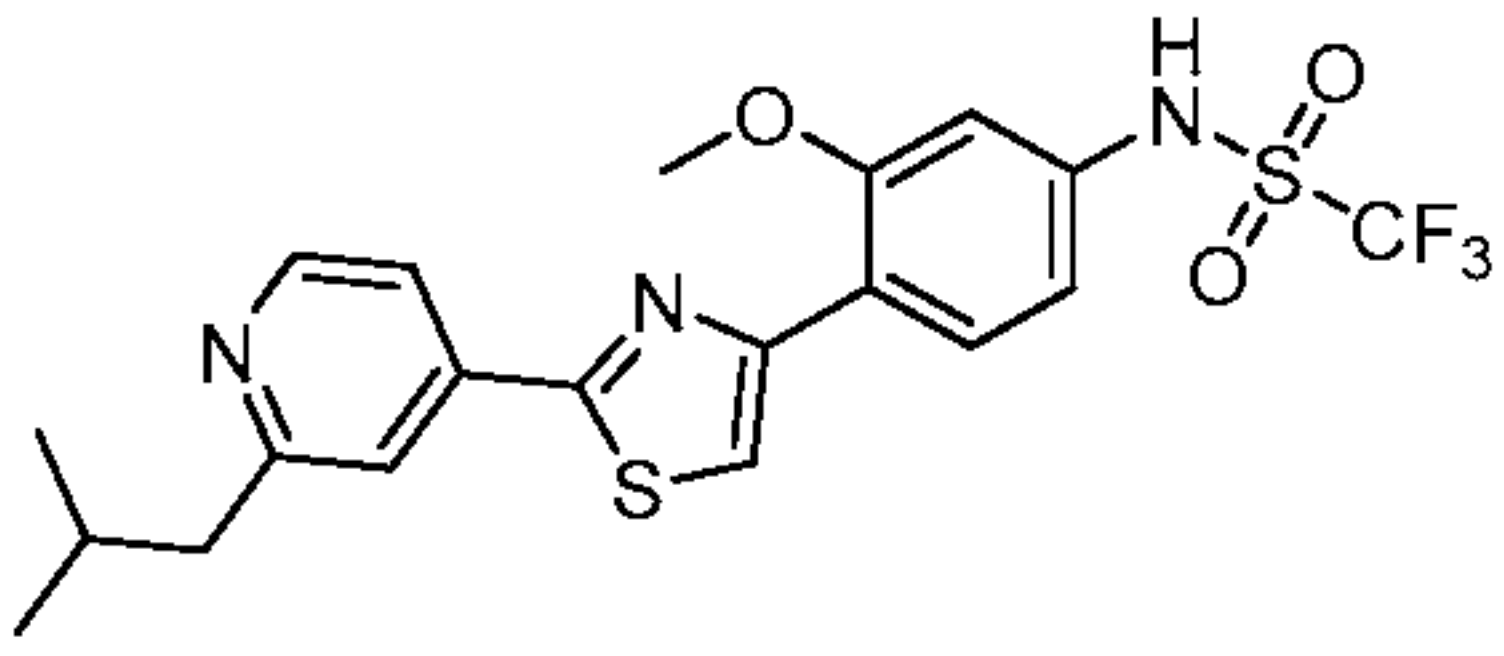
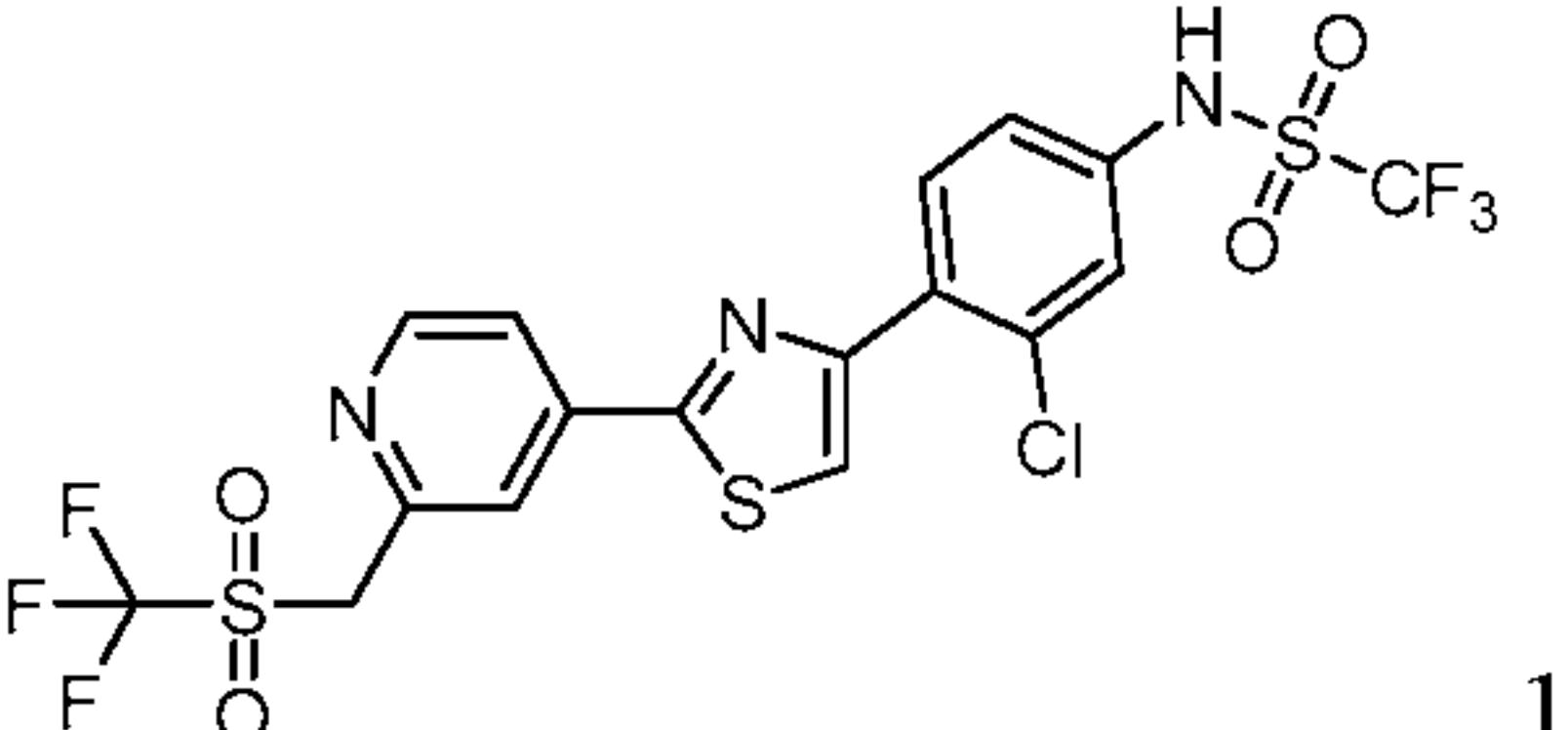
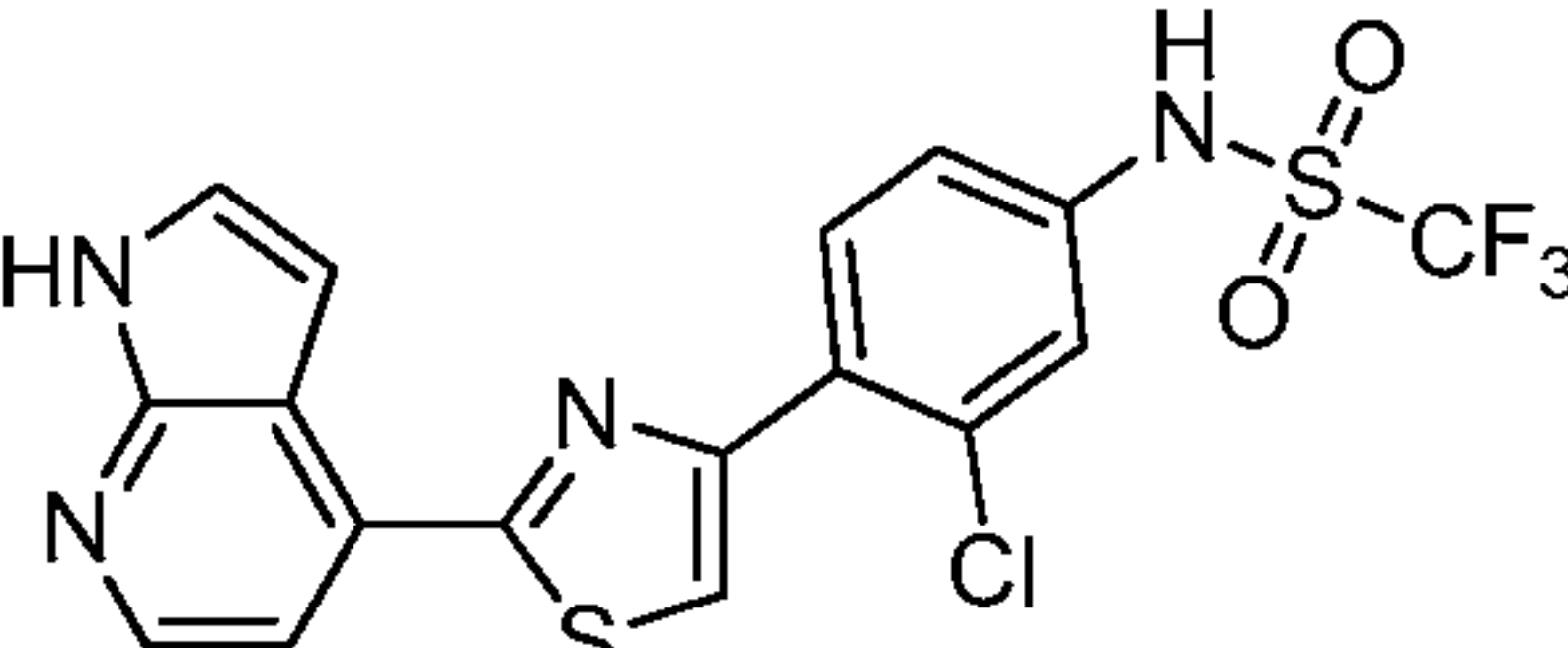
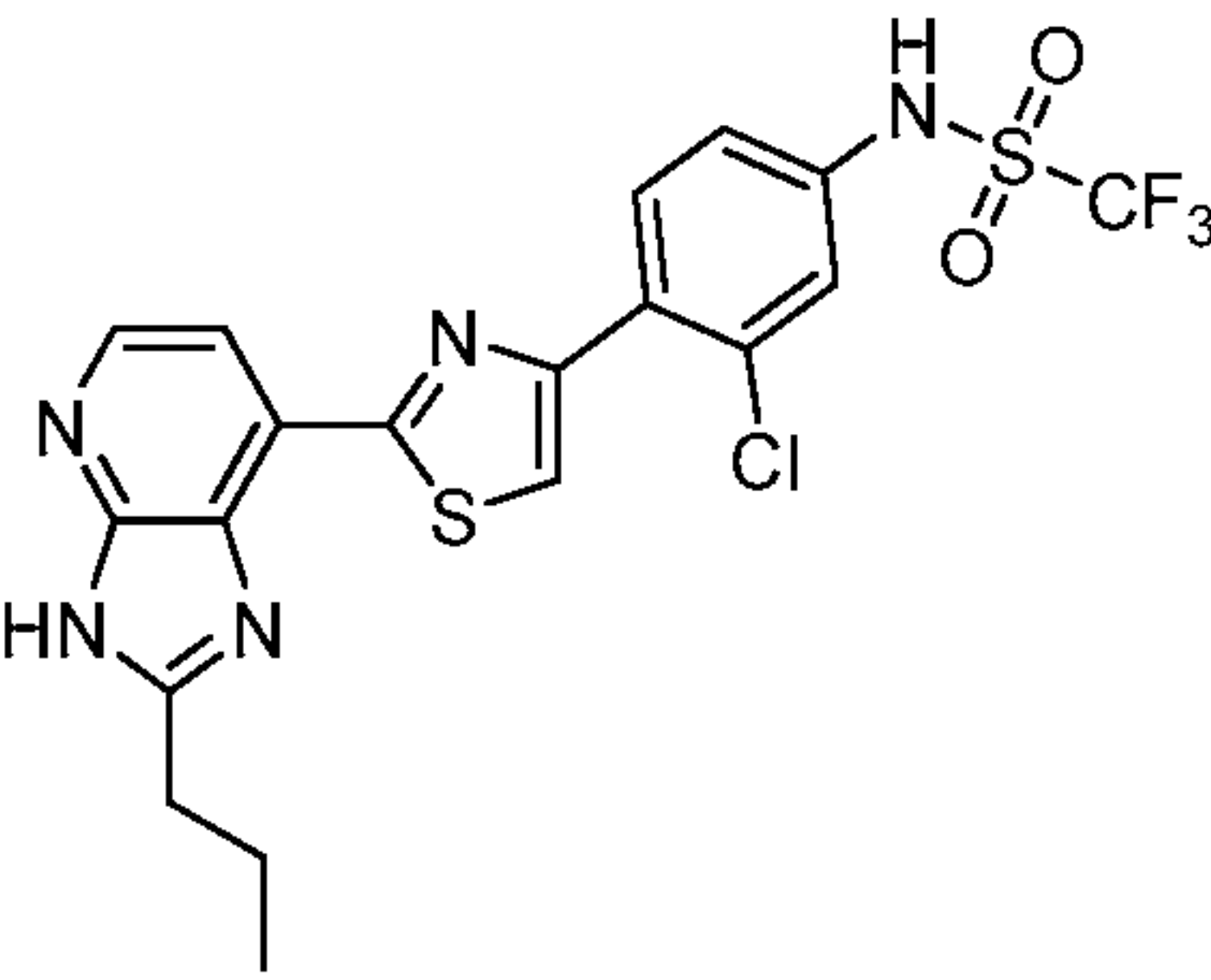
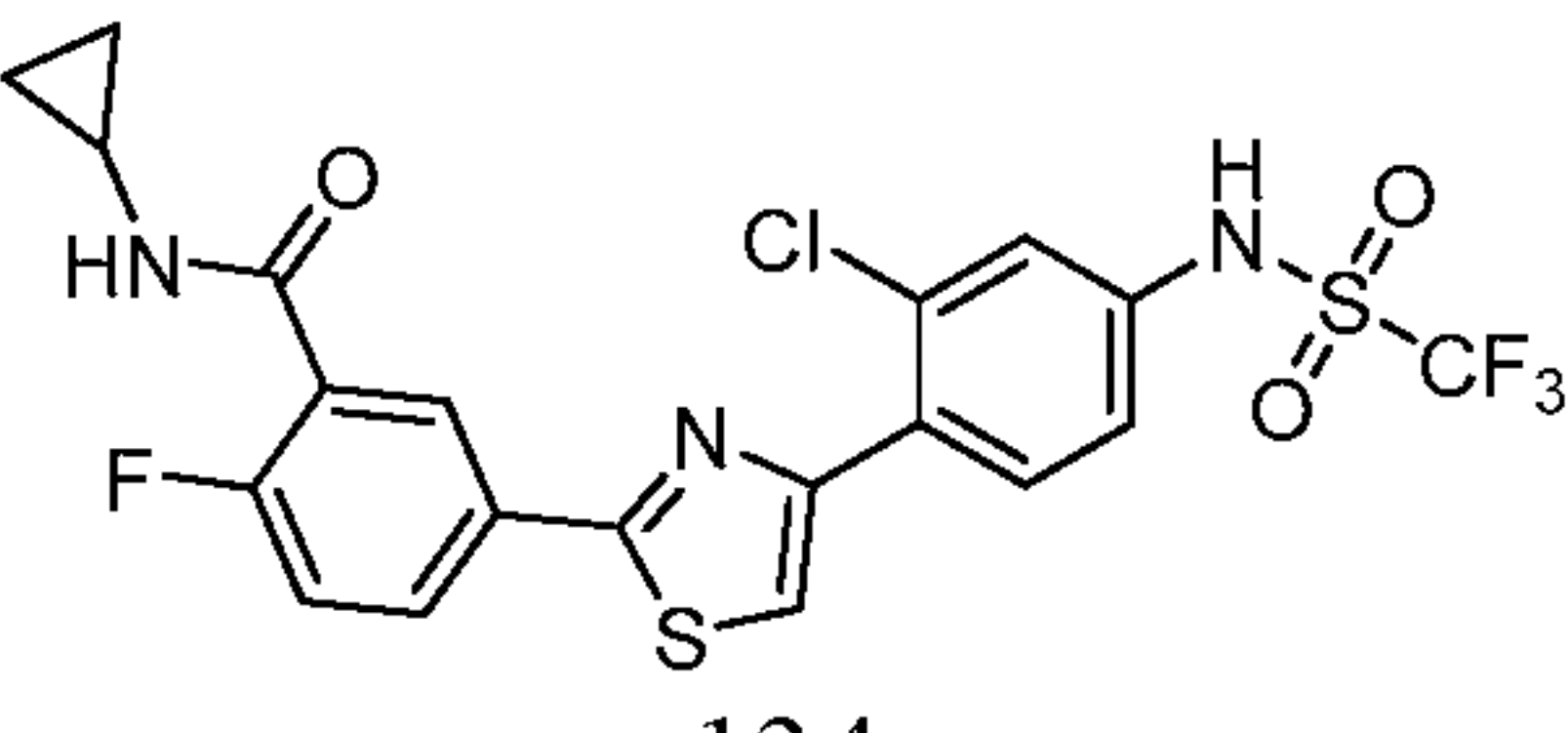
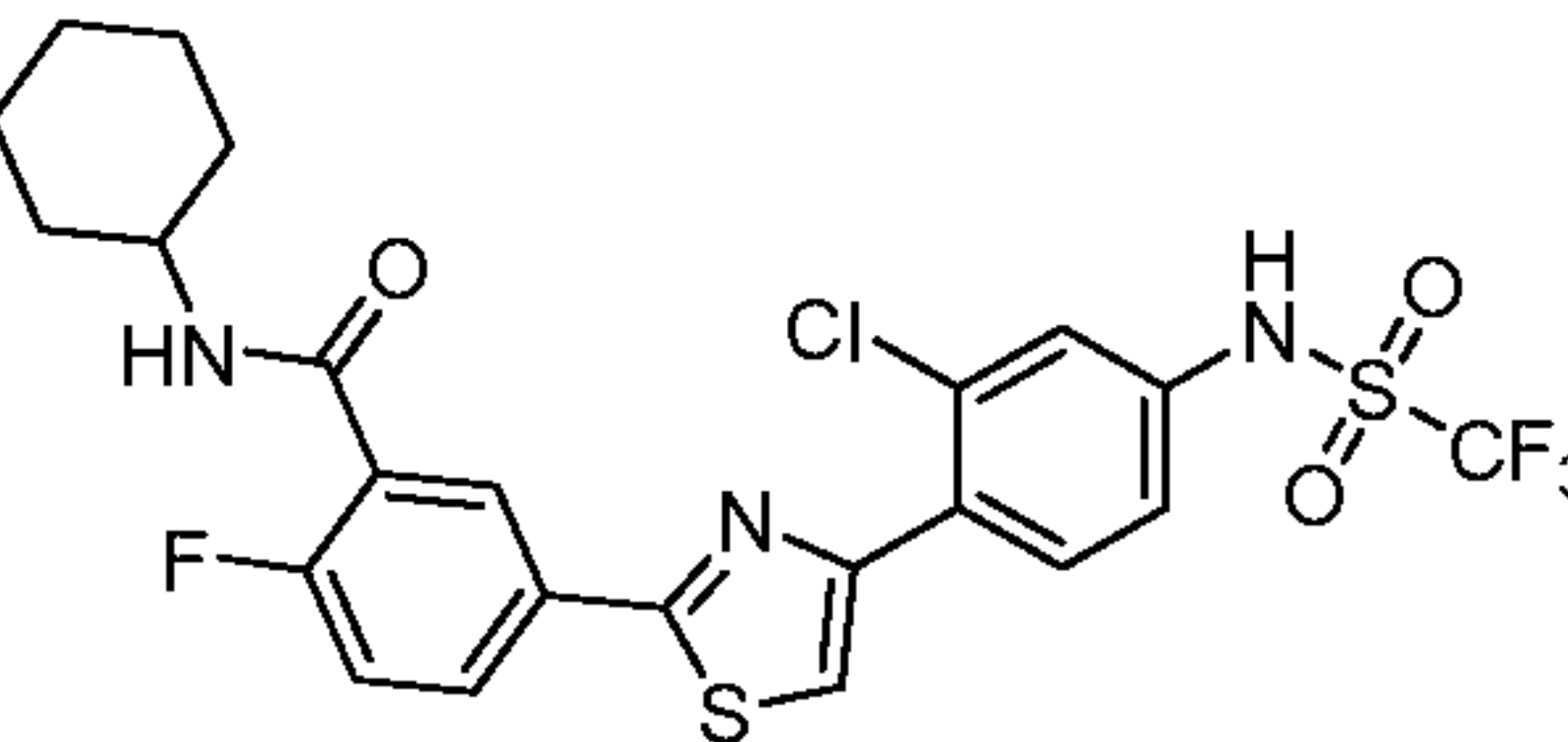
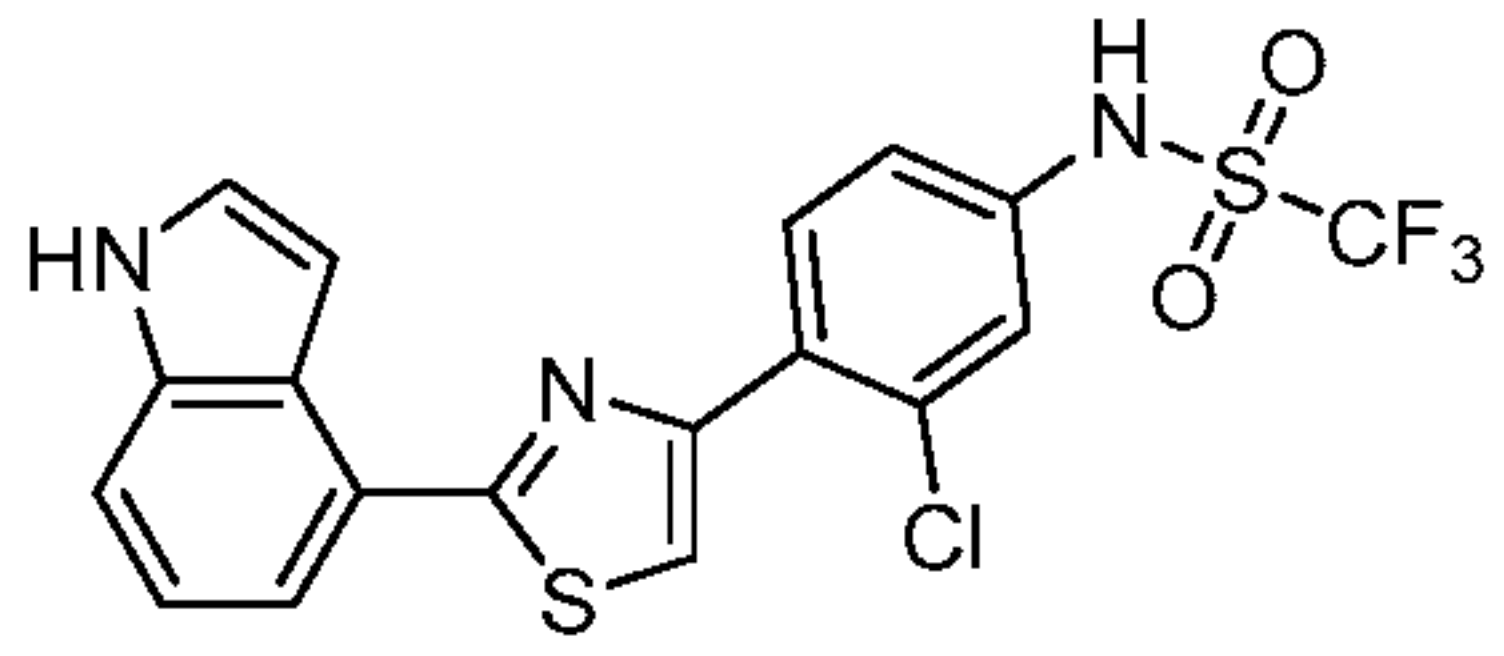
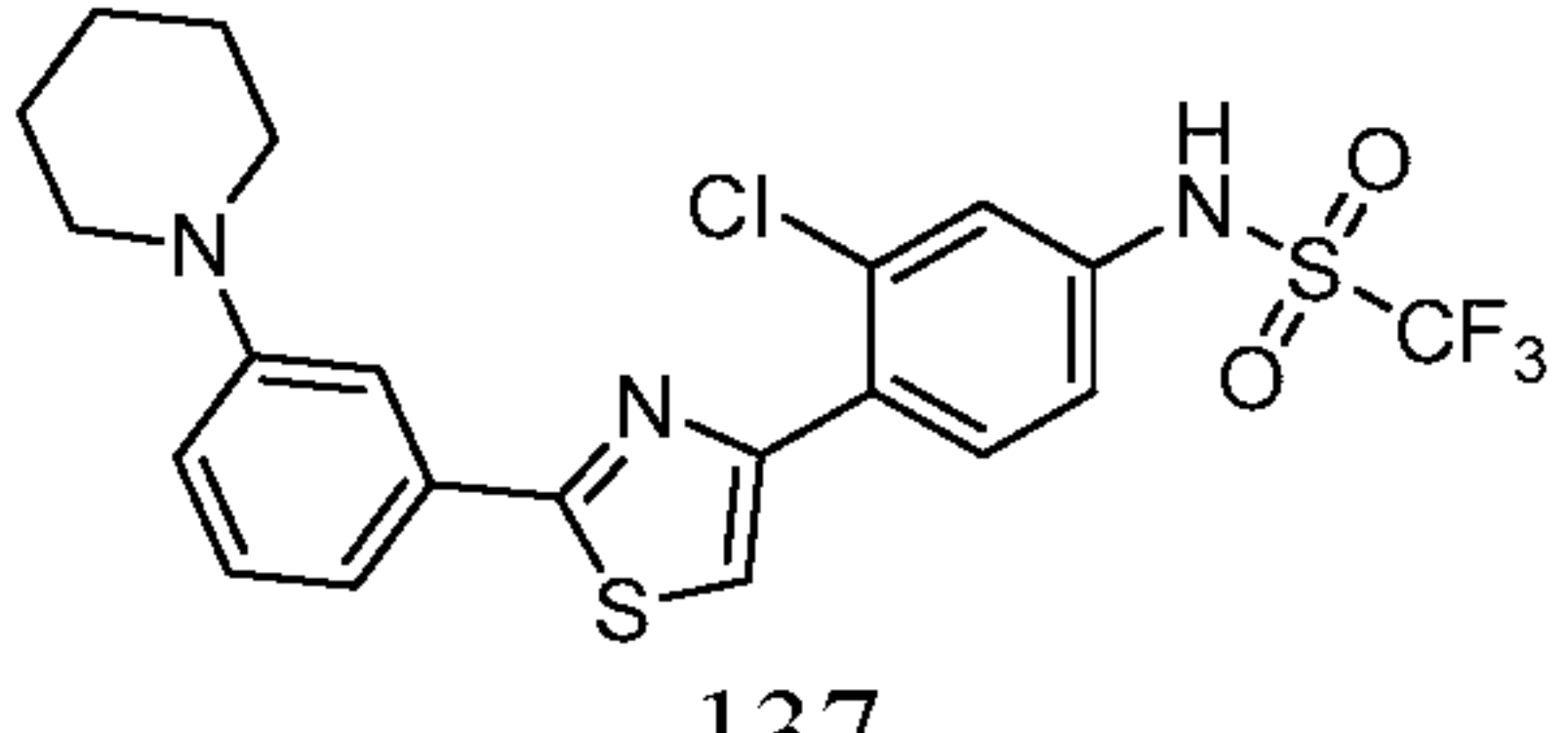
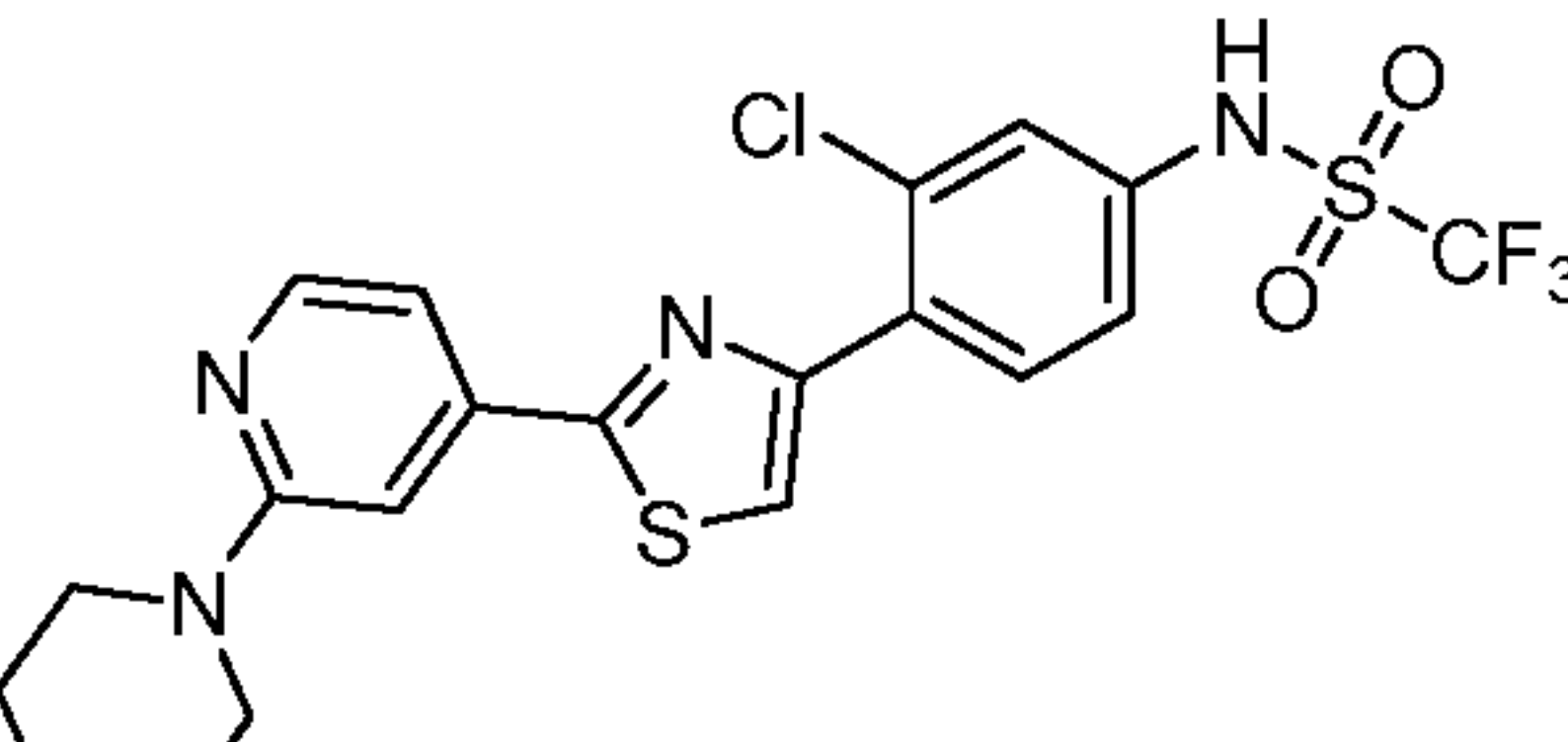
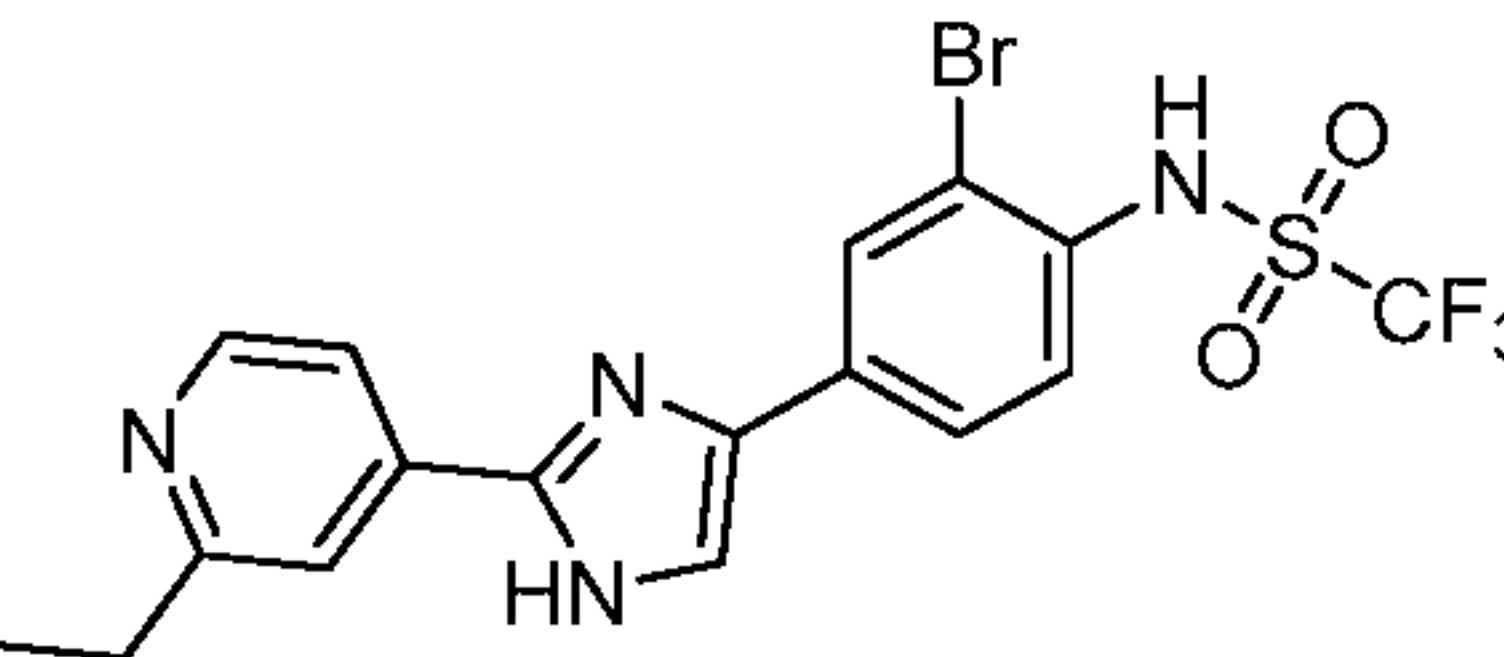
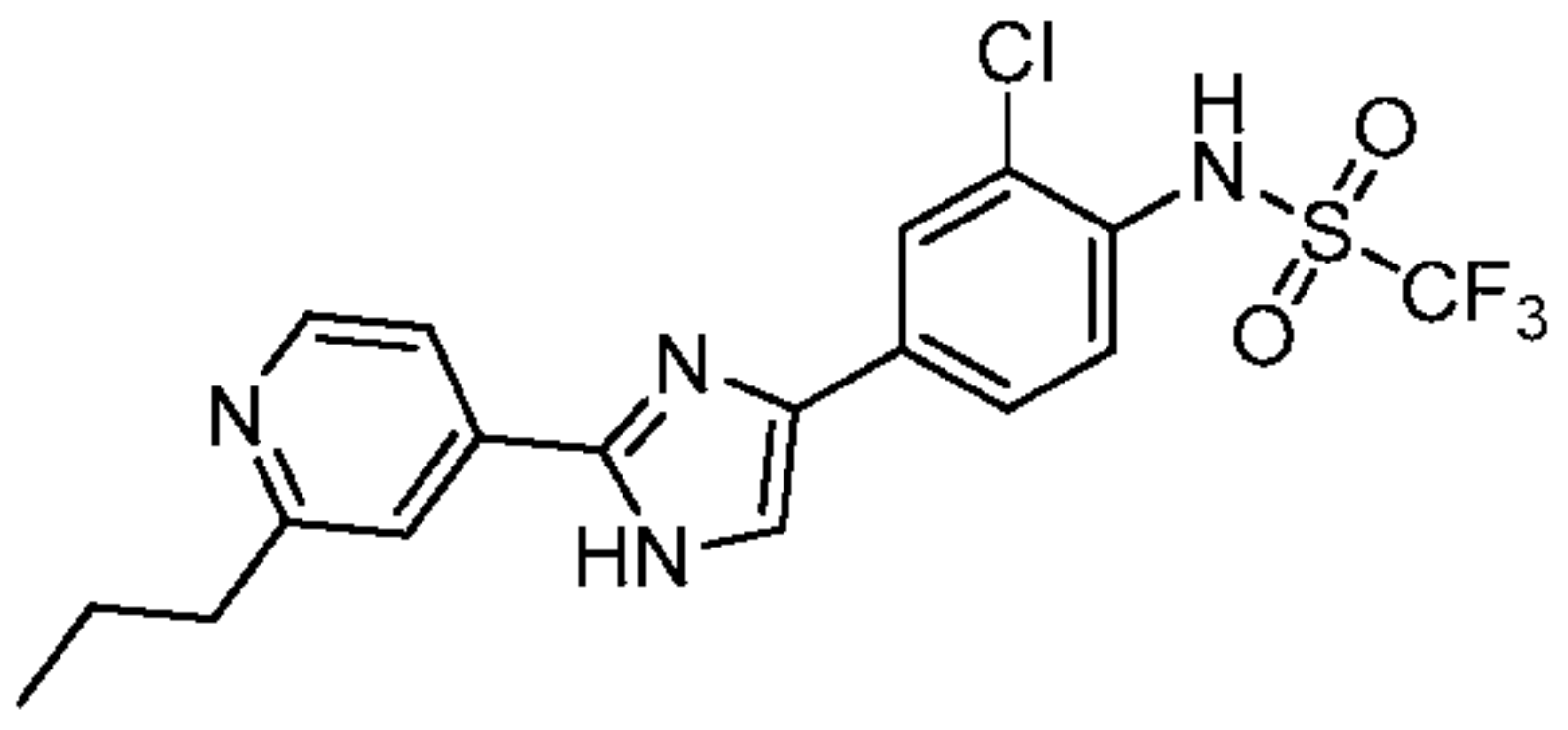
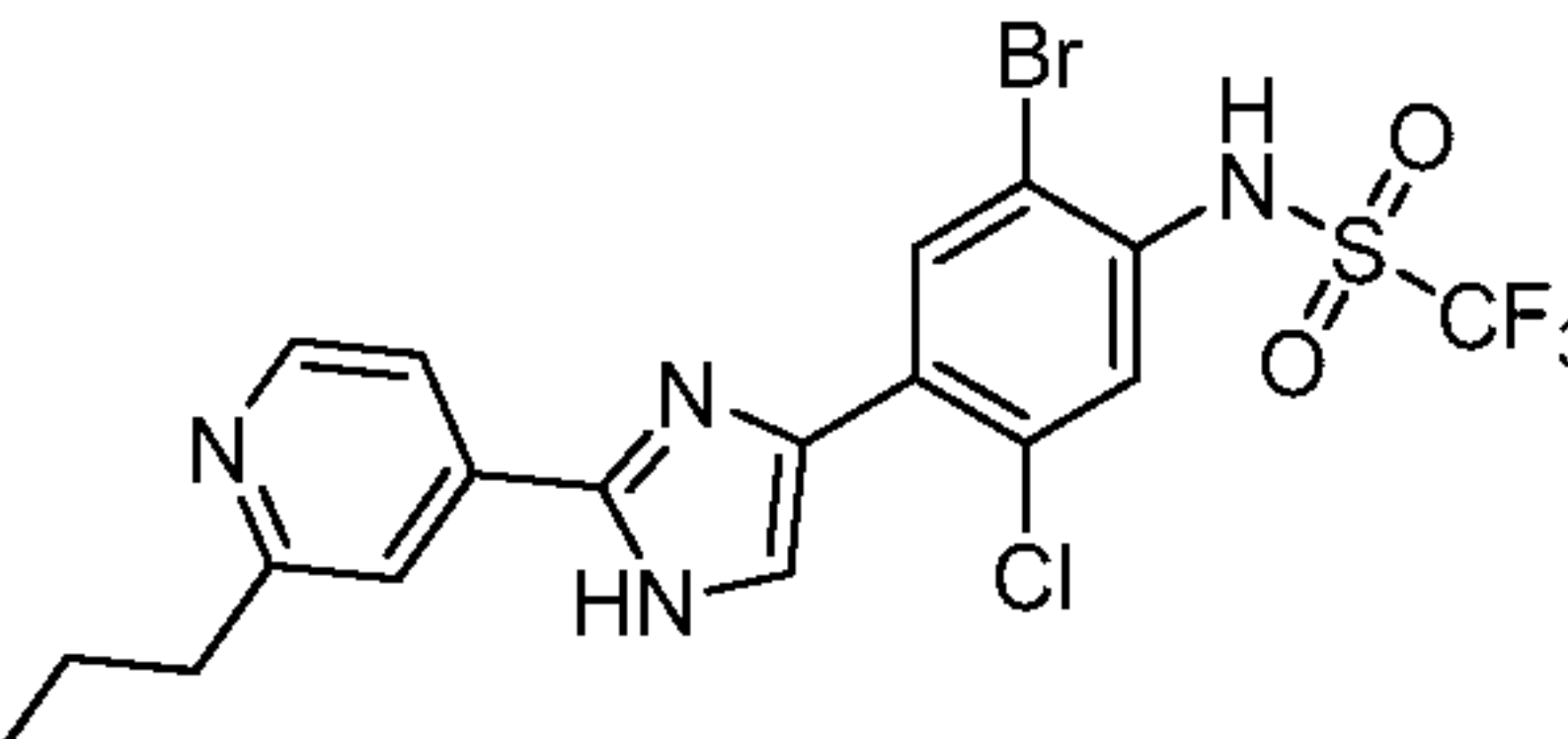
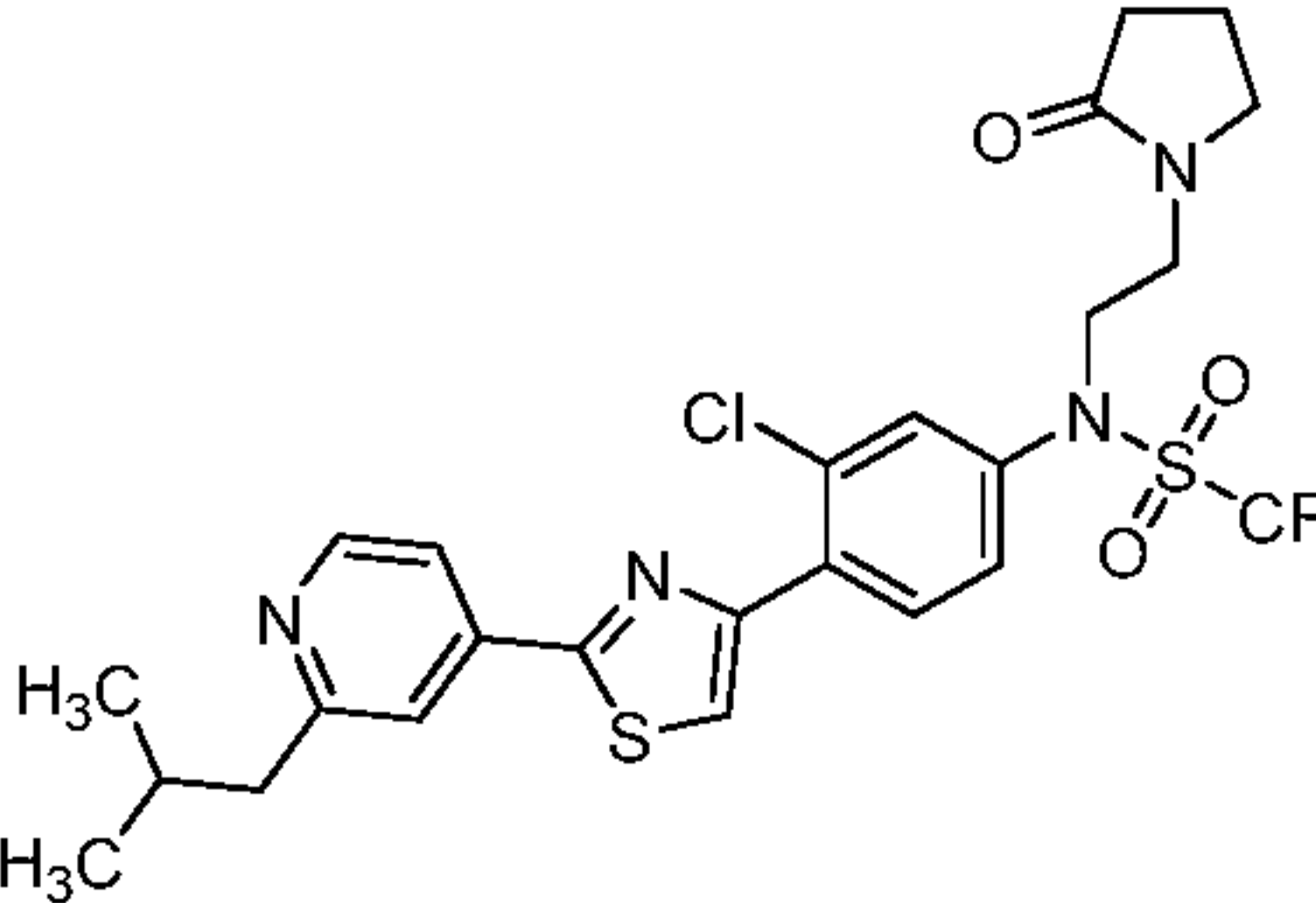
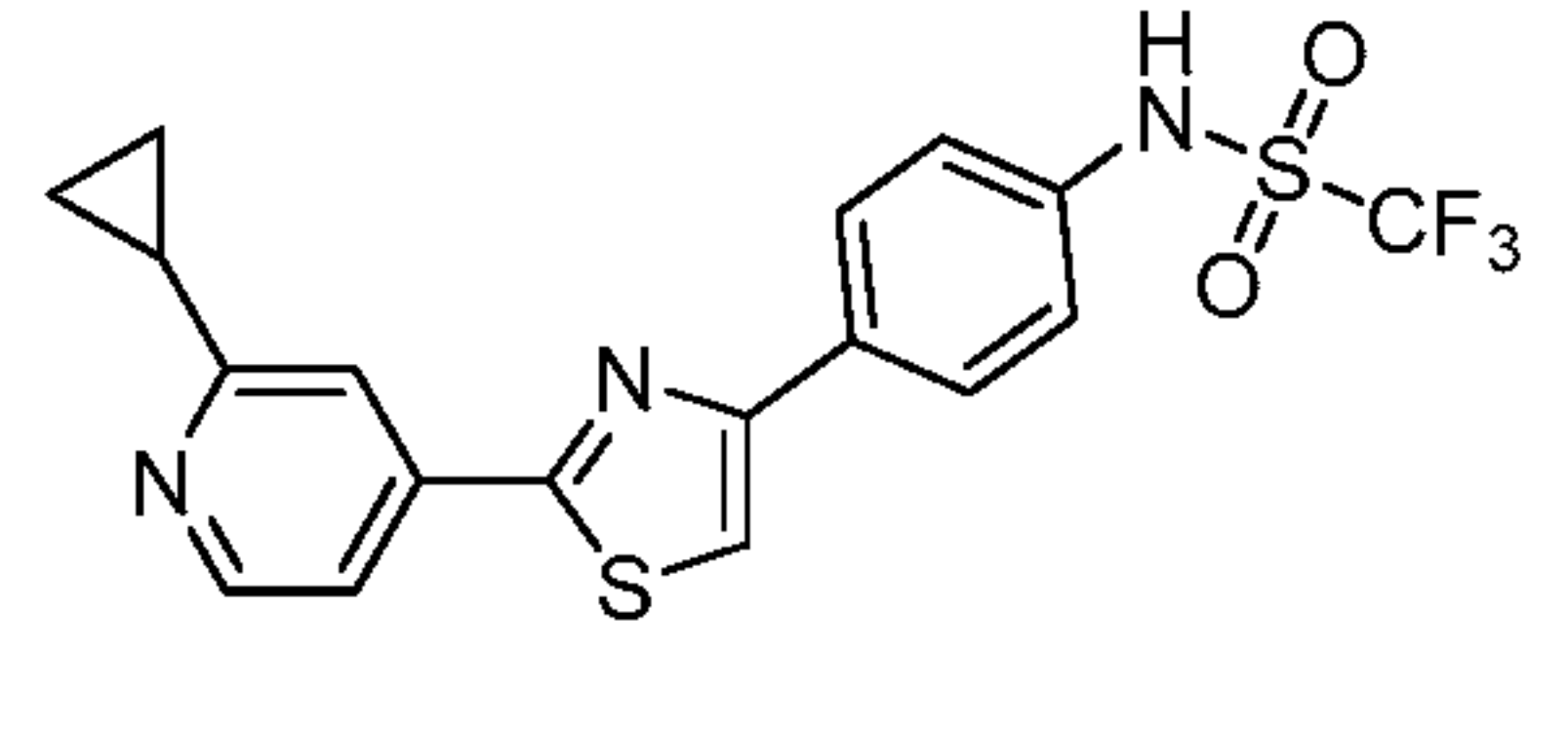
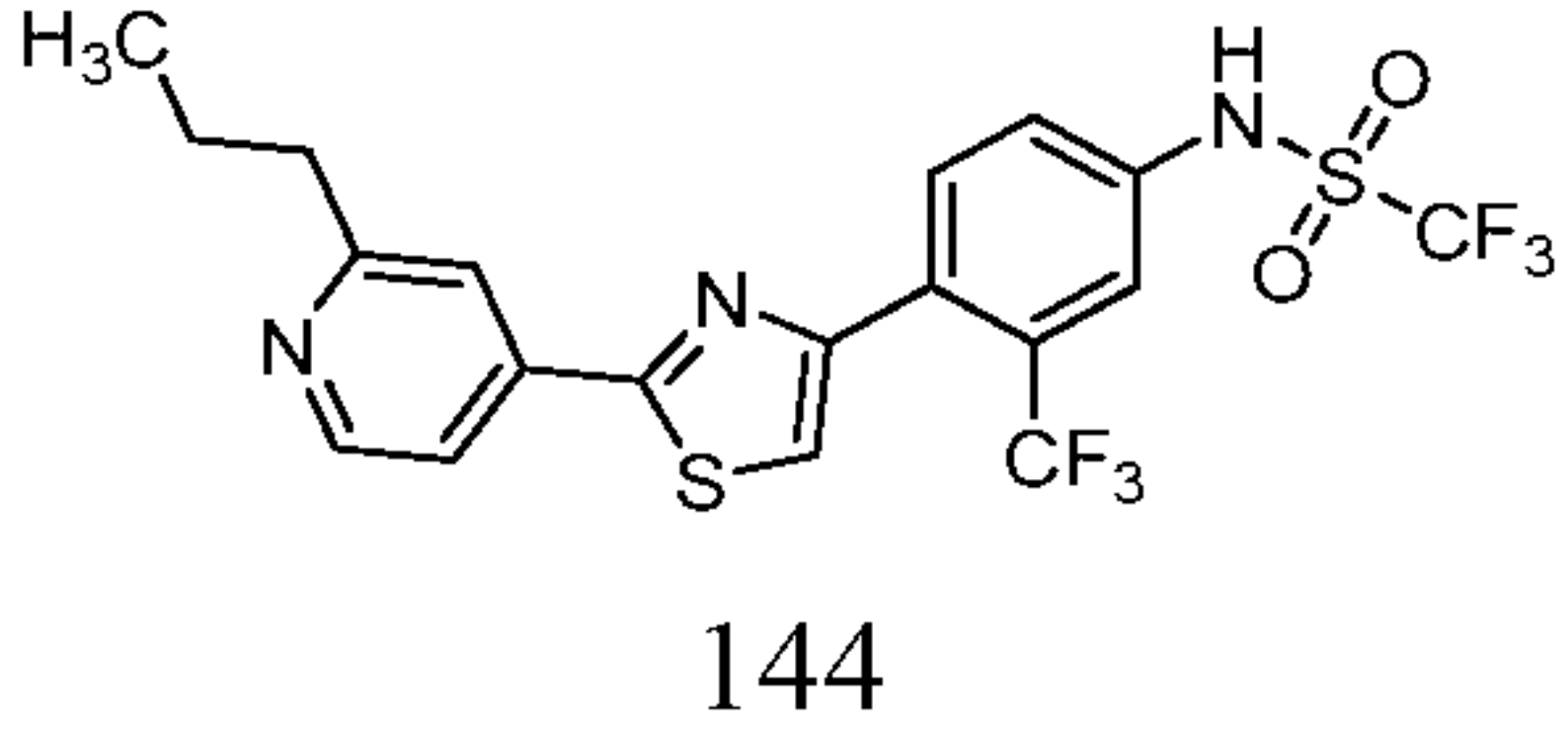
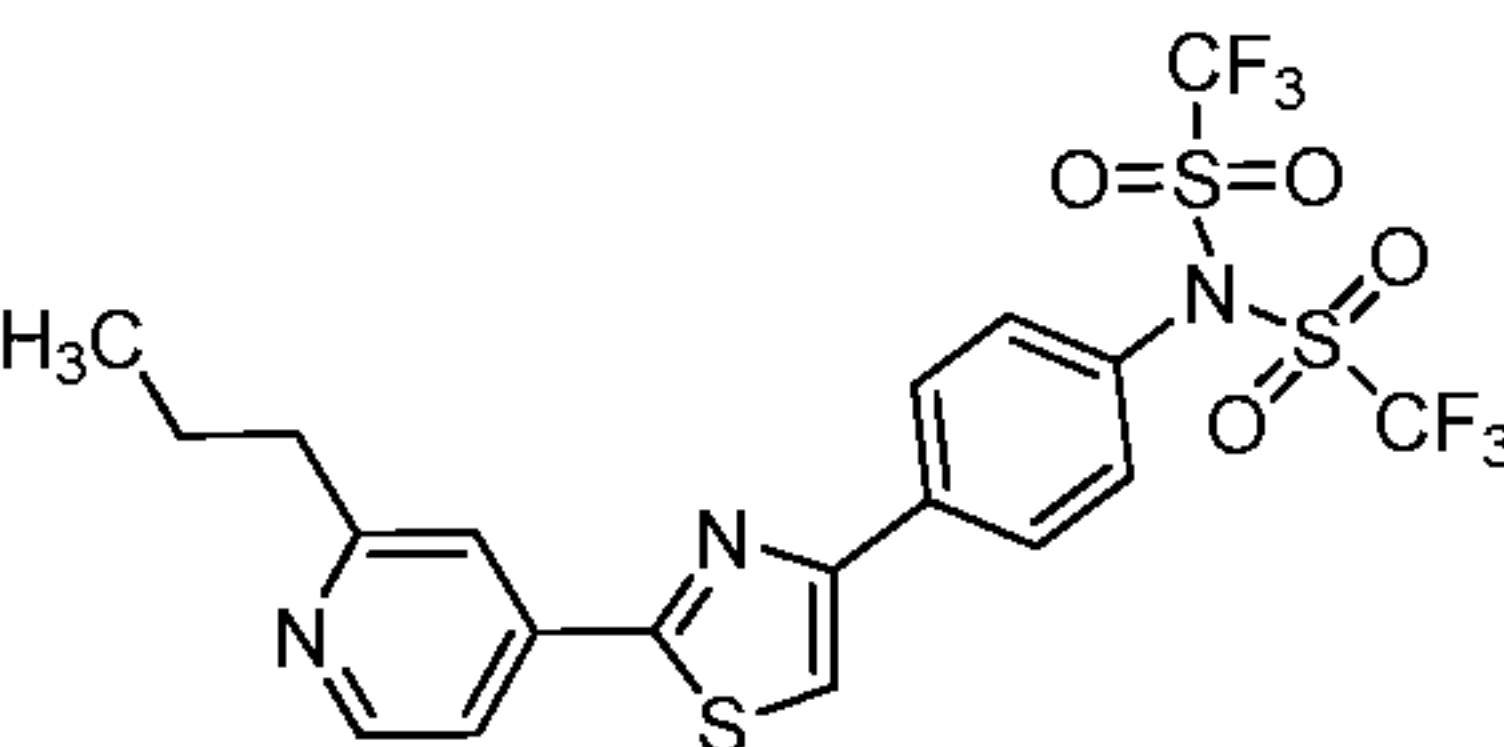
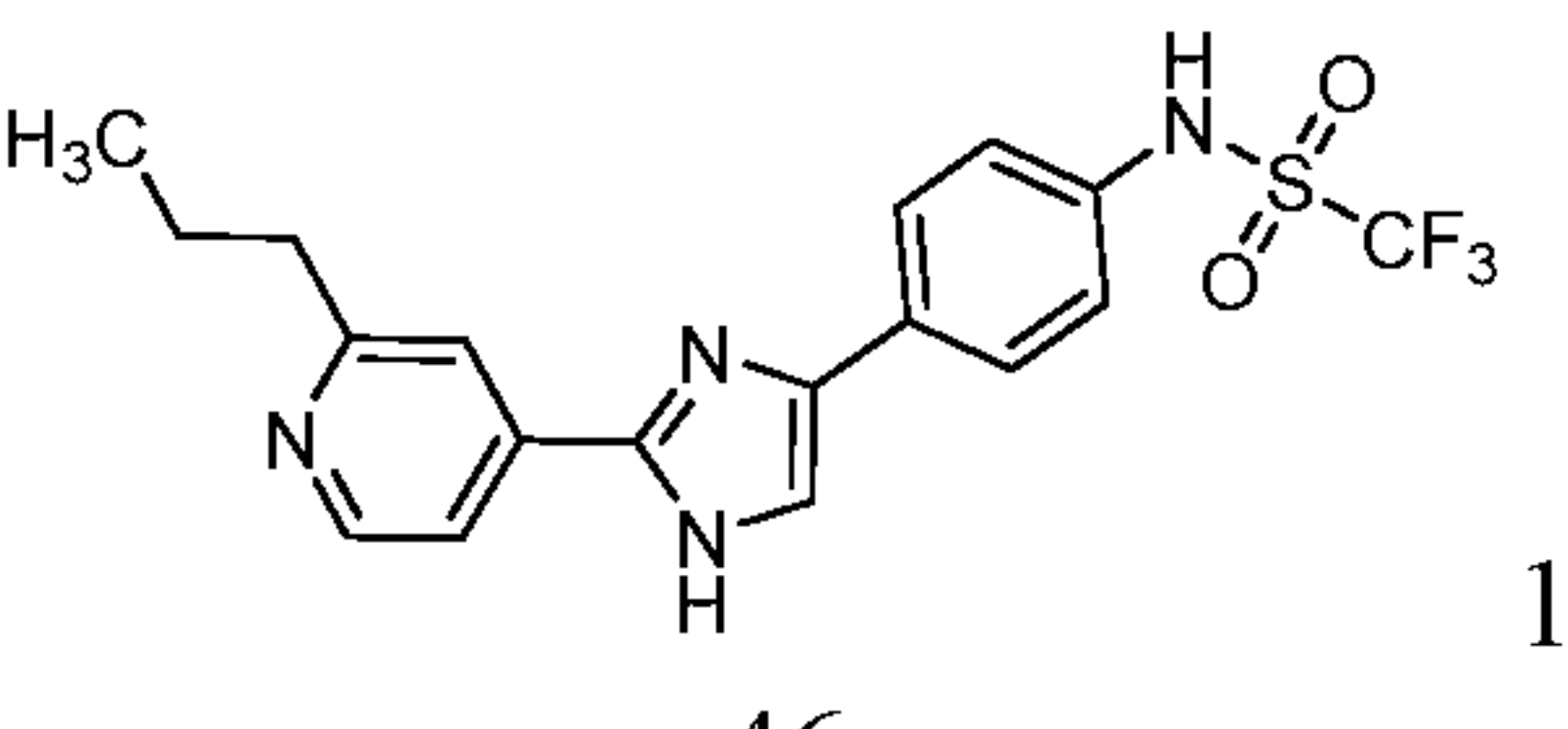
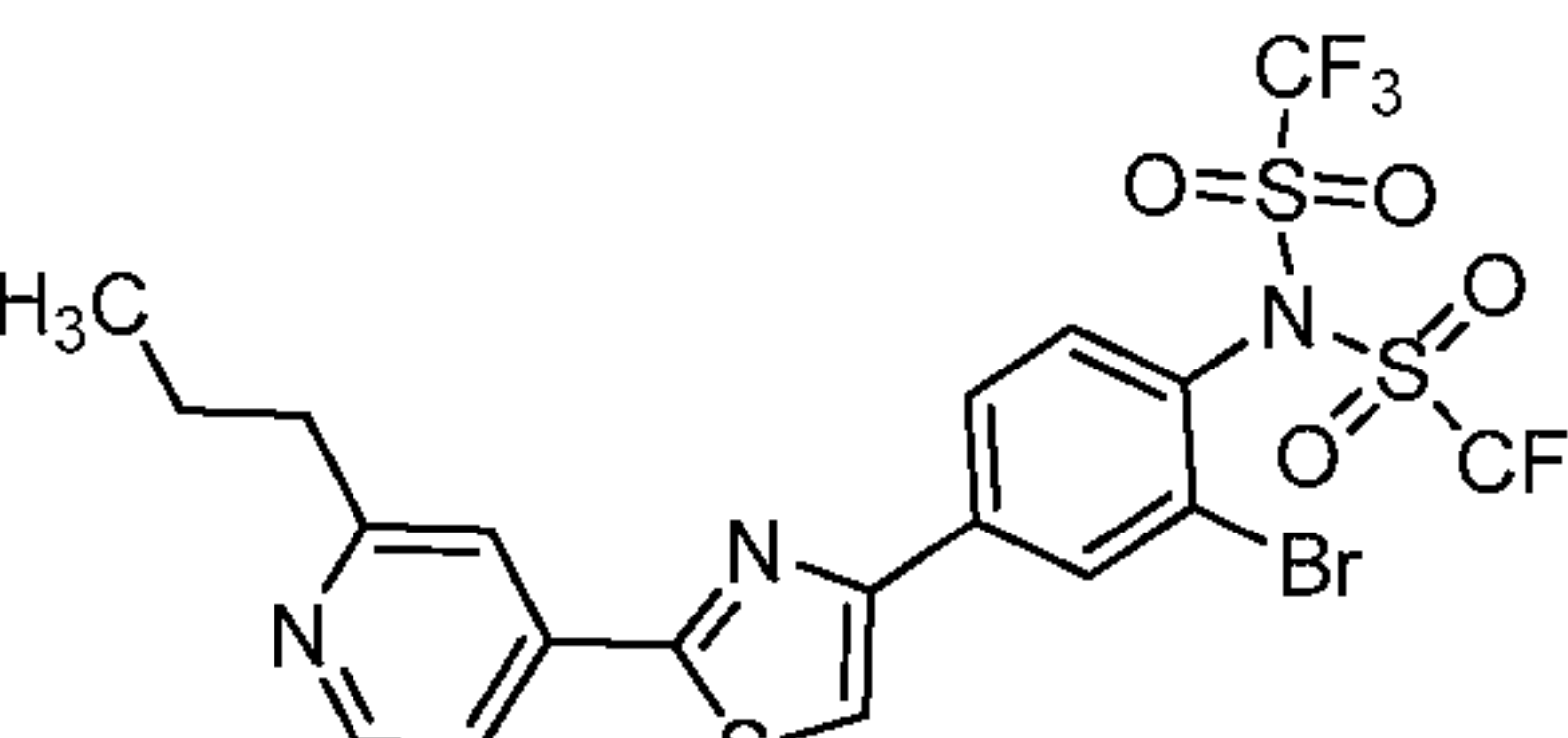
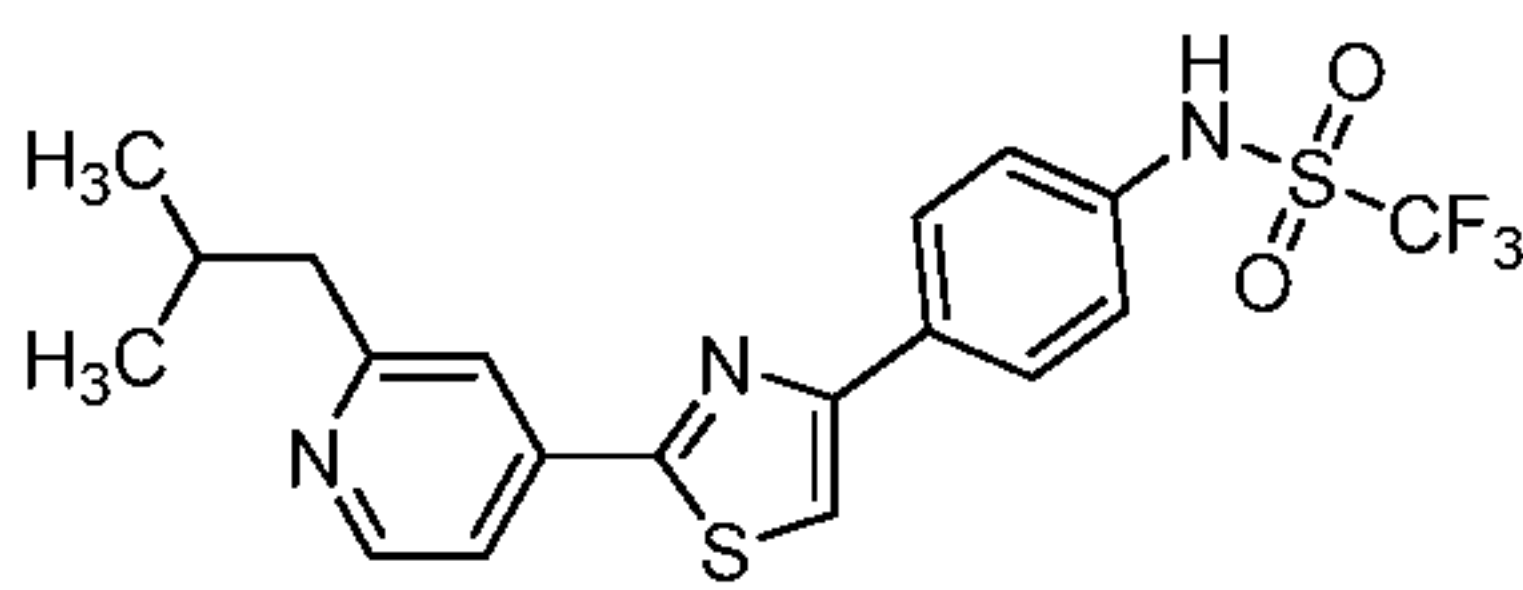
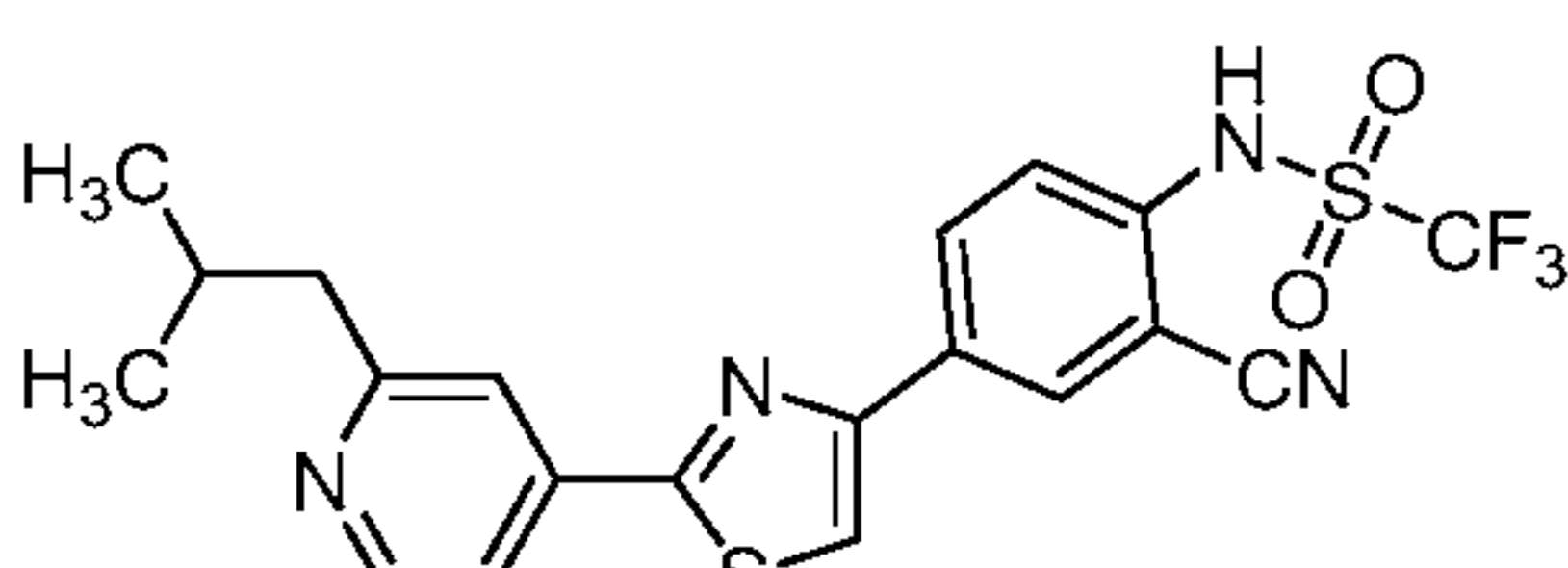
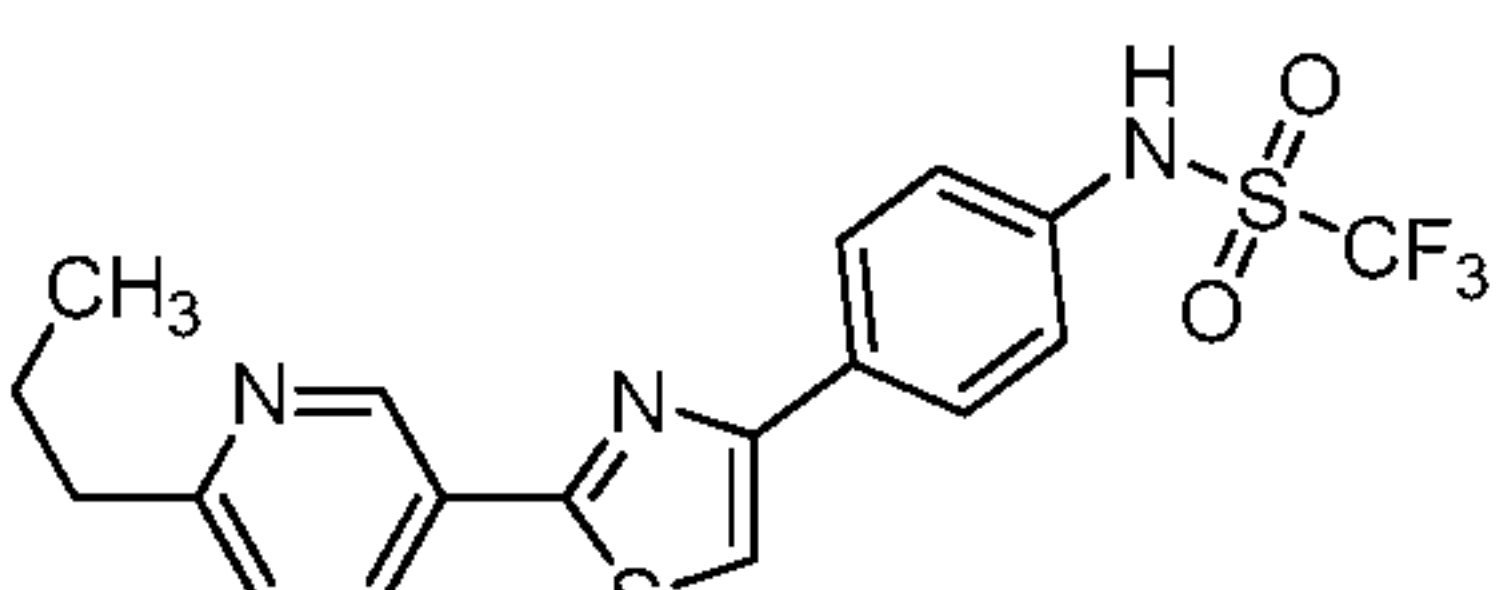
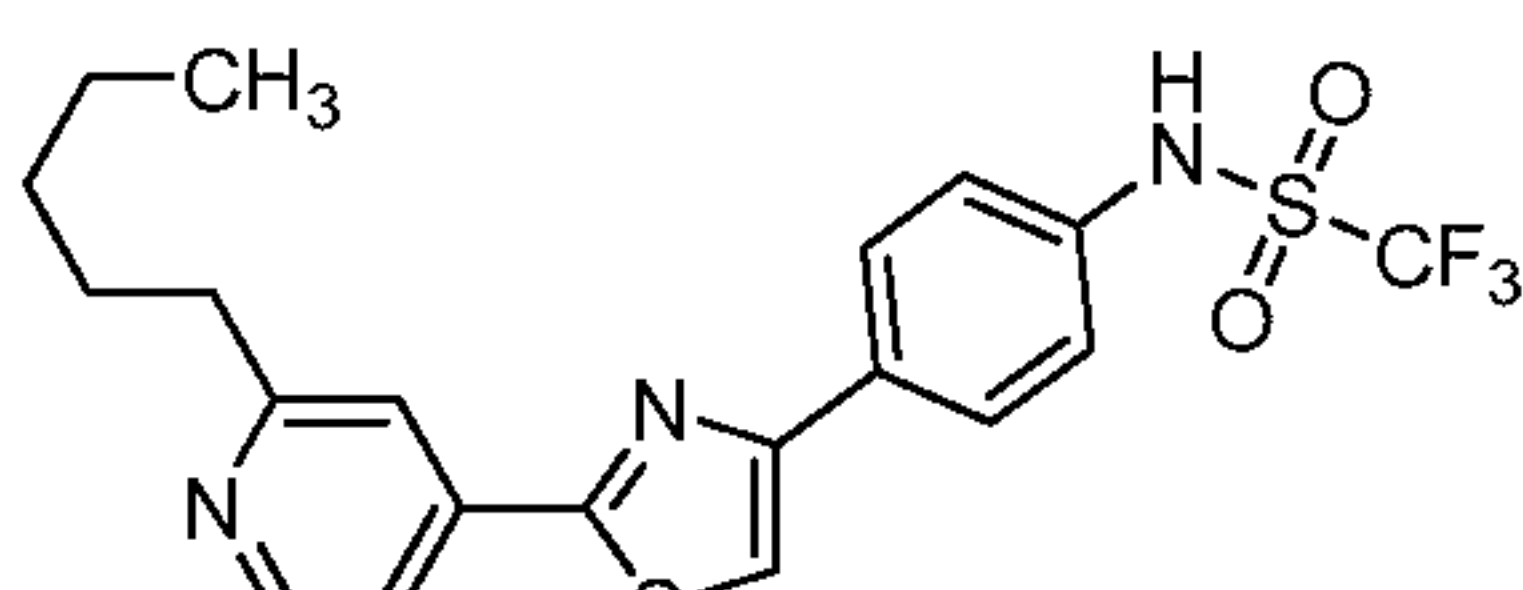
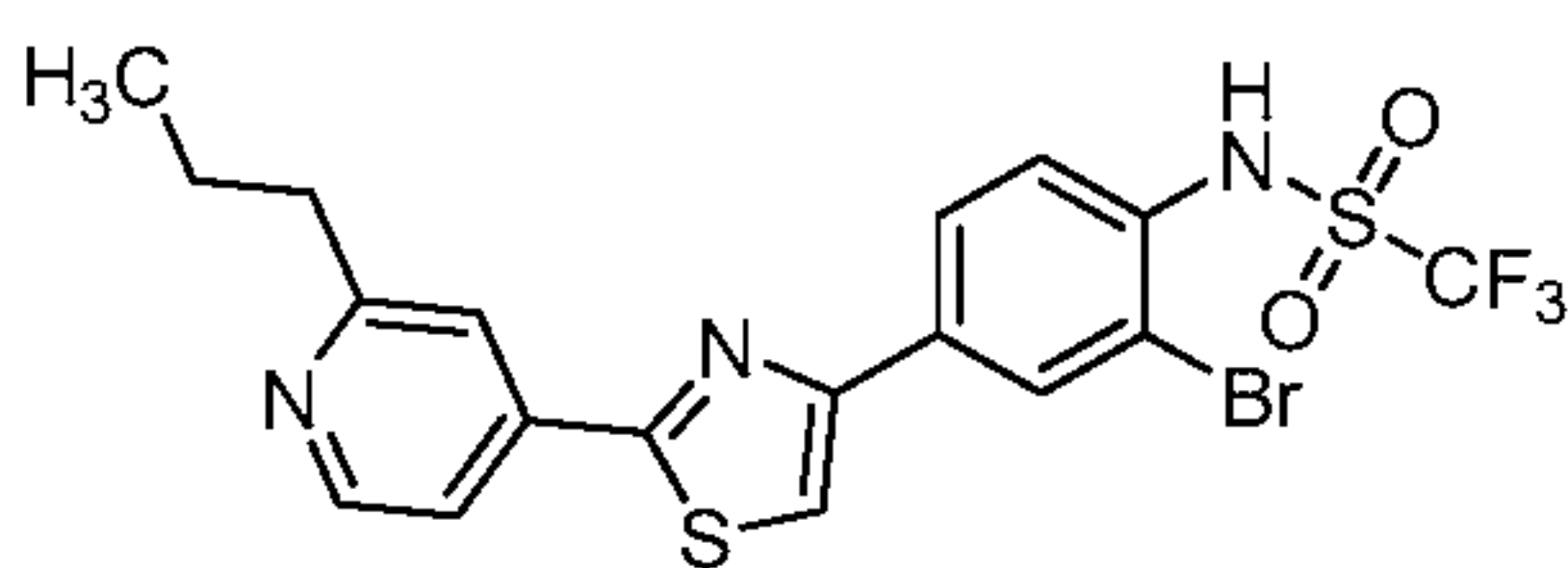
 130	 31	 132
 133	 134	 135
 136	 137	 138
 139	 140	 141
 142	 143	 144
 145	 46	 147

Table 1		
 148	 149	 15
 151	 152	

[076] In some embodiments, the compound is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, or 152.

[077] In some embodiments, the compound is 1, 2, 3, 4, 5, 37, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, or 94.

[078] Representative examples of compounds detailed herein, including intermediates and final compounds, are depicted in Table 1 and elsewhere herein. It is understood that in one aspect, any of the compounds may be used in the methods detailed herein, including, where applicable, intermediate compounds that may be isolated and administered to an individual.

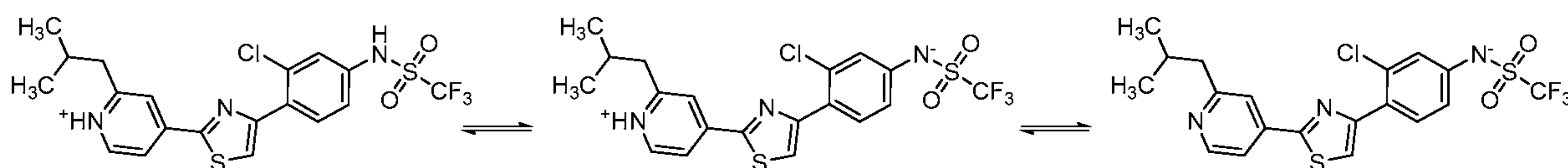
[079] The compounds depicted herein may be present as salts even if salts are not depicted, and it is understood that the compositions and methods provided herein embrace all salts and solvates of the compounds depicted here, as well as the non-salt and non-solvate form of the compound, as is well understood by the skilled artisan. In some embodiments, the salts of the compounds provided herein are pharmaceutically acceptable salts.

[080] In one embodiment, the compound is a pharmaceutically acceptable salt of a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, or a pharmaceutically acceptable salt thereof.

[081] In some embodiments, certain compounds presented herein are considered to be “prodrug” forms of other compounds herein. Prodrugs are precursor derivatives that, upon administration to a patient, undergo metabolism *in-vivo* such as, for example, hydrolysis to release the active form of the compound – the ‘parent’ compound. The prodrug form itself is either inactive or less active than the parent. Prodrugs are designed to improve bioavailability or to improve selective administration to particular organs, such as the liver [see, for example, Erion, et al. *PNAS* (2007) 104:39, pp 15490-15495; Erion, et al. *J. Pharmacol. Exp. Ther.* (2005) 312:2, pp 554-560; Meyer, et al. *Patent Publication US 2006-0281695A1*]. Compounds provided herein such as, for example, compound nos. 106-111 can be considered prodrug forms of the ‘parent’ compound no. 5. In some embodiments, prodrug forms of compounds presented herein are provided. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in “*Design of Prodrugs*”, ed. H. Bundgaard, Elsevier, 1985; Beaumont; K. et al. *Curr. Drug Metab.* (2003) 4, pp 461-485; Mizen, L, et al. *Pharm. Biotechnol.* (1998) 11, pp 345-365. In addition to prodrugs, this disclosure provides the salts, esters, amides, and other protected or derivatized forms of the described compounds.

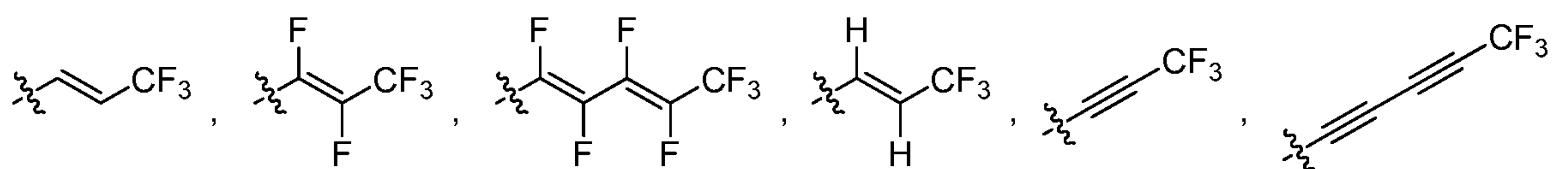
[082] As has been described above, the inherent pKa(s) of molecules can be assessed by potentiometric methods known to the skilled artisan, typically UV spectrophotometry [see, for example, Julémont, et al. *J. Med. Chem.* (2002), 45, pp 5182-5185]. In-silico methods can be used as a predictive tool, and software is commercially available from, for example, ACD/Labs, Molecular Discovery, ChemAxon, and other vendors. Without being bound by theory, it is presented that compounds provided herein possess unexpected physicochemical properties presumed to arise from the presence of the trifluoromethylsulfonamide moiety and its effect on the acidity of the remaining structure of the provided compounds as a whole. The compounds provided herein contain several ionizable centers including, for example, the trifluoromethylsulfonamide nitrogen atom; the thiazole ring nitrogen atom; the “ring A” pyridine nitrogen atom, etc.

[083] As one example to describe the theory, compound #37 could exist in the following forms:



Other ionized forms are conceivable, but those presented here are a protonated form; a neutral or internal zwitterionic form; and an anionic form. Which form would exist is dependent upon the pH of the aqueous or physiological solution in which the compound is placed. Calculated pKa values of compound #37 [provided by I-Lab 2.0 (ACD/Labs, Inc.)] give two values of 3.4 and 5.4. These values are similar to those experimentally obtained under potentiometric and spectrophotometric methods [courtesy of Pion, Inc.], found to be 3.09 and 5.27. When the CF₃ group is replaced by a CH₃ group, the calculated pKa values become 5.1 and 7.5 – both notably higher. It is postulated that the more electronegative nature of the CF₃ group results in a more highly acidic nature of the compound. Based on the calculated / measured pKa values of the trifluoromethylsulfonamide containing compounds claimed herein, it is likely that at a pH of 6-8, these compounds will predominantly exist in the anionic form, with the above equilibrium lying to the right at higher pH values. The anionic form renders the compound more aqueous soluble and therefore better absorbed. A solubility study [courtesy of Pion, Inc.] showed average solubilities of 13µg/mL @ pH 6.0, 104µg/mL @ pH 7.0, and >130µg/mL @ pH 8.0. When a compound is dosed orally, most of the absorption occurs in the intestines where the pH ranges from 6-8. Therefore it is likely that the trifluoromethylsulfonamide containing compounds claimed herein will have significantly better solubility and absorption when dose orally relative to the methylsulfonamides which the anionic form would be present to a significantly lower extent at pH 6-8, compared to its neutral/zwitterionic form).

[084] Examples of perhaloalkylsulfonamide groups are presented hereinabove. In some embodiments, also provided are compounds bearing perhaloalkenylsulfonamide groups, perhaloalkynylsulfonamide groups, or alkylsulfonamide groups bearing 1 or more halogen atoms. Such compounds can include, for example, the following:



Without being bound by theory, it is expected that each of these particular groups, and variations therein, has varying degrees of electronegativity, affording subtle changes in pKa, and allowing a tuning of the acidity of the disclosed compounds, where required by the skilled artisan.

Pharmaceutically acceptable salts

[085] “Pharmaceutically acceptable salts” are those salts which retain at least some of the biological activity of the free (non-salt) compound and which can be administered as drugs or pharmaceuticals to an individual. Such salts, for example, include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid, maleic acid, tartaric acid and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth metal ion, or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Further examples of pharmaceutically acceptable salts include those listed in Berge *et al.*, Pharmaceutical Salts, *J. Pharm. Sci.* 1977 Jan; 66(1):1-19. Pharmaceutically acceptable salts can be prepared *in situ* in the manufacturing process, or by separately reacting a purified compound disclosed herein in its free acid or base form with a suitable organic or inorganic base or acid, respectively, and isolating the salt thus formed during subsequent purification. In one embodiment, a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

Pharmaceutical Compositions

[086] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, typically is provided in a pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or excipient. A “pharmaceutically acceptable” carrier or excipient is a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a pharmaceutical composition administered to an individual without

causing significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition, wherein it is contained. Pharmaceutically acceptable carriers or excipients meet the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[087] A pharmaceutical composition can comprise one or more compounds of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein. In some embodiments, a pharmaceutical composition further comprises chemotherapeutic agent, as described below.

[088] Preferably a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, is bioavailable orally. However, the compounds may also be formulated for parenteral (*e.g.*, intravenous) administration.

[089] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, can be used in the preparation of a medicament by combining the compound or compounds as an active ingredient with a pharmacologically acceptable carrier, which is known in the art. Depending on the therapeutic form of the medication, the carrier may be in various forms. In one variation, the manufacture of a medicament is for use in any of the methods disclosed herein.

[090] Methods as provided herein may comprise administering to an individual a pharmacological composition that contains an effective amount of a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, and a pharmaceutically acceptable carrier. The effective amount of the compound may in one aspect be a dose of between about 0.01 and about 100 mg.

[091] The compound may be formulated for any available delivery route, including an oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal or rectal), parenteral (*e.g.*, intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A compound may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (*e.g.*, nasal spray or inhalers), gels, suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

[092] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compound or compounds as an active ingredient with a pharmaceutically acceptable carrier, such as those mentioned above. Depending on the therapeutic form of the system (*e.g.*, transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the compound may also contain other substances which have valuable therapeutic properties.

Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable formulations can be found, *e.g.*, in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 20th ed. (2000), which is incorporated herein by reference.

[093] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, may be administered to individuals in a form of generally accepted oral compositions, such as tablets, coated tablets, gel capsules in a hard or in soft shell, emulsions or suspensions.

Examples of carriers, which may be used for the preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate or its salts, *etc.* Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax, fats, semisolid and liquid poly-ols, and so on. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

[094] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, can be formulated in a tablet in any dosage form described, for example, a compound as described herein or a pharmaceutically acceptable salt thereof can be formulated as a 10 mg tablet.

[095] A compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer, which in some variations may be for the duration of the individual's life. In one variation, a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, is administered on a daily or intermittent schedule. The compound can be administered to an individual continuously (for example, at least once daily) over a period of time. The dosing

frequency can also be less than once daily, *e.g.*, about a once weekly dosing. The dosing frequency can be more than once daily, *e.g.*, twice or three times daily. The dosing frequency can also be intermittent (*e.g.*, once daily dosing for 7 days followed by no doses for 7 days, repeated for any 14 day time period, such as about 2 months, about 4 months, about 6 months or more). Any of the dosing frequencies can employ any of the compounds described herein together with any of the dosages described herein.

[096] In some embodiments, a pharmaceutical composition is provided as a unit dosage form, such as a tablet, capsule, or individually packaged container (*e.g.*, an ampoule, syringe, or vial).

[097] In some embodiments, the unit dosage form contains a daily dose of a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein. In some embodiments, the unit dosage form contains a daily sub-dose of the compound.

[098] In some embodiments, the unit dosage form contains a daily dose of each of two or more compounds of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein. In some embodiments, the unit dosage form contains a daily sub-dose of each of two or more compounds.

[099] In some embodiments, the unit dosage form contains a daily dose of compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, and a daily dose of each of one or more chemotherapeutic agents. In some embodiments, the unit dosage form contains a daily sub-dose of the compound and a daily sub-dose of each of one or more chemotherapeutic agents.

[0100] In some embodiments, the unit dosage form contains a daily dose of each of two or more compounds of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, and a daily dose of each of one or more chemotherapeutic agents. In some embodiments, the unit dosage form contains a daily sub-dose of each of two or more compounds and a daily dose of each of one or more chemotherapeutic agents.

Kits and Articles of Manufacture

[0101] This disclosure also provides kits and articles of manufacture comprising one or more compounds of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, or a pharmacological composition comprising a compound of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein,. The kits may employ any of the compounds disclosed herein.

In one variation, the kit employs a compound described herein or a pharmaceutically acceptable salt thereof.

[0102] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

[0103] The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein and/or a second pharmaceutically active compound useful for a disease detailed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (*e.g.*, hospital pharmacies and compounding pharmacies).

[0104] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (*e.g.*, magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the disclosed methods. The instructions included with the kit generally include information as to the components and their administration to an individual.

Therapeutic Uses

[0105] Compounds of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, can be used to treat liver fibrosis, elevated cholesterol levels, and insulin resistance. Unless otherwise defined, “treat,” as used herein, refers to the reduction of one or more symptoms associated with a disorder or to slowing the progression of one or more such symptoms.

a. Liver Fibrosis

[0106] Compounds disclosed herein can be administered to an individual to treat liver fibrosis. In some embodiments, the liver fibrosis is secondary to chronic hepatitis C virus infection. In some embodiments, the liver fibrosis is secondary to alcohol abuse. In some embodiments, the liver fibrosis is a precursor to, is concurrent with, is associated with, or is secondary to nonalcoholic steatohepatitis (NASH).

[0107] In some embodiments in which the liver fibrosis is a precursor to, is concurrent with, is associated with, or is secondary to NASH, the individual has been diagnosed with NASH following a liver biopsy in which one or more of steatosis, hepatocyte ballooning, lobular inflammation, Mallory hyaline bodies, mixed inflammatory infiltrate, pericellular fibrosis, and perisinusoidal fibrosis is detected.

[0108] In other embodiments in which the liver fibrosis is a precursor to, is concurrent with, is associated with, or is secondary to NASH, the individual is suspected of having or developing NASH based on one or more symptoms such as such as elevated serum levels of liver enzymes (*e.g.*, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyltransferase, alkaline phosphatase); focal or diffuse accumulation of lipid as detected by imaging techniques such as magnetic resonance spectroscopy, ultrasonography, computed tomography; abdominal discomfort, acanthosis nigricans, bowel dysmotility, coma, constipation, disseminated intravascular coagulopathy, epigastric pain, fatigue, fluid retention, hepatomegaly, hypoglycemia, intestinal bleeding, jaundice, lipomatosis, lipodystrophy, lipodystrophy, muscle wasting, nausea, neurological defects, Palmer erythema, panniculitis, periumbilical pain, small bowel bacterial overgrowth, spider angiomas, splenomegaly, subacute liver failure, or vomiting.

[0109] In some embodiments, the individual is overweight or obese. In some embodiments, the individual has symptoms of insulin resistance, as described below; *i.e.*, the individual is pre-diabetic or has type II diabetes.

[0110] In some embodiments, administration of one or more disclosed compounds prevents or slows the histologic progression of liver fibrosis and the clinical progression to cirrhosis in patients who have NASH or who are suspected of having NASH.

[0111] In some embodiments, administration of one or more disclosed compounds reduces the patient's risk of developing NASH.

[0112] Treatment or prevention can be assessed by one or more of the following:

- reduction in average liver fat concentration (measured, *e.g.*, by NMRS or MRI);
- reduction of serum ALT;
- reduction of serum AST;
- reduction of serum γ -glutamyltransferase;
- reduction of serum alkaline phosphatase;

increased in plasma concentrations of the cholesterol synthesis intermediate
 lathosterol;
 improved NASH activity index or NAFLD activity score (NAS) (Kleiner *et al.*,
 Hepatology 41, 1313-21, 2005);
 improved SAF score (Bedossa *et al.*, Hepatology 56, 1751-59, 2012;
 changes in insulin resistance (measured, *e.g.*, by Homeostatis Model Assessment of
 Insulin Resistance (HOMA-IR);
 reduced hemoglobin A1c levels;
 adiponectin level;
 leptin:adiponectin ratio (LAR);
 reduction in one or more markers of inflammation or fibrosis such as fibrinogen, CK-
 18, C-reactive protein (CRP), TNF α , IL-6;
 reduction in body weight; or
 reduced histological features such as cholestasis, fat cysts, fibrosis, granular iron,
 hepatocellular ballooning, increased numbers of eosinophils, inflammation, lobular
 disarray, lobular inflammation, macrovesicular steatosis, Mallory bodies,
 megamitochondria, necrosis, periodic acid-Schiff stained globulines, portal
 inflammation, microvesicular steatosis, or steatosis.

b. Elevated Cholesterol Levels

[0113] Compounds disclosed herein can be administered to an individual to treat elevated
 cholesterol levels, *e.g.*, cholesterol levels above 200 mg/dL (5.2 mmol/L), such as 200-239
 mg/dL (5.2-6.2 mmol/L) or 240 mg/dL (6.2 mmol/L) and above. In some embodiments, the
 individual has LDL cholesterol levels in the range of 130-159 mg/dL (3.4-4.1 mmol/L). In
 some embodiments, the individual has LDL cholesterol levels in the range of 160-189 mg/dL
 (4.1-4.9 mmol/L). In some embodiments, the individual has LDL cholesterol levels in the
 range of 190 mg/dL (4.9 mmol/L) and above. In some embodiments, the individual has HDL
 cholesterol levels below 40 mg/dL (1 mmol/L; men) or below 50 mg/dL (1.3 mmol/L;
 women). In some embodiments, the individual has HDL cholesterol levels in the range of 50-
 59 mg/dL (1.3-1.5 mmol/L). In some embodiments, the individual has triglyceride levels in
 the range of 150-199 mg/dL (1.7-2.2 mmol/L). In some embodiments, the individual has
 triglyceride levels in the range of 200-499 mg/dL (2.3-5.6 mmol/L). In some embodiments,
 the individual has triglyceride levels in the range of 500 mg/dL (5.6 mmol/L) and above.

[0114] In some embodiments, the elevated cholesterol levels are a precursor to NASH or the individual has NASH or is suspected of having NASH, as described above.

[0115] In some embodiments, the individual has symptoms of insulin resistance, as described below.

c. Insulin Resistance

[0116] Compounds disclosed herein can be administered to an individual to treat insulin resistance. In some embodiments, the individual has pre-diabetes, *e.g.*, the individual has a hemoglobin A1C level between 5.7 and 6.4 percent and/or a fasting blood sugar level from 100-125 mg/dL (5.6-6.9 mmol/L). In some embodiments, the individual has type II diabetes *e.g.*, the individual has a hemoglobin A1C level of 6.5 percent or higher and/or a fasting blood sugar level of 126 mg/dL (7 mmol/L) or higher.

[0117] In some embodiments, the individual has one or more of the following symptoms, which may improve upon treatment with one or more compounds disclosed herein: increased thirst and frequent urination, increased hunger; weight loss; fatigue; blurred vision; slow-healing sores or frequent infections; and acanthosis nigricans.

[0118] In some embodiments, the insulin resistance is a precursor to NASH or the individual has NASH or is suspected of having NASH, as described above.

d. Combination Therapies

[0119] Compounds of Formulae (Ia), (Ib), (IIa) or (IIb), or any variation presented herein, can be administered in combination with other therapeutic interventions for treating elevated cholesterol levels, liver fibrosis, or insulin resistance. Unless otherwise defined, “in combination” includes any coordinated administration of such therapeutic interventions with one or more therapeutic compounds disclosed herein, including sequential administration, alternating administration, and substantially simultaneous administration.

[0120] Therapeutic interventions for treating elevated cholesterol levels include, but are not limited to, statins, such as atorvastatin (*e.g.*, LIPITOR®), fluvastatin (*e.g.*, LESCOL®), lovastatin (*e.g.*, ALTOPREV®, MEVACOR®), pitavastatin (*E.G.*, LIVALO®), pravastatin (*e.g.*, PRAVACHOL®), rosuvastatin (*e.g.*, CRESTOR®), and SIMVASTATIN (*e.g.*, ZOCOR®); bile acid binding resins, such as cholestyramine (*e.g.*, PREVALITE®), colestevlam (*e.g.*, WELCHOL®), and colestipol (*e.g.*, COLESTID®); and cholesterol absorption inhibitors such as ezetimibe (*e.g.*, ZETIA®).

[0121] Therapeutic interventions for treating liver fibrosis include, but are not limited to, angiotensin inhibitors, colchicine, corticosteroids, endothelin inhibitors, interferon- α , interleukin 10, pentoxifylline or oxpentifylline (*e.g.*, TRENTAL®), phosphatidylcholine, PPAR antagonists, S-adenosyl-methionine, TGF- β inhibitors, and tocopherol.

[0122] Therapeutic interventions for treating insulin resistance include, but are not limited to, insulin-sensitizing agents such as metformin (*e.g.*, GLUCOPHAGE®), thiazolidinediones such as pioglitazone (*e.g.*, ACTOS®) and rosiglitazone (*e.g.*, AVANDIA®); and leptin); α -glucosidase inhibitors such as miglitol (*e.g.*, GIYSET®); insulin; meglitinides such as repaglinide (*e.g.*, PRANDIN®) and nateglinide (*e.g.*, STARLIX®); sulfonylureas such as glyburide (*e.g.*, ORINASE®, TOLINASE®, MICRONASE®, GLYNASE®, DIABETA®, AMARYL®) and chlorpropamide (*e.g.*, DIABINASE®, GLUTROL®, GLUCOTROL XL®; and combinations such as AVANDAMET® (metformin and rosiglitazone).

Dosing and Method of Administration

[0123] The dose of a compound administered to an individual (such as a human) may vary with the particular compound or salt thereof, the method of administration, and the particular stage of the disorder being treated. For therapeutic purposes, “effective dose” or “effective amount” refers to that amount of each active compound or pharmaceutical agent, alone or in combination, that elicits the biological or medicinal response in a tissue system, animal, or human that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. For prophylactic purposes (*i.e.*, preventing or inhibiting the onset or progression of a disorder), the term “effective dose” or “effective amount” refers to that amount of each active compound or pharmaceutical agent, alone or in combination, that inhibits in a subject the onset or progression of a disorder as being sought by a researcher, veterinarian, medical doctor, or other clinician, the delaying of which disorder is mediated, at least in part, by blocking of SREBP function. The amount should be sufficient to produce a desirable response, such as a therapeutic or prophylactic response against the disorder. In some embodiments, the amount of the compound or salt thereof is a therapeutically effective amount. In some embodiments, the amount of the compound or salt thereof is a prophylactically effective amount. In some embodiments, the amount of compound or salt thereof is below the level that induces a toxicological effect (*e.g.*, an effect above a clinically acceptable level of toxicity) or is at a level where a potential side effect can be controlled or tolerated when the composition is administered to the individual.

[0124] The effective amount of the compound may in one aspect be a dose of between about 0.01 and about 100 mg/kg.

[0125] Any of the methods provided herein may in one aspect comprise administering to an individual a pharmaceutical composition that contains an effective amount of a compound provided herein or a salt thereof and a pharmaceutically acceptable excipient.

[0126] A compound or composition provided herein may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer, which in some variations may be for the duration of the individual's life. In one variation, the compound is administered on a daily or intermittent schedule. The compound can be administered to an individual continuously (for example, at least once daily) over a period of time. The dosing frequency can also be less than once daily, *e.g.*, about a once weekly dosing. The dosing frequency can be more than once daily, *e.g.*, twice or three times daily. The dosing frequency can also be intermittent (*e.g.*, once daily dosing for 7 days followed by no doses for 7 days, repeated for any 14 day time period, such as about 2 months, about 4 months, about 6 months or more). Any of the dosing frequencies can employ any of the compounds described herein together with any of the dosages described herein.

[0127] The compounds provided herein or a salt thereof may be administered to an individual via various routes, including, *e.g.*, intravenous, intramuscular, subcutaneous, oral and transdermal.

[0128] In one aspect, provided is a method of treating one or more of liver fibrosis, elevated cholesterol levels, and insulin resistance in an individual by parenterally administering to the individual (*e.g.*, a human) an effective amount of a compound or salt thereof. In some embodiments, the route of administration is intravenous, intra-arterial, intramuscular, or subcutaneous. In some embodiments, the route of administration is oral. In still other embodiments, the route of administration is transdermal. *e.g.*. Also provided are articles of manufacture, comprising a compound provided herein or a salt thereof, composition, and unit dosages described herein in suitable packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

General Synthetic Methods

[0129] The compounds may be prepared by a number of processes as generally described below in the General Synthetic Schemes and more specifically in the Examples hereinafter. In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

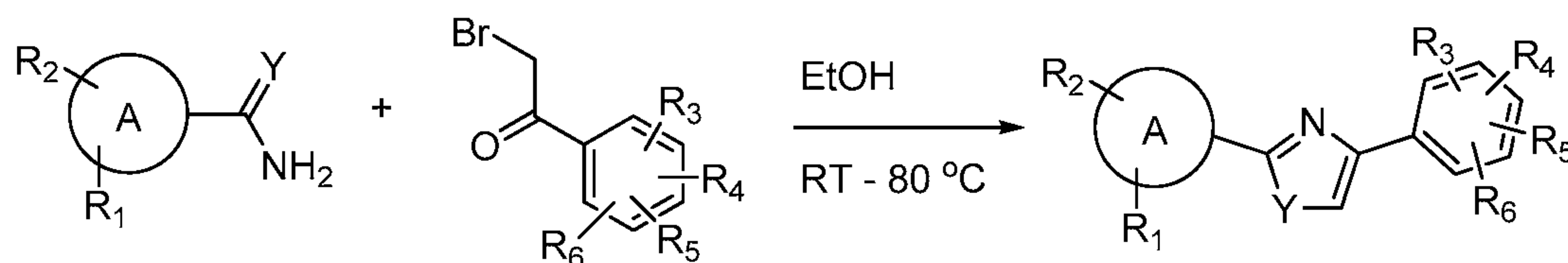
[0130] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

[0131] The following abbreviations are used herein: thin layer chromatography (TLC); hour (h); minute (min); second (sec); ethanol (EtOH); dimethylsulfoxide (DMSO); *N,N*-dimethylformamide (DMF); trifluoroacetic acid (TFA); tetrahydrofuran (THF); Normal(N); aqueous (aq.); methanol (MeOH); dichloromethane (DCM); ethyl acetate (EtOAc); Retention factor (Rf); room temperature (RT).

[0132] The following General Synthetic Schemes and Examples are provided to illustrate and not to be limiting. Those skilled in the art will be familiar with many of the reaction steps described. Particular publications are presented to assist with certain steps of the synthetic route.

General Synthetic Scheme 1

[0133] General Synthetic Scheme 1 provides methods to prepare compounds with a thiazole or imidazole B-ring as presented herein. Substituents R₁-R₆ are as exemplified in the Examples below. Syntheses of tricyclic substituted thiazoles, oxazoles and imidazoles, such as those presented herein, will be familiar to those skilled in the art. An example to illustrate a synthesis of a substituted thiazole is presented below. Complete details for syntheses of the compounds presented herein are provided in the Examples.



A = aromatic or heteroaromatic ring
Y = O, S, NH

[0134] **General procedure:** The corresponding substituted pyridine-4-carbothioamide or isonicotinamide and the corresponding substituted 2-bromoacetylbenzene are dissolved in

EtOH. The resultant reaction mixture is stirred at between RT and 70 °C for between 30 min and 2 h. The progress of the reaction is monitored by TLC and LCMS. The reaction mixture is cooled to RT, basified with aq. sodium bicarbonate solution and the mixture extracted with EtOAc. The organic layer is dried over sodium sulfate and concentrated to obtain the crude product, which is purified by silica gel (100-200 mesh) column chromatography / by HPLC to obtain the desired product.

EXAMPLES

Example 1. Preparation of Compound No. 1

[0135] Pyridine (0.02 mL, 0.248 mmol) was added to a solution of triflic anhydride (0.05 mL, 0.297 mmol) at 0 °C under nitrogen in DCM (2 mL). After 15 min, 4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)aniline (70 mg, 0.236 mmol) was added dropwise at 0 °C in DCM (3 mL). The reaction was allowed to stir at RT for additional 30 min, monitored by TLC. After completion, the reaction mixture was diluted with water (10 mL) and the mixture extracted with EtOAc (2x20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product, which was purified by reverse phase preparative HPLC to obtain 17 mg of 1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide (yellow solid). This was treated with 2N aq. HCl for salt formation. ¹H NMR (400 MHz, CD₃OD) δ (ppm): 8.77 (d, J = 6.2 Hz, 1H), 8.54 (s, 1H), 8.48 (d, J = 6.2 Hz, 1H), 8.36 (s, 1H), 8.13 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 3.18-2.98 (m, 2H), 1.91 (p, J = 7.7 Hz, 2H), 1.10 (t, J = 7.4 Hz, 3H).

Example 2. Preparation of Compound No. 2

[0136] 2-Propylpyridine-4-carbothioamide (50 mg, 0.118 mmol) and N-(3-(2,2-dibromoacetyl)phenyl)-1,1,1-trifluoromethanesulfonamide (16.9 mg, 0.09 mmol) were charged in acetic acid (1 mL) and the reaction mixture was stirred at 80 °C for 30 min. The reaction was monitored by LCMS and acetic acid was evaporated under vacuum. The crude reaction mixture was purified using reverse phase chromatography to get 2.4 mg of 1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide. ¹H NMR (CD₃OD) δ (ppm): 8.59 (d, J = 5.3 Hz, 1H), 8.08 (s, 1H), 8.00 (s, 1H), 7.94 (m, 2H), 7.49 (m, 1H), 7.33 (d, J = 8.1 Hz, 1H), 2.99-2.77 (m, 3H), 1.83 (m, 2H), 1.03 (t, J = 7.3 Hz, 3H).

Example 3. Preparation of Compound No. 4

[0137] N-(4-(2-Bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (50mg, 0.132 mmol) and 2-propylpyridine-4-carbothioamide (23.8 mg, 0.132mmol) were charged in

EtOH (10 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated and purified through reverse phase HPLC. Yield: 17 mg TFA salt. ¹H NMR (TFA salt, CD₃OD) δ (ppm): 8.72 (d, J=6.0 Hz, 1H), 8.38 (d, J=7.6 Hz, 1H), 8.31 (d, J=6.0 Hz, 2H), 8.07 (d, J=8.5 Hz, 1H), 7.49 (s, 1H), 3.04 (t, J=7.8 Hz, 3H), 1.88 (m, 2H), 1.07 (s, J=7.3 Hz, 3H).

Example 4. Preparation of Compound No. 5

[0138] 2-tert-Butylpyridine-4-carbothioamide (100 mg, 0.26 mmol) and N-(4-(2-bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (51 mg, 0.26 mmol) were charged in EtOH (5 mL) and the reaction mixture was stirred at 80 °C for 30 min. The reaction was monitored by LCMS, and then the EtOH was evaporated under vacuum. The reaction mixture was purified using reverse phase chromatography to get 43mg of N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide. ¹H NMR (HCl salt, CD₃OD) δ (ppm): 8.76 (d, J =6.1 Hz, 1H), 8.50 (s, 1H), 8.43 (m, 2H), 8.06 (d, J=8.5 Hz, 1H), 7.50 (d, J=2.2Hz, 1H), 7.4 (m, 1H), 1.58 (s, 9H).

Example 5. Preparation of Compound No. 57

Synthesis of 1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide

Step-1: Synthesis of 3-methoxy-4-nitrobenzoyl chloride

[0139] 3-Methoxy-4-nitrobenzoicacid (5) (3 g) and thionyl chloride (10 mL) were added dropwise at 0 °C. The reaction mixture was allowed to come to RT and heated to reflux overnight. Thionyl chloride was evaporated and ice was added to the reaction mixture. The organic layer was extracted in ethyl acetate (2x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to get 6 g of 3-methoxy-4-nitrobenzoyl chloride.

Step-2: Synthesis of 1-(3-methoxy-4-nitrophenyl)ethanone

[0140] A suspension of anhydrous magnesium chloride (932 mg, 9.8 mmol) in toluene (13 mL) was treated with triethylamine (4.7 mL, 33.4 mmol) and diethylmalonate (2.7 mL, 16.74 mmol). The reaction mixture was stirred at RT for 1.5 h. Finally, 3-methoxy-4-nitrobenzoyl chloride (6) (3 g, 13.9 mmol) was added and the reaction mixture was stirred at RT for 18 h. Concentrated hydrochloric acid (10 mL) was added and the organic layer was separated. DMSO (11.5 mL) and water (0.5 mL) were added and the mixture was heated to reflux for 2

h. The reaction mixture was allowed to come to RT and partitioned between water and EtOAc. The organic phase was washed subsequently with saturated sodium bicarbonate solution and brine and concentrated to get 2.5 g of 1-(3-methoxy-4-nitrophenyl)ethanone.

Step-3: Synthesis of 1-(4-amino-3-methoxyphenyl)ethanone

[0141] 1-(3-Methoxy-4-nitrophenyl)ethanone (2 g, 10.25 mmol) was charged in MeOH (30 mL). Iron powder (1.72 g, 30.76 mmol) was added and concentrated HCl (10 mL) was added dropwise with constant stirring. The reaction mixture was heated at 60 °C for 1 h. The iron powder was filtered off and MeOH was concentrated. Water (10 mL) was added and the organic layer was extracted in EtOAc (3x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to get 1.2 g of 1-(4-amino-3-methoxyphenyl)ethanone.

Step-4: Synthesis of N-(4-acetyl-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0142] Triflic anhydride (0.6ml 3.6 mmol) was charged in DCM (20 mL). The reaction mixture was cooled to 0 °C and pyridine was added dropwise with constant stirring. After 15 min, 1-(4-amino-3-methoxyphenyl)ethanone (500mg, 3.03 mmol) was dissolved in DCM (10 mL) and added slowly to the reaction mixture. The reaction mixture was allowed to come to RT and the reaction mixture was stirred at RT for 1 h. The reaction was monitored by TLC. Water (15 mL) was added and the organic layer was extracted in DCM (3x100 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to get 700 mg of N-(4-acetyl-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide.

Step-5: Synthesis of N-(4-(2-bromoacetyl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0143] N-(4-Acetyl-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide (700 mg, 2.35 mmol) was charged in chloroform (50 mL) and the reaction mixture was cooled to 0 °C. Liquid bromine (0.125 mL, 2.35 mmol) was added dropwise and the reaction mixture was stirred at RT for 18 h. A saturated solution of sodium thiosulfate (20 mL) was added and the chloroform layer was isolated and concentrated under reduced pressure to get 525 mg of N-(4-(2-bromoacetyl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide.

Step-6: Synthesis of 1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)methanesulfonamide

[0144] N-(4-(2-Bromoacetyl)-3-chlorophenyl)methanesulfonamide (50 mg, 0.133 mmol) and 2-isobutylpyridine-4-carbothioamide compound (20.6 mg, 0.10 mmol) were charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture

was concentrated under reduced pressure and purified through reverse phase HPLC to get 16 mg of 1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide. ¹H NMR (400 MHz, Methanol-d₄) : δ (ppm): 8.56 (d, J = 5.2 Hz, 1H), 7.96 – 7.70 (m, 3H), 7.58 (d, J = 1.9 Hz, 1H), 7.48 (dd, J = 8.3, 1.9 Hz, 1H), 7.33 (dd, J = 8.3, 2.1 Hz, 2H), 3.92 (s, 3H), 2.76 (d, J = 7.3 Hz, 2H), 2.12 (td, J = 14.0, 7.2 Hz, 1H), 0.98 (d, J = 6.6 Hz, 6H). LCMS: 473.2 (M+1).

Example 6. Preparation of Compound No. 58

Steps 1-5: Synthesis of N-(4-(2-bromoacetyl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0145] See Example 6.

Step-6: Synthesis of N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide:

[0146] N-(4-(2-Bromoacetyl)-3-chlorophenyl)methanesulfonamide (50 mg, 0.133 mmol) and 2-propylpyridine-4-carbothioamide (18 mg, 0.1 mmol) were charged in ethanol (10 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified through reverse phase HPLC to get 17 mg of N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide. ¹H NMR (400 MHz, Methanol-d₄) : δ (ppm): 8.68 (d, J = 5.8 Hz, 1H), 8.28 (d, J = 5.9 Hz, 1H), 8.22 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.68 (dd, J = 8.4, 1.8 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 4.02 (s, 3H), 3.01 (m, 2H), 1.87 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H). LCMS: (M+1) 458.3.

Example 7. Preparation of Compound No. 59

Steps 1-5: Synthesis of N-(4-(2-bromoacetyl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0147] See Example 6.

Step-6: Synthesis of N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0148] N-(4-(2-Bromoacetyl)-3-chlorophenyl)methanesulfonamide (50 mg, 0.133 mmol) and 2-tert-butylpyridine-4-carbothioamide (20.6 mg, 0.10 mmol) were charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified through reverse phase HPLC to get 15 mg of N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide. ¹H NMR (400 MHz, Methanol-d₄): δ (ppm): 8.61 (d, J = 5.1 Hz, 1H), 8.03 (d, J = 3.3 Hz, 2H),

7.82 (dd, J = 5.2, 1.6 Hz, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.60 (dd, J = 8.3, 1.9 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 3.98 (s, 3H), 1.45 (s, 9H). LCMS: (M+1) 472.5.

Example 8. Preparation of Compound No. 60

[0149] N-(4-(2-Bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.263 mol) and 2-benzylpyridine-4-carbothioamide (54.1 mg, 0.237 mol) were charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 1 h. A yellow solid reaction mixture was obtained, which was filtered and the residue was washed with diethyl ether (15 mL) to get N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide (33 mg) as a brown solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.85-8.68 (d, J = 6.2 Hz, 1H), 8.55-8.39 (m, 2H), 8.03 (d, J=8.5 Hz, 1H), 7.49 (d, J=2.3 Hz, 1H), 7.48-7.31 (m, 7H), 4.51 (s, 2H). LCMS (M+1): 510.1.

Example 9. Preparation of Compound No. 61

Step-1: Synthesis of 2-aminopyridine-4-carbothioamide

[0150] To a solution of 2-aminoisonicotinamide (100 mg, 0.0729 mol, 1 eq.) in pyridine (3 mL), phosphorus pentasulfide (83 mg, 0.0365 mol, 0.5 eq.) was added. The reaction was heated at 100 °C for 3 h. The reaction was monitored by LCMS. After completion, pyridine was concentrated under reduced pressure and residue was dissolved in water (5 mL) and the mixture extracted with EtOAc (3x15 mL). The EtOAc extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to get 33 mg of 2-aminopyridine-4-carbothioamide as a yellow solid.

Step-2: Synthesis of 2-chloro-4-nitrobenzoyl chloride

[0151] To a two neck RBF (1 liter) placed in ice bath, 2-chloro-4-nitrobenzoic acid (50 g, 0.248 mol, 1 eq.) was charged. Thionyl chloride (110 mL, 1.51 mol, 6.1 eq.) was added dropwise at 0 °C. The reaction mixture was allowed to come to RT and then heated to reflux. The reflux was continued overnight. Thionyl chloride was evaporated and ice (approx. 150 g) was added into the reaction mixture. The aqueous reaction mass was extracted with DCM (2x200 mL). The DCM extracts were combined dried over anhydrous sodium sulfate and concentrated under vacuum to get 50 g (91.7 %) of 2-chloro-4-nitrobenzoyl chloride as a light yellow liquid.

Step-3: Synthesis of 1-(2-chloro-4-nitrophenyl) ethanone

[0152] A suspension of anhydrous magnesium chloride (47 g, 0.214 mol, 0.7 eq.) in toluene (300 mL) was treated with triethylamine (75.04 mL, 0.535 mol, 2.5 eq.) and diethylmalonate (41.09 g, 0.257 mol, 1.2 eq.). The reaction mixture was stirred at RT for 1.5 h. To this was added 2-chloro-4-nitrobenzoyl chloride (4) (47 g, 0.214 mol, 1 eq.) was added dropwise (an exothermic reaction up to 50 °C was observed during addition). Toluene (50 mL) was used for complete transfer of 2-chloro-4-nitrobenzoyl chloride to the reaction mixture. The reaction mixture was stirred at RT for 18 h. The reaction was monitored by TLC and NMR. After complete consumption of starting material, concentrated hydrochloric acid (35 % solution) (300 mL) was added and the upper toluene layer was separated. Toluene was evaporated under reduced pressure below 50 °C. To the residue after concentration, DMSO (200 mL) and water (10 mL) were added and the mixture was heated at 160 °C for 12 h. The reaction was monitored by TLC and NMR. The reaction mixture was allowed to come to RT and water (40 mL) was added to the reaction mixture. The reaction mixture was extracted with EtOAc (3x200 mL). The EtOAc extracts were combined was washed brine solution (3x300 mL) and dried over anhydrous sodium sulfate. The EtOAc layer was concentrated to get 43 g (100%) of 1-(2-chloro-4-nitrophenyl) ethanone as a yellow liquid which solidified upon refrigeration.

Step-4: Synthesis of 1-(4-amino-2-chlorophenyl) ethanone

[0153] 1-(2-Chloro-4-nitrophenyl) ethanone (126 g, 0.63 mole 1 eq.) was dissolved in MeOH (600 mL). Iron powder (105.8 g, 1.89 mol, 3 eq.) was added to the solution. Concentrated HCl (130 mL, 1.89 mol, 3 eq.) was added dropwise with constant stirring. The reaction mixture was then heated at 70 °C for 12 h. The reaction was monitored by TLC and NMR. The reaction mixture showed presence of starting material. The same quantity of iron powder and concentrated HCl were added again at 70 °C and the heating was continued at 70 °C for 4 h. The reaction mixture was again monitored by TLC and NMR. After completion of reaction, Iron powder was filtered through a celite bed and the MeOH filtrate was concentrated. Water (100 mL) was added and the reaction mixture was extracted in EtOAc (5x300 mL). The EtOAc extracts were combined, dried over anhydrous sodium sulfate and concentrated to get 100 g of crude product. 71 g of the crude product was purified through silica column (#100-200) using 0-20% EtOAc: hexane as eluant to get 38.6 g (52.5 %) of 1-(4-amino-3-methoxyphenyl) ethanone (6) as pink solid. ¹H NMR (400 MHz, Chloroform-d):

δ (ppm): 7.62 (d, J = 8.5 Hz, 1H), 6.66 (d, J = 2.3 Hz, 1H), 6.54 (dd, J = 8.5, 2.3 Hz, 1H), 4.07 (s, 2H), 2.61 (s, 3H).

Step-5: Synthesis of N-(4-acetyl-3-chlorophenyl)-1, 1, 1-trifluoromethanesulfonamide

[0154] A solution of triflic anhydride (75.1 g, 0.266 mol, 1.5 eq.) in DCM (600 mL) was cooled to 0 °C. Pyridine (21.4 mL, 0.266 mol, 1.5 eq.) was added dropwise with constant stirring over 30 min. The reaction mixture was stirred at same temperature for 1 h. A solution of 1-(4-amino-2-chlorophenyl)ethanone (30 g, 0.177 mol, 1 eq.) in DCM (400 mL) was added dropwise maintaining the temperature 0 °C with constant stirring over a period of 45 min. The reaction mixture was then allowed to come to RT and stirred for 1 h at RT. The reaction was monitored by TLC and NMR. Upon completion, ice water (500 mL) was added and the DCM layer was separated. The aqueous layer was again extracted with DCM (2x100 mL). The DCM extracts were combined washed with ice water (2x500 mL). The DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure below 40 °C to obtain the crude product. Diethyl ether (200 mL) and pentane (600 mL) were added into the reaction mixture and stirred for 30 min. The reaction mixture was filtered and the mother liquor was concentrated and triturated in pentane to get 28 g (52.8%) of N-(4-acetyl-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide as a light pink solid.

Step-6: Synthesis of N-(4-(2-bromoacetyl)-3-chlorophenyl)-1, 1, 1-trifluoromethanesulfonamide

[0155] A solution of N-(4-acetyl-3-chlorophenyl)-1, 1, 1-trifluoromethanesulfonamide (21 g, 0.07 mol, 1 eq.) in chloroform (600 mL) was cooled to 0 °C. Liquid bromine (2.9 mL, 0.004 mol, 0.8 eq.) dissolved in chloroform (400 mL) was added dropwise over a period of 40 min, maintaining the temperature between 0-10 °C. The reaction mixture was allowed to come to RT and was stirred at RT for 18 h. The reaction was monitored by TLC and NMR, which indicated the presence of starting material and desired compound along with some amount of N-(3-chloro-4-(2,2-dibromoacetyl)phenyl)-1,1,1-trifluoromethanesulfonamide (dibromo impurity). A saturated solution of sodium thiosulfate (200 mL) was added and the chloroform layer was separated. The aqueous layer was extracted with chloroform (2x100 mL). The main chloroform layer and the chloroform extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. A clear liquid was obtained as a residue. To this were added diethylether (50 mL) and pentane (250 mL) and the mixture stirred for 10 min. The reaction mixture was filtered off and mother liquor was concentrated. The crude product obtained was triturated with pentane (~50 mL) to obtain a white solid. The white

solid obtained was filtered off and dried under vacuum to get 20 g of N-(4-(2-bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide with contained approximately 35% of starting material *i.e.* N-(4-acetyl-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide by NMR. The mixture of both was directly used in the next step.

Step-7: Synthesis of N-(4-(2-(2-aminopyridin-4-yl)thiazol-5-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide:

[0156] N-(4-(2-Bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (50 mg, 0.132 mmol, 1 eq.) and 2-aminopyridine-4-carbothioamide (32.8 mg, 0.132 mmol, 1 eq.) were charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 12 h. The reaction mixture was concentrated and purified by reverse phase chromatography to get 6.8 mg of N-(4-(2-(2-aminopyridin-4-yl) thiazol-5-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide. ¹H NMR (400 MHz, Methanol-d₄): δ (ppm): 8.25 (s, 1H), 8.01 – 7.89 (m, 2H), 7.55 (d, J = 1.6 Hz, 1H), 7.46 – 7.40(m, 1H), 7.33 (dd, J = 8.5, 2.2 Hz, 1H). LCMS: (M+1) 435.1.

Example 10. Preparation of Compound No. 62

Steps 1-7: Synthesis of N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide

[0157] See Example 10.

Step-8: Synthesis of N-(3-chloro-4-(2-(2-(methylsulfonamido)pyridin-4-yl)thiazol-5-yl)phenyl)-1,1,1-trifluoromethanesulfonamide

[0158] N-(4-(2-(2-Aminopyridin-4-yl)thiazol-5-yl)-3-chlorophenyl)-1,1,1-trifluoro methane sulfonamide (50 mg, 0.115 mmol, 1 eq.) was charged in pyridine (3 mL). The reaction mixture was cooled to 0 °C and methane sulfonyl chloride (0.01 mL, 0.115 mol, 1 eq.) was added dropwise with constant stirring. The reaction mixture was allowed to come to RT and the reaction mixture was stirred at RT for 1 h. Pyridine was evaporated and water was added and the mixture extracted in EtOAc (3x100 mL). The combined organic layer was concentrated and purified using reverse phase chromatography to get 1.3 mg of N-(3-chloro-4-(2-(2-(methylsulfonamido)pyridin-4-yl)thiazol-5-yl)phenyl)-1,1,1-trifluoromethanesulfonamide. ¹H NMR (400 MHz, Methanol-d₄): δ (ppm): 8.32 (d, J = 5.6 Hz, 1H), 8.17 (s, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.66 (s, 1H), 7.59 (dd, J = 5.6, 1.6 Hz, 1H), 7.47 (d, J = 2.3 Hz, 1H), 7.35 (dd, J = 8.6, 2.3 Hz, 1H), 3.2 (s, 1H). LCMS: 513 (M+1).

Example 11. Preparation of Compound No. 63

Steps 1-6: Synthesis of N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide:

[0159] See Example 7.

Step-7: Synthesis of 1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide

[0160] 1,1,1-Trifluoro-N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide (17 mg, 0.037 mmol, 1 eq.) charged in DCM (5 mL) and the reaction mixture was cooled at 0 °C. A 1M solution of boron tribromide (0.12 mL, 0.11mmol) was added dropwise. The reaction mixture was allowed to come to RT and stirred at RT for 12 h. The reaction was monitored by LCMS. A saturated sodium bicarbonate was added and the mixture extracted in EtOAc (3x25 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure and the crude reaction mixture was purified using reverse phase HPLC to get (1.5 mg) of 1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide as the TFA salt. ¹H NMR (400 MHz, Methanol-d₄): δ (ppm): 8.63 (d, J = 5.6 Hz, 1H), 8.13 – 8.00 (m, 2H), 7.63 (d, J = 1.9 Hz, 1H), 7.53 – 7.38 (m, 2H), 2.94 (t, J = 7.7 Hz, 2H), 1.84 (p, J = 7.5 Hz, 2H), 1.05 (t, J = 7.4 Hz, 3H) LCMS (M+1): 444.4.

Example 12. Preparation of Compound No. 64

[0161] N-(4-(2-Bromoacetyl)-3-chlorophenyl)1,1,1-trifluoro methane sulfonamide (100 mg, 0.263 mol) and 2-(3,3,3-trifluoropropyl) pyridine-4-carbothioamide (55.5 mg, 0.237 mol) were charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 1h. The resultant reaction mixture was concentrated under reduced pressure and purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (27 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.84 (d, J = 6.2 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H), 8.52 (d, J = 6.1 Hz, 1H), 8.42 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 2.3Hz, 1H), 7.40 (d, J = 8.5Hz, 1H), 3.42 (m 2H), 2.87 (m, 2H). LCMS (M+1): 516.1.

Example 13. Preparation of Compound No. 65

Steps 1-5: Synthesis of N-(4-(2-bromoacetyl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide

[0162] See Example 6

Step-6: Synthesis of 1,1,1-trifluoro-N-(2-methoxy-4-(2-(2-neopentylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide

[0163] N-(4-(2-Bromoacetyl)-3-chlorophenyl)methanesulfonamide (50 mg, 0.133 mmol) and 2-neopentylpyridine-4-carbothioamide (50 mg, 0.10 mmol) was charged in ethanol (5 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and purified through reverse phase HPLC to get 14 mg of 1,1,1-trifluoro-N-(2-methoxy-4-(2-(2-neopentylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide. ¹H NMR (400 MHz, Methanol-d₄): δ (ppm): 8.71 (d, J = 5.8 Hz, 1H), 8.33 – 8.14 (m, 2H), 7.76 (d, J = 1.9 Hz, 1H), 7.68 (dd, J = 8.4, 1.9 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 4.01 (s, 3H), 2.95 (s, 2H), 1.06 (s, 9H). LCMS: 486 (M+1).

Example 14. Preparation of Compound No. 66

[0164] A solution of triflic anhydride (0.03ml, 0.17 mmol, 1.5 eq.) in DCM (8 mL) was cooled to 0 °C. Pyridine (0.01 mL, 0.17 mmol, 1.5 eq.) was added dropwise with constant stirring over 30 min. A solution of N-(4-(2-(2-aminopyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (50 mg, 0.115 mmol, 1 eq.) in DCM (2 mL) was added dropwise maintaining the temperature at 0 °C with constant stirring over a period of 5 min. The reaction mixture was then allowed to come to RT and stirred for 1 h at RT. The reaction was monitored by LCMS and NMR. Upon completion, ice water (10 mL) was added and the DCM layer was separated. The aqueous layer was again extracted with DCM (2x20 mL). The DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure and purified using reverse phase chromatography to get 9.26 mg of N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide. ¹H NMR (400 MHz, Methanol-d₄): δ (ppm): 8.40 – 8.22 (m, 2H), 8.06 (dd, J = 7.6, 3.6 Hz, 2H), 7.72 (dd, J = 6.6, 1.7 Hz, 1H), 7.49 (d, J = 2.3 Hz, 1H), 7.37 (dd, J = 8.6, 2.3 Hz, 1H). LCMS (M+1): 566.8.

Example 15. Preparation of Compound No. 67

[0165] N-[4-(2-Bromothiazol-4-yl)-3-chloro-phenyl]-1,1,1-trifluoro-methanesulfonamide (300 mg, 0.71 mmol, 1 eq.), [4-(piperidine-1-carbonyl)phenyl]boronic acid (233 mg, 1.4 eq.) and sodium carbonate (189 mg, 2.5 eq. in 1 mL water) were charged in 5 mL of DMF in a 25

mL glass bottle and aerated with nitrogen gas for 7 min. After adding Pd(PPh₃)₄ (82.5 mg, 0.1 mmol) the mixture was further purged for 3 min and was heated to 100 °C overnight. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT; water (10 mL) was added and the mixture extracted with EtOAc (3x50 mL). The combined organic layer was washed with water (4x50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[4-(piperidine-1-carbonyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (207 mg) as a white solid as the free base. ¹H NMR (400 MHz, Chloroform-d) δ (ppm): 7.98 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.82 (s, 1H), 7.36 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 2.2 Hz, 1H), 6.98 (dd, J = 8.5, 2.3 Hz, 1H), 3.78 (s, 2H), 3.37 (s, 2H), 1.72 (s, 4H), 1.55 (s, 2H). LCMS (M+1): 530.1.

Example 16. Preparation of Compound No. 68

[0166] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (200 mg, 0.4761 mmol) and 1-isopentyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (150.9 mg, 0.5714 mmol), sodium carbonate (100 mg, 0.952 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (55 mg, 0.0476 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT; water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (135 mg) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.05 (s, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.47 (d, J = 2.2 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 4.75 (m, 2H), 1.77 (m, J = 9.4 Hz, 2H), 1.60 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H). LCMS (M+1): 479.1.

Example 17. Preparation of Compound No. 69

Step-1: Synthesis of N-[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanesulfonamide

[0167] 3-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (506 mg, 1 mmol, 1 eq.) was suspended in DCM (18 mL) then TEA (808 mg, 4 eq.) added and stirred for 5 min at RT. The mixture was maintained at ice-bath condition and mesyl chloride (458 mg, 2 eq.)

was added dropwise and stirred for 2 h at the same temperature. The reaction was monitored by ¹H-NMR. After completion of the reaction, the solvent was evaporated to get the desired product as a solid which was used for next step without any further purification.

Step-2: Synthesis of 4-(4-bromo-2-thienyl)-2-tert-butyl-pyridine

[0168] 2,4-Dibromothiophene (150 mg, 0.62 mmol), 2-tert-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (242 mg, 1.5 equiv) and sodium carbonate (164 mg, 1.54 mmol, 2.5 eq. in 1.0 mL water) in dimethyl formamide (5 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 8 min. After adding Pd(PPh₃)₄ (35 mg, 0.05 mmol) and Xantphos (35.8 mg, 0.1 eq.), the mixture was further purged for 3 min, and was heated to 100 °C overnight. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT; water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain crude 4-(4-bromo-2-thienyl)-2-tert-butyl-pyridine, which was used as such for the next step of synthesis without any further purification.

Step-3: Synthesis of N-[4-[5-(2-tert-butyl-4-pyridyl)-3-thienyl]-3-chlorophenyl]methanesulfonamide

[0169] 4-(4-Bromo-2-thienyl)-2-tert-butyl-pyridine (170 mg, 0.576 mmol, 1 eq.), N-[3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl] methanesulfonamide (286 mg, 1.5 eq.) and sodium carbonate (152 mg, 2.5 equiv) were charged in DMF (5 mL) in a 25 mL glass bottle and aerated with nitrogen gas for 7 min. After adding Pd(PPh₃)₄ (66 mg, 0.1 mmol) the mixture was further purged for 3 min and was heated to 100 °C overnight. The reaction was monitored by LCMS. The reaction mixture was allowed to come to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-chlorophenyl}methanesulfonamide (64 mg) as a light yellow solid as the formate salt. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.53 (d, J = 5.2 Hz, 1H), 7.99 (s, 1H), 7.82 (s, 1H), 7.65 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 5.2 Hz, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.24 (dd, J = 8.2, 2.1 Hz, 1H), 3.07 (s, 3H), 1.36 (s, 9H). LCMS (M+1): 421.1.

Example 19. Preparation of Compound No. 70

[0170] N-(4-(2-Bromoacetyl)-3-chlorophenyl) 1, 1, 1-trifluoro methane sulfonamide (200 mg, 0.527 mol) and 2-(cyclohexylmethyl) pyridine-4-carbothioamide (111.2 mg, 0.475 mol) were charged in ethanol (10 mL) and the reaction mixture was heated at 80 °C for 1h. The resultant reaction mixture was concentrated under reduced pressure and purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (45 mg) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.75 (d, J = 6.2 Hz, 1H), 8.46-8.36 (m, 3H), 8.07 (d, J=8.5 Hz, 1H), 7.49 (d, J=2.3Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 2.98 (d, J = 7.3Hz, 2H), 1.88 (m, J = 10.9Hz, 1H), 1.76 (m 5H), 1.35 (m, 5H). LCMS (M+1): 516.1.

Example 19. Preparation of Compound No. 71

[0171] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and naphthalene-1-yl-boronic acid (61.3 mg, 0.3571 mmol), cesium carbonate (155 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (40 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.69-8.60 (d, J = 6.2 Hz, 1H), 8.18 (s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.04-7.96 (m, 2H), 7.92 (d, J = 7.2 Hz, 1H), 7.6 (m, 3H), 7.53 (d, J = 2.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H). LCMS (M+1): 469.0.

Example 20. Preparation of Compound No. 72

[0172] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 1H-indole-6-yl-boronic acid (57.4 mg, 0.357mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol) the reaction mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and

the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (43 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.10 (d, J = 6.2 Hz, 1H), 8.04 (d, J = 1.9 Hz, 1H), 7.88 (s, 1H), 7.65 (m, 2H), 7.48 (d, J = 2.2 Hz, 1H), 7.39 (m, 2H), 6.52 (d, J = 7.2 Hz, 1H). LCMS (M+1): 457.9.

Example 21. Preparation of Compound No. 73

[0173] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 3-(benzyloxy)-4-(trifluoromethyl)phenylboronic acid (105.7 mg, 0.357 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (10 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.06-7.94 (m, 2H), 7.91-7.80 (d, J = 1.9 Hz, 1H), 7.71-7.67 (d, J = 1.9 Hz, 1H), 7.65-7.60 (m, 1H), 7.48-7.40 (m, 3H), 7.38-7.27 (m, 4H), 3.33 (d, J = 15.4 Hz, 2H). LCMS (M+1): 593.2.

Example 22. Preparation of Compound No. 74

[0174] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and biphenyl-2-ylboronic acid (70 mg, 0.357 mmol), potassium carbonate (65 mg, 0.476mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.238 mol), the mixture was heated to 100 °C for 18h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-

thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (18 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 7.92 (d, J = 7.8 Hz, 2H), 7.72-7.59 (m, 2H), 7.57-7.47 (m, 2H), 7.43 (d, J = 2.2 Hz, 1H), 7.43-7.35 (m, 3H), 7.28 (m, 3H). LCMS (M+1): 495.

Example 23. Preparation of Compound No. 75

[0175] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and isoquinolin-4-ylboronic acid (61.7mg, 0.357 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (18 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 9.41 (s, 1H), 9.08 (d, J = 8.5 Hz, 1H), 8.95 (s, 1H), 8.38 (d, J = 2.3 Hz, 1H), 8.28 (s, 1H), 7.98-8.12 (m, 2H), 7.88 (m, 1H), 7.58 (s, 1H), 7.39 (d, J = 5.5 Hz, 1H). LCMS (M+1): 469.9.

Example 24. Preparation of Compound No. 76

[0176] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-2-yl)piperazine (108 mg, 0.357 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (54.2 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.28 (d, J = 5.6 Hz, 1H), 8.19 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.67 (s, 1H), 7.52-7.43 (m, 2H), 7.38 (d, J = 8.4 Hz, 1H), 4.60 (d, J = 14.5 Hz,

2H), 3.67 (d, J = 12.5 Hz, 2H), 3.42 (s, 2H), 3.22 (d, J = 10.5 Hz, 2H), 2.99 (s, 3H). LCMS (M+1): 518.06.

Example 25. Preparation of Compound No. 77

[0177] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (79.6 mg, 0.357 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (3.2 mg) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.20 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 2.73 (s, 3H), 2.52 (s, 3H). LCMS (M+1): 437.9.

Example 26. Preparation of Compound No. 78

[0178] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 4-methyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzenesulfonamide (133 mg, 0.357 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-methylbenzene-1-sulfonamide (35.2 mg) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 10.48 (s, 1H), 8.11 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.78-7.66 (m, 3H), 7.62 (d, J = 7.8 Hz, 1H), 7.43-7.34 (m, 2H), 7.37-7.27 (m, 2H), 7.23 (d, J = 8.0 Hz, 1H), 2.32 (s, 3H). LCMS (M+1): 588.

Example 27. Preparation of Compound No. 79

[0179] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and (3,4-dimethoxy phenyl) boronic acid (64.9 mg, 0.3571 mmol), cesium carbonate (155 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (11 mg) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 7.70 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 2.1 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.90(s, 3H). LCMS (M+1): 479.0.

Example 28. Preparation of Compound No. 80

[0180] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 1H-indole-4-yl-boronic acid (57.5 mg, 0.3571 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (30 mg) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.10 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.72 (d, J = 7.4 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.43 (t, J = 2.8 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 5.4 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H). LCMS (M+1): 457.7.

Example 29. Preparation of Compound No. 81*Step-1: Synthesis of 4-fluoro-2-(trifluoromethyl)benzamide*

[0181] A solution of 4-fluoro-2-(trifluoromethyl)benzonitrile (100 mg, 0.528 mmol) in conc. sulfuric acid (1.2 mL) and glacial acetic acid (0.8 mL) was heated at 120 °C for 0.5h, monitored by TLC. The reaction was diluted with water and the mixture extracted with EtOAc (2x30 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 80 mg of 4-fluoro-2-(trifluoromethyl)benzamide as an off-white solid.

Step-2: Synthesis of 4-fluoro-2-(trifluoromethyl)benzenecarbothioamide

[0182] A solution of 4-fluoro-2-(trifluoromethyl)benzamide (500 mg, 2.414 mmol) and Lawesson's Reagent (1.95 g, 4.821 mmol) in toluene (30 mL) was heated at 80 °C for 1h. The progress of the reaction was monitored by TLC. The reaction was diluted with water (30 mL) and the mixture extracted with EtOAc (2x50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a crude product, which was purified by column chromatography (silica-gel, 230-400 mesh) using 10 % EtOAc in hexane as eluent to obtain 100 mg of 4-fluoro-2-(trifluoromethyl)benzenecarbothioamide as a yellow sticky compound.

Step-3: Synthesis of N-[3-chloro-4-[2-[4-fluoro-2-(trifluoromethyl)phenyl]thiazol-4-yl]phenyl]-1,1,1-trifluoro-methanesulfonamide

[0183] A solution of 4-fluoro-2-(trifluoromethyl)benzenecarbothioamide (50 mg, 0.224 mmol) and N-[4-(2-bromoacetyl)-3-chloro-phenyl]-1,1,1-trifluoro-methanesulfonamide (170 mg, 0.446 mmol) in ethanol (10 mL) was heated at 70 °C for 40 min, monitored by TLC. The reaction was diluted with aqueous saturated NaHCO₃ solution (25 mL) and the mixture extracted with EtOAc (2x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a crude product, which was purified by reverse phase preparative HPLC to obtain N-[3-chloro-4-[2-[4-fluoro-2-(trifluoromethyl)phenyl]thiazol-4-yl]phenyl]-1,1,1-trifluoro-methanesulfonamide (22 mg) as an off-white solid. ¹H NMR (400 MHz, Methanol-d₄): δ (ppm): 7.98 (s, 1H), 7.81 (dd, J = 8.6, 5.4 Hz, 1H), 7.68 (dd, J = 8.9, 3.0 Hz, 2H), 7.53 (td, J = 8.4, 2.6 Hz, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.11 (dd, J = 8.4, 2.1 Hz, 1H).

Example 30. Preparation of Compound No. 82

[0184] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 2,3-dihydrobenzofuran-5-boronic acid (58.5 mg, 0.3571 mmol), potassium carbonate (65 mg, 0.476 mmol), dimethyl formamide (5 mL), water (0.5 mL) were charged in a 2 neck round bottom flask and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol), the mixture was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT; water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (15 mg) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 7.97 (d, J = 8.5 Hz, 1H), 7.88 (s, 1H), 7.82 (s, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.44 (s, 1H), 7.32 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 4.63 (t, J = 8.7 Hz, 2H), 2.17 (t, J = 9.3 Hz, 2H). LCMS (M+1): 460.6.

Example 31. Preparation of Compound No. 83

[0185] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and [3-(bromomethyl)phenyl]boronic acid (61.3 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol), the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (9 mg) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.13 (s, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.97 – 7.79 (m, 1H), 7.51 – 7.43 (m, 2H), 7.41 (d, J = 2.2 Hz, 1H), 7.33 (dd, J = 8.6, 2.2 Hz, 1H), 4.59 (s, 2H). LCMS (M+1): 448.9.

Example 32. Preparation of Compound No. 84

[0186] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and [2-(bromomethyl)phenyl]boronic acid (56 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (25 mg) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.20 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.81 – 7.79 (m, 1H), 7.79 – 7.71 (m, 1H), 7.54 (dd, J = 7.5, 1.3 Hz, 1H), 7.43 (dt, J = 3.7, 1.9 Hz, 2H), 7.35 (dd, J = 8.5, 2.3 Hz, 1H), 4.87 (s, 2H). LCMS (M+1): 449.1.

Example 33. Preparation of Compound No. 85

[0187] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and [2-(1-piperidyl)-4-pyridyl]boronic acid (53 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (56 mg) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.23 – 8.07 (m, 2H), 7.38 (s, 1H) 7.83 (d, J = 8.5 Hz, 1H), 7.35 (s, 1H), 7.19 – 7.09 (m, 2H), 3.62 (t, J = 5.1 Hz, 4H), 3.17 (s, 2H), 1.60 (dt, J = 9.7, 5.7 Hz, 4H). LCMS (M+1): 504.0.

Example 34. Preparation of Compound No. 86

[0188] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and (3-methyl-4-pyridyl)boronic acid (35 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (13 mg) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.80 (s, 1H), 8.70 (s, 1H), 8.41 (s, 2H), 8.04 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 8.5, 2.3 Hz, 1H), 2.86 (s, 3H). LCMS (M+1): 434.4.

Example 35. Preparation of Compound No. 87

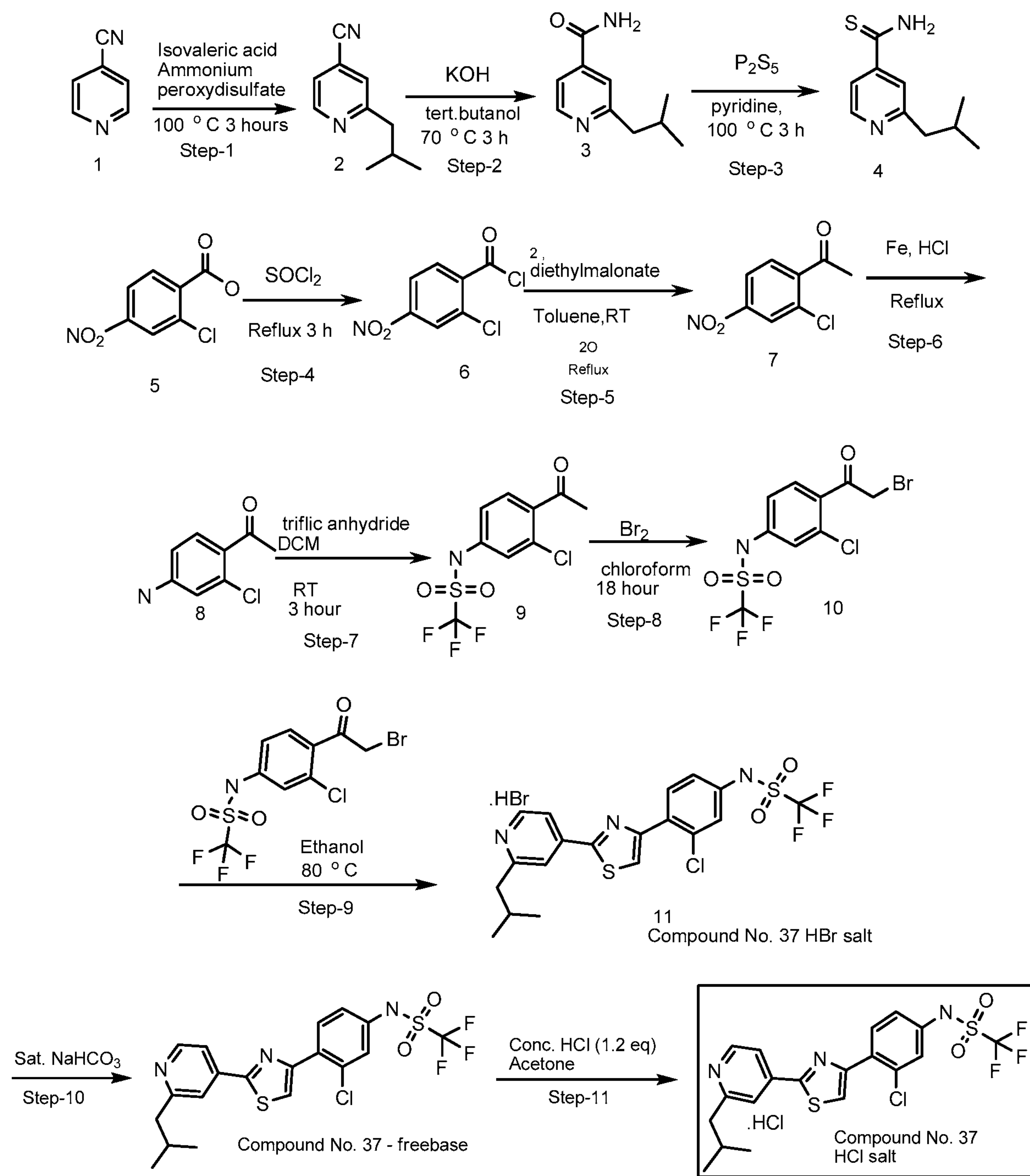
[0189] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (63 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide (37 mg) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.39 (d, J = 5.6 Hz, 1H), 8.29 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 5.6 Hz, 1H), 7.69 (d, J = 3.5 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.43 – 7.33 (m, 2H). LCMS (M+1): 459.5.

Example 36. Preparation of Compound No. 37

[0190] N-(4-(2-Bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (50mg, 0.132 mmol) and 2-isobutylpyridine-4-carbothioamide (25.34 mg, 0.132mmol) were charged

in EtOH (10 mL) and the reaction mixture was heated at 80 °C for 1 h. The reaction mixture was concentrated and purified through reverse phase HPLC. (Yield: 17 mg TFA salt). ¹H NMR (TFA salt, CD₃OD) δ (ppm): 8.73 (d, J=5.9 Hz, 1H), 8.38 (d, J=2.9 Hz, 1H), 8.31 (d, J = 6.2 Hz, 1H), 8.07 (d, J= 8.5 Hz, 1H), 7.49 (s, 1H), 7.39 (d, J=8.2 Hz, 1H), 2.94 (d, J=7.3 Hz, 2H), 2.19 (m, 2H), 1.07 (d, J=6.6 Hz, 6H).

Complete synthesis of Compound No. 37



Step 1: Synthesis of 2-isobutylpyridine-4-carbonitrile (2)

[0191] To a suspension of 4-cyano pyridine (**1**) (30 g, 0.288 mol, 1 equiv.) in water (210 mL), concentrated sulfuric acid (15.3 mL, 0.288 mol, 1 equiv.) was added dropwise maintaining the temperature at 20-25 °C. After formation of a clear solution, AgNO₃ (4.9 g, 0.028 mmol, 0.0001 equiv.) followed by isovaleric acid (160 mL, 1.47 mol, 5 equiv.) were added in to the reaction mixture. A white hazy solution formed. Ammonium peroxydisulfate (66 g, 0.288 mol, 1 equiv.) dissolved in water (90 mL) was then added. A black clear solution formed. The reaction mixture was then heated to reflux at 100 °C for 3 h. The reaction was monitored by TLC. After completion, the reaction mixture was basified (pH = 7-8) using a saturated solution of sodium bicarbonate, and extracted with EtOAc (3x750 mL). The extracts were combined and were washed with brine (3x300 mL) and dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel: #100-200) using 0-6 % EtOAc in hexane as eluant to afford 2-isobutylpyridine-4-carbonitrile (**2**) (15 g (32.5 % yield)) as a pale yellow liquid. ¹H NMR (400 MHz, Chloroform-*d*): δ (ppm): 8.78 – 8.63 (m, 1H), 7.41 – 7.27 (m, 2H), 2.72 (d, *J* = 7.2 Hz, 2H), 1.35 – 1.23 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 6H).

Step 2: Synthesis of 2-isobutylpyridine-4-carboxamide (3)

[0192] 2-Isobutylpyridine-4-carbonitrile (**2**) (15 g, 0.093 mol, 1 equiv.) and KOH (15.7 g, 0.281 mol, 3 equiv.) was dissolved in *tert*-butanol (160 mL). The reaction mixture was stirred at 70 °C for 90 min. The reaction was monitored by TLC. After completion, the *tert*-butanol was removed under reduced pressure; the residue was dissolved in water and extracted with EtOAc (3x275 mL). The extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was triturated with *n*-hexane (3x200 mL). To the residue was added diethyl ether (50 mL) and then concentrated under reduced pressure to afford 2-isobutylpyridine-4-carboxamide (**3**) (13.5 g (81.3 % yield)) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*): δ (ppm): 8.68 (d, *J* = 5.1 Hz, 1H), 7.49 (s, 1H), 7.42 (d, *J* = 5.1 Hz, 1H), 6.14(s, 1H), 5.81 (s, 1H), 2.73 (d, *J* = 7.3 Hz, 2H), 2.13 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 6H).

Step 3: Synthesis of 2-isobutylpyridine-4-carbothioamide (4)

[0193] To a solution of 2-isobutylpyridine-4-carboxamide (**3**) (13.5 g, 0.075mol, 1 equiv.) in pyridine (135 ml), was added P₂S₅ (8.45 g, 0.037 mol, 0.5 equiv.). The reaction was heated at 100 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the

pyridine was evaporated under reduced pressure; the residue was dissolved in water (100 mL) and extracted with EtOAc (3x250 mL). The EtOAc extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product obtained was triturated with *n*-hexane (3x200 mL) to afford 2-isobutylpyridine-4-carbothioamide (**4**) (8 g (54.4 % yield)) as a yellow solid. ¹H NMR (400 MHz, Chloroform-*d*): δ (ppm): 8.62 (d, *J* = 5.1 Hz, 1H), 7.73 – 7.64 (broad, 1H), 7.52 – 7.40 (m, 2H), 7.32 – 7.25 (m, 1H), 2.72 (d, *J* = 7.2 Hz, 2H), 2.13 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 6H).

Step 4: Synthesis of 2-chloro-4-nitrobenzoyl chloride (6)

[0194] To a two neck flask (1L) placed in ice bath was placed 2-chloro-4-nitrobenzoic acid (**5**) (50 g, 0.248 mol, 1 equiv.). Thionyl chloride (110 ml, 1.51 mol, 6.1 equiv.) was added dropwise at 0 °C. The reaction mixture was allowed to come to RT and then heated to reflux. The heating was continued overnight. The thionyl chloride was evaporated and ice (approx. 150 g) was added to the reaction mixture. The aqueous reaction mixture was extracted with DCM (2x200 mL). The DCM extracts were combined dried over anhydrous sodium sulfate and concentrated under vacuum to get 2-chloro-4-nitrobenzoyl chloride (**6**) (50 g (91.7 % yield)) as a light yellow liquid. ¹H NMR (400 MHz, Chloroform-*d*): δ (ppm): 8.37 (d, *J* = 2.2 Hz, 1H), 8.25 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.15 (d, *J* = 8.7 Hz, 1H).

Step 5: Synthesis of 1-(2-chloro-4-nitrophenyl)ethanone (7)

[0195] A suspension of anhydrous magnesium chloride (47 g, 0.214 mol, 0.7 equiv.) in toluene (300 mL) was treated with triethylamine (75.04 mL, 0.535 mol, 2.5 equiv.) and diethylmalonate (41.09 g, 0.257 mol, 1.2 equiv.). The reaction mixture was stirred at RT for 1.5 h. To this was added 2-chloro-4-nitrobenzoyl chloride (**6**) (47 g, 0.214 mol, 1 equiv.) dropwise (an exothermic reaction up to 50 °C was observed during addition). Toluene (50 mL) was used for complete transfer of 2-chloro-4-nitrobenzoyl chloride to the reaction mixture. The reaction mixture was stirred at RT for 18 h. The reaction was monitored by TLC and NMR. After complete consumption of starting material, concentrated hydrochloric acid (35 % solution) (300 mL) was added and the upper toluene layer was separated. The toluene was evaporated under reduced pressure below 50 °C. To the residue were added DMSO (200 mL) and water (10 mL), and the mixture heated at 160 °C for 12 h. The reaction was monitored by TLC and NMR. The reaction mixture was allowed to come to RT and water (40 mL) was added. The reaction mixture was extracted with EtOAc (3x200 mL). The EtOAc extracts were combined and washed with brine solution (3x300 mL) and dried over

anhydrous sodium sulfate. The EtOAc layer was concentrated to get 1-(2-chloro-4-nitrophenyl) ethanone (**7**) (43 g (84 % yield)) as a yellow liquid which solidified upon refrigeration. ¹H NMR (400 MHz, Chloroform-*d*): δ (ppm): 8.29 (d, *J* = 2.2 Hz, 1H), 8.17 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 2.66 (s, 3H).

Step 6: Synthesis of 1-(4-amino-2-chlorophenyl) ethanone (8)

[0196] 1-(2-Chloro-4-nitrophenyl) ethanone (87.8 g, 0.43 mol, 1 equiv.) was charged in methanol (600 mL). The reaction mixture was heated to 70 °C and concentrated HCl (131 mL, 1.29 mol, 3 equiv.) was added dropwise with constant stirring. After the completion of addition, iron powder (98.2 g, 1.75 mol, 4 equiv.) was added in four parts at 5 minute intervals. The reaction mixture was heated at 70 °C for 7 h and the reaction monitored by TLC and NMR. After completion of reaction, the mixture was allowed to come to RT and then filtered through a celite bed. The filtrate was concentrated under reduced pressure and celite bed was washed with EtOAc to obtain further crude product. Both portions were combined and water (200 mL) was added. The EtOAc layer was separated and aqueous layer was extracted with EtOAc (2x500 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to get crude product (57 g). This crude product was precipitated in pentane to get 1-(4-amino-3-methoxyphenyl) ethanone (**8**) (50g (67 % yield)) as a pink solid. ¹H NMR (400 MHz, Chloroform-*d*): δ (ppm): 7.62 (d, *J* = 8.5 Hz, 1H), 6.66 (d, *J* = 2.3 Hz, 1H), 6.54 (dd, *J* = 8.5, 2.3 Hz, 1H), 4.07 (s, 2H), 2.61 (s, 3H).

Step 7: Synthesis of N-(4-acetyl-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (9)

[0197] A solution of triflic anhydride (75.1 g, 0.266 mol, 1.5 equiv.) in DCM (600 mL) was cooled to 0 °C. Pyridine (23.4 mL, 0.266 mol, 1.5 equiv.) was added dropwise with constant stirring over 30 min. The reaction mixture was stirred at the same temperature for 1 h. A solution of 1-(4-amino-2-chlorophenyl)ethanone (**8**) (30 g, 0.177 mol, 1 equiv.) in DCM (400 mL) was added dropwise maintaining the temperature at 0 °C with constant stirring over a period of 45 min. The reaction mixture was then allowed to come to RT and stirred for 1 h at RT. The reaction was monitored by TLC and NMR. Upon completion, ice cold water (500 mL) was added and the DCM layer was separated. The aqueous layer was again extracted with DCM (2x100 mL). The DCM extracts were combined washed with ice cold water (2x500 mL). The DCM layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure below 40 °C to obtain the crude product. Diethyl ether (200 mL) and pentane (600 mL) were added to the mixture which was then stirred for 30 min. The mixture

was filtered and the filtrate concentrated and triturated in pentane to get N-(4-acetyl-3-chlorophenyl)-1, 1,1-trifluoromethanesulfonamide (**9**) (28 g (52.8% yield)) as a light pink solid. ¹H NMR (400 MHz, Chloroform-*d*): δ (ppm): 7.63 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 2.2 Hz, 1H), 7.28 – 7.21(m, 1H), 2.66 (s, 3H).

Step 8: Synthesis of N-(4-(2-bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (10)

[0198] A solution of N-(4-acetyl-3-chlorophenyl)-1, 1, 1-trifluoromethanesulfonamide (**9**) (21 g, 0.07 mol, 1 equiv.) in chloroform (600 mL) was cooled to 0 °C. Liquid bromine (2.9 mL, 0.004 mol, 0.8 equiv.) dissolved in chloroform (400 mL) was added dropwise over a period of 40 min, maintaining the reaction temperature between 0-10 °C. The mixture was allowed to come to RT and then stirred at RT for 18 h. The reaction was monitored by TLC and NMR. There was an indication of the presence of starting material and desired compound along with some amount of N-(3-chloro-4-(2,2-dibromoacetyl)phenyl)-1,1,1-trifluoromethanesulfonamide (dibromo impurity). A saturated solution of sodium thiosulfate (200 mL) was added and the chloroform layer was separated. The aqueous layer was extracted with chloroform (2x100 mL). The main chloroform layer and the chloroform extracts were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure. A clear liquid was obtained as the residue. To this were added diethylether (50 mL) and pentane (250 mL) and the mixture stirred for 10 min. The reaction mixture was filtered and the filtrate concentrated. The crude product obtained was triturated with pentane (~50 mL) to obtain a white solid. This white solid was filtered and dried under vacuum to get N-(4-(2-bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (**10**) (20 g) which contained approximately 35% of starting material *i.e.* N-(4-acetyl-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (**9**) by NMR. The mixture of products was directly used for the next step without any further purification. ¹H NMR (400 MHz, Chloroform-*d*): δ (ppm): 7.64 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 2.2 Hz, 1H), 7.30 – 7.27 (m, 1H), 4.51 (s, 2H).

Step 9: Synthesis of N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide (11)

[0199] N-(4-(2-Bromoacetyl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (**10**) (15.5 g, 0.041 mol, 1 equiv.) and 2-isobutylpyridine-4-carbothioamide (5.2 g, 0.027 mol, 0.65 equiv.) were charged in ethanol (40 mL) and the reaction mixture was heated at 80 °C for 30 min. The reaction mixture was cooled in an ice bath and stirred at 0 °C for 30 min. The solid obtained was isolated by filtration and washed with cold ethanol (2x5 mL). The solid obtained was dried under vacuum to get N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-

yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide (**11**) (10.2 g (53.6% yield)) as the hydrobromide salt. ¹H NMR (400 MHz, Methanol-*d*₄): δ (ppm): 8.80 (d, *J* = 6.3 Hz, 1H), 8.57 – 8.45 (m, 3H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 2.2 Hz, 1H), 7.40 (dd, *J* = 8.6, 2.3 Hz, 1H), 3.01 (d, *J* = 7.4 Hz, 2H), 2.21 (m, 1H), 1.06 (d, *J* = 6.6 Hz, 6H). UPLC: In method, Column Type : ACQUITY BEH SHIELD C18, Column ID: 2.1*50 mm, 1.7μ; Flow Rate - 0.35 mL/min, Mobile Phase A: 0.05% TFA; Mobile Phase B: acetonitrile. Gradient: 10% B To 50% B in 1min., hold for 0.5 min, 50% B to 90% B in 0.1 min, hold for 1 min, 90% B to 10% B in 0.4 min compound eluted at a retention time of 2.66 min.

Step 10: Synthesis of N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide - free base (12)

[0200] N-(3-Chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide hydrobromide salt (**11**) (88.5 g) was charged in a flask and a saturated solution of sodium bicarbonate (300 mL) was added so that the pH became slightly basic (pH=7-8). EtOAc (3x500 mL) was added and the reaction mixture was stirred at RT until the mixture became clear. The organic layer was separated and washed with water (50 mL). The EtOAc layer was dried over anhydrous sodium sulfate and concentrated to get N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide (**12**) (46.3g (61% yield)) as the free base. ¹H NMR (400 MHz, Methanol-*d*₄): δ (ppm): 8.56 (d, *J* = 5.3 Hz, 1H), 8.10 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.92 – 7.80 (m, 2H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.31 (dd, *J* = 8.5, 2.3 Hz, 1H), 3.06 (s, 3H), 2.86 (dd, *J* = 8.6, 6.7 Hz, 2H), 1.88 – 1.74 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H).

Step 11: Synthesis of N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide Hydrochloride (13)

[0201] N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide - free base (**12**) (46.4 g, 0.097 mol, 1 equiv.) was charged in acetone (1.5 L) and stirred at RT for 5-10 min until a clear solution was obtained. A solution of concentrated hydrochloric acid [~35% v/v] (13.3 mL, 0.126 mol, 1.3 equiv.) in acetone (85 mL) was added dropwise with constant stirring. After addition, the pH of the reaction mixture was 1-2. The reaction mixture was stirred for 30 min at RT. The solid obtained was filtered under vacuum and washed with acetone (3x100 mL) (the washing was performed without vacuum and once acetone was absorbed by the solid, the solvent was removed by vacuum filtration). The washing was repeated until the filtrate was colorless. The light yellow solid obtained was dried at 50 °C under reduced pressure for 2 h to get N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl) thiazol-4-yl) phenyl)-1, 1, 1-trifluoromethanesulfonamide -

hydrochloride salt (13) (44 g (88 % yield)). ¹H NMR (400 MHz, Methanol-*d*₄): δ (ppm): 8.81 (d, *J* = 6.3 Hz, 1H), 8.58 – 8.45 (m, 3H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.49 (t, *J* = 2.8 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.4 Hz, 1H), 3.02 (d, *J* = 7.3 Hz, 2H), 2.22 (m, 1H), 1.06 (d, *J* = 6.6 Hz, 6H). Melting point: 165 °C – 173 °C (FB). LCMS – (M+1): 475.9 (99.5%). In method, Column type : HYPERSILGOLD, C18, Column_ID: 4.6*50 mm, 5μ; Mobile Phase A: 0.05% formic acid in H₂O; Mobile Phase B: 0.01% formic acid in acetonitrile. Gradient: 10% B to 90% B From 0.2 to 2 min, hold for 2.5 min, 10%B in 0.1 min. Flow: 0.7 mL/min. The desired compound has RT of 4.514 min. UPLC – In method, Column Type: ACQUITY BEH C18; Column ID: 2.1*50 mm, 1.7μ; Flow Rate: 0.35 mL/min. Mobile phase A: 0.05% TFA Mobile phase B: Acetonitrile, Gradient: 10% B to 90% B in 2.5 min, hold for 1 min, 90% B to 10% B in 0.3 min. The desired compound had RT of 2.793 min. Melting point: 220 °C - 227 °C (Hydrochloride salt).

Example 37. Preparation of Compound No. 88

[0202] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and [3-(1-piperidyl)phenyl]boronic acid (53 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd-acetate (8 mg, 0.035 mmol) and xantphos (27.5 mg, .0476 mmol), the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (25 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ (ppm): 8.23 (s, 1H), 8.11 – 7.94 (m, 3H), 7.71 – 7.59 (m, 2H), 7.47 (d, *J* = 2.2 Hz, 1H), 7.37 (dd, *J* = 8.6, 2.2 Hz, 1H), 3.63 (t, *J* = 5.5 Hz, 4H), 2.01 (q, *J* = 6.2 Hz, 4H), 1.80 (q, *J* = 6.0 Hz, 2H). LCMS (M+1): 502.5.

Example 38. Preparation of Compound No. 89

[0203] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and [5-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolo[2,3-*b*]pyridin-1-yl]-triisopropyl-silane (109 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle

and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide (35 mg) as a white color solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 12.10 (s, 1H), 8.43 (d, J = 2.2 Hz, 2H), 8.08 (d, J = 8.5 Hz, 1H), 7.74 (t, J = 3.0 Hz, 1H), 7.47 (d, J = 2.2 Hz, 1H), 7.45 – 7.36 (m, 2H). LCMS (M+1): 477.1.

Example 39. Preparation of Compound No. 90

[0204] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380mmol) and benzothiophen-3-ylboronic acid (47 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide (59 mg) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.80 (d, J = 8.0 Hz, 1H), 8.26 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.99 (s, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.51 – 7.43 (m, 2H), 7.38 (dd, J = 8.6, 2.3 Hz, 1H). LCMS (M+1): 475.

Example 40. Preparation of Compound No. 91

[0205] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 1-[[5-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]pyrrolidine (80 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by

LCMS. The reaction mixture was cooled to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (80 mg) as a pale red solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.11 (dd, J = 8.7, 5.4 Hz, 1H), 7.98 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.56 (dd, J = 9.0, 2.7 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.33 (dd, J = 8.4, 2.2 Hz, 1H), 4.61 (s, 2H), 3.43 (t, 2H), 3.25 (t, 2H), 2.17 (m, 2H), 1.97 (m, 2H). LCMS (M+1): 521.4.

Example 41. Preparation of Compound No. 92

[0206] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and N-cyclopentyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-amine (76 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled to RT; water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide (96 mg) as a yellow solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.25 (s, 1H), 7.94 (dd, J = 14.6, 7.6 Hz, 2H), 7.57 (d, J = 1.6 Hz, 1H), 7.44 (d, J = 2.3 Hz, 1H), 7.40 (d, J = 1.7 Hz, 1H), 7.38 – 7.29 (m, 1H), 4.11 (q, J = 6.1 Hz, 1H), 2.14 (dt, J = 13.2, 6.4 Hz, 2H), 1.84 (dt, J = 6.6 Hz, 2H), 1.71 (tt, J = 24.6, 11.7, 6.0 Hz, 4H). LCMS (M+1): 503.8.

Example 42. Preparation of Compound No. 93

[0207] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (64 mg, 0.261 mmol), sodium carbonate (63 mg, 0.595), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol) the mixture was further purged for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was cooled

to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase HPLC to afford N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide (42 mg) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 8.24 – 8.19 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.50 – 7.45 (m, 2H), 7.36 (dd, J = 8.5, 2.3 Hz, 1H), 7.26 – 7.20 (m, 2H). LCMS (M+1): 458.3.

Example 43. Preparation of Compound No. 94

[0208] N-(4-(2-Bromothiazol-4-yl)-3-chlorophenyl)-1, 1, 1-trifluoromethane sulfonamide (100 mg, 0.2380 mmol) and 4-quinolyl boronic acid (61.7 mg, 0.3571 mol), sodium carbonate (63 mg, 0.595 mmol), dimethyl formamide (4 mL), water (1.0 mL) were charged in a 25 mL glass bottle and aerated with nitrogen gas for 5 min. After adding Pd(PPh₃)₄ (27.4 mg, 0.0238 mmol) re-purged the mixture for 2 min and was heated to 100 °C for 18 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool to RT, water (10 mL) was added and the mixture extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (4x30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product, which was purified by reverse phase HPLC to afford N-[3-chloro-4-[2-(4-quinolyl)thiazol-4-yl]phenyl]-1,1,1-trifluoromethanesulfonamide (37 mg) as a white solid. ¹H NMR (400 MHz, Methanol-d₄) δ (ppm): 7.94 (s, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.46 – 7.38 (m, 4H), 7.31 (dd, J = 8.5, 2.3 Hz, 2H), 6.16 (s, 1H), 5.64 (s, 1H). LCMS (M+1): 445.3.

Example 44. Preparation of Compound Nos. 6-36, 38-56, and 95-152

[0209] Compound nos. 6-36, 38-56, and 95-152 can be prepared using conditions analogous to those in both the General Methods and Examples provided above.

Example B1A. Effect of Compounds on SREBP2 Cleavage and Cell Viability in HepG2 Cells.

[0210] Cancer cells such as HepG2 cells depend on SREBP activation and de novo lipogenesis to survive, particularly in low serum or serum-free conditions. Using this model, compounds were screened over 24 hours for the ability to block cleavage of SREBP to its active form and over 72 hours for an effect on cell viability under serum-free conditions.

[0211] Average SREBP2 cleavage in HepG2 cells was measured in the presence of compounds disclosed in Table 1. HepG2 cells were seeded at 500,000 cells per well in 6-well

plates in DMEM supplemented with 10% FBS. After 2 days, cells were treated with compounds (20 μ M) for 1 day in DMEM without FBS. Western blots were normalized with respect to actin.

[0212] For viability measurements, HepG2 cells were seeded at 5,000 cells per well in 96-well plates in DMEM supplemented with 10% FBS. After 1 day in culture, cells were treated with compounds (20 μ M & 5 μ M) for 3 days in DMEM without FBS. Viability was measured by MTS (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). Treatment with compounds (20 μ M & 5 μ M) was carried out in medium without FBS, and viability was measured by MTS.

[0213] The results are shown in Table 2 as percent inhibition @ 20 μ M, and in Table 3 as percent inhibition @ 5 μ M.

Table 2 (20 μ M)		
Compound No.	Average SREBP2 cleavage (% Inhibition, n=3)	Average Viability (% Inhibition, n=3)
1	73.7	92.07
2	73	80.5
4	96.07	94.38
5	81.7	99.2
37	94.59	95.03
57	46.9	56.4
58	29.4	67.9
59	60.6	99.8
60	99.0	100.0
61	2.0	43.0
62	0.0	0.0
63	39.0	47.0
64	97.0	100.0
66	0.0	11.0
67	3.0	20.0

Table 3 (5 μ M)		
Compound No.	Average SREBP2 cleavage (% Inhibition, n=3)	Average Viability (% Inhibition, n=3)
37	75	94
70	73	100
71	77	97
72	61	94

Table 3 (5 μ M)		
Compound No.	Average SREBP2 cleavage (% Inhibition, n=3)	Average Viability (% Inhibition, n=3)
73	64	99
74	76	97
75	55	88
76	7	3
77	56	41
78	38	87
79	65	74
80	90	86
81	44	88
82	77	82
83	2	0
84	20	18
85	82	93
86	54	27
87	50	9
88	90	19
89	53	5100
90	64	99
91	16	4
92	59	94
93	28	82
94	35	84
95	39	86

[0214] Compound #37 reduces SREBP cleavage in a concentration-dependent manner with an IC₅₀ of 4.6 μ M in HepG2 cells when analyzed by Western blot following 24 hours of treatment (**FIG.1A** and **FIG. 1B**).

[0215] Inhibition of SREBP activity by Compound #37 was further demonstrated in a HepG2 reporter cell line with luciferase synthesis driven by an SREBP-responsible promoter (HepG2_LSSprom). HepG2_LSSprom cells were cultured in DMEM with 10% fetal bovine serum and 1% penicillin/streptomycin for 24 hours. Cells were then treated with increasing concentrations of Compound #37 or an equal volume of DMSO in culture medium without serum. Luciferase expression was measured and compared after 6 hours of treatment. The results are shown in **FIG. 1C**. Similar to the results shown by Western blot, Compound #37 reduced luciferase expression in a dose-dependent manner with an IC₅₀ of 2.7 μ M .

[0216] In these complementary SREBP cell-based activity assays, Compound #37 consistently exhibited an IC₅₀ between 2 and 5 μ M for inhibiting SREBP activation. Consistent with the dependence on de novo lipogenesis, inhibition of SREBP activation by Compound #37 in this cell-based model led to decreased viability of HepG2 cells with an IC₅₀ of 2.1 μ M, as shown in **FIG. 1B**.

Example B1B. Effect of Compound #37 on Gene Expression in HepG2 Cells

[0217] HepG2 cells were incubated with 10 μ M Compound #37 in DMSO in serum-free conditions for 16 hours followed by microarray analysis of SREBP-driven gene expression performed with Ingenuity Pathway Analysis software. This analysis revealed that the major SREBP pathways involved in lipid and cholesterol biosynthesis were down-regulated in Compound #37-treated cells. Many of the genes altered are direct transcriptional targets of SREBP, indicating that inhibition of SREBP cleavage by Compound #37 is sufficient to reduce expression of SREBP target genes. A summary of lipid and cholesterol pathways down-regulated by Compound #37 is presented in **FIG. 3**.

[0218] Overall, the in vitro studies in Examples B1A and B1B demonstrate that Compound #37 prevents SREBP cleavage activation, and as a consequence, down-regulates SREBP target gene expression. These data are consistent with the inhibition of SREBP activation demonstrated by fatostatin (Kamisuki et al, 2009).

Example B2. PK data for representative compounds.

[0219] Standard PK parameters were collected in Mouse and Dog for Compound #37 in mouse (**FIG. 2A**) and dog (**FIG. 2B**). Data for additional compounds was collected and is presented in Table 4:

Table 4: PK parameters for representative compounds

Cpd No.	i.v. @ 2 mg/kg					p.o. @ 10 mg/kg				Bioavailability
	C _{max} (μ M)	AUC _{last} (μ M*h)	Terminal t _{1/2} (h)	CL (L/h/kg)	V _d (L/kg)	C _{max} (μ M)	T _{max} (h)	AUC _{last} (μ M*h)	Terminal t _{1/2} (h)	
5	10.2	41	2.51	0.095	0.345	20.3	1	302	6.96	149.0%
60	3.38	12.6	3.08	0.288	1.28	6.58	4	57.1	>8hrs	90.20%
64	7.13	38.5		0.055	1.95	32.1	24	526	>8hrs	273%
70	4	2.2	1.1	3.28	5.22	2.2	0.5	5.19	1.04	46.4%
71	3.57	13.6	3.5	0.251	1.27	7.57	4	51.5	>8hrs	75.9%
80	3.63	8.94	2.8	4.25	1.72	20.6	4	130	>8hrs	291.0%
82	12.6	25.4	3.64	0.137	0.719	25.8	4	175	>8hrs	138.0%
85	0.241	0.655	4.08	4.63	27.3	0.45	2	2.27	>8hrs	69.3%
88	3.44	10.6	3.35	0.3	1.45	8.41	2	51.5	>8hrs	96.8%

Example B3. Effects of Compound #37 on liver injuries in a short-term (21 day) induced NASH mouse model

[0220] This example demonstrates the effects of Compound #37 on liver injuries in a short-term (21 day) induced NASH mouse model generated using a 60% high fat Paigen diet.

[0221] C57BL/6J mice who are fed an atherogenic Paigen diet, a high-fat (60% fat), high-cholesterol (1.25%) diet supplemented with cholate (0.5%) have been shown to have acute liver damage with significant, predominantly mononuclear, leukocyte infiltration in the liver, severe hepatic steatosis, elevated hepatic expression of inflammatory cytokines (MCP-1, RANTES, and MIP-2), increased serum liver transaminase concentrations, and increased molecular markers of fibrosis (Desai et al, 2008; Vergnes et al, 2003; Nishina et al, 1993).

[0222] To investigate whether Compound #37 prevents the development of pathology associated with NASH and steatosis in an acute exploratory disease model, a study was conducted using a diet-induced acute liver steatosis model in mice. As described below, in this study, C57BL/6J mice were initiated on the Paigen diet and simultaneously treated with Compound #37 (5, 20, and 40 mg/kg/day) or vehicle control (20% HP β CD 10 mL/kg/day) by oral gavage for 21 days.

[0223] After acclimation, 8-week old male C57BL/6J mice (Charles River) weighing about 25 g were randomized in 4 groups according their body weight and treated once daily around noon by oral gavage with vehicle, or Compound #37 at various for 21 days as follows: Group 1: vehicle- 20% (2-hydroxypropyl)- β -cyclodextrin (HP- β -CD) (n=10); Group 2: Compound #37, 5 mg/kg (n=10) Group 3: Compound #37, 20 mg/kg (n=10) Group 4: Compound #37, 40 mg/kg (n=10). During the treatment period, body weight and food intake (measured over 24h) were measured 3 times per week and once a week, respectively. During the acclimation, all mice were fed a standard diet (Special Diets Services RM1 (E), product no. 801492) and tap water *ad libitum*. After the acclimation period, mice were fed until the end of the experiment with a 60% high fat Paigen diet (60 kcal% fat, 1.25% cholesterol, and 0.5% cholate; D11061901, Research Diet) and tap water *ad libitum*.

[0224] After 21 days of treatment, mice were 4-hour fasted (9 am to 1 pm). One hour after the last dosing (noon), blood was collected by retro-orbital bleeding (maximal volume on EDTA) under isoflurane anesthesia to measure plasma triglycerides, total cholesterol, non-esterified fatty acid, ALT and AST. Mice were then sacrificed by cervical dislocation, and livers were harvested and weighed. Liver samples from the same lobe were dissected, frozen, and analyzed as described below.

[0225] Data Analysis. Values are presented as mean $\pm$ standard error of the mean (sem). To assess the compound effect, treated groups were compared to vehicle with a 1-way ANOVA + Dunnett's post-test. When variances were significantly different a Kruskal-Wallis test was performed. For RT-qPCR and score Kruskal-Wallis test was performed with Dunns post-test. For body weight evolution the treated groups were compared to vehicle with a 2-way ANOVA with Bonferroni post-test. For each test, a $p < 0.05$ was considered significant.

[0226] Results. The day following the start of diet and treatment, Compound #37 at 20mg/kg and at 40mg/kg induced a body weight decrease and death in some mice. Treatment with Compound #37 at 40 mg/kg was stopped after 4 administrations. Mice were maintained on specific diet and were sacrificed after 9 days of diet. The treatment with Compound #37 at 20mg/kg was maintained, and the mice that were still alive recovered. Body weight evolution of Compound #37-treated groups was similar to vehicle and was associated with similar food intake.

[0227] After 21 days of diet, treatment with Compound #37 at 5mg/kg and 20mg/kg tended to prevent plasma ALT and AST increase. Mice treated with Compound #37 at 40mg/kg displayed very high ALT and AST levels at day 9, which may be related to an acute effect of the diet or the potential liver toxicity effect of Compound #37 at 40mg/kg in combination with the diet. After 21 days, treatment with Compound #37 at 20mg/kg significantly decreased free fatty acids and tended to prevent triglyceride plasma levels. Plasma cholesterol levels were unchanged. See Tables 5A and 5B.

Table 5A. Plasma levels of cholesterol, triglycerides, and free fatty acids after 21 days of diet and treatment

Group	animal #	ALT (U/L)	AST (U/L)	AST/ALT ratio
vehicle	7	960	1415	1.47
	15	1800	1260	0.7
	17	507	615	1.21
	20	344	416	1.21
	24	309	425	1.38
	26	634	619	0.98
	27	372	480	1.29
	31	200	221	1.11
	35	278	434	1.56
	39	359	439	1.22
	mean	576.3	632.4	1.2
	SD	482.8	389.6	0.2
	sem	152.7	123.2	0.1
	n	10	10	10

Group	animal #	ALT (U/L)	AST (U/L)	AST/ALT ratio
5 mg/kg	2	382	350	0.92
	5	620	ND	ND
	6	346	416	1.20
	8	825	710	0.86
	12	267	405	1.52
	19	246	286	1.16
	23	255	392	1.54
	36	447	481	1.08
	37	435	528	1.21
	38	370	477	1.29
	mean	419.3	449.4	1.2
	sd	181.1	121.9	0.2
	sem	57.3	40.6	0.1
	n	10	9	9
20 mg/kg	3	266	362	1.36
	16	587	467	0.80
	21	432	344	0.80
	28	413	615	1.49
	32	385	424	1.10
	40	338	375	1.11
	mean	403.5	431.2	1.1
	sd	107.8	100.7	0.3
	sem	44.0	41.1	0.1
	n	6	6	6

Table 5B. Plasma levels of cholesterol, triglycerides, and free fatty acids after 9 days of diet and treatment

Group	animal #	ALT (U/L)	AST (U/L)	AST/ALT ratio
40 mg/kg	25	1095	1165	1.1
	30	1160	1555	1.3
	33	12560	3900	0.3
	34	13360	4120	0.3
	mean	7043.8	2685.0	0.8
	sd	6839.4	1540.9	0.5
	sem	3419.7	770.4	0.3
	n	4	4	4

[0228] At the end of the treatment period, livers were weighed, and their lipid content was analyzed. The liver weights were unchanged by the treatment. An increase of liver cholesterol and fatty acid levels were observed in the group treated with Compound #37 at 20mg/kg. An increase in liver triglycerides tended to be prevented in the groups treated with Compound #37. See Tables 6A and 6B.

Table 6A. Liver cholesterol, triglycerides, and fatty acid levels at 21 days of diet and treatment.

Group	animal #	cholesterol ($\mu\text{g}/\text{mg}$ tissue)	triglycerides ($\mu\text{g}/\text{mg}$ tissue)	fatty acids (nmol/mg tissue)
vehicle	7	35.43	8.85	56.5
	15	27.12	20.11	46.3
	17	24.55	7.29	44.7
	20	25.59	6.90	46.5
	24	32.85	4.42	56.9
	26	27.78	5.39	47.5
	27	27.03	5.47	41.4
	31	28.57	6.24	45.1
	35	32.61	4.04	53.2
	39	36.99	7.26	70.8
	mean	29.9	7.6	50.9
	sd	4.3	4.6	8.7
	sem	1.4	1.5	2.8
	n	10	10	10
5 mg/kg	2	42.24	6.91	65.4
	5	37.91	7.18	66.6
	6	31.39	4.64	53.5
	8	23.12	9.62	47.5
	12	31.47	6.13	55.2
	19	25.31	5.69	35.5
	23	29.76	5.49	55.0
	36	37.34	6.13	55.2
	37	49.15	3.62	77.4
	38	36.57	6.16	65.2
	mean	34.4	6.2	57.6
	sd	7.8	1.6	11.6
	sem	2.5	0.5	3.7
	n	10	10	10
20 mg/kg	3	38.32	6.75	63.4
	16	42.07	2.65	66.5
	21	39.38	2.83	65.0
	28	32.61	3.72	50.0
	32	40.02	9.84	62.7
	40	42.44	6.82	72.5
	mean	39.1	5.4	63.3
	sd	3.6	2.8	7.4
	sem	1.5	1.2	3.0
	n	6	6	6

Table 6B. Liver cholesterol, triglycerides, and fatty acid levels at 9 days of diet and treatment.

Group	animal #	cholesterol ($\mu\text{g}/\text{mg}$ tissue)	triglycerides ($\mu\text{g}/\text{mg}$ tissue)	fatty acids (nmol/mg tissue)
40 mg/kg	25	20.18	11.15	43.1
	30	20.88	14.68	43.5
	33	17.60	11.77	41.8
	34	22.40	9.11	43.6
	mean	20.3	11.7	43.0
	sd	2.0	2.3	0.8
	sem	1.0	1.2	0.4
	n	4	4	4

[0229] Oil Red O staining. One 0.5 cm^3 piece of liver was frozen in OCT in isopentane and stored at -80°C for neutral lipid coloration with quantification to evaluate accumulation of neutral lipids in the liver. One section (thickness 5-7 μm) per block was deposited on superfrost + slides for Red Oil staining. Red Oil-stained slides were digitalized at X20 with the Nanozoomer 2.0 HT. Red Oil labeling was quantified (surface, density): the stained slides were analyzed using an image. All the samples were analyzed within the same range of labeling intensity (0-130), allowing comparison between animals. The intensity scale ranged from 0 to 255 grey levels, in which 0 is the value of a black pixel, and 255 is the value of a white pixel. The staining intensity was calculated as the mean intensity of each pixel composing the labeling signal. For each slide, the percentage (%) of labeling was also calculated: $\% = (\text{Surface of labeling} \times 100) / \text{section area}$.

[0230] There were deposits in the OCT, which contributed to the red oil signal from the lipids. A high variability of response in the vehicle group was observed, due in part to one animal. However, treatment with Compound #37 tended to prevent the accumulation of neutral lipids, which was correlated with the tendency of liver triglycerides to decrease. Liver lipids and cholesterol metabolism genes were analyzed by RT-qPCR and were unchanged by the treatment except for the ACC1 gene. Compound #37 decreased ACC1 liver gene expression in a dose-dependent manner. See Tables 7A and 7B.

Table 7A. Liver O red Oil staining at 21 days of diet and treatment.

group	animal #	% labeling
vehicle	7	3.05
	15	11.17
	17	2.91
	20	4.61
	24	0.50
	26	0.36
	27	0.76
	31	0.67
	35	0.09*
	39	1.90
	mean	2.88
	sd	3.43
	sem	1.14
	n	9
5 mg/kg	2	2.08
	5	2.02
	6	1.19
	8	2.18
	12	1.64
	19	1.09
	23	1.16
	36	1.50
	37	0.70
	38	1.39
	mean	1.50
	sd	0.48
	sem	0.15
	n	10
20 mg/kg	3	1.53
	16	0.81
	21	0.29
	28	1.11
	32	0.92
	40	0.92
	mean	0.93
	sd	0.40
	sem	0.16
	n	6

Table 7B. Liver O red Oil staining at 9 days of diet and treatment

Group	animal #	% labeling
40 mg/kg	25	2.53
	30	2.54
	33	1.12
	34	1.28
	mean	1.87
	sd	0.77
	sem	0.39
	n	4

[0231] Gene expression analysis. Hepatic expression levels of genes involved in lipid metabolism (FAS, SREBP1, ACC1, SCD1), cholesterol metabolism (HMG-CoAR, LDLR), SREBP proteolysis (SCAP, INSIG1), ER stress (PERK), oxidative stress (NRF2), inflammation (MCP-1), and fibrosis (collagen 1 α 1) were quantified by RTqPCR. Expression level was normalized to 18S gene expression and relative expression to vehicle group was calculated with the 2-t method.

[0232] The 60% high fat Paigen diet induced accumulation of liver lipids, inflammation, oxidative stress, and then fibrosis. Compound #37 at 5mg/kg tended to decrease in a non-significant manner some gene expression markers of inflammation and oxidative stress, but no clear modifications were observed. Expression of these genes was unchanged in the group treated with Compound #37 at 20mg/kg, but a tendency to prevent increase in liver IL-6 levels was observed. Compound #37 treatment tended to decrease expression of the collagen 1 α 1 gene in a dose-dependent manner. The results are shown in Tables 8-13.

Table 8A. Lipid metabolism gene expression (21 days): FAS

Group	N°	18S	FAS	Dct	DDct	2DDct
Vehicle	7	12.96	22.25	9.29	-0.62	1.54
	15	11.15	21.28	10.13	0.22	0.86
	17	11.14	20.72	9.58	-0.33	1.26
	20	13.25	22.42	9.17	-0.74	1.67
	24	11.65	22.16	10.51	0.6	0.66
	26	12.41	23.01	10.6	0.69	0.62
	27	13.25	21.37	8.12	-1.79	3.46
	31	11.38	21.57	10.19	0.28	0.82
	35	11.26	22	10.74	0.83	0.56
	39	11.5	22.26	10.76	0.85	0.55
	mean	12	21.9	9.9	0	1.2
	sd	0.9	0.7	0.9	0.86	0.89
	sem	0.3	0.2	0.3	0.27	0.28
	n	10	10	10	10	10
5 mg/kg	2	13.46	22.23	8.77	-1.14	2.2
	5	13.11	22.4	9.29	-0.62	1.54
	6	11.61	20.89	9.28	-0.63	1.55
	8	13.35	22.03	8.68	-1.23	2.34
	12	12.03	22.49	10.46	0.55	0.68
	19	13.35	24.63	11.28	1.37	0.39
	23	11.6	21.65	10.05	0.14	0.91
	36	11.79	22.31	10.52	0.61	0.65
	37	11.14	22.66	11.52	1.61	0.33
	38	11.12	21.79	10.67	0.76	0.59
	mean	12.3	22.3	10.1	0.14	1.12
	sd	1	1	1	1.01	0.74
	sem	0.3	0.3	0.3	0.32	0.23
	n	10	10	10	10	10
20 mg/kg	3	12.91	22.25	9.34	-0.57	1.48
	16	12.29	23.04	10.75	0.84	0.56
	21	12.2	22.78	10.58	0.67	0.63
	28	13.03	22.22	9.19	-0.72	1.65
	32	11.49	21.55	10.06	0.15	0.9
	40	11.26	20.26	9	-0.91	1.88
	mean	12.2	22	9.8	-0.09	1.18
	sd	0.7	1	0.7	0.75	0.56
	sem	0.3	0.4	0.3	0.31	0.23
	n	6	6	6	6	6

Table 8B. Lipid metabolism gene expression (21 days): SCD1

Group	N°	18S	SCD1	Dct	DDct	2DDct
Vehicle	7	12.96	19.94	6.98	1.16	0.45
	15	11.15	16.71	5.56	-0.26	1.19
	17	11.14	17.76	6.62	0.8	0.57
	20	13.25	17.23	3.98	-1.84	3.57
	24	11.65	17.71	6.06	0.24	0.84
	26	12.41	18.17	5.76	-0.06	1.04
	27	13.25	17.58	4.33	-1.49	2.8
	31	11.38	18.1	6.72	0.9	0.53
	35	11.26	17.62	6.36	0.54	0.69
	39	11.5	17.3	5.8	-0.02	1.01
	mean	12	17.8	5.8	0	1.27
	sd	0.9	0.9	1	0.99	1.05
	sem	0.3	0.3	0.3	0.31	0.33
	n	10	10	10	10	10
5 mg/kg	2	13.46	17.71	4.25	-1.57	2.96
	5	13.11	18.94	5.83	0.01	0.99
	6	11.61	18.03	6.42	0.6	0.66
	8	13.35	18.15	4.8	-1.02	2.02
	12	12.03	18.23	6.2	0.38	0.77
	19	13.35	21.37	8.02	2.2	0.22
	23	11.6	17.52	5.92	0.1	0.93
	36	11.79	18.01	6.22	0.4	0.76
	37	11.14	17.69	6.55	0.73	0.6
	38	11.12	17.7	6.58	0.76	0.59
	mean	12.3	18.3	6.1	0.26	1.05
	sd	1	1.1	1	1.03	0.82
	sem	0.3	0.4	0.3	0.32	0.26
	n	10	10	10	10	10
20 mg/kg	3	12.91	18.75	5.84	0.02	0.98
	16	12.29	19.21	6.92	1.1	0.47
	21	12.2	18.2	6	0.18	0.88
	28	13.03	17.66	4.63	-1.19	2.28
	32	11.49	18.39	6.9	1.08	0.47
	40	11.26	16.08	4.82	-1	2
	mean	12.2	18	5.9	0.03	1.18
	sd	0.7	1.1	1	0.98	0.78
	sem	0.3	0.4	0.4	0.4	0.32
	n	6	6	6	6	6

Table 8C. Lipid metabolism gene expression (21 days): SREBP1C

Group	N°	18S	SREBP1C	Dct	DDct	2DDct
Vehicle	7	12.96	27.64	14.68	0.9	0.54
	15	11.15	24.42	13.27	-0.51	1.43
	17	11.14	26.39	15.25	1.47	0.36
	20	13.25	26.73	13.48	-0.3	1.23
	24	11.65	25.69	14.04	0.26	0.84
	26	12.41	26.37	13.96	0.18	0.88
	27	13.25	25.05	11.8	-1.98	3.95
	31	11.38	25.31	13.93	0.15	0.9
	35	11.26	25.23	13.97	0.19	0.88
	39	11.5	24.95	13.45	-0.33	1.26
	mean	12	25.8	13.8	0	1.23
	sd	0.9	1	0.9	0.91	1.01
	sem	0.3	0.3	0.3	0.29	0.32
	n	10	10	10	10	10
5 mg/kg	2	13.46	27.03	13.57	-0.21	1.16
	5	13.11	27.79	14.68	0.9	0.54
	6	11.61	25.45	13.84	0.06	0.96
	8	13.35	26.15	12.8	-0.98	1.98
	12	12.03	27.27	15.24	1.46	0.36
	19	13.35	28.65	15.3	1.52	0.35
	23	11.6	25.29	13.69	-0.09	1.07
	36	11.79	25.3	13.51	-0.27	1.21
	37	11.14	25.09	13.95	0.17	0.89
	38	11.12	24.92	13.8	0.02	0.99
	mean	12.3	26.3	14	0.26	0.95
	sd	1	1.3	0.8	0.8	0.48
	sem	0.3	0.4	0.3	0.25	0.15
	n	10	10	10	10	10
20 mg/kg	3	12.91	27.19	14.28	0.5	0.71
	16	12.29	26.45	14.16	0.38	0.77
	21	12.2	26.09	13.89	0.11	0.93
	28	13.03	25.45	12.42	-1.36	2.57
	32	11.49	25.93	14.44	0.66	0.63
	40	11.26	23.96	12.7	-1.08	2.12
	mean	12.2	25.8	13.6	-0.13	1.29
	sd	0.7	1.1	0.9	0.87	0.84
	sem	0.3	0.4	0.4	0.35	0.34
	n	6	6	6	6	6

Table 8D. Lipid metabolism gene expression (21 days): ACC1

Group	N°	18S	ACC1	Dct	DDct	2DDct
Vehicle	7	12.96	32.8	19.84	1.92	0.26
	15	11.15	28.48	17.33	-0.59	1.51
	17	11.14	30.19	19.05	1.13	0.46
	20	13.25	30.61	17.36	-0.56	1.47
	24	11.65	29.85	18.2	0.28	0.82
	26	12.41	29.78	17.37	-0.55	1.46
	27	13.25	28.92	15.67	-2.25	4.76
	31	11.38	25.26	13.88*	-3.64*	12.43*
	35	11.26	30.65	19.39	1.47	0.36
	39	11.5	28.57	17.07	-0.85	1.8
	mean	12	29.5	17.9	0	1.43
	sd	0.9	2	1.3	1.32	1.37
	sem	0.3	0.6	0.4	0.44	0.46
	n	10	10	9	9	9
5 mg/kg	2	13.46	32.46	19	1.08	0.47
	5	13.11	31.81	18.7	0.78	0.58
	6	11.61	31.41	19.8	1.88	0.27
	8	13.35	34.39	21.04	3.12	0.12
	12	12.03	ND	ND	ND	ND
	19	13.35	ND	ND	ND	ND
	23	11.6	28.99	17.39	-0.53	1.44
	36	11.79	28.84	17.05	-0.87	1.83
	37	11.14	30.07	18.93	1.01	0.5
	38	11.12	29.05	17.93	0.01	0.99
	mean	12.3	30.9	18.7	0.81	0.78
	sd	1	2	1.3	1.3	0.6
	sem	0.3	0.7	0.5	0.46	0.21
	n	10	8	8	8	8
20 mg/kg	3	12.91	31.43	18.52	0.6	0.66
	16	12.29	37.36	25.07	7.15	0.01
	21	12.2	33.78	21.58	3.66	0.08
	28	13.03	31.41	18.38	0.46	0.73
	32	11.49	33.32	21.83	3.91	0.07
	40	11.26	29.63	18.37	0.45	0.73
	mean	12.2	32.8	20.6	2.71	0.38
	sd	0.7	2.7	2.7	2.71	0.36
	sem	0.3	1.1	1.1	1.11	0.15
	n	6	6	6	6	6

Table 8E. Lipid metabolism gene expression (21 days): SCAP

Group	N°	18S	SCAP	Dct	DDct	2DDct
Vehicle	7	12.96	26.59	13.6	0.97	0.51
	15	11.15	23.78	12.63	-0.03	1.02
	17	11.14	25.51	14.37	1.71	0.31
	20	13.25	25.19	11.94	-0.72	1.65
	24	11.65	24.43	12.78	0.12	0.92
	26	12.41	25.13	12.72	0.06	0.96
	27	13.25	23.95	10.7	-1.96	3.89
	31	11.38	24.59	13.21	0.55	0.68
	35	11.26	23.84	12.58	-0.08	1.06
	39	11.5	23.53	12.03	-0.63	1.55
	mean	12	24.7	12.7	0	1.25
	sd	0.9	1	1	1	1.01
	sem	0.3	0.3	0.3	0.32	0.32
	n	10	10	10	10	10
5 mg/kg	2	13.46	25.42	11.96	-0.7	1.62
	5	13.11	26.49	13.38	0.72	0.61
	6	11.61	24.17	12.56	-0.1	1.07
	8	13.35	25.83	12.48	-0.18	1.13
	12	12.03	25.9	13.87	1.21	0.43
	19	13.35	26.71	13.36	0.7	0.62
	23	11.6	24.53	12.93	0.27	0.83
	36	11.79	24.24	12.45	-0.21	1.16
	37	11.14	23.78	12.64	-0.02	1.01
	38	11.12	23.95	12.83	0.17	0.89
	mean	12.3	25.1	12.8	0.19	0.94
	sd	1	1.1	0.6	0.56	0.34
	sem	0.3	0.3	0.2	0.18	0.11
	n	10	10	10	10	10
20 mg/kg	3	12.91	26.17	13.26	0.6	0.66
	16	12.29	25.78	13.49	0.83	0.56
	21	12.2	25.19	12.99	0.33	0.79
	28	13.03	24.4	11.37	-1.29	2.44
	32	11.49	25.05	13.56	0.9	0.54
	40	11.26	22.98	11.72	-0.94	1.92
	mean	12.2	24.9	12.7	0.07	1.15
	sd	0.7	1.1	0.9	0.95	0.82
	sem	0.3	0.5	0.4	0.39	0.33
	n	6	6	6	6	6

Table 8F. Lipid metabolism gene expression (21 days): INSIG1

Group	N°	18S	INSIG1	Dct	DDct	2DDct
Vehicle	7	12.96	25.29	12.33	0.65	0.64
	15	11.15	22.6	11.45	-0.23	1.18
	17	11.14	23.06	11.92	0.24	0.85
	20	13.25	24.5	11.25	-0.43	1.35
	24	11.65	23.76	12.11	0.43	0.74
	26	12.41	24.06	11.65	-0.03	1.02
	27	13.25	24.05	10.8	-0.88	1.85
	31	11.38	23.49	12.11	0.43	0.74
	35	11.26	23.08	11.82	0.14	0.91
	39	11.5	22.9	11.4	-0.28	1.22
	mean	12	23.7	11.7	0	1.05
	sd	0.9	0.8	0.5	0.47	0.36
	sem	0.3	0.3	0.1	0.15	0.11
	n	10	10	10	10	10
5 mg/kg	2	13.46	24.56	11.1	-0.58	1.5
	5	13.11	25	11.89	0.21	0.87
	6	11.61	23.77	12.16	0.48	0.72
	8	13.35	25	11.65	-0.03	1.02
	12	12.03	24.05	12.02	0.34	0.79
	19	13.35	26.48	13.13	1.45	0.37
	23	11.6	23.37	11.77	0.09	0.94
	36	11.79	23.99	12.2	0.52	0.7
	37	11.14	23.14	12	0.32	0.8
	38	11.12	22.85	11.73	0.05	0.97
	mean	12.3	24.2	12	0.28	0.87
	sd	1	1.1	0.5	0.52	0.29
	sem	0.3	0.3	0.2	0.16	0.09
	n	10	10	10	10	10
20 mg/kg	3	12.91	25.09	12.18	0.5	0.71
	16	12.29	24.72	12.43	0.75	0.6
	21	12.2	24.39	12.19	0.51	0.7
	28	13.03	24.04	11.01	-0.67	1.6
	32	11.49	23.79	12.3	0.62	0.65
	40	11.26	22.18	10.92	-0.76	1.7
	mean	12.2	24	11.8	0.15	0.99
	sd	0.7	1	0.7	0.68	0.51
	sem	0.3	0.4	0.3	0.28	0.21
	n	6	6	6	6	6

Table 9A. Cholesterol metabolism genes expression: HMGC_oA

Group	N°	18S	HMGC _o A	Dct	DDct	2DDct
Vehicle	7	12.96	26.27	13.31	0.44	0.74
	15	11.15	23.46	12.31	-0.56	1.47
	17	11.14	24.5	13.36	0.49	0.71
	20	13.25	26.15	12.9	0.03	0.98
	24	11.65	24.92	13.27	0.40	0.76
	26	12.41	25.17	12.76	-0.11	1.08
	27	13.25	25.14	11.89	-0.98	1.97
	31	11.38	24.76	13.38	0.51	0.70
	35	11.26	24.19	12.93	0.06	0.96
	39	11.5	24.05	12.55	-0.32	1.24
	mean	12.0	24.9	12.9	0.00	1.06
	sd	0.9	0.9	0.5	0.50	0.41
	sem	0.3	0.3	0.2	0.16	0.13
	n	10	10	10	10	10
5 mg/kg	2	13.46	25.94	12.48	-0.39	1.31
	5	13.11	26.3	13.19	0.32	0.80
	6	11.61	24.57	12.96	0.09	0.94
	8	13.35	26.14	12.79	-0.08	1.05
	12	12.03	25.77	13.74	0.87	0.55
	19	13.35	26.85	13.5	0.63	0.64
	23	11.6	24.44	12.84	-0.03	1.02
	36	11.79	24.76	12.97	0.10	0.93
	37	11.14	24.36	13.22	0.35	0.78
	38	11.12	24.19	13.07	0.20	0.87
	mean	12.3	25.3	13.1	0.21	0.89
	sd	1.0	1.0	0.4	0.36	0.22
	sem	0.3	0.3	0.1	0.11	0.07
	n	10	10	10	10	10
20 mg/kg	3	12.91	26.35	13.44	0.57	0.67
	16	12.29	26.22	13.93	1.06	0.48
	21	12.2	25.65	13.45	0.58	0.67
	28	13.03	25.5	12.47	-0.40	1.32
	32	11.49	25.13	13.64	0.77	0.58
	40	11.26	23.49	12.23	-0.64	1.55
	mean	12.2	25.4	13.2	0.33	0.88
	sd	0.7	1.0	0.7	0.68	0.44
	sem	0.3	0.4	0.3	0.28	0.18
	n	6	6	6	6	6

Table 9B. Cholesterol metabolism genes expression: LDLR

Group	N°	18S	LDLR	Dct	DDct	2DDct
Vehicle	7	12.96	26.32	13.36	0.70	0.61
	15	11.15	23.24	12.09	-0.57	1.48
	17	11.14	24.91	13.77	1.11	0.46
	20	13.25	25.49	12.24	-0.42	1.34
	24	11.65	24.71	13.06	0.40	0.76
	26	12.41	25.81	13.4	0.74	0.60
	27	13.25	24.04	10.79	-1.87	3.65
	31	11.38	24.63	13.25	0.59	0.66
	35	11.26	23.72	12.46	-0.20	1.15
	39	11.5	23.66	12.16	-0.50	1.41
	mean	12.0	24.7	12.7	0.00	1.21
	sd	0.9	1.0	0.9	0.89	0.94
	sem	0.3	0.3	0.3	0.28	0.30
	n	10	10	10	10	10
5 mg/kg	2	13.46	25.2	11.74	-0.92	1.89
	5	13.11	25.9	12.79	0.13	0.91
	6	11.61	23.67	12.06	-0.60	1.51
	8	13.35	25.03	11.68	-0.98	1.97
	12	12.03	26.15	14.12	1.46	0.36
	19	13.35	27.4	14.05	1.39	0.38
	23	11.6	24.3	12.7	0.04	0.97
	36	11.79	24.78	12.99	0.33	0.79
	37	11.14	24.32	13.18	0.52	0.70
	38	11.12	24.15	13.03	0.37	0.77
	mean	12.3	25.1	12.8	0.18	1.03
	sd	1.0	1.1	0.8	0.85	0.57
	sem	0.3	0.4	0.3	0.27	0.18
	n	10	10	10	10	10
20 mg/kg	3	12.91	25.95	13.04	0.38	0.77
	16	12.29	25.86	13.57	0.91	0.53
	21	12.2	25.18	12.98	0.32	0.80
	28	13.03	24.47	11.44	-1.22	2.33
	32	11.49	24.57	13.08	0.42	0.75
	40	11.26	22.55	11.29	-1.37	2.58
	mean	12.2	24.8	12.6	-0.09	1.29
	sd	0.7	1.2	1.0	0.96	0.91
	sem	0.3	0.5	0.4	0.39	0.37
	n	6	6	6	6	6

Table 10. MCP-1 gene expression (21 days)

Group	N°	18S	MCP-1	Dct	DDct	2DDct
Vehicle	7	12.96	25.15	12.19	-1.14	2.2
	15	11.15	25.35	14.2	0.87	0.55
	17	11.14	23.92	12.78	-0.55	1.46
	20	13.25	25.1	11.85	-1.48	2.79
	24	11.65	25.61	13.96	0.63	0.65
	26	12.41	25.96	13.55	0.22	0.86
	27	13.25	24.49	11.24	-2.09	4.25
	31	11.38	26.59	15.21	1.88	0.27
	35	11.26	25.64	14.38	1.05	0.48
	39	11.5	25.43	13.93	0.6	0.66
	mean	12	25.3	13.3	0	1.42
	sd	0.9	0.7	1.3	1.26	1.29
	sem	0.3	0.2	0.4	0.4	0.41
	n	10	10	10	10	10
5 mg/kg	2	13.46	26.68	13.2	-0.11	1.08
	5	13.11	26.47	13.36	0.03	0.98
	6	11.61	26.76	15.15	1.82	0.28
	8	13.35	26.19	12.84	-0.49	1.4
	12	12.03	26.35	14.32	0.99	0.5
	19	13.35	27.79	14.44	1.11	0.46
	23	11.6	25.17	13.57	0.24	0.85
	36	11.79	25.06	13.27	-0.06	1.04
	37	11.14	25.54	14.4	1.07	0.48
	38	11.12	26.04	14.92	1.59	0.33
	mean	12.3	26.2	13.9	0.62	0.74
	sd	1	0.8	0.8	0.79	0.38
	sem	0.3	0.3	0.3	0.25	0.12
	n	10	10	10	10	10
20 mg/kg	3	12.91	25.89	12.98	-0.35	1.27
	16	12.29	24.04	11.75	-1.58	2.99
	21	12.2	23.5	11.3	-2.03	4.08
	28	13.03	24.46	11.43	-1.9	3.73
	32	11.49	25.7	14.21	0.88	0.54
	40	11.26	26.54	15.28	1.95	0.26
	mean	12.2	25	12.8	-0.5	2.15
	sd	0.7	1.2	1.6	1.64	1.66
	sem	0.3	0.5	0.7	0.67	0.68
	n	6	6	6	6	6

Table 11A. ER and oxidative stress gene expression (21 days): PERK

Group	N°	18S	PERK	Dct	DDct	2DDct
Vehicle	7	12.96	28.22	15.26	0.22	0.86
	15	11.15	25.95	14.8	-0.24	1.18
	17	11.14	27.09	15.95	0.91	0.53
	20	13.25	27.67	14.42	-0.62	1.54
	24	11.65	27.17	15.52	0.48	0.72
	26	12.41	27.67	15.26	0.22	0.86
	27	13.25	26.37	13.12	-1.92	3.79
	31	11.38	27.17	15.79	0.75	0.6
	35	11.26	26.93	15.67	0.63	0.65
	39	11.5	26.13	14.63	-0.41	1.33
	mean	12	27	15	0	1.21
	sd	0.9	0.7	0.8	0.84	0.97
	sem	0.3	0.2	0.3	0.27	0.31
	n	10	10	10	10	10
5 mg/kg	2	13.46	28.14	14.68	-0.36	1.29
	5	13.11	29.05	15.94	0.9	0.54
	6	11.61	28.17	16.56	1.52	0.35
	8	13.35	27.81	14.46	-0.58	1.5
	12	12.03	28.31	16.28	1.24	0.42
	19	13.35	29.19	15.84	0.8	0.58
	23	11.6	26.56	14.96	-0.08	1.06
	36	11.79	26.19	14.4	-0.64	1.56
	37	11.14	26.22	15.08	0.04	0.97
	38	11.12	26.5	15.38	0.34	0.79
	mean	12.3	27.6	15.4	0.32	0.91
	sd	1	1.2	0.8	0.77	0.44
	sem	0.3	0.4	0.2	0.24	0.14
	n	10	10	10	10	10
20 mg/kg	3	12.91	27.9	14.99	-0.05	1.04
	16	12.29	27.26	14.97	-0.07	1.05
	21	12.2	26.9	14.7	-0.34	1.27
	28	13.03	26.65	13.62	-1.42	2.68
	32	11.49	27.25	15.76	0.72	0.61
	40	11.26	25.88	14.62	-0.42	1.34
	mean	12.2	27	14.8	-0.27	1.33
	sd	0.7	0.7	0.7	0.7	0.71
	sem	0.3	0.3	0.3	0.28	0.29
	n	6	6	6	6	6

Table 11B. ER and oxidative stress gene expression (21 days): NRF2

Group	N°	18S	NRF2	Dct	DDct	2DDct
Vehicle	7	12.96	24.42	11.46	0.52	0.7
	15	11.15	21.92	10.77	-0.17	1.13
	17	11.14	23.26	12.12	1.18	0.44
	20	13.25	23.32	10.07	-0.87	1.83
	24	11.65	22.91	11.26	0.32	0.8
	26	12.41	23.66	11.25	0.31	0.81
	27	13.25	22.13	8.88	-2.06	4.17
	31	11.38	23	11.62	0.68	0.62
	35	11.26	22.61	11.35	0.41	0.75
	39	11.5	22.12	10.62	-0.32	1.25
	mean	12	22.9	10.9	0	1.25
	sd	0.9	0.8	0.9	0.92	1.1
	sem	0.3	0.2	0.3	0.29	0.35
	n	10	10	10	10	10
5 mg/kg	2	13.46	24.8	11.34	0.4	0.76
	5	13.11	25.07	11.96	1.02	0.49
	6	11.61	23.36	11.75	0.81	0.57
	8	13.35	23.36	10.01	-0.93	1.91
	12	12.03	24.63	12.6	1.66	0.32
	19	13.35	25.61	12.26	1.32	0.4
	23	11.6	22.83	11.23	0.29	0.82
	36	11.79	22.7	10.91	-0.03	1.02
	37	11.14	22.66	11.52	0.58	0.67
	38	11.12	22.62	11.5	0.56	0.68
	mean	12.3	23.8	11.5	0.57	0.76
	sd	1	1.1	0.7	0.72	0.45
	sem	0.3	0.4	0.2	0.23	0.14
	n	10	10	10	10	10
20 mg/kg	3	12.91	24.24	11.33	0.39	0.76
	16	12.29	23.63	11.34	0.4	0.76
	21	12.2	23.27	11.07	0.13	0.91
	28	13.03	22.81	9.78	-1.16	2.23
	32	11.49	23.05	11.56	0.62	0.65
	40	11.26	22.02	10.76	-0.18	1.13
	mean	12.2	23.2	11	0.03	1.08
	sd	0.7	0.8	0.6	0.65	0.59
	sem	0.3	0.3	0.3	0.26	0.24
	n	6	6	6	6	6

Table 12A. IL-6 expression (21 days)

group	animal #	IL-6 (pg /mg tissue)
Vehicle	7	875
	15	622
	17	1041
	20	713
	24	935
	26	1170
	27	794
	31	1250
	35	1183
	39	1218
	mean	980
	sd	225
	sem	71
	n	10
5 mg/kg	2	1444
	5	845
	6	1107
	8	650
	12	1305
	19	957
	23	770
	36	1296
	37	883
	38	863
	mean	1012
	sd	263
	sem	83
	n	10
20 mg/kg	3	904
	16	737
	21	760
	28	705
	32	970
	40	826
	mean	817
	sd	103
	sem	42
	n	6

Table 12B. IL-6 expression (9 days)

group	animal #	IL-6 (pg /mg tissue)
40 mg/kg	25	1005
	30	569
	33	535
	34	566
	mean	669
	sd	225
	sem	112
	n	4

Table 13. Fibrosis gene expression (21 days): Coll1a1

Group	N°	18S	Coll1a1	Dct	DDct	2DDct
Vehicle	7	12.96	28.29	15.3	1.19	0.44
	15	11.15	23.38	12.2	-1.91	3.75
	17	11.14	27.86	16.72	2.58	0.17
	20	13.25	27.11	13.86	-0.28	1.21
	24	11.65	25.32	13.67	-0.47	1.38
	26	12.41	26.57	14.16	0.02	0.98
	27	13.25	25.29	12.04	-2.1	4.28
	31	11.38	27.22	15.84	1.7	0.31
	35	11.26	25.67	14.41	0.27	0.83
	39	11.5	24.6	13.1	-1.04	2.05
	mean	12	26.1	14.1	0	1.54
	sd	0.9	1.5	1.5	1.51	1.42
	sem	0.3	0.5	0.5	0.48	0.45
	n	10	10	10	10	10
5 mg/kg	2	13.46	27.81	14.4	0.21	0.86
	5	13.11	29.15	16.04	1.9	0.27
	6	11.61	25.8	14.19	0.05	0.96
	8	13.35	28.03	14.68	0.54	0.69
	12	12.03	28.92	16.89	2.75	0.15
	19	13.35	31.82	18.47	4.33	0.05
	23	11.6	24.93	13.33	-0.81	1.75
	36	11.79	24.75	12.96	-1.18	2.26
	37	11.14	25.01	13.87	-0.27	1.2
	38	11.12	26.07	14.95	0.81	0.57
	mean	12.3	27.2	15	0.84	0.88
	sd	1	2.3	1.7	1.7	0.71
	sem	0.3	0.7	0.5	0.54	0.22
	n	10	10	10	10	10
20 mg/kg	3	12.91	28.9	15.99	1.85	0.28
	16	12.29	26.66	14.37	0.23	0.85
	21	12.2	26.93	14.73	0.59	0.66
	28	13.03	27.17	14.14	0	1
	32	11.49	26.34	14.85	0.71	0.61
	40	11.26	23.43	12.17	-1.97	3.91*
	mean	12.2	26.6	14.4	0.24	0.68
	sd	0.7	1.8	1.3	1.26	0.27
	sem	0.3	0.7	0.5	0.51	0.12
	n	6	6	6	6	5

[0233] NAFLD score analysis. A 0.5 cm³ piece of liver was fixed in 10% formalin for 48-72h, stored in ethanol 70° at 4°C, and processed for eosin/hematoxylin staining and NAFLD score analysis. One section (thickness 3-5µm) per block was deposited on Superfrost + slides for hematoxylin-eosin staining. Individual slides having a single hepatic lobe section stained with H&E were digitized using a Nanozoomer from Hamamatsu. Sections were evaluated with knowledge of groups. Each section was evaluated and individually scored. A NAFLD scoring system (NAS) adapted from Kleiner *et al.* (Hepatology 41, 1313-21, 2005), Wu *et al.* (BMC Vet. Res. 10, 162, 2014), and Lee *et al.* (J. Lipid Res. 48, 1885-96, 2007). A total of four variables were qualitatively assessed and ranked with a score: (1) hepatocellular steatosis, (2) liver inflammation, (3) lobular fibrosis, and (4) hepatocyte ballooning. The criteria for score assignments are presented in the table below.

Score	Steatosis	Inflammation	Fibrosis	Hepatocyte ballooning
0	<5% of liver parenchyma	no foci	none	none
1	5-33% of liver parenchyma	<2 foci at 20x field	zone 3 and/or perisinusoidal fibrosis	minimal to mild focal involving fewer than 3 hepatocytes
2	34-66% of liver parenchyma	2-4 foci at 20x field	As grade 1 and portal fibrosis	moderate multifocal involving more than 3 hepatocytes
3	>66% of liver parenchyma	>4 foci at 20x field	As grade 2 and bridging fibrosis	prominent multifocal involving large number of hepatocytes
4	not applicable	not applicable	cirrhosis	not applicable

[0234] NAS scores were determined based on histopathological analysis of steatosis, inflammation, hepatocyte ballooning, and fibrosis. The most remarkable lesion contributing to the NAS scores in the vehicle group and in the groups treated with Compound #37 at 5mg/kg and 20mg/kg was interstitial inflammation ranging from a Grade 1 to a Grade 3 in all animals in all three groups. A grade-3 inflammation was noted in 2/10 animals in the vehicle-treated group, 4/10 animals in the group treated with Compound #37 at 5mg/kg, and 1/6 animals in the group treated with Compound #37 at 20mg/kg. Inflammation was accompanied by limited periportal fibrosis (mostly Grade 1) in 9/10 animals in the vehicle-treated group, 10/10 animals in the group treated with Compound #37 at 5mg/kg, and 3/6 animals in the group treated with Compound #37 at 20mg/kg. Grade 1 hepatocellular steatosis was observed in 7/10 animals in the vehicle-treated group, 9/10 animals in the group treated with Compound #37 at 5mg/kg, and 3/6 animals in the group treated with Compound

#37 at 20mg/kg. A grade 2 hepatocellular steatosis was also observed in one animal each in the vehicle-treated group and the group treated with Compound #37 at 5mg/kg, but not in animals treated with Compound #37 at 20mg/kg.

[0235] There was no inflammation noted in the animals treated with Compound #37 at 40mg/kg. Inflammation was accompanied by limited periportal fibrosis but was not observed at day 9 in animals treated with Compound #37 at 40mg/kg. The hepatocellular steatosis was more pronounced (Grade 2) in that group. The steatosis was accompanied by hepatocellular ballooning, which was inconsistently noted in vehicle-treated group and the group treated with Compound #37 at 5mg/kg group, but was absent in the group treated with Compound #37 at 20mg/kg.

[0236] Overall, the NAS scores in the vehicle-treated group and the group treated with Compound #37 at 5mg/kg were slightly higher than that observed in the group treated with Compound #37 at 20mg/kg, reflecting an apparent difference severity and extent of the inflammatory and lipidic changes. The group treated with Compound #37 at 20mg/kg was the least severely affected.

[0237] Lesions of NAFLD observed in this study were consistent to that previously described and reviewed by Imajo et al. (2013). The hyper-inflammatory response was accompanied by some evidence of fibrosis.

[0238] Although this experiment did not demonstrate a clear dose-dependent effect of treatment with Compound #37, treatment at 20mg/kg appeared to be the most effective in reducing most of the liver injuries induced in this specific diet-induced NASH mouse model. Plasma ALT and ALT levels were reduced as well as liver steatosis. Finally NAS score assessed by histopathological analysis was also improved with reduced inflammation, steatosis, and hepatocyte ballooning as well as fibrosis.

[0239] The results are shown in Tables 14A and 14B.

Table 14A. NAS Scores (21 days)

group	animal #	steatose	inflammation	fibrosis	hepatocyte ballooning	total
Vehicle	7	1	2	1	0	4
	15	2	1	1	2	6
	17	1	1	0	0	2
	20	1	2	1	0	4
	24	1	3	1	0	5
	26	0	1	1	0	2
	27	1	3	1	0	5
	31	1	2	1	0	4
	35	0	2	1	0	3
	39	1	2	1	0	4
	mean	0.9	1.9	0.9	0.2	3.9
	sd	0.57	0.74	0.32	0.63	1.29
	sem	0.18	0.23	0.1	0.2	0.41
	n	10	10	10	10	10
5 mg/kg	2	1	1	1	1	4
	5	1	2	1	1	5
	6	1	3	1	0	5
	8	1	1	1	0	3
	12	1	1	1	0	3
	19	2	1	1	1	5
	23	1	3	2	0	6
	36	1	3	1	0	5
	37	1	3	2	0	6
	38	1	2	1	0	4
	mean	1.1	2	1.2	0.3	4.6
	sd	0.3	0.9	0.4	0.5	1.1
	sem	0.1	0.3	0.1	0.2	0.3
	n	10	10	10	10	10
20 mg/kg	3	1	1	0	0	2
	16	0	2	1	0	3
	21	0	2	1	0	3
	28	1	3	1	0	5
	32	0	1	0	0	1
	40	1	1	0	0	2
	mean	0.5	1.67	0.5	0	2.67
	sd	0.55	0.82	0.55	0	1.37
	sem	0.22	0.33	0.22	0	0.56
	n	6	6	6	6	6

Table 14B. NAS Scores (9 days)

group	animal #	steatose	inflammation	fibrosis	hepatocyte ballooning	total
40 mg/kg	25	2	0	0	1	3
	30	2	0	0	1	3
	33	2	0	0	1	3
	34	2	0	0	1	3
	mean	2	0	0	1	3
	sd	0	0	0	0	0
	sem	0	0	0	0	0
	n	4	4	4	4	4

[0240] Summary of the Results and Discussion. The Paigen diet in the C57Bl/6J mouse strain typically results in an initial acute weight loss that recovers over time (Hebbard & George, 2011; vendor historical unpublished data). Animals receiving this diet with Compound #37 were observed to have an added dose-dependent decrease in food intake within the first week of dosing that led to marked weight loss and resulting toxicity. The Compound #37 40 mg/kg/day treatment group (10 mice) exhibited a marked decrease in food intake and > 20% mean weight loss over 4 days of treatment, leading to the death of 3 mice by day 7 and the death of an additional 3 mice by day 9. Dosing of this group was stopped on day 4 and the surviving mice were sacrificed on day 9, 1 hour after a final dose to analyze drug exposure. The Compound #37 20 mg/kg/day group (10 mice) also demonstrated decreased food intake and weight loss; 4 mice with the most pronounced weight loss died (1 on day 7, 2 on day 9, 1 on day 11). The other 6 mice in the group exhibited less dramatic weight loss, survived, and regained weight similar to vehicle group animals. No mice died in the Compound #37 5 mg/kg/day or vehicle control groups (10 mice each group).

[0241] The death of animals in the Compound #37 40 mg/kg/day and 20 mg/kg/day groups appears to be related to synergistic weight loss due to a combination of the Paigen diet and the inappetence effects of Compound #37 observed in repeat-dose toxicity studies in rats and dogs. By the end of the 3-week dosing period, no differences in weight were observed among the animals that survived the full study in the vehicle control, Compound #37 5 mg/kg/day, and Compound #37 20 mg/kg/day treatment groups (Table B3). Compound #37 mean plasma concentration 1 hour after final dose administration on day 21 was 20.4 μM ($\pm 4.33 \mu\text{M}$) and 112 μM ($\pm 26.0 \mu\text{M}$) for the 5 mg/kg and 20 mg/kg groups, respectively. The Compound #37 mean plasma concentration 1 hour after final dose administration for the 4 animals on day 9

in the 40 mg/kg group was 136 μM (± 37.1 μM). These exposures at 1 hour after dosing are approximately 2-fold higher than those observed in healthy mice and may be related to altered Compound #37 metabolism in this acute liver injury model.

Table B3.

Treatment		Days of Treatment										
		0	2	4	7	9	11	14	16	18	21	
Vehicle	Mean (g)	27.5	26.9	25.9	25.3	24.6	24.3	24.1	24.6	25.0	25.6	
	SD	1.7	2.1	1.6	1.5	2.1	2.6	2.7	2.6	2.2	1.3	
	N	10	10	10	10	10	10	10	10	10	10	
MDV4463 5 mg/kg	Mean (g)	27.8	26.6	26.3	26.9	26.5	25.9	25.8	25.1	25.4	25.8	
	SD	1.6	1.5	1.4	2.0	1.5	1.7	2.0	2.2	2.5	2.0	
	N	10	10	10	10	10	10	10	10	10	10	
MDV4463 20 mg/kg	Mean (g)	27.7	25.7	23.9	23.7	25.6	27.2	27.2	26.9	27.3	27.0	
	SD	1.5	1.4	2.9	4.2	4.5	1.4	1.2	1.4	1.5	1.7	
	N	10	10	10	9	7	6	6	6	6	6	
MDV4463 40 mg/kg	Mean (g)	28.0	25.8	22.03	19.73	23.28	--	--	--	--	--	
	SD	1.4	1.2	0.8	1.3	1.4	--	--	--	--	--	
	N	10	10	10	7	4	--	--	--	--	--	

[0242] The severe food intake decrease and animal deaths confound the interpretation of the results in this cholate-based model. No consistent observations in hepatic lipid concentrations or SREBP-related target gene expression levels were evident in surviving animals receiving Compound #37 compared with the vehicle control group; however, lower plasma triglyceride and free fatty acid concentrations were observed in a dose-dependent manner. Of note, after 21 days of treatment in this model, liver transaminases were markedly increased for all treatment groups, consistent with the diet-induced liver injury, but trended toward lower values in the Compound #37 treatment groups compared with the vehicle control group (Table 5A). The 4 surviving animals in the 40 mg/kg group were found to have markedly elevated liver transaminases at the time of sacrifice on day 9 (mean AST and ALT > 2500 U/L); however, no control animals were sacrificed at this time point for comparison.

Example B4. Effect of Compound #37 in an Obese Insulin-Resistant Mouse Diet-Induced NASH Model (DIN Model)

[0243] This example demonstrates that Compound #37 tends to improve insulin resistance and reduced liver fibrosis in a diet-induced NASH obese insulin resistant mice.

[0244] Male C57Bl/6J mice (8 weeks old) were housed in enriched ventilated cages (31 X 12.5 X 12.7 cm) throughout the experimental phase. Animals' cages litters were changed at least once a week. Animal were housed 5 per cage on inverted 12-hour light cycle (at 09:00 am lights off), 22 ± 2 °C and 55 ± 10 % relative humidity. The acclimation period was 20 days. During the acclimation period, all mice were fed a standard diet (RM1 (E) 801492, SDS) and tap water *ad libitum*. After the acclimation period, mice were fed with the DIN diet (60% fat, cholesterol enriched) and fructose-enriched tap water *ad libitum* until the end of the experiment.

[0245] At 6 weeks of diet, mice were 4-hour fasted (09:00 am to 1:00 pm) and blood (150 µl/EDTA) was collected at 01:00 pm by retro-orbital bleeding under isoflurane anesthesia. Mice were then allocated in 2 homogenous groups (n=12/group) according to their plasma levels of ALT (average levels: 685U/L), AST (average levels: 627U/L) and HOMA-IR index (average value: 4.7), into 2 homogenous groups (see values at day 0 in Tables 15A and 15B ALT/AST and Tables 16A and 16B for HOMA-IR). Mice were then treated once daily by oral gavage with vehicle (Group 1) or Compound #37 at 20 mg/kg (Group 2) for 70 days.

[0246] Results. A non-significant trend towards lower body weight and body weight gain was observed in mice treated with Compound #37, with no major change observed regarding food intake. Water intake tended to be higher in mice treated with, resulting in a 17% increase in cumulative water intake ($p < 0.05$ vs. vehicle). One animal in the 20mg/kg/day treatment group died on day 48.

[0247] Although a trend towards lower AST plasma levels was observed in mice treated with Compound #37, no significant change was observed in plasma ALT/AST levels and area under the curve during the 70-day treatment (Tables 15A and 15B).

[0248] Blood glucose levels were not altered by Compound #37 treatment. However, plasma insulin levels tended to be reduced with Compound #37, leading to lower HOMA-IR index at day 42 and day 70 (50 and 40% reduction), although this trend was not significant. At the end of the treatment period, plasma leptin levels were significantly reduced by 38% with Compound #37 ($p < 0.05$ vs. vehicle). These results are presented in Tables 16A and 16B.

[0249] Although mice treated with Compound #37 showed increased HDL-cholesterol by 31% ($p < 0.05$ vs. vehicle), no significant change was observed in plasma lipids levels at the end of the treatment period. See Table 17.

[0250] Liver weight was significantly higher (by 21%) in mice treated with Compound #37. Hepatic total cholesterol levels were raised by 17% ($p < 0.05$ vs. vehicle). However, liver fatty acids and triglycerides levels remained unchanged. See Table 18A. Hepatic MCP-1 levels were reduced by 70% ($p < 0.001$ vs. vehicle) in mice treated with Compound #37; see Table 18B.

[0251] Slides having a single hepatic lobe section stained with H&E and Sirius red were digitized using a Nanozoomer from Hamamatsu. Sections were evaluated with knowledge of groups. In agreement with the unchanged hepatic triglycerides levels, oil red O staining and % labeling was not changed with Compound #37. A substantial reduction in Sirius Red labeling was also observed, leading to a 61% reduction ($p < 0.001$ vs. vehicle) in % labeling. These results are presented in Table 18B.

[0252] Each section was evaluated and individually scored using the modified NAFLD scoring system described above. The results of the NAS scoring are shown in Table 19. Although inflammation scores were low in both groups (0-1), NAS scoring (figure 10) showed a significant 81% increase in the inflammation score ($p < 0.05$ vs. vehicle) for mice treated with Compound #37. In agreement with the Sirius Red % labeling, fibrosis score was

reduced by 45%, although this did not reach significance ($p=0.055$ vs. vehicle). While steatosis and hepatocyte ballooning scores remained unchanged, total NAS score did not change with Compound #37.

[0253] The results of the gene expression analysis are presented in Tables 20A-20L. Hepatic expression levels of genes involved in lipid (FAS, SREBP1, ACC1, SCD1), cholesterol metabolism (HMG-CoAR, LDLR), in SREBP proteolysis (SCAP, INSIG1), in ER stress (PERK), oxidative stress (NRF2), and inflammation (MCP-1) were not changed. However, expression of collagen 1 α 1, involved in liver fibrosis, was reduced by 66% in mice treated with Compound #37 ($p<0.05$ vs. vehicle).

[0254] Conclusion. In the diet-induced NASH obese insulin resistant mice, Compound #37 tends to improve insulin resistance and reduce liver fibrosis.

Table 15A. Plasma ALT and AST Levels (Vehicle Group)

[illegible]

Table 15B. Plasma ALT and AST Levels (20 mg/kg Compound #37 group)

group	animal #	days of treatment / ALAT (U/L)						days of treatment / ASAT (U/L)						ALAT		ASAT	
		0	14	28	42	56	70	0	14	28	42	56	70	U/L.day	U/L.day		
20 mg/kg	1	830	690	160	66	534	142	725	440	222	130	182	182	16954	13167		
	3	662	134	208	50	70	142	730	248	288	76	130	198	8862	11690		
	4	260	252	38	370	74	104	283	428	68	174	164	192	7686	9163		
	6	1065	106	136	322	dead	dead	860	126	190	296	dead	dead	dead	dead		
	8	1520	250	176	68	276	364	1440	296	238	88	346	258	18578	18662		
	10	698	252	118	280	80	1030	875	268	98	132	122	648	17206	15001		
	17	955	218	96	52	48	326	584	206	84	80	92	162	11865	8456		
	18	551	200	68	50	68	372	435	228	76	110	108	206	9163	8141		
	19	226	92	58	136	52	210	217	124	80	140	60	180	5418	5607		
	21	365	198	316	58	54	342	269	150	168	96	96	160	9331	6573		
	22	625	256	226	168	112	1150	464	190	140	200	132	524	17759	11550		
	24	563	410	154	92	130	358	500	288	102	106	112	376	11949	10388		
	mean	693	255	146	143	136	413	615	249	146	136	126	281	12252	10763		
	sd	365	161	79	117	147	350	343	104	74	63	37	165	4630	3830		
	sem	105	46	23	34	44	106	99	30	21	18	13	50	1396	1155		
	n	12	12	12	12	11	11	12	12	12	12	11	11	11	11		

Table 16A. Blood Glucose and Plasma Insulin Levels

group	animal #	blood glucose (mg/dL)			plasma insulin (μ U/mL)		
		day 0	day 42	day 70	day 0	day 42	day 70
Vehicle	2	97	135	159	21.8	26.0	14.1
	5	117	145	141	51.9	22.3	59.4
	7	123	109	153	7.8	12.1	13.2
	9	135	136	145	8.1	16.9	16.7
	11	118	144	172	9.6	31.0	13.6
	12	106	112	133	5.1	6.5	7.0
	13	92	166	154	13.1	9.5	18.1
	14	131	142	156	9.0	8.9	33.2
	15	117	138	109	9.9	16.2	39.9
	16	100	150	119	32.4	57.8	23.3
	20	96	90	111	26.7	62.8	6.0
	23	90	99	145	10.2	7.2	9.8
	mean	110	131	141	17.1	23.1	21.2
	sd	15	23	20	13.8	19	15.7
	sem	4	7	6	4	5.5	4.5
	n	12	12	12	12	12	12
20 mg/kg	1	97	133	138	11.3	11.6	21.9
	3	113	139	132	14.7	9.5	8.0
	4	123	112	135	77.6	18.0	18.1
	6	106	126	dead	8.1	24.8	dead
	8	79	128	157	11.9	8.9	15.1
	10	113	132	136	6.9	11.8	11.5
	17	95	131	124	7.5	5.8	9.3
	18	114	138	127	13.6	8.2	20.6
	19	102	139	100	8.4	8.2	10.3
	21	89	151	114	7.5	10.0	13.4
	22	112	140	130	31.9	10.2	9.8
	24	103	127	141	9	10.7	12.9
	mean	104	133	130	17	11.5	13.7
	sd	12	10	15	20	5.1	4.7
	sem	4	3	4	6	1.5	1.4
	n	12	12	11	12	12	11

Table 16B. Homeostasis Model Assessment of Insulin Resistance and Plasma Leptin Levels

group	animal #	HOMA-IR			plasma leptin
		([mM X μ U/mL]/22.5)			(pg/mL)
		day 0	day 42	day 70	day 70
Vehicle	2	5.2	8.7	5.5	397
	5	15.0	8.0	20.7	311
	7	2.4	1.6	5.0	675
	9	2.7	5.7	6.0	842
	11	2.8	11.0	5.8	480
	12	1.3	1.8	2.3	95
	13	3.0	3.9	6.9	334
	14	2.9	3.1	12.8	653
	15	2.9	5.5	10.7	630
	16	8.0	21.4	6.8	490
	20	6.3	14.0	1.7	44
	23	2.3	1.8	3.5	165
	mean	4.6	7.2	7.3	426
	sd	3.8	5.9	5.3	249
	sem	1.1	1.7	1.5	72
	n	12	12	12	12
20 mg/kg	1	2.7	3.8	7.5	454
	3	4.1	3.3	2.6	330
	4	23.6	5.0	6.0	202
	6	2.1	7.7	dead	dead
	8	2.3	2.8	5.8	280
	10	1.9	3.8	3.9	341
	17	1.8	1.9	2.8	144
	18	3.8	2.8	6.5	294
	19	2.1	2.8	2.5	46
	21	1.6	3.7	3.8	269
	22	8.8	3.5	3.1	374
	24	2.3	3.4	4.5	187
	mean	4.8	3.7	4.5	265
	sd	6.2	1.5	1.7	114
	sem	1.8	0.4	0.5	35
	n	12	12	11	11

Table 17. Plasma Lipid Levels

Group	Animal #	cholesterol (g/L)	HDL cholesterol (g/L)	triglycerides (g/L)	free fatty acids (mM)
Vehicle	2	1.50	1.01	0.50	0.56
	5	1.63	1.12	0.39	0.54
	7	1.94	1.20	0.40	0.65
	9	2.49	1.47	0.40	0.57
	11	2.04	1.41	0.40	0.67
	12	1.34	1.02	0.42	0.69
	13	1.61	0.92	0.40	0.84
	14	1.64	1.16	0.50	0.62
	15	1.98	1.22	0.60	0.81
	16	1.72	0.98	0.34	0.46
	20	2.75	0.58	1.03	1.08
	23	1.31	0.88	0.42	0.93
	mean	1.83	1.08	0.48	0.7
	sd	0.44	0.24	0.19	0.18
	sem	0.13	0.07	0.05	0.05
	n	12	12	12	12
20 mg/kg	1	2.49	1.65	0.37	0.73
	3	2.36	1.68	0.3	0.63
	4	1.95	1.10	0.42	0.59
	6	dead	dead	dead	dead
	8	1.67	1.47	0.35	0.29
	10	2.12	1.90	0.40	0.65
	17	1.38	1.12	0.34	0.56
	18	1.62	1.43	0.45	0.71
	19	1.15	0.62	0.50	0.44
	21	1.57	1.47	0.47	0.59
	22	1.86	1.62	0.37	0.59
	24	1.90	1.56	0.39	0.67
	mean	1.82	1.42	0.40	0.59
	sd	0.4	0.36	0.06	0.13
	sem	0.12	0.11	0.02	0.04
	n	11	11	11	11

Table 18A. Liver Lipid Levels

Group	animal #	liver weight	cholesterol (µg/mg)	triglycerides (µg/mg)	fatty acids (nmol/mg)
Vehicle	2	1.65	20.5	128.5	67.2
	5	1.72	20.0	62.4	41.3
	7	2.35	35.0	197.5	92.5
	9	2.61	25.6	165.2	67.8
	11	2.29	32.2	151.5	85.5
	12	1.57	18.8	103.3	48.9
	13	2.14	21.7	90.6	51.5
	14	2.44	30.4	181.3	75.2
	15	2.62	23.3	178.2	64.6
	16	2.08	18.7	85.7	45.3
	20	2.40	22.8	67.8	46.8
	23	1.60	20.0	107.0	45.3
	mean	2.12	24.1	126.6	61.0
	sd	0.39	5.5	47	17.1
	sem	0.11	1.6	13.6	4.9
	n	12	12	12	12
20 mg/kg	1	3.24	27.4	262.5	72.2
	3	2.72	32.2	203.3	67.2
	4	1.97	25.8	72.2	56.2
	6	dead	dead	dead	dead
	8	2.74	28.4	162.3	82.8
	10	2.39	28.3	101.9	56.8
	17	1.97	27.1	53.6	47.8
	18	2.54	29.9	178.1	68.4
	19	2.44	20.7	48.9	43.9
	21	2.67	31.3	91.5	70.0
	22	3.05	34.0	195	76.7
	24	2.40	25.3	102.6	53.2
	mean	2.56	28.2	133.8	63.2
	sd	0.39	3.7	70.1	12.4
	sem	0.12	1.1	21.1	3.7
	n	11	11	11	11

Table 18B. MCP1 and % Labeling

Group	animal #	MCP1 (pg/mg liver)	O red Oil labeling (%)	Sirius red labeling (%)
Vehicle	2	1.96	8.8	0.6
	5	3.04	6.2	1.1
	7	3.3	28.8	1.2
	9	3.73	5.7	1.4
	11	3.31	10.6	1.9
	12	5.91	9.7	2.7
	13	2.79	10.8	1.6
	14	4.74	13.6	0.9
	15	1.87	8.3	1.0
	16	3.16	5.2	2.0
	20	31.66	5.1	6.6
	23	1.68	4.3	1.9
	mean	5.6	9.8	1.9
	sd	8.3	6.6	1.6
	sem	2.4	1.9	0.5
	n	12	12	12
20 mg/kg	1	1.34	12.9	0.5
	3	1.53	15.1	0.8
	4	0.60	0.9	0.8
	6	dead	ND	ND
	8	2.54	18.6	0.6
	10	1.76	19.3	1.0
	17	1.72	21.3	0.9
	18	1.42	0.3	0.8
	19	1.21	8.3	0.7
	21	1.78	19.5	0.6
	22	1.90	13.0	0.7
	24	2.59	4.2	0.8
	mean	1.7	12.1	0.7
	sd	0.6	7.7	0.1
	sem	0.2	2.3	0
	n	11	11	11

Table 19. NAS Scores

group	animal #	steatosis	inflammation	fibrosis	hepatocyte ballooning	total
Vehicle	2	1	0	1	1	3
	5	1	1	1	1	4
	7	3	0	2	3	8
	9	2	0	1	2	5
	11	2	1	1	2	6
	12	1	1	1	1	4
	13	2	0	1	2	5
	14	2	0	1	2	5
	15	3	0	1	3	7
	16	1	1	0	1	3
	20	2	1	3	2	8
	23	1	1	1	1	4
	mean	1.75	0.50	1.17	1.75	5.17
	sd	0.75	0.52	0.72	0.75	1.75
	sem	0.22	0.15	0.21	0.22	0.51
	n	12	12	12	12	12
20 mg/kg	1	3	0	1	3	7
	3	3	1	1	3	8
	4	1	1	0	1	3
	8	2	1	0	2	5
	10	2	1	1	2	6
	17	1	1	1	1	4
	18	2	1	0	2	5
	19	1	1	0	1	3
	21	2	1	1	2	6
	22	2	1	1	2	6
	24	2	1	1	2	6
	mean	1.91	0.91	0.64	1.91	5.36
	sd	0.70	0.30	0.50	0.70	1.57
	sem	0.21	0.09	0.15	0.21	0.47
	n	11	11	11	11	11

Table 20A. Gene Expression: FAS

group	animal #	FAS				
		18S	FAS	Dct	DDct	2 ^{DDct}
vehicle	2	12.42	21.64	9.22	0.72	0.61
	5	12.38	20.75	8.37	-0.13	1.09
	7	12.58	20.74	8.16	-0.34	1.27
	9	12.32	20.89	8.57	0.07	0.95
	11	12.58	20.77	8.19	-0.31	1.24
	12	12.11	23.11	11	2.50	0.18
	13	12.34	20.65	8.31	-0.19	1.14
	14	12.37	18.82	6.45	-2.05	4.14
	15	12.16	18.85	6.69	-1.81	3.51
	16	12.59	21.25	8.66	0.16	0.90
	20	12.33	21.59	9.26	0.76	0.59
	23	12.52	21.64	9.12	0.62	0.65
	mean	12.4	20.9	8.5	0.00	1.36
	sd	0.2	1.2	1.2	1.19	1.20
	sem	0.0	0.3	0.3	0.34	0.35
	n	12	12	12	12	12
20 mg/kg	1	12.55	19.75	7.2	-1.30	2.46
	3	12.55	20.68	8.13	-0.37	1.29
	4	12.84	22.79	9.95	1.45	0.37
	6	ND	ND	ND	ND	ND
	8	12.43	20.37	7.94	-0.56	1.47
	10	12.35	22.33	9.98	1.48	0.36
	17	12.59	20.71	8.12	-0.38	1.30
	18	11.73	20.54	8.81	0.31	0.81
	19	12.51	21.65	9.14	0.64	0.64
	21	11.5	21.62	10.12	1.62	0.33
	22	11.55	22.33	10.78	2.28	0.21
	24	12.35	20.03	7.68	-0.82	1.77
	mean	12.3	21.2	8.9	0.40	1
	sd	0.5	1	1.2	1.18	0.72
	sem	0.1	0.3	0.4	0.35	0.22
	n	11	11	11	11	11

Table 20B. Gene Expression: SCD1

group	animal #	SCD1				
		18S	SCD1	Dct	DDct	2 ^{DDct}
vehicle	2	12.42	17.7	5.28	-0.03	1.02
	5	12.38	17.75	5.37	0.06	0.96
	7	12.58	17.25	4.67	-0.64	1.56
	9	12.32	18.04	5.72	0.41	0.75
	11	12.58	17.53	4.95	-0.36	1.29
	12	12.11	18.91	6.8	1.49	0.36
	13	12.34	17.62	5.28	-0.03	1.02
	14	12.37	16.47	4.1	-1.21	2.32
	15	12.16	16.63	4.47	-0.84	1.80
	16	12.59	18.4	5.81	0.5	0.71
	20	12.33	18.26	5.93	0.62	0.65
	23	12.52	17.91	5.39	0.08	0.95
	mean	12.4	17.7	5.3	0.00	1.12
	sd	0.2	0.7	0.7	0.72	0.55
	sem	0.0	0.2	0.2	0.21	0.16
	n	12	12	12	12	12
20 mg/kg	1	12.55	17.05	4.5	-0.81	1.76
	3	12.55	16.66	4.11	-1.20	2.30
	4	12.84	18.93	6.09	0.78	0.58
	6	ND	ND	ND	ND	ND
	8	12.43	17.94	5.51	0.20	0.87
	10	12.35	17.92	5.57	0.26	0.84
	17	12.59	17.42	4.83	-0.48	1.40
	18	11.73	16.42	4.69	-0.62	1.54
	19	12.51	17.11	4.6	-0.71	1.64
	21	11.5	17.53	6.03	0.72	0.61
	22	11.55	18.11	6.56	1.25	0.42
	24	12.35	16.3	3.95	-1.36	2.57
	mean	12.3	17.4	5.1	-0.18	1.32
	sd	0.5	0.8	0.9	0.87	0.72
	sem	0.1	0.2	0.3	0.26	0.22
	n	11	11	11	11	11

Table 20C. Gene Expression: SREBP1C

group	animal #	SREBP1C				
		18S	SREBP1C	Dct	DDct	2 ^{DDct}
vehicle	2	12.42	26.04	13.62	0.26	0.84
	5	12.38	25.85	13.47	0.11	0.93
	7	12.58	25.84	13.26	-0.10	1.07
	9	12.32	26	13.68	0.32	0.8
	11	12.58	25.98	13.4	0.04	0.97
	12	12.11	26.29	14.18	0.82	0.57
	13	12.34	26.15	13.81	0.45	0.73
	14	12.37	24.53	12.16	-1.20	2.30
	15	12.16	25.26	13.1	-0.26	1.20
	16	12.59	26.19	13.6	0.24	0.85
	20	12.33	25	12.67	-0.69	1.62
	23	12.52	25.92	13.4	0.04	0.97
	mean	12.4	25.8	13.4	0.00	1.07
	sd	0.2	0.5	0.5	0.53	0.47
	sem	0.0	0.2	0.2	0.15	0.14
	n	12	12	12	12	12
20 mg/kg	1	12.55	25.53	12.98	-0.38	1.30
	3	12.55	25.64	13.09	-0.27	1.21
	4	12.84	27.5	14.66	1.30	0.41
	6	ND	ND	ND	ND	ND
	8	12.43	26.83	14.4	1.04	0.49
	10	12.35	26.25	13.9	0.54	0.69
	17	12.59	25.81	13.22	-0.14	1.10
	18	11.73	25.1	13.37	0.01	0.99
	19	12.51	25.42	12.91	-0.45	1.37
	21	11.5	26.32	14.82	1.46	0.36
	22	11.55	26.01	14.46	1.10	0.47
	24	12.35	24.62	12.27	-1.09	2.13
	mean	12.3	25.9	13.6	0.28	0.96
	sd	0.5	0.8	0.8	0.85	0.54
	sem	0.1	0.2	0.3	0.25	0.16
	n	11	11	11	11	11

Table 20D. Gene Expression: ACC1

group	animal#	ACC1				
		18S	ACC1	Dct	DDct	2 ^{DDct}
vehicle	2	12.42	28.34	15.92	0.04	0.97
	5	12.38	28.51	16.13	0.25	0.84
	7	12.58	28.12	15.54	-0.34	1.27
	9	12.32	28.17	15.85	-0.03	1.02
	11	12.58	28.43	15.85	-0.03	1.02
	12	12.11	29.9	17.79	1.91	0.27
	13	12.34	28.36	16.02	0.14	0.91
	14	12.37	26.48	14.11	-1.77	3.42
	15	12.16	26.85	14.69	-1.19	2.29
	16	12.59	28.75	16.16	0.28	0.83
	20	12.33	29	16.67	0.79	0.58
	23	12.52	28.38	15.86	-0.02	1.02
	mean	12.4	28.3	15.9	0.00	1.20
	sd	0.2	0.9	0.9	0.91	0.84
	sem	0.0	0.3	0.3	0.26	0.24
	n	12	12	12	12	12
20 mg/kg	1	12.55	27.74	15.19	-0.69	1.62
	3	12.55	28.17	15.62	-0.26	1.20
	4	12.84	31	18.16	2.28	0.21
	6	ND	ND	ND	ND	ND
	8	12.43	28.06	15.63	-0.25	1.19
	10	12.35	30.55	18.2	2.32	0.20
	17	12.59	28.11	15.52	-0.36	1.29
	18	11.73	27.95	16.22	0.34	0.79
	19	12.51	28.97	16.46	0.58	0.67
	21	11.5	28.95	17.45	1.57	0.34
	22	11.55	29.55	18	2.12	0.23
	24	12.35	27.41	15.06	-0.82	1.77
	mean	12.3	28.8	16.5	0.62	0.86
	sd	0.5	1.2	1.2	1.23	0.58
	sem	0.1	0.4	0.4	0.37	0.18
	n	11	11	11	11	11

Table 20E. Gene Expression: SCAP

group	animal #	SCAP				
		18S	SCAP	Dct	DDct	2 ^{DDct}
vehicle	2	12.42	24.25	11.83	-0.23	1.17
	5	12.38	24.57	12.19	0.13	0.91
	7	12.58	24.17	11.59	-0.47	1.39
	9	12.32	25.05	12.73	0.67	0.63
	11	12.58	24.81	12.23	0.17	0.89
	12	12.11	25	12.89	0.83	0.56
	13	12.34	24.73	12.39	0.33	0.80
	14	12.37	23.28	10.91	-1.15	2.22
	15	12.16	24.06	11.9	-0.16	1.12
	16	12.59	24.66	12.07	0.01	0.99
	20	12.33	24.76	12.43	0.37	0.77
	23	12.52	24.1	11.58	-0.48	1.4
	mean	12.4	24.5	12.1	0.00	1.07
	sd	0.2	0.5	0.5	0.55	0.45
	sem	0.0	0.1	0.2	0.16	0.13
	n	12	12	12	12	12
20 mg/kg	1	12.55	24.16	11.61	-0.45	1.37
	3	12.55	23.83	11.28	-0.78	1.72
	4	12.84	25.53	12.69	0.63	0.65
	6	ND	ND	ND	ND	ND
	8	12.43	24.98	12.55	0.49	0.71
	10	12.35	24.54	12.19	0.13	0.91
	17	12.59	24.11	11.52	-0.54	1.46
	18	11.73	23.32	11.59	-0.47	1.39
	19	12.51	23.79	11.28	-0.78	1.72
	21	11.5	24.21	12.71	0.65	0.64
	22	11.55	24.38	12.83	0.77	0.59
	24	12.35	23.73	11.38	-0.68	1.60
	mean	12.3	24.2	12.0	-0.10	1.16
	sd	0.5	0.6	0.6	0.63	0.46
	sem	0.1	0.2	0.2	0.19	0.14
	n	11	11	11	11	11

Table 20F. Gene Expression: INSIG1

group	animal #	INSIG1				
		18S	INSIG1	Dct	DDct	2 ^{DDct}
vehicle	2	12.42	23.1	10.68	-0.22	1.16
	5	12.38	22.61	10.23	-0.67	1.59
	7	12.58	22.83	10.25	-0.65	1.57
	9	12.32	23.3	10.98	0.08	0.94
	11	12.58	23.27	10.69	-0.21	1.15
	12	12.11	24.36	12.25	1.35	0.39
	13	12.34	23.78	11.44	0.54	0.69
	14	12.37	22.17	9.8	-1.10	2.14
	15	12.16	22.89	10.73	-0.17	1.12
	16	12.59	24.03	11.44	0.54	0.69
	20	12.33	24.68	12.35	1.45	0.37
	23	12.52	22.44	9.92	-0.98	1.97
	mean	12.4	23.3	10.9	0.00	1.15
	sd	0.2	0.8	0.8	0.84	0.58
	sem	0.0	0.2	0.2	0.24	0.17
	n	12	12	12	12	12
20 mg/kg	1	12.55	22.4	9.85	-1.05	2.07
	3	12.55	22.28	9.73	-1.17	2.24
	4	12.84	24.1	11.26	0.36	0.78
	6	ND	ND	ND	ND	ND
	8	12.43	22.7	10.27	-0.63	1.54
	10	12.35	22.65	10.3	-0.60	1.51
	17	12.59	22.76	10.17	-0.73	1.65
	18	11.73	22.09	10.36	-0.54	1.45
	19	12.51	22.89	10.38	-0.52	1.43
	21	11.5	22.76	11.26	0.36	0.78
	22	11.55	23.58	12.03	1.13	0.46
	24	12.35	21.74	9.39	-1.51	2.84
	mean	12.3	22.7	10.5	-0.44	1.52
	sd	0.5	0.7	0.8	0.77	0.7
	sem	0.1	0.2	0.2	0.23	0.21
	n	11	11	11	11	11

Table 20G. Gene Expression: HMGCOA

group	animal #	HMGCOA				
		18S	HMGCoA	Dct	DDct	2 ^{DDct}
vehicle	2	12.42	25.68	13.26	0.04	0.97
	5	12.38	25.07	12.69	-0.53	1.44
	7	12.58	25.26	12.68	-0.54	1.45
	9	12.32	26.03	13.71	0.49	0.71
	11	12.58	25.79	13.21	-0.01	1.01
	12	12.11	26.44	14.33	1.11	0.46
	13	12.34	26.48	14.14	0.92	0.53
	14	12.37	24.43	12.06	-1.16	2.24
	15	12.16	25.33	13.17	-0.05	1.04
	16	12.59	26.00	13.41	0.19	0.88
	20	12.33	25.97	13.64	0.42	0.75
	23	12.52	24.87	12.35	-0.87	1.83
	mean	12.4	25.6	13.2	0.00	1.11
	sd	0.2	0.6	0.7	0.69	0.54
	sem	0.0	0.2	0.2	0.20	0.15
	n	12	12	12	12	12
20 mg/kg	1	12.55	25.35	12.8	-0.42	1.34
	3	12.55	24.69	12.14	-1.08	2.12
	4	12.84	26.62	13.78	0.56	0.68
	6	ND	ND	ND	ND	ND
	8	12.43	25.08	12.65	-0.57	1.49
	10	12.35	25.92	13.57	0.35	0.79
	17	12.59	25.42	12.83	-0.39	1.31
	18	11.73	24.76	13.03	-0.19	1.14
	19	12.51	25.37	12.86	-0.36	1.28
	21	11.5	25.99	14.49	1.27	0.41
	22	11.55	26.18	14.63	1.41	0.38
	24	12.35	24.72	12.37	-0.85	1.8
	mean	12.3	25.5	13.2	-0.03	1.16
	sd	0.5	0.6	0.8	0.82	0.55
	sem	0.1	0.2	0.2	0.25	0.17
	n	11	11	11	11	11

Table 20H. Gene Expression: LDLR

Group	animal #	LDLR				
		18S	LDLR	Dct	DDct	2 ^{DDct}
Vehicle	2	12.42	26.06	13.64	0.54	0.69
	5	12.38	24.71	12.33	-0.77	1.70
	7	12.58	24.85	12.27	-0.83	1.77
	9	12.32	26.25	13.93	0.83	0.56
	11	12.58	25.02	12.44	-0.66	1.58
	12	12.11	26.93	14.82	1.72	0.30
	13	12.34	25.93	13.59	0.49	0.71
	14	12.37	24.05	11.68	-1.42	2.67
	15	12.16	24.96	12.8	-0.3	1.23
	16	12.59	25.41	12.82	-0.28	1.21
	20	12.33	26.6	14.27	1.17	0.44
	23	12.52	25.08	12.56	-0.54	1.45
	mean	12.4	25.5	13.1	0.00	1.19
	sd	0.2	0.9	0.9	0.94	0.69
	sem	0.0	0.2	0.3	0.27	0.20
	n	12	12	12	12	12
20 mg/kg	1	12.55	24.92	12.37	-0.73	1.65
	3	12.55	24.3	11.75	-1.35	2.54
	4	12.84	27.14	14.3	1.2	0.43
	6	ND	ND	ND	ND	ND
	8	12.43	25.37	12.94	-0.16	1.11
	10	12.35	25.85	13.5	0.4	0.76
	17	12.59	24.92	12.33	-0.77	1.7
	18	11.73	23.76	12.03	-1.07	2.09
	19	12.51	24.73	12.22	-0.88	1.84
	21	11.5	24.47	12.97	-0.13	1.09
	22	11.55	24.99	13.44	0.34	0.79
	24	12.35	23.63	11.28	-1.82	3.52
	mean	12.3	24.9	12.6	-0.45	1.59
	sd	0.5	1.0	0.9	0.88	0.90
	sem	0.1	0.3	0.3	0.26	0.27
	n	11	11	11	11	11

Table 20I. Gene Expression: PERK

group	animal #	PERK				
		18S	PERK	Dct	DDct	2 ^{DDct}
Vehicle	2	12.42	27.4	14.98	0.48	0.71
	5	12.38	27.25	14.87	0.37	0.77
	7	12.58	26.77	14.19	-0.31	1.24
	9	12.32	26.82	14.5	0.00	1.00
	11	12.58	27.18	14.6	0.1	0.93
	12	12.11	27.22	15.11	0.61	0.65
	13	12.34	27.27	14.93	0.43	0.74
	14	12.37	25.93	13.56	-0.94	1.91
	15	12.16	26.19	14.03	-0.47	1.38
	16	12.59	27.55	14.96	0.46	0.72
	20	12.33	26.25	13.92	-0.58	1.49
	23	12.52	26.82	14.30	-0.20	1.15
	mean	12.4	26.9	14.50	0.00	1.06
	sd	0.2	0.5	0.5	0.5	0.39
	sem	0	0.2	0.1	0.14	0.11
	n	12	12	12	12	12
20 mg/kg	1	12.55	26.78	14.23	-0.27	1.2
	3	12.55	26.96	14.41	-0.09	1.06
	4	12.84	28.95	16.11	1.61	0.33
	6	ND	ND	ND	ND	ND
	8	12.43	27.32	14.89	0.39	0.76
	10	12.35	27.3	14.95	0.45	0.73
	17	12.59	26.77	14.18	-0.32	1.24
	18	11.73	26.58	14.85	0.35	0.78
	19	12.51	26.81	14.3	-0.2	1.15
	21	11.5	27.25	15.75	1.25	0.42
	22	11.55	27.62	16.07	1.57	0.34
	24	12.35	25.25	12.9	-1.6	3.02
	mean	12.3	27.1	14.8	0.29	1.00
	sd	0.5	0.9	0.9	0.95	0.75
	sem	0.1	0.2	0.3	0.29	0.23
	n	11	11	11	11	11

Table 20J. Gene Expression: NRF2

Group	animal #	NRF2				
		18S	NRF2	Dct	DDct	2 ^{DDct}
Vehicle	2	12.42	23.83	11.41	0.37	0.77
	5	12.38	23.87	11.49	0.45	0.73
	7	12.58	23.16	10.58	-0.46	1.38
	9	12.32	23.29	10.97	-0.07	1.05
	11	12.58	24.02	11.44	0.40	0.76
	12	12.11	23.91	11.8	0.76	0.59
	13	12.34	23.45	11.11	0.07	0.95
	14	12.37	22.15	9.78	-1.26	2.40
	15	12.16	22.53	10.37	-0.67	1.59
	16	12.59	24.02	11.43	0.39	0.76
	20	12.33	23.13	10.8	-0.24	1.18
	23	12.52	23.84	11.32	0.28	0.82
	mean	12.4	23.4	11.0	0.00	1.08
	sd	0.2	0.6	0.6	0.57	0.51
	sem	0.0	0.2	0.2	0.17	0.15
	n	12	12	12	12	12
20 mg/kg	1	12.55	23.17	10.62	-0.42	1.34
	3	12.55	23.25	10.7	-0.34	1.27
	4	12.84	25.41	12.57	1.53	0.35
	6	ND	ND	ND	ND	ND
	8	12.43	23.7	11.27	0.23	0.85
	10	12.35	23.66	11.31	0.27	0.83
	17	12.59	23.47	10.88	-0.16	1.12
	18	11.73	22.83	11.1	0.06	0.96
	19	12.51	23.25	10.74	-0.3	1.23
	21	11.5	23.73	12.23	1.19	0.44
	22	11.55	23.44	11.89	0.85	0.56
	24	12.35	22.25	9.9	-1.14	2.21
	mean	12.3	23.5	11.2	0.16	1.01
	sd	0.5	0.8	0.8	0.78	0.52
	sem	0.1	0.2	0.2	0.23	0.16
	n	11	11	11	11	11

Table20K. Gene Expression: MCP-1

Group	animal #	MCP-1				
		18S	MCP-1	Dct	DDct	2 ^{DDct}
Vehicle	2	12.42	27.14	14.72	1.1	0.47
	5	12.38	26.01	13.63	0.01	0.99
	7	12.58	25.58	13	-0.62	1.54
	9	12.32	25.75	13.43	-0.19	1.14
	11	12.58	26.44	13.86	0.24	0.85
	12	12.11	25.87	13.76	0.14	0.91
	13	12.34	26.2	13.86	0.24	0.85
	14	12.37	25.42	13.05	-0.57	1.48
	15	12.16	25.66	13.5	-0.12	1.09
	16	12.59	27.42	14.83	1.21	0.43
	20	12.33	24.06	11.73	-1.89	3.7
	23	12.52	26.57	14.05	0.43	0.74
	mean	12.4	26.0	13.6	0.00	1.18
	sd	0.2	0.9	0.8	0.82	0.86
	sem	0.0	0.3	0.2	0.24	0.25
	n	12	12	12	12	12
20 mg/kg	1	12.55	26.89	14.34	0.72	0.61
	3	12.55	26.18	13.63	0.01	0.99
	4	12.84	28.45	15.61	1.99	0.25
	6	ND	ND	ND	ND	ND
	8	12.43	26.02	13.59	-0.03	1.02
	10	12.35	25.89	13.54	-0.08	1.06
	17	12.59	26.25	13.66	0.04	0.97
	18	11.73	26.62	14.89	1.27	0.41
	19	12.51	28.83	16.32	2.7	0.15
	21	11.5	27	15.5	1.88	0.27
	22	11.55	27.29	15.74	2.12	0.23
	24	12.35	24.14	11.79	-1.83	3.55
	mean	12.3	26.7	14.4	0.80	0.87
	sd	0.5	1.3	1.3	1.33	0.96
	sem	0.1	0.4	0.4	0.40	0.29
	n	11	11	11	11	11

Table 20L. Gene Expression: Coll1a1

Group	animal #	Coll1a1				
		18S	Coll1a1	Dct	DDct	2 ^{DDct}
Vehicle	2	12.42	29.06	16.64	2.69	0.15
	5	12.38	28.03	15.65	1.70	0.31
	7	12.58	26.08	13.5	-0.45	1.37
	9	12.32	26.57	14.25	0.30	0.81
	11	12.58	26.7	14.12	0.17	0.89
	12	12.11	26.28	14.17	0.22	0.86
	13	12.34	26.14	13.8	-0.15	1.11
	14	12.37	24.13	11.76	-2.19	4.56
	15	12.16	25.13	12.97	-0.98	1.97
	16	12.59	26.77	14.18	0.23	0.85
	20	12.33	24.38	12.05	-1.90	3.73
	23	12.52	26.83	14.31	0.36	0.78
	mean	12.4	26.3	14	0.00	1.45
	sd	0.2	1.4	1.4	1.35	1.35
	sem	0	0.4	0.4	0.39	0.39
	n	12	12	12	12	12
20 mg/kg	1	12.55	27.55	15	1.05	0.48
	3	12.55	26.78	14.23	0.28	0.82
	4	12.84	30.66	17.82	3.87	0.07
	6	ND	ND	ND	ND	ND
	8	12.43	28.81	16.38	2.43	0.19
	10	12.35	27.72	15.37	1.42	0.37
	17	12.59	28.24	15.65	1.7	0.31
	18	11.73	26.86	15.13	1.18	0.44
	19	12.51	28.61	16.1	2.15	0.23
	21	11.5	27.64	16.14	2.19	0.22
	22	11.55	29.03	17.48	3.53	0.09
	24	12.35	25.17	12.82	-1.13	2.19
	mean	12.3	27.9	15.6	1.70	0.49
	sd	0.5	1.4	1.4	1.41	0.60
	sem	0.1	0.4	0.4	0.42	0.18
	n	11	11	11	11	11

Example B5. Effect of Compound #37 on plasma and liver lipid levels in ob/ob mice

[0255] This example demonstrates the effect of Compound #37 on plasma and liver lipid levels in ob/ob mice.

[0256] Groups of mice were either untreated (group 1) or treated for 8 weeks with vehicle (group 2), or with Compound #37 at 5 mg/kg (group 3), 10 mg/kg (group 4), or 20 mg/kg (group 5). Treatment was daily by oral gavage in vehicle (20% HP β CD). Values are presented as mean $\pm$ standard error of the mean (sem). A t test was performed to compare the untreated group and the vehicle group. Then Compound #37-treated groups were compared to the vehicle-treated group with a 1-way ANOVA + Dunnett's post-test. When variances were significantly different, a Kruskaii-Wallis test was performed. For each test, a $p < 0.05$ was considered significant. Of note, animal #39, group 1 was excluded from the statistical analysis, due to low values for all parameters measured. Some other values were considered as out-liners and excluded from the statistical analysis when the value was far below the mean minus 2 SD. Excluded values are marked with an asterisk in Tables 21-23.

[0257] Results. At the end of experiment, the ob/ob mice treated with vehicle alone, in comparison to the untreated mice, displayed a significant increase in plasma triglyceride levels ($p < 0.01$) and, inversely, a significant plasma insulin level decrease ($p < 0.01$). The plasma total cholesterol and non-esterified fatty acids levels were unchanged (Table 21).

[0258] Treatment with Compound #37 at 10 mg/kg treatment tended to decrease plasma triglycerides levels. Compound #37 decreased dose-dependently levels of non-esterified fatty acids and total cholesterol levels. Plasma insulin levels were unchanged with the treatment or tended to increase with treatment with Compound #37 at 20 mg/kg. See Table 21.

[0259] Treatment with 5 mg/kg of Compound #37 significantly decreased liver triglyceride and fatty acids levels, as shown in Table 22. This decrease was correlated with results obtained with Oil red O staining at the same dose; see Table 23.

[0260] The treatment was generally well tolerated over 8 weeks, with no significant differences in weight gain and food intake across all treatment groups (Compound #37P042). Compound #37 treatment resulted in a reduction in plasma triglyceride, as well as a statistically significant ($p < 0.05$) dose-dependent reduction in plasma free fatty acids and total cholesterol concentrations. These plasma lipid results are consistent with SCAP/SREBP pathway inhibition seen in tissue-specific SCAP knockout mice (Horton et al, 2002) and with inhibition of SREBP in vivo (Moon et al, 2012).

[0261] Lipid accumulation was reduced in the livers of Compound #37-treated ob/ob mice (Compound #37P042), as indicated by a reduction in triglycerides, fatty acids, total cholesterol, and Oil Red O staining of hepatic neutral lipids; however, these reductions were

variable (Compound #37P054, Table 2.6.2-2). Quantification of Oil Red O staining showed a decrease at the 5 mg/kg/day and 20 mg/kg/day doses; however, these decreases were not statistically significant. The 10 mg/kg/day dose resulted in no reduction in Oil Red O staining despite reducing plasma lipids. Compound #37 had no effect on hepatic cholesterol concentrations. The variability in these findings may be due to the severity of steatosis that develops in this model or the quantification methods used. Fasting blood glucose and insulin concentrations were highly variable across groups without significant changes from the vehicle control group.

[0262] Conclusion. Vehicle alone modified plasma triglycerides and insulin levels.

Treatment with Compound #37 decreased in a dose-dependent manner non-esterified fatty acid levels and total cholesterol and tended to decrease triglycerides. At 5 mg/kg, Compound #37 significantly decreased liver triglycerides and fatty acids, indicating that treatment with Compound #37 improves liver steatosis in ob/ob mice.

Table 21. Plasma triglycerides, non-esterified free fatty acids, total cholesterol, and insulin levels

Group	animal #	triglycerides (g/L)	non-esterified fatty acids (mM)	total cholesterol (g/L)	plasma insulin (μU/mL)
no treatment	15	0.777	1.33	1.954	499.9
	17	0.728	1.009	1.903	643.5
	23	0.663	1.131	1.891	866.9
	25	0.973	0.886	1.802	511.4
	30	1.348	0.494	1.752	905.3
	33	0.908	0.552	1.676	1019.5
	36	0.875	0.777	2.055	783.6
	39	2.147*	0.552*	1.133*	11.4*
	48	1.984	0.873	2.055	310.3
	mean	1.0	0.9	1.9	695.1
	sd	0.4	0.3	0.1	244.0
	sem	0.2	0.1	0.0	86.3
	n	8	8	8	8
vehicle	1	1.576	1.562	2.232	16.5*
	3	1.625	1.157	2.118	202.0
	12	2.115	1.221	1.827	121.3
	13	1.886	0.893	1.966	65.4
	22	1.152	0.803	1.764	496.8
	26	1.935	0.751	1.651	504.0
	28	1.674	0.88	1.663	464.6
	43	1.544	0.835	2.087	394.6
	44	1.788	0.848	2.029	170.9

	mean	1.7	1.0	1.9	302.4
	sd	0.3	0.3	0.2	181.1
	sem	0.1	0.1	0.1	64.0
	n	9	9	9	9
5 mg/kg	4	1.283	1.028	1.587	198.7
	8	1.152	0.77	1.903	262.7
	10	1.038	0.616	1.916	181.1
	18	1.397	0.552	1.853	250.5
	19	1.593	0.68	2.017	118.7
	20	1.201	1.092	1.537	394.6
	40	1.397	0.783	2.08	24.6*
	41	1.609	0.655	1.625	374.6
	47	2.408	0.539	1.347	512.6
	50	2.504	0.68	1.638	173.1
	mean	1.6	0.7	1.8	274.1
	sd	0.5	0.2	0.2	127.9
	sem	0.2	0.1	0.1	42.6
	n	10	10	10	10

Table 21, cont.

Group	animal #	triglycerides (g/L)	non-esterified fatty acids (mM)	total cholesterol (g/L)	plasma insulin (μU/mL)
10 mg/kg	2	0.94	1.009	1.587	123.8
	6	1.12	0.474	1.865	457.7
	11	0.875	0.828	1.865	81.9
	14	1.218	0.7	1.891	949.0
	21	1.528	0.564	1.827	153.3
	29	1.299	0.951	1.827	62.6
	31	1.968	0.738	1.234	508.2
	42	1.381	0.661	1.891	904.4
	45	1.593	0.809	1.651	194.4
	46	0.777	0.307	1.183	137.5
	mean	1.3	0.7	1.7	357.3
	sd	0.4	0.2	0.3	336.0
	sem	0.1	0.1	0.1	106.2
	n	10	10	10	10
20 mg/kg	5	0.875	0.429	1.234	447.3
	9	1.886	0.642	0.893	10.5
	16	1.511	0.494	1.499	730.1
	24	1.642	0.481	1.714	505.0
	27	1.854	0.423	1.663	254.3
	34	1.283	0.513	1.625	881.0
	35	1.308	0.423	1.587	810.7
	37	1.381	0.397	1.36	483.7
	38	1.511	0.687	1.272	62.6
	49	1.968	0.597	1.663	256.2
	mean	1.5	0.5	1.5	444.1
	sd	0.4	0.1	0.3	301.3
	sem	0.1	0.0	0.1	95.3
	n	10	10	10	10

Table 22. Liver triglycerides, fatty acids, and total cholesterol levels

Group	animal #	triglycerides ($\mu\text{g}/\text{mg}$ liver)	fatty acids (nmol/mg liver)	total cholesterol ($\mu\text{g}/\text{mg}$ liver)
no treatment	15	106.20	45.19	5.66
	17	124.97	45.88	14.51
	23	94.27	35.16	11.82
	25	116.95	42.26	13.05
	30	137.18	45.36	14.25
	33	128.14	51.02	14.52
	36	115.83	41.64	13.72
	39	11.203*	12.58*	9.83*
	48	98.37	43.67	13.79
	mean	115.2	43.8	12.7
	sd	14.9	4.5	3.0
	sem	5.3	1.6	1.0
	n	8	8	8
vehicle	1	155.04	51.45	14.77
	3	132.12	53.84	13.67
	12	100.72	36.40	10.92
	13	126.81	47.45	17.15
	22	172.66	45.61	15.29
	26	119.53	41.60	12.06
	28	110.38	40.42	12.48
	43	102.33	53.25	13.47
	44	212.91	56.63	13.92
	mean	136.9	47.4	13.7
	sd	37.1	6.9	1.9
	sem	12.4	2.3	0.6
	n	9	9	9
5 mg/kg	4	32.54	21.39	9.57
	8	89.34	38.65	13.21
	10	118.92	43.56	16.08
	18	123.01	43.68	15.08
	19	111.66	42.30	14.41
	20	54.15	26.81	9.18
	40	66.99	31.47	10.40
	41	69.20	34.22	12.19
	47	107.70	40.04	13.20
	50	29.81	36.50	13.39
	mean	80.3	35.9	12.5
	sd	34.9	7.5	2.3
	sem	11.0	2.4	0.7
	n	10	10	10

Table 22, cont.

Group	animal #	triglycerides ($\mu\text{g}/\text{mg}$ liver)	fatty acids (nmol/mg liver)	total cholesterol ($\mu\text{g}/\text{mg}$ liver)
10 mg/kg	2	71.81	29.78	11.02
	6	110.46	49.10	14.95
	11	96.59	42.91	15.25
	14	67.76	39.50	11.27
	21	106.16	43.38	14.07
	29	153.12	48.06	16.04
	31	128.22	58.06	17.20
	42	157.22	46.42	13.65
	45	124.56	53.47	14.90
	46	138.07	59.33	17.30
	mean	115.44	47.00	14.47
	sd	30.9	8.8	2.2
	sem	9.8	2.8	0.7
	n	10	10	10
20 mg/kg	5	115.27	46.82	16.75
	9	10.45*	11.67*	7.14*
	16	99.74	43.19	13.56
	24	160.82	56.93	17.52
	27	71.59	36.64	11.98
	34	95.60	43.21	14.67
	35	114.62	40.58	14.39
	37	92.80	33.97	13.53
	38	91.36	38.27	12.83
	49	115.09	41.87	9.07
	mean	106.3	42.4	13.8
	sd	24.9	6.7	2.5
	sem	8.3	2.2	0.8
	n	9	9	9

*excluded from statistical analysis

Table 23. Liver Oil Red O

Group	animal #	oil-red-O quantification (%)
no treatment	15	9.01
	17	14.17
	23	10.38
	25	21.79
	30	16.52
	33	17.11
	36	5.43
	39	0.19*
	48	4.74
	mean	12.4
	sd	6.0
	sem	2.1
	n	8
vehicle	1	5.01
	3	10.20
	12	14.84
	13	5.99
	22	3.94
	26	5.55
	28	22.20
	43	19.93
	44	13.80
	mean	11.3
	sd	6.8
	sem	2.3
	n	9
5 mg/kg	4	0.67
	8	2.91
	10	8.82
	18	9.22
	19	4.41
	20	6.15
	40	8.06
	41	8.93
	47	8.85
	50	9.33
	mean	6.7
	sd	3.1
	sem	1.0
	n	10

Table 23, cont.

Group	animal #	oil-red-O quantification (%)
10 mg/kg	2	19.18
	6	18.46
	11	13.25
	14	3.65
	21	8.46
	29	8.67
	31	16.07
	42	17.12
	45	16.00
	46	11.43
	mean	13.23
	sd	5.1
	sem	1.6
	n	10
20 mg/kg	5	13.45
	9	0.42
	16	15.53
	24	9.89
	27	4.95
	34	8.17
	35	4.74
	37	7.06
	38	15.71
	49	5.38
	mean	8.5
	sd	5.1
	sem	1.6
	n	10

Example B6. Effect of Compound #37 in a diet-induced chronic steatosis/NASH model

[0263] To investigate whether Compound #37 improves pre-existing steatosis / NASH pathology, a study was conducted using a 16-week diet-induced NASH mouse model. In this model, mice develop steatosis that progresses with inflammation and fibrosis that mimic many of the observed pathologies in human nonalcoholic fatty liver disease (NAFLD) and NASH (Hebbard & George, 2010). For 6 weeks, mice were fed a high-fat, high-cholesterol diet and provided drinking water containing fructose to induce liver pathology (Charlton et al, 2011). After 6 weeks, the mice were divided into 2 groups with similar mean aspartate

aminotransferase (AST) and alanine aminotransferase (ALT) values (n = 12 mice), although it should be noted that AST and ALT concentrations within both groups were higher and with greater variability than anticipated (*e.g.*, mean ALT 677 U/L [SD, 401 U/L] in the vehicle control group and 693 U/L [SD, 365 U/L] in the Compound #37 group). After the animals were divided into 2 groups, the diet was continued for 10 additional weeks during which time 1 group received vehicle and the other was treated with 20 mg/kg/day Compound #37.

[0264] Compound #37 was generally well tolerated in this model with no important differences in weight gain between treatment groups after the first week of treatment. One animal in the Compound #37 treatment group died after 48 days of treatment with no obvious cause of death; gavage error in dosing could not be ruled out. This death rate is within historical norms for long-term diet-induced NASH studies at this vendor.

[0265] Overall, no consistent findings were observed in plasma or hepatic lipid concentrations, degree of steatosis, or SREBP-related target gene expression levels between treatment groups, although the degree of variability of liver injury in the animals at baseline makes the results difficult to interpret. No evidence of hepatotoxicity with Compound #37 was observed in this study; transaminase concentrations were similar between treatment groups throughout the study.

[0266] Notably, while Compound #37 did not cause an overt reduction in liver lipid content, a significant reduction in the formation of collagen fiber formation was demonstrated by decreased Sirius Red staining (**FIG. 4**). Furthermore, mean liver collagen $\alpha 1(I)$ mRNA was also significantly down-regulated by Compound #37 treatment (1.45% vs 0.49%; $p < 0.05$), suggesting a potential effect on liver fibrosis.

[0267] Compound #37 treatment also resulted in a trend toward lower homeostasis model assessment-estimated insulin resistance (HOMA-IR) scores due to reduced plasma insulin. Glucose concentrations were in the normal range and were largely unchanged for the Compound #37-treated mice, indicating an improvement in insulin sensitivity without concurrent hypoglycemia (**FIG. 5A-C**). Compound #37-treated mice also had a 38% reduction in plasma leptin concentrations, a hormone associated with adiposity, but these findings were not statistically significant.

Example B7. Pharmacology Data From 28-Day Repeat-Dose Toxicity Studies in Healthy Rats and Dogs

[0268] In addition to standard safety endpoints, pharmacology endpoints were assessed as part of a 28-day repeat-dose toxicity studies in healthy rats and dogs.

[0269] In the repeat-dose toxicity study in rats (Compound #37P018), Compound #37 was given at 0 (vehicle control), 50, 100/75, and 200/150 mg/kg/day for 28 days; some animals from each dose group continued into a 28-day recovery period. After 28 days of treatment, liver neutral lipids from treated and control animals were analyzed with Oil Red O staining. This analysis demonstrated a trend towards decreased concentrations of neutral lipids in the liver in an Compound #37 dose-dependent manner (summarized in Table B7; representative micrographs are presented in **FIG. 6**) without effects on liver glycogen.

Table B7.

	ALT (U/L)		AST (U/L)	
	Mean	SD	Mean	SD
Vehicle	576.30	482.79	632.40	389.57
Compound #37, 5 mg/kg	419.30	181.14	449.44	121.87
Compound #37, 20 mg/kg	403.50	107.81	431.17	100.66

[0270] The more pronounced effects in female rats compared with male rats is consistent with the observed higher plasma exposure (> 4-fold higher area under the curve over 24 hours [AUC_{24h}]) at day 28 in females compared with males. Evidence of an effect of Compound #37 on leptin concentrations was also observed in female rats in a dose-dependent manner. As animals gain weight, leptin concentrations naturally increase due to its origin from adipose tissue. Female rats treated with Compound #37 had lower concentrations of leptin compared with the vehicle control group during the treatment period (day 4 and day 28), which was not observed after treatment termination and recovery (day 56) (**FIG. 7**). In male rats, decreases in leptin concentrations were only observed at the highest dose group, likely due to lower systemic exposures of Compound #37 as noted above..

[0271] In the repeat-dose toxicity study in dogs, Compound #37 was given at 0 (vehicle control), 0.5, 2, 5, and 10/7.5 mg/kg/day for 28 days; some animals from each dose group continued into a 28-day recovery period (vehicle, 5, and 10/7.5 mg/kg/day groups only). Observations included trends of mild to moderate decreases in serum triglyceride (**FIGS. 8A-B**) and cholesterol concentrations (**FIGS. 9A-B**) at Compound #37 doses $\geq$ 5 mg/kg/day.

These Compound #37-related changes were reversible at the end of the 28-day recovery period. Findings were similar between male and female dogs, and consistent with the lack of sex differences in plasma exposure.

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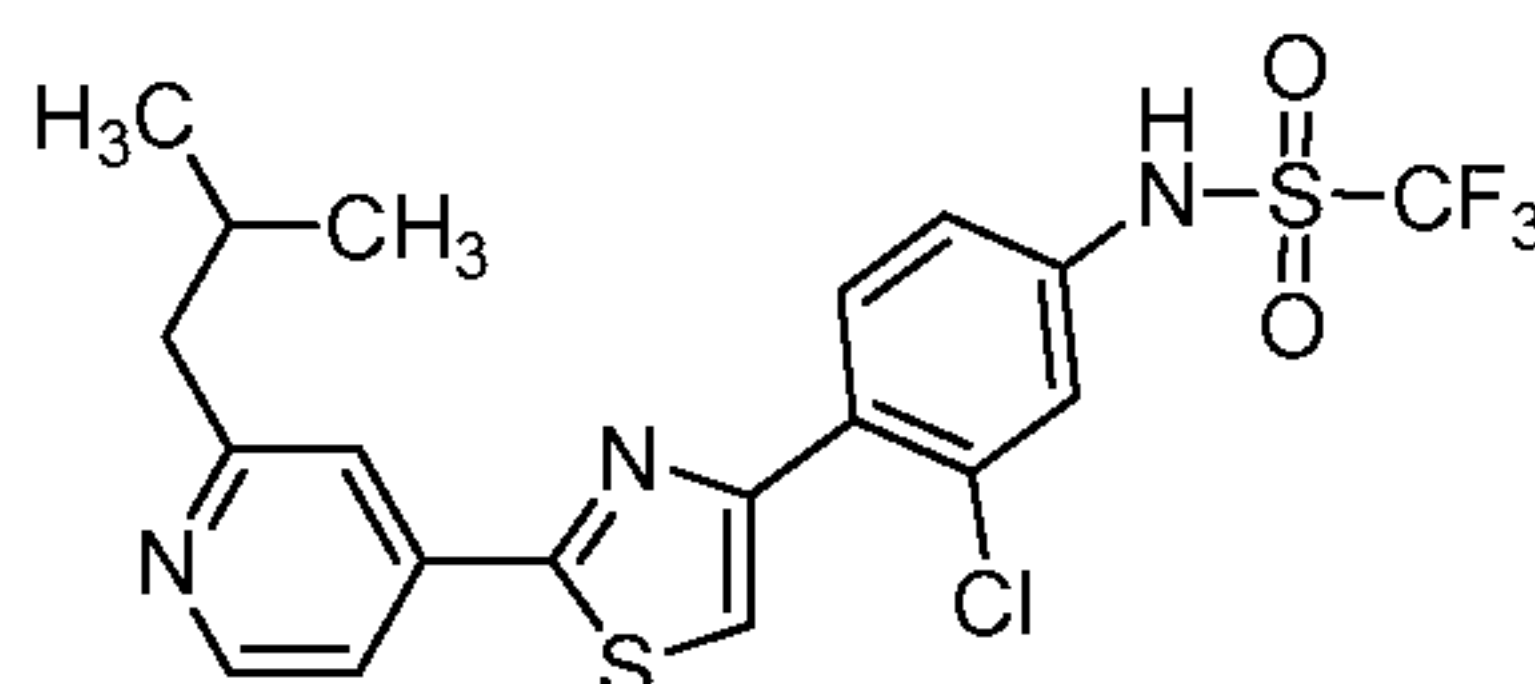
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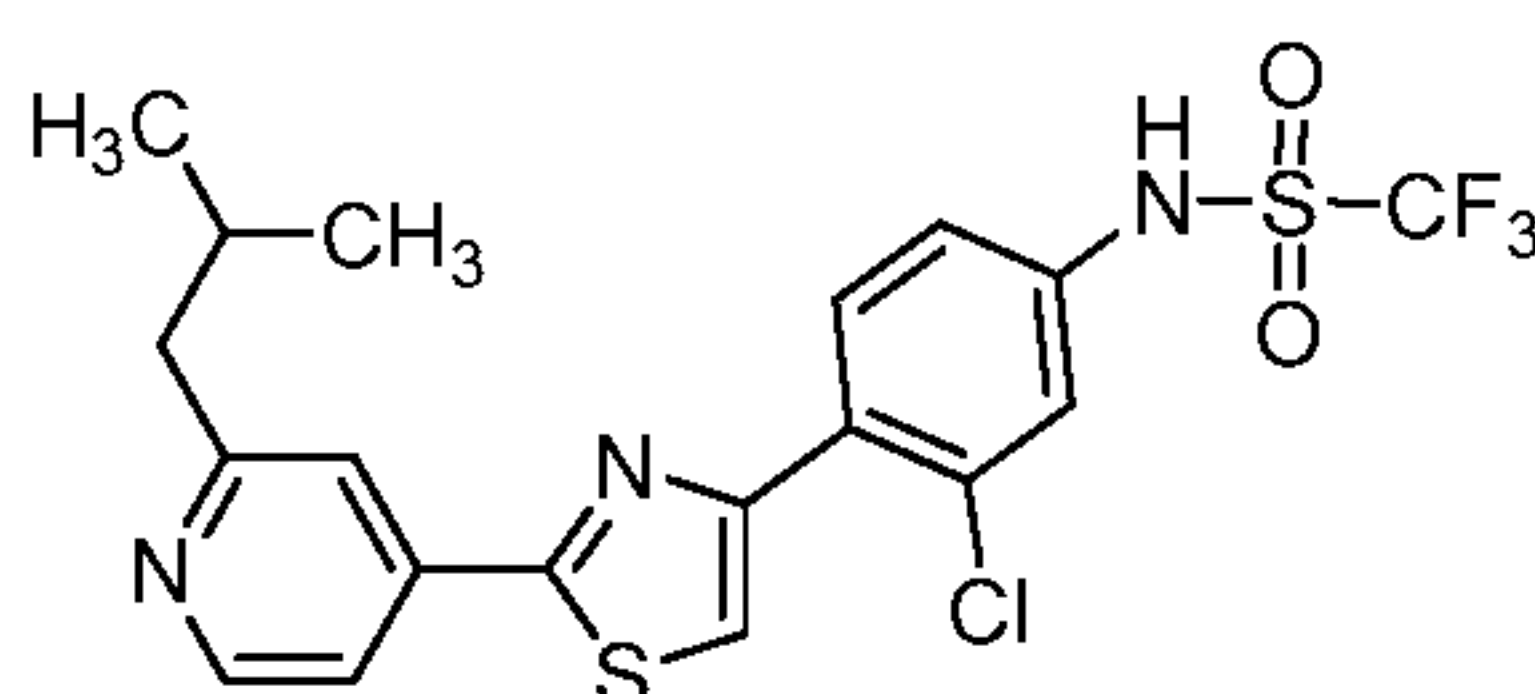
CLAIMS

1. A compound for treating a disorder selected from the group consisting of liver fibrosis, elevated cholesterol levels, and insulin resistance, wherein the compound is N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide:

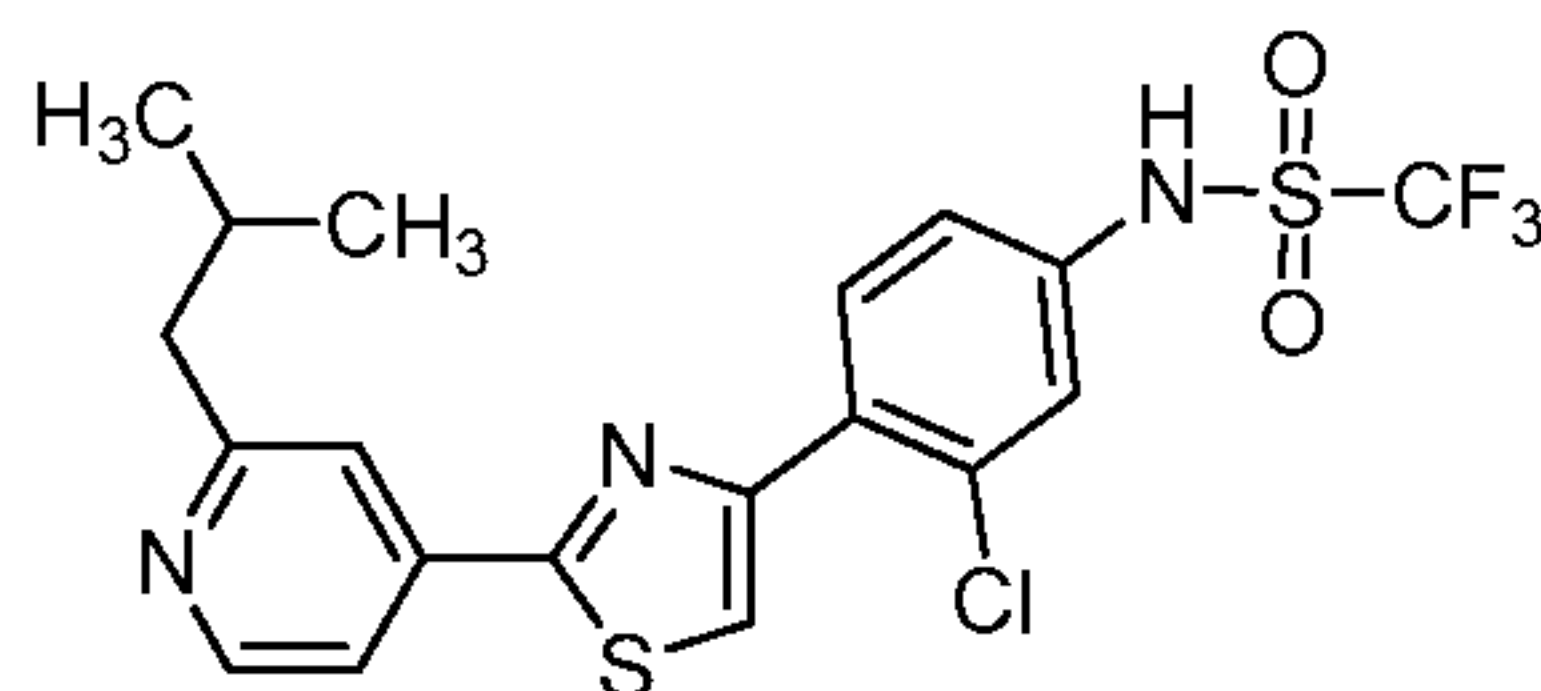


or a pharmaceutically acceptable salt thereof.

2. The compound for use according to claim 7, wherein the disorder is selected from the group consisting of liver fibrosis, elevated cholesterol levels, and insulin resistance in a patient who has non-alcoholic steatohepatitis (NASH).
3. Use of a compound or a pharmaceutically acceptable salt of the compound in the manufacture of a medicament for treating a disorder selected from the group consisting of liver fibrosis, elevated cholesterol levels, and insulin resistance, wherein the compound is N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide:

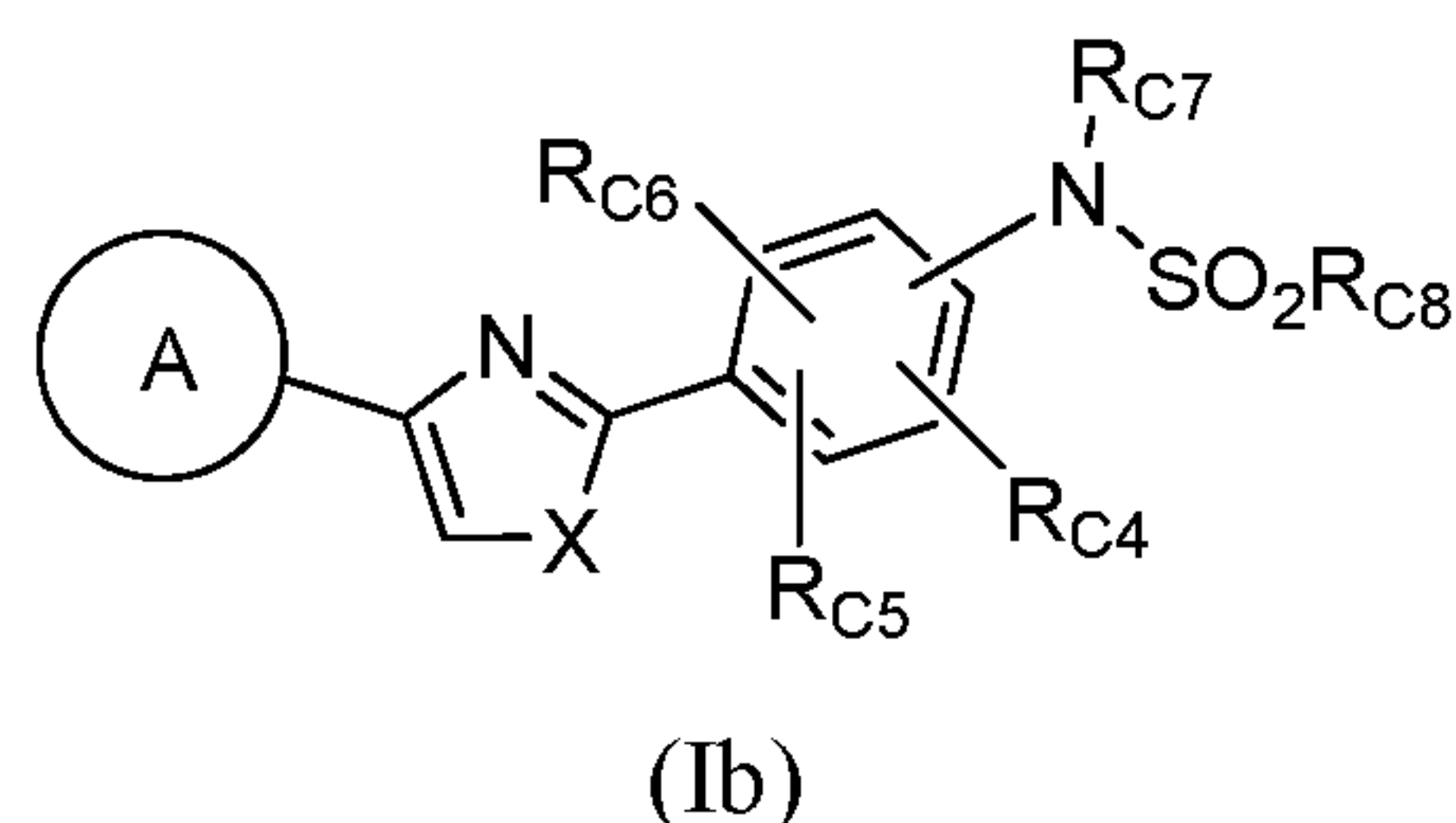
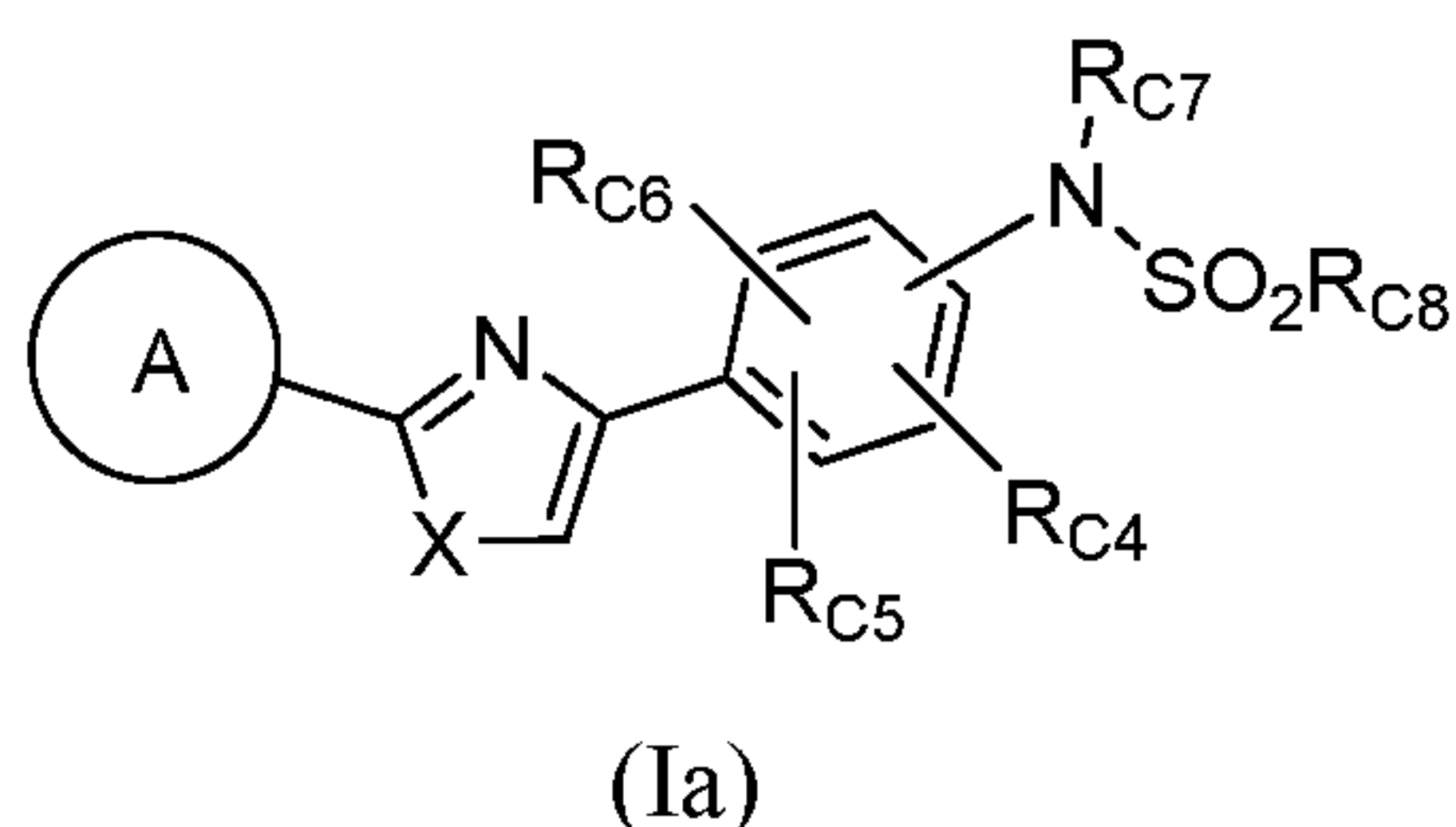


4. The use of claim 3, wherein the disorder is selected from the group consisting of liver fibrosis, elevated cholesterol levels, and insulin resistance in a patient who has non-alcoholic steatohepatitis (NASH).
5. A method of treating a disorder selected from the group consisting of liver fibrosis, elevated cholesterol levels, and insulin resistance, comprising administering to a patient in need thereof an effective amount of the compound N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide:



or a pharmaceutically acceptable salt thereof

6. The method of claim 5, wherein the patient has non-alcoholic steatohepatitis (NASH).
7. The method of claim 5, wherein administration of the compound or the pharmaceutically acceptable salt of the compound reduces the risk of NASH in the patient.
8. A method of treating a disorder selected from the group consisting of liver fibrosis, elevated cholesterol levels, and insulin resistance, comprising administering to a patient in need thereof an effective amount of a compound of Formulae (Ia) or (Ib):



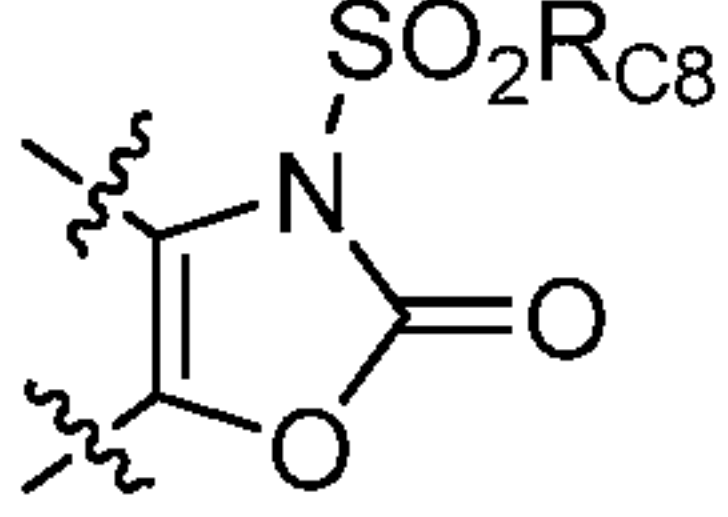
or a pharmaceutically acceptable salt thereof, wherein:

A is either:

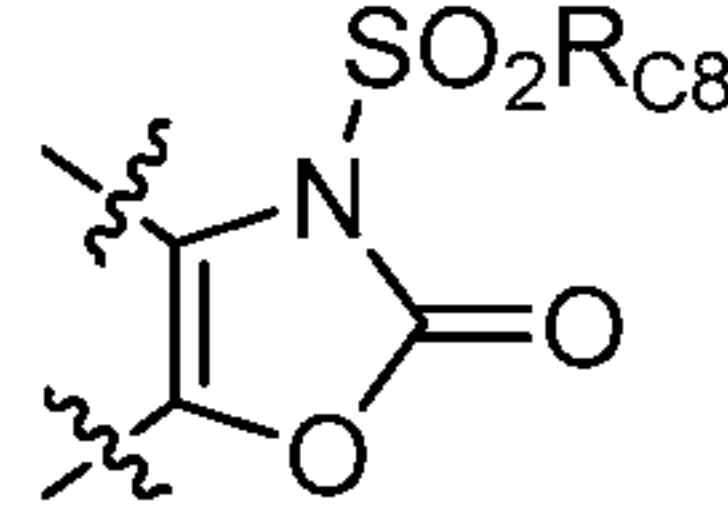
- i. an aryl or heteroaryl, each having only one ring, substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF₃, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -(CH₂)_mCF₃, =O, -CH₂OCH₃, -OBn, -CO₂H, -CO₂-Alkyl, -NR₁₀R₁₁, and -CONR₁₀R₁₁; or
- ii. an aryl or heteroaryl, each having more than one ring, optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF₃, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -(CH₂)_mCF₃,

=O, -CH₂OCH₃, -CH₂OH, -OBn, -CO₂H, -CO₂-Alkyl, -NR₁₀R₁₁, and -CONR₁₀R₁₁;

each **R_{C4}**, **R_{C5}**, and **R_{C6}**, is independently hydrogen, halogen, CN, CF₃, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, -CO₂H, -CONR₁₀R₁₁,

or -NHCONH₂; or is taken with **R_{C7}** to form the moiety  ;

R_{C7} is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -(CR_{9a}R_{9b})_mNR₁₀R₁₁, -CO₂-Alkyl, -(CR_{9a}R_{9b})_mO-Alkyl, -(CR_{9a}R_{9b})_mOPO₃Na₂, -(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO-Alkyl, -(CR_{9a}R_{9b})_mO(C=O)-Alkyl, -(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)-Alkyl, -(C=O)CH=CH₂, -SO₂R_{C8'};

or is taken with one of **R_{C4}**, **R_{C5}** or **R_{C6}** to form the moiety  ;

R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

R_{C8'} is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

each **R_{9a}** and **R_{9b}**, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

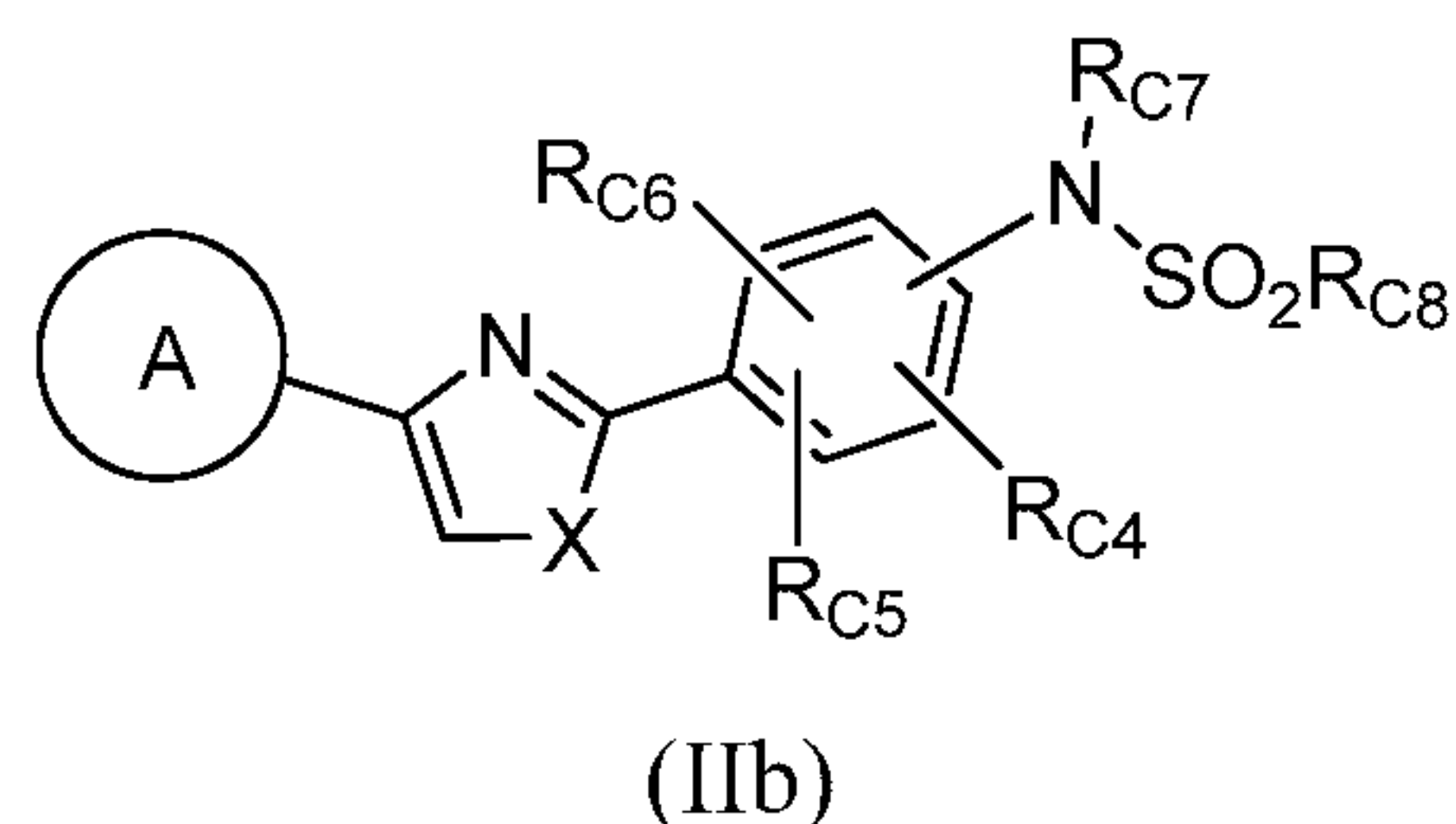
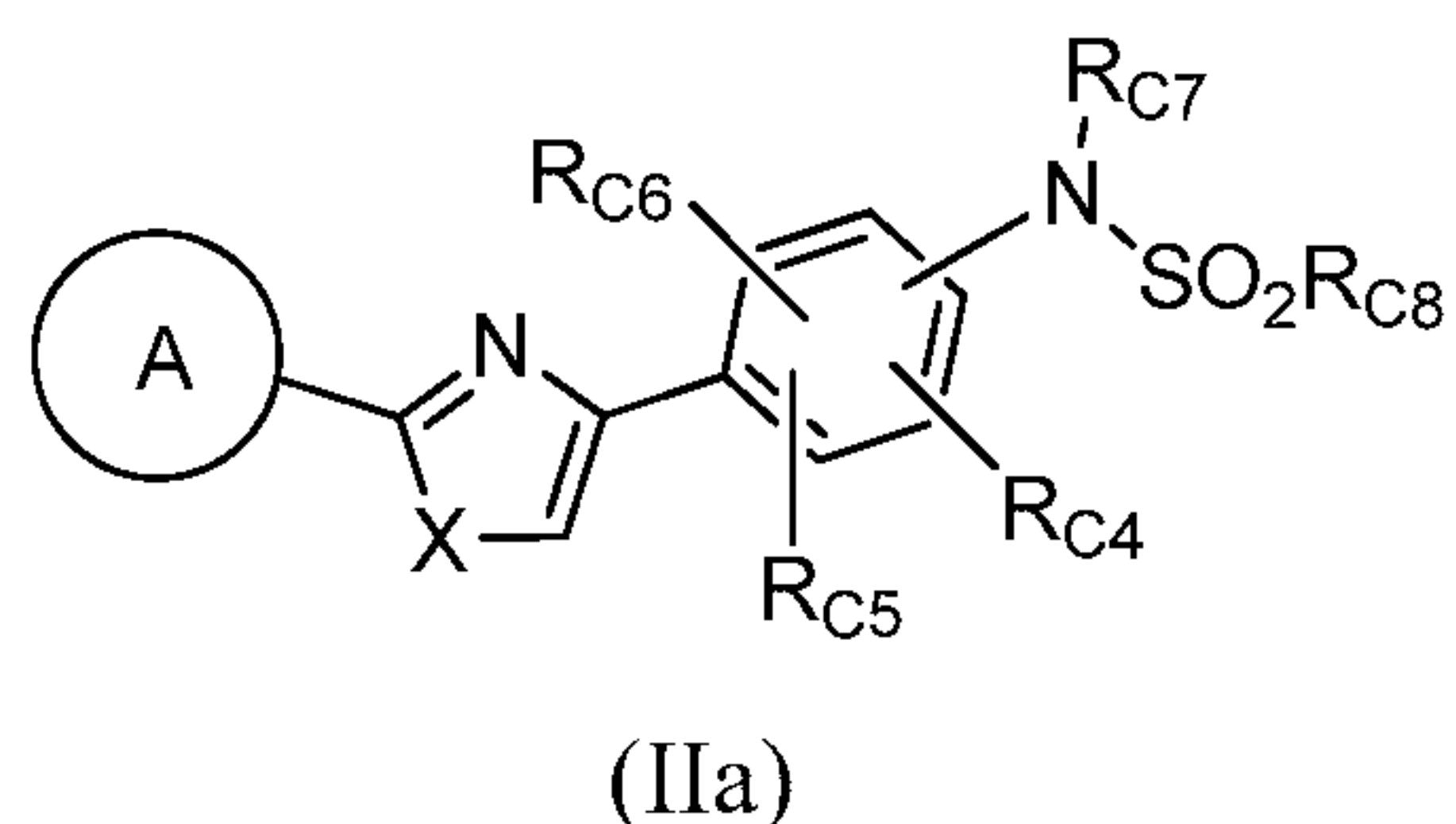
R₁₀ and **R₁₁** are independently hydrogen, -SO₂R_{C8'}, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone,

imidazolidinone, tetrahydropyrimidin-2(1H)-one, a
 $1\lambda^6,2$ -thiazolidine-1,1-dione, a $1,2\lambda^6,3$ -oxathiazolidine-2,2-dione, or a
 $1\lambda^6,2,5$ -thiadiazolidine-1,1-dione;

X is a heteroatom selected from S, O; or NR_B wherein R_B is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

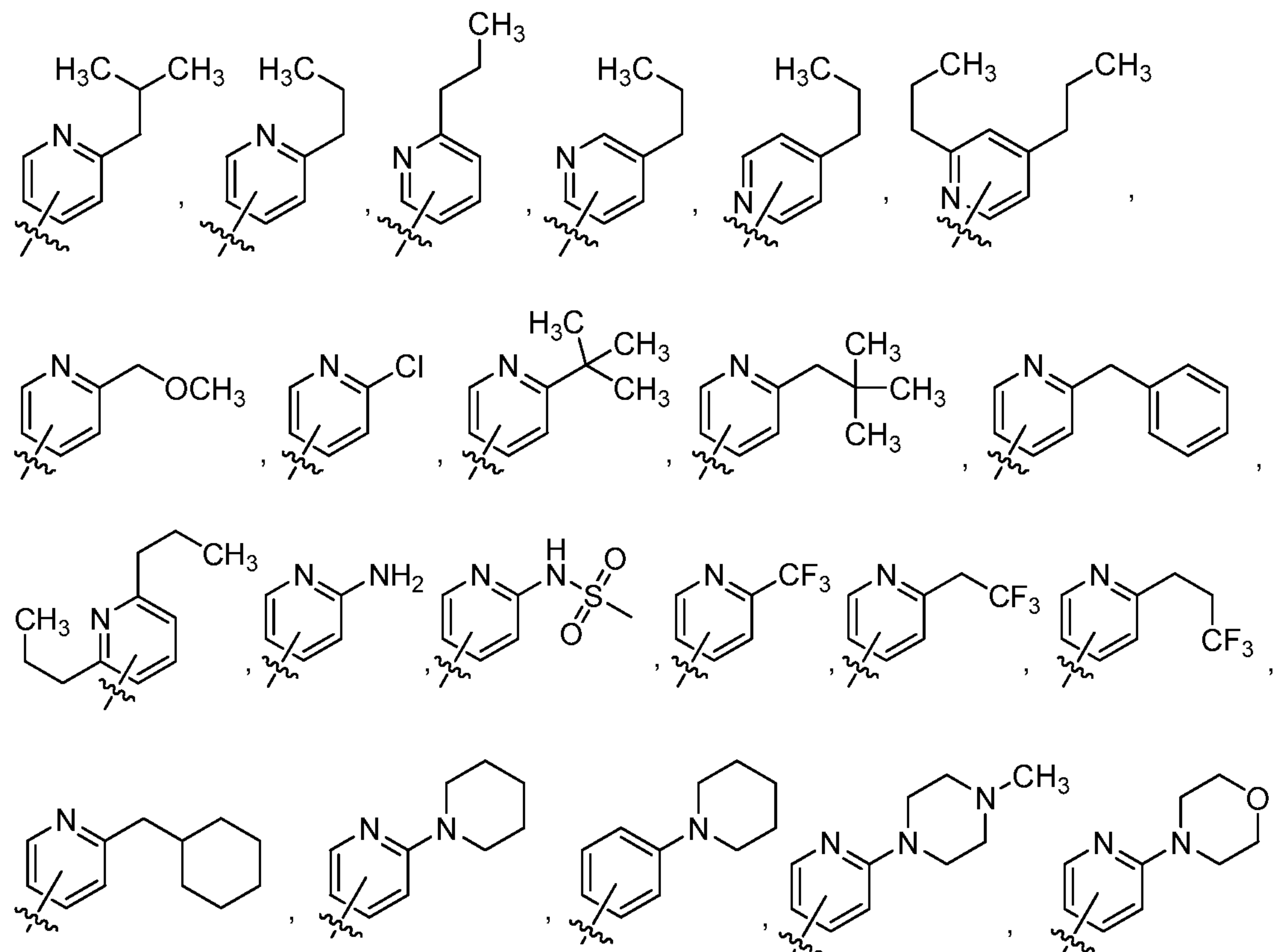
each *m* and *n* is 1, 2 or 3.

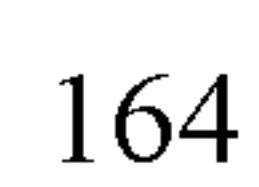
9. The method of claim 8, wherein compound is of formulae (IIa) or (IIb):



or a pharmaceutically acceptable salt thereof, wherein:

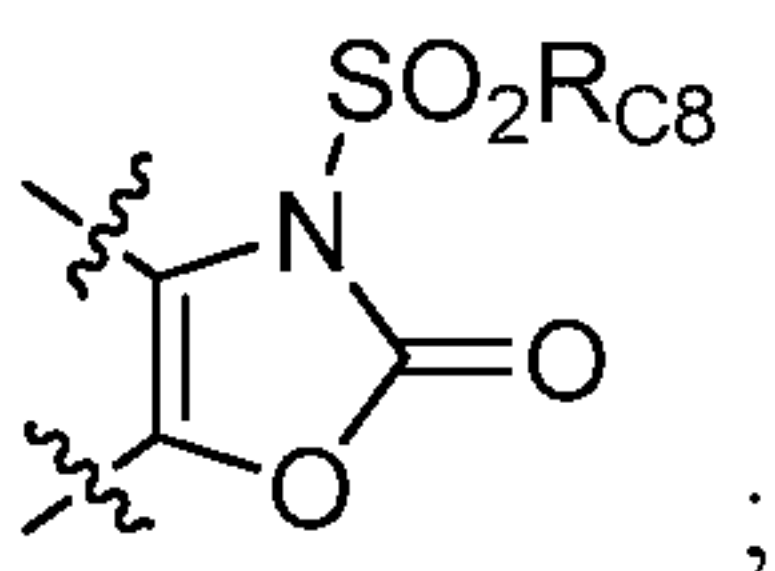
A is a moiety selected from the group consisting of:



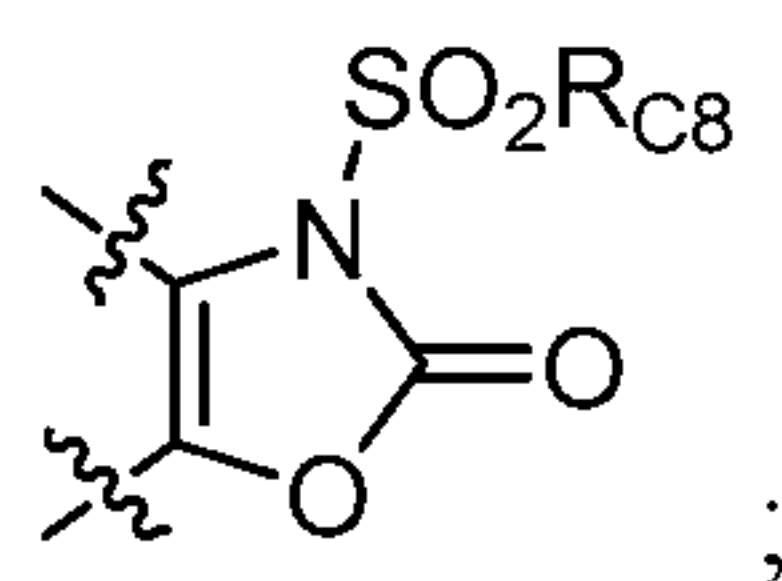


wherein the ring containing X is linked to ring A at any available position on ring A;

Each **R_{C4}**, **R_{C5}**, and **R_{C6}**, is independently hydrogen, halogen, CN, CF₃, OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, -CO₂H, -CONR¹⁰R¹¹,

or -NHCONH₂; or is taken with **R_{C7}** to form the moiety  ;

R_{C7} is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, -(CR_{9a}R_{9b})_mNR¹⁰R¹¹, -CO₂-Alkyl, -(CR_{9a}R_{9b})_mO-Alkyl, -(CR_{9a}R_{9b})_mOPO₃Na₂, -(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO-Alkyl, -(CR_{9a}R_{9b})_mO(C=O)-Alkyl, -(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)-Alkyl, -(C=O)CH=CH₂, -SO₂R_{C8};

or is taken with one of **R_{C4}**, **R_{C5}** or **R_{C6}** to form the moiety  ;

R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

R_{C8}' is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

Each **R_{9a}** and **R_{9b}**, where present, is independently hydrogen or C1-C6 linear or branched alkyl;

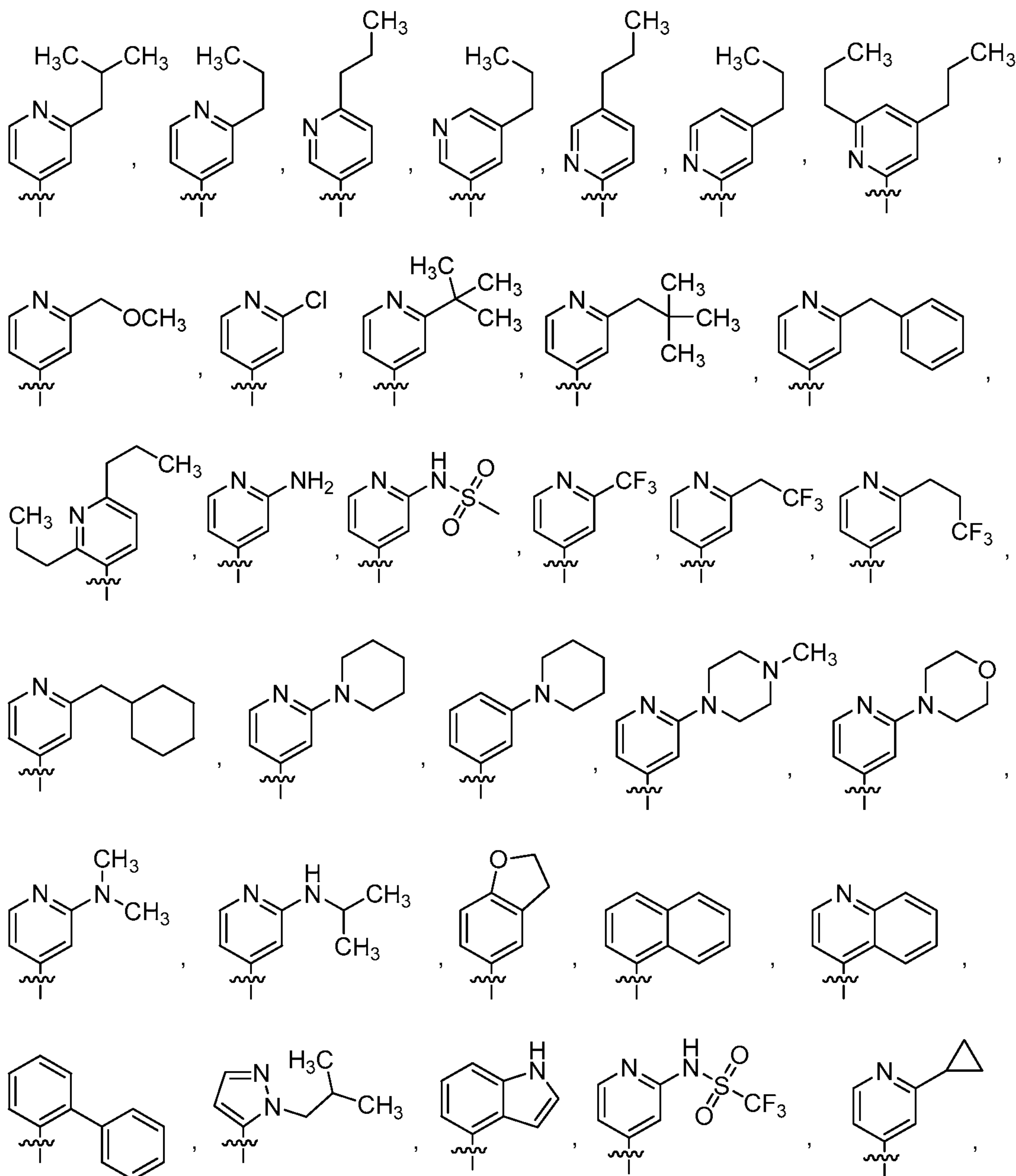
R¹⁰ and **R¹¹** are independently hydrogen, -SO₂R_{C8}', C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a

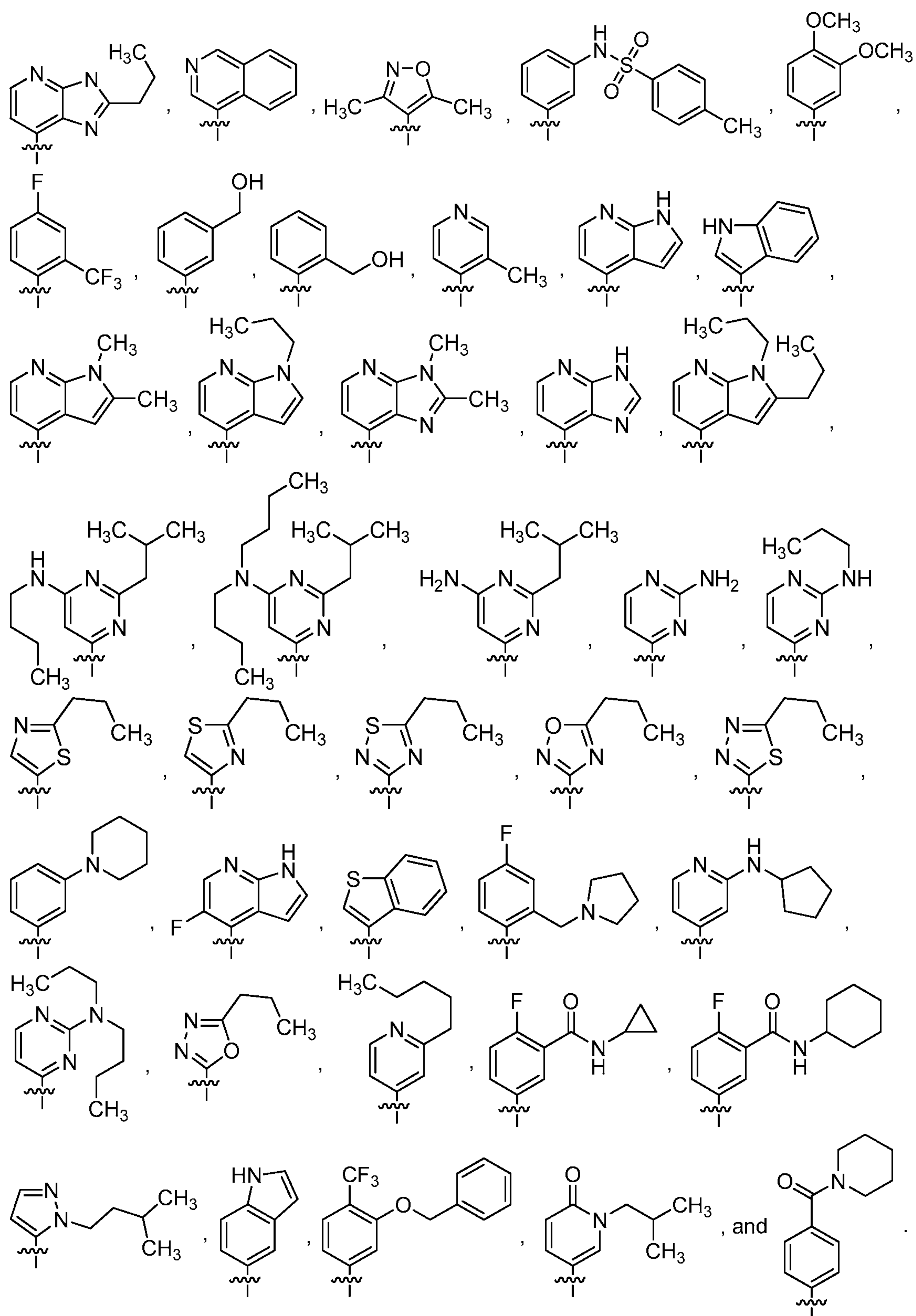
1 λ^6 ,2-thiazolidine-1,1-dione, a 1,2 λ^6 ,3-oxathiazolidine-2,2-dione, or a 1 λ^6 ,2,5-thiadiazolidine-1,1-dione;

X is a heteroatom selected from S, O; or NR_B wherein **R_B** is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

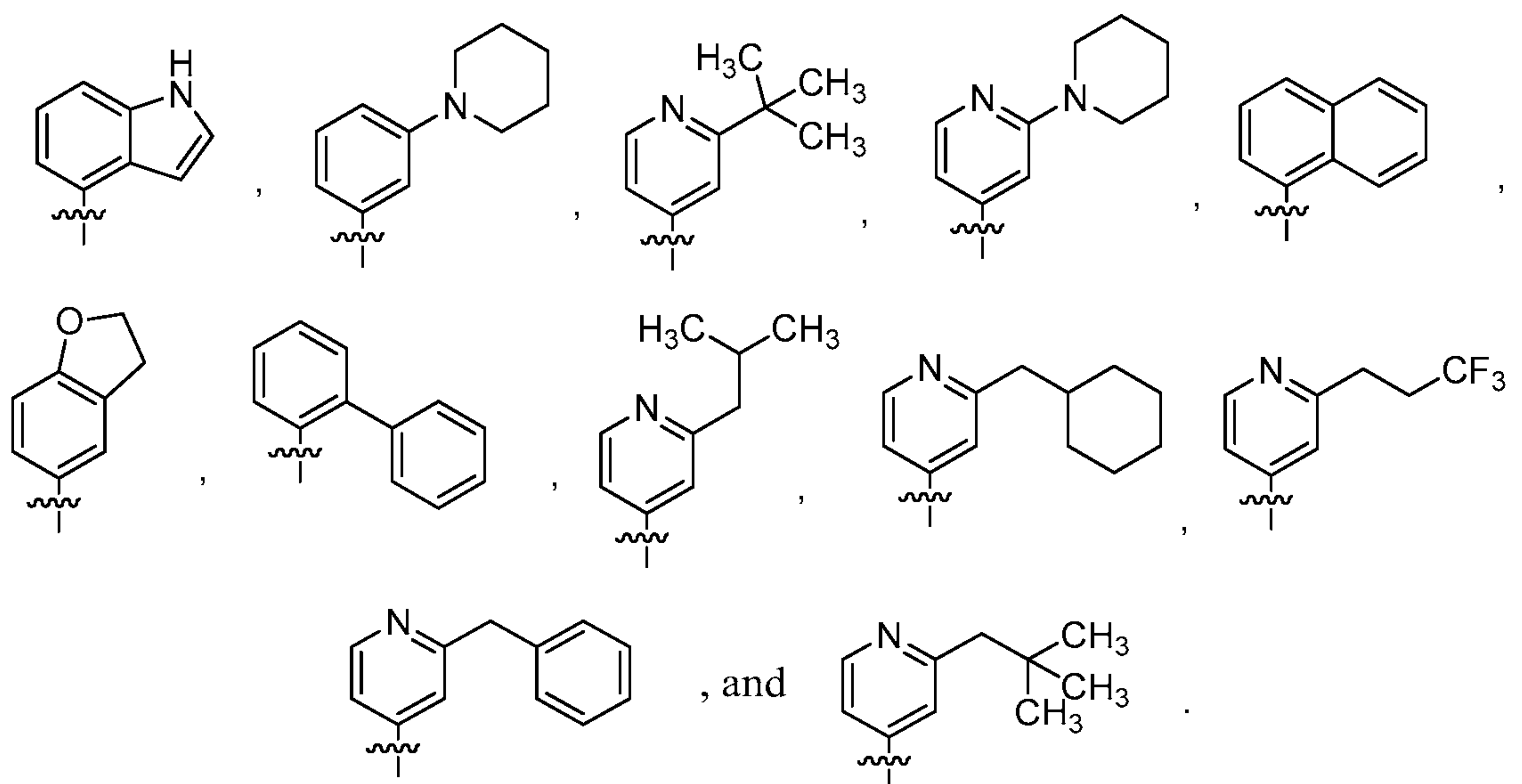
Each *m* and *n* is 1, 2 or 3.

10. The method of claim 9, wherein A is a moiety selected from the group consisting of:

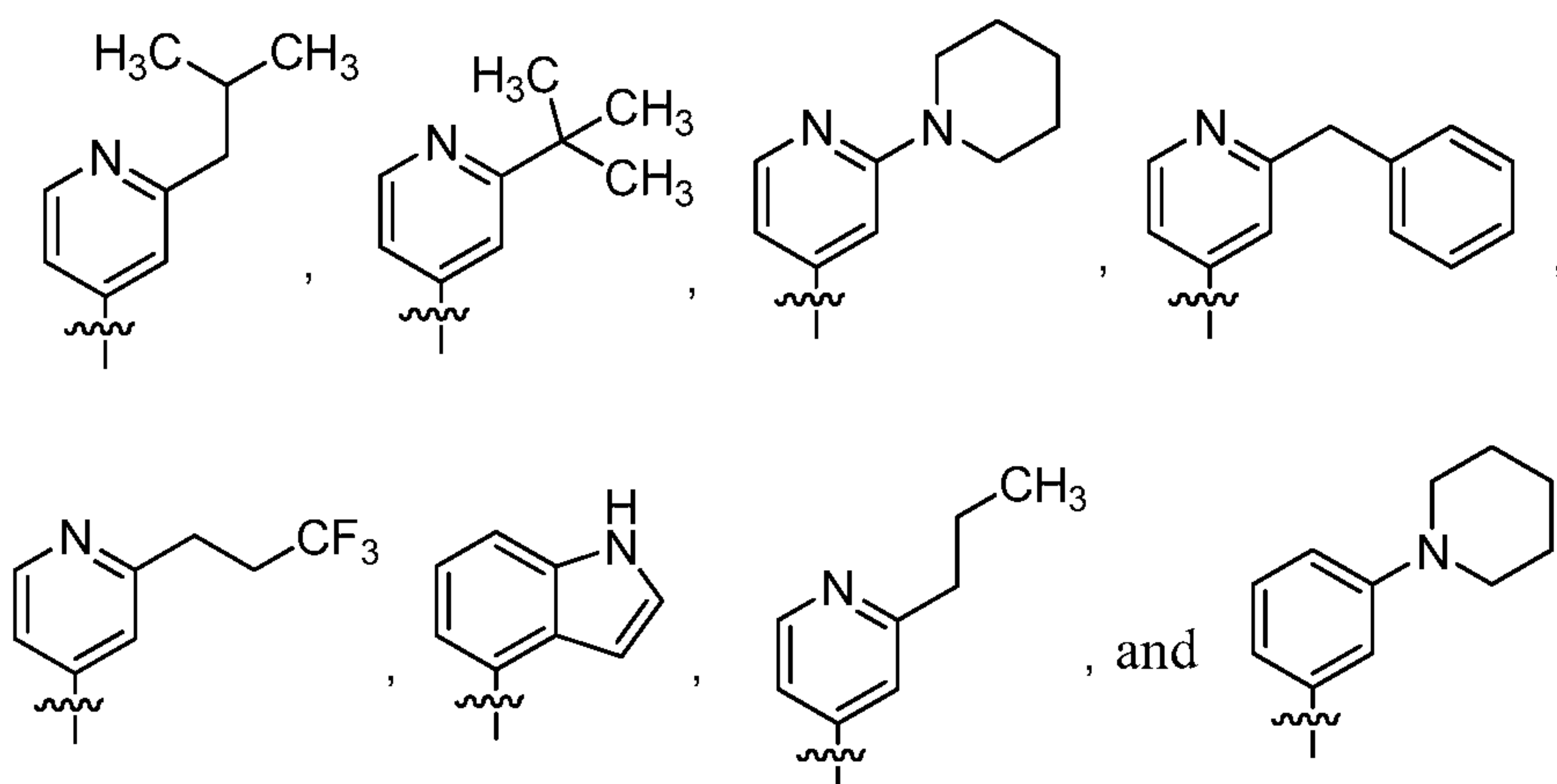




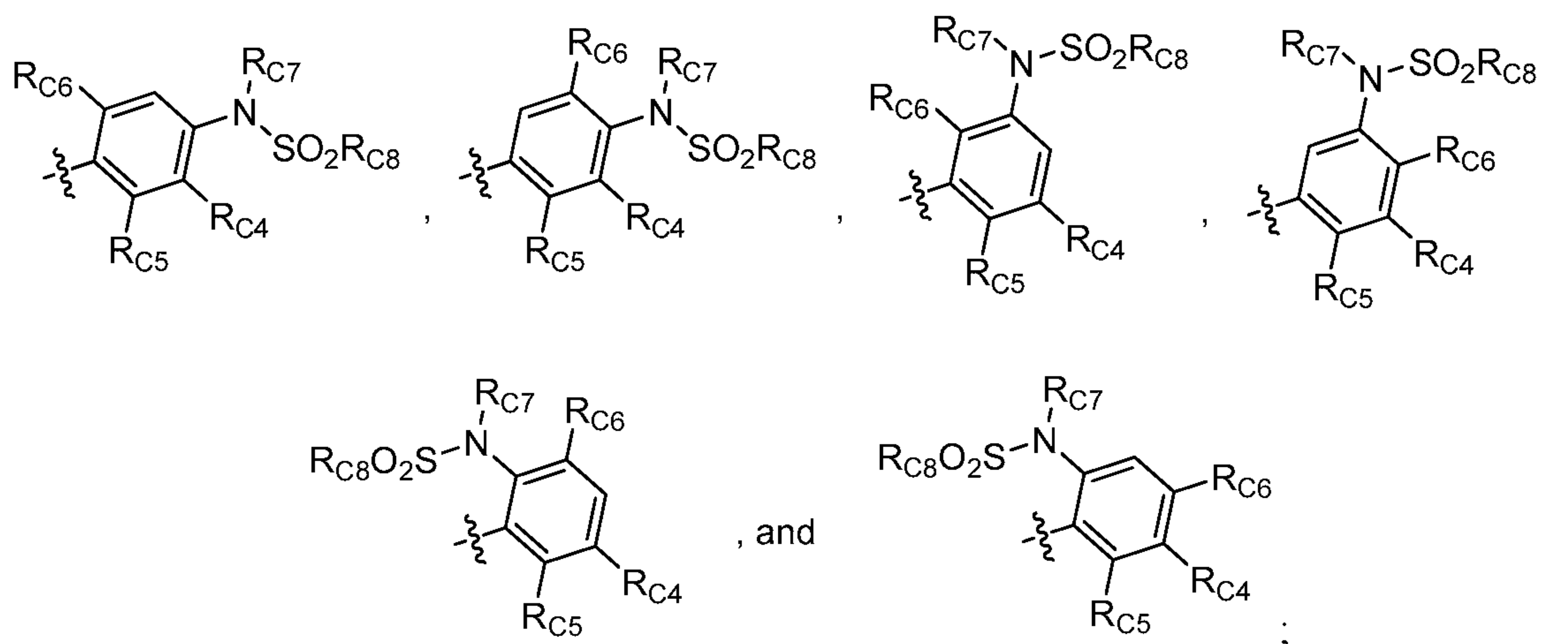
11. The method of claim 10, wherein A is a moiety selected from the group consisting of:



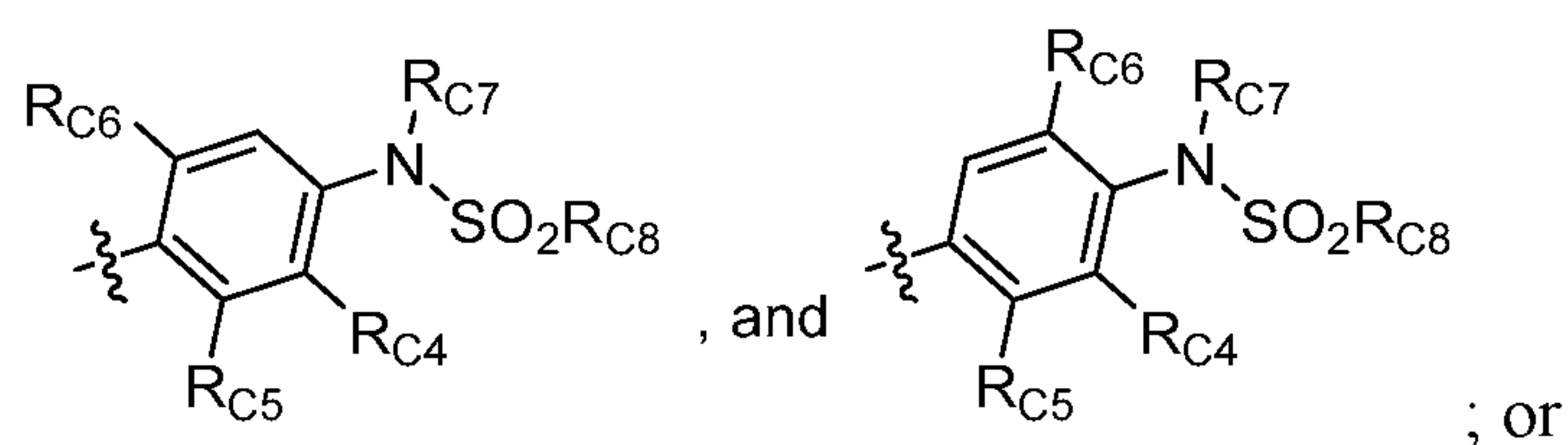
12. The method of claim 10, wherein A is a moiety selected from the group consisting of:



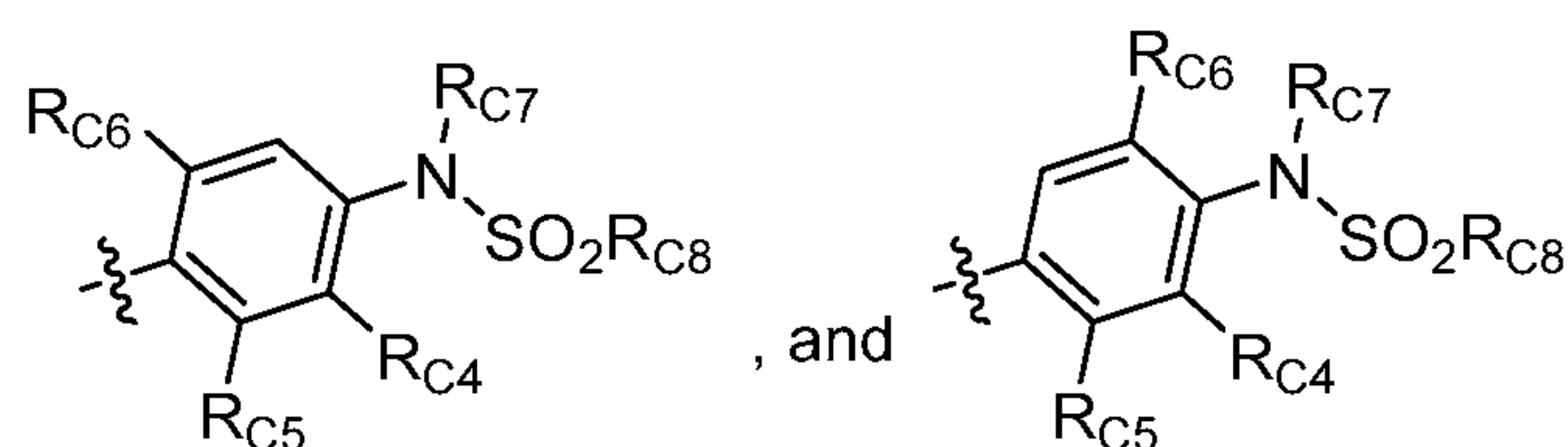
13. The method of any of claims 8-11, wherein X is S.
14. The method of any of claims 8-114, wherein:
- (a) X is NR_B , wherein R_B is a linear or branched C1-C6 alkyl;
 - (b) X is NR_B , wherein R_B is a linear C1-C6 alkyl selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl and n-hexyl;
 - (c) X is NR_B , wherein R_B is a branched C1-C6 alkyl selected from iso-propyl, iso-pentyl, and tert-butyl.
15. The method of any of claims 8-14, wherein:
- (a) the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-\text{NR}_{C7}\text{SO}_2R_{C8}$, is a moiety selected from:



(b) the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is a moiety selected from:

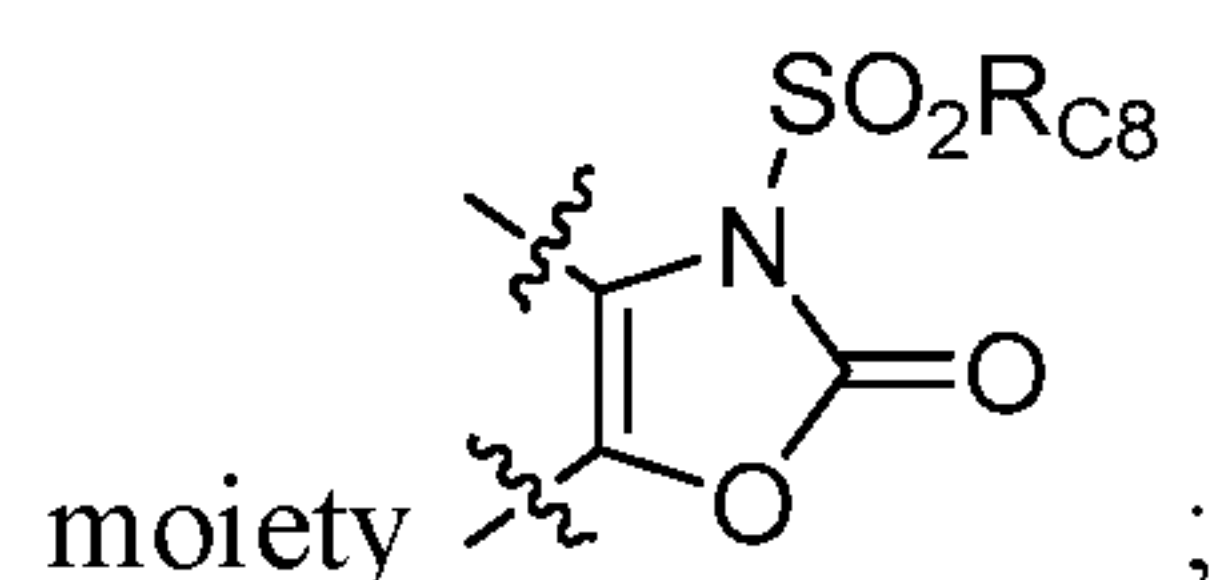


(c) the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is a moiety selected from:



16. The method of any of claims 8-15, wherein:

(a) each R_{C4} , R_{C5} and R_{C6} , is independently hydrogen, halogen, CN, CF_3 , OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, $-CO_2H$, $-CONR_{10}R_{11}$, or $-NHCONH_2$; or is taken with R_{C7} to form the



(b) at least one of R_{C4} , R_{C5} and R_{C6} is hydrogen;

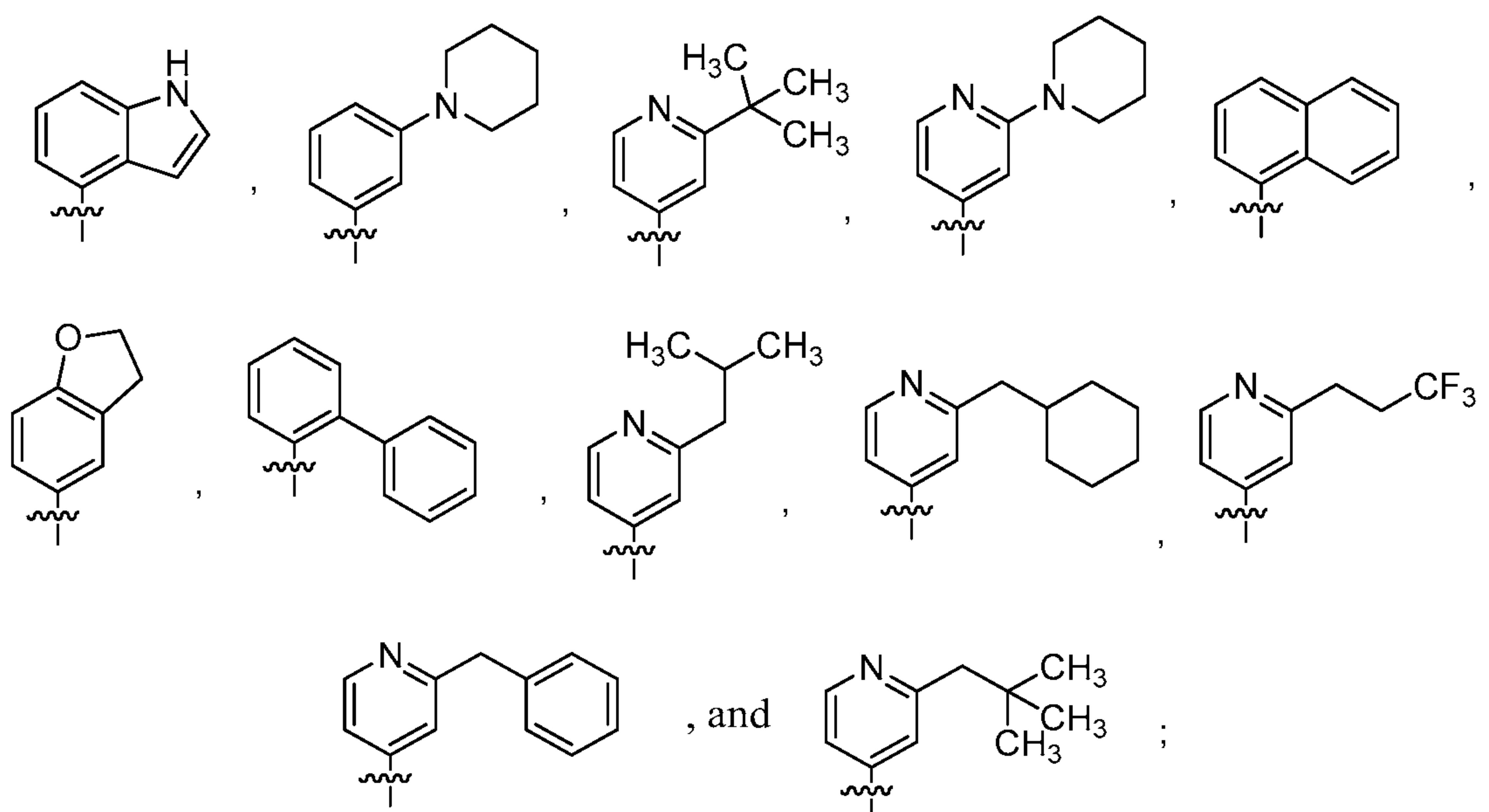
(c) two of R_{C4} , R_{C5} and R_{C6} are hydrogen;

(d) each R_{C4} , R_{C5} and R_{C6} is hydrogen;

- (e) at least one of R_{C4} , R_{C5} and R_{C6} is halogen;
- (f) two of R_{C4} , R_{C5} and R_{C6} are halogen;
- (g) each R_{C4} , R_{C5} and R_{C6} is halogen;
- (h) one of R_{C4} , R_{C5} and R_{C6} is hydrogen, and the remaining two of R_{C4} , R_{C5} and R_{C6} are halogen; or
- (i) two of R_{C4} , R_{C5} and R_{C6} are hydrogen, and the remaining one of R_{C4} , R_{C5} and R_{C6} is halogen.

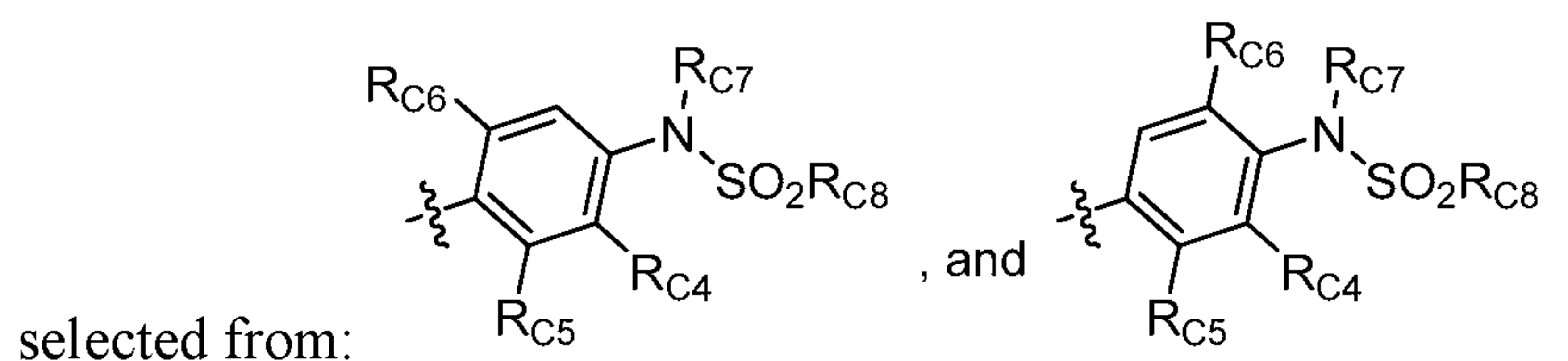
17. The method of any of claims 8, 13, 14, 15, or 16, wherein:

A is a moiety selected from



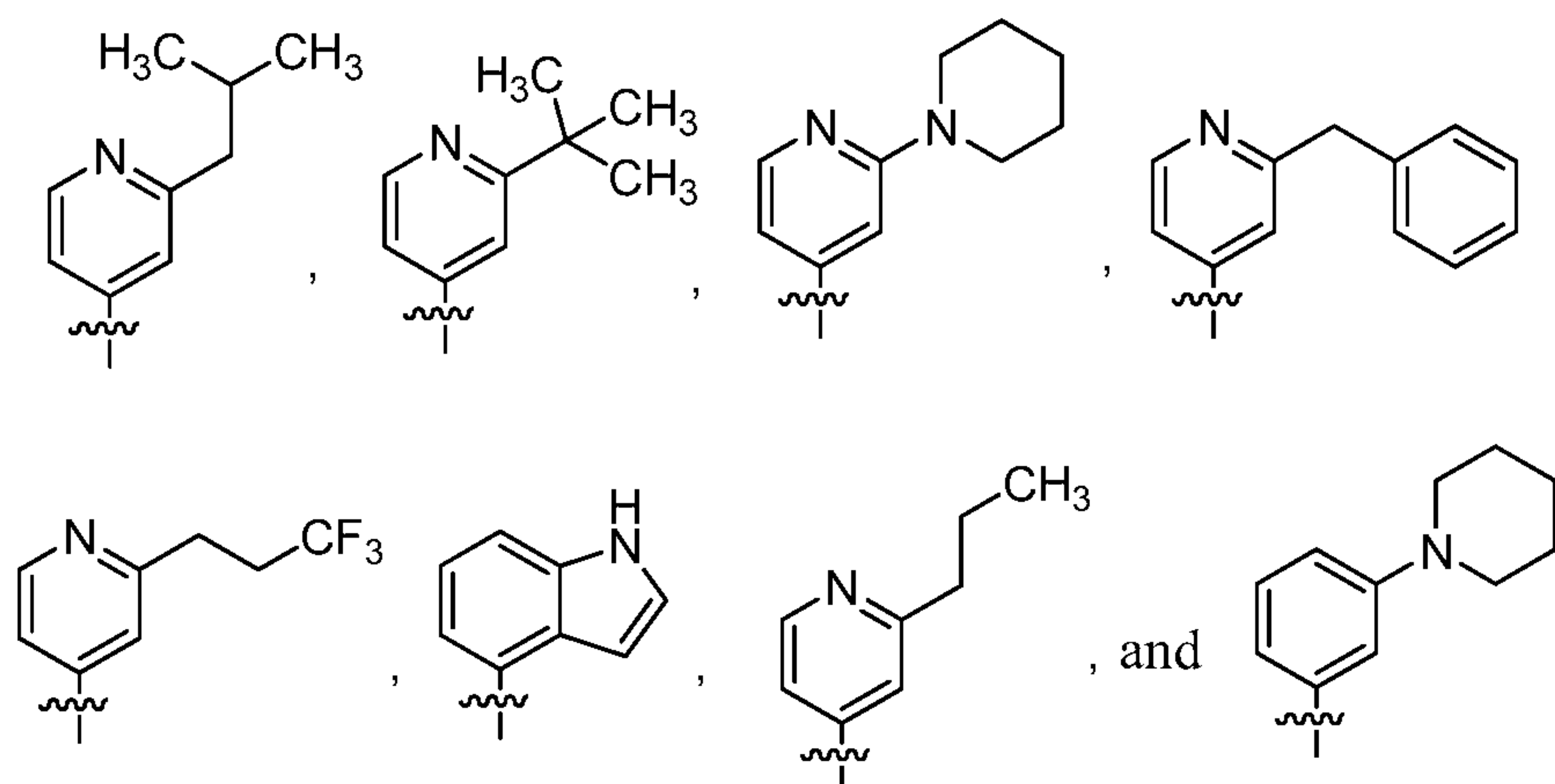
X is S; and

the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is a moiety



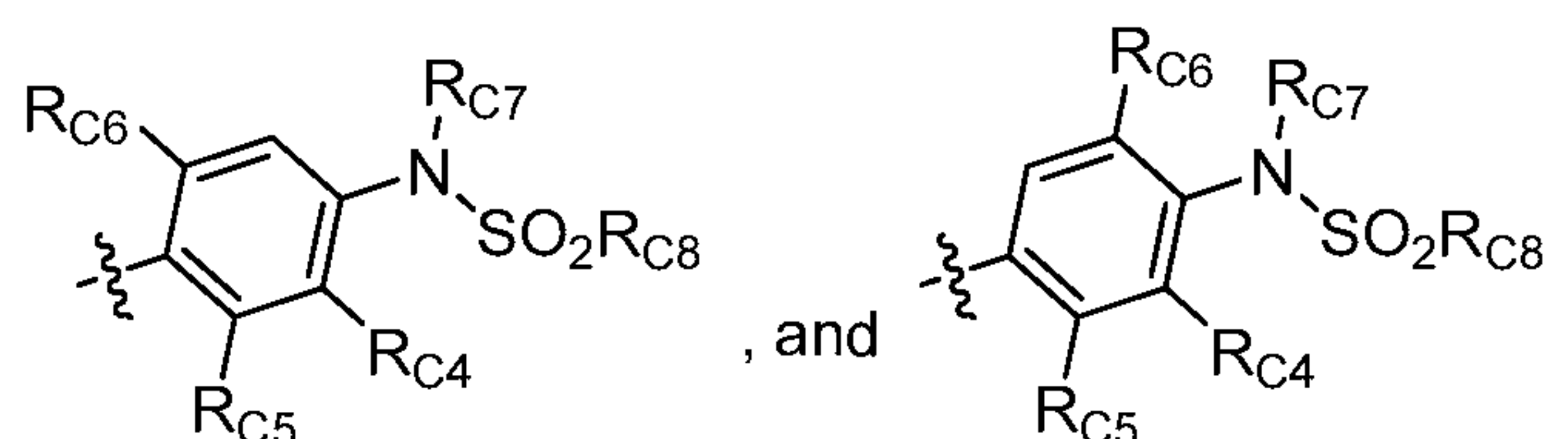
18. The method of claim 8, wherein:

A is a moiety selected from

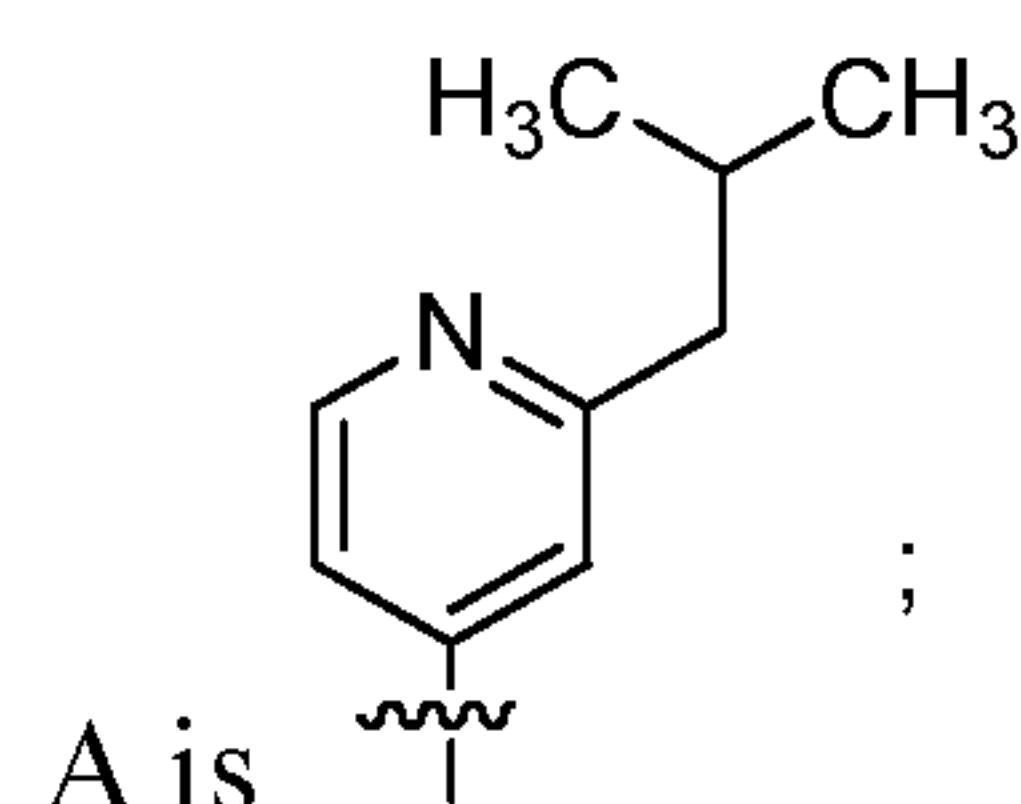


X is S; and

the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} and $-NR_{C7}SO_2R_{C8}$, is a moiety selected from

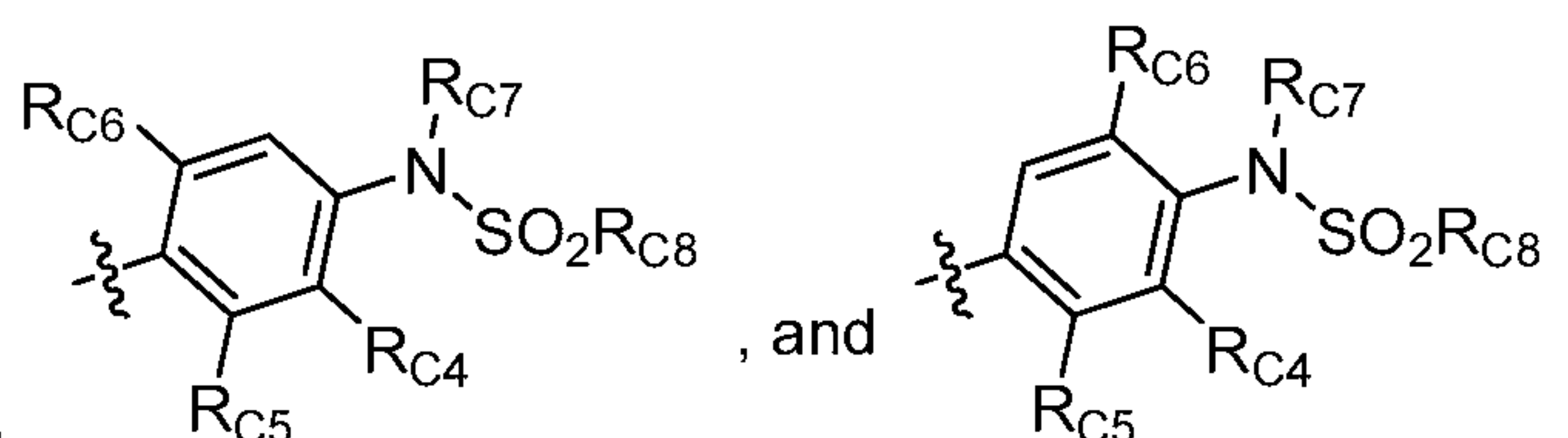


19. The method of claim 8, wherein:



X is S; and

the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is

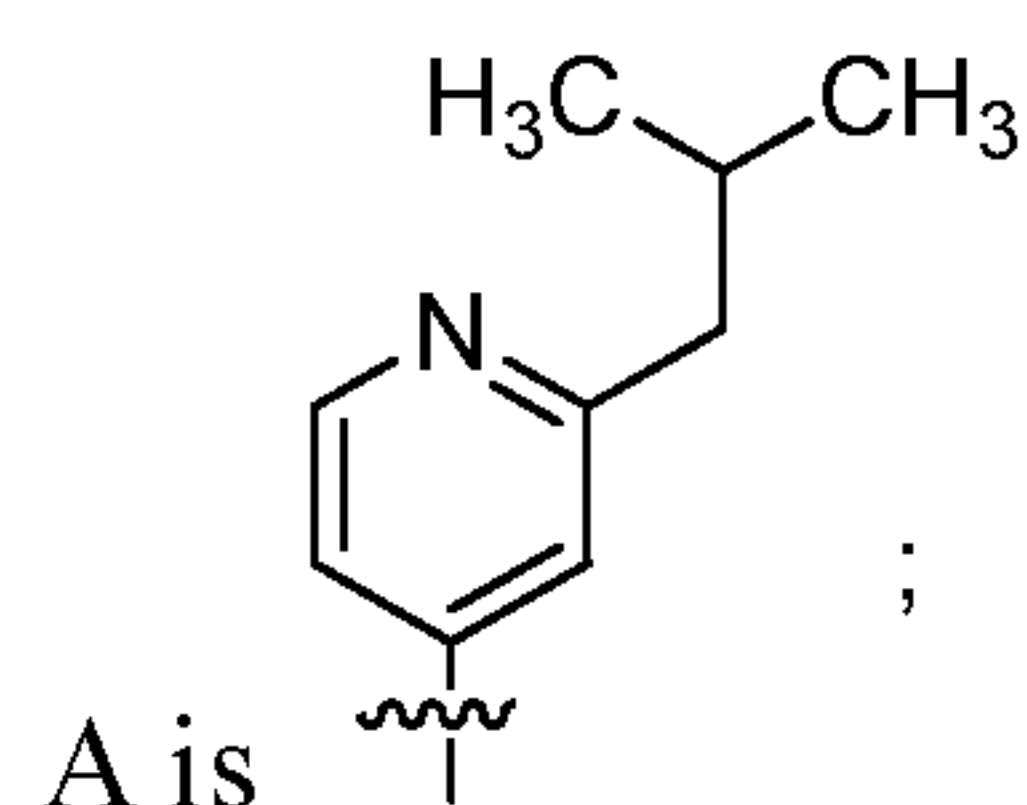


selected from

20. The method of any of claims 8-19, wherein the compound is of Formula (IIa).

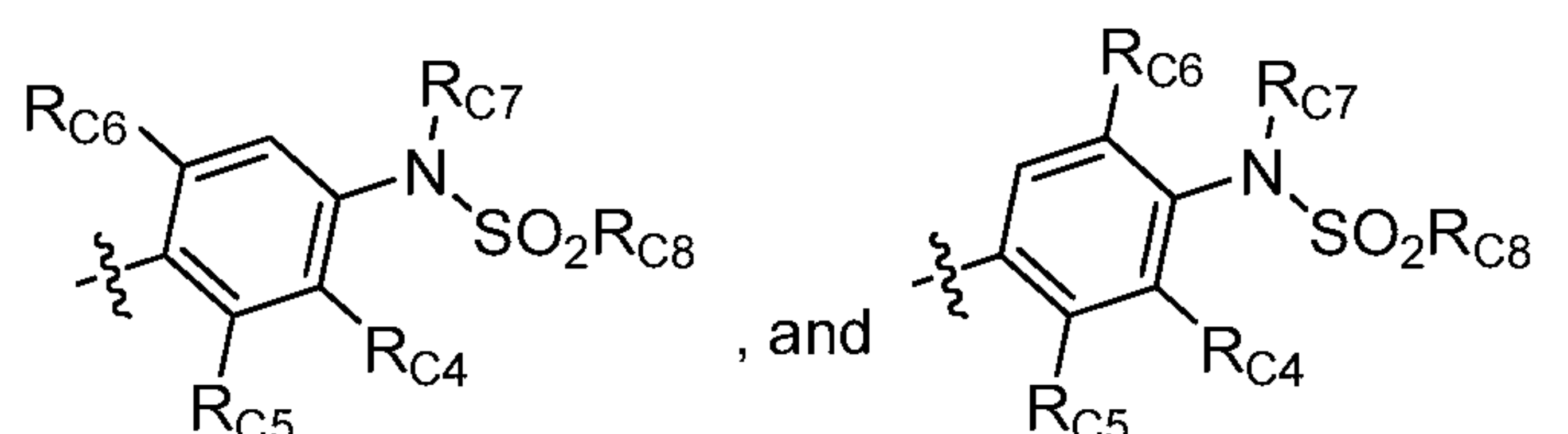
21. The method of any of claims 8-19, wherein the compound is of Formula (IIb).

22. The method of any of claims 8-20, wherein the compound is of Formula (IIa), wherein:



X is S; and

the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is selected from



23. The method of claim 8, wherein the compound is selected from the group consisting of:
- 1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 - 1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 - N-(3-chloro-4-(2-(1-isobutyl-1H-pyrazol-5-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 - N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 - N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 - N-(3-chloro-4-(2-(1,2-dimethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 - N-(3-chloro-4-(2-(1-propyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 - N-(3-chloro-4-(2-(2,3-dimethyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 - N-(3-chloro-4-(2-(3-propyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 - N-(4-(2-(3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1,2-dipropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(6-(butylamino)-2-isobutylpyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(6-(dibutylamino)-2-isobutylpyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(6-amino-2-isobutylpyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-aminopyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(propylamino)pyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(dibutylamino)pyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2'-propyl-2,4'-bithiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,2,4-thiadiazol-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,2,4-oxadiazol-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2'-propyl-2,5'-bithiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,3,4-thiadiazol-2-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(5-propyl-1,3,4-oxadiazol-2-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1-isobutyl-6-oxo-1,6-dihydropyridin-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(4-fluoro-3-isobutylphenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3,5-dichloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-(trifluoromethyl)phenyl)methanesulfonamide;

N-(2-cyclopropyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methylphenyl)methanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-isopropylphenyl)methanesulfonamide;

N-(2-ethynyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-ethynyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-6-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-6-methylphenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(4-(2-tert-butylpyridin-4-yl)-1-methyl-1H-imidazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(1-methyl-2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-5-chloro-4-(1-methyl-2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(4-(2-tert-butylpyridin-4-yl)oxazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)oxazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(dimethylamino)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(trifluoromethylsulfonyl)acrylamide;

N-(3-chloro-4-(2-(2-(methylsulfonamido)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-(3,3,3-trifluoropropyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-hydroxyphenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-(trifluoromethyl)phenyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-neopentylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 6-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-(trifluoromethylsulfonyl)benzo[d]oxazol-2(3H)-one;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,2,2,2-pentafluoroethanesulfonamide;
 1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide;
 1,1,1-trifluoro-N-{2-methoxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;
 N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-2-methoxyphenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(2-aminopyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-
 1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-{2-hydroxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-
 yl]phenyl}methanesulfonamide;
 N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-(4-{2-[2-(2,2-dimethylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}-2-methoxyphenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-
 yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(4-(piperidine-1-carbonyl)phenyl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-
 chlorophenyl}methanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-
 chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-
 methylbenzene-1-sulfonamide;

N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(quinolin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-chloropyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxopyrrolidin-1-yl)ethyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-yl)ethyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxoimidazolidin-1-yl)ethyl)methanesulfonamide;
 N-(2-bromo-4-(2-(2-(piperidin-1-yl)pyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 2-(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)ethyl acetate;
 (2-(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)ethoxy)methyl acetate;
 N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-N-(2-{[4-(3-chlorophenyl)-2-oxo-1,3,2λ⁵-dioxaphosphinan-2-yl]oxy}ethyl)-1,1,1-trifluoromethanesulfonamide;
 (N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)methyl acetate;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(methoxymethyl)methanesulfonamide;
 N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-N-([4-(3-chlorophenyl)-2-oxo-1,3,2λ⁵-dioxaphosphinan-2-yl]oxy)methyl)-1,1,1-trifluoromethanesulfonamide;
 methyl 4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl(trifluoromethylsulfonyl)carbamate;
 sodium (N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)methyl phosphate;

1-(N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethylsulfonamido)ethyl isobutyrate;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-yl)ethyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-(pyrrolidin-1-yl)ethyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(2-(diethylamino)ethyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(2-(dimethylamino)ethyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(3-fluoro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-methylmethanesulfonamide;
 1,1,1-trifluoro-N-(3-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 N-(2-bromo-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-methyl-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 N-(4-(2-(2-butylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide
 1,1,1-trifluoro-N-(4-(2-(2-(methoxymethyl)pyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 N-(4-(2-(4,6-dipropylpyridin-2-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(4-(2-(4-propylpyridin-2-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(2,6-dipropylpyridin-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(2-(cyclohexylmethyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-methoxyphenyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-((trifluoromethylsulfonyl)methyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-propyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 5-(4-(2-chloro-4-(trifluoromethylsulfonamido)phenyl)thiazol-2-yl)-N-cyclopropyl-2-fluorobenzamide;
 5-(4-(2-chloro-4-(trifluoromethylsulfonamido)phenyl)thiazol-2-yl)-N-cyclohexyl-2-fluorobenzamide;
 N-(4-(2-(1H-indol-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(3-(piperidin-1-yl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-(piperidin-1-yl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-5-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide; and
 N-(2-bromo-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

24. The method of claim 8, wherein the compound is selected from the group consisting of:

1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(1-isobutyl-1H-pyrazol-5-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide;

1,1,1-trifluoro-N-{2-methoxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-2-methoxyphenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-aminopyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-{2-hydroxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-{2-[2-(2,2-dimethylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(4-(piperidine-1-carbonyl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-
 chlorophenyl}methanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-
 chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-
 methylbenzene-1-sulfonamide;
 N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-
 trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide; and
 N-(3-chloro-4-(2-(quinolin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

25. The method of claim 8, wherein the compound is selected from the group consisting of:

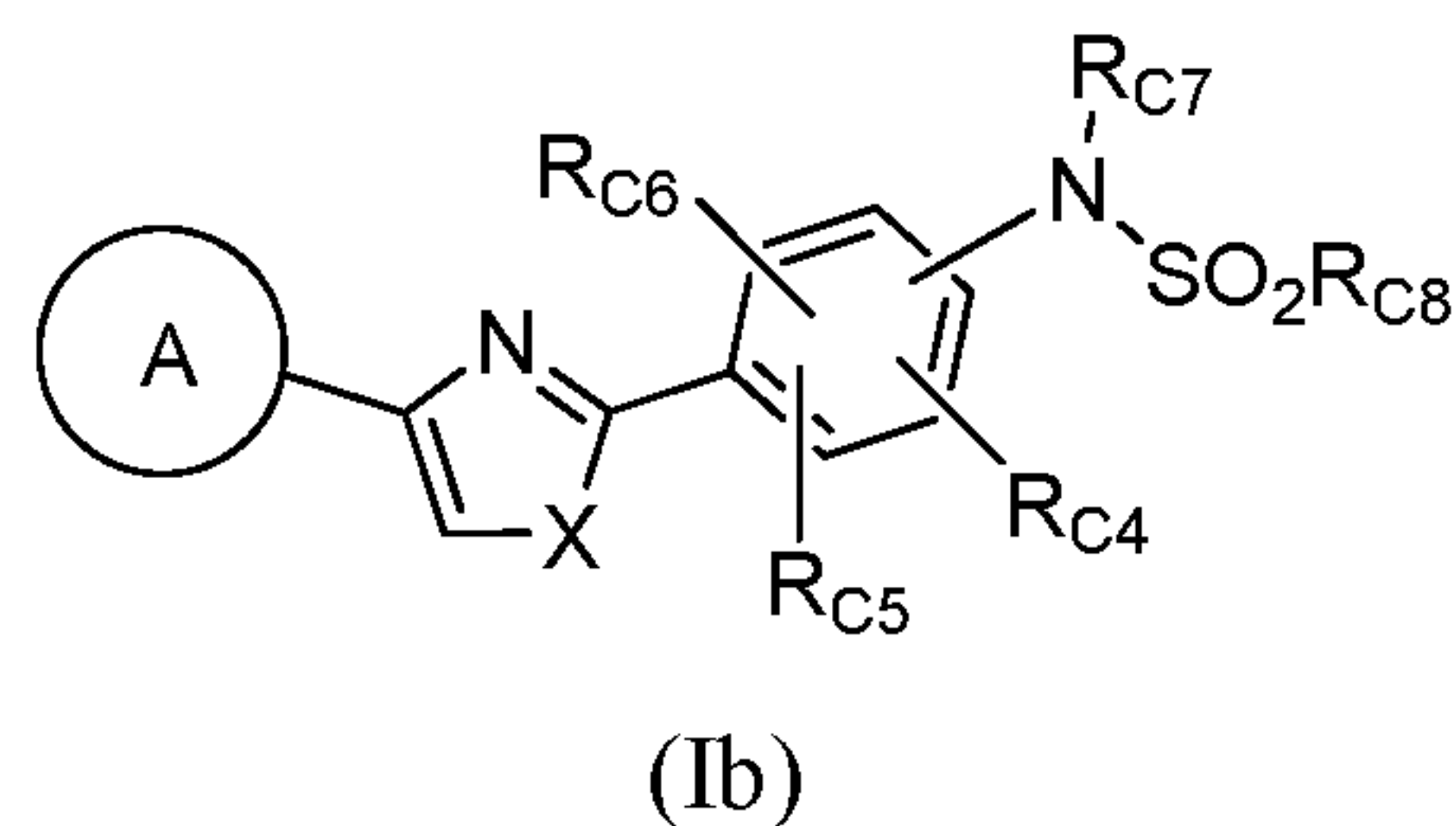
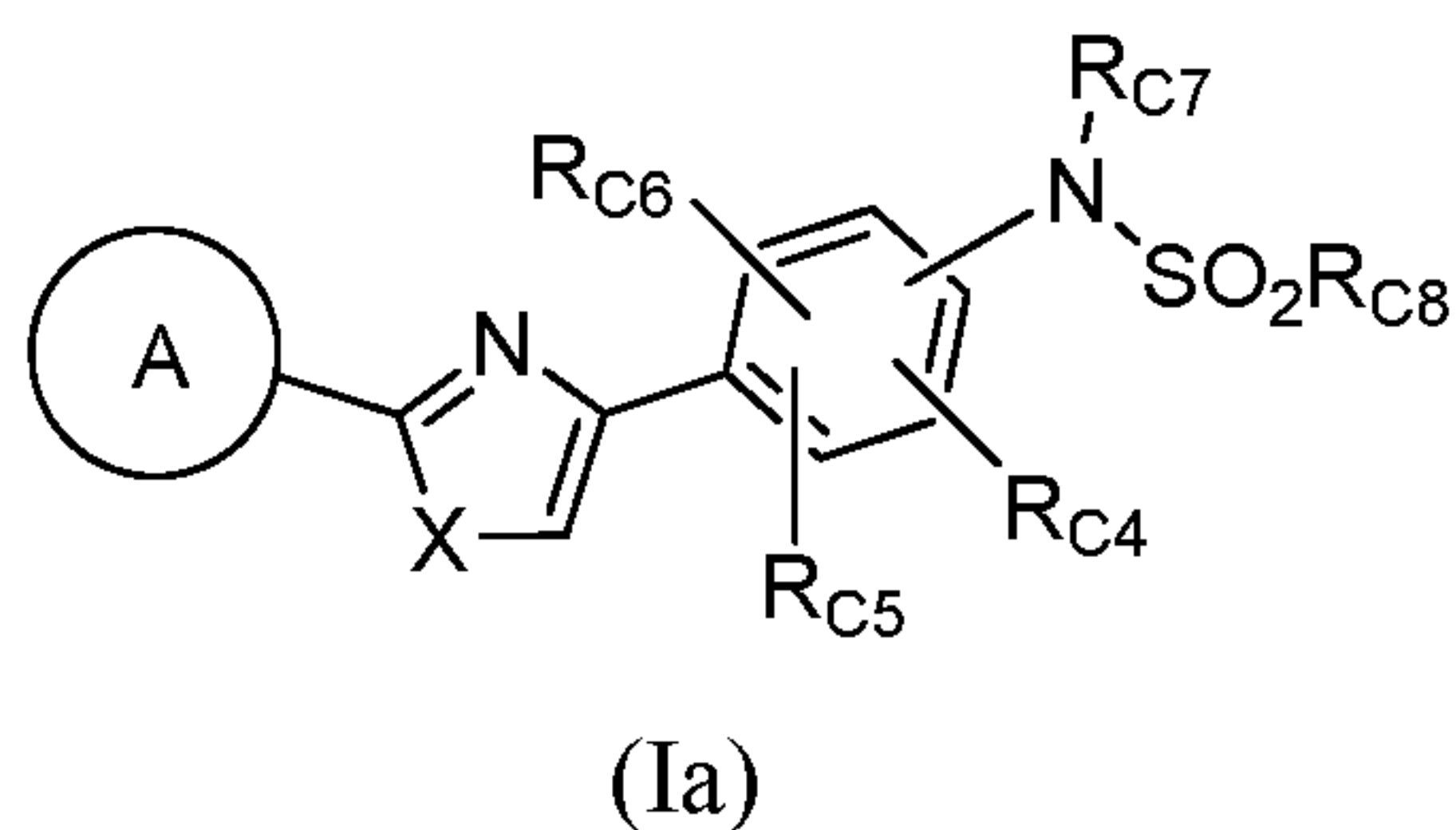
N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide; and

N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide.

26. The method of any of claim 8-19, wherein the patient has non-alcoholic steatohepatitis (NASH).
27. The method of claim 8, wherein administration of the compound or the pharmaceutically acceptable salt of the compound reduces the risk of NASH in the patient.
28. A compound for treating elevated a disorder selected from the group consisting of liver fibrosis, elevated cholesterol levels, and insulin resistance, wherein the compound is a compound of Formula (Ia) or Formula (Ib):



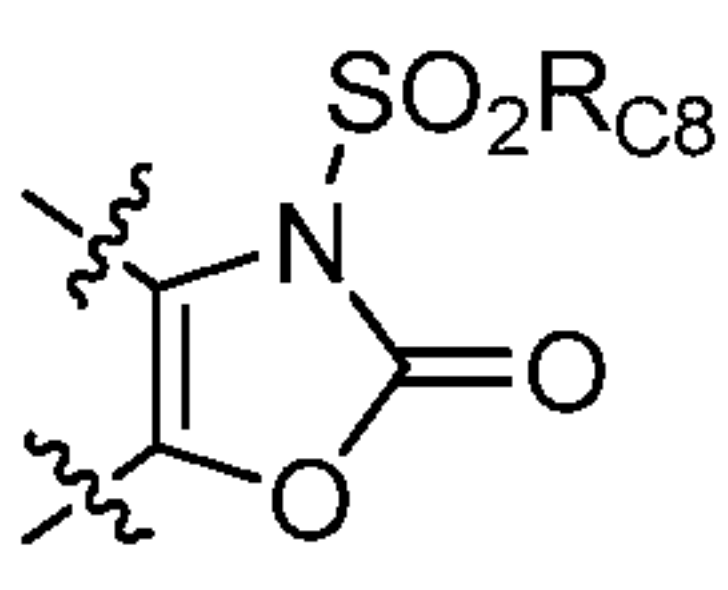
or a pharmaceutically acceptable salt thereof, wherein:

A is either:

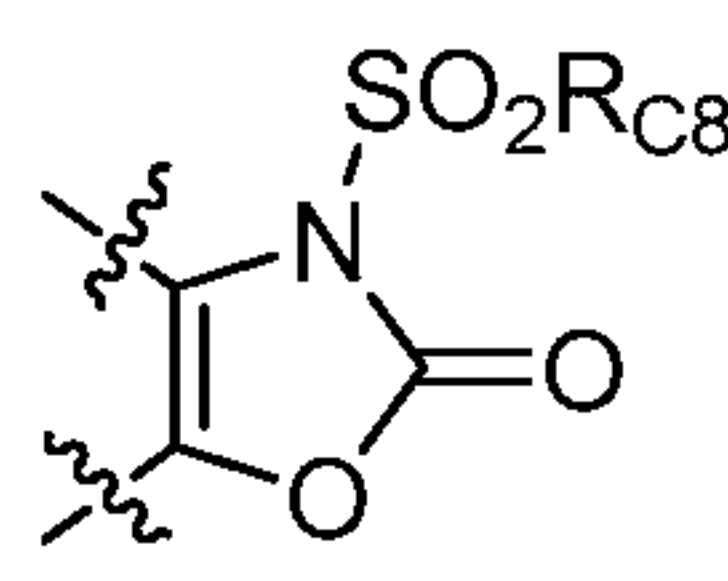
- i. an aryl or heteroaryl, each having only one ring, substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF₃, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -(CH₂)_mCF₃, =O, -CH₂OCH₃, -OBn, -CO₂H, -CO₂-Alkyl, -NR₁₀R₁₁, and -CONR₁₀R₁₁; or
- ii. an aryl or heteroaryl, each having more than one ring, optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF₃, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl,

C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, $-(\text{CH}_2)_m\text{CF}_3$, $=\text{O}$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OH}$, $-\text{OBn}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{-Alkyl}$, $-\text{NR}_{10}\text{R}_{11}$, and $-\text{CONR}_{10}\text{R}_{11}$;

each $\text{R}_{\text{C}4}$, $\text{R}_{\text{C}5}$, and $\text{R}_{\text{C}6}$, is independently hydrogen, halogen, CN, CF_3 , OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, $-\text{CO}_2\text{H}$, $-\text{CONR}_{10}\text{R}_{11}$,

or $-\text{NHCONH}_2$; or is taken with $\text{R}_{\text{C}7}$ to form the moiety  ;

$\text{R}_{\text{C}7}$ is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{NR}_{10}\text{R}_{11}$, $-\text{CO}_2\text{-Alkyl}$, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{O-Alkyl}$, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{OPO}_3\text{Na}_2$, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{O}(\text{CR}_{9a}\text{R}_{9b})_n\text{O-Alkyl}$, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{O}(\text{C}=\text{O})\text{-Alkyl}$, $-(\text{CR}_{9a}\text{R}_{9b})_m\text{O}(\text{CR}_{9a}\text{R}_{9b})_n\text{O}(\text{C}=\text{O})\text{-Alkyl}$, $-(\text{C}=\text{O})\text{CH}=\text{CH}_2$, $-\text{SO}_2\text{R}_{\text{C}8}$;

or is taken with one of $\text{R}_{\text{C}4}$, $\text{R}_{\text{C}5}$ or $\text{R}_{\text{C}6}$ to form the moiety  ;

$\text{R}_{\text{C}8}$ is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

$\text{R}_{\text{C}8'}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

each R_{9a} and R_{9b} , where present, is independently hydrogen or C1-C6 linear or branched alkyl;

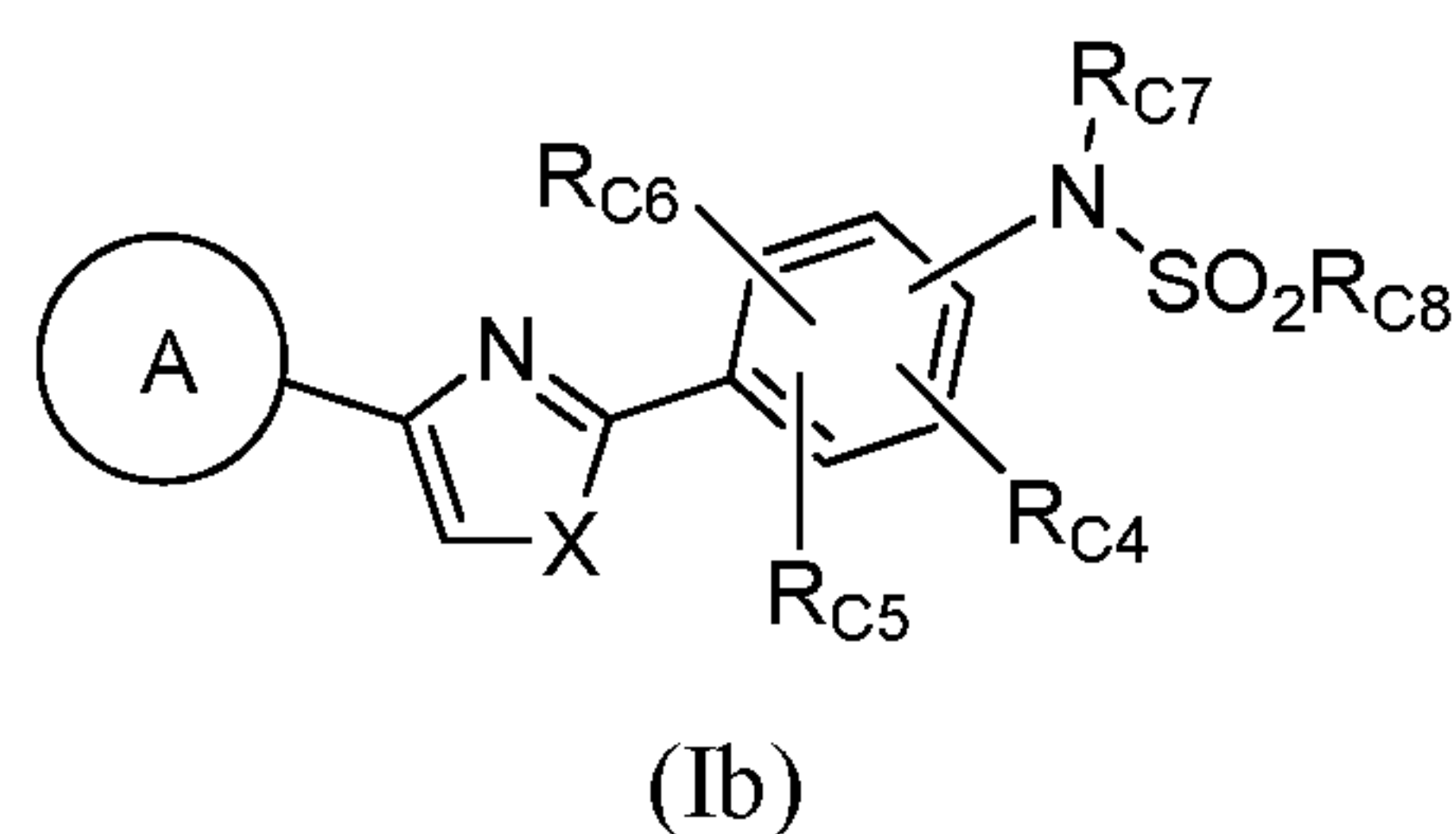
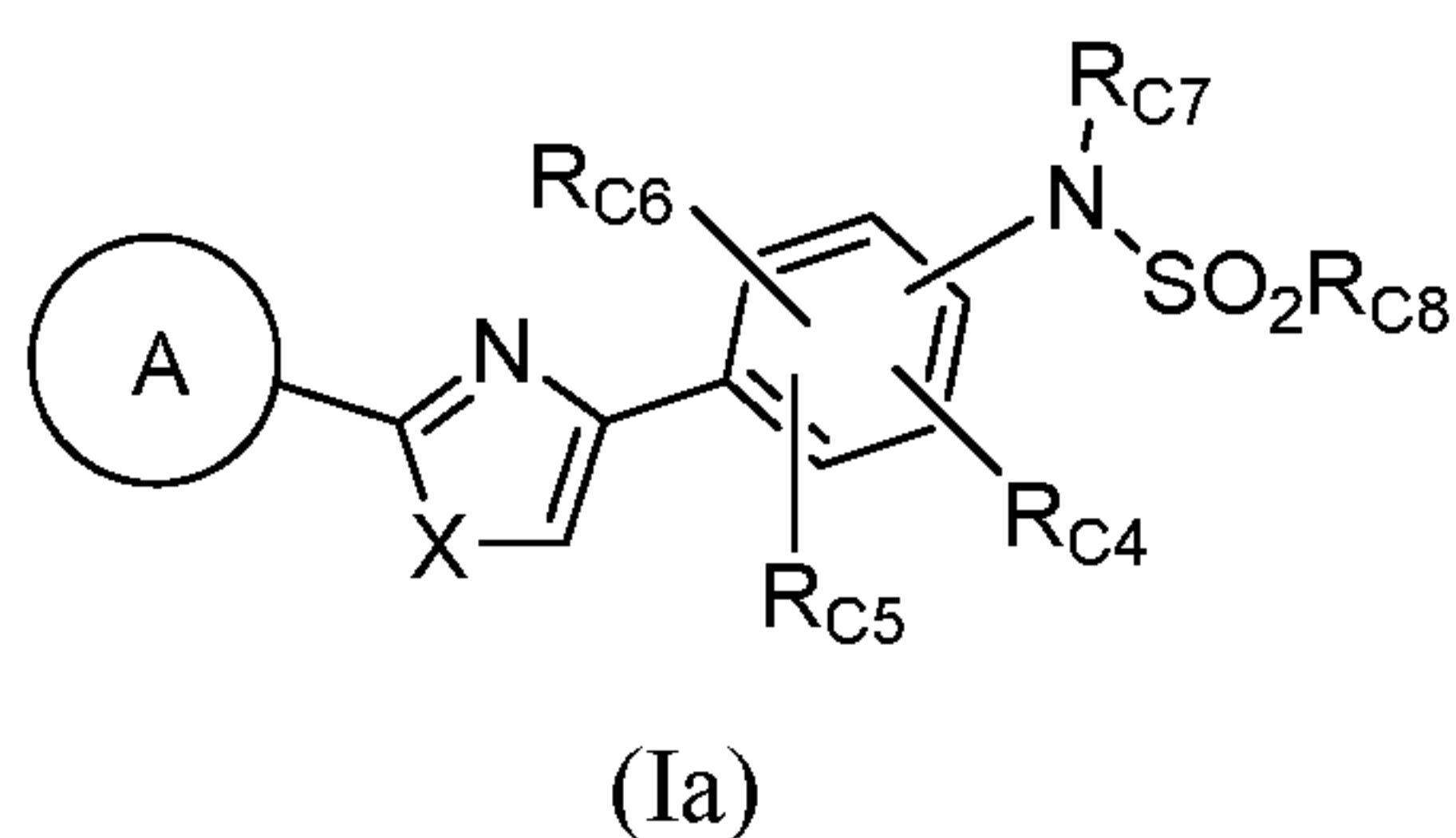
R_{10} and R_{11} are independently hydrogen, $-\text{SO}_2\text{R}_{\text{C}8'}$, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6

heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6$,2-thiazolidine-1,1-dione, a $1,2\lambda^6$,3-oxathiazolidine-2,2-dione, or a $1\lambda^6$,2,5-thiadiazolidine-1,1-dione;

X is a heteroatom selected from S, O; or **NR_B** wherein **R_B** is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

each **m** and **n** is 1, 2 or 3.

29. The compound of claim 28 for treating a disorder selected from the group consisting of liver fibrosis, elevated cholesterol levels, and insulin resistance in a patient who has non-alcoholic steatohepatitis (NASH).
30. Use of a compound in the manufacture of a medicament for treating a disorder selected from the group consisting of liver fibrosis, elevated cholesterol levels, and insulin resistance, wherein the compound is a compound of Formula (Ia) or Formula (Ib):



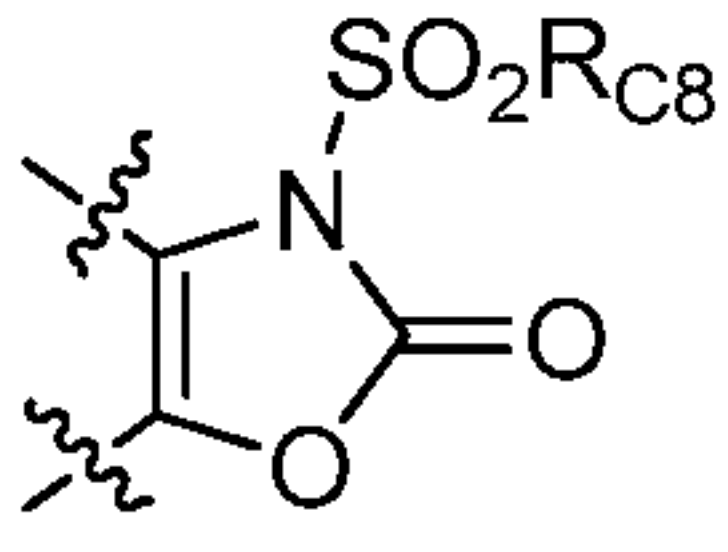
or a pharmaceutically acceptable salt thereof, wherein:

A is either:

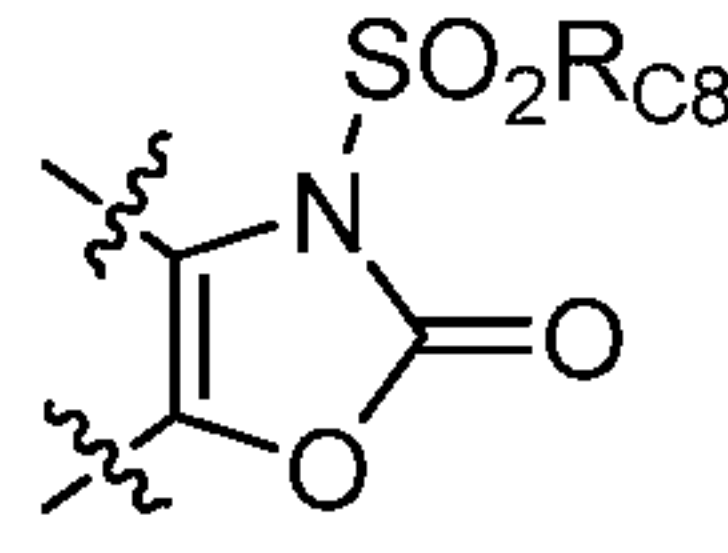
- i. an aryl or heteroaryl, each having only one ring, substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF₃, OH, C1-C6 linear or branched alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, -(CH₂)_mCF₃, =O, -CH₂OCH₃, -OBn, -CO₂H, -CO₂-Alkyl, -NR₁₀R₁₁, and -CONR₁₀R₁₁; or
- ii. an aryl or heteroaryl, each having more than one ring, optionally substituted with 1, 2, or 3 substituents selected from the group consisting of halogen, CN, CF₃, OH, C1-C6 linear or branched alkyl, C3-C6

cycloalkyl, C3-C6 cycloalkenyl, C1-C6 linear or branched hydroxyalkyl, C1-C3 linear or branched alkoxy, C3-C6 cycloalkylmethyl, $-(CH_2)_mCF_3$, $=O$, $-CH_2OCH_3$, $-CH_2OH$, $-OBn$, $-CO_2H$, $-CO_2$ -Alkyl, $-NR_{10}R_{11}$, and $-CONR_{10}R_{11}$;

each R_{C4} , R_{C5} , and R_{C6} , is independently hydrogen, halogen, CN, CF_3 , OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, $-CO_2H$, $-CONR_{10}R_{11}$,

or $-NHCONH_2$; or is taken with R_{C7} to form the moiety  ;

R_{C7} is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, $-(CR_{9a}R_{9b})_mNR_{10}R_{11}$, $-CO_2$ -Alkyl, $-(CR_{9a}R_{9b})_mO$ -Alkyl, $-(CR_{9a}R_{9b})_mOPO_3Na_2$, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO$ -Alkyl, $-(CR_{9a}R_{9b})_mO(C=O)$ -Alkyl, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)$ -Alkyl, $-(C=O)CH=CH_2$, $-SO_2R_{C8'}$;

or is taken with one of R_{C4} , R_{C5} or R_{C6} to form the moiety  ;

R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

$R_{C8'}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

each R_{9a} and R_{9b} , where present, is independently hydrogen or C1-C6 linear or branched alkyl;

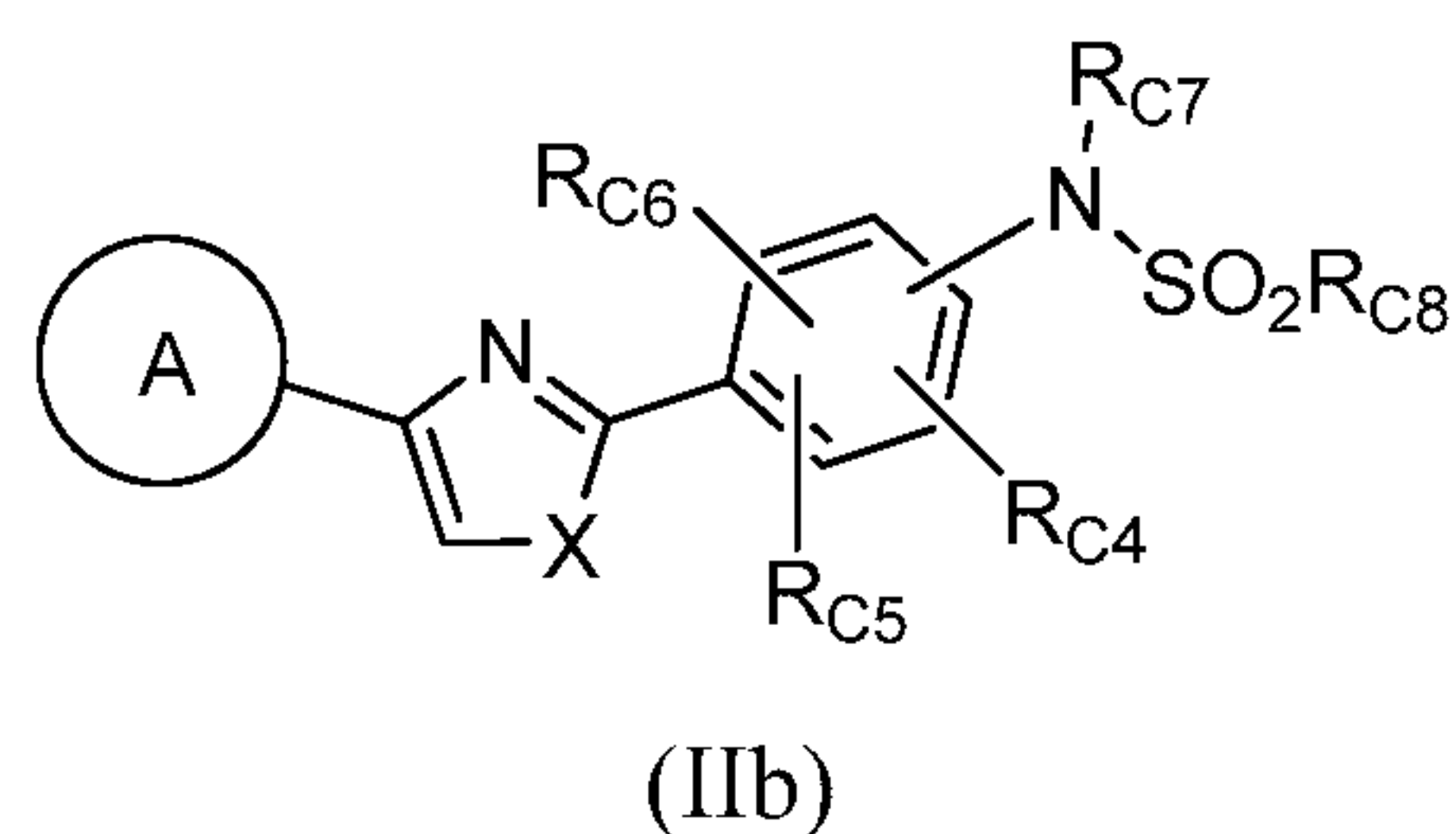
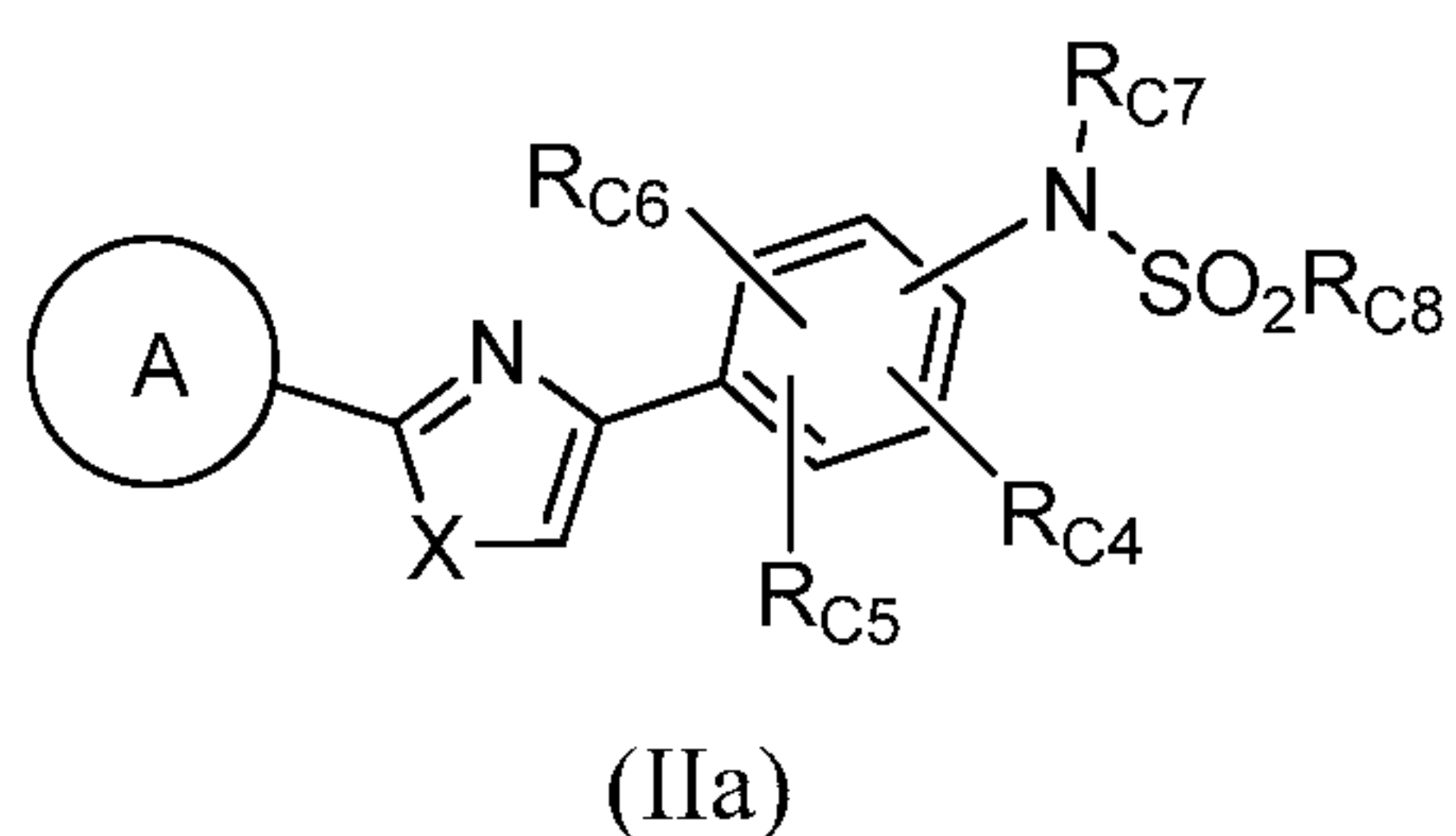
R_{10} and R_{11} are independently hydrogen, $-SO_2R_{C8'}$, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl;

or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6,2$ -thiazolidine-1,1-dione, a $1,2\lambda^6,3$ -oxathiazolidine-2,2-dione, or a $1\lambda^6,2,5$ -thiadiazolidine-1,1-dione;

X is a heteroatom selected from S, O; or NR_B wherein R_B is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

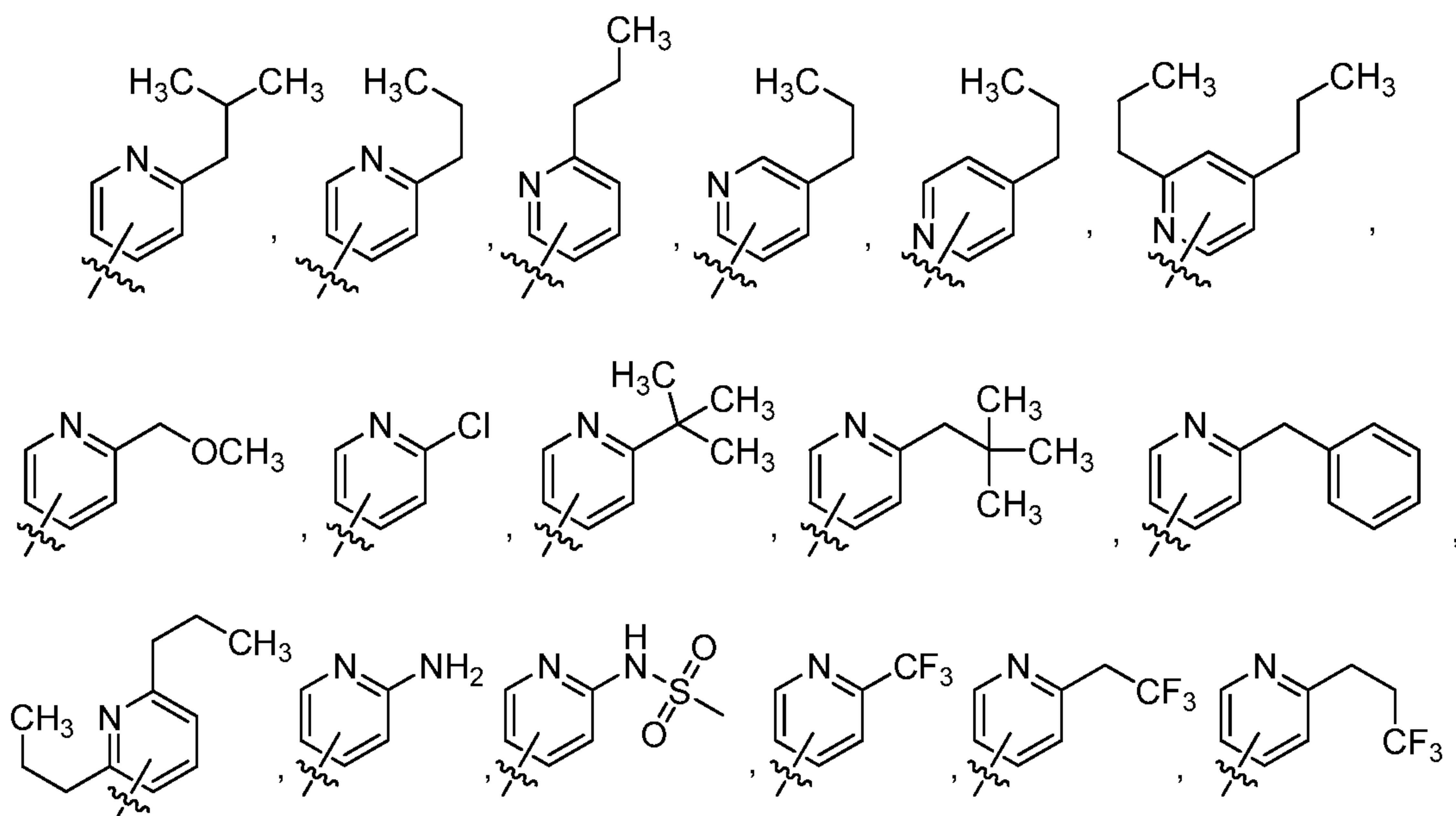
each *m* and *n* is 1, 2 or 3.

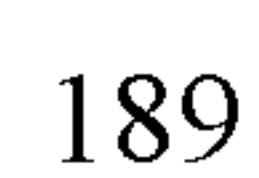
31. The use of claim 30, wherein the medicament is for treating a disorder selected from the group consisting of liver fibrosis, elevated cholesterol levels, and insulin resistance in a patient who has non-alcoholic steatohepatitis (NASH).
32. The compound of claim 28 or 29 or the use of claim 30 or 31, wherein compound is of formula (IIa) or formula (IIb):

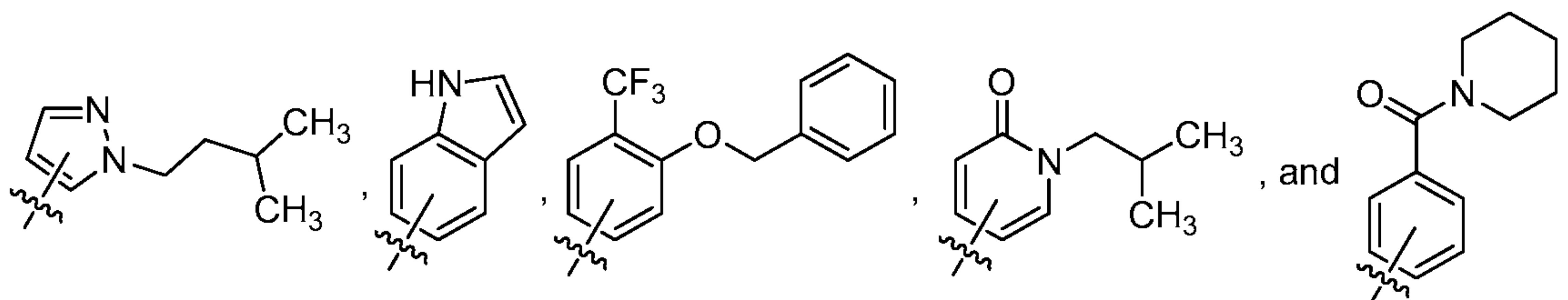


or a pharmaceutically acceptable salt thereof, wherein:

A is a moiety selected from the group consisting of:

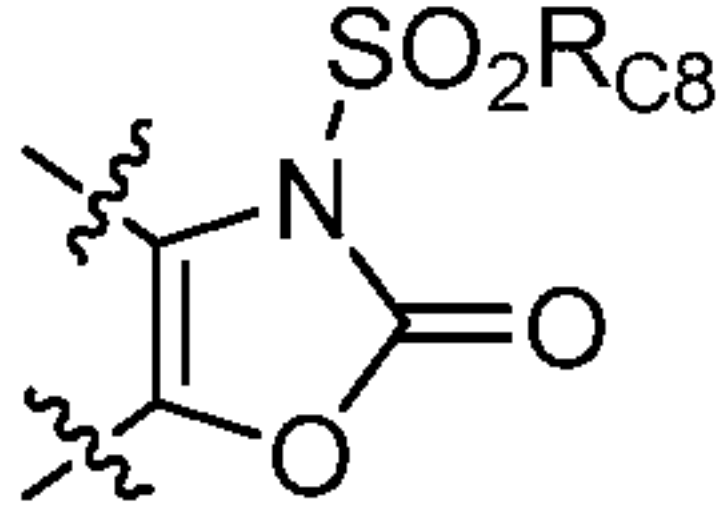




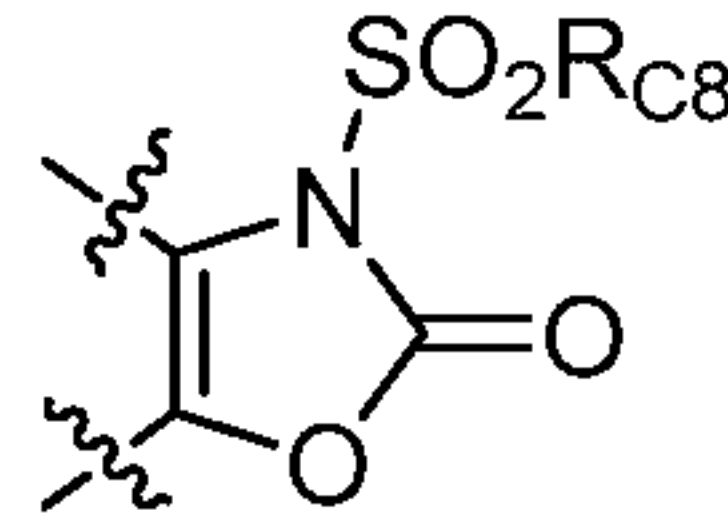


wherein the ring containing X is linked to ring A at any available position on ring A;

each R_{C4} , R_{C5} , and R_{C6} , is independently hydrogen, halogen, CN, CF_3 , OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, $-CO_2H$, $-CONR_{10}R_{11}$,

or $-NHCONH_2$; or is taken with R_{C7} to form the moiety  ;

R_{C7} is hydrogen, C1-C6 linear or branched alkyl, C1-C6 linear or branched hydroxyalkyl, $-(CR_{9a}R_{9b})_mNR_{10}R_{11}$, $-CO_2$ -Alkyl, $-(CR_{9a}R_{9b})_mO$ -Alkyl, $-(CR_{9a}R_{9b})_mOPO_3Na_2$, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO$ -Alkyl, $-(CR_{9a}R_{9b})_mO(C=O)$ -Alkyl, $-(CR_{9a}R_{9b})_mO(CR_{9a}R_{9b})_nO(C=O)$ -Alkyl, $-(C=O)CH=CH_2$, $-SO_2R_{C8'}$;

or is taken with one of R_{C4} , R_{C5} or R_{C6} to form the moiety  ;

R_{C8} is a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

$R_{C8'}$ is a linear or branched C1-C6 alkyl, a linear or branched C1-C6 perhaloalkyl, a linear or branched C2-C6 perhaloalkenyl, a linear or branched C2-C6 perhaloalkynyl, a linear or branched C1-C6 alkyl having at least one halogen atom, a linear or branched C2-C6 alkenyl having at least one halogen atom, or a linear or branched C2-C6 alkynyl having at least one halogen atom;

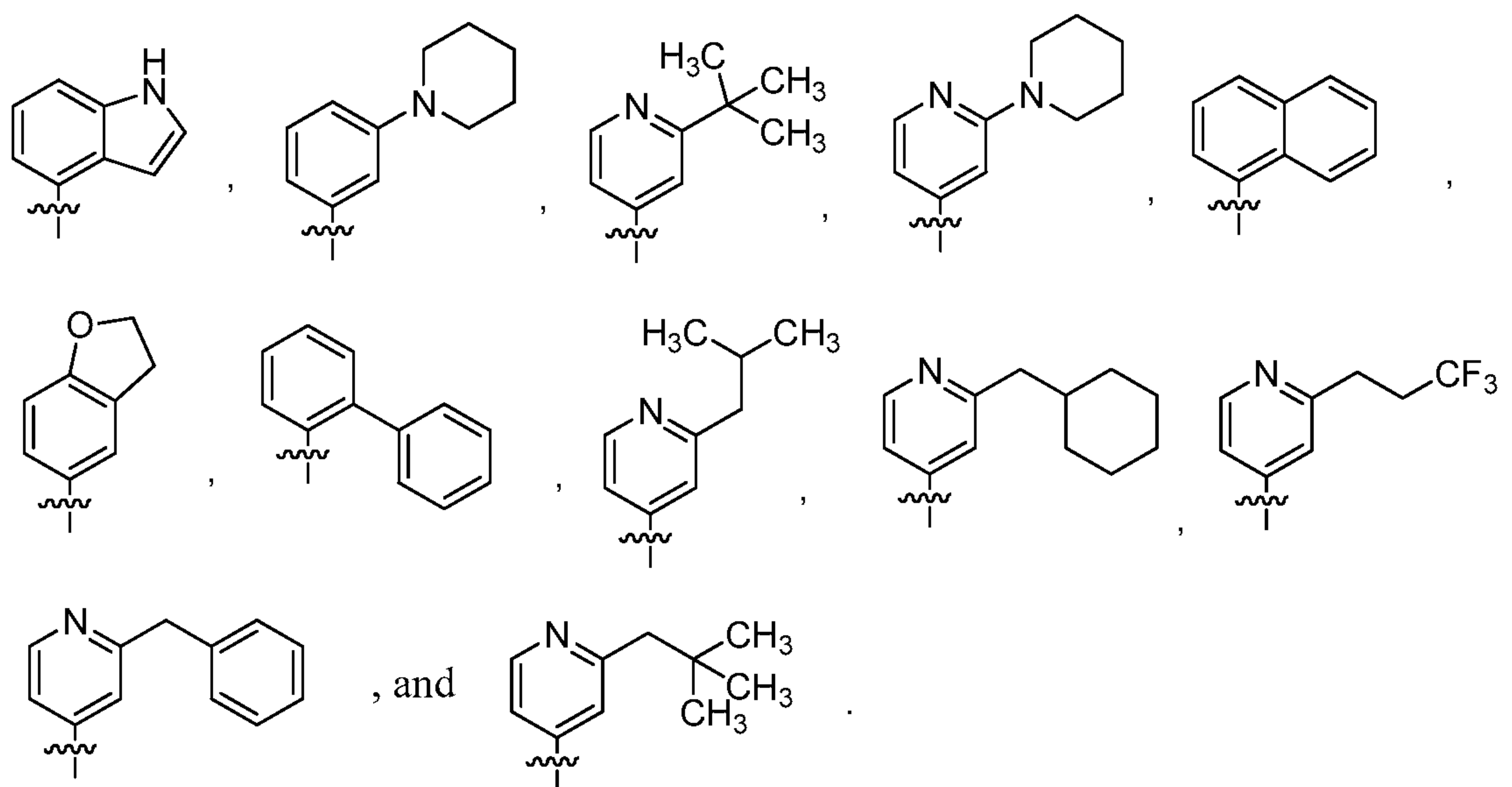
each R_{9a} and R_{9b} , where present, is independently hydrogen or C1-C6 linear or branched alkyl;

R10 and **R11** are independently hydrogen, $-\text{SO}_2\text{R}_{\text{C8}}$, C1-C6 linear or branched alkyl, C2-C6 linear or branched alkenyl, C3-C6 cycloalkyl, or C3-C6 cycloalkenyl; or are taken together with the N to which they are attached to form a C3-C6 heterocycle, pyrrolidinone, piperidinone, oxazolidinone, oxazinanone, imidazolidinone, tetrahydropyrimidin-2(1H)-one, a $1\lambda^6,2$ -thiazolidine-1,1-dione, a $1,2\lambda^6,3$ -oxathiazolidine-2,2-dione, or a $1\lambda^6,2,5$ -thiadiazolidine-1,1-dione;

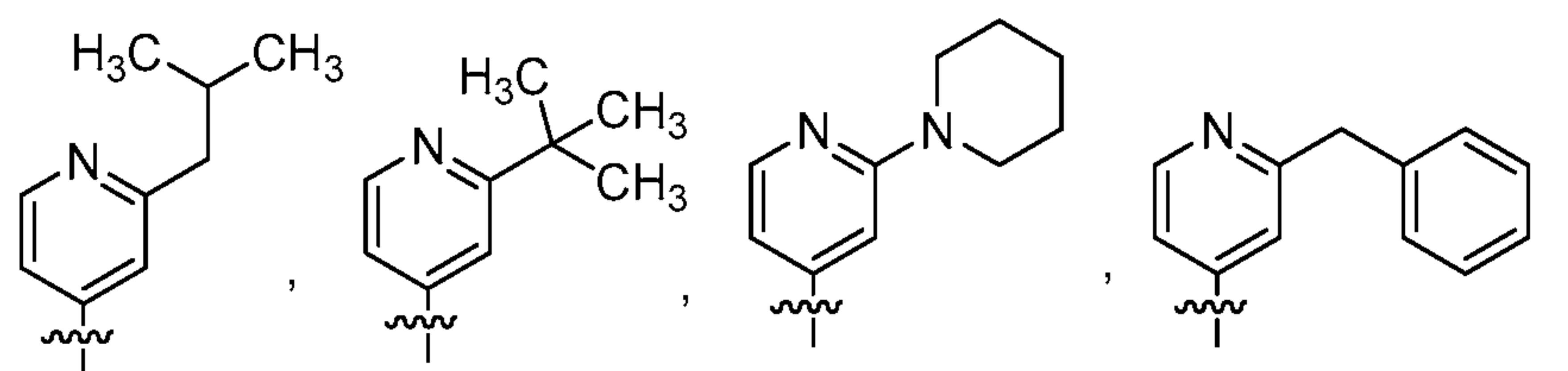
X is a heteroatom selected from S, O; or NR_{B} wherein **R_B** is hydrogen, a C1-C6 linear or branched alkyl, or a C3-C6 cycloalkyl; and

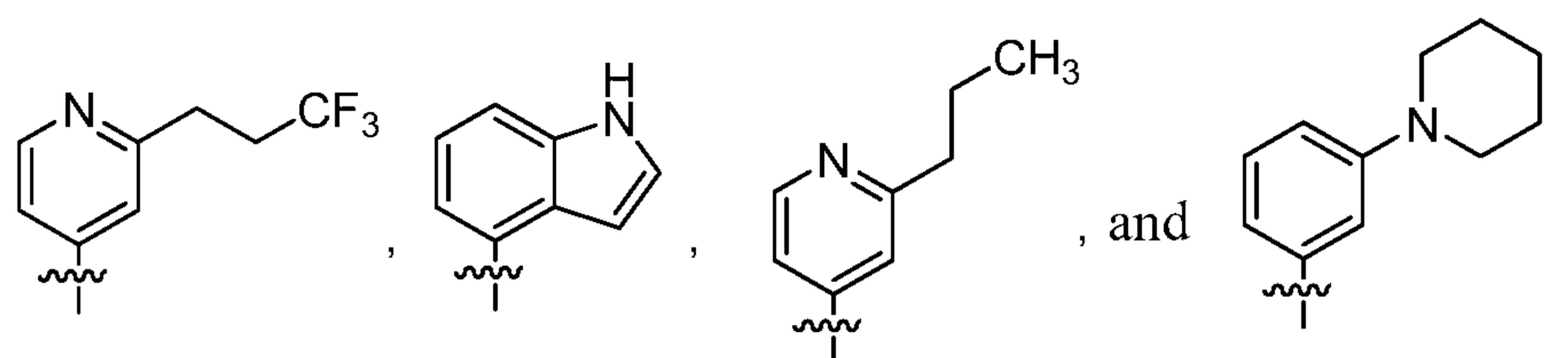
each *m* and *n* is 1, 2 or 3.

33. The compound of claim 28 or 29 or the use of claim 30 or 31, wherein A is a moiety selected from the group consisting of:



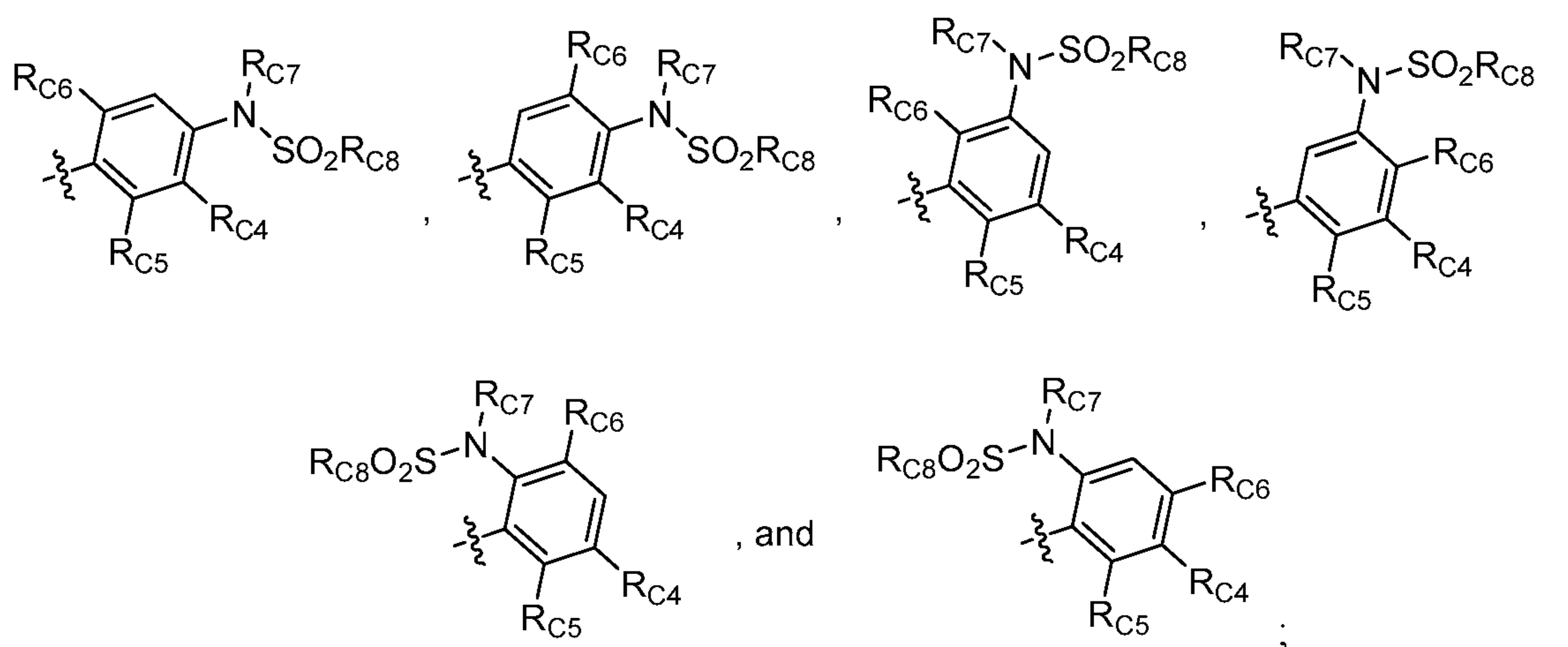
34. The compound or the use of claim 26, wherein A is a moiety selected from the group consisting of:



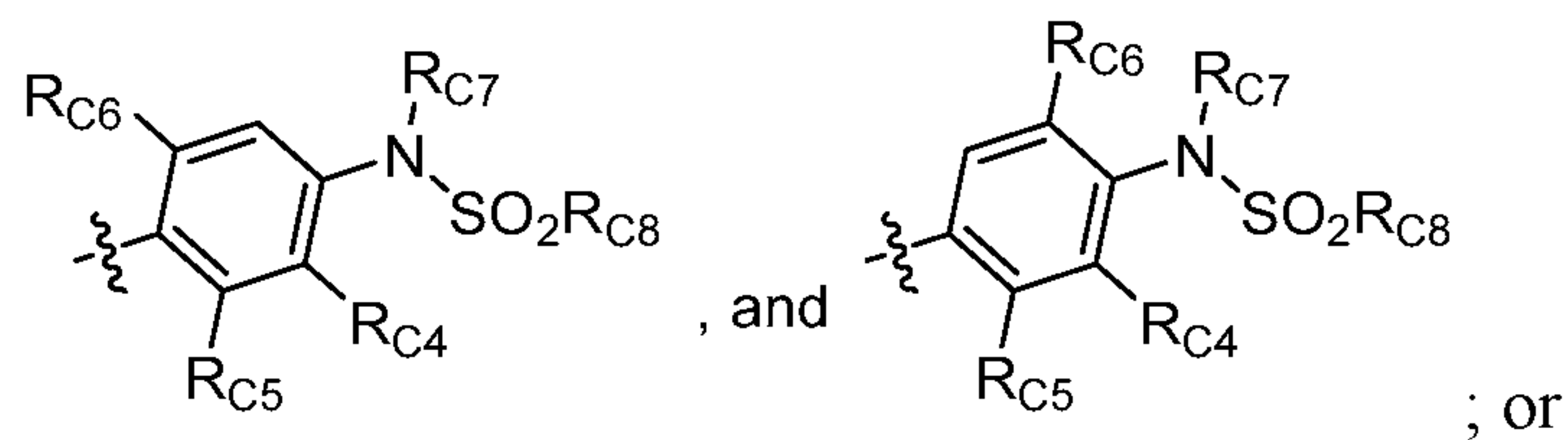


35. The compound of claim 28 or 29, the use of claim 30 or 31, or the compound or use of any of claims 31-33, wherein X is S.
36. The compound of claim 28 or 29, the use of claim 30 or 31, or the compound or use of any of claims 31-34, wherein:
- (a) X is NR_B , wherein R_B is a linear or branched C1-C6 alkyl;
 - (b) X is NR_B , wherein R_B is a linear C1-C6 alkyl selected from methyl, ethyl, n-propyl, n-butyl, n-pentyl and n-hexyl;
 - (c) X is NR_B , wherein R_B is a branched C1-C6 alkyl selected from iso-propyl, iso-pentyl, and tert-butyl.
37. The compound of claim 28 or 29, the use of claim 30 or 31, or the compound or use of any of claims 31-36, wherein:

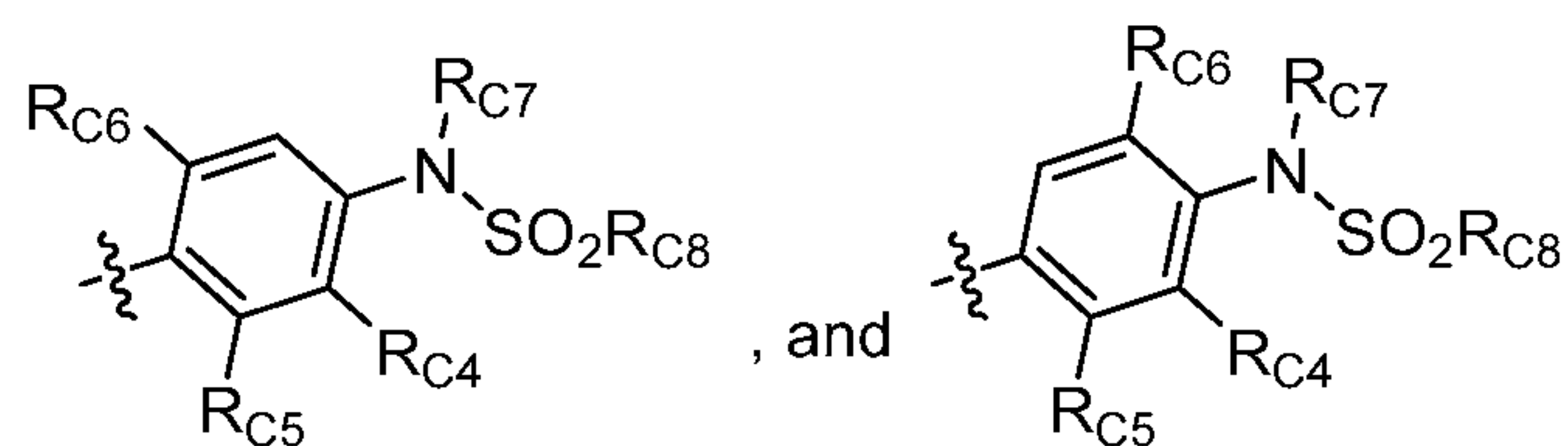
- (a) the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-\text{NR}_{C7}\text{SO}_2R_{C8}$, is a moiety selected from:



- (b) the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-\text{NR}_{C7}\text{SO}_2R_{C8}$, is a moiety selected from:

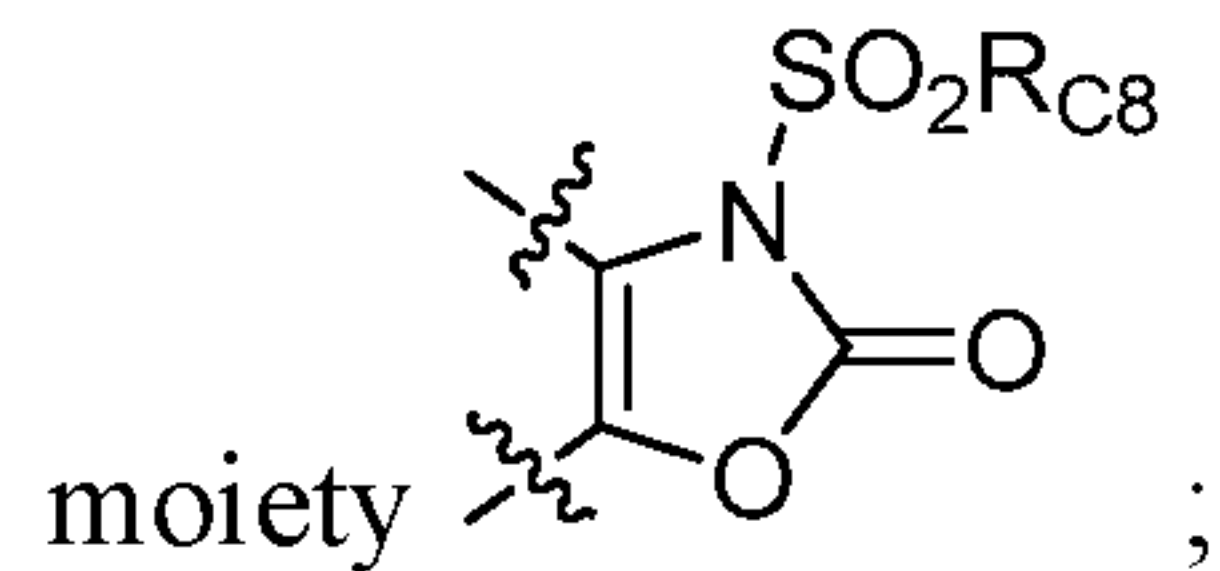


(c) the phenyl ring containing the groups $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$, $\mathbf{R}_{C6}$, and $-\mathbf{NR}_{C7}\mathbf{SO}_2\mathbf{R}_{C8}$, is a moiety selected from:



38. The compound of claim 28 or 29, the use of claim 30 or 31, or the compound or use of any of claims 31-37, wherein:

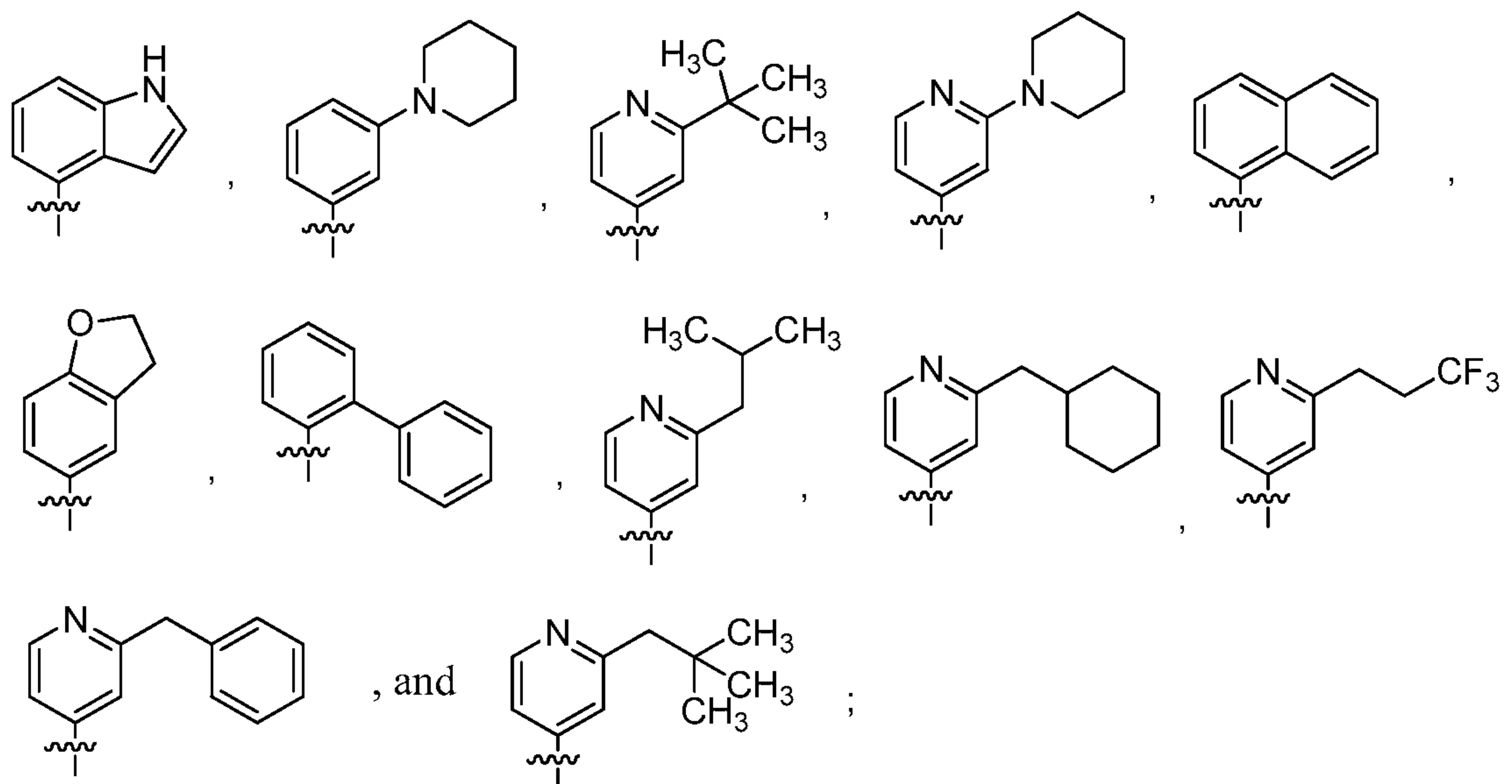
- (a) each $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$ and $\mathbf{R}_{C6}$, is independently hydrogen, halogen, CN, CF_3 , OH, C1-C3 linear or branched alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C6 cycloalkyl, C3-C6 cycloalkenyl, C1-C3 linear or branched alkoxy, $-\text{CO}_2\text{H}$, $-\text{CONR}_{10}\text{R}_{11}$, or $-\text{NHCONH}_2$; or is taken with $\mathbf{R}_{C7}$ to form the



- (b) at least one of $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$ and $\mathbf{R}_{C6}$ is hydrogen;
- (c) two of $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$ and $\mathbf{R}_{C6}$ are hydrogen;
- (d) each $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$ and $\mathbf{R}_{C6}$ is hydrogen;
- (e) at least one of $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$ and $\mathbf{R}_{C6}$ is halogen;
- (f) two of $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$ and $\mathbf{R}_{C6}$ are halogen;
- (g) each $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$ and $\mathbf{R}_{C6}$ is halogen;
- (h) one of $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$ and $\mathbf{R}_{C6}$ is hydrogen, and the remaining two of $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$ and $\mathbf{R}_{C6}$ are halogen; or
- (i) two of $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$ and $\mathbf{R}_{C6}$ are hydrogen, and the remaining one of $\mathbf{R}_{C4}$, $\mathbf{R}_{C5}$ and $\mathbf{R}_{C6}$ is halogen.

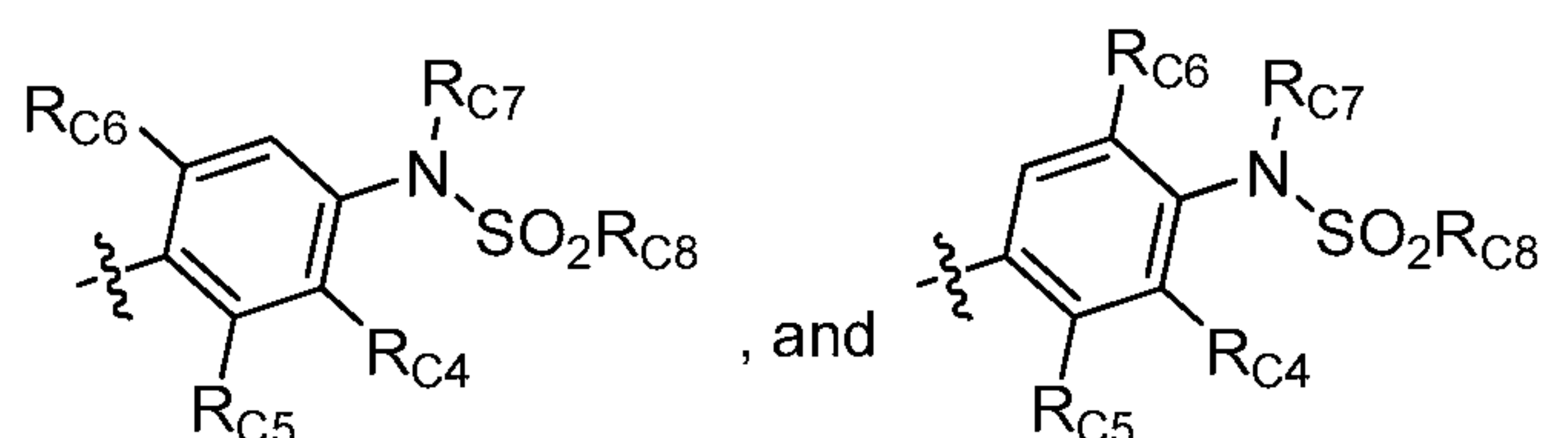
39. The compound of claim 28 or 29, the use of claim 30 or 31, or the compound or use of any of claims 31-38, wherein:

A is a moiety selected from



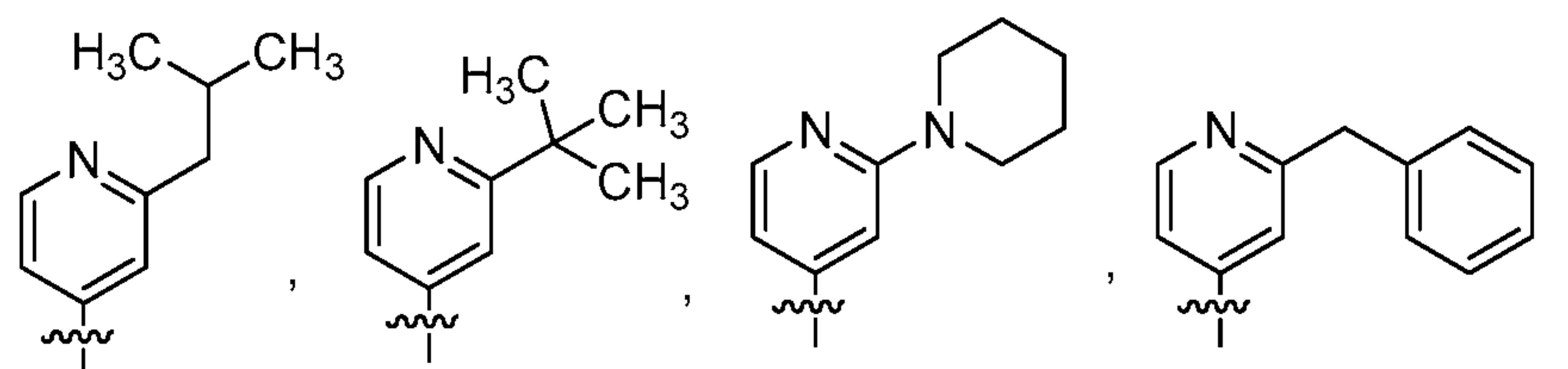
X is S, and

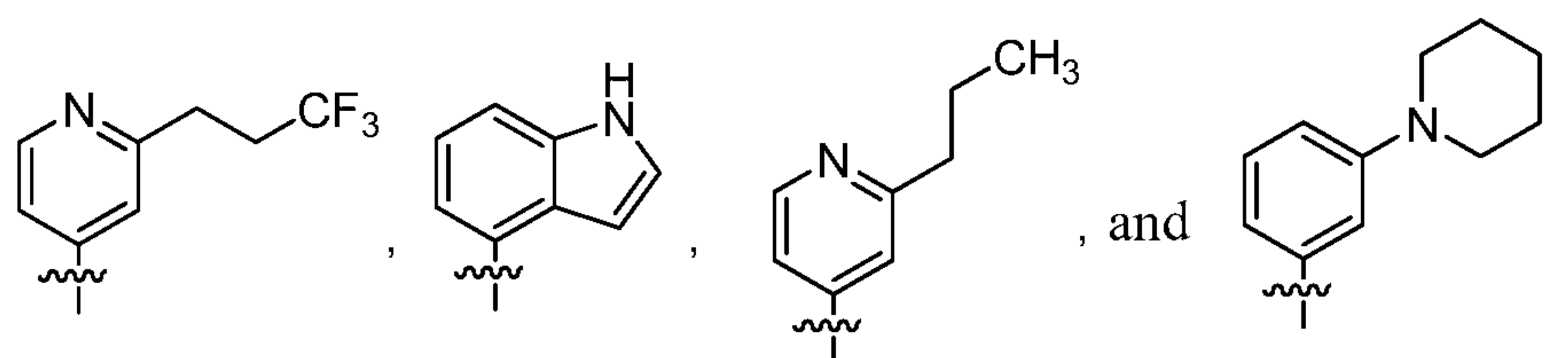
the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is a moiety selected from:



40. The compound of claim 28 or 29, the use of claim 30 or 31, or the compound or use of any of claims 31-38, wherein:

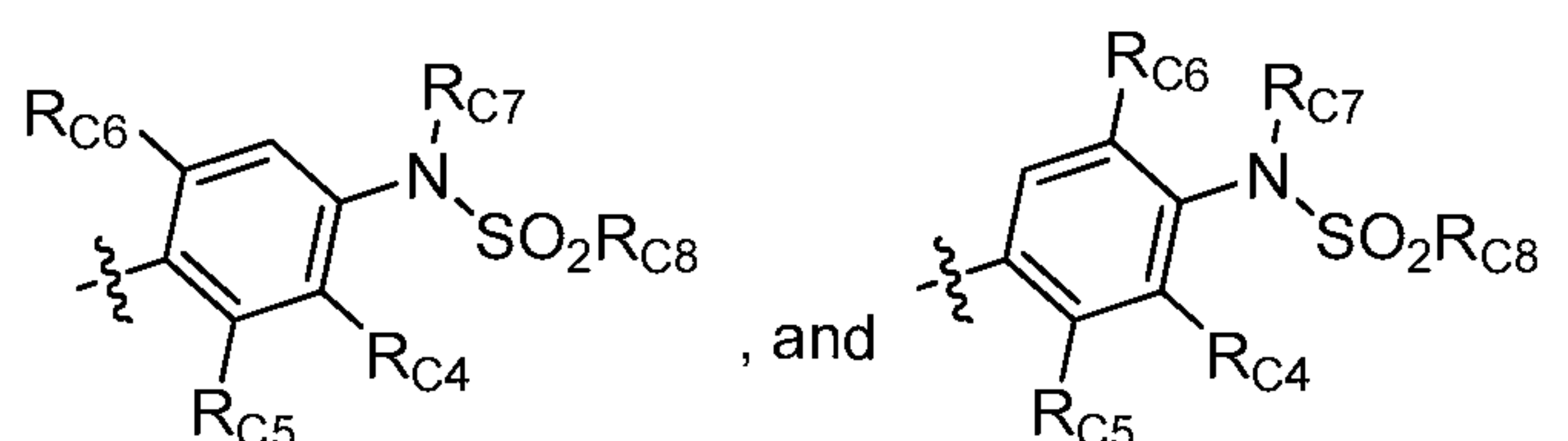
A is a moiety selected from



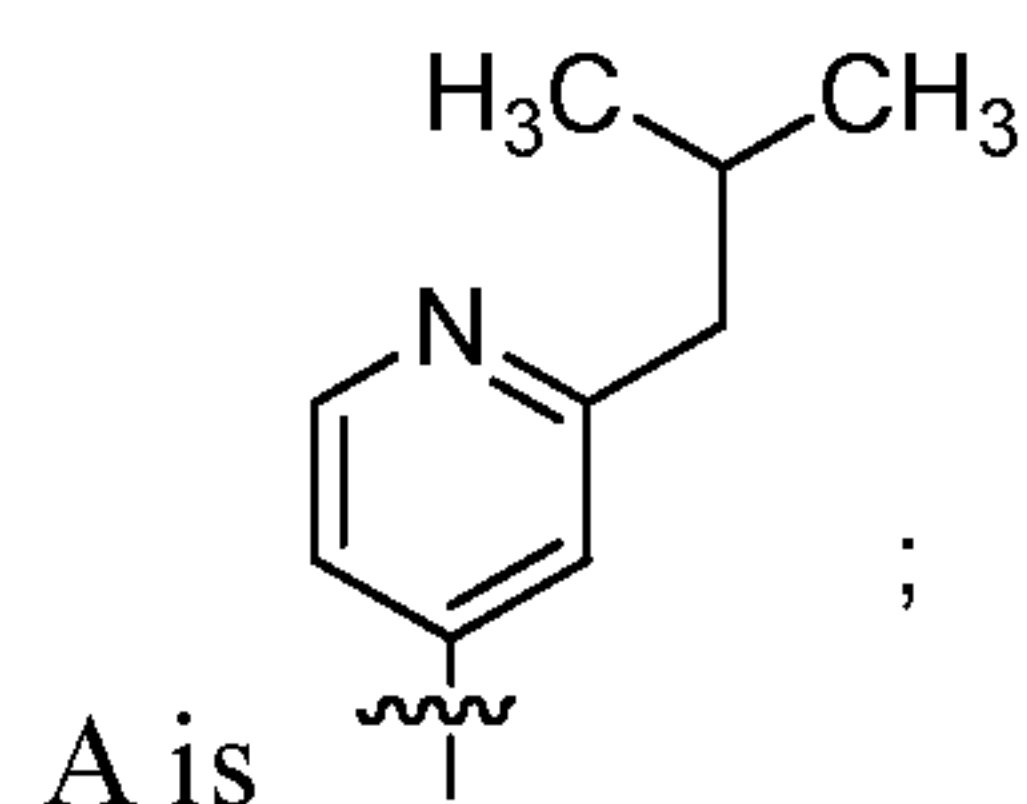


X is S, and

the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} and $-NR_{C7}SO_2R_{C8}$, is a moiety selected from

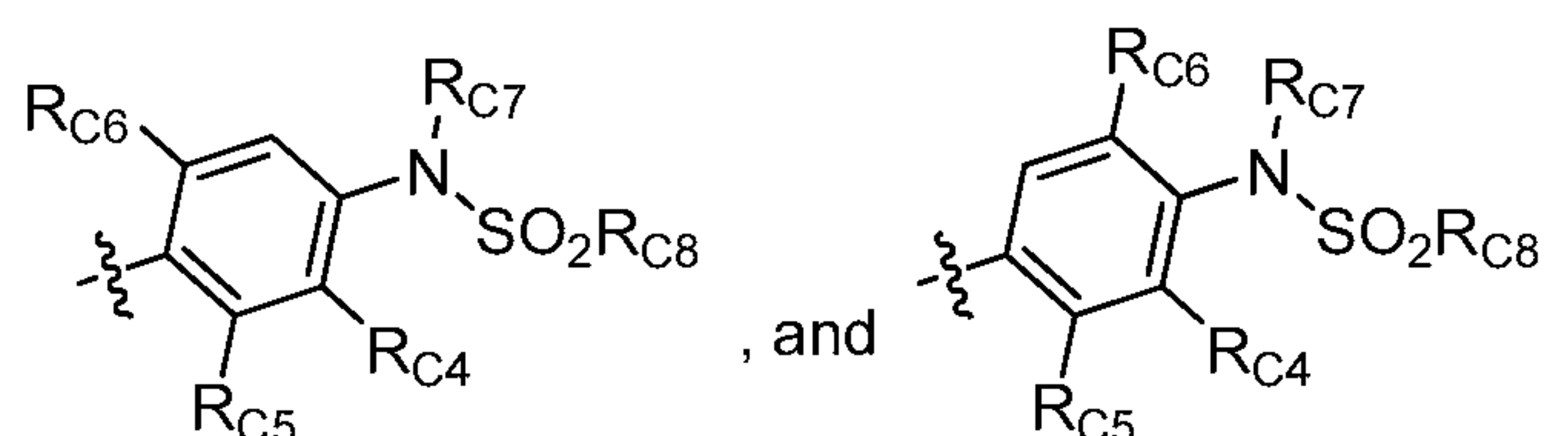


41. The compound of claim 28 or 29, the use of claim 30 or 31, or the compound or use of any of claims 31-40, wherein:

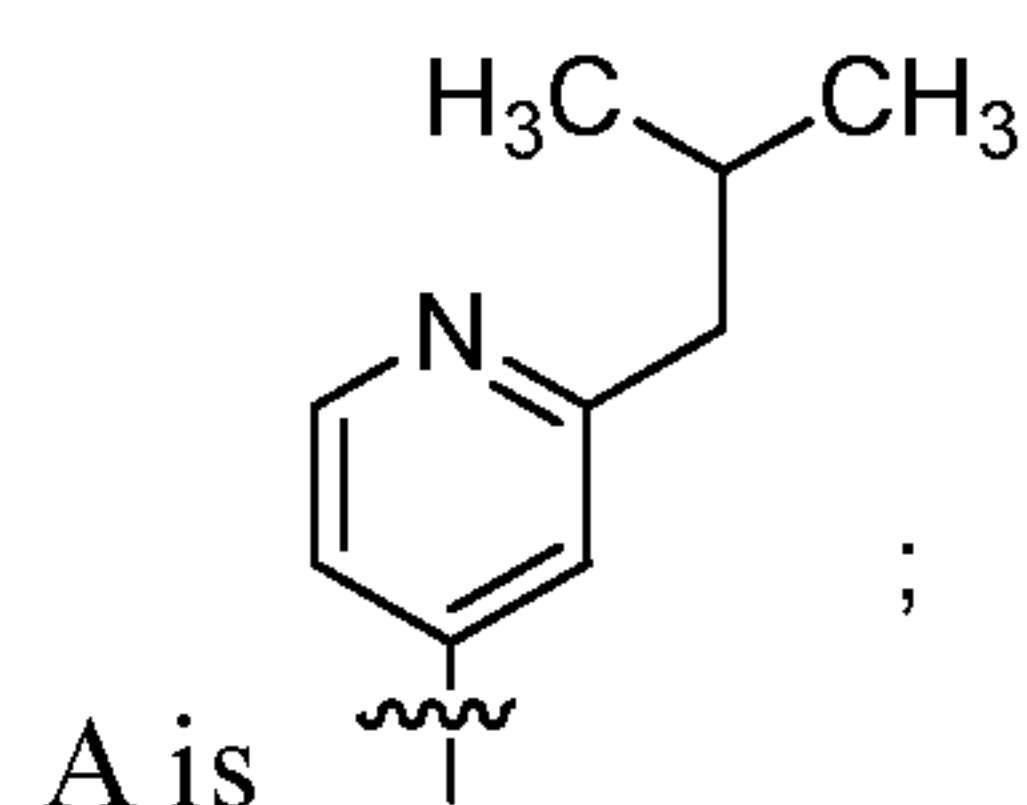


X is S, and

the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is selected from

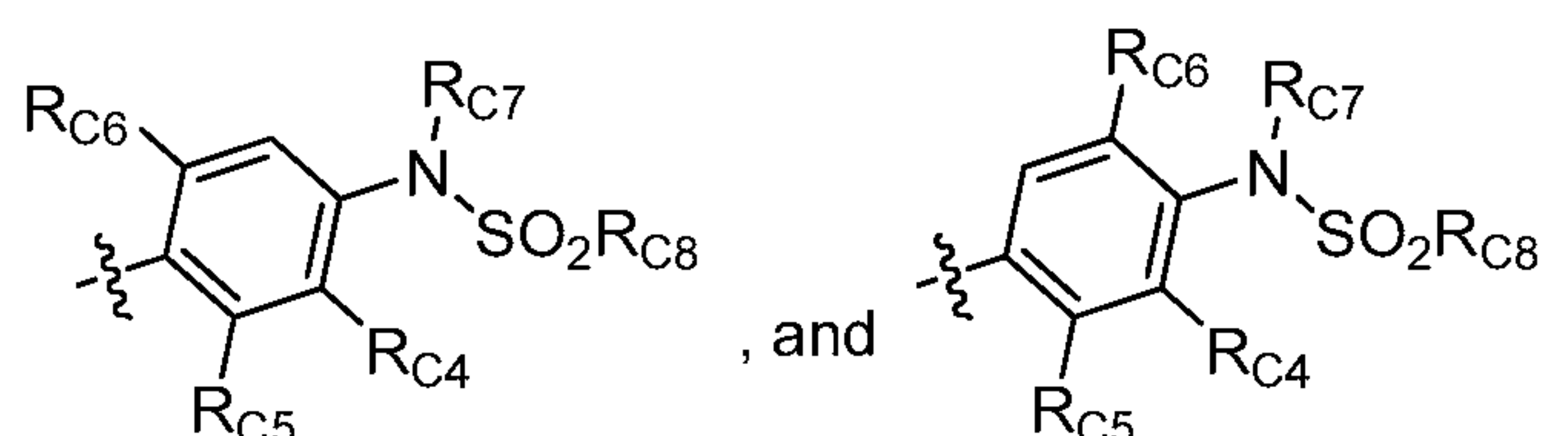


42. The compound of claim 28 or 29, the use of claim 30 or 31, or the compound or use of any of claims 31-41, wherein the compound is of Formula (IIa).
43. The compound of claim 28 or 29, the use of claim 30 or 31, or the compound or use of any of claims 31-41, wherein the compound is of Formula (IIb).
44. The compound of claim 28 or 29, the use of claim 30 or 31, or the compound or use of any of claims 31-34, wherein the compound is of Formula (IIa), wherein:



X is S;

the phenyl ring containing the groups R_{C4} , R_{C5} , R_{C6} , and $-NR_{C7}SO_2R_{C8}$, is selected from



45. The compound of claim 28 or 29 or the use of claim 30 or 31, wherein the compound is selected from the group consisting of:

1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(1-isobutyl-1H-pyrazol-5-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1,2-dimethyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1-propyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2,3-dimethyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(3-propyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(1,2-dipropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(6-(butylamino)-2-isobutylpyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(6-(dibutylamino)-2-isobutylpyrimidin-4-yl)thiazol-4-yl)phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(6-amino-2-isobutylpyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(4-(2-(2-aminopyrimidin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-(propylamino)pyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-(dibutylamino)pyrimidin-4-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2'-propyl-2,4'-bithiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(5-propyl-1,2,4-thiadiazol-3-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(5-propyl-1,2,4-oxadiazol-3-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2'-propyl-2,5'-bithiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(5-propyl-1,3,4-thiadiazol-2-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(5-propyl-1,3,4-oxadiazol-2-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(1-isobutyl-6-oxo-1,6-dihydropyridin-3-yl)thiazol-4-yl)phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(4-fluoro-3-isobutylphenyl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(2-bromo-3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3,5-dichloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-(trifluoromethyl)phenyl)methanesulfonamide;

N-(2-cyclopropyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methylphenyl)methanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-isopropylphenyl)methanesulfonamide;

N-(2-ethynyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-ethynyl-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-6-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-6-methylphenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(4-(2-tert-butylpyridin-4-yl)-1-methyl-1H-imidazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(1-methyl-2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-3-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-5-chloro-4-(1-methyl-2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(4-(2-tert-butylpyridin-4-yl)oxazol-2-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)oxazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-(dimethylamino)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(trifluoromethylsulfonyl)acrylamide;

N-(3-chloro-4-(2-(2-(methylsulfonamido)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-(3,3,3-trifluoropropyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 1,1,1-trifluoro-N-(2-hydroxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-hydroxyphenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(2-methoxy-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;
 1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-(trifluoromethyl)phenyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-neopentylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 6-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-(trifluoromethylsulfonyl)benzo[d]oxazol-2(3H)-one;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,2,2,2-pentafluoroethanesulfonamide;
 1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide;
 1,1,1-trifluoro-N-{2-methoxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;
 N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-2-methoxyphenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(2-aminopyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-
 1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-{2-hydroxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-
 yl]phenyl}methanesulfonamide;
 N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-(4-{2-[2-(2,2-dimethylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}-2-methoxyphenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-
 yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(4-(piperidine-1-carbonyl)phenyl)thiazol-4-yl)phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-
 chlorophenyl}methanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-
 chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-
 methylbenzene-1-sulfonamide;

N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(quinolin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-chloropyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxopyrrolidin-1-yl)ethyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-yl)ethyl)methanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-(2-oxoimidazolidin-1-yl)ethyl)methanesulfonamide;
 N-(2-bromo-4-(2-(2-(piperidin-1-yl)pyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 2-(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)ethyl acetate;
 (2-(N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)ethoxy)methyl acetate;
 N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-N-(2-{[4-(3-chlorophenyl)-2-oxo-1,3,2λ⁵-dioxaphosphinan-2-yl]oxy}ethyl)-1,1,1-trifluoromethanesulfonamide;
 (N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)methyl acetate;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(methoxymethyl)methanesulfonamide;
 N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-N-([4-(3-chlorophenyl)-2-oxo-1,3,2λ⁵-dioxaphosphinan-2-yl]oxy)methyl)-1,1,1-trifluoromethanesulfonamide;
 methyl 4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl(trifluoromethylsulfonyl)carbamate;
 sodium (N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethylsulfonamido)methyl phosphate;

1-(N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethylsulfonamido)ethyl isobutyrate;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-(2-oxooxazolidin-3-yl)ethyl)methanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-(pyrrolidin-1-yl)ethyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(2-(diethylamino)ethyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-N-(2-(dimethylamino)ethyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(3-fluoro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-(2-hydroxyethyl)methanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoro-N-methylmethanesulfonamide;

1,1,1-trifluoro-N-(3-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(2-bromo-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-methyl-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(2-butylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide

1,1,1-trifluoro-N-(4-(2-(2-(methoxymethyl)pyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(4,6-dipropylpyridin-2-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(4-(2-(4-propylpyridin-2-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(4-(2-(2,6-dipropylpyridin-3-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(2-(cyclohexylmethyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 1,1,1-trifluoro-N-(4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)-3-methoxyphenyl)methanesulfonamide;
 N-(3-chloro-4-(2-(2-((trifluoromethylsulfonyl)methyl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(1H-pyrrolo[2,3-b]pyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-propyl-3H-imidazo[4,5-b]pyridin-7-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 5-(4-(2-chloro-4-(trifluoromethylsulfonamido)phenyl)thiazol-2-yl)-N-cyclopropyl-2-fluorobenzamide;
 5-(4-(2-chloro-4-(trifluoromethylsulfonamido)phenyl)thiazol-2-yl)-N-cyclohexyl-2-fluorobenzamide;
 N-(4-(2-(1H-indol-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(3-(piperidin-1-yl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-(piperidin-1-yl)pyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-4-(2-(2-tert-butylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(2-bromo-5-chloro-4-(2-(2-propylpyridin-4-yl)-1H-imidazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide; and
 N-(2-bromo-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

46. The compound of claim 28 or 29 or the use of claim 30 or 31, wherein the compound is selected from the group consisting of:

1,1,1-trifluoro-N-(4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

1,1,1-trifluoro-N-(3-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)methanesulfonamide;

N-(3-chloro-4-(2-(1-isobutyl-1H-pyrazol-5-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-(2-methoxy-4-{2-[2-(2-methylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)methanesulfonamide;

1,1,1-trifluoro-N-{2-methoxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-{4-[2-(2-tert-butylpyridin-4-yl)-1,3-thiazol-4-yl]-2-methoxyphenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{4-[2-(2-aminopyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-methanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

1,1,1-trifluoro-N-{2-hydroxy-4-[2-(2-propylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}methanesulfonamide;

N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(4-{2-[2-(2,2-dimethylpropyl)pyridin-4-yl]-1,3-thiazol-4-yl}-2-methoxyphenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(2-trifluoromethanesulfonamidopyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-(2-(4-(piperidine-1-carbonyl)phenyl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[1-(3-methylbutyl)-1H-pyrazol-5-yl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{4-[5-(2-tert-butylpyridin-4-yl)thiophen-3-yl]-3-
 chlorophenyl}methanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclohexylmethyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(naphthalen-1-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-6-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(4-{2-[3-(benzyloxy)-4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}-3-
 chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2-phenylphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(isoquinolin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(4-methylpiperazin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(dimethyl-1,2-oxazol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-[4-(2-chloro-4-trifluoromethanesulfonamidophenyl)-1,3-thiazol-2-yl]phenyl}-4-
 methylbenzene-1-sulfonamide;
 N-{3-chloro-4-[2-(3,4-dimethoxyphenyl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-
 1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(2,3-dihydro-1-benzofuran-5-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-
 trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(hydroxymethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-
 trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(3-methylpyridin-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-[3-chloro-4-(2-{5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl}-1,3-thiazol-4-yl)phenyl]-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(1-benzothiophen-3-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[4-fluoro-2-(pyrrolidin-1-ylmethyl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(cyclopentylamino)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{3-chloro-4-[2-(1H-indol-3-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide; and
 N-(3-chloro-4-(2-(quinolin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide.

47. The compound of claim 28 or 29 or the use of claim 30 or 31, wherein the compound is selected from the group consisting of:

N-(3-chloro-4-(2-(2-propylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(4-(2-(2-tert-butylpyridin-4-yl)thiazol-4-yl)-3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-(2-(2-isobutylpyridin-4-yl)thiazol-4-yl)phenyl)-1,1,1-trifluoromethanesulfonamide;
 N-{4-[2-(2-benzylpyridin-4-yl)-1,3-thiazol-4-yl]-3-chlorophenyl}-1,1,1-trifluoromethanesulfonamide;
 N-(3-chloro-4-{2-[2-(3,3,3-trifluoropropyl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide;

N-{3-chloro-4-[2-(1H-indol-4-yl)-1,3-thiazol-4-yl]phenyl}-1,1,1-trifluoromethanesulfonamide;

N-(3-chloro-4-{2-[2-(piperidin-1-yl)pyridin-4-yl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide; and

N-(3-chloro-4-{2-[3-(piperidin-1-yl)phenyl]-1,3-thiazol-4-yl}phenyl)-1,1,1-trifluoromethanesulfonamide.

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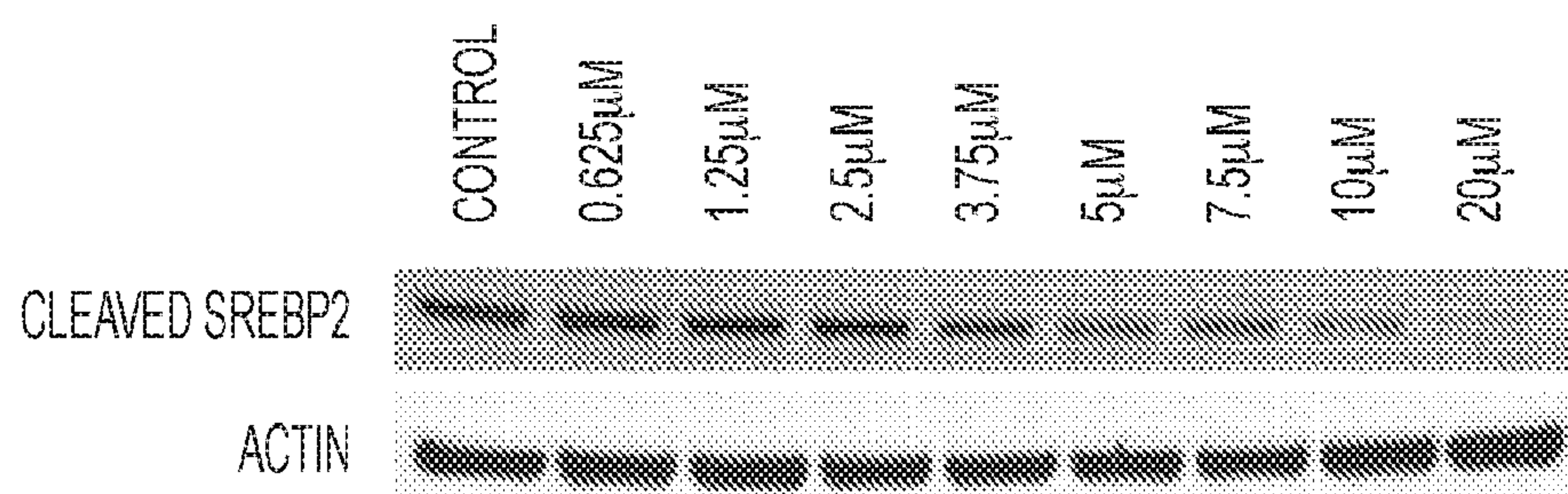


FIG. 1A

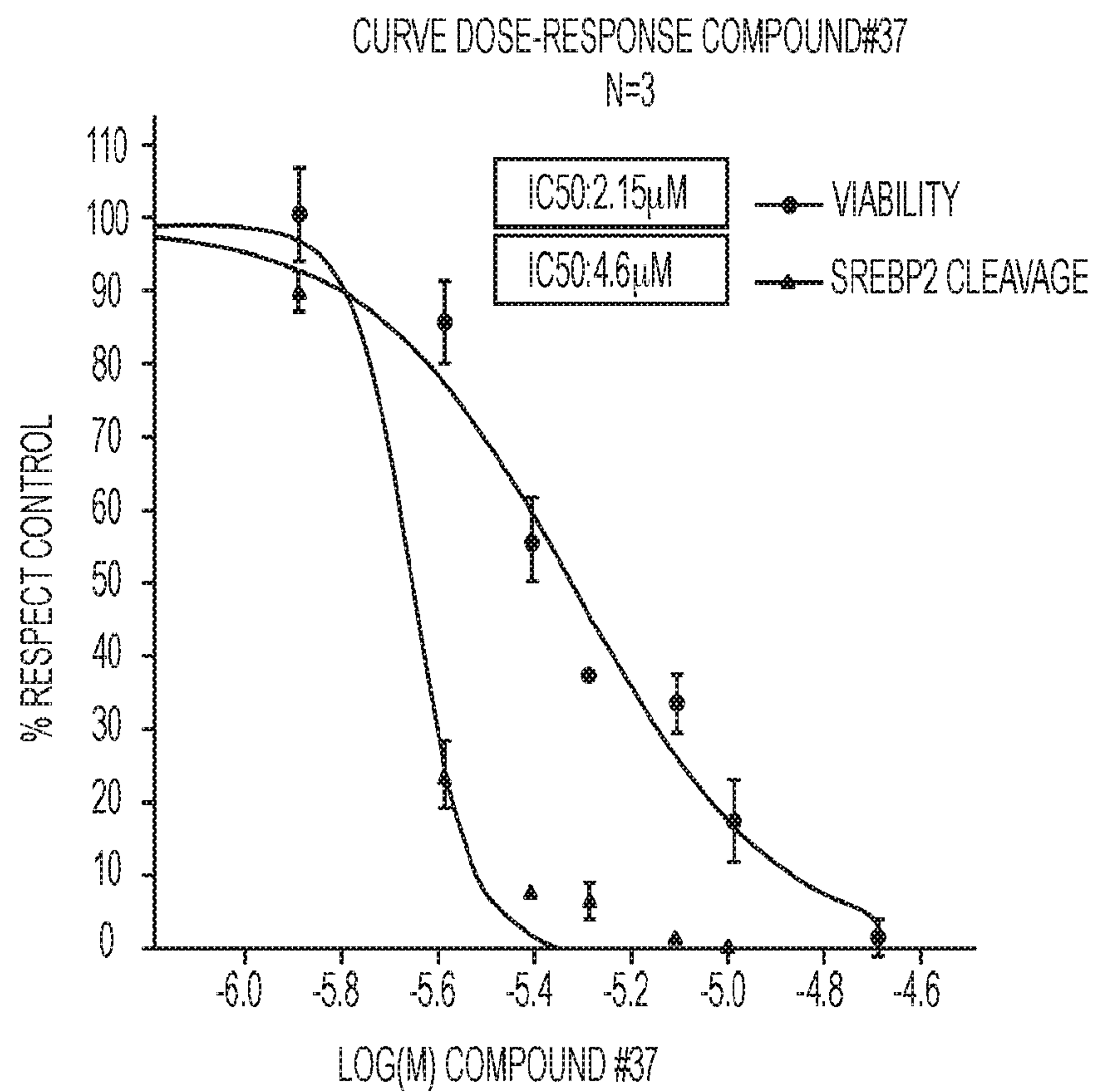


FIG. 1B

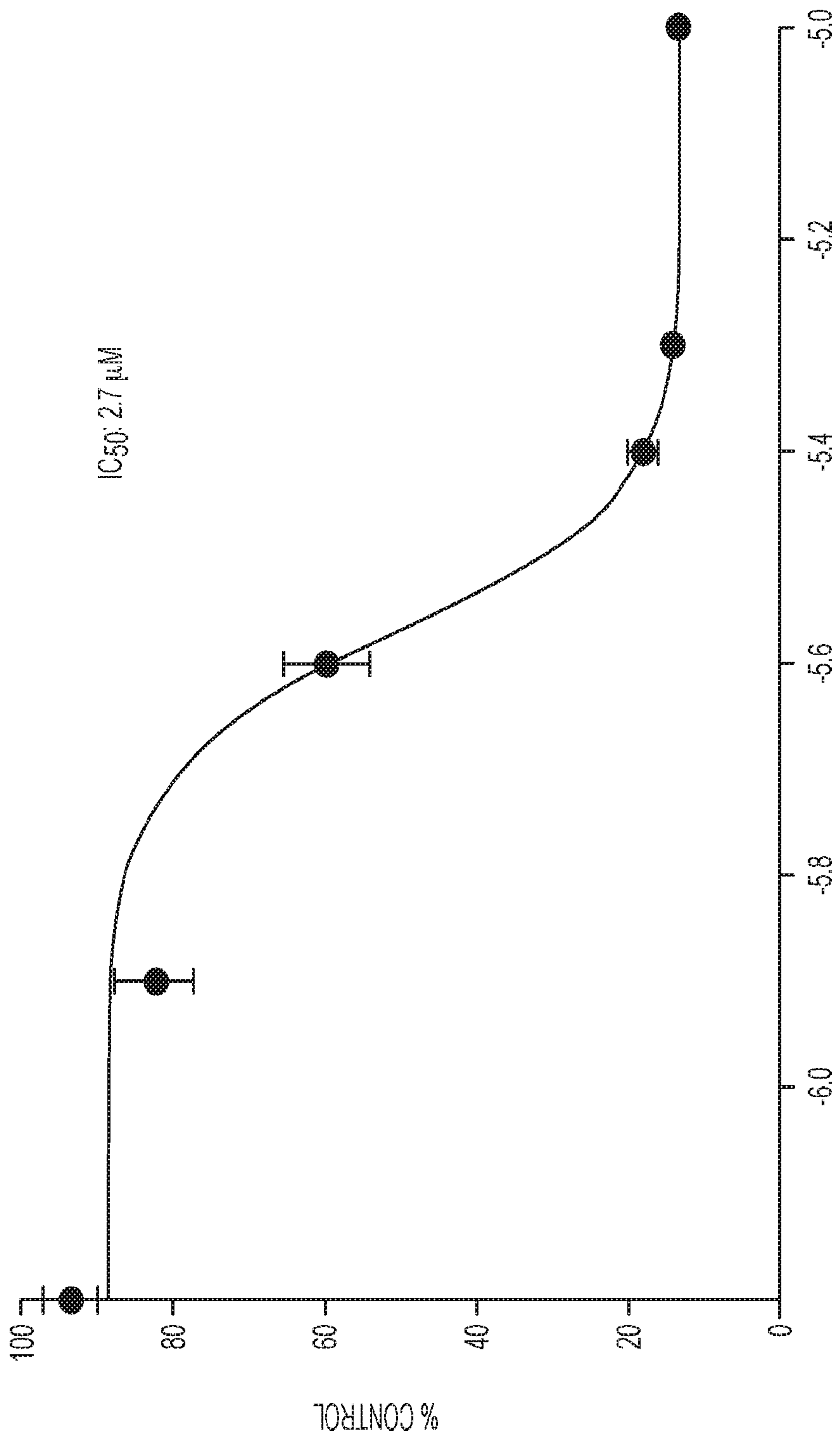


FIG. 1C

COMPOUND #37
MOUSE PK

PO(10MG/KG)	
PK PARAMETERS	MEAN
C MAX (μM)	32.4
T MAX (h)	1
AUC FAST (μM*h)	294
TERMINAL t _{1/2} (h)	4.23
BIOAVAILABILITY(%)	151%

FIG. 2A

COMPOUND #37
DOG ORAL PK

PO DOSE LEVEL (MG/KG)	2(N=3)		10(N=1)	
PK PARAMETERS	MEAN	SD	DOG2002	SD
C MAX (μM)	27.0	1.21	182	-
T MAX (h)	1.5	0	1.5	-
AUC FAST (μM*h)	449	17.3	4200	-
TERMINAL t _{1/2} (h)	10.7	2.05	11.3	-
BIOAVAILABILITY	99.3%	20.1%	62.9%	-

FIG. 2B

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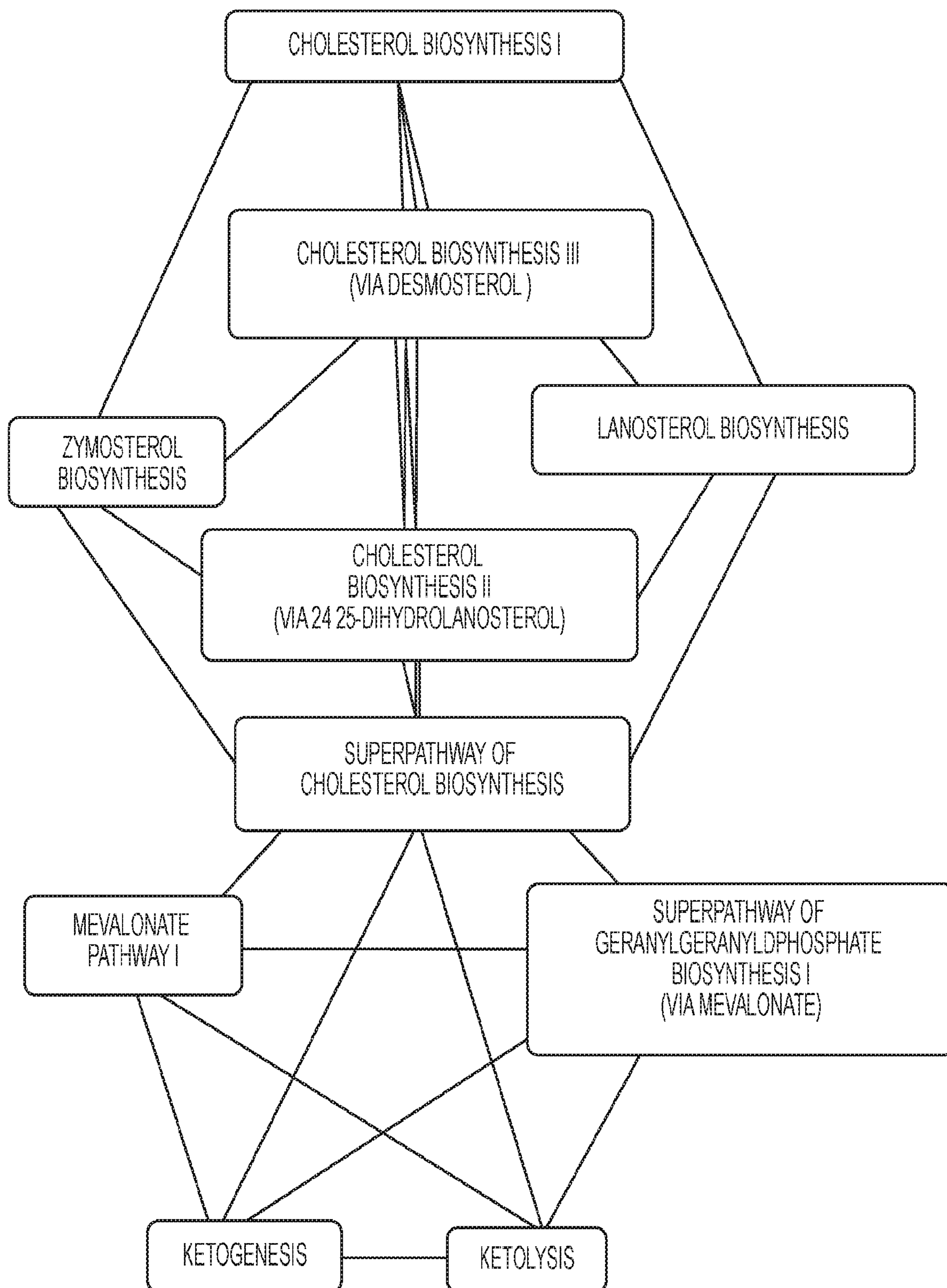


FIG. 3

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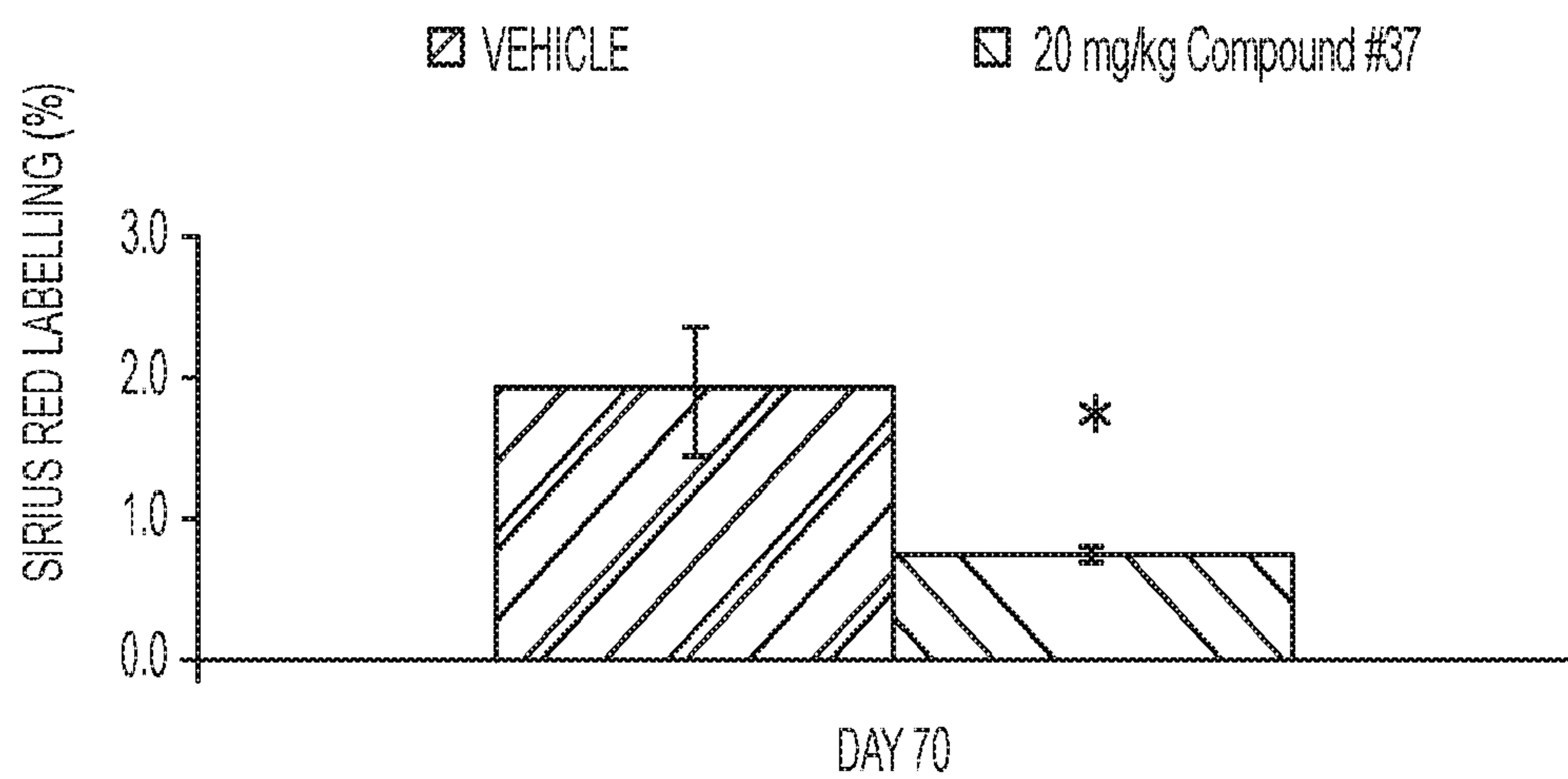


FIG. 4

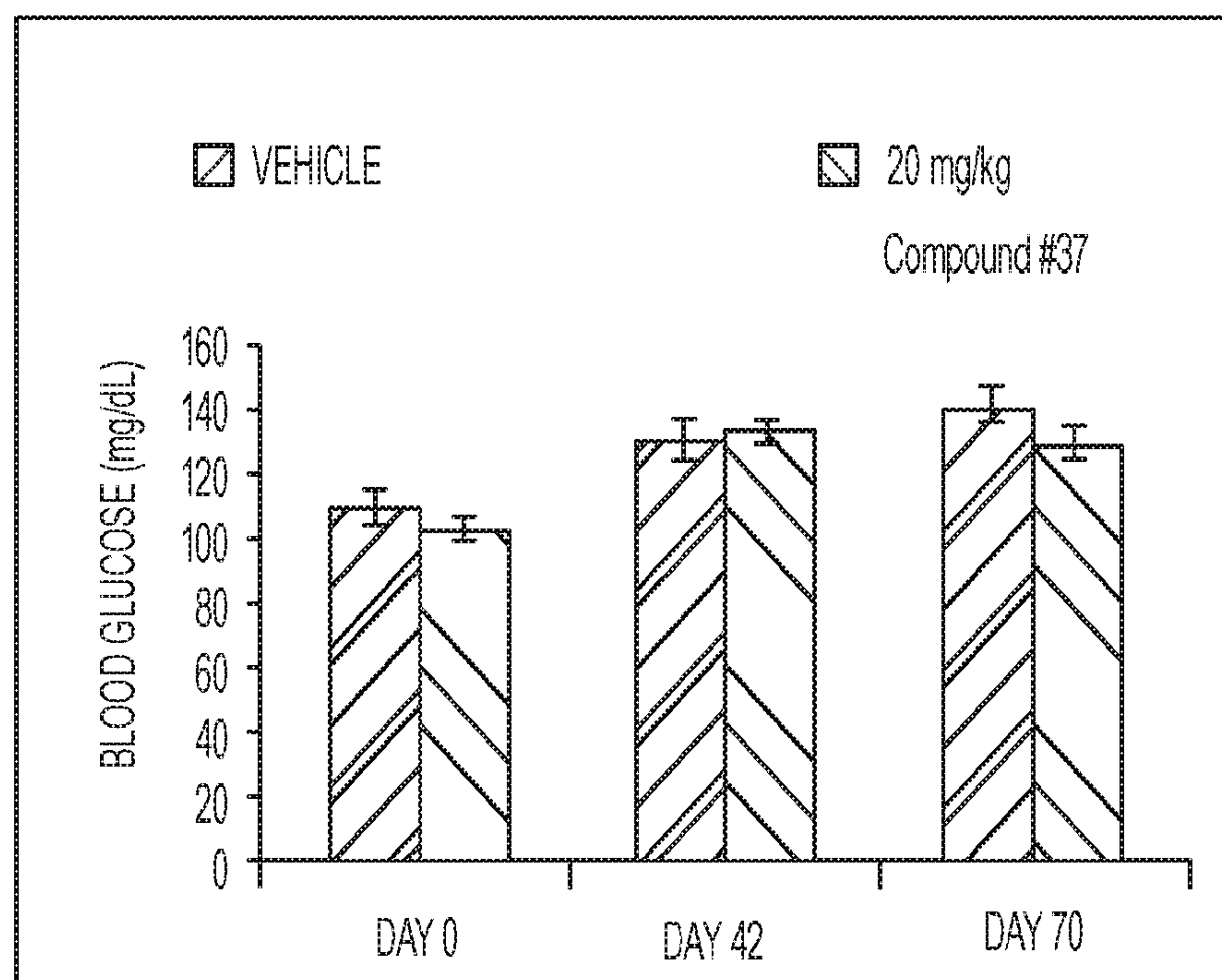


FIG. 5A

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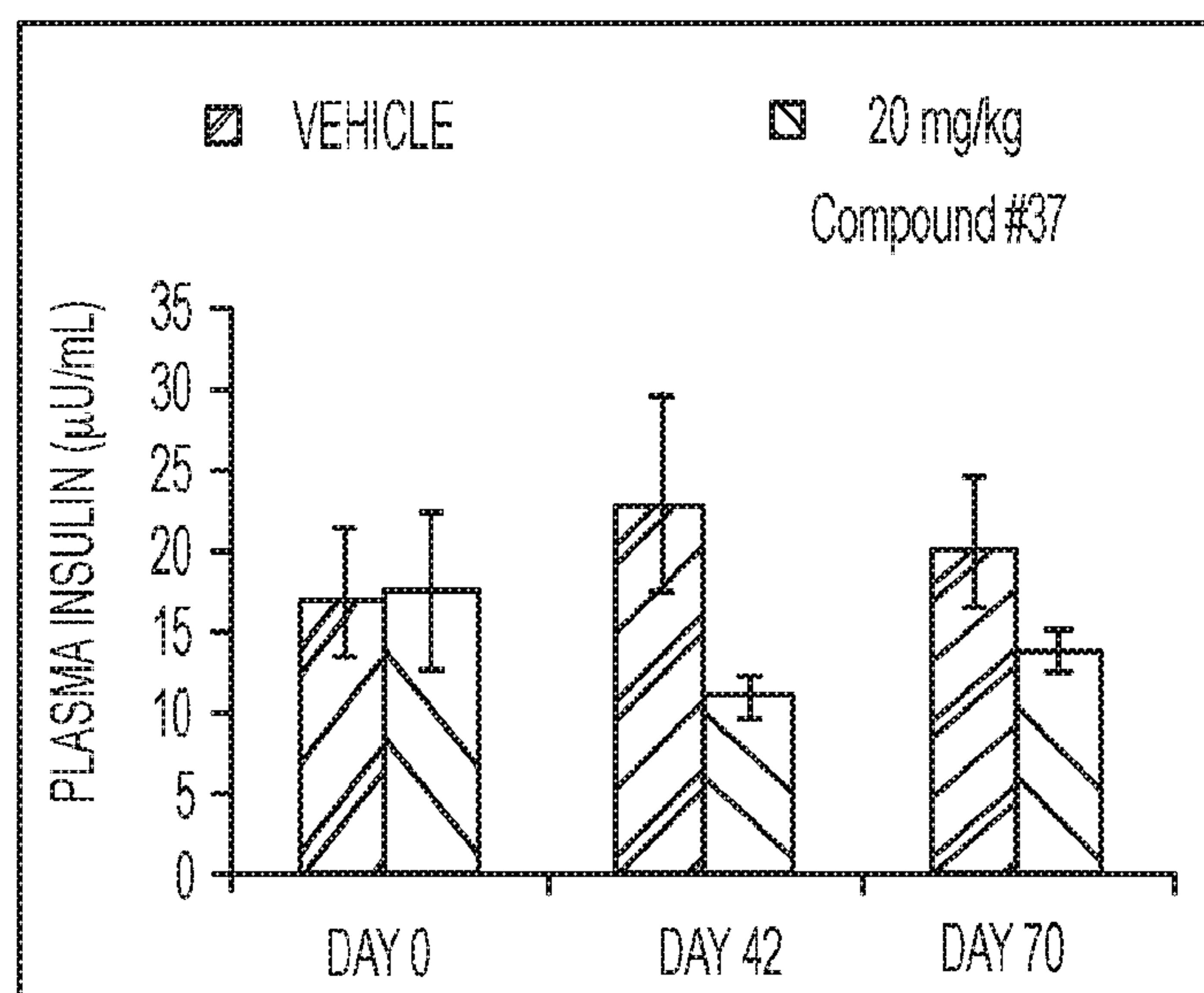


FIG. 5B

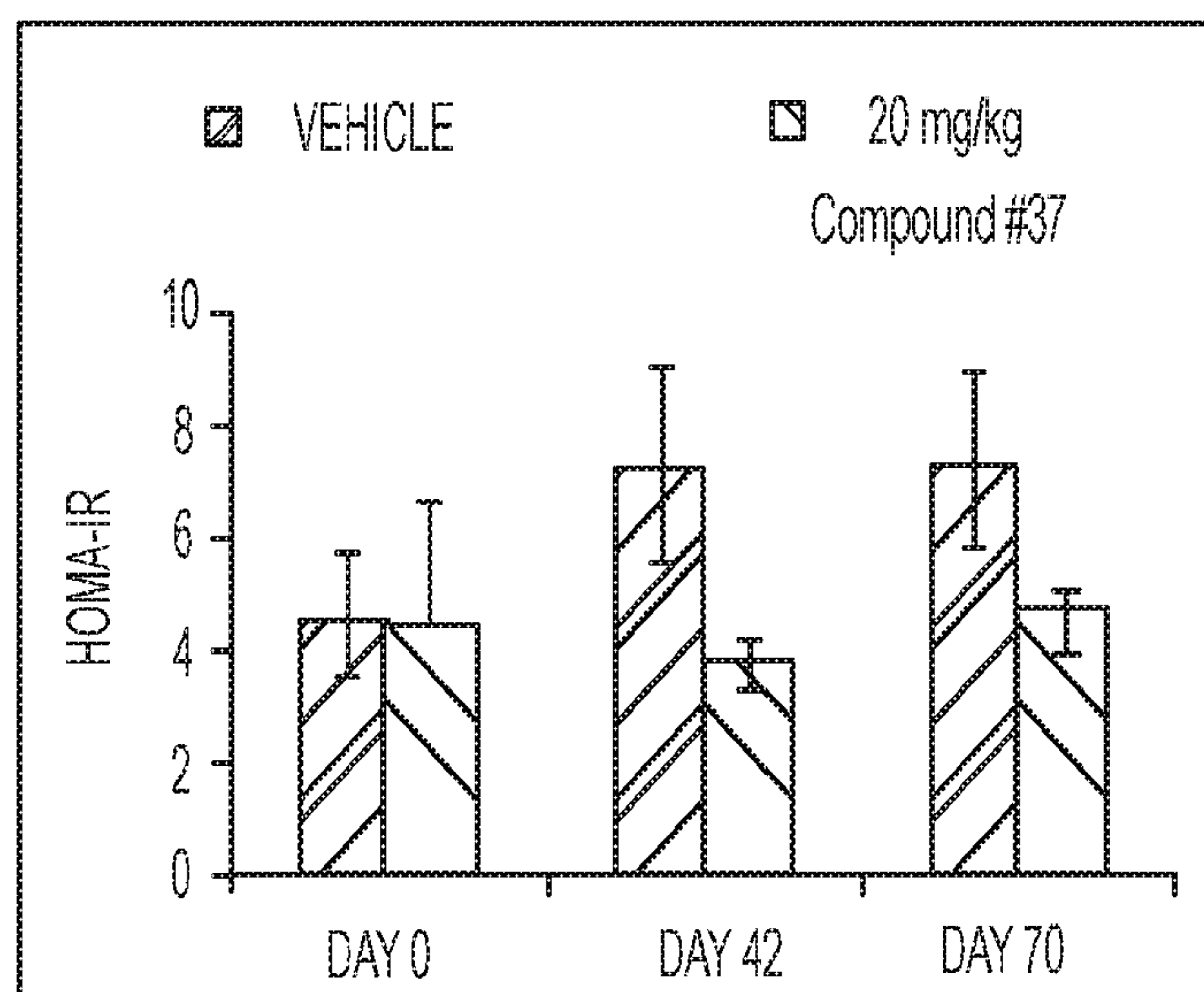


FIG. 5C

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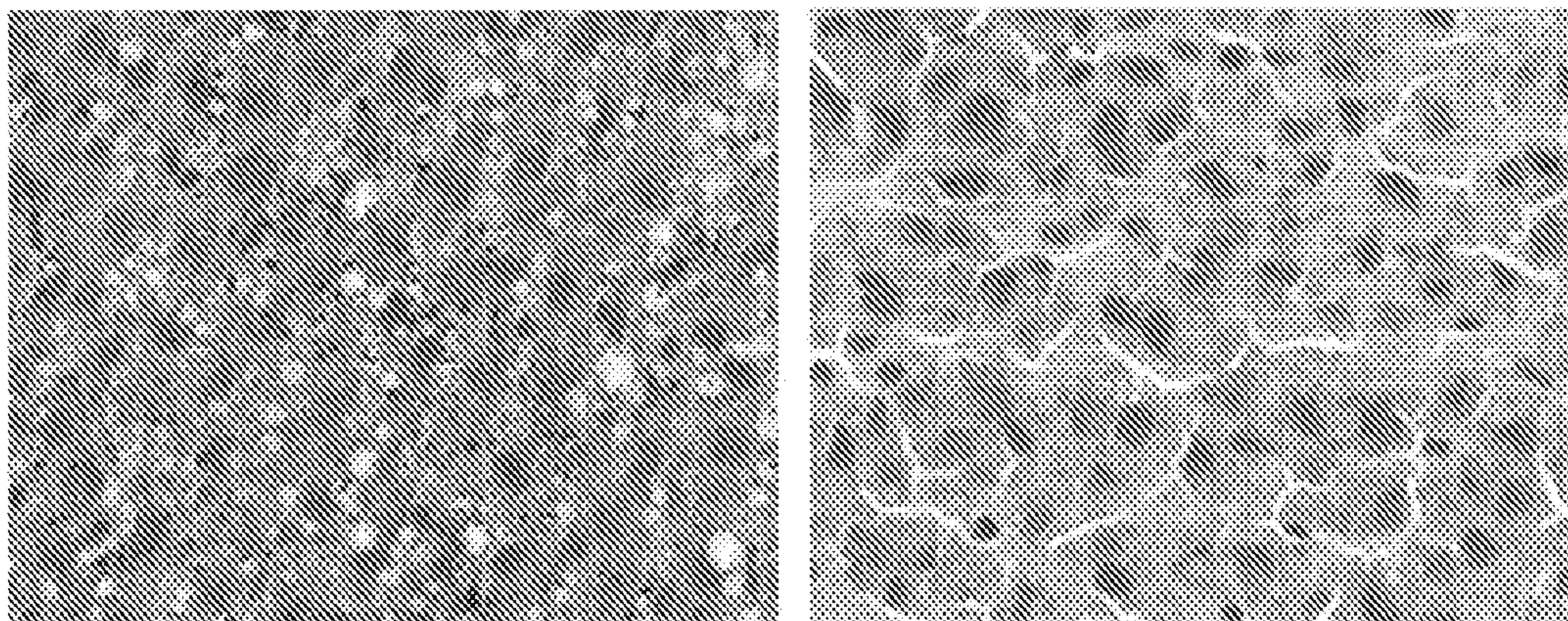


FIG. 6

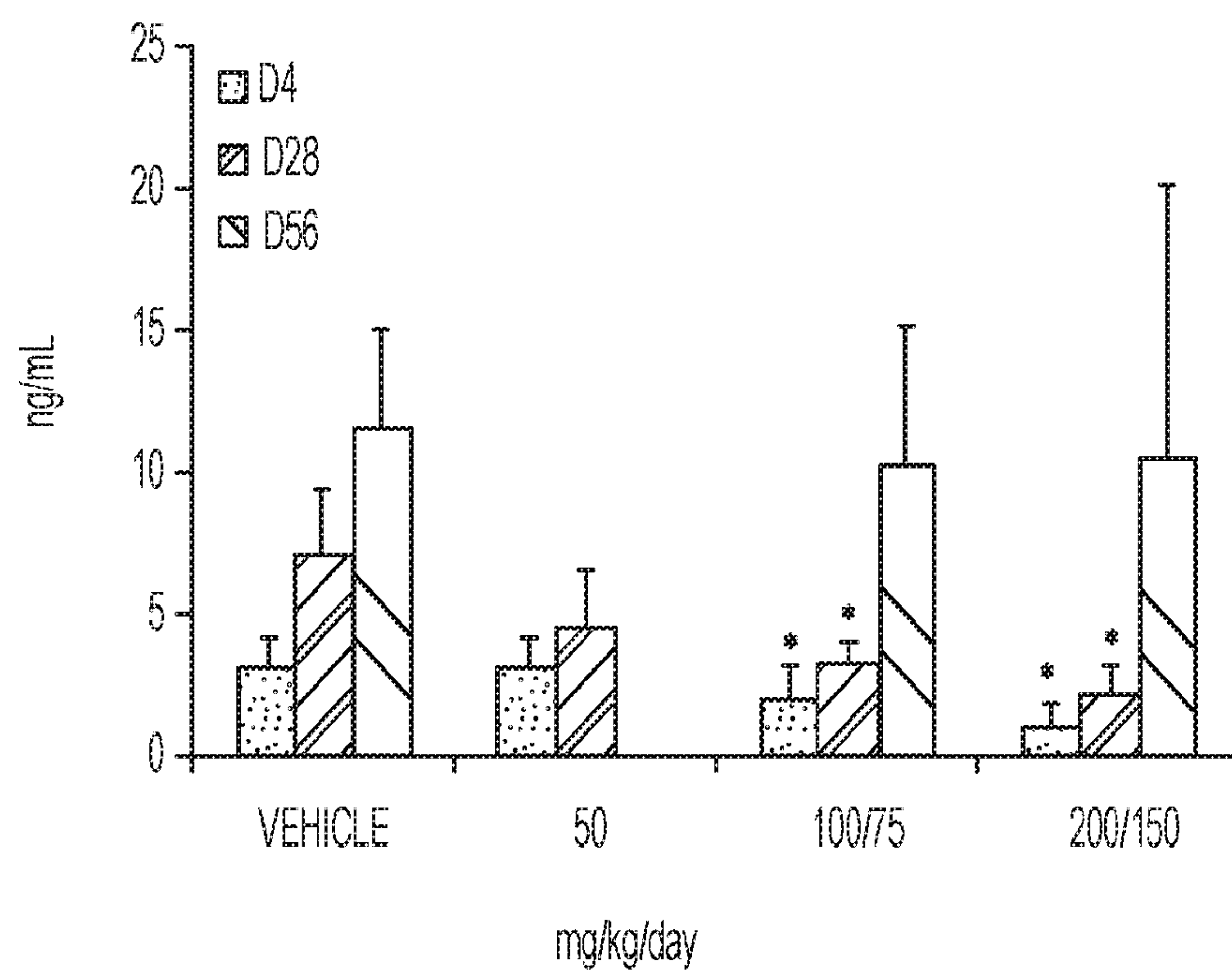


FIG. 7

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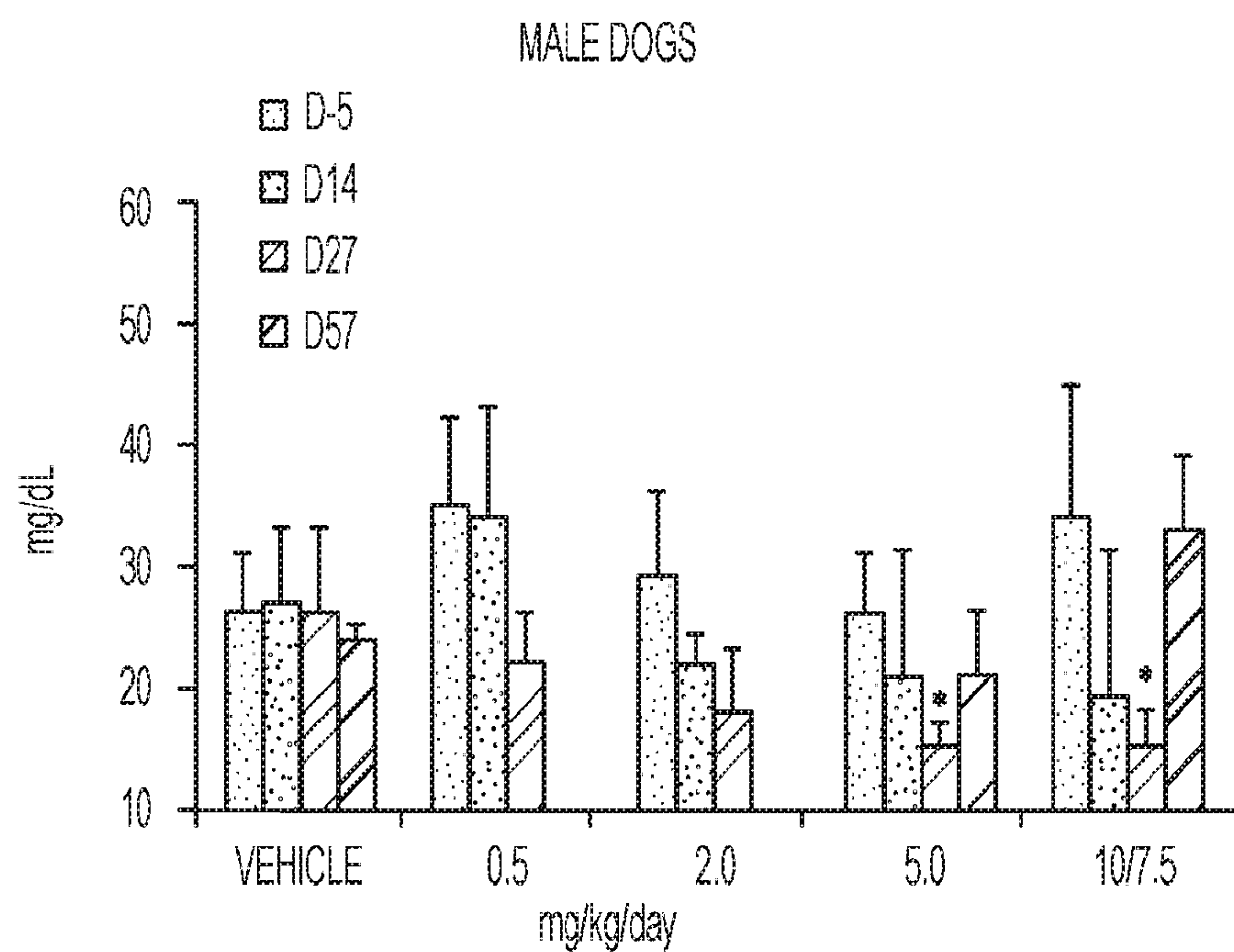


FIG. 8A

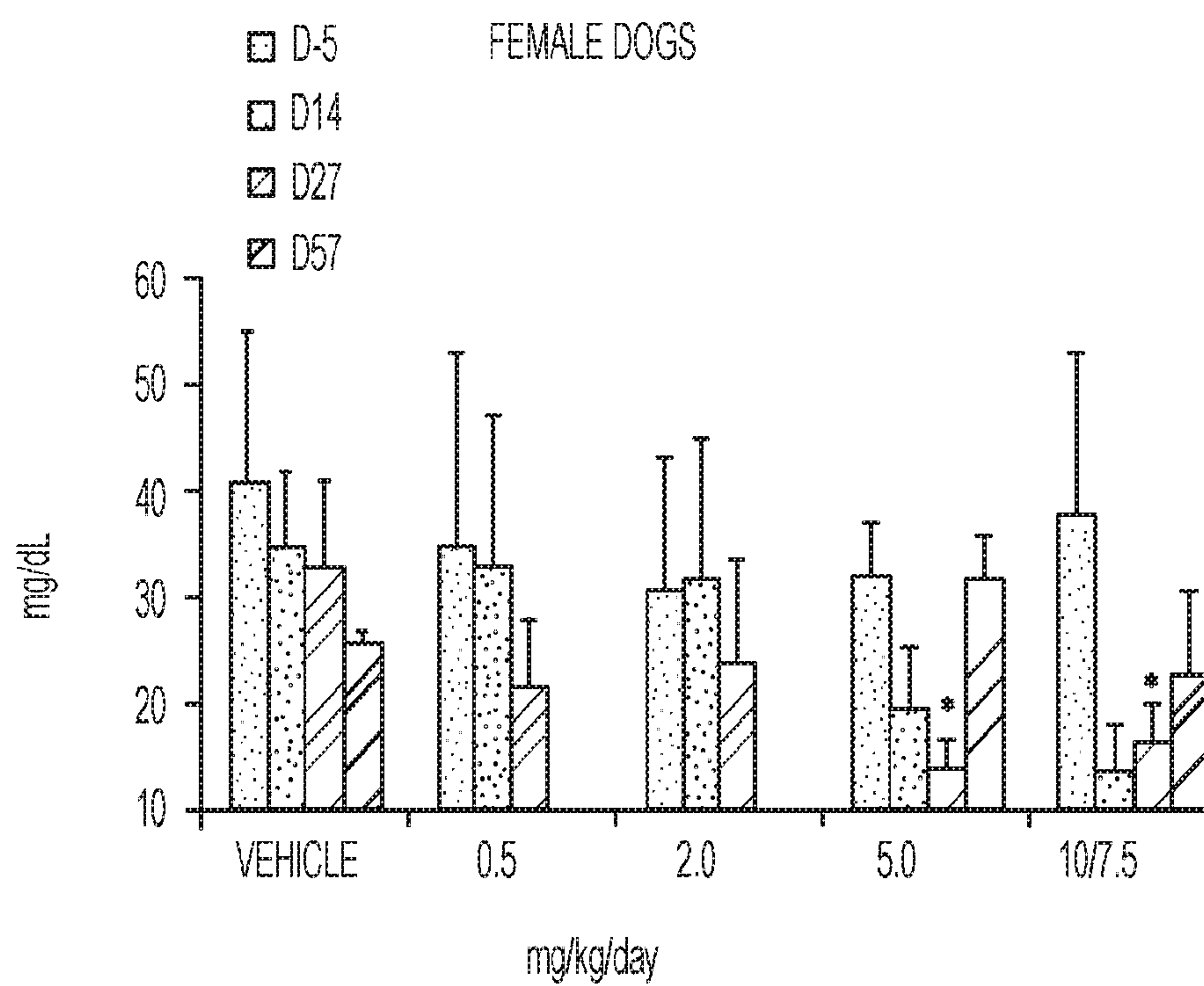


FIG. 8B

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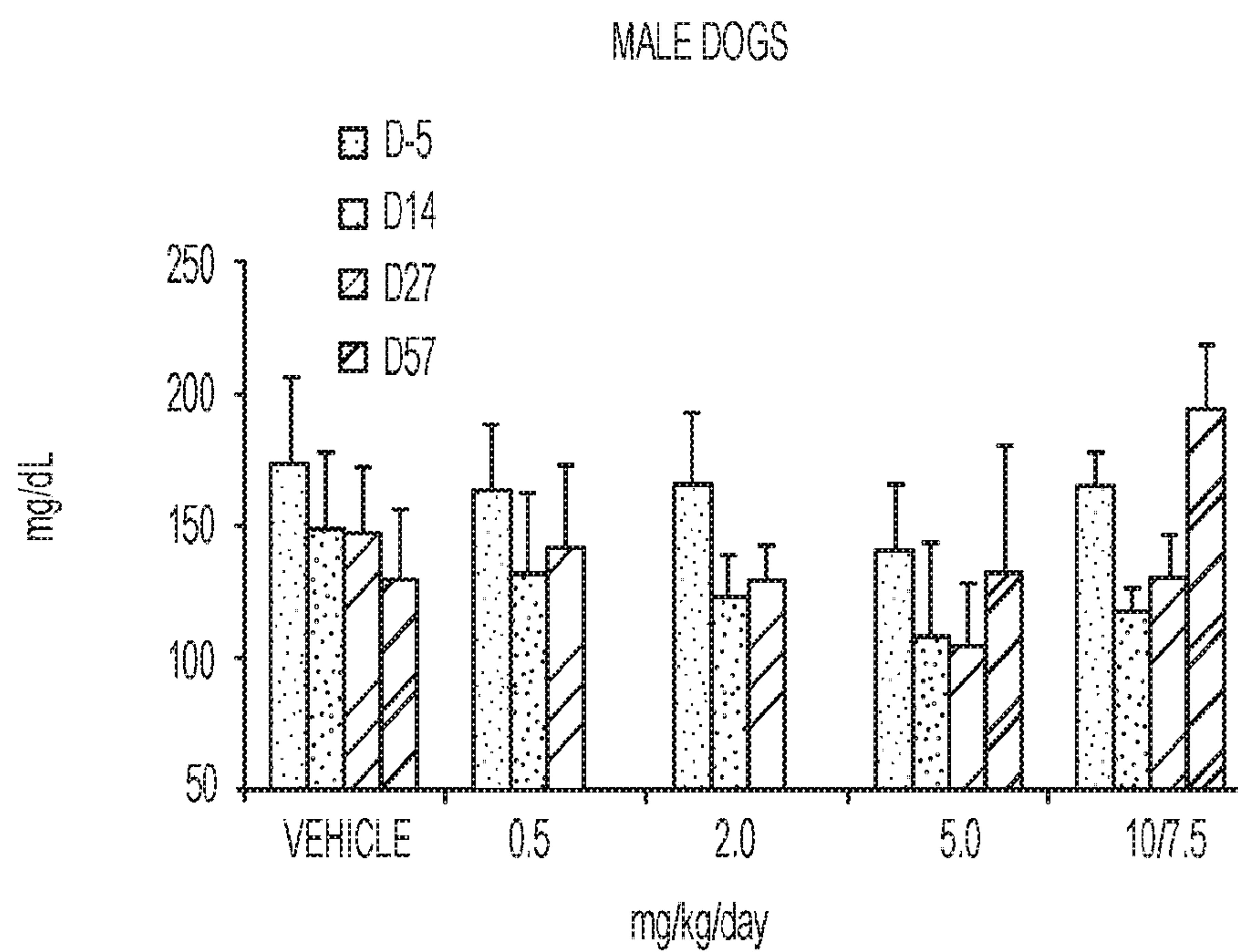


FIG. 9A

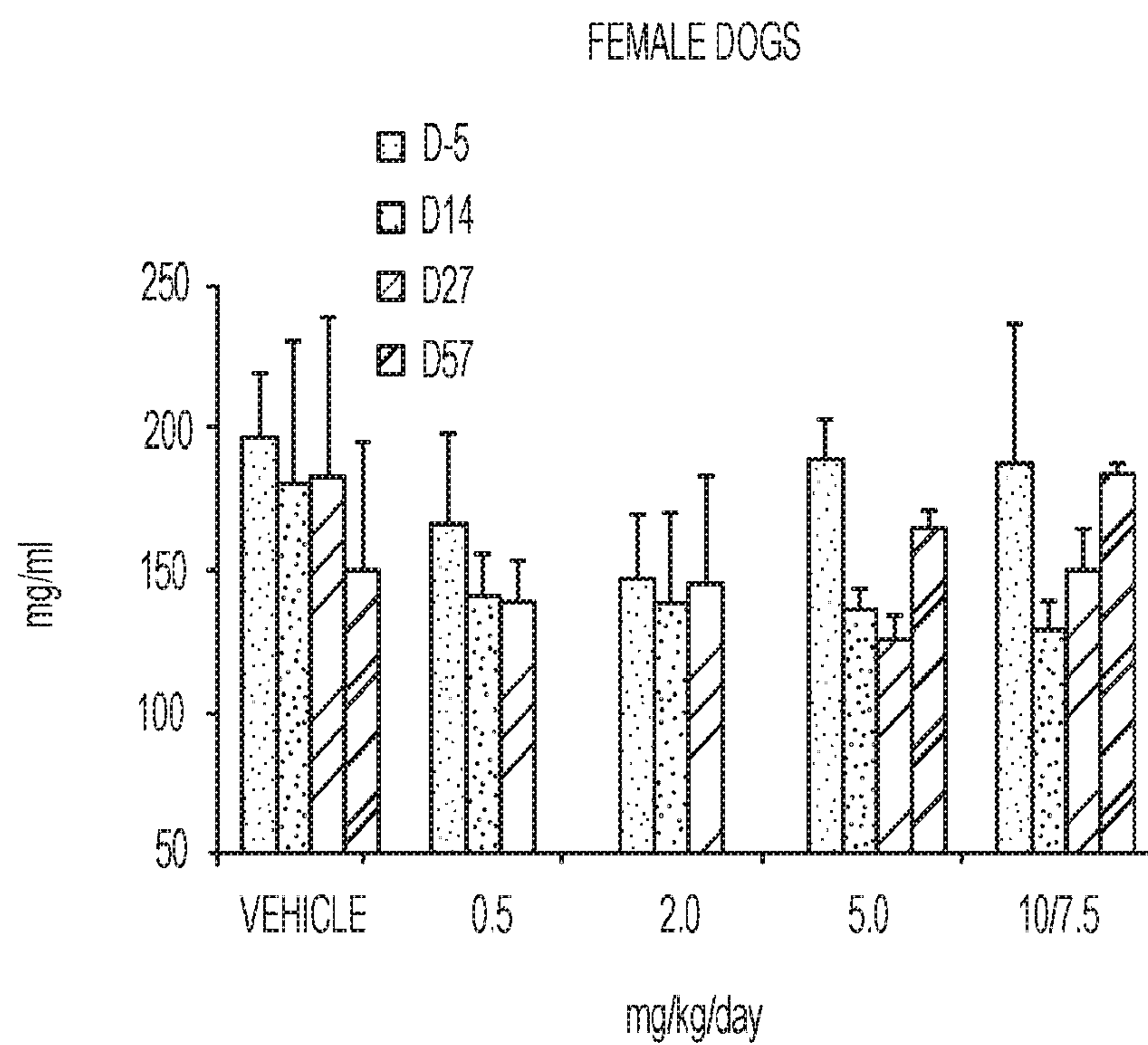


FIG. 9B