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(54) **Title:** METHODS AND MATERIALS FOR INHIBITING NF-kB ACTIVITY

(57) **Abstract:** This document provides compounds that are inhibitors of NF-κB activity, as well as the methods of using such compounds for treating diseases and conditions such as cancer, inflammatory conditions, or autoimmune diseases.

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METHODS AND MATERIALS FOR INHIBITING NF-κB ACTIVITY

CLAIM OF PRIORITY

This application claims priority to U.S. Provisional Patent Application Serial No. 63/059,488, filed on July 31, 2020, and U.S. Provisional Patent Application Serial No. 62/938,820, filed on November 21, 2019, the entire contents of which are hereby incorporated by reference.

FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

This invention was made with government support under grant numbers HL139860, HL142777, HL143663, and HL142589 awarded by National Institutes of Health (NIH). The government has certain rights in the invention.

TECHNICAL FIELD

This document relates to methods and materials for inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity. For example, this document provides compounds (e.g., organic compounds) having the ability to inhibit NF-κB activity within cells, formulations containing one or more compounds having the ability to inhibit NF-κB activity within cells, methods for making one or more compounds having the ability to inhibit NF-κB activity within cells, methods for inhibiting NF-κB activity within cells, and methods for treating mammals (e.g., humans) having a condition responsive to inhibition of NF-κB activity.

BACKGROUND

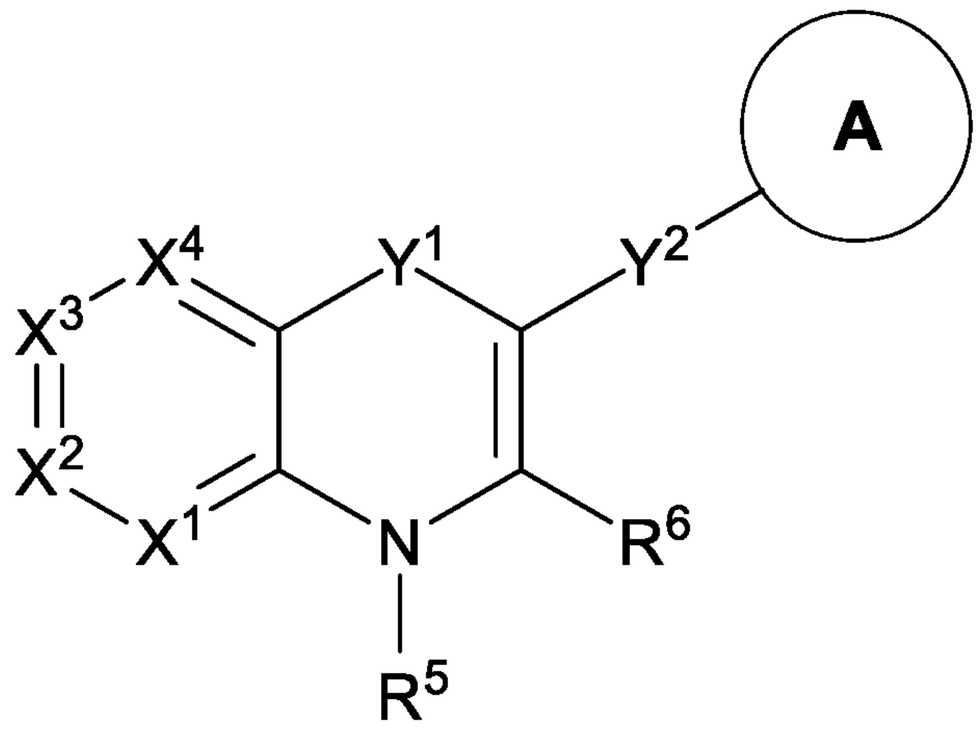
The transcription factor NF-κB is a key regulator of both the innate and adaptive immune response to various pathogens. Activated by an array of stressors, NF-κB protein complexes initiate expression of a wide array of cytokines and other inflammatory mediators. Inappropriate or excessive activation of an NF-κB regulatory pathway can lead to excessive inflammation, which may be harmful to an individual and may lead to numerous disease states. Reducing excessive inflammation, acute or chronic, may be beneficial, for example, in a number of auto-immune conditions.

SUMMARY

This document provides methods and materials for inhibiting NF-κB activity. For example, the document provides compounds (e.g., organic compounds) having the ability to inhibit NF-κB activity within cells, formulations containing one or more compounds having the ability to inhibit NF-κB activity within cells, methods for making one or more compounds having the ability to inhibit NF-κB activity within cells, methods for making formulations containing one or more compounds having the ability to inhibit NF-κB activity within cells, methods for inhibiting NF-κB activity within cells, and methods for treating mammals (e.g., humans) having a condition responsive to inhibition of NF-κB activity. Suitable examples of conditions responsive to inhibition of NF-κB activity within cells include autoimmune conditions, such as Crohn's disease, ulcerative colitis, colitis, psoriatic arthritis, systemic lupus, erythematosis (SLE), and psoriasis.

As described herein, the methods and materials provided herein can be used to inhibit NF-κB activity within cells *in vitro*, *in vivo*, or *ex vivo*. In some cases, the compounds provided herein can be used to treat mammals (e.g., humans) having a disease, disorder, or condition associated with activation of an NF-κB polypeptide complex within cells. In some cases, one or more compounds provided herein can be used to treat mammals (e.g., humans) having a disease, disorder, or condition that is responsive to inhibition of NF-κB activity.

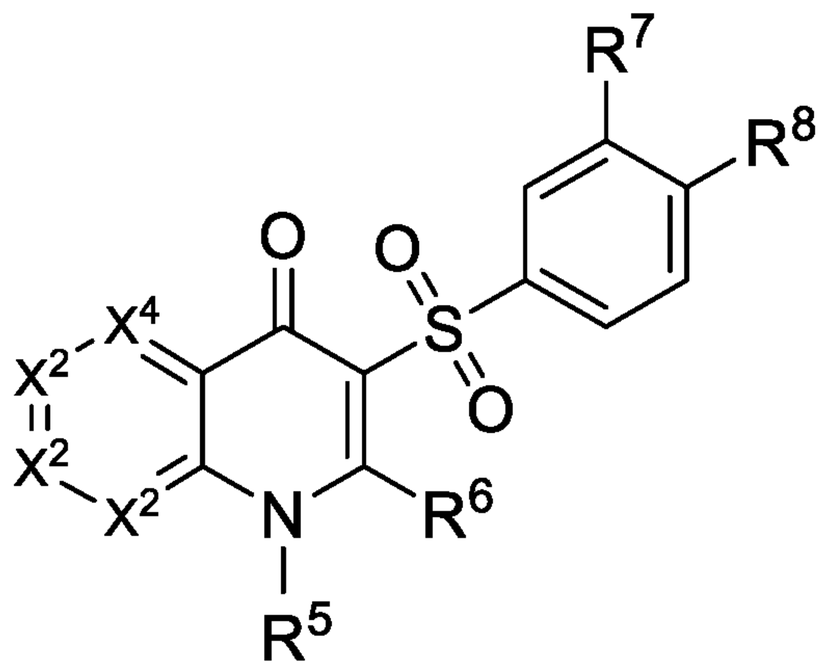
In one general aspect, the present disclosure provides a method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt thereof, wherein X^1, X^2, X^3, X^4, Y^1, Y^2, R^5, R^6, and ring A are as described herein.

In another general aspect, the present disclosure provides a compound of Formula (Ib):

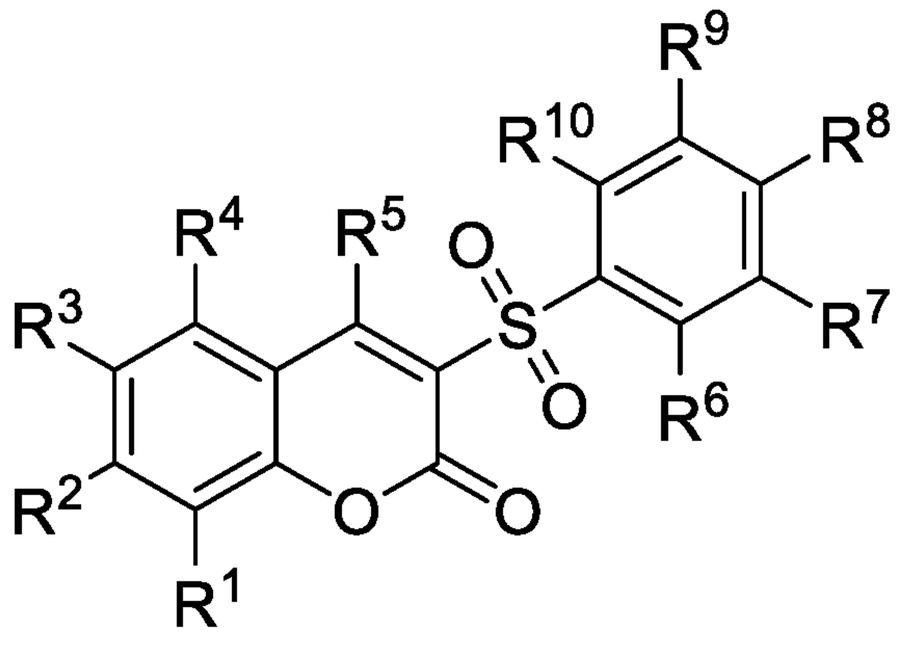


(Ib),

or a pharmaceutically acceptable salt thereof, wherein X^1, X^2, X^3, X^4, R^5, R^6, R^7, and R^8 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, and a pharmaceutically available carrier.

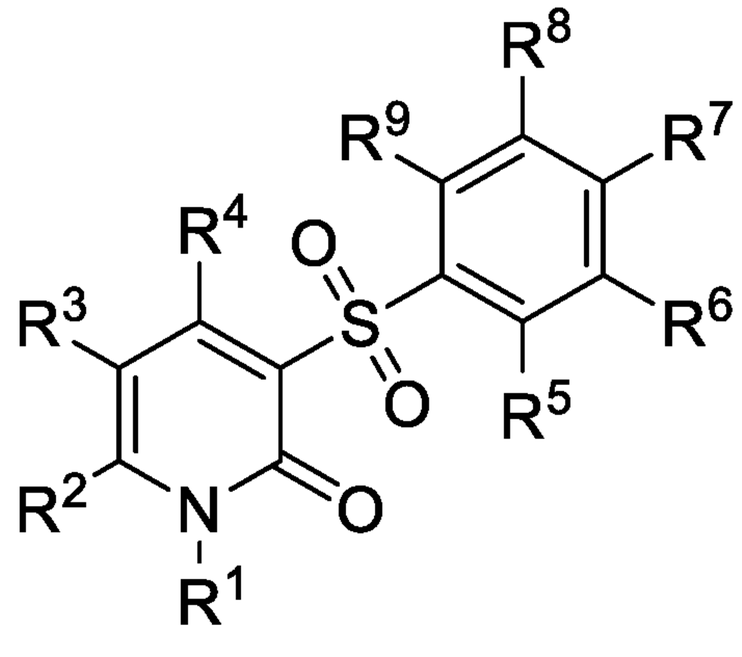
In yet another general aspect, the present disclosure provides a method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (Ic):



(Ic),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are as described herein.

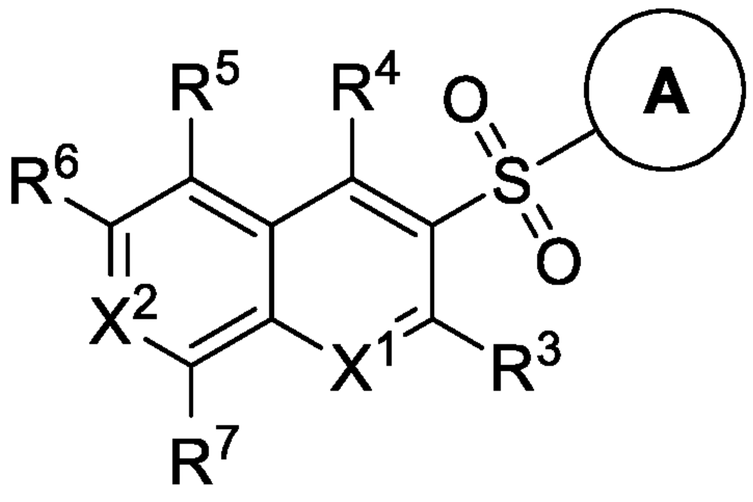
In yet another general aspect, the present disclosure provides a method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (Id):



(Id),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are as described herein.

In yet another general aspect, the present disclosure provides a compound of Formula (Ie):

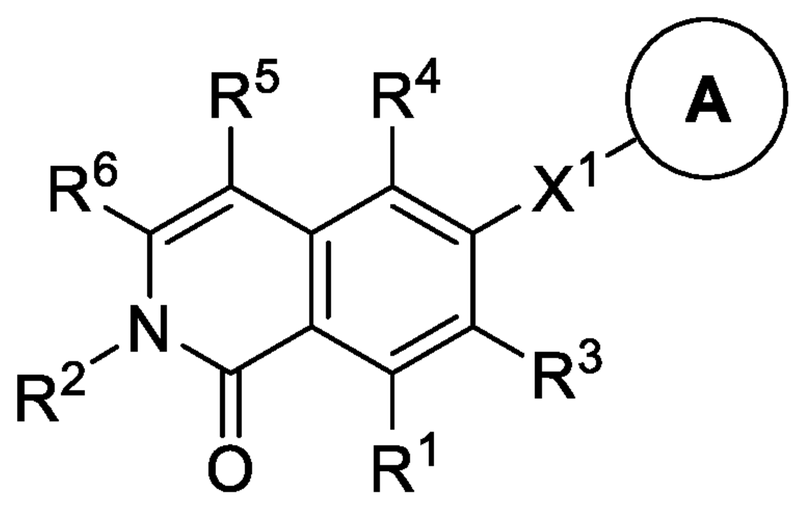


(Ie),

or a pharmaceutically acceptable salt thereof, wherein X^1, X^2, ring A, R^3, R^4, R^5, R^6, and R^7 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (Ie), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (If):

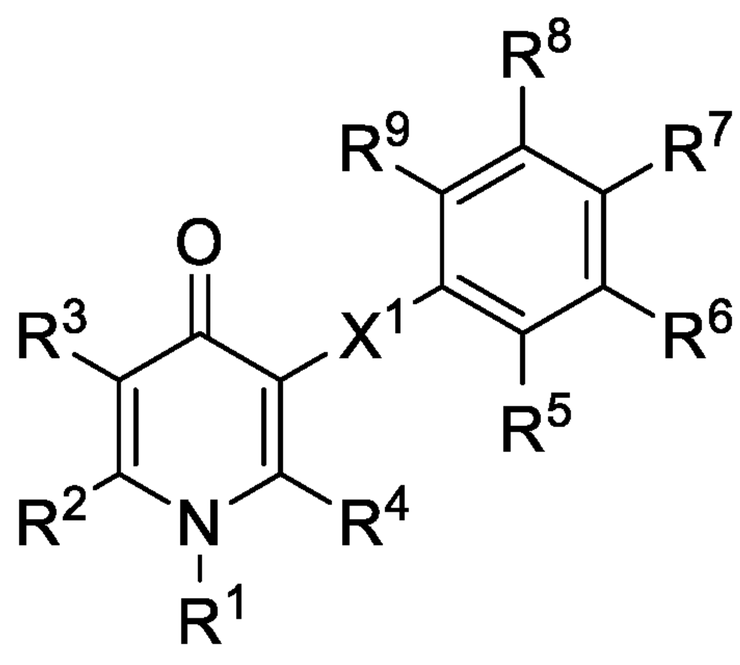


(If),

or a pharmaceutically acceptable salt thereof, wherein X^1, ring A, R^1, R^2, R^3, R^4, R^5, and R^6 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (If), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (Ig):

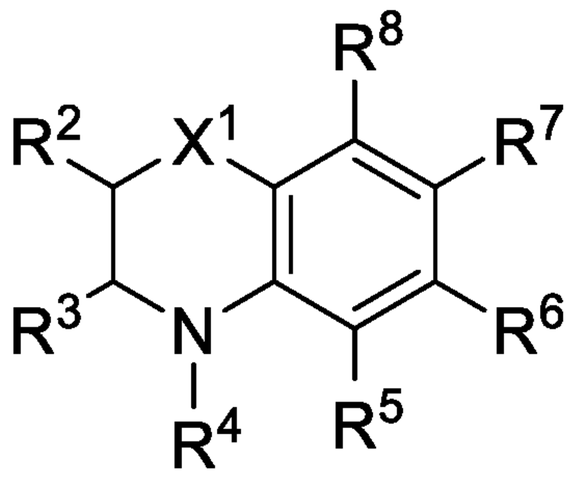


(Ig),

or a pharmaceutically acceptable salt thereof, wherein X^1, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (Ig), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

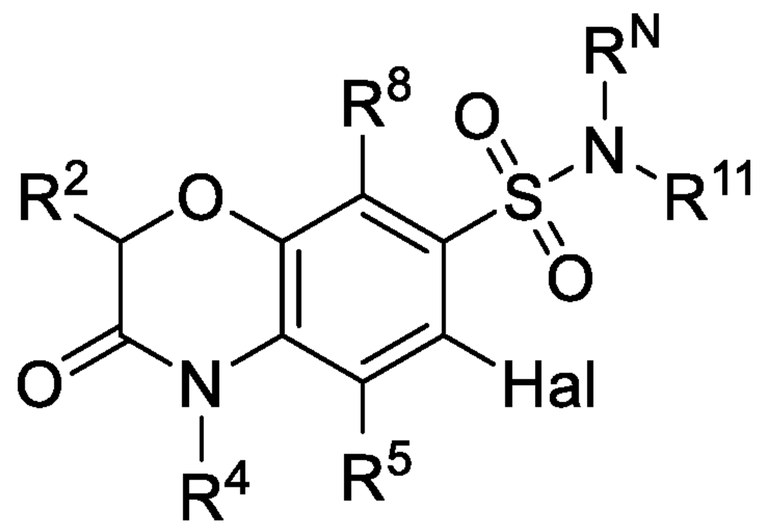
In yet another general aspect, the present disclosure provides a method of inhibiting activation of an NF-κB pathway within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (IIa):



(IIa),

or a pharmaceutically acceptable salt thereof, wherein X^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are as described herein.

In yet another general aspect, the present disclosure provides a compound of Formula (IIb):

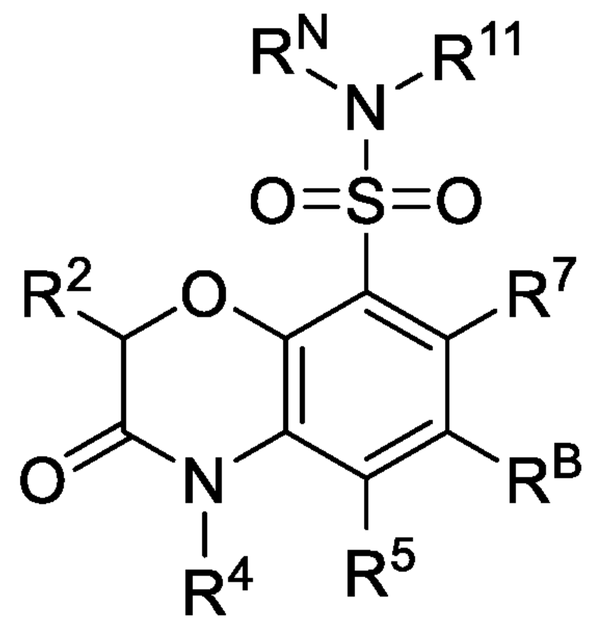


(IIb),

or a pharmaceutically acceptable salt thereof, wherein R^N, Hal, R^2, R^4, R^5, R^8 and R^{11} are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIb), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIc):

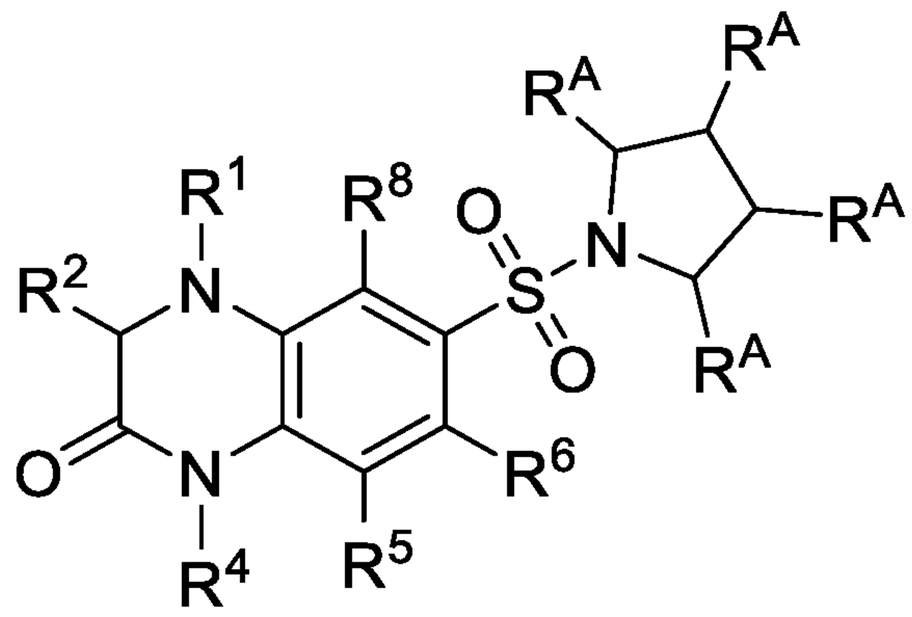


(IIc),

or a pharmaceutically acceptable salt thereof, wherein R^N, R^B, R^2, R^4, R^5, R^7 and R^{11} are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIc), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IId):

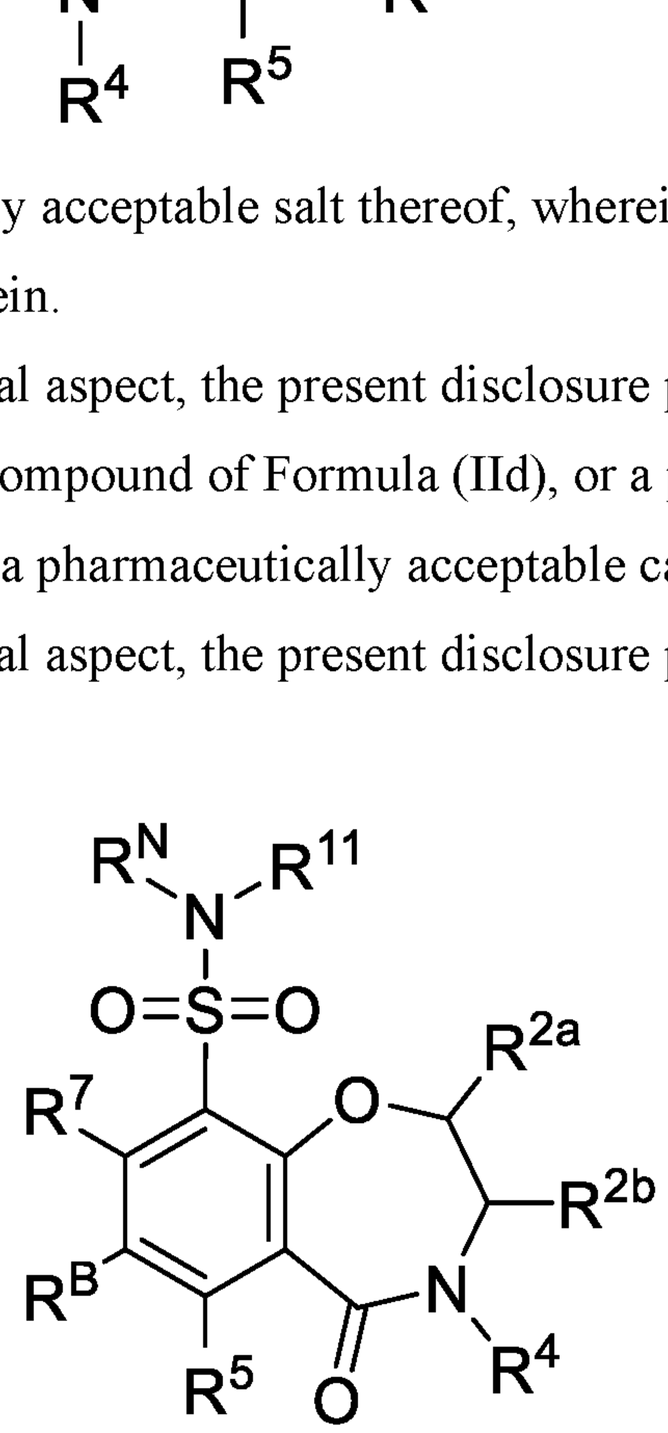


(IId),

or a pharmaceutically acceptable salt thereof, wherein R^A, R^1, R^2, R^4, R^5, R^6, and R^8 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IId), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIe):

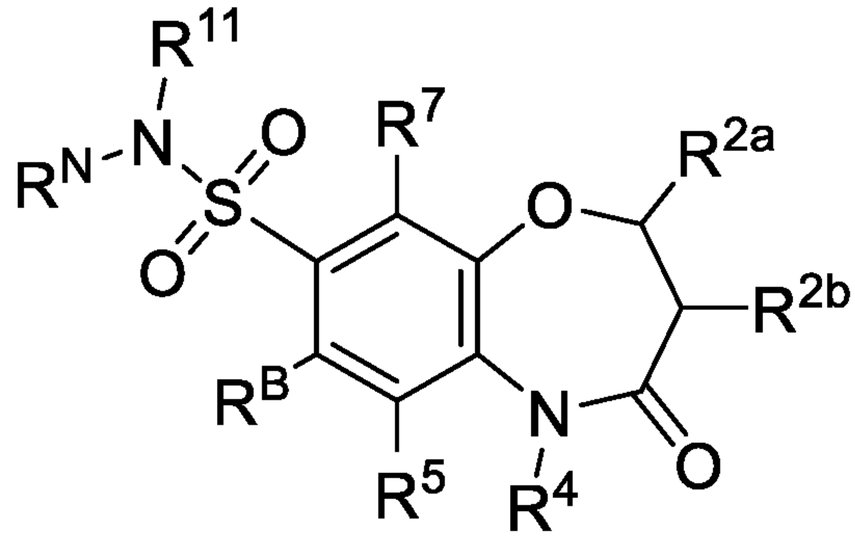


(IIe),

or a pharmaceutically acceptable salt thereof, wherein R^N, R^{2a}, R^{2b}, R^4, R^5, R^B, R^7, and R^{11} are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIe), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIf):

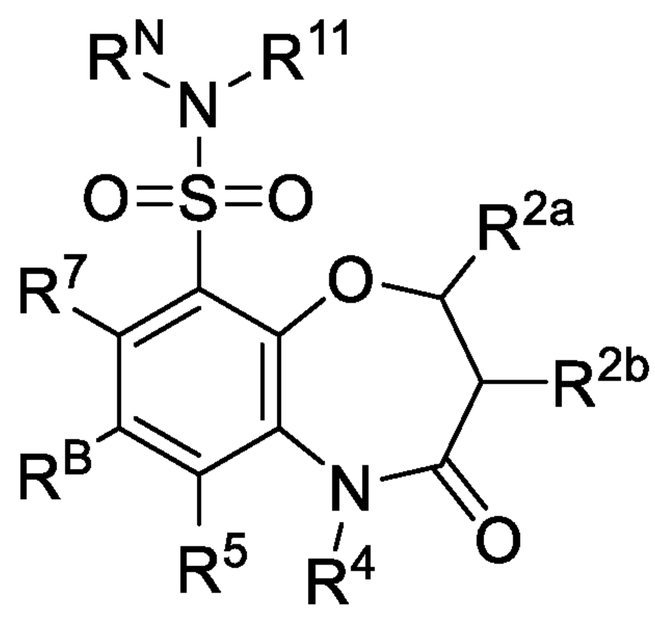


(IIf),

or a pharmaceutically acceptable salt thereof, wherein R^N, R^{2a}, R^{2b}, R^4, R^5, R^B, R^7, and R^{11} are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIf), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIg):

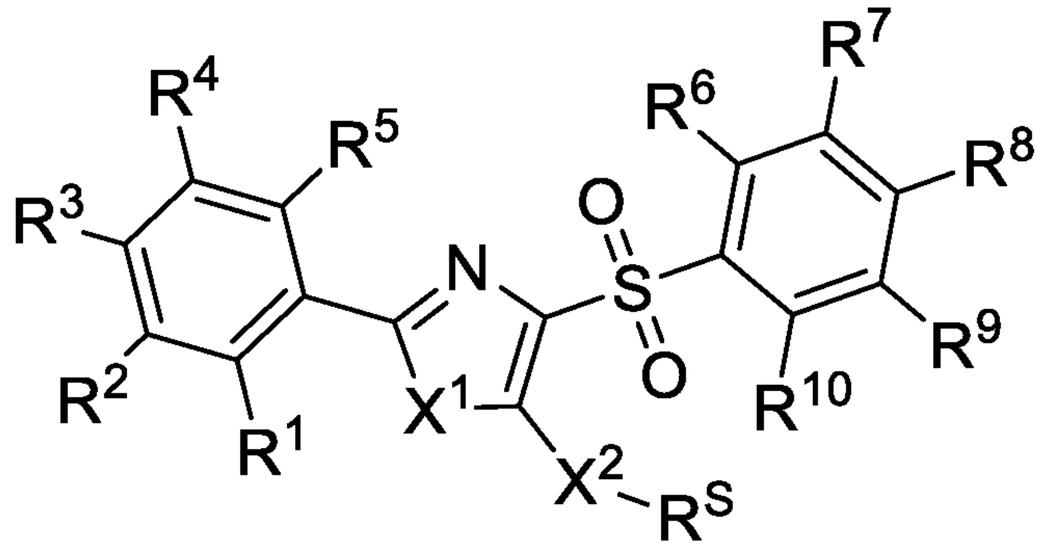


(IIg),

or a pharmaceutically acceptable salt thereof, wherein R^N, R^{2a}, R^{2b}, R^4, R^5, R^B, R^7, and R^{11} are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIg), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (IIIa):



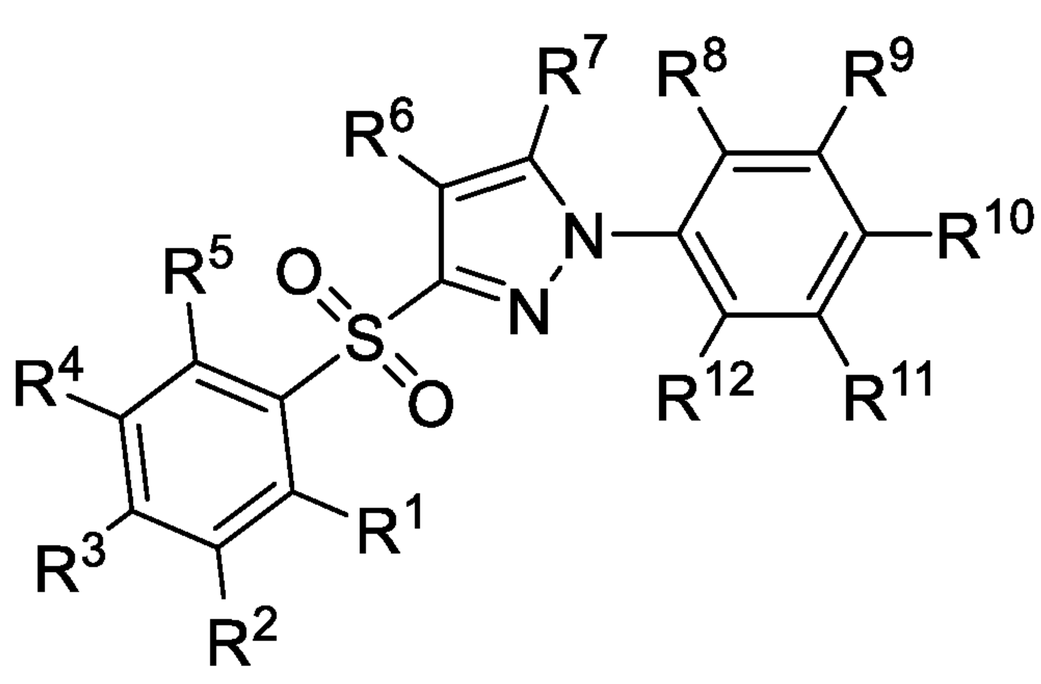
(IIIa),

or a pharmaceutically acceptable salt thereof, wherein X^1, X^2, R^S, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are as described herein.

In yet another general aspect, the present disclosure provides a compound selected from any one of the compounds of Table 3b, or a pharmaceutically acceptable salt thereof.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising any one of the compound of Table 3b, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIIc):

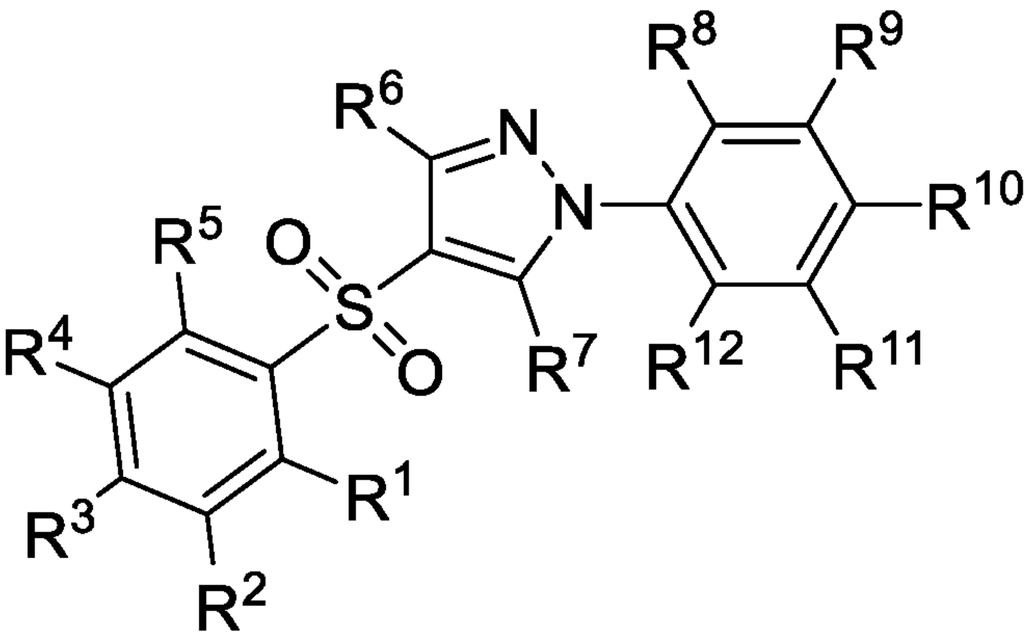


(IIIc),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIIc), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIId):

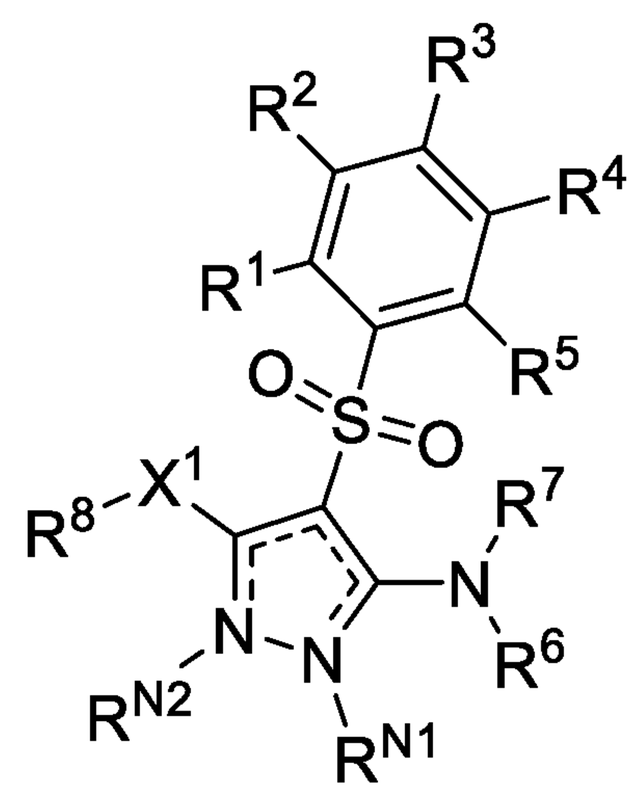


(IIId),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIId), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIIe):

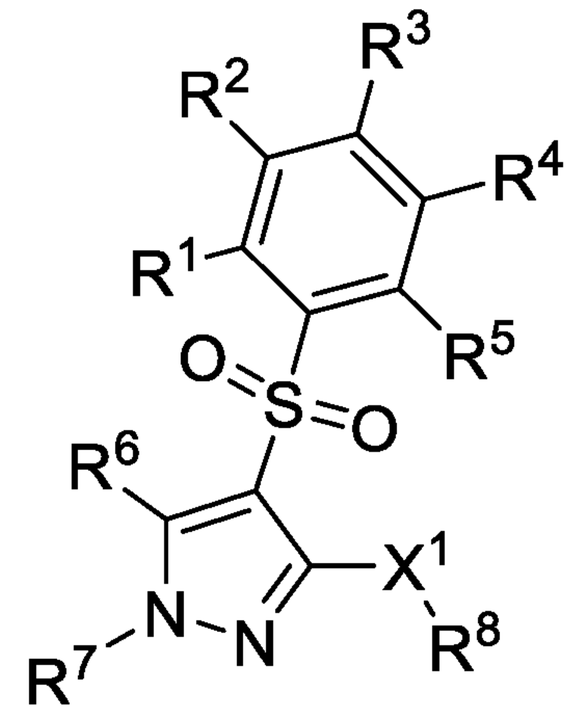


(IIIe),

or a pharmaceutically acceptable salt thereof, wherein X^1, R^{N2}, R^{N1}, R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIIe), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIIf):

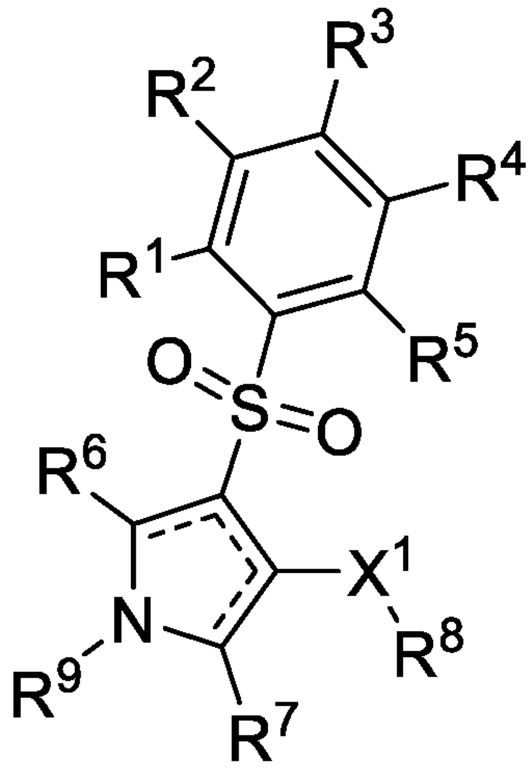


(IIIf),

or a pharmaceutically acceptable salt thereof, wherein X^1, R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIIf), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIIg-2):

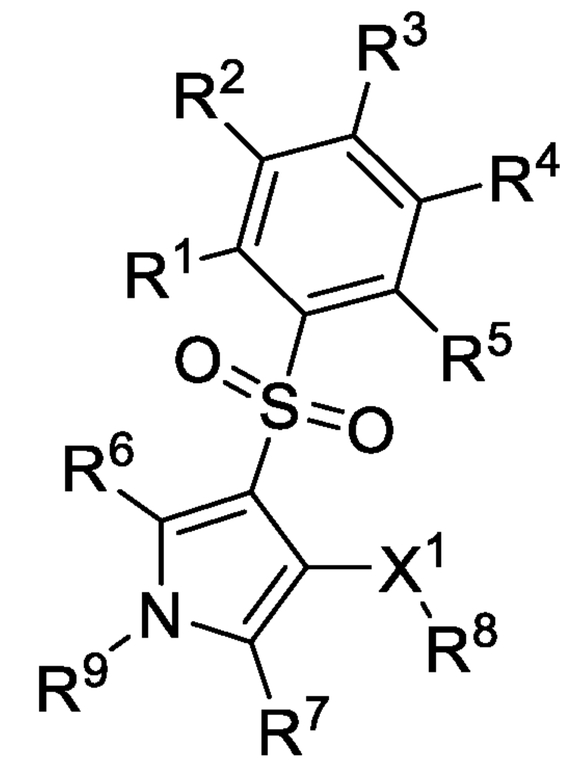


(IIIg-2),

or a pharmaceutically acceptable salt thereof, wherein X^1, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIIg-2), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIIg):

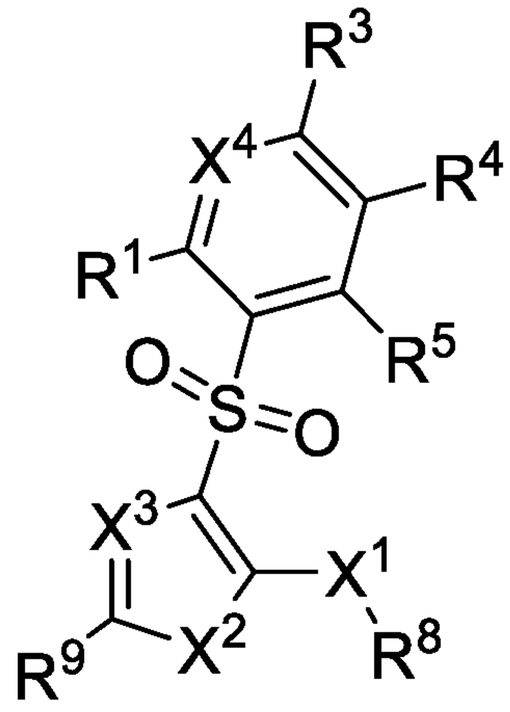


(IIIg),

or a pharmaceutically acceptable salt thereof, wherein X^1, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIIg), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIIh):

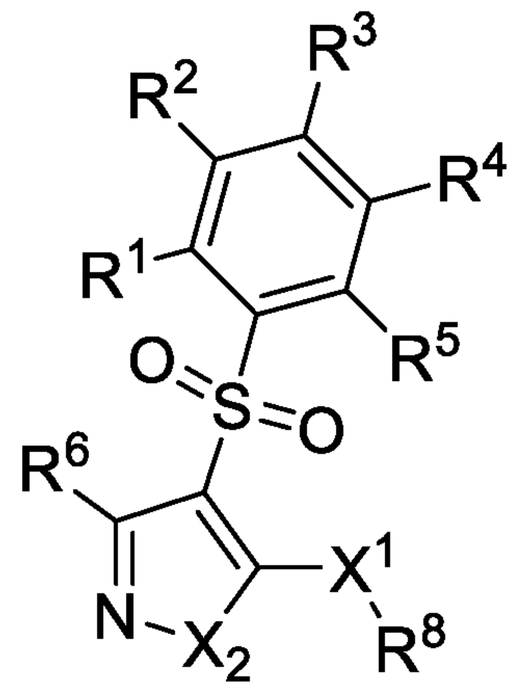


(IIIh),

or a pharmaceutically acceptable salt thereof, wherein X^1, X^2, X^3, X^4, R^3, R^4, R^5, R^8 and R^9 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIIh), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IIIi):

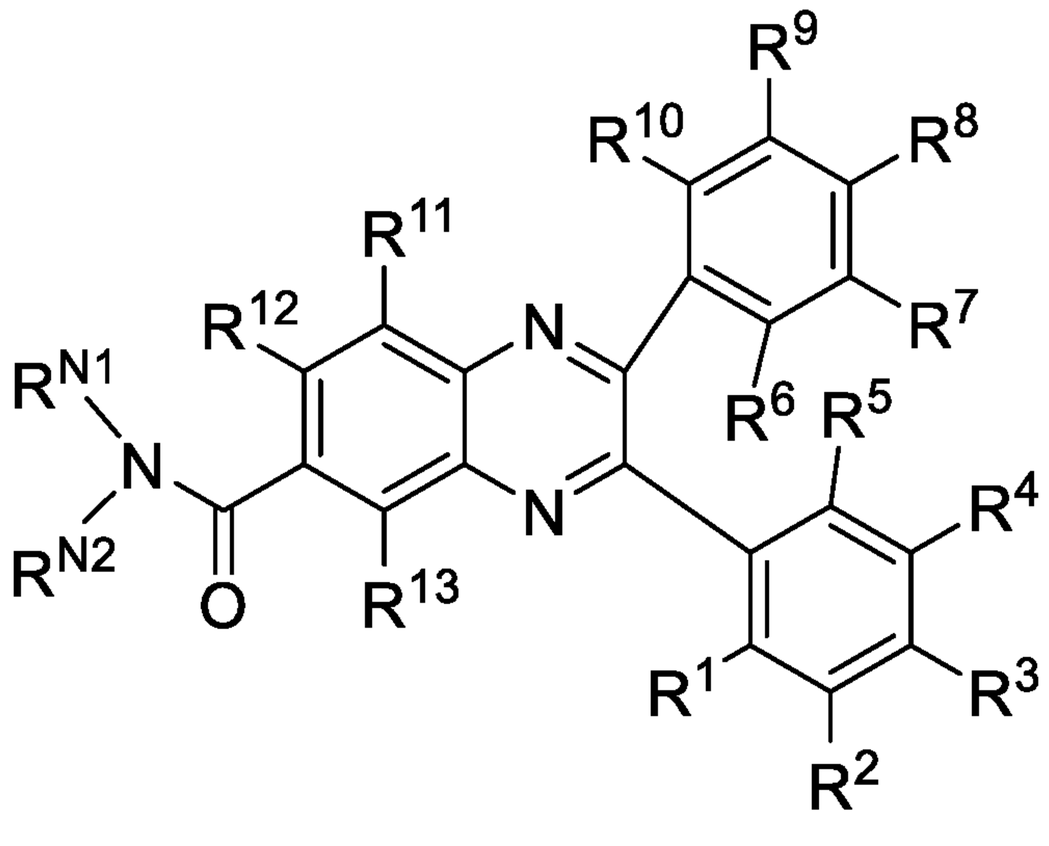


(IIIi)

or a pharmaceutically acceptable salt thereof, wherein X^1, X^2, R^1, R^2, R^3, R^4, R^5, R^6 and R^8 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IIIi), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (IVa):



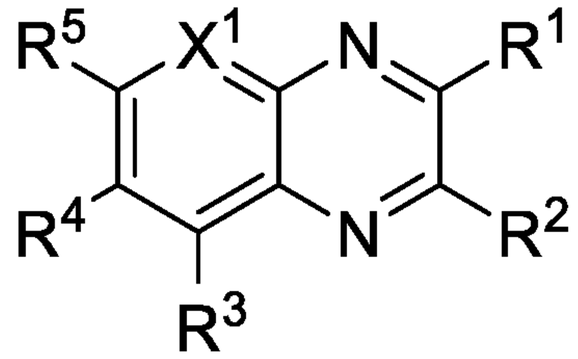
(IVa),

or a pharmaceutically acceptable salt thereof, wherein R^{N1}, R^{N2}, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are as described herein.

In yet another general aspect, the present disclosure provides a compound selected from any one of the compounds of Table 4b, or a pharmaceutically acceptable salt thereof.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising any one of the compounds of Table 4b, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IVb):

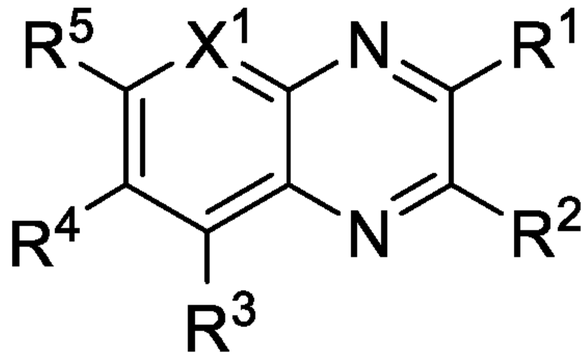


(IVb),

or a pharmaceutically acceptable salt thereof, wherein X^1, R^1, R^2, R^3, R^4, and R^5 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IVb), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IVc):

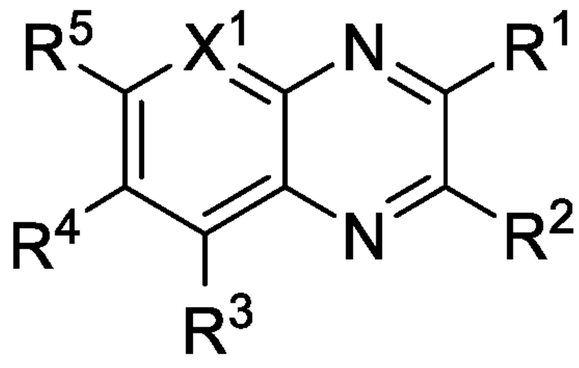


(IVc),

or a pharmaceutically acceptable salt thereof, wherein X^1, R^1, R^2, R^3, R^4, and R^5 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IVc), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IVd):



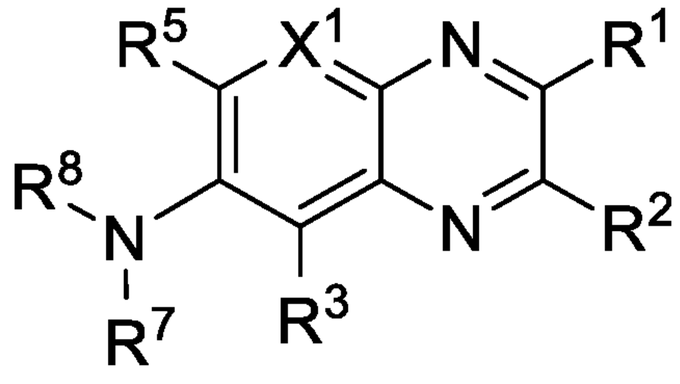
(IVd),

or a pharmaceutically acceptable salt thereof, wherein X^1, R^1, R^2, R^3, R^4, and

R^5 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IVd), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IVe):

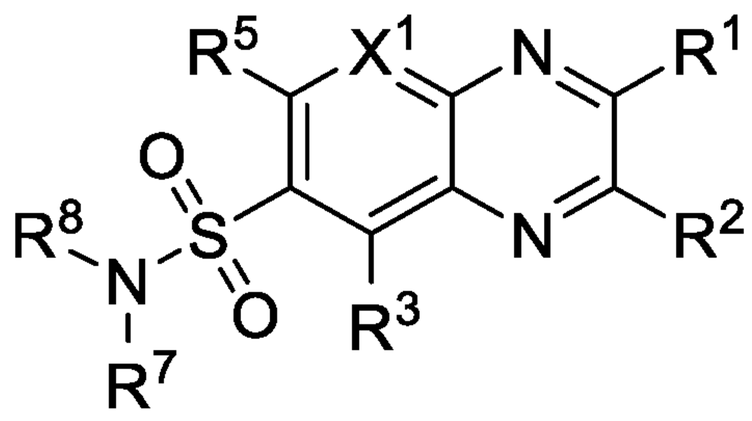


(IVe),

or a pharmaceutically acceptable salt thereof, wherein X^1, R^1, R^2, R^3, R^5, R^7, and R^8 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IVe), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IVf):

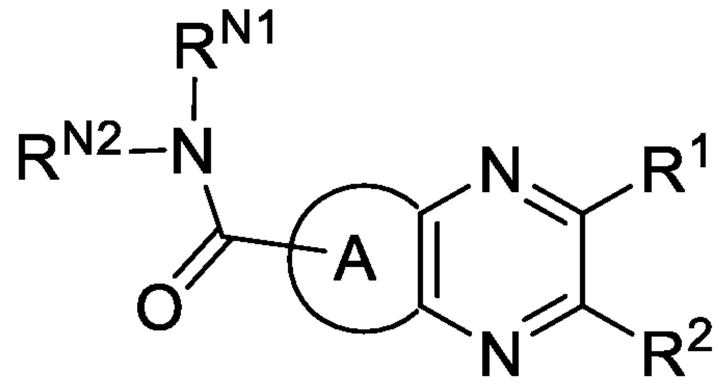


(IVf),

or a pharmaceutically acceptable salt thereof, wherein X^1, R^1, R^2, R^3, R^5, R^7, and R^8 are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IVf), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a compound of Formula (IVg):



(IVg),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, ring A, R^{N1}, and R^{N2} are as described herein.

In yet another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (IVg), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another general aspect, the present disclosure provides a method of treating a mammal having a disease, disorder, or condition responsive to inhibiting NF-κB activity within a cell, wherein said method comprises administering, to said mammal, any one of the compounds described herein, or a pharmaceutical composition comprising same. In some embodiments, the mammal is a human. In some embodiments, the method comprises treating a mammal having a cancer. In some embodiments, the method comprises treating a mammal having an inflammation. In some embodiments, the inflammation is an autoimmune disease.

In yet another general aspect, the present disclosure provides a method for inhibiting NF-κB activity within cells of a mammal, wherein said method comprises administering, to said mammal, any one of the compounds described herein or a pharmaceutical composition comprising same.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the present application belongs. Methods and materials are described herein for use in the present application; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. Other features and advantages of the present application will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 contains line plots showing NF-κB activity of exemplified compounds. 25k THP1-NF-κB-LUC cells were dispensed into 384 well plate (per well). Cells were treated with compounds (2 μM and 0.2 μM) for 2 hours before addition of LPS (10 ng/mL) for 18 hours. Secreted luciferase activity were measured using quant-luc reagents (1 bag of luc reagent dilute to 40 mL, use 10 μL per well). Data were normalized to vehicle control and graphed. Structures of selected exemplified compounds are shown.

FIG. 2 contains heat charts showing NF-κB activity of exemplified compounds as a function of concentration. 25k THP1-NF-κB-LUC cells were dispensed into 384 well plate (per well). Cells were treated with compounds (with serial dilution) for 2 hours before addition of LPS (10 ng/mL) for 18 hours. Secreted luciferase activity were measured using quant-luc reagents (1 bag of luc reagent dilute to 40 mL, use 10 μL per well). Structures of selected exemplified compounds are shown.

FIG. 3 contains heat charts showing NF-κB activity of exemplified compounds as a function of concentration. 25k THP1-NF-κB-LUC cells were dispensed into 384 well plate (per well). Cells were treated with compounds (with serial dilution) for 2 hours before addition of Pam3CSK4 (1 g/mL) for 18 hours. Secreted luciferase activity were measured using quant-luc reagents (1 bag of luc reagent dilute to 40 mL, use 10 μL per well). Structures of selected exemplified compounds are shown.

FIG. 4 contains heat charts showing NF-κB activity of exemplified compounds as a function of concentration. 25k THP1-NF-κB-LUC cells were dispensed into 384 well plate (per well). Cells were treated with compounds (with serial dilution) for 2 hours before addition of R848 (1 μg/mL) for 18 hours. Secreted luciferase activity were measured using quant-luc reagents (1 bag of luc reagent dilute to 40 mL, use 10 μL per well). Structures of selected exemplified compounds are shown.

FIG. 5 contains a bar graph showing TNFα inhibitory activity for selected exemplified compounds. Mouse bone marrow macrophages were cultured in 96 well and differentiated before compound treatment at various concentrations for 2 hours. Cells were further treated with LPS (10 ng/mL) for 2 hours, and supernatants were collected and assayed for TNF.

DETAILED DESCRIPTION

This document provides methods and materials for inhibiting NF-κB activity. For example, the document provides compounds (e.g., organic compounds) having the ability to inhibit NF-κB activity within cells, formulations containing one or more compounds having the ability to inhibit NF-κB activity within cells, methods for making one or more compounds having the ability to inhibit NF-κB activity within cells, methods for making formulations containing one or more compounds having the ability to inhibit NF-κB activity within cells, methods for inhibiting NF-κB activity within cells, and methods for treating mammals (e.g., humans) having a condition responsive to inhibition of NF-κB activity. Suitable examples of conditions responsive to inhibition of NF-κB activity within cells include autoimmune conditions, such as Crohn's disease, ulcerative colitis, colitis, psoriatic arthritis, systemic lupus, erythematosis (SLE), and psoriasis.

Methods of treatment using one or more inhibitors of NF-κB activity

In some cases, this document provides methods for inhibiting NF-κB activity within a cell by contacting the cell with one or more compounds provided herein (e.g., a compound set forth in any one of the Formulae (I)-(IV), or a pharmaceutically acceptable salt thereof).

In some cases, methods for inhibiting NF-κB activity within cells can be performed *in vivo*. For example, one or more compounds provided herein (e.g., a compound set forth in any one of the Formulae (I)-(IV), or a pharmaceutically acceptable salt thereof) can be administered to a mammal (e.g., a human) to inhibit NF-κB activity within cells within that mammal. In some cases, methods for inhibiting NF-κB activity within cells can be performed *in vitro*. For example, one or more compounds provided herein (e.g., a compound set forth in any one of the Formulae (I)-(IV), or a pharmaceutically acceptable salt thereof) can be added to a cell culture containing cells (e.g., human cells) to inhibit NF-κB activity within those cells. In some cases, such intervention can improve the quality of the cell while in culture or subsequently.

This document also provides methods for treating diseases, disorders, and conditions in a mammal by administering one or more compounds provided herein (e.g., a compound set forth in any one of the Formulae (I)-(IV), or a pharmaceutically acceptable salt thereof) to a mammal in need thereof. In some cases, the disease,

disorder, or condition being treated can be a disease, disorder, or condition that is responsive to inhibiting NF-κB activity within cells within the mammal. In some cases, the disease, disorder, or condition being treated can be a disease, disorder, or condition that is associated with enhanced NF-κB activity within the mammal.

Examples of diseases, disorders, and conditions that can be treated with one or more compounds provided herein include, without limitation, cancer and inflammation disorders (e.g., acute or chronic inflammation, or viral or influenza-induced inflammation such as HIV-related inflammation).

Suitable examples of disorders associated with inflammation include asthma, chronic obstructive lung disease, pulmonary fibrosis, pneumonitis (e.g., hypersensitivity pneumonitis and radiation pneumonitis), pneumonia, cystic fibrosis, psoriasis, arthritis, rheumatoid arthritis, rhinitis, pharyngitis, cystitis, prostatitis, dermatitis, allergy (e.g., hay fever), nephritis, conjunctivitis, encephalitis, meningitis, opthalmitis, uveitis, pleuritis, pericarditis, myocarditis, atherosclerosis, diabetes, osteoarthritis, psoriatic arthritis, autoimmune diseases or conditions, inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis), colitis, sepsis, vasculitis, bursitis, connective tissue disease, systemic lupus erythematosis (SLE), polymyalgia rheumatica, scleroderma, Wegener's granulomatosis, temporal arteritis, vasculitis, cryoglobulinemia, multiple sclerosis, and edema.

Suitable examples of cancers include prostate cancer, pancreatic cancer, ovarian cancer, breast cancer, lung cancer (*e.g.*, bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); kidney cancer (*e.g.*, nephroblastoma, *a.k.a.* Wilms' tumor, renal cell carcinoma); acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.*, cholangiocarcinoma); bladder cancer; breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (*e.g.*, meningioma, glioblastomas, glioma (*e.g.*, astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.*, cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.*, Kaposi's sarcoma, multiple idiopathic hemorrhagic

sarcoma); endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma); esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett's adenocarcinoma); Ewing's sarcoma; ocular cancer (*e.g.*, intraocular melanoma, retinoblastoma); familiar hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.*, stomach adenocarcinoma); gastroesophageal cancer, gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease; hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma, hepatobiliary cancer); leiomyosarcoma (LMS); mastocytosis (*e.g.*, systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendoctrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.*,bone cancer); ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.*, pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.*, Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasmlungrectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (*e.g.*, appendix cancer); soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma; testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma); thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary

thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (*e.g.*, Paget's disease of the vulva).

In some cases, provided herein are methods for treating a cancer (e.g., any one of the cancers described herein) in a mammal (e.g., human) by administering one or more compounds provided herein (e.g., a compound set forth in any one of the Formulae (I)-(IV), or a pharmaceutically acceptable salt thereof) to a mammal in need thereof.

In some cases, provided herein are methods for treating inflammation (e.g., any one of the inflammation disorders described herein) in a mammal (e.g., human) by administering one or more compounds provided herein (e.g., a compound set forth in any one of the Formulae (I)-(IV), or a pharmaceutically acceptable salt thereof) to a mammal in need thereof.

In some cases, provided herein are methods for treating autoimmune disease (e.g., any one of the autoimmune diseases described herein) in a mammal (e.g., human) by administering one or more compounds provided herein (e.g., a compound set forth in any one of the Formulae (I)-(IV), or a pharmaceutically acceptable salt thereof) to a mammal in need thereof.

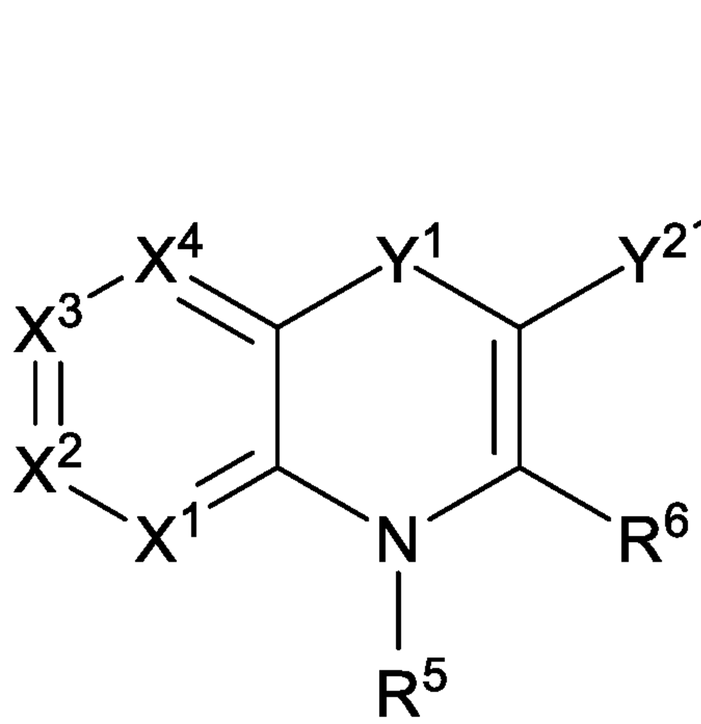
In some cases, one or more compounds provided herein (e.g., a compound set forth in any one of the Formulae (I)-(IV), or a pharmaceutically acceptable salt thereof) can be used as described herein (e.g., to inhibit NF-κB activity within cells and/or to treat a disease, disorder, or condition as described herein) as the sole active ingredient(s). For example, a composition containing a compound set forth in any one of the Formulae (I)-(IV), or a pharmaceutically acceptable salt thereof, can lack any other active ingredients that inhibit NF-κB activity within cells. In some cases, a composition containing a compound set forth in any one of the Formulae (I)-(IV), or a pharmaceutically acceptable salt thereof, can lack any other active ingredients that are effective to treat a disease, disorder, or condition as described herein.

Therapeutic compounds

As described herein, any one or more of the compounds provided herein can be used to inhibit NF-κB activity within cells and/or can be used to treat (or prevent) a disease, disorder, and condition in a mammal (e.g., a human) as described herein.

Formula (Ia)

In one general aspect, the present disclosure provides a compound of Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is selected from C(O) and $S(O)_2$;

Y^2 is selected from C(O) and $S(O)_2$;

X^1 is selected from N and CR^1;

X^2 is selected from N and CR^2;

X^3 is selected from N and CR^3;

X^4 is selected from N and CR^4;

provided that no more than two of X^1, X^2, X^3, and X^4 are N;

each of R^1, R^2, R^3, R^4, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^5 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from Cy^1, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$,

$S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

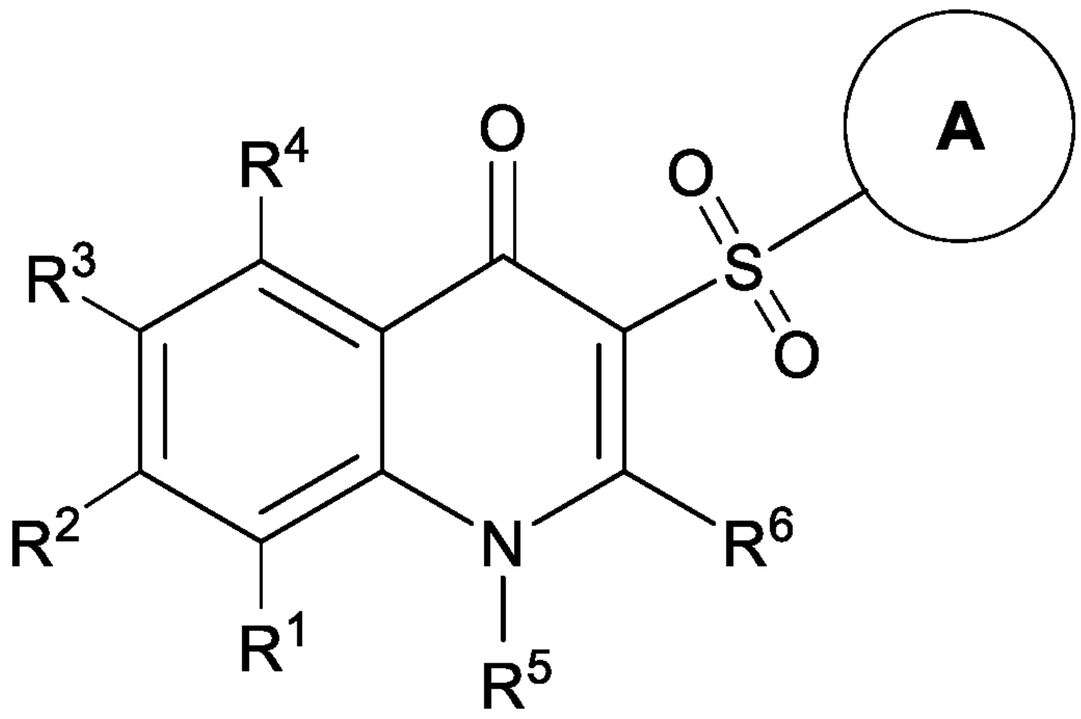
In some embodiments, Y^1 is C(O). In some embodiments, Y^1 is $S(O)_2$.

In some embodiments, Y^2 is C(O). In some embodiments, Y^2 is $S(O)_2$.

In some embodiments, Y^1 is C(O) and Y^2 is $S(O)_2$. In some embodiments, Y^1 is C(O) and Y^2 is C(O). In some embodiments, Y^1 is $S(O)_2$ and Y^2 is $S(O)_2$. In some embodiments, Y^1 is $S(O)_2$ and Y^2 is C(O).

In some embodiments, X^1 is N. In some embodiments, X^1 is CR^1. In some embodiments, X^2 is N. In some embodiments, X^2 is CR^2. In some embodiments, X^3 is N. In some embodiments, X^3 is CR^3. In some embodiments, X^4 is N. In some embodiments, X^4 is CR^1. In some embodiments, one of X^1, X^2, X^3, and X^4 is N. In some embodiments, two of X^1, X^2, X^3, and X^4 are N.

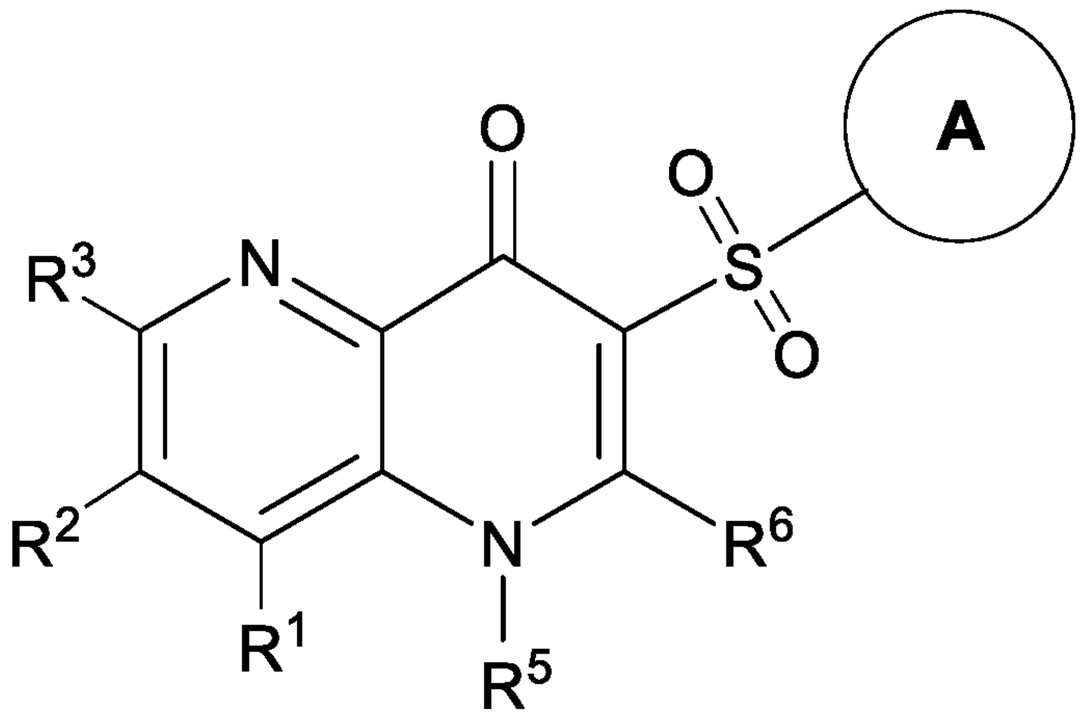
In some embodiments, the compound of Formula (Ia) has formula:



,

or a pharmaceutically acceptable salt thereof.

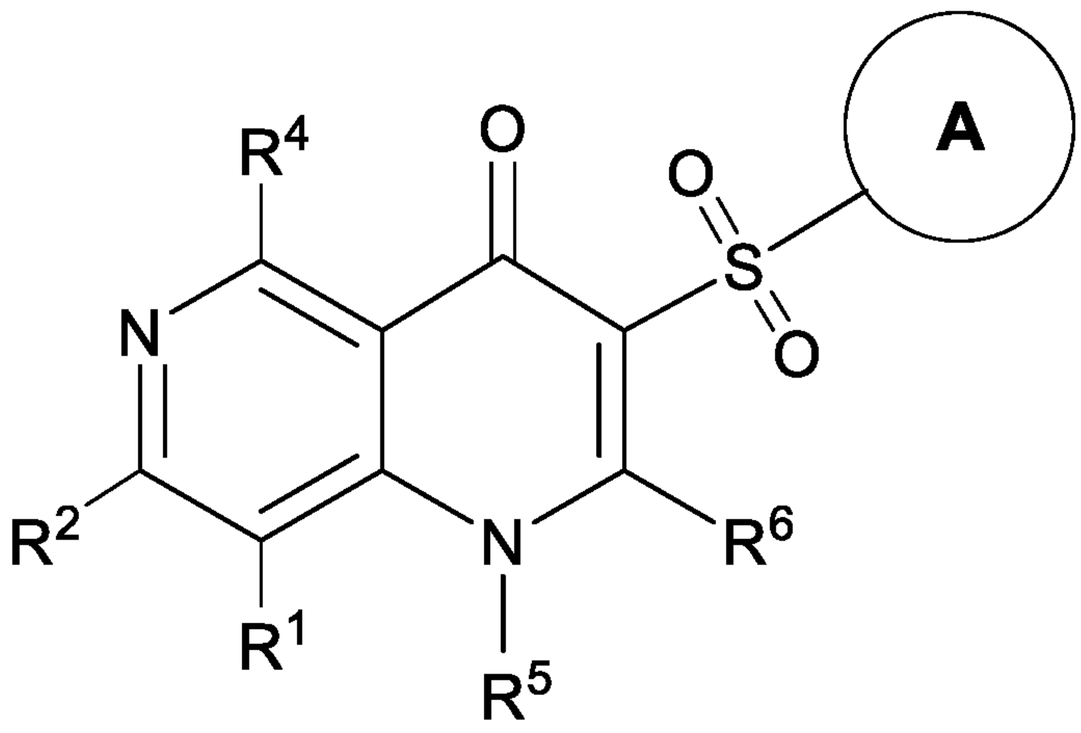
In some embodiments, the compound of Formula (Ia) has formula:



,

or a pharmaceutically acceptable salt thereof.

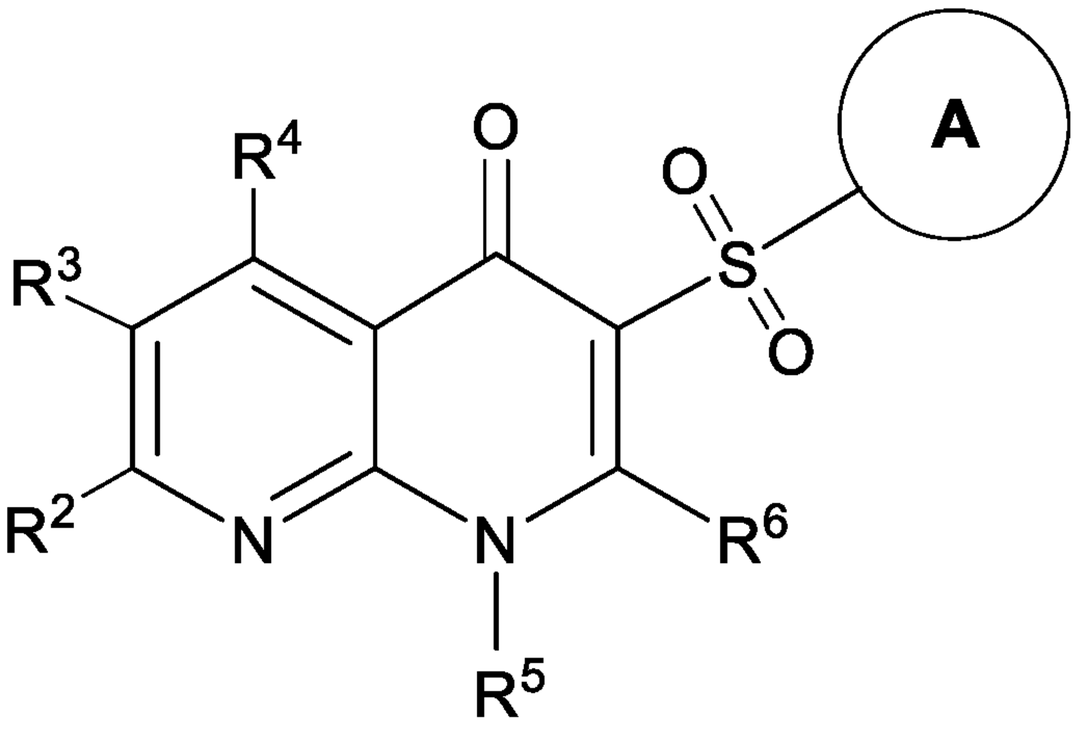
In some embodiments, the compound of Formula (Ia) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) has formula:



,

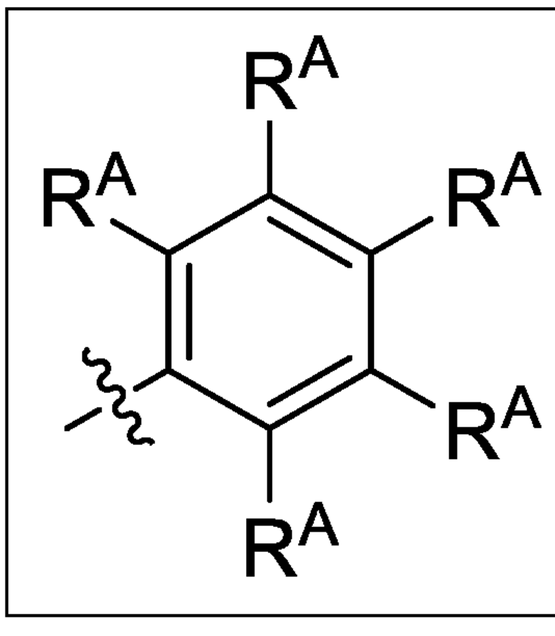
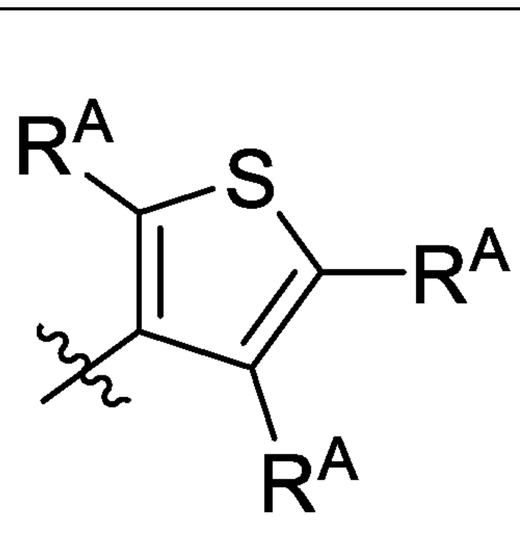
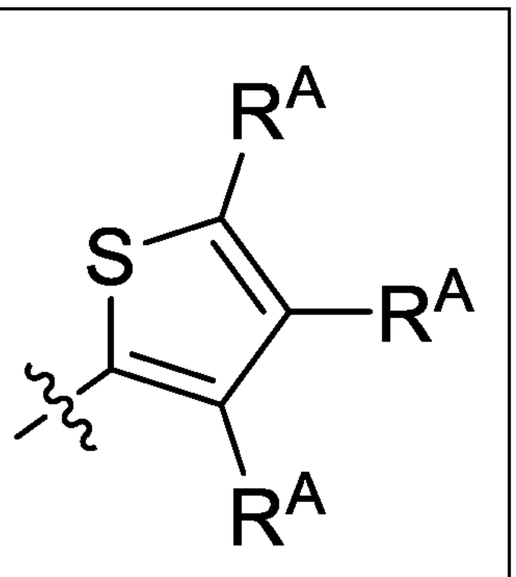
or a pharmaceutically acceptable salt thereof.

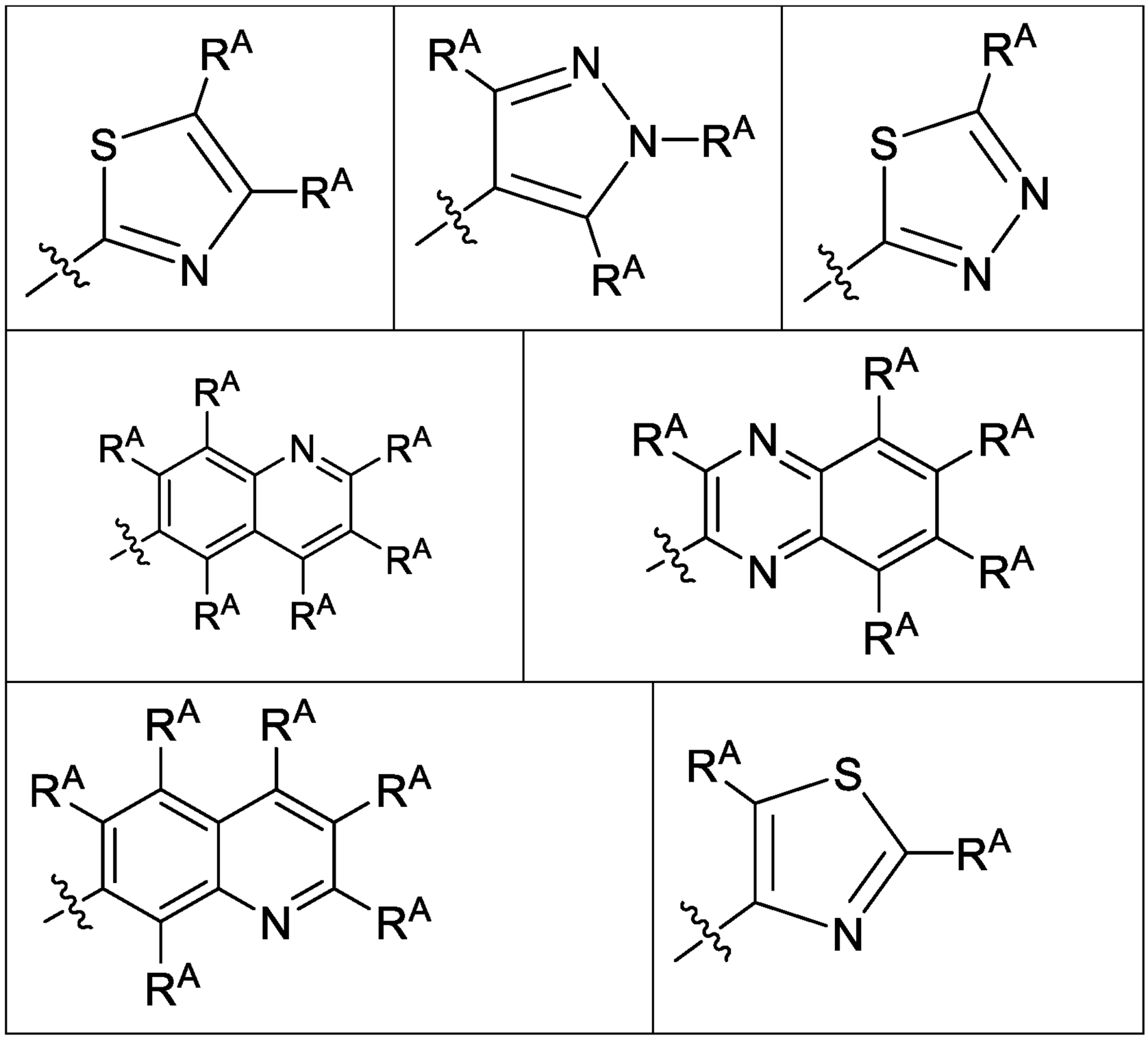
In some embodiments, ring A is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is substituted with 1-6 substituents independently selected from R^A.

In some embodiments, ring A is C_{6-10} aryl, substituted with 1-5 substituents independently selected from R^A. In some embodiments, ring A is phenyl, optionally substituted with 1-5 substituents independently selected from R^A. In some embodiments, ring A is naphthyl, optionally substituted with 1-5 substituents independently selected from R^A.

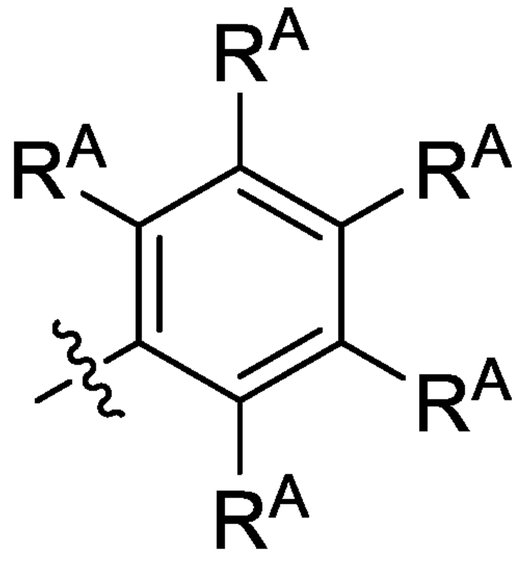
In some embodiments, ring A is 5-10 membered heteroaryl, substituted with 1-6 substituents independently selected from R^A. In some embodiments, ring A is selected from pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, thiophen-2-yl, thiophen-3-yl, pyrazol-3-yl, pyrazlol-4-yl, pyrazol-5-yl, quinolin-6-yl, quinolin-7-yl, thiazolyl, 1,3,4-thiadiazolyl, and quinoxaline-6-yl, each of which is optionally substituted with 1-6 substituents independently selected from R^A.

In some embodiments, ring A is selected from any one of the following moieties:

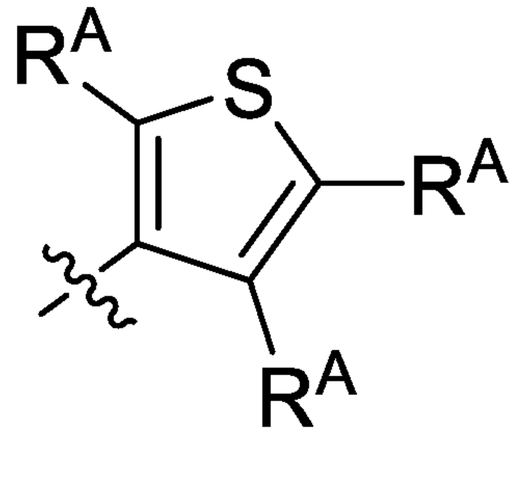
		



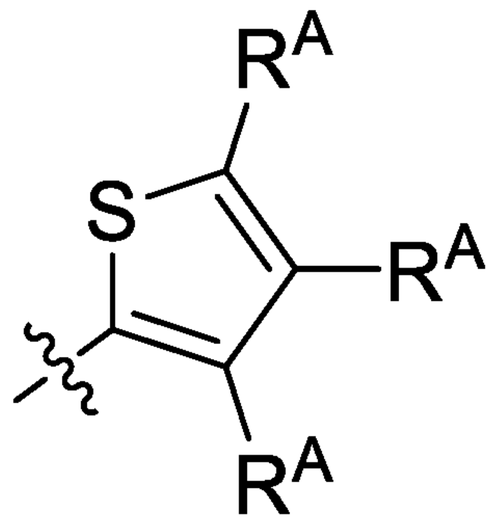
In some embodiments, ring A is:



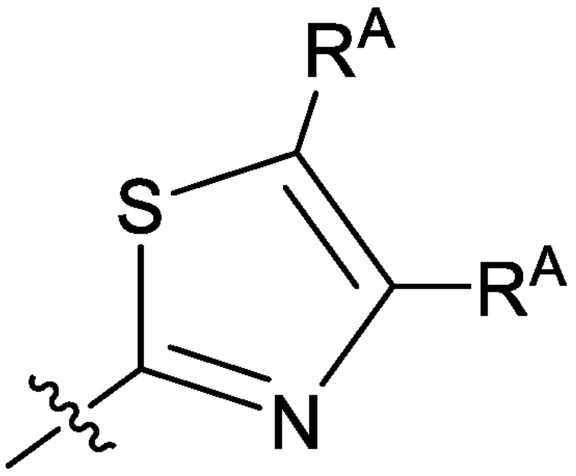
In some embodiments, ring A is:



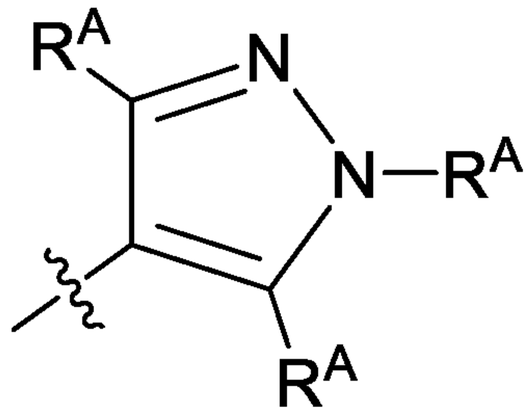
In some embodiments, ring A is:



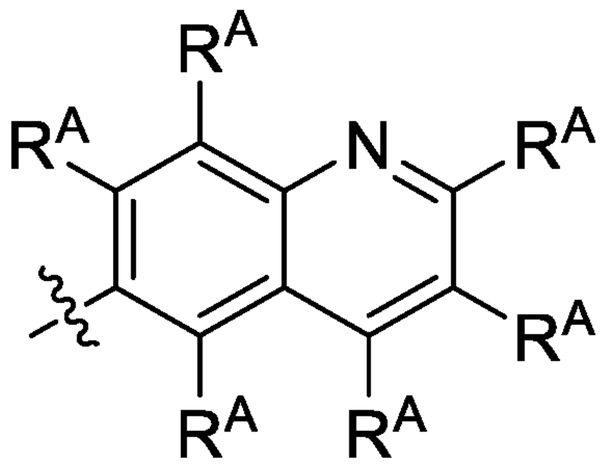
In some embodiments, ring A is:



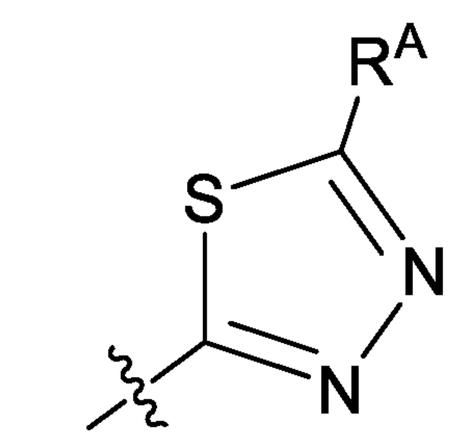
In some embodiments, ring A is:



In some embodiments, ring A is:

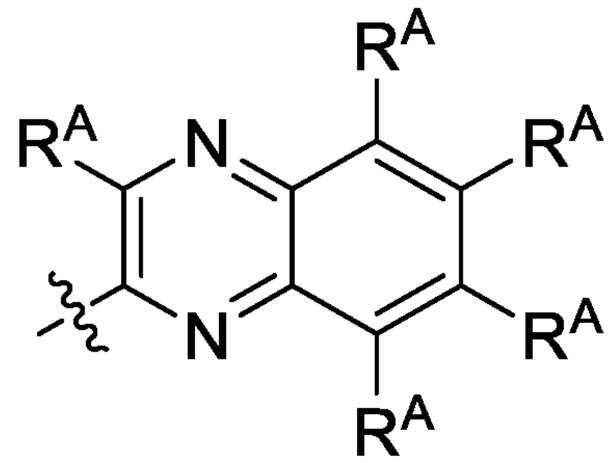


In some embodiments, ring A is:

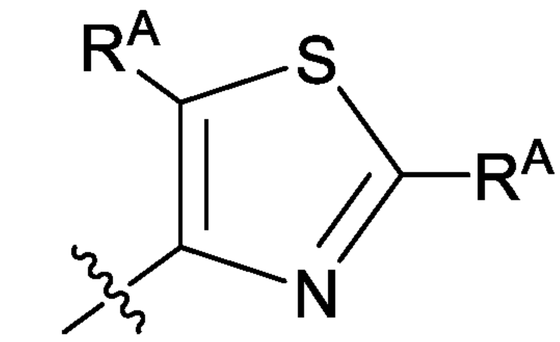


In some embodiments, ring A is:

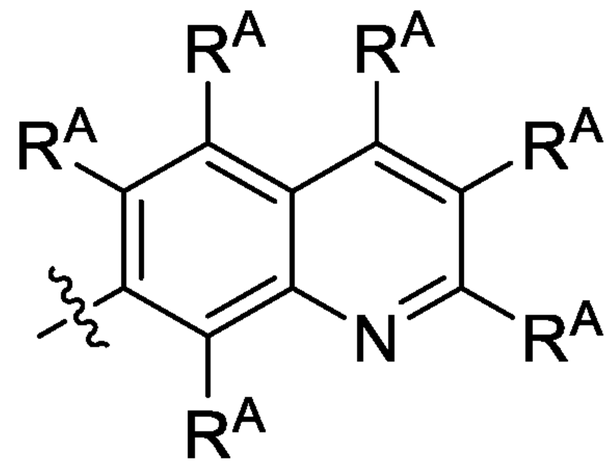
In some embodiments, ring A is:



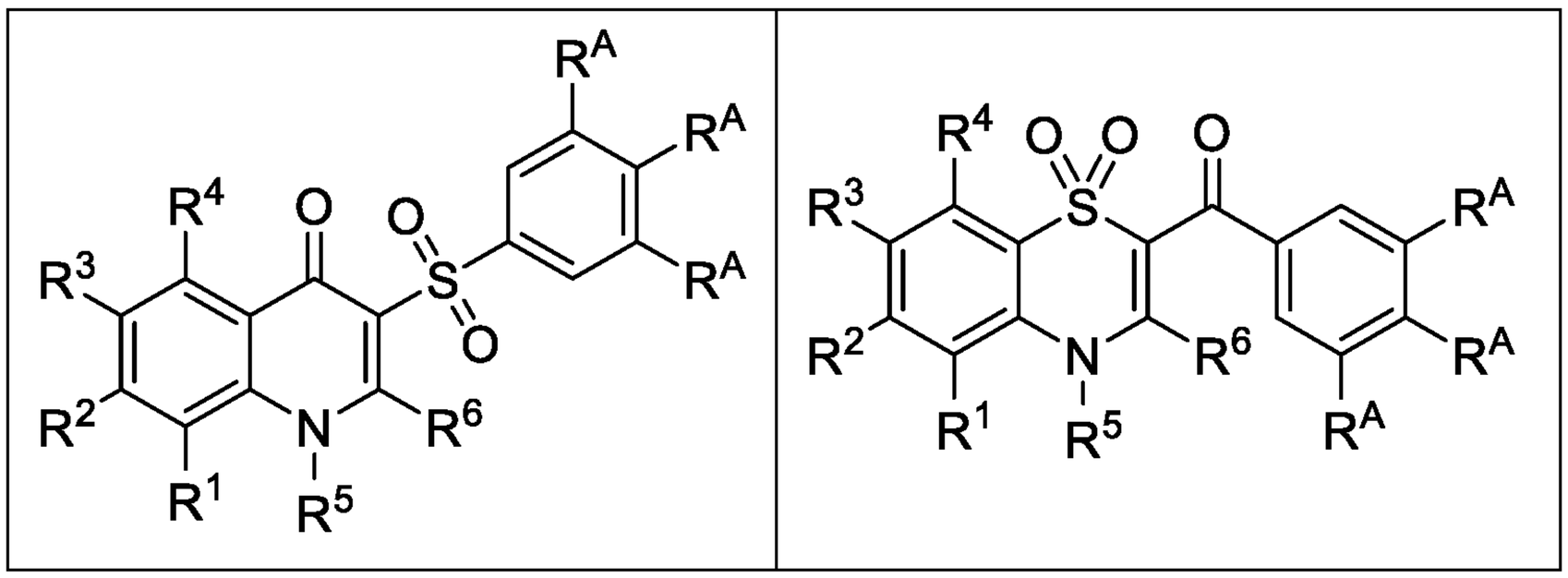
In some embodiments, ring A is:

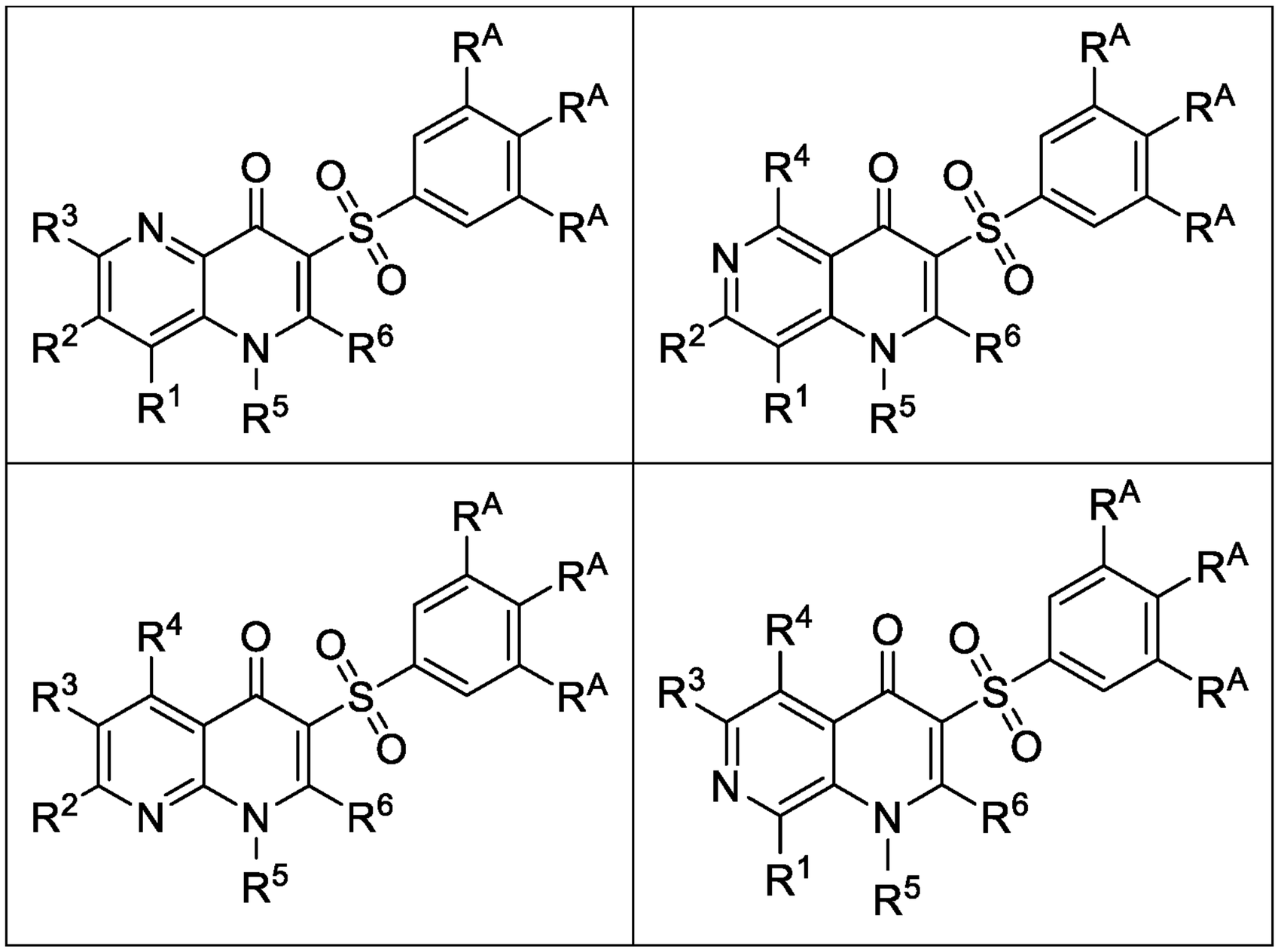


In some embodiments, ring A is:



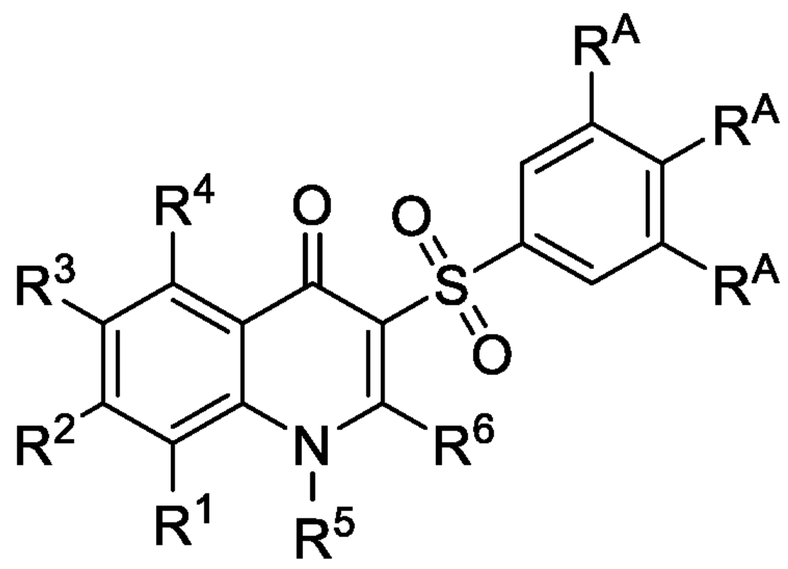
In some embodiments, the compound of Formula (Ia) is selected from any one of the following compounds:





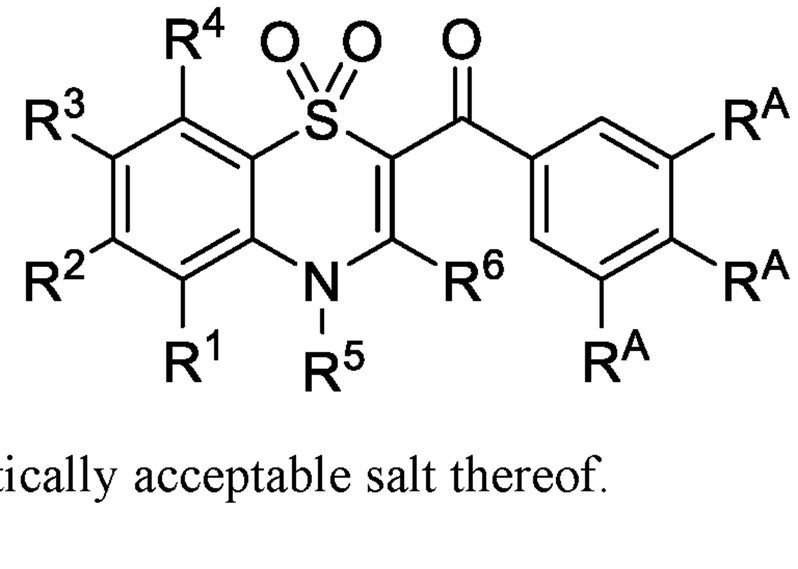
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) has formula:



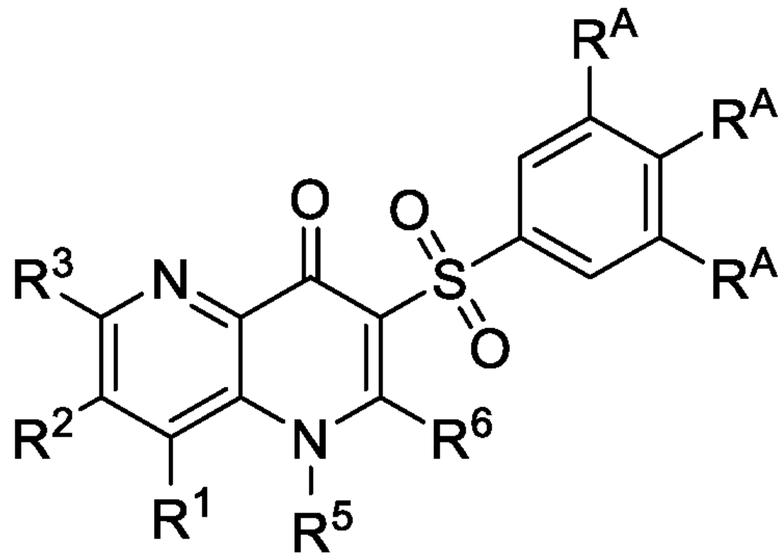
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) has formula:



or a pharmaceutically acceptable salt thereof.

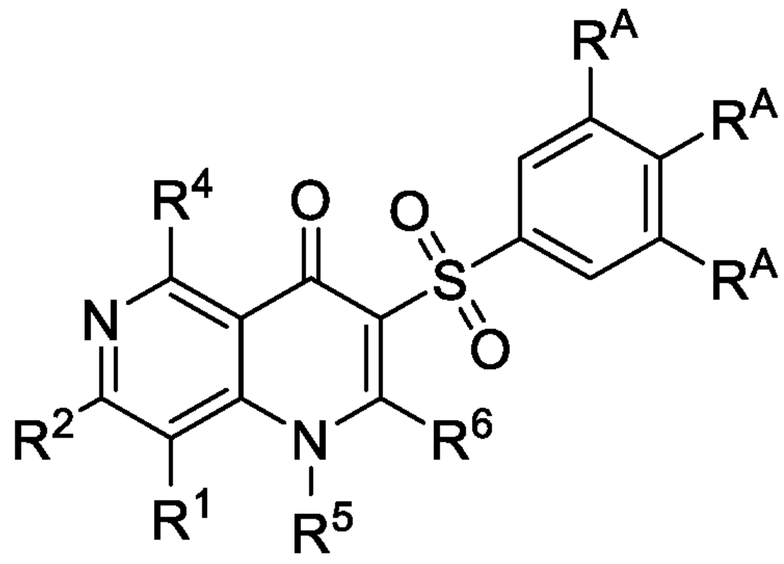
In some embodiments, the compound of Formula (Ia) has formula:



,

or a pharmaceutically acceptable salt thereof.

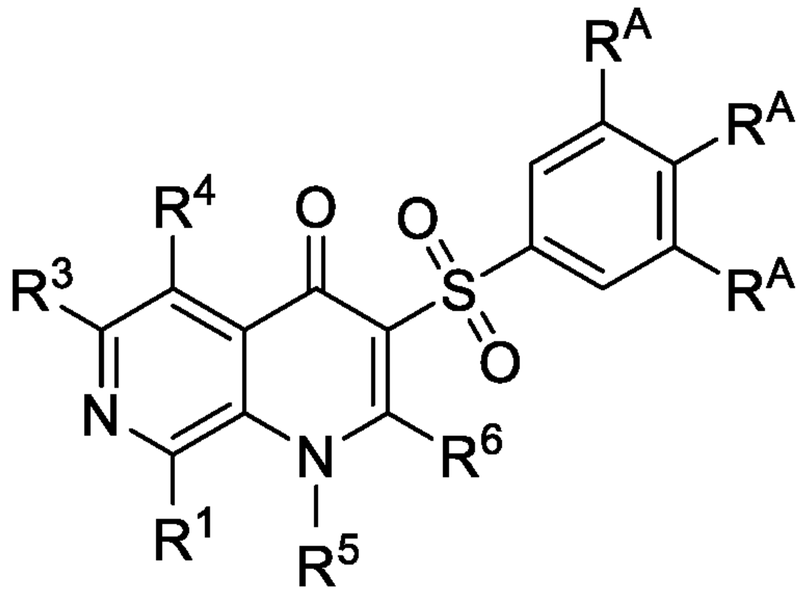
In some embodiments, the compound of Formula (Ia) has formula:



,

or a pharmaceutically acceptable salt thereof.

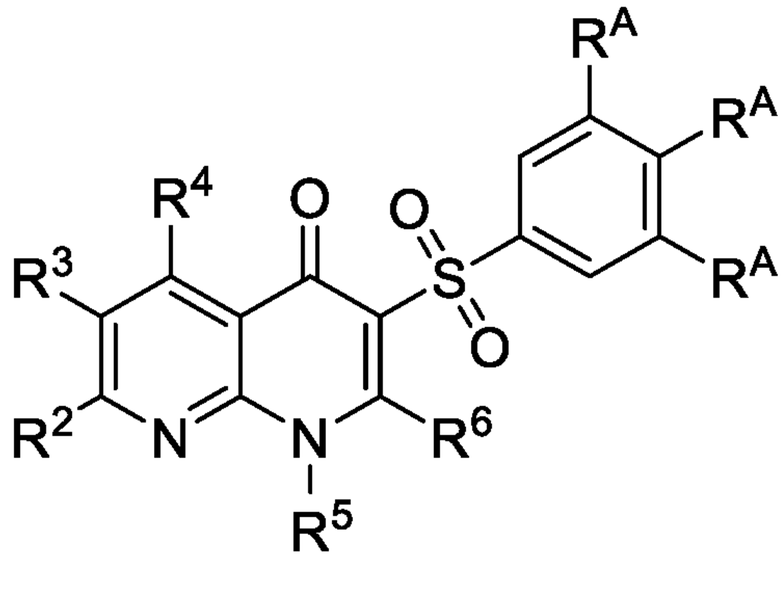
In some embodiments, the compound of Formula (Ia) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, each R^9 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$.

In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, R^A is H. In some embodiments, R^A is halo. In some embodiments, R^A is CN. In some embodiments, R^A is C_{1-6} alkyl. In some embodiments, R^A is C_{1-6} alkoxy.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^7.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, C_{1-6} alkyl, and OR^{a1}. In some embodiments, at least one of R^1, R^2, R^3, R^4, and R^6 is H. In some embodiments, at least one of R^1, R^2, R^3, R^4, and R^6 is halo. In some embodiments, at least one of R^1, R^2, R^3, R^4, and R^6 is CN. In some embodiments, at least one of R^1, R^2, R^3, R^4, and R^6 is C_{1-6} alkyl. In some embodiments, at least one of R^1, R^2, R^3, R^4, and R^6 is OR^{a1}.

In some embodiments, R^1, if present in the compound of Formula (Ia), is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy; R^2, if present in the compound of Formula (Ia), is selected from H, CN, halo, C_{1-6} alkoxy, and C_{1-6} alkyl; R^3, if present

in the compound of Formula (Ia), is selected from H, CN, halo, C_{1-6} alkoxy, and C_{1-6} alkyl; R^4, if present in the compound of Formula (Ia), is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy; and R^6, if present in the compound of Formula (Ia), is selected from H and OH. In some embodiments, R^6 is OH.

In some embodiments, R^7 is selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$.

In some embodiments, R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8.

In some embodiments, R^8 is selected from Cy^1, CN, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, R^8 is selected from Cy^1 and $C(O)NR^{c1}R^{d1}$. In some embodiments, R^8 is Cy^1. In some embodiments, R^8 is $C(O)NR^{c1}R^{d1}$.

In some embodiments, R^5 is H.

In some embodiments, R^5 is Cy^1.

In some embodiments, R^5 is C_{1-6} alkyl, optionally substituted with Cy^1. In some embodiments, R^5 is C_{1-6} alkyl substituted with Cy^1. I In some embodiments, R^5 is C_{1-6} alkyl, optionally substituted with $C(O)NR^{c1}R^{d1}$. In some embodiments, R^5 is C_{1-6} alkyl substituted with $C(O)NR^{c1}R^{d1}$.

In some embodiments, Cy^1 is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1}.

In some embodiments, Cy^1 is C_{6-10} aryl, optionally substituted with R^{Cy1}.

In some embodiments, R^{Cy1} is selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl. In some embodiments, R^{Cy1} is halo.

In some embodiments, Cy^1 is C_{6-10} aryl, optionally substituted with halo.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, each R^g is independently selected from halo and C_{1-6} alkyl.

In some embodiments of Formula (Ia):

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$;

each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

R^7 is selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$;

R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from Cy^1, CN, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments of Formula (Ia):

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy;

each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, C_{1-6} alkyl, and OR^{a1};

R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from Cy^1 and $C(O)NR^{c1}R^{d1}$;

Cy^1 is C_{6-10} aryl, optionally substituted with R^{Cy1};

R^{Cy1} is selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

wherein each R^g is independently selected from halo and C_{1-6} alkyl.

In some embodiments:

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^1, if present in the compound of Formula (Ia), is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^2, if present in the compound of Formula (Ia), is selected from H, CN, halo, C_{1-6} alkoxy, and C_{1-6} alkyl;

R^3, if present in the compound of Formula (Ia), is selected from H, CN, halo, C_{1-6} alkoxy, and C_{1-6} alkyl;

R^4, if present in the compound of Formula (Ia), is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R^6, if present in the compound of Formula (Ia), is selected from H and OH.

R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from Cy^1 and $C(O)NR^{c1}R^{d1}$;

Cy^1 is C_{6-10} aryl, optionally substituted with halo;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from halo and C_{1-6} alkyl.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

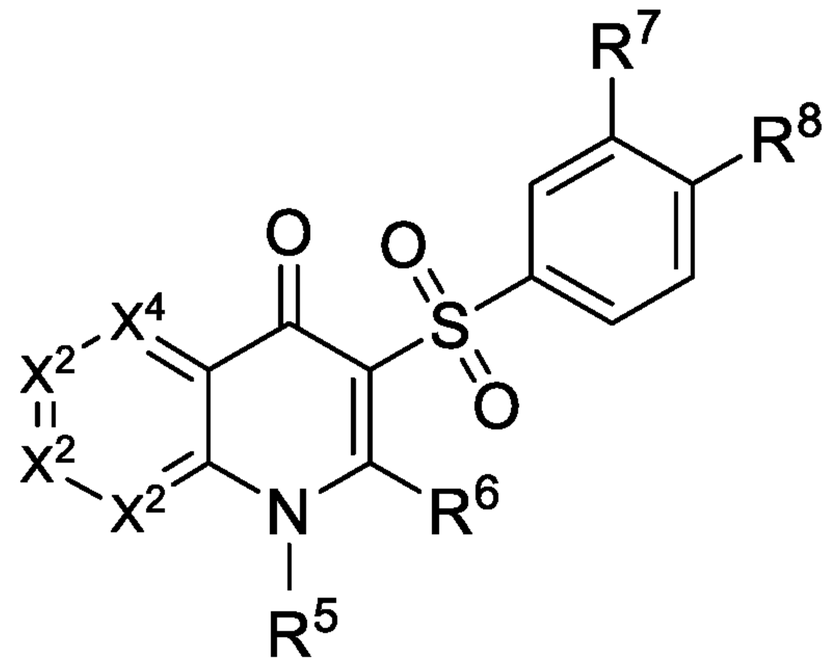
In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (Ia) is selected from any one of the compounds of Table 1a, Table 1d, or Table 1e, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (Ia) is selected from any one of the compounds of Table 1a, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (Ia) is selected from any one of the compounds of Table 1d, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (Ia) is selected from any one of the compounds of Table 1e, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (Ia) has Formula (Ib), or a pharmaceutically acceptable salt thereof.

Formula (Ib):

In one general aspect, the present disclosure provides a compound of Formula (Ib):



(Ib),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^1;

X^2 is selected from N and CR^2;

X^3 is selected from N and CR^3;

X^4 is selected from N and CR^4;

provided that at least one of X^1, X^2, X^3, and X^4 is N;

each of R^1, R^2, R^3, R^4, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^5 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from Cy^1, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^7 and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$,

$NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{12};

each R^{12} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

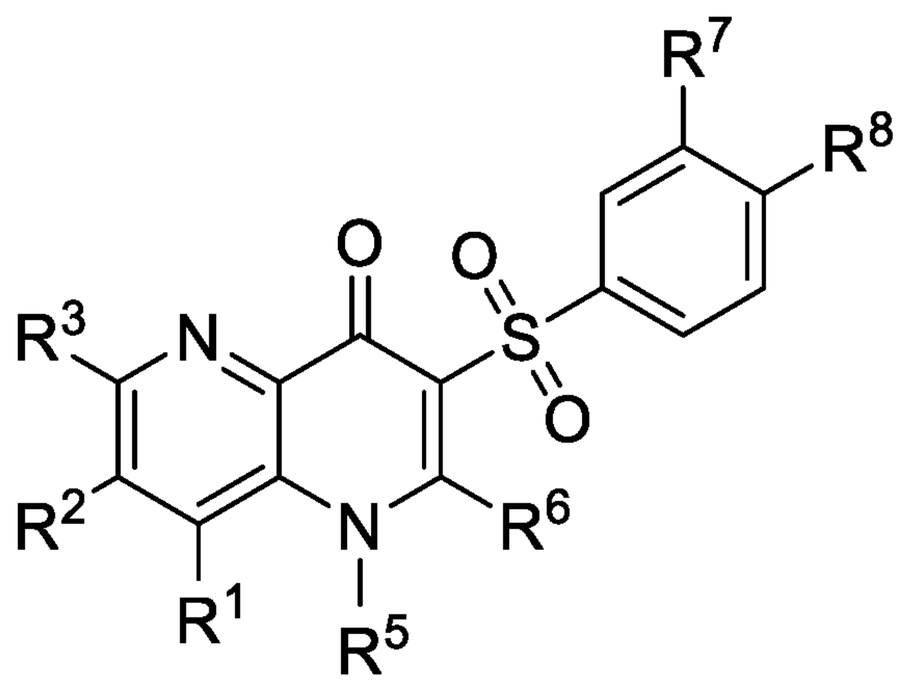
or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-

C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, X^1 is N. In some embodiments, X^1 is CR^1. In some embodiments, X^2 is N. In some embodiments, X^2 is CR^2. In some embodiments, X^3 is N. In some embodiments, X^3 is CR^3. In some embodiments, X^4 is N. In some embodiments, X^4 is CR^1. In some embodiments, one of X^1, X^2, X^3, and X^4 is N. In some embodiments, two of X^1, X^2, X^3, and X^4 are N.

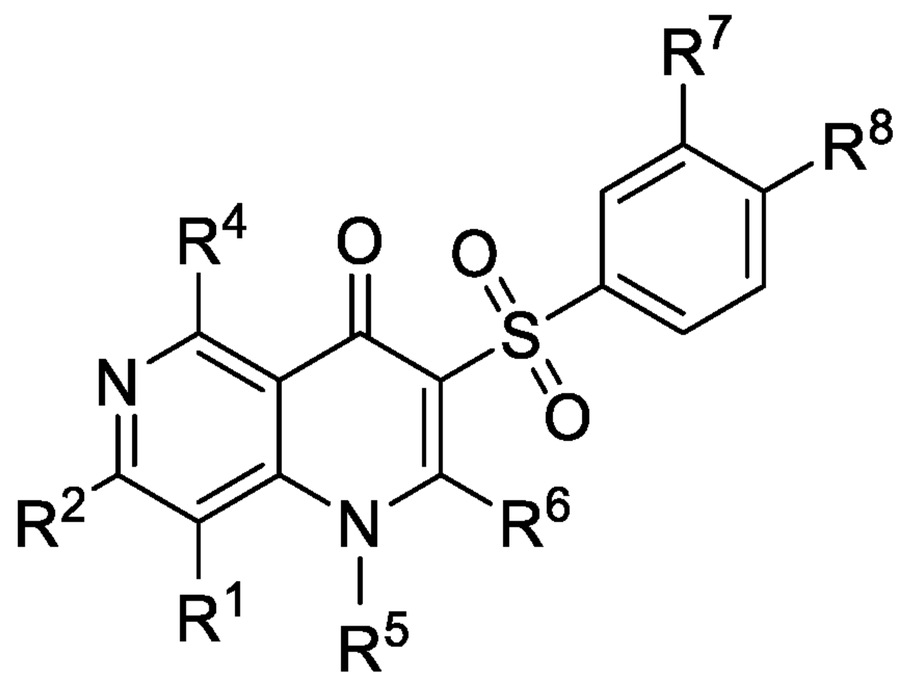
In some embodiments, the compound of Formula (Ib) has formula:



,

or a pharmaceutically acceptable salt thereof.

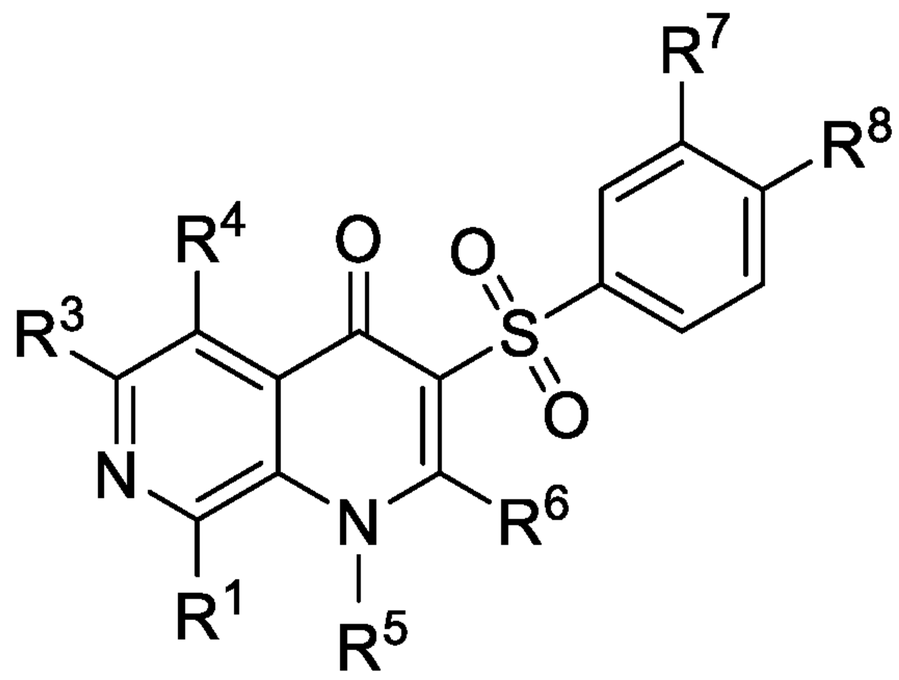
In some embodiments, the compound of Formula (Ib) has formula:



,

or a pharmaceutically acceptable salt thereof.

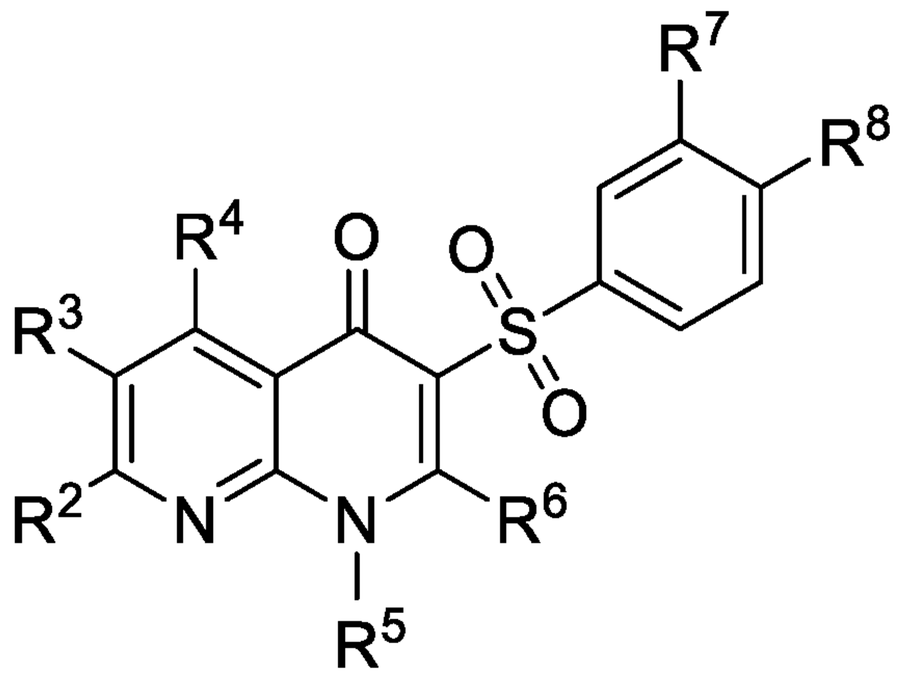
In some embodiments, the compound of Formula (Ib) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ib) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, R^7 and R^8 are each independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments, R^7 and R^8 are each independently selected from H, halo, and C_{1-6} alkyl. In some embodiments, R^7 is H and R^8 is halo. In some embodiments, R^7 is halo and R^8 is H. In some embodiments, R^7 is C_{1-6} alkyl and R^8 is halo. In some embodiments, R^7 is halo and R^8 is C_{1-6} alkyl. In some embodiments, R^7 and R^8 are each halo. In some embodiments, R^8 is F.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ib), is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ib), is independently selected from H, halo, and OR^{a1}. In some embodiments, at least one of R^1, R^2, R^3, and R^4 is selected from halo and C_{1-6} alkoxy. In some embodiments, R^6 is H. In some embodiments, R^6 is OH.

In some embodiments:

each of R^1, R^2, R^3, and R^4, if present in the compound of Formula (Ib), is independently selected from H, halo, and C_{1-6} alkoxy; and

R^6 is selected from H and OH.

In some embodiments, R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^5 is selected from H and C_{1-6} alkyl.

In some embodiments, R^5 is H.

In some embodiments, R^5 is Cy^1.

In some embodiments, R^5 is C_{1-6} alkyl, optionally substituted with R^{10}.

In some embodiments, R^{10} is selected from Cy^1, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$. In some embodiments, R^{10} is OR^{a1}. In some embodiments, R^{10} is $C(O)NR^{c1}R^{d1}$. In some embodiments, R^{10} is $C(O)OR^{a1}$. In some embodiments, R^{10} is $NR^{c1}R^{d1}$.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H and C_{1-6} alkyl.

In some embodiments:

R^7 and R^8 are each independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ib), is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6}

alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments:

R^7 and R^8 are each independently selected from H, halo, and C_{1-6} alkyl;

each of R^1, R^2, R^3, and R^4, if present in the compound of Formula (Ib), is independently selected from H, halo, and C_{1-6} alkoxy;

R^6 is selected from H and OH;

R^5 is selected from H and C_{1-6} alkyl; and

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

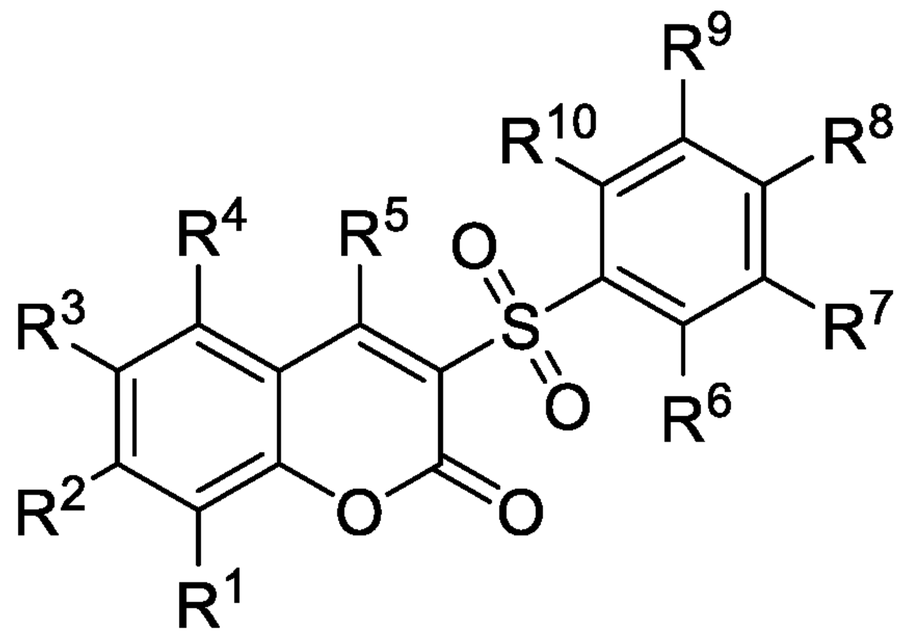
In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (Ib) is selected from any one of the compounds of Table 1d, or a pharmaceutically acceptable salt thereof.

In one general aspect, the present disclosure provides a compound selected from any one of the compounds of Table 1e, or a pharmaceutically acceptable salt thereof.

Formula (Ic):

In a general aspect, the present disclosure provides a compound of Formula (Ic):



(Ic),

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^B;

each R^B is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^C;

each R^C is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered

heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^B.

In some embodiments, each R^B is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, and $C(O)OR^{a1}$.

In some embodiments, at least one of R^1, R^2, R^3, R^4, and R^5 is halo. In some embodiments, at least one of R^1, R^2, R^3, R^4, and R^5 is OR^{a1}. In some embodiments, at least one of R^1, R^2, R^3, R^4, and R^5 is C_{1-6} alkoxy.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, and C_{1-6} alkoxy.

In some embodiments, each of R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^C.

In some embodiments, each R^C is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, each of R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, and C_{1-6} alkyl. In some embodiments, at least one of R^6, R^7, R^8, R^9, and R^{10} is halo. In some embodiments, at least one of R^6, R^7, R^8, R^9, and R^{10} is CN. In some embodiments, at least one of R^6, R^7, R^8, R^9, and R^{10} is C_{1-6} alkyl.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H and C_{1-6} alkyl.

In some embodiments:

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^B;

each R^B is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^C;

each R^C is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, and C_{1-6} alkoxy; and each of R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, and C_{1-6} alkyl.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

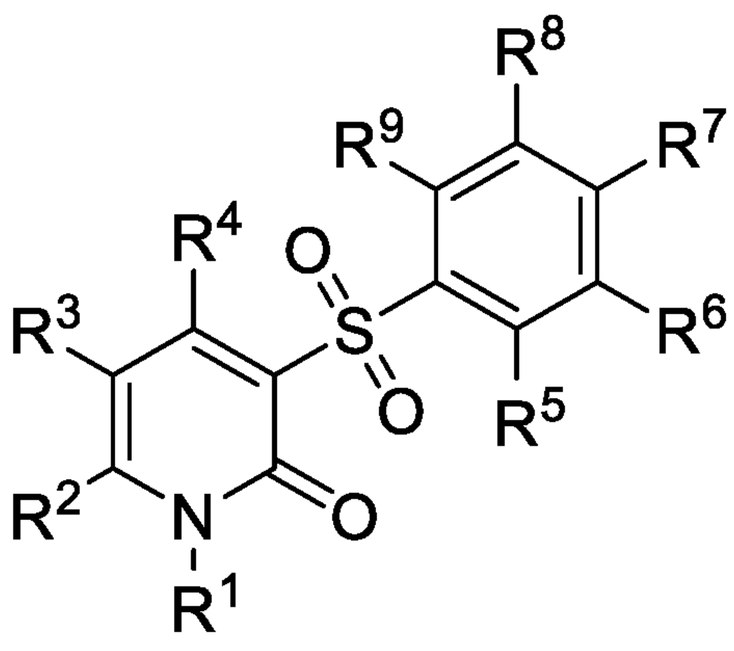
In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (Ic) is selected from any one of the compound of Table 1b, or a pharmaceutically acceptable salt thereof.

Formula (Id):

In one general aspect, the present disclosure provides a compound of Formula (Id):



(Id),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^2, R^3, and R^4 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^B;

each R^B independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^C;

each R^C is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene,

HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, R^1 is H. In some embodiments, R^1 is C_{1-6} alkyl. In some embodiments, R^1 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments, R^1 is selected from H and C_{1-6} alkyl. In some embodiments, R^1 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, each R^{10} is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$. In some embodiments, each R^{10} is independently selected from OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$.

In some embodiments, each of R^2, R^3, and R^4 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}; wherein said C_{1-6} alkyl is each optionally substituted with 1, 2, or 3 substituents independently selected from R^B.

In some embodiments, each R^B is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$. In some embodiments, each R^B is independently selected from OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$.

In some embodiments, each of R^2, R^3, and R^4 is independently selected from H and C_{1-6} alkyl. In some embodiments, R^3 is H, and R^2 and R^4 are each C_{1-6} alkyl.

In some embodiments, each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^C.

In some embodiments, each R^C is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$. In some embodiments, each R^C is independently selected from OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$. In some embodiments, each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H and halo. In some embodiments, at least one of R^5, R^6, R^7, R^8, and R^9 is halo.

In some embodiments, each of R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g.

In some embodiments, each of R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H and C_{1-6} alkyl.

In some embodiments:

R^1 is H;

each of R^2, R^3, and R^4 is independently selected from H and C_{1-6} alkyl; and

each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H and halo.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

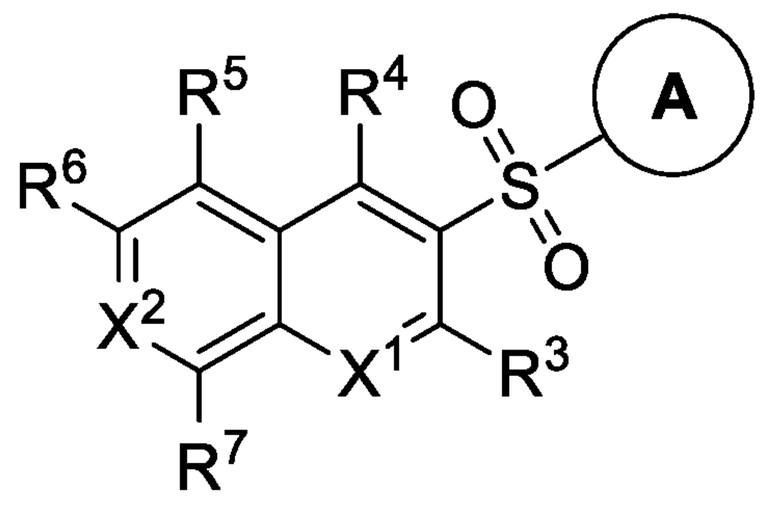
In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (Id) is selected from any one of the compounds of Table 1c, or a pharmaceutically acceptable salt thereof.

Formula (Ie)

In one general aspect, the present disclosure provides a compound of Formula (Ie):



(Ie),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^1;

X^2 is selected from N and CR^2;

each R^1, R^2, R^3, R^4, R^5, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^7 is selected from OR^{a2} and $NR^{c2}R^{d2}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

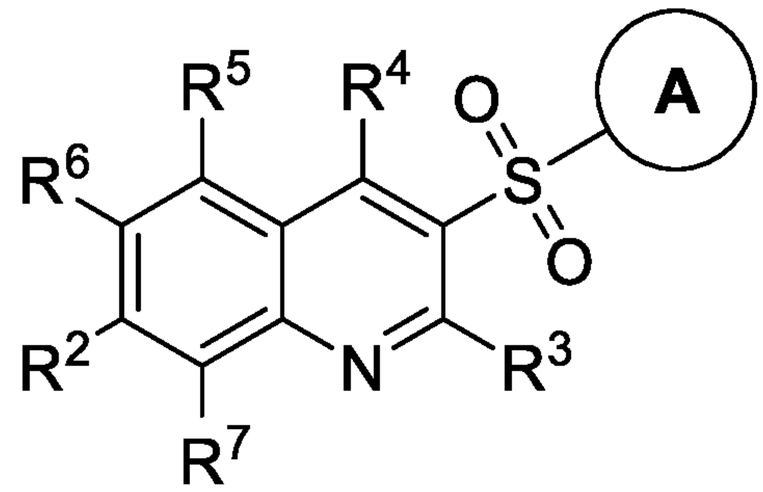
each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

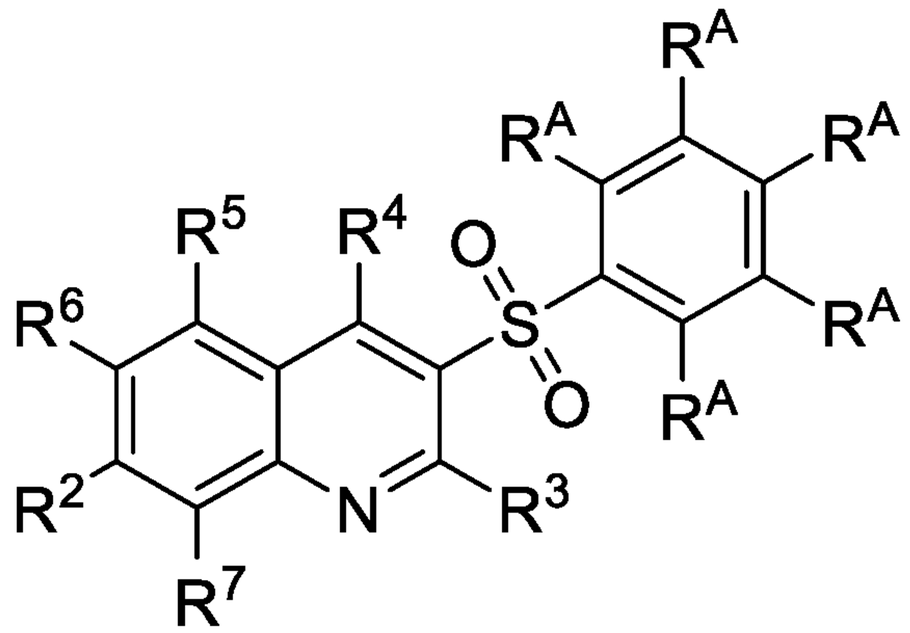
In some embodiments, the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

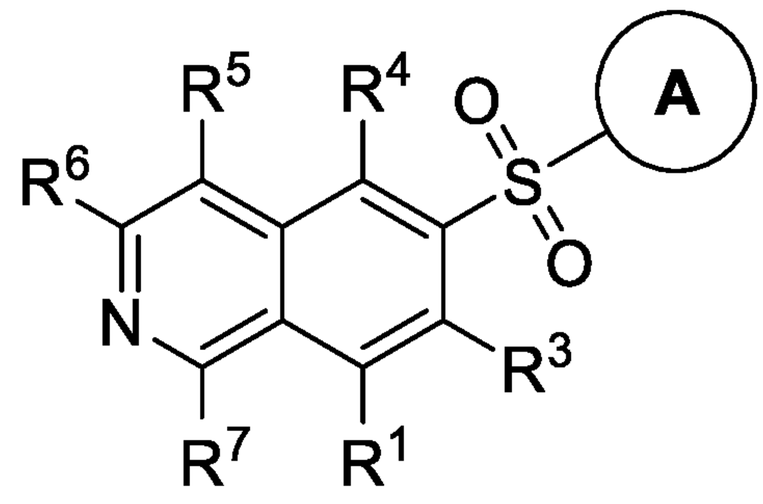
In some embodiments, the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

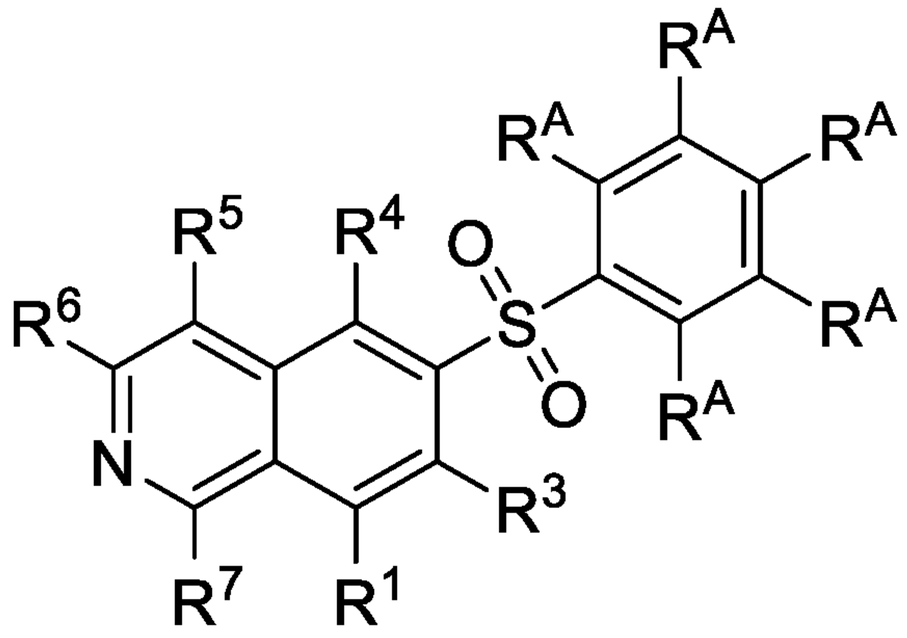
In some embodiments, the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

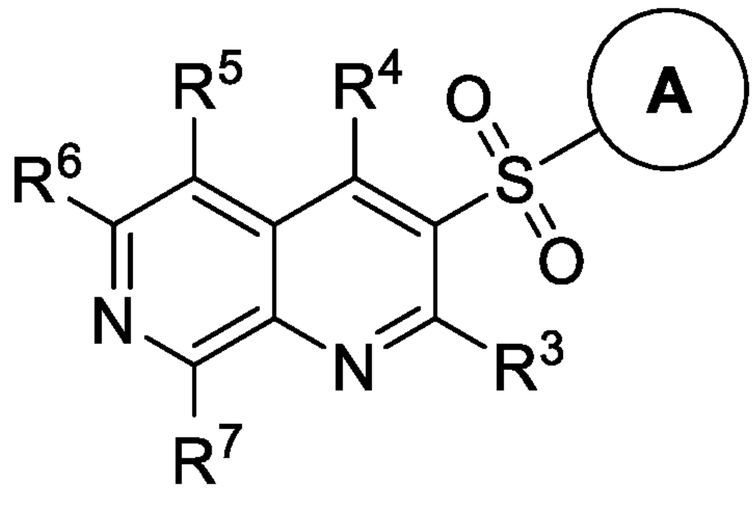
In some embodiments, the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

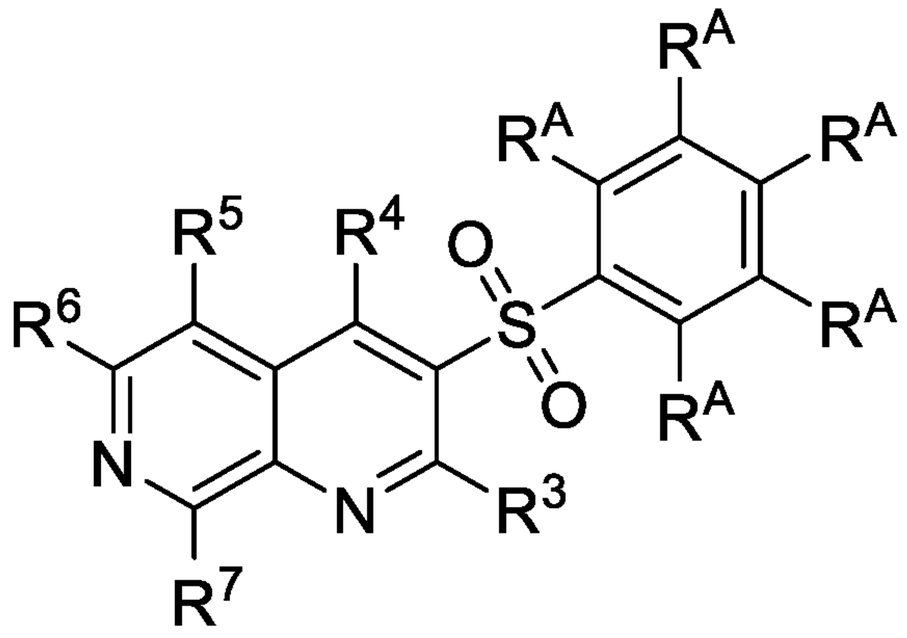
In some embodiments, the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^6 is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8.

In some embodiments, each R^8 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, OH, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H and C_{1-6} alkyl.

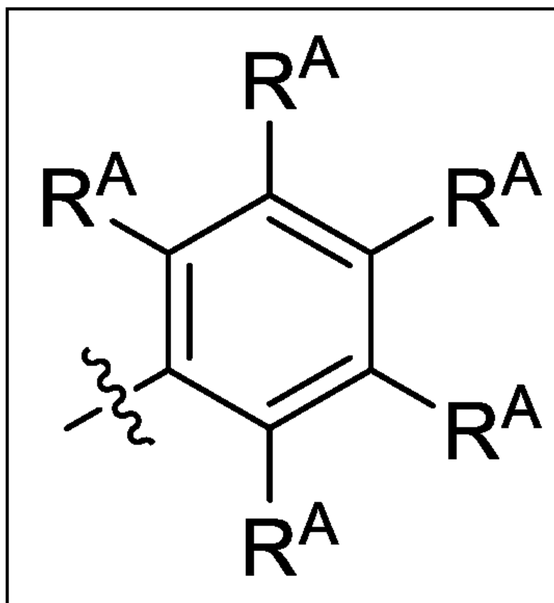
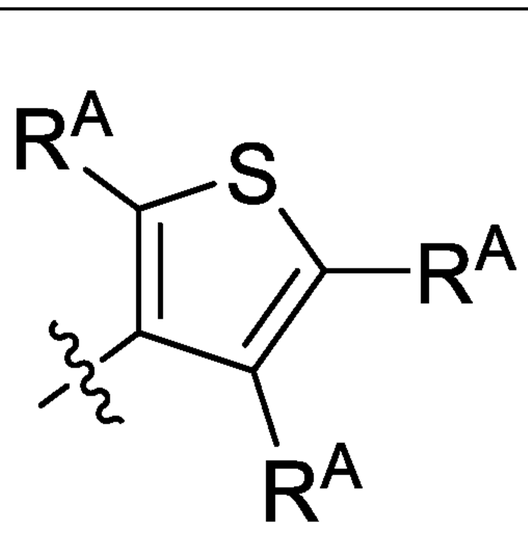
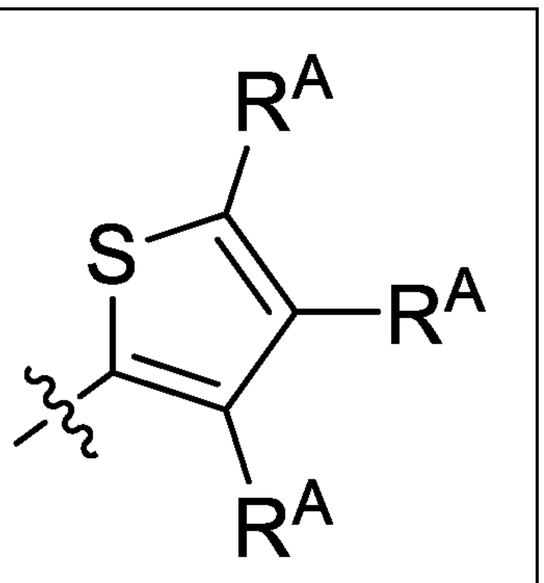
In some embodiments, R^7 is OR^{a2}. In some embodiments, R^7 is OH. In some embodiments, R^7 is C_{1-6} alkoxy. In some embodiments, R^7 is $NR^{c2}R^{d2}$. In some embodiments, R^7 is amino. In some embodiments, R^7 is C_{1-6} alkylamino. In some embodiments, R^7 is di(C_{1-6} alkyl)amino.

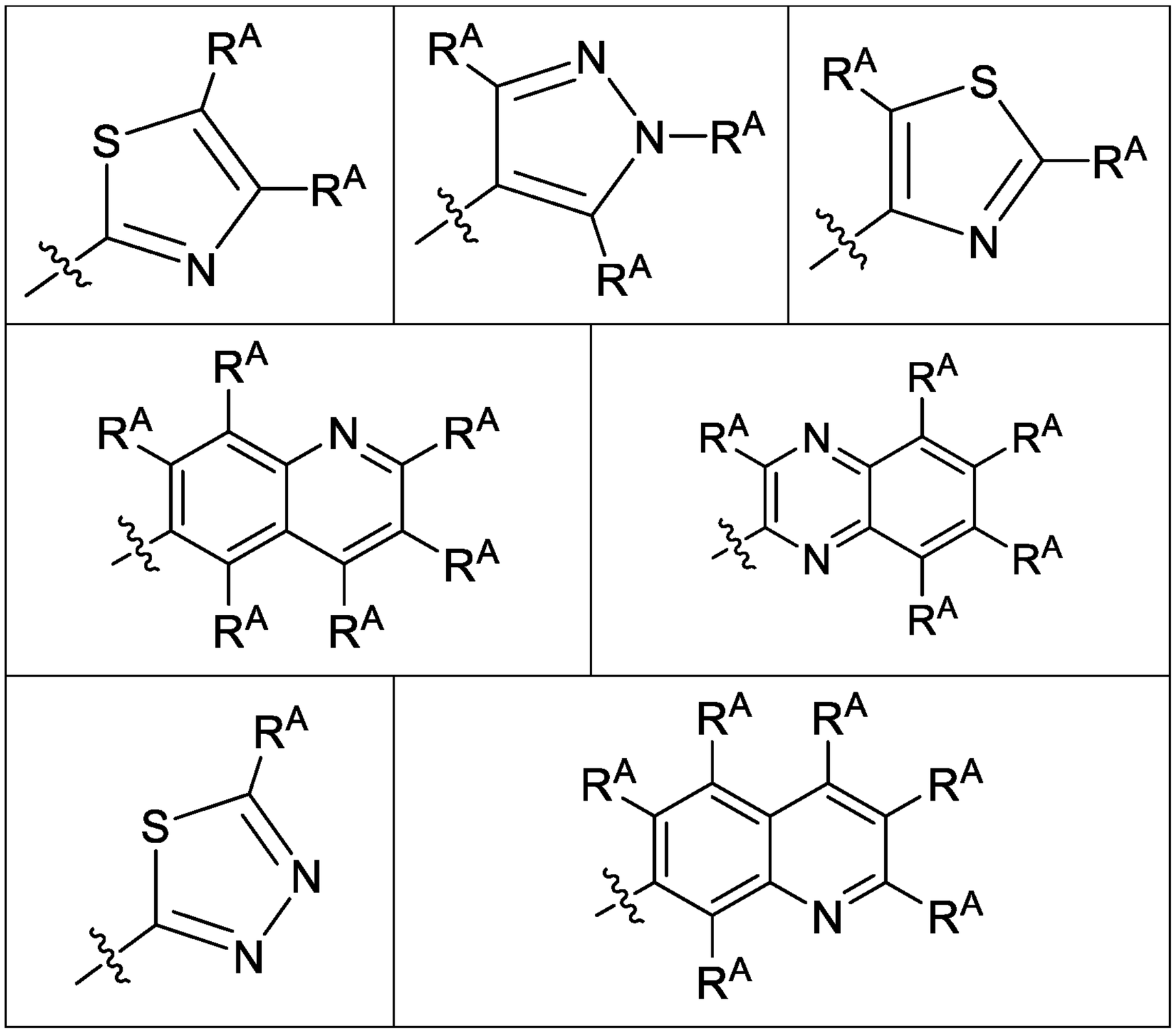
In some embodiments, ring A is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1-6 substituents independently selected from R^A.

In some embodiments, ring A is C_{6-10} aryl, substituted with 1-5 substituents independently selected from R^A. In some embodiments, ring A is phenyl, optionally substituted with 1-5 substituents independently selected from R^A. In some embodiments, ring A is naphthyl, optionally substituted with 1-5 substituents independently selected from R^A.

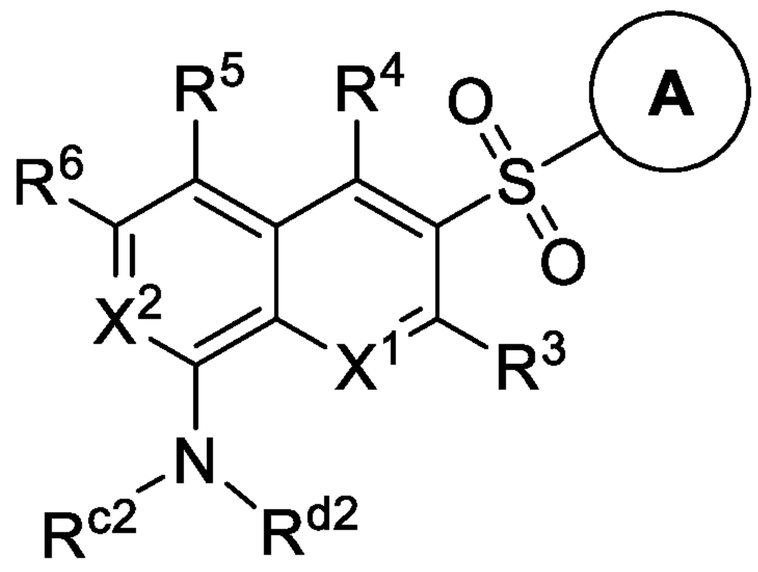
In some embodiments, ring A is 5-10 membered heteroaryl, substituted with 1-6 substituents independently selected from R^A. In some embodiments, ring A is selected from pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, thiophen-2-yl, thiophen-3-yl, pyrazol-3-yl, pyrazlol-4-yl, pyrazol-5-yl, quinolin-6-yl, quinolin-7-yl, thiazolyl, 1,3,4-thiadiazolyl, and quinoxaline-6-yl, each of which is optionally substituted with 1-6 substituents independently selected from R^A.

In some embodiments, ring A is selected from any one of the following moieties:



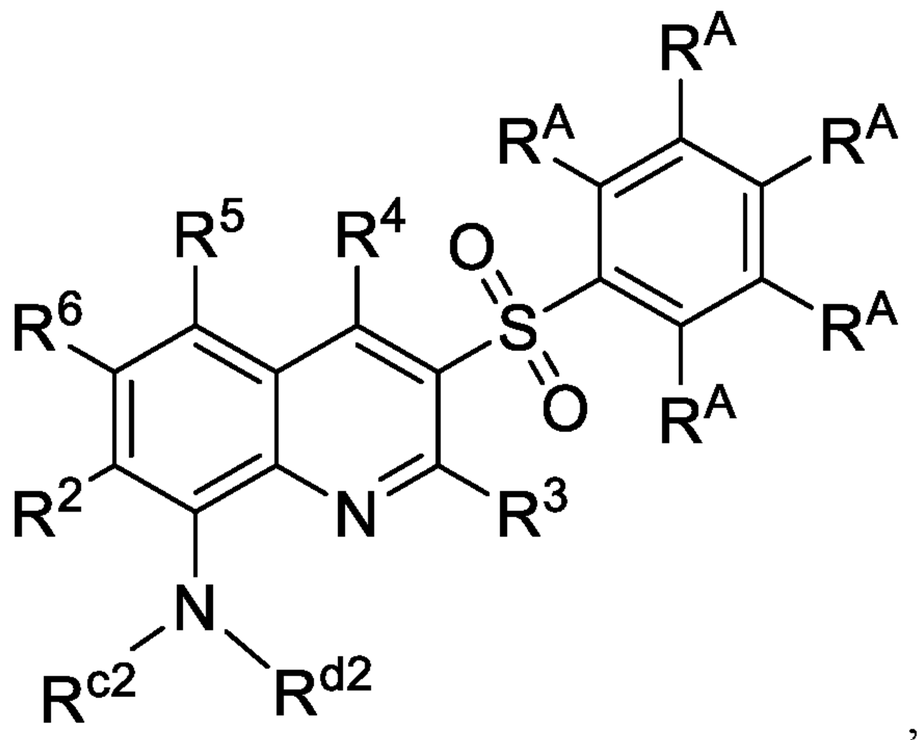
In some embodiments, the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

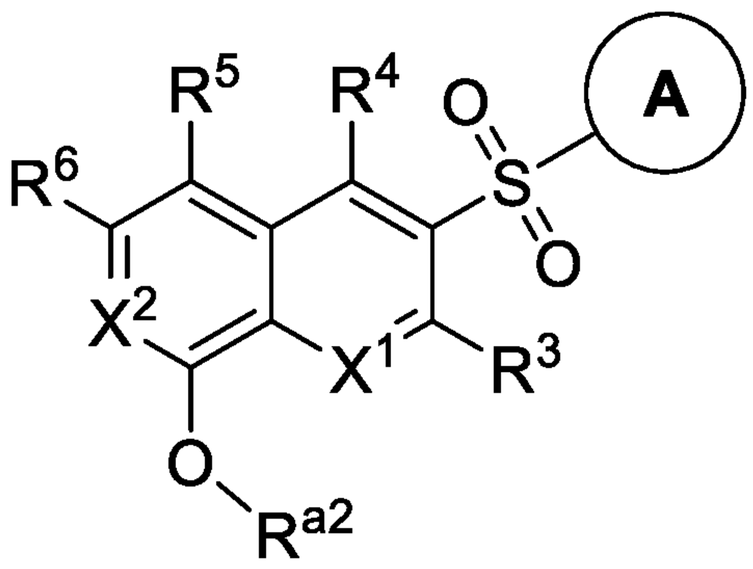
In some embodiments, the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

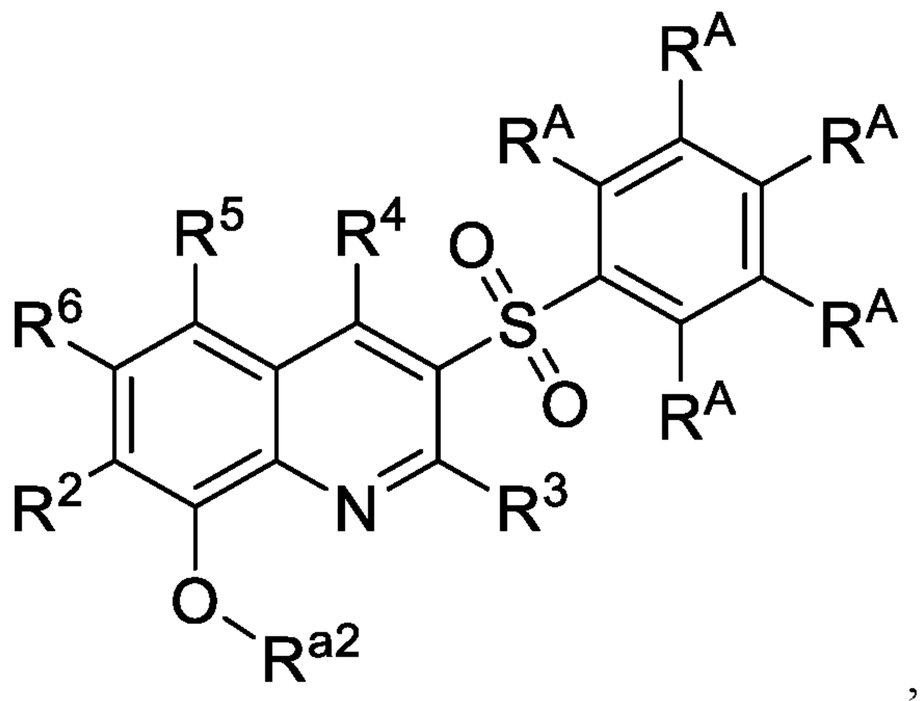
In some embodiments, the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, each R^9 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$.

In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, R^A is H. In some embodiments, at least one R^A is halo. In some embodiments, at least one R^A is CN. In some embodiments, at least one R^A is C_{1-6} alkyl. In some embodiments, at least one R^A is C_{1-6} alkoxy.

In some embodiments, each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H and C_{1-6} alkyl. In some embodiments, R^{c2} is H and R^{d2} is C_{1-6} alkyl. In some embodiments, R^{c2} and R^{d2} are both H. In some embodiments, R^{c2} and R^{d2} are both C_{1-6} alkyl.

In some embodiments:

R^1, R^2, R^3, R^4, and R^6 is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$;

ring A is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1-6 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$;

each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments:

each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, OH, C_{1-6} alkyl, and C_{1-6} alkoxy;

ring A is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1-6 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy; and

each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

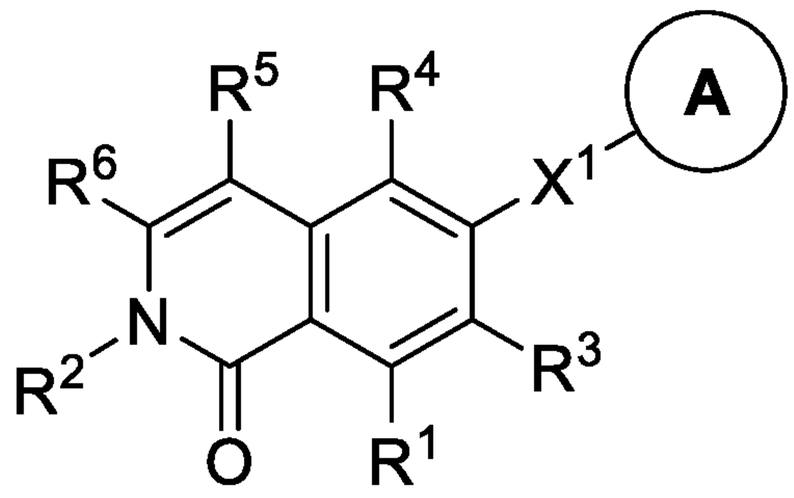
In some embodiments, each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (Ie) is selected from any one of the compounds of Table 1f, or a pharmaceutically acceptable salt thereof.

Formula (If)

In one general aspect, the present disclosure provides a compound of Formula (If):



(If),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

R^1, R^3, R^4, R^5, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, X^1 is S.

In some embodiments, X^1 is S(O).

In some embodiments, X^1 is $S(O)_2$.

In some embodiments, R^1, R^3, R^4, R^5, and R^6 is independently selected from H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

In some embodiments, R^1, R^3, R^4, R^5, and R^6 are each H.

In some embodiments, R^2 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl.

In some embodiments, ring A is C_{6-10} aryl, optionally substituted with 1 or 2 substituents independently selected from halo and C_{1-6} alkyl.

In some embodiments:

R^1, R^3, R^4, R^5, and R^6 is independently selected from H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino;

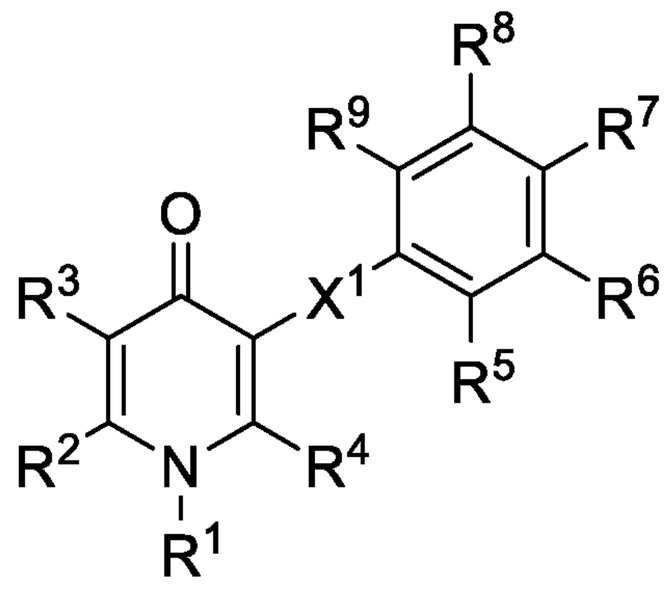
R^2 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

ring A is C_{6-10} aryl, optionally substituted with 1 or 2 substituents independently selected from halo and C_{1-6} alkyl.

In some embodiments, the compound of Formula (If) is selected from any one of the compound of Table 1g, or a pharmaceutically acceptable salt thereof.

Formula (Ig)

In one general aspect, the present disclosure provides a compound of Formula (Ig):



(Ig),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

R^1 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^2, R^3, and R^4 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^B;

each R^B independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^C;

each R^C is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, X^1 is selected from S(O) and $S(O)_2$.

In some embodiments, R^1 is H.

In some embodiments, each of R^2, R^3, and R^4 is independently selected from H and C_{1-6} alkyl.

In some embodiments, each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H, halo, and C_{1-6} alkyl.

In some embodiments:

X^1 is S(O) or $S(O)_2$;

R^1 is H;

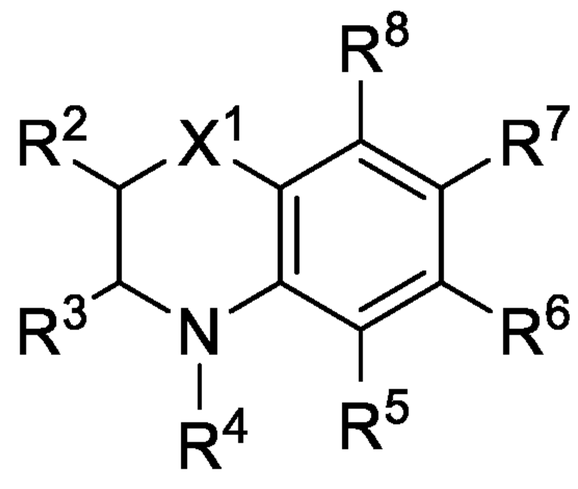
each of R^2, R^3, and R^4 is independently selected from H and C_{1-6} alkyl; and

each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H, C_{1-6} alkyl and halo.

In some embodiments, the compound of Formula (Ig) is selected from any one of the compounds of Table 1h, or a pharmaceutically acceptable salt thereof.

Formula (IIa)

In one general aspect, the present disclosure provides a compound of Formula (IIa):



(IIa),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from O and NR^1;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^3 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

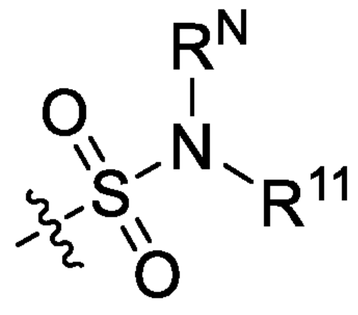
R^1 and R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^1 and R^2, together with N atom to which R^1 is attached and C atom to which R^2 is attached, form a 4-10 membered heterocycloalkyl ring, which is substituted with

1, 2, or 3 substituents independently selected from R^9;

R^5 and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$; and a group of formula (i):



(i),

wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

provided that at least one of R^7 and R^8 is a group of formula (i);

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a -10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

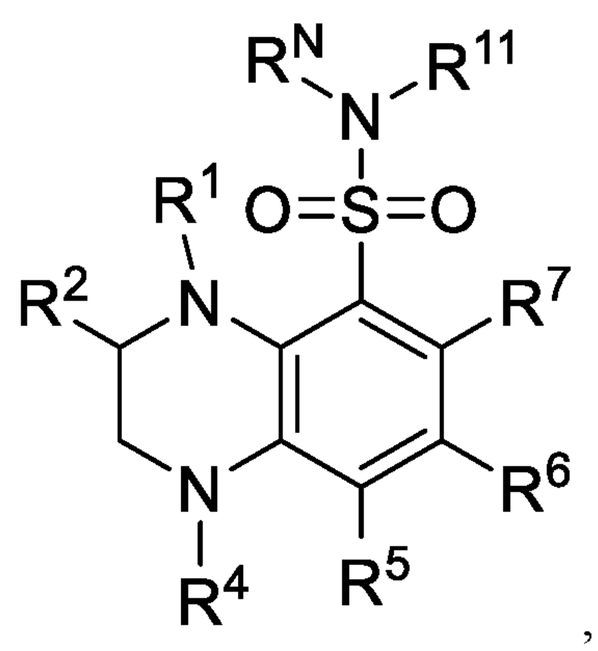
each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

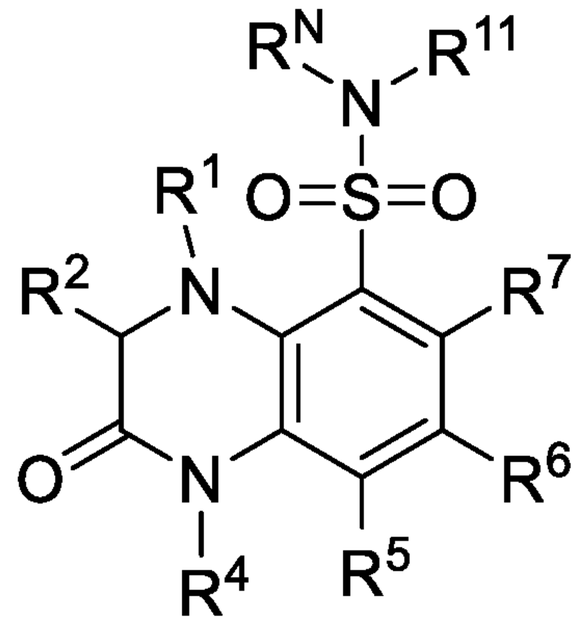
each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, the compound of Formula (IIa) has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIa) has formula:



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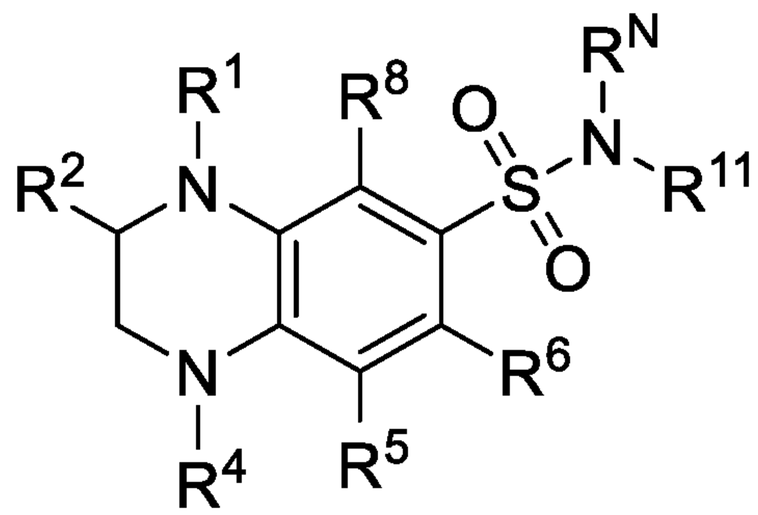
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIa) has formula:



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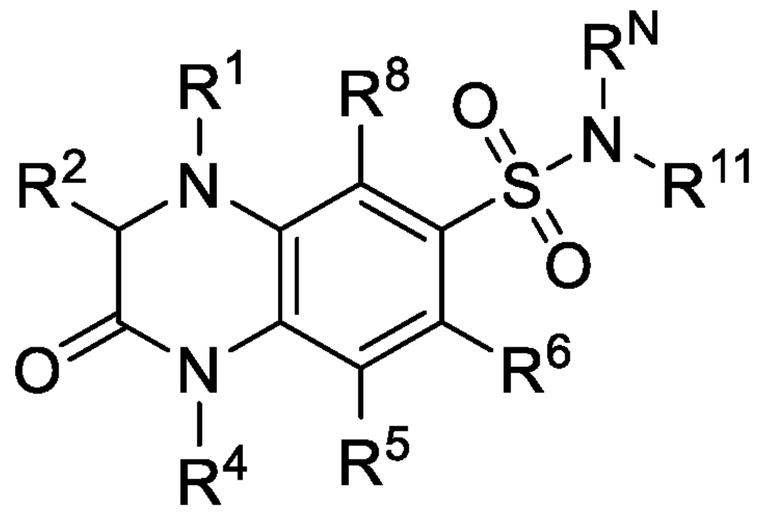
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIa) has formula:

,

or a pharmaceutically acceptable salt thereof.

In some embodiments:

R^2 is selected from H and C_{1-6} alkyl;

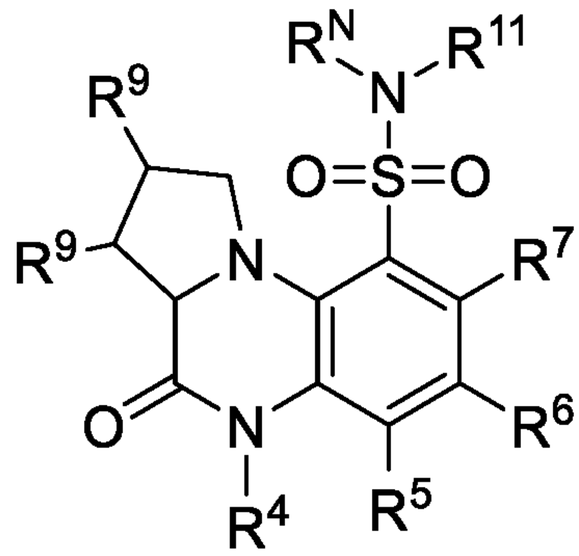
R^1 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments:

R^2 is selected from H and C_{1-6} alkyl;

R^1 is selected from C_{1-6} alkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$.

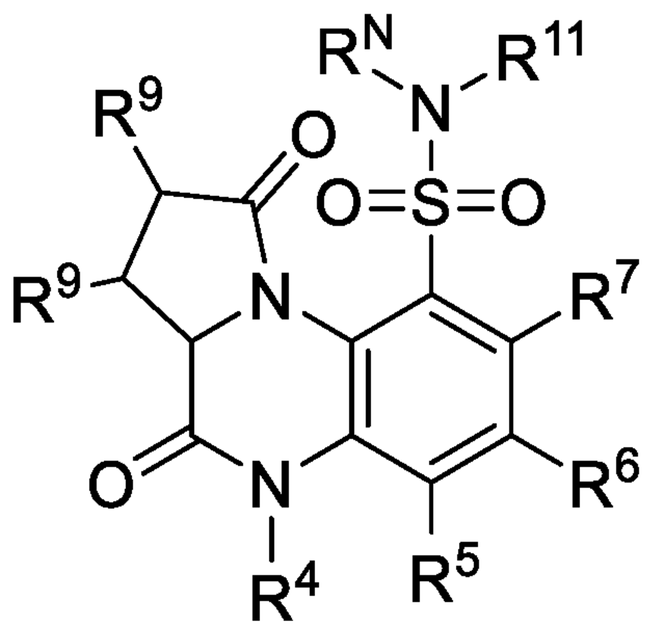
In some embodiments, the compound of Formula (IIa) has formula:



;

or a pharmaceutically acceptable salt thereof.

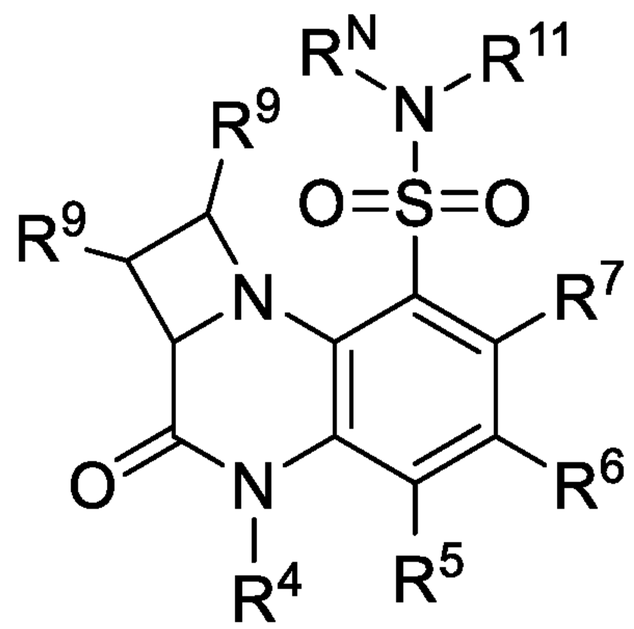
In some embodiments, the compound of Formula (IIa) has formula:



;

or a pharmaceutically acceptable salt thereof.

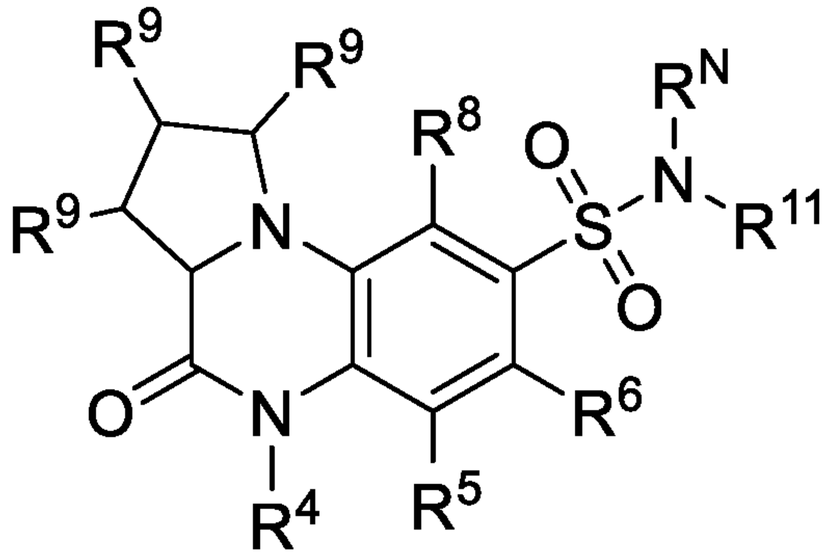
In some embodiments, the compound of Formula (IIa) has formula:



;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIa) has formula:



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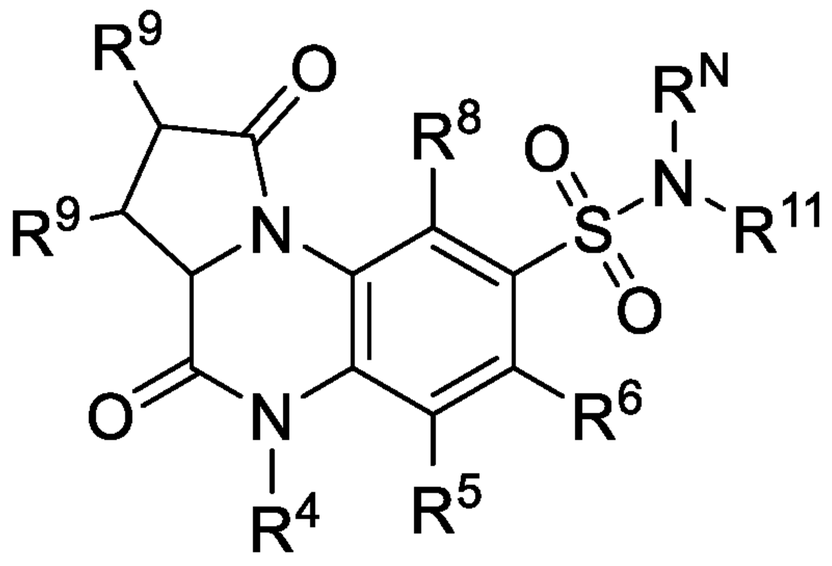
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIa) has formula:



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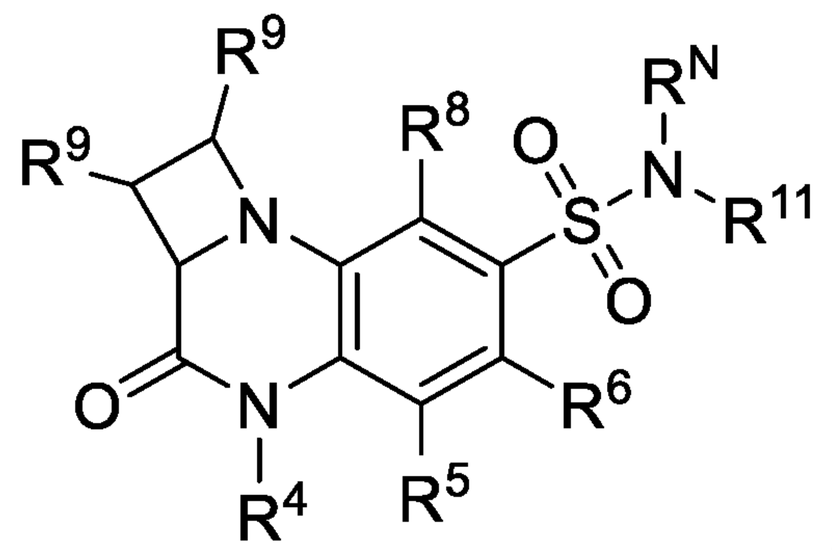
or a pharmaceutically acceptable salt thereof.

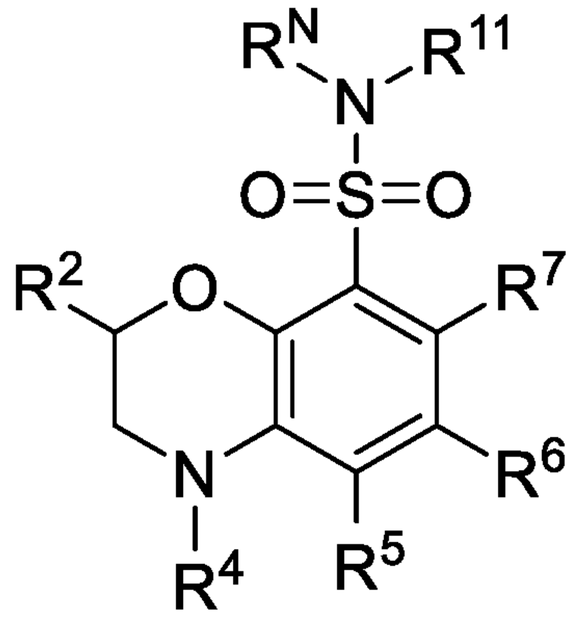
In some embodiments, the compound of Formula (IIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

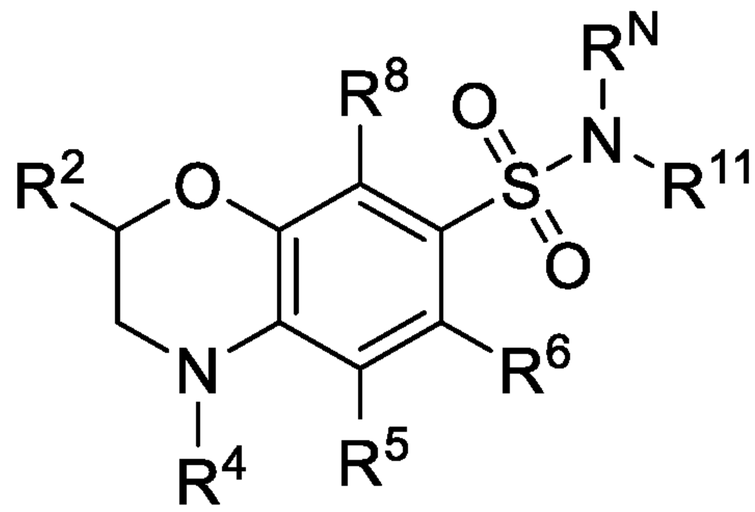
In some embodiments, the compound of Formula (IIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

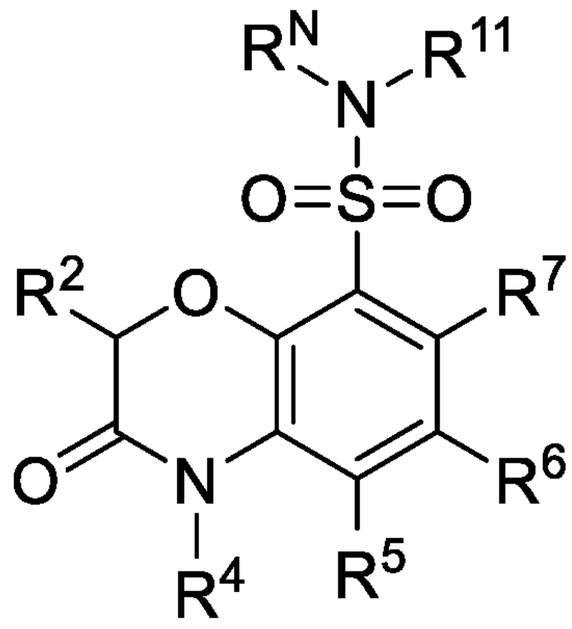
In some embodiments, the compound of Formula (IIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

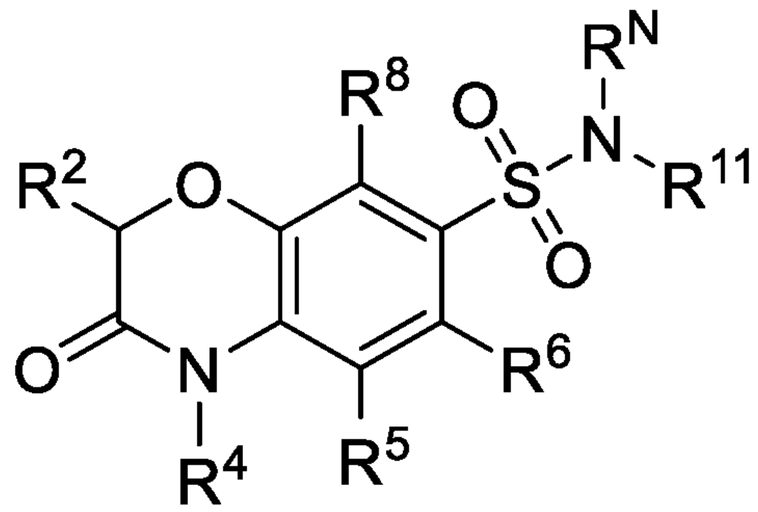
In some embodiments, the compound of Formula (IIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, R^2 is selected from H and C_{1-6} alkyl. In some embodiments, R^2 is H. In some embodiments, R^2 is C_{1-6} alkyl.

In some embodiments, R^4 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^4 is H. In some embodiments, R^4 is C_{1-6} alkyl.

In some embodiments, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with R^9.

In some embodiments, R^5 is H and R^6 is C_{1-6} alkyl, optionally substituted with $NR^{c1}R^{d1}$. In some embodiments, R^5 is H and R^6 is halo. In some embodiments, R^5 is H and R^6 is $S(O)_2R^{b1}$.

In some embodiments, R^7 is selected from H and C_{1-6} alkyl (and R^8 is a moiety of formula (i)). In some embodiments, R^8 is selected from H and C_{1-6} alkyl (and R^7 is a moiety of formula (i)).

In some embodiments, R^N is selected from H and C_{1-6} alkyl. In some embodiments, R^N is H. In some embodiments, R^N is C_{1-6} alkyl.

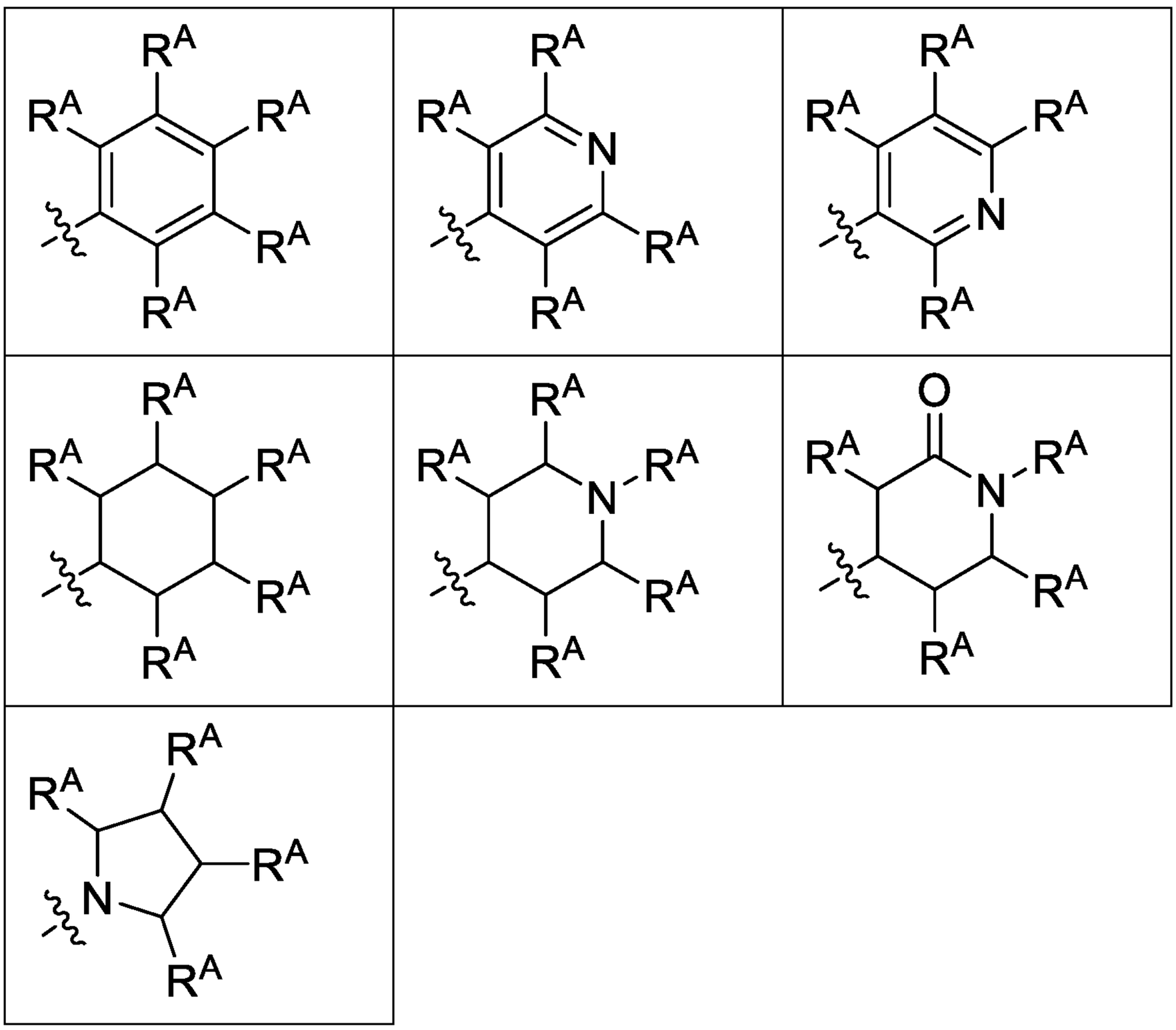
In some embodiments, R^{11} is ring A.

In some embodiments, R^{11} is C_{1-6} alkyl, optionally substituted with ring A.

In some embodiments, R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from morpholinyl, piperidinyl, and piperazinyl, each of

which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, ring A is selected from any one of the following moieties:



In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, and $NR^{c1}C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments, each R^{11} is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, each R^A is independently selected from H, halo, CN,

C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, and $NR^{c1}C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with $C(O)OR^{a1}$.

In some embodiments, each R^9 is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OH, C_{1-6} alkoxy, carboxy, amino, $C(O)NH_2$, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and C_{1-6} haloalkoxy. In some embodiments, each R^9 is independently selected from OH, C_{1-6} alkoxy, carboxy, $C(O)NH_2$, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, $C(O)NH_2$, and carboxy.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments:

R^2 is selected from H and C_{1-6} alkyl;

R^1 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^1 and R^2, together with N atom to which R^1 is attached and C atom to which R^2 is attached, form a 4-10 membered heterocycloalkyl ring, which is substituted with 1, 2, or 3 substituents independently selected from R^9;

R^3 is selected from H and oxo;

R^4 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3

substituents independently selected from R^9;

R^7 and R^8 are independently selected from H, C_{1-6} alkyl, and a moiety of formula (i);

R^N is selected from H and C_{1-6} alkyl; or

R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from morpholinyl, piperidinyl, and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

R^{11} is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments:

R^2 is selected from H and C_{1-6} alkyl;

R^1 is selected from C_{1-6} alkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$.

R^1 and R^2, together with N atom to which R^1 is attached and C atom to which R^2 is attached, form a 4-10 membered heterocycloalkyl ring, which is substituted with 1, 2, or 3 substituents independently selected from R^9;

R^3 is selected from H and oxo;

R^4 is H;

R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with R^9;

R^7 and R^8 are independently selected from H, C_{1-6} alkyl, and a moiety of formula (i);

R^N is selected from H and C_{1-6} alkyl; or

R^N and R^{11}, together with the N atom to which they are attached, form a ring

selected from morpholinyl, piperidinyl, and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, and $NR^{c1}C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with $C(O)OR^{a1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (IIa) is selected from any one of the compounds of Table 2a, Table 2c, Table 2c-2, Table 2d, Table 2d-2, Table 2e, or Table 16, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIa) is selected from any one of the compounds of Table 2a, Table 2c, Table 2d, or Table 2e, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIa) is selected from any one of the compounds of Table 2a, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIa) is selected from any one of the compounds of Table 2c, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIa) is selected from any one of the compounds of Table 2d, or a

pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIa) is selected from any one of the compounds of Table 2e, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIa) is selected from any one of the compounds of Table 2c-2, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIa) is selected from any one of the compounds of Table 2d-2, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIa) is selected from any one of the compounds of Table 16, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure privdes a compound selected from any one of the compounds of Table 16, or a pharmaceutically acceptable salt thereof.

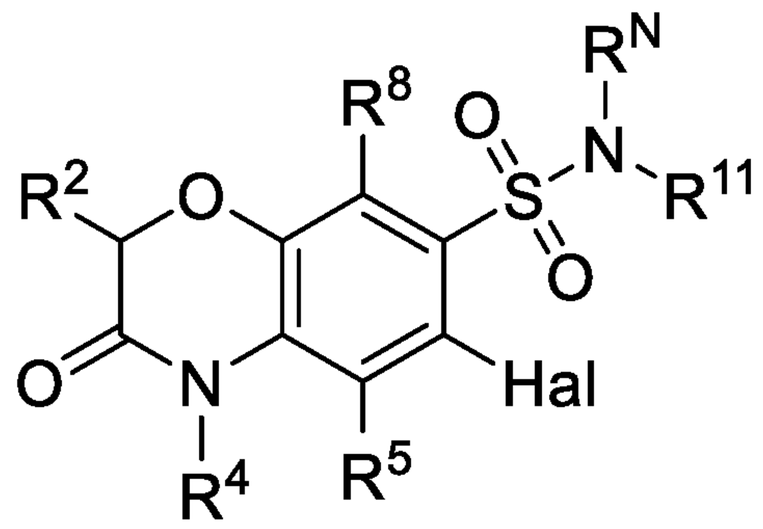
In some embodiments, the compound of Formula (IIa) has Formula (IIb), or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIa) has Formula (IIc), or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIa) has Formula (IId), or a pharmaceutically acceptable salt thereof.

Formula (IIb)

In one general aspect, the present disclosure provides a compound of Formula (IIb):



(IIb),

or a pharmaceutically acceptable salt thereof, wherein:

Hal is a halogen, and

R^2, R^4, R^5, R^8, R^N, and R^{11} are as described herein for Formula (IIa).

In some embodiments:

Hal is a halogen;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl,

each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, for a -10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, R^2 is H or C_{1-6} alkyl.

In some embodiments, R^4 is H or C_{1-6} alkyl.

In some embodiments, R^5 is H or C_{1-6} alkyl.

In some embodiments, R^8 is H or C_{1-6} alkyl.

In some embodiments, R^4, R^5, and R^8 are each H.

In some embodiments, R^N is H.

In some embodiments, R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from pyrrolidinyl, morpholinyl, piperidinyl, and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from pyrrolidinyl, morpholinyl, and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, R^{11} is ring A. In some embodiments, R^{11} is C_{1-6} alkyl, optionally substituted with ring A.

In some embodiments, ring A is selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1-10 substituents independently selected from R^A.

In some embodiments, ring A is C_{6-10} aryl, optionally substituted with 1-10 substituents independently selected from R^A.

In some embodiments, ring A is C_{3-10} cycloalkyl, optionally substituted with 1-10 substituents independently selected from R^A.

In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, and $C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments, each R^A is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, and $C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments:

R^2 is selected from H and C_{1-6} alkyl;

R^4, R^5, and R^8 are each H;

R^N is H; or

R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from pyrrolidinyl, morpholinyl, and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

ring A is selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1-10 substituents independently selected from R^A; and

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, and $C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments, R^A is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, and $C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

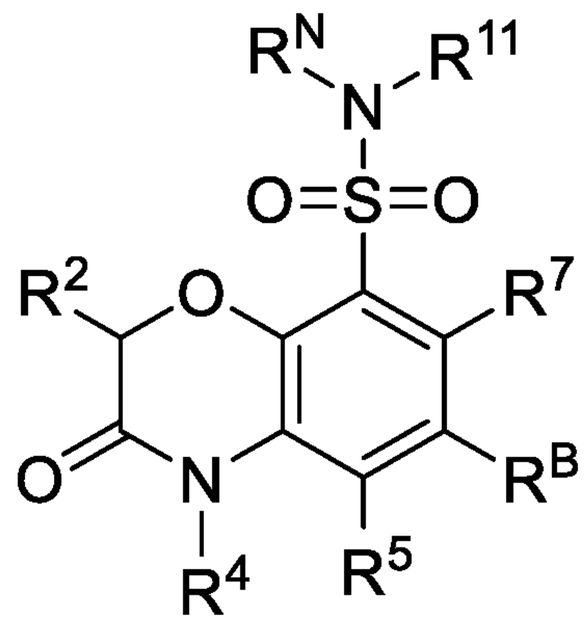
In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (IIb) is selected from any one of the compounds of Table 2c or Table 2c-2, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIb) is selected from any one of the compounds of Table 2c, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIb) is selected from any one of the compounds of Table 2c-2, or a pharmaceutically acceptable salt thereof.

Formula (IIc)

In one general aspect, the present disclosure provides a compound of Formula (IIc):



(IIc),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$; and

R^2, R^4, R^5, R^7, R^N, and R^{11} are as described herein for Formula (IIa).

In some embodiments:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-

C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, R^B is a halogen (e.g., Cl, F, or Br). In some embodiments, R^B is Cl. In some embodiments, R^B is $S(O)_2R^{b1}$ (e.g., R^{b1} is C_{1-6} alkyl). In some embodiments, R^B is ethylsulfonyl.

In some embodiments, R^2 is selected H and C_{1-6} alkyl.

In some embodiments, R^4 is H.

In some embodiments, R^5 is H.

In some embodiments, R^7 is selected H and C_{1-6} alkyl.

In some embodiments, R^N is H.

In some embodiments, R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from morpholinyl and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, R^{11} is ring A. In some embodiments, R^{11} is C_{1-6} alkyl, optionally substituted with ring A.

In some embodiments, ring A is selected from C_{6-10} aryl and C_{3-10} cycloalkyl, optionally substituted with 1-10 substituents independently selected from R^A.

In some embodiments, ring A is C_{6-10} aryl, optionally substituted with 1-10 substituents independently selected from R^A.

In some embodiments, ring A is C_{3-10} cycloalkyl, optionally substituted with 1-10 substituents independently selected from R^A.

In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments:

R^2 is selected H and C_{1-6} alkyl;

R^4 is H;

R^5 is H;

R^7 is selected H and C_{1-6} alkyl;

R^N is H; or

R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from morpholinyl and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

ring A is selected from C_{6-10} aryl and C_{3-10} cycloalkyl, optionally substituted with 1-10 substituents independently selected from R^A; and

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

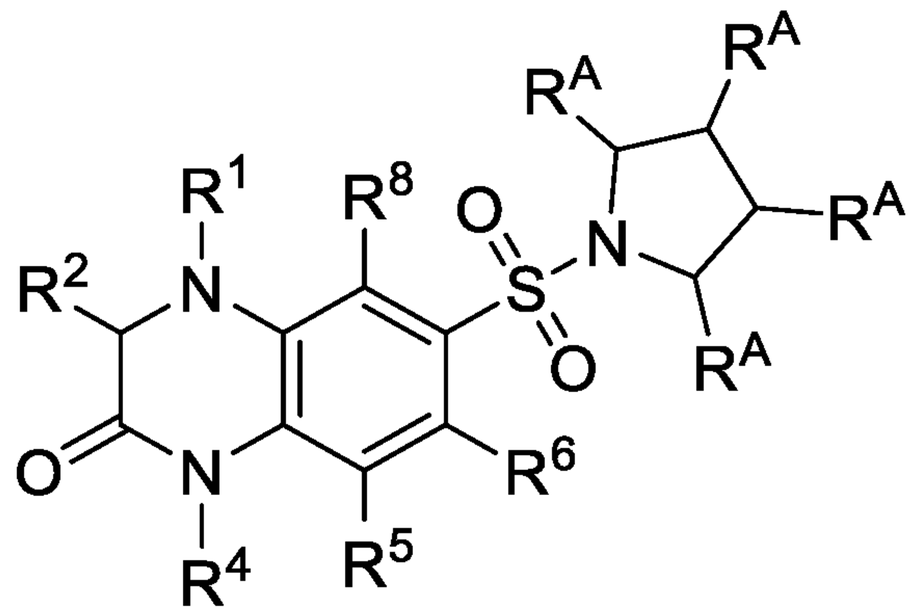
In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (IIc) is selected from any one of the compounds of Table 2d or Table 2d-2, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIc) is selected from any one of the compounds of Table 2d, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIc) is selected from any one of the compounds of Table 2d-2, or a pharmaceutically acceptable salt thereof.

Formula (IId)

In one general aspect, the present disclosure provides a compound of Formula (IId):



(IId),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^4, R^5, R^6, R^8, and R^A are as described herein for Formula (IIa).

In some embodiments:

R^1 and R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5, R^6, and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, R^2 is selected from H and C_{1-6} alkyl.

In some embodiments, R^4 is H.

In some embodiments, R^1 is selected from H, C_{1-6} alkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, each R^9 is independently selected from OH, C_{1-6} alkoxy, carboxy, $C(O)NH_2$, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

In some embodiments, R^5, R^6, and R^8 are each independently selected from H,

halo, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy. In some embodiments, R^5, R^6, and R^8 are each H.

In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, and $NR^{c1}C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments, each R^A is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, halo, CN, OH, C_{1-6} alkoxy, carboxy, amino, $C(O)NH_2$, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and C_{1-6} haloalkoxy. In some embodiments, each R^A is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, halo, and C_{1-6} alkoxy. In some embodiments, each R^A is independently selected from H and C_{1-6} alkyl. In some embodiments, each R^A is H.

In some embodiments:

R^2 is selected from H and C_{1-6} alkyl;

R^4 is H;

R^5, R^6, and R^8 are each H;

R^1 is selected from H, C_{1-6} alkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OH, C_{1-6} alkoxy, carboxy, $C(O)NH_2$, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino; and

each R^A is H.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

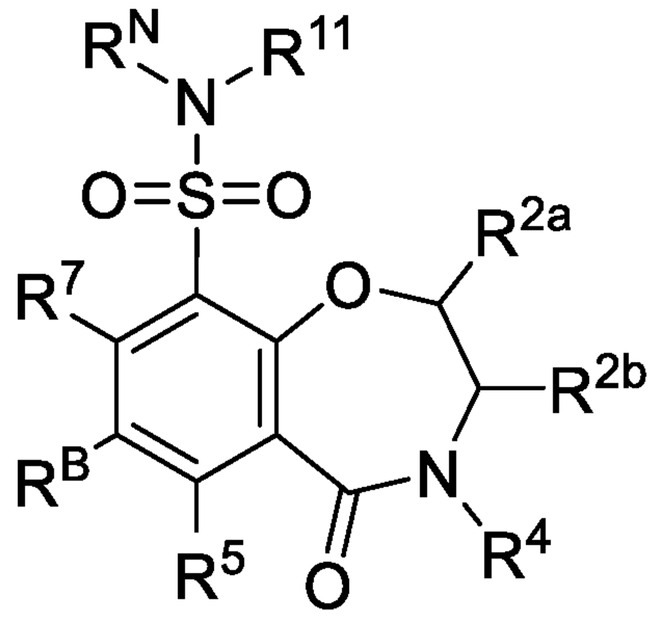
In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (IId) is selected from any one of the compounds of Table 2e, or a pharmaceutically acceptable salt thereof.

Formula (IIe)

In one general aspect, the present disclosure provides a compound of Formula (IIe):



(IIe),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6}

alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, R^B is a halogen.

In some embodiments, R^B is $S(O)_2R^{b1}$.

In some embodiments, R^{2a} and R^{2b} are each independently selected from H and C_{1-6} alkyl.

In some embodiments, R^4 is H.

In some embodiments, R^5 is H.

In some embodiments, R^7 is selected H and C_{1-6} alkyl.

In some embodiments, R^N is H.

In some embodiments, ring A is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A.

In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments:

R^{2a} and R^{2b} are each independently selected H and C_{1-6} alkyl;

R^4 is H;

R^5 is H;

R^7 is selected H and C_{1-6} alkyl;

R^N is H;

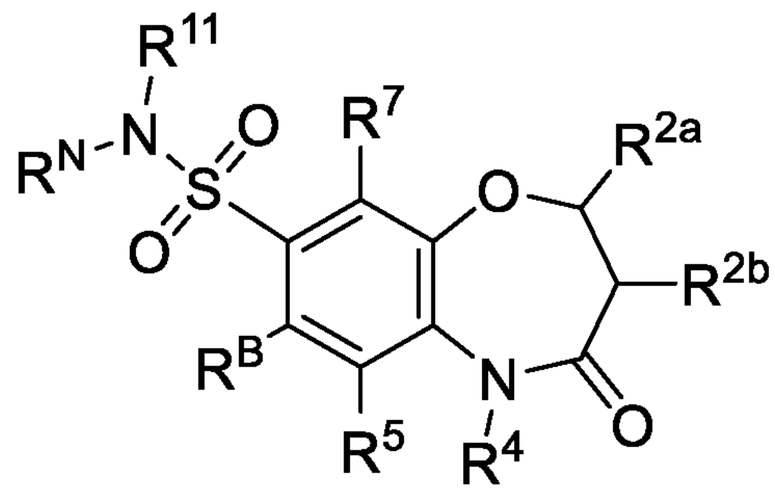
R^{11} is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A; and

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, the compound of Formula (IIe) is selected from any one of the compounds of Table 2f, or a pharmaceutically acceptable salt thereof.

Formula (IIf)

In one general aspect, the present disclosure provides a compound of Formula (IIf):



(IIf),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, R^B is a halogen.

In some embodiments, R^B is $S(O)_2R^{b1}$.

In some embodiments, R^{2a} and R^{2b} are each independently selected from H and C_{1-6} alkyl.

In some embodiments, R^4 is H.

In some embodiments, R^5 is H.

In some embodiments, R^7 is selected H and C_{1-6} alkyl.

In some embodiments, R^N is H.

In some embodiments, ring A is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A.

In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments:

R^{2a} and R^{2b} are each independently selected H and C_{1-6} alkyl;

R^4 is H;

R^5 is H;

R^7 is selected H and C_{1-6} alkyl;

R^N is H;

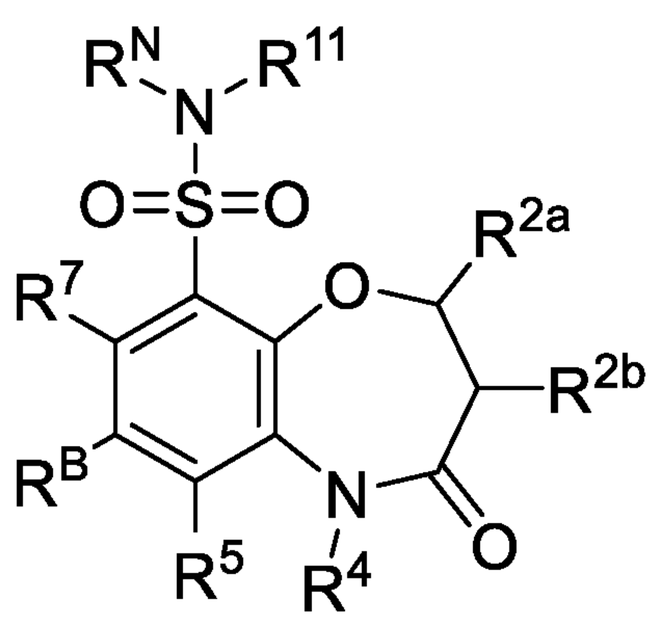
R^{11} is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A; and

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, the compound of Formula (IIf) is selected from any one of the compounds of Table 2g, or a pharmaceutically acceptable salt thereof.

Formula (IIg)

In one general aspect, the present disclosure provides a compound of Formula (IIg):



(IIg),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, R^B is a halogen.

In some embodiments, R^B is $S(O)_2R^{b1}$.

In some embodiments, R^{2a} and R^{2b} are each independently selected from H and C_{1-6} alkyl.

In some embodiments, R^4 is H.

In some embodiments, R^5 is H.

In some embodiments, R^7 is selected H and C_{1-6} alkyl.

In some embodiments, R^N is H.

In some embodiments, ring A is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A.

In some embodiments, each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments:

R^{2a} and R^{2b} are each independently selected H and C_{1-6} alkyl;

R^4 is H;

R^5 is H;

R^7 is selected H and C_{1-6} alkyl;

R^N is H;

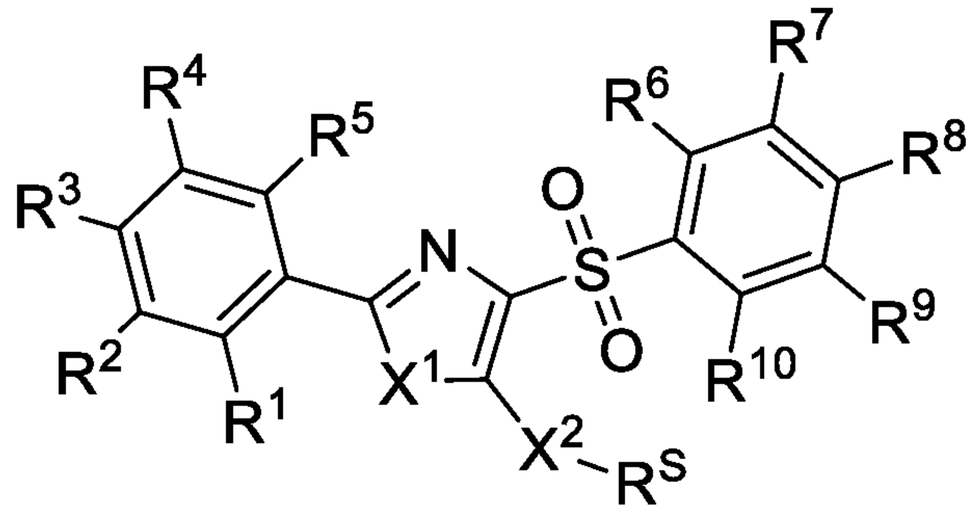
R^{11} is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A; and

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, the compound of Formula (IIg) is selected from any one of the compounds of Table 2h, or a pharmaceutically acceptable salt thereof.

Formula (IIIa)

In one general aspect, the present disclosure provides a compound of Formula (IIIa):



(IIIa),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from O, S, and NR^N;

R^N is selected from H and C_{1-6} alkyl;

X^2 is selected from S, S(O), and $S(O)_2$;

R^S is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

or any two adjacent R^1, R^2, R^3, R^4, and R^5 groups, together with the carbon atoms to which they are attached, form a C_{6-10} aryl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{12};

each R^{12} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments:

X^1 is selected from O, S, and NR^N;

R^N is selected from H and C_{1-6} alkyl;

X^2 is selected from S, S(O), and $S(O)_2$;

R^S is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{12};

each R^{12} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

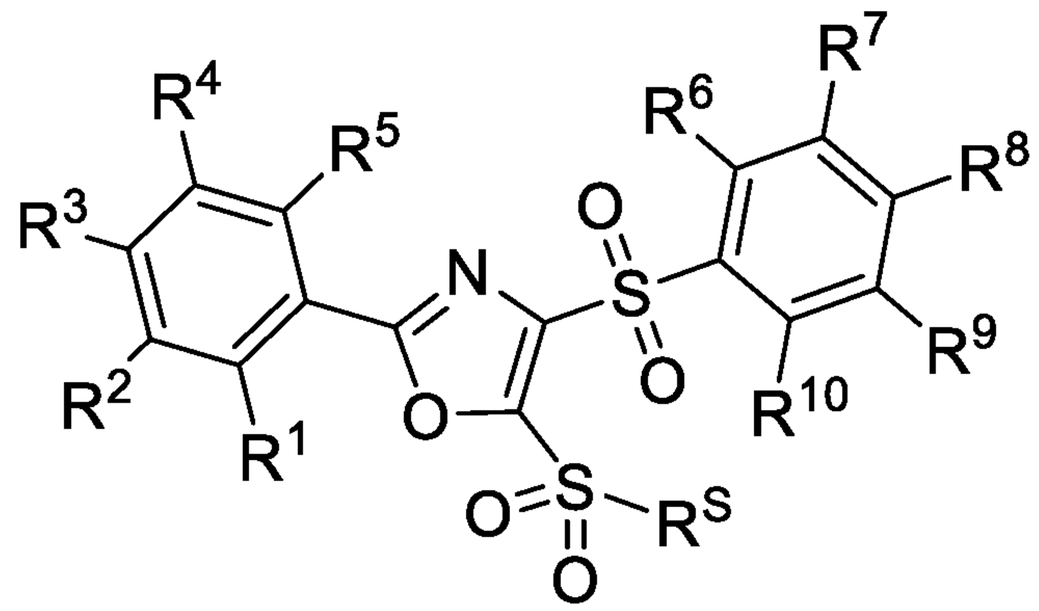
or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, X^1 is O. In some embodiments, X^1 is S. In some embodiments, X^1 is NR^N. In some embodiments, X^2 is S. In some embodiments, X^2 is S(O). In some embodiments, X^2 is $S(O)_2$.

In some embodiments, X^1 is O and X^2 is S. In some embodiments, X^1 is O and X^2 is S(O). In some embodiments, X^1 is O and X^2 is $S(O)_2$. In some embodiments, X^1 is S and X^2 is S. In some embodiments, X^1 is S and X^2 is S(O). In some embodiments, X^1 is S and X^2 is $S(O)_2$. In some embodiments, X^1 is NR^N and X^2 is S. In some embodiments, X^1 is NR^N and X^2 is S(O). In some embodiments, X^1 is NR^N and X^2 is $S(O)_2$.

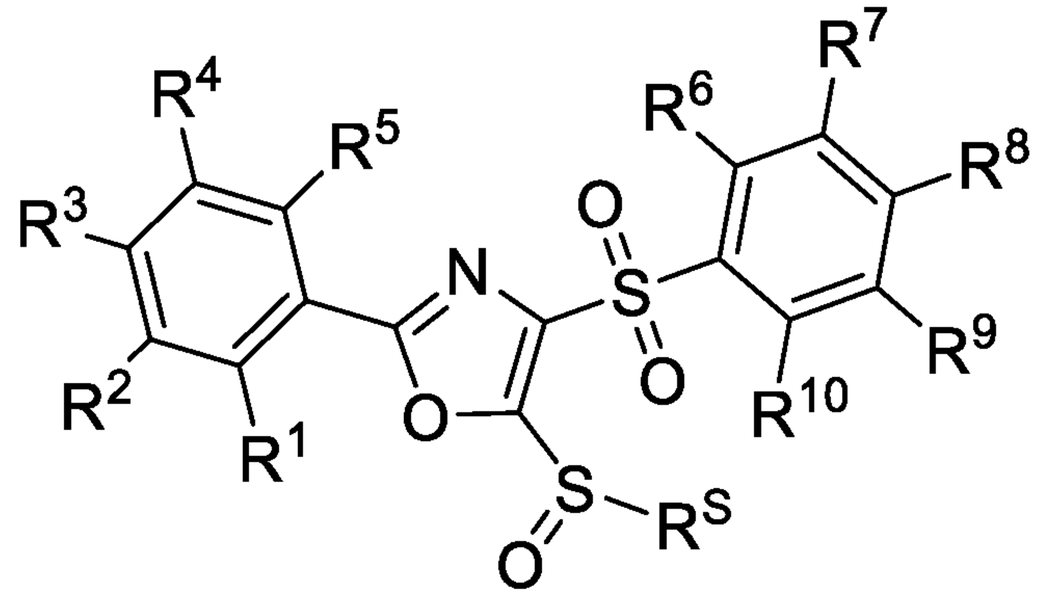
In some embodiments, the compound of Formula (IIIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, R^S is selected from C_{1-6} alkyl, C_{6-10} aryl, and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}.

In some embodiments, R^S is C_{1-6} alkyl, optionally substituted with Cy^1, OR^{a1}, $C(O)R^{b1}$, $NR^{c1}R^{d1}$, and $C(O)NR^{c1}R^{d1}$.

In some embodiments, R^S is C_{1-6} alkyl, optionally substituted with Cy^1, OR^{a1}, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$. In some embodiments, R^S is C_{1-6} alkyl. In some embodiments, R^S is C_{1-6} alkyl, optionally substituted with Cy^1. In some embodiments, R^S is C_{1-6} alkyl, optionally substituted with OR^{a1}. In some embodiments, R^S is C_{1-6} alkyl, optionally substituted with C_{1-6} alkoxy. In some embodiments, R^S is C_{1-6} alkyl, optionally substituted with $C(O)R^{b1}$. In some embodiments, R^S is C_{1-6} alkyl, optionally substituted with $C(O)NR^{c1}R^{d1}$.

In some embodiments, R^S is selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}. In some embodiments, R^S is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}. In some embodiments, R^S is C_{3-10} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments, R^S is selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from halo and C_{1-6} alkyl. In some embodiments, R^S is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from halo and C_{1-6} alkyl. In some embodiments, R^S is C_{3-10} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from halo and C_{1-6} alkyl.

In some embodiments, each R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$. In some embodiments, R^{11} is Cy^1. In some embodiments, R^{11} is halo. In some embodiments, R^{11} is C_{1-6} alkyl. In some embodiments, R^{11} is OR^{a1}. In some embodiments, R^{11} is C_{1-6} alkoxy. In some embodiments, R^{11} is $C(O)R^{b1}$. In some embodiments, R^{11} is $C(O)NR^{c1}R^{d1}$.

In some embodiments, each Cy^1 is independently selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1}. In some embodiments, Cy^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1}. In some embodiments, Cy^1 is C_{3-10} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1}.

In some embodiments, each R^{Cy1} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{12}. In some embodiments, R^{Cy1} is halo. In some embodiments, R^{Cy1} is

C_{1-6} alkyl. In some embodiments, R^{Cy1} is C_{1-6} haloalkyl. In some embodiments, R^{Cy1} is OR^{a1}. In some embodiments, R^{Cy1} is C_{1-6} alkoxy. In some embodiments, R^{Cy1} is $C(O)R^{b1}$. In some embodiments, R^{Cy1} is $NR^{c1}R^{d1}$. In some embodiments, each R^{Cy1} is independently selected from halo, CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and $S(O)_2NH_2$.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy. In some embodiments, R^g is halo. In some embodiments, R^g is C_{1-6} alkyl.

In some embodiments:

R^S is selected from C_{1-6} alkyl, C_{6-10} aryl, and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, or 3, 4, or 5 substituents independently selected from R^{11};

R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, $NR^{c1}R^{d1}$, and $C(O)NR^{c1}R^{d1}$;

Cy^1 is independently selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{12};

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino,

and carboxy. In some aspects of these embodiments, R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$.

In some embodiments:

R^S is selected from C_{1-6} alkyl, C_{6-10} aryl, and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, or 3, 4, or 5 substituents independently selected from R^{11};

R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, $NR^{c1}R^{d1}$, and $C(O)NR^{c1}R^{d1}$;

Cy^1 is independently selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and $S(O)_2NH_2$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy. In some aspects of these embodiments, R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

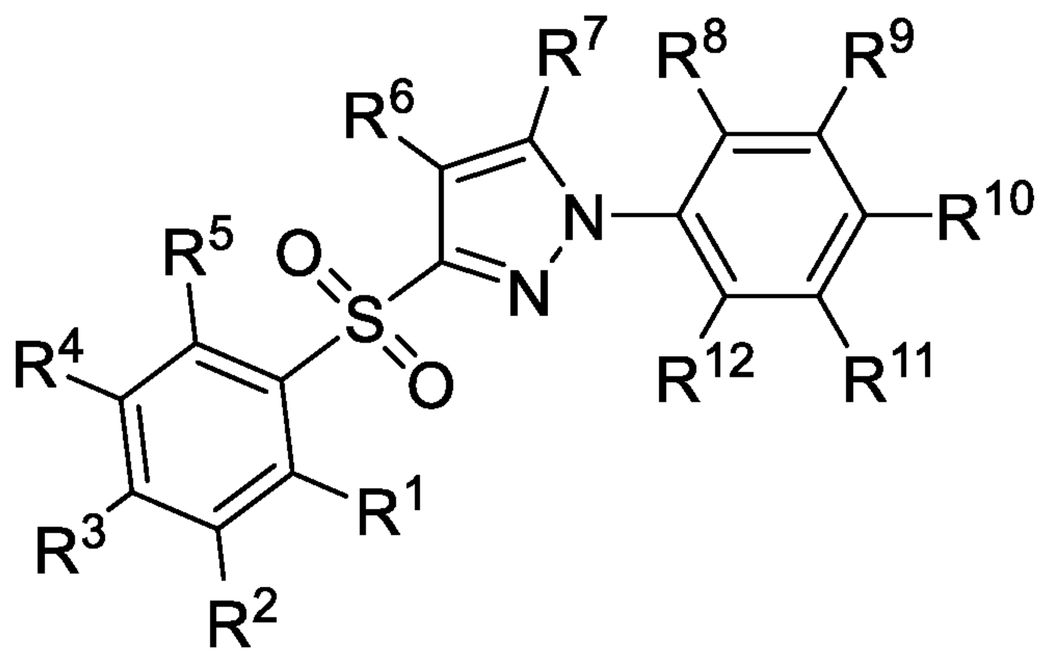
In some embodiments, the compound of Formula (IIIa) is selected from any one of the compounds of Table 3a, Table 3b, Table 3b-2, Table 10, or Table 11.

In some embodiments, the compound of Formula (IIIa) is selected from any one of the compounds of Table 3a or Table 3b, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIIa) is selected from any one of the compounds of Table 3a, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIIa) is selected from any one of the compounds of Table 3b, or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides a compound selected from any one of the compounds of Table 3b or Table 3b-2, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a compound selected from any one of the compounds of Table 3b, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a compound selected from any one of the compounds of Table 3b-2, or a pharmaceutically acceptable salt thereof.

Formula (IIIc)

In a general aspect, the present disclosure provides a compound of Formula (IIIc):



(IIIc),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as described herein.

In some embodiments:

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and

C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{13};

each R^{13} independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy.

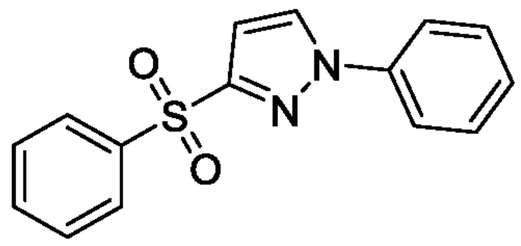
In some embodiments, each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, OH, C_{1-6} alkyl, and C_{1-6} alkoxy.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (IIIc) is:

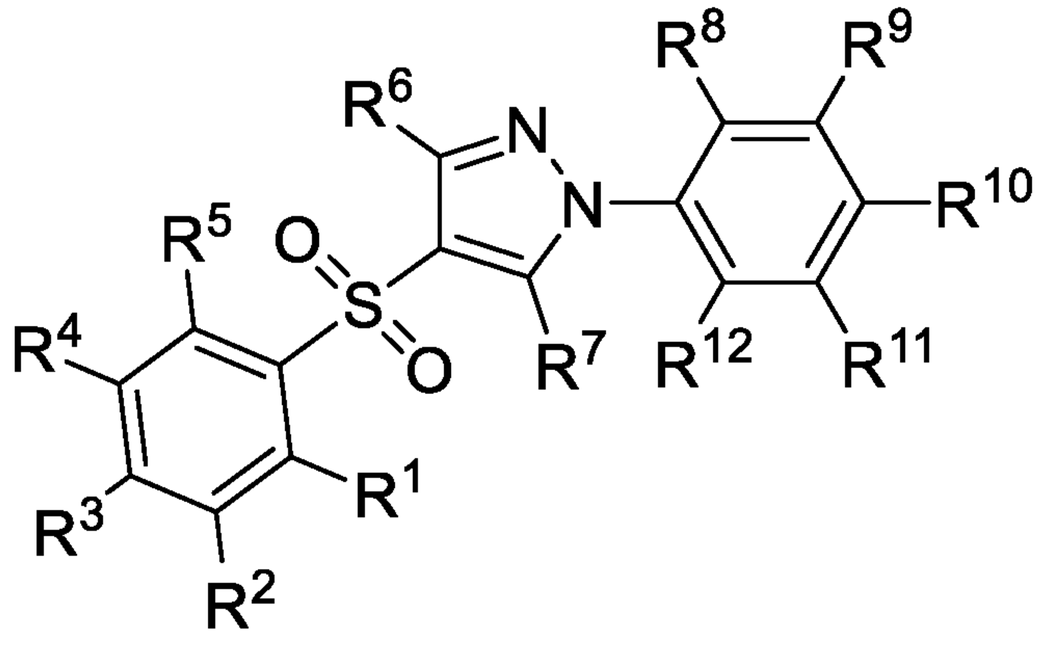


,

or a pharmaceutically acceptable salt thereof.

Formula (IIId)

In some embodiments, the present disclosure provides a compound of Formula (IIId):



(IIId),

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as described herein.

In some embodiments:

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{13};

each R^{13} independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy.

In some embodiments, each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, OH, C_{1-6} alkyl, and C_{1-6} alkoxy.

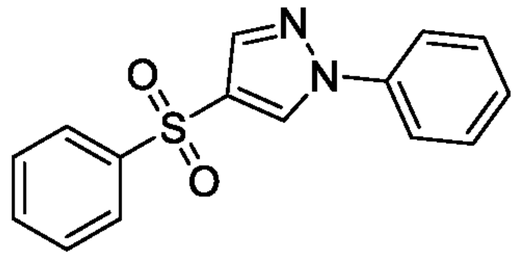
In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4}

alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (IIId) is:

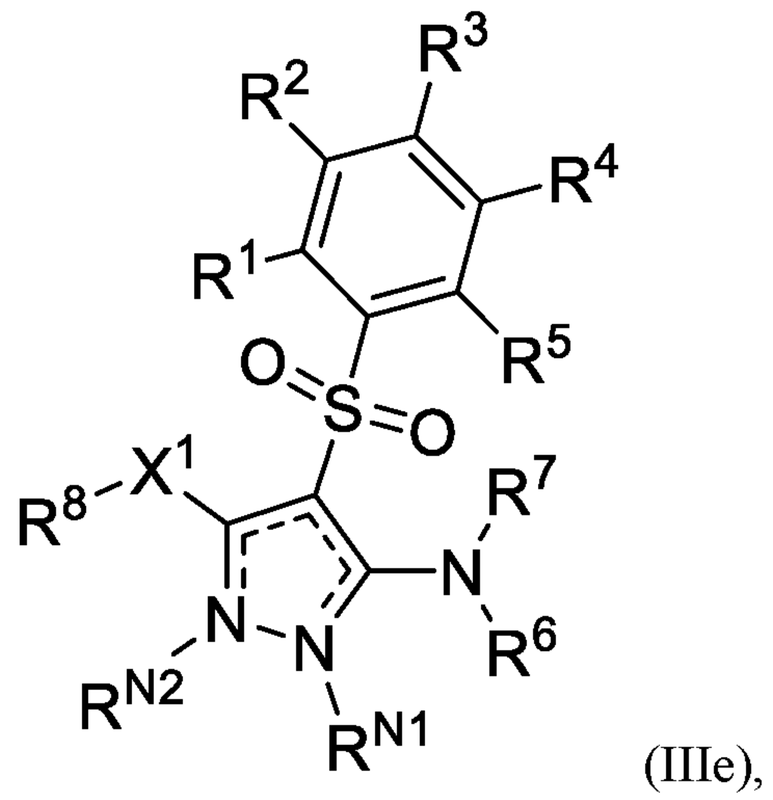


,

or a pharmaceutically acceptable salt thereof.

Formula (IIIe)

In one general aspect, the present disclosure provides a compound of Formula (IIIe):



(IIIe),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

each ⋮ represents a single bond or a double bond, provided that not more than two of ⋮ are double bonds;

R^{N2} is absent if ⋮ between the N atom to which R^{N2} is attached and the C atom to which X^1 is attached is a double bond; or

R^{N2} is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3

substituents independently selected from R^9;

R^{N1} is absent if ⋮ between the N atom to which R^{N1} is attached and the C atom to which NR^6R^7 is attached is a double bond; or

R^{N1} is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^9;

R^6 and R^7 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

or R^6 and R^{N1} together with the N atoms to which they are attached from a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^9 independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{10} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered

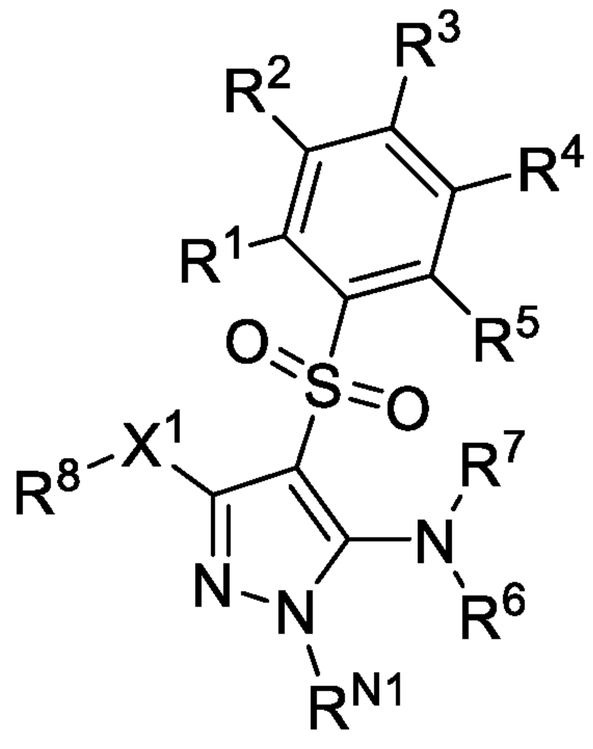
heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, X^1 is selected from S(O) and $S(O)_2$. In some embodiments, $X^1$is S(O). In some embodiments, X^1 is $S(O)_2$. In some embodiments, X^1 is S.

In some embodiments, the compound of Formula (IIIe) has formula:



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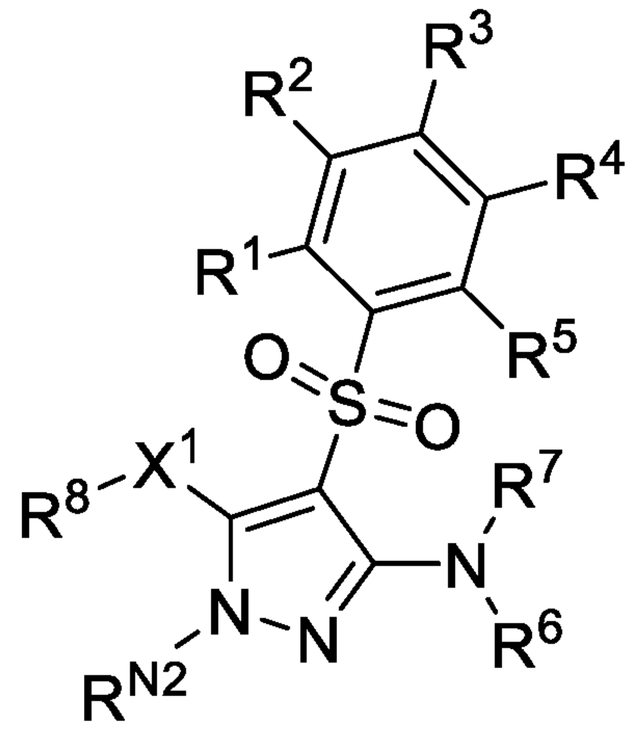
or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{N1} is selected from H and C_{1-6} alkyl. In some embodiments, R^{N1} is H. In some embodiments, R^{N1} is C_{1-6} alkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, the compound of Formula (IIIe) has formula:



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or a pharmaceutically acceptable salt thereof.

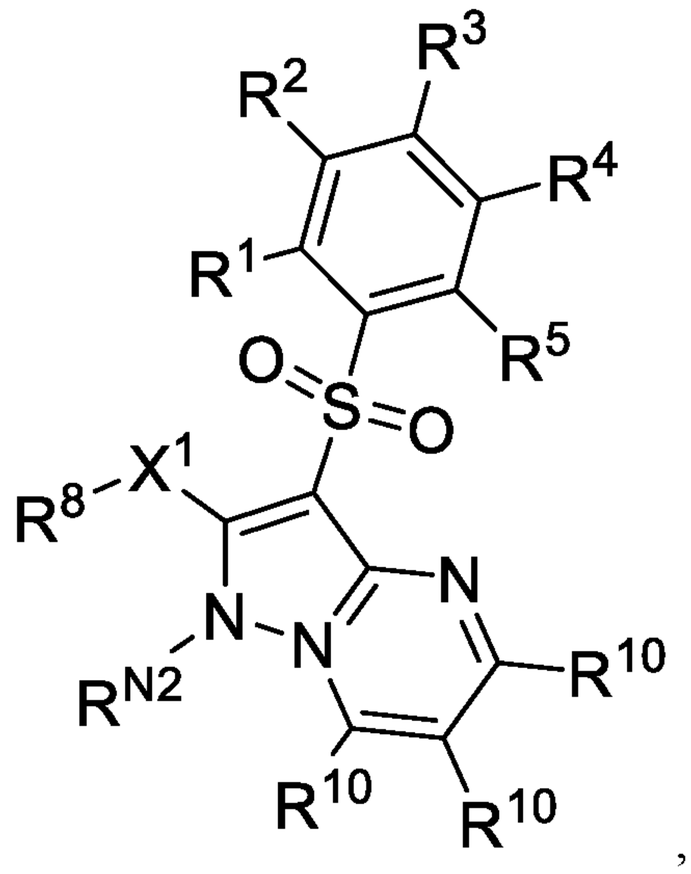
In some embodiments, R^6 is H. In some embodiments, R^7 is H. In some embodiments, R^6 and R^7 are each independently selected from H and C_{1-6} alkyl. In some embodiments, R^6 and R^7 are both H. In some embodiments, R^6 is H and R^7 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, R^6 and R^7 are each independently selected from H and C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^6 is H and R^7 is C_{6-10} aryl (e.g., phenyl, naphthyl), optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^6 is H and R^7 is C_{3-10} cycloalkyl (e.g., cyclohexyl, cyclopropyl), optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^6 is H and R^7 is 5-10 membered heteroaryl (e.g., pyridine), optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^6 is H and R^7 is 4-10 membered heterocycloalkyl (e.g., piperidine, tetrahydropyran), optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, R^6 and R^{N1} together with the N atoms to which they are attached from a 5-10 membered heteroaryl, substituted with 1, 2, or 3 substituents independently selected from R^{10} (e.g., pyrimidine, triazine).

In some embodiments, R^6 and R^{N1} together with the N atoms to which they are attached from a 4-10 membered heterocycloalkyl, substituted with 1, 2, or 3 substituents independently selected from R^{10} (e.g., hexahydropyrimidine).

In some embodiments, the compound of Formula (IIIe) has formula:



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or a pharmaceutically acceptable salt thereof.

In some embodiments, each R^{10} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$. In some embodiments, each R^{10} is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy. In some embodiments, each R^{10} is independently selected from H, halo, OH, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, each R^{10} is independently selected from H, OH, and C_{1-6} alkyl.

In some embodiments, R^{N2} is selected from H and C_{1-6} alkyl. In some embodiments, R^{N2} is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^{N2} is H.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy. In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H and C_{1-}

6 alkyl. In some embodiments, R^1, R^2, R^3, R^4, and R^5 are all H.

In some embodiments, R^8 is C_{1-6} alkyl. In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^8 is selected from C_{1-6} alkyl and C_{1-6} haloalkyl. In some embodiments, R^8 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^8 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^8 is C_{3-10} cycloalkyl (e.g., cyclopentyl, cyclohexyl), optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^8 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^8 is 4-10 membered heterocycloalkyl (e.g., tetrahydrofuran), optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1}. In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with C_{1-6} alkoxy. In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with $NR^{c1}R^{d1}$.

In some embodiments, each R^9 independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$. In some embodiments, each R^9 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy. In some embodiments, each R^9 is independently selected from H, halo, OH, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, each R^9 is independently selected from H and C_{1-6} alkyl.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein said C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6}

alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments (when R^6 and R^{N1} together with the N atoms to which they are attached form a ring):

X^1 is selected from S(O) and $S(O)_2$;

each R^{10} is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy;

R^{N2} is selected from H and C_{1-6} alkyl;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

R^8 is C_{1-6} alkyl.

In some embodiments (when R^6 and R^{N1} together with the N atoms to which they are attached form a ring):

X^1 is selected from S(O) and $S(O)_2$;

each R^{10} is independently selected from H, OH, and C_{1-6} alkyl;

R^{N2} is H;

R^1, R^2, R^3, R^4, and R^5 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R^8 is C_{1-6} alkyl.

In some embodiments:

X^1 is selected from S(O) and $S(O)_2$;

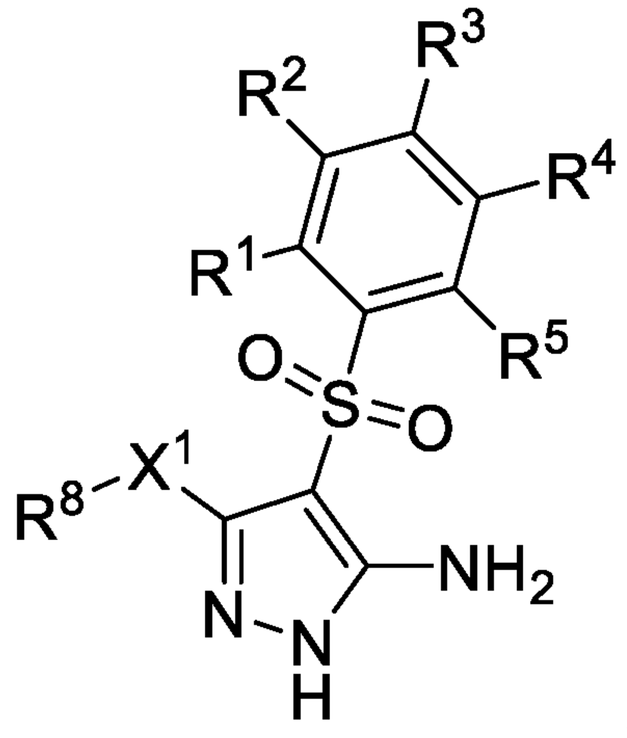
each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl;

R^{N1} is selected from H and C_{1-6} alkyl; and

R^6 and R^7 are each independently selected from H and C_{1-6} alkyl.

In some embodiments, the compound of Formula (IIIe) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments:

X^1 is selected from S(O) and $S(O)_2$;

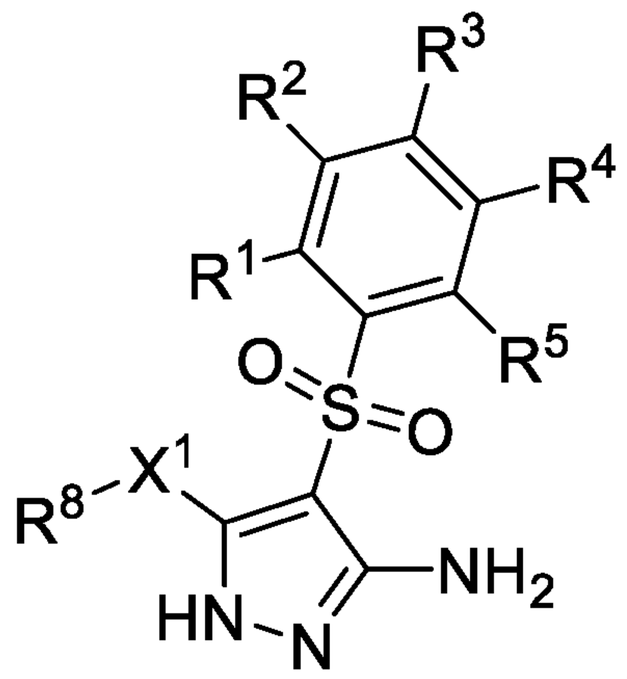
each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl;

R^{N2} is selected from H and C_{1-6} alkyl; and

R^6 and R^7 are each independently selected from H and C_{1-6} alkyl.

In some embodiments, the compound of Formula (IIIe) has formula:



,

or a pharmaceutically acceptable salt thereof.

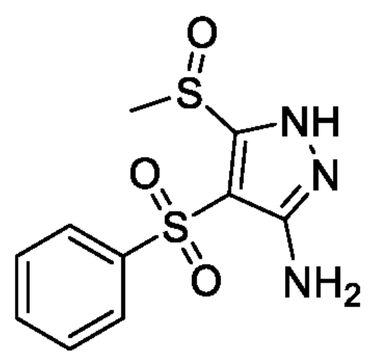
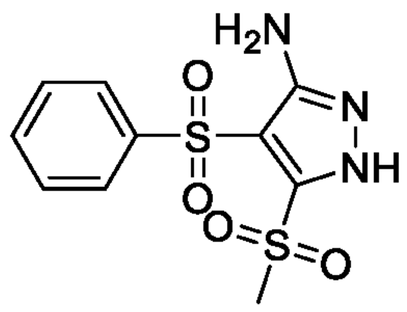
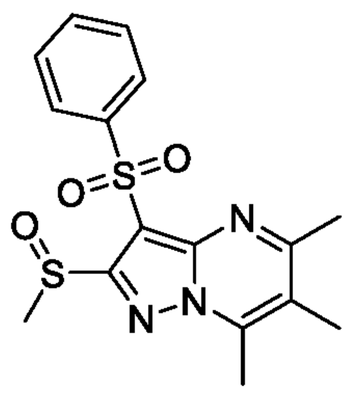
In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected

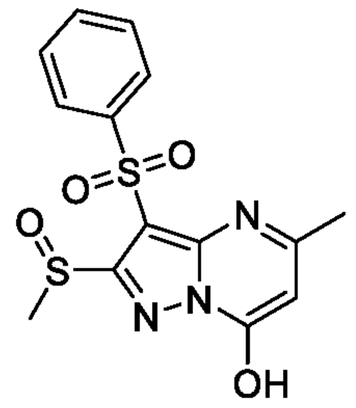
from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (IIIe) is selected from any one of the following compounds:

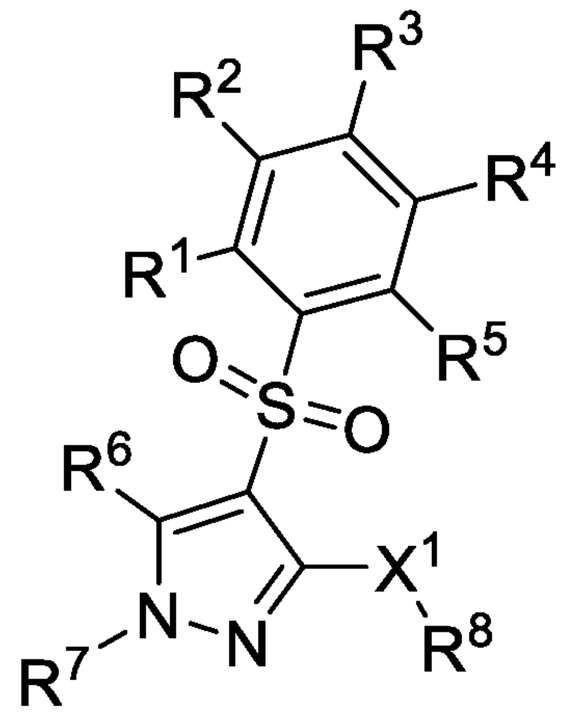
BC19338	ZE23-0091	
BC19339	ZE23-0092	
BC19340	ZE23-0096	

BC19341	ZE23-0098	

or a pharmaceutically acceptable salt thereof.

Formula (IIIf)

In one general aspect, the present disclosure provides a compound of Formula (IIIf):



(IIIf),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^9;

R^6 and R^7 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3

substituents independently selected from R^9;

provided that at least one of R^6 and R^7 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

or R^6 and R^7, together with the C atom to which R^6 is attached and N atom to which R^7 is attached, from a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^9 independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{10} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6}

alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, X^1 is selected from S(O) and $S(O)_2$.

In some embodiments, $X^1$is S.

In some embodiments, $X^1$is S(O).

In some embodiments, X^1 is $S(O)_2$.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$. In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with OH. In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with C_{1-6} alkoxy. In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with $NR^{c1}R^{d1}$.

In some embodiments, R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^8 is C_{3-10} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^8 is 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments:

R^6 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

R^7 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments:

R^6 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^7 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl,

and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments:

R^7 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

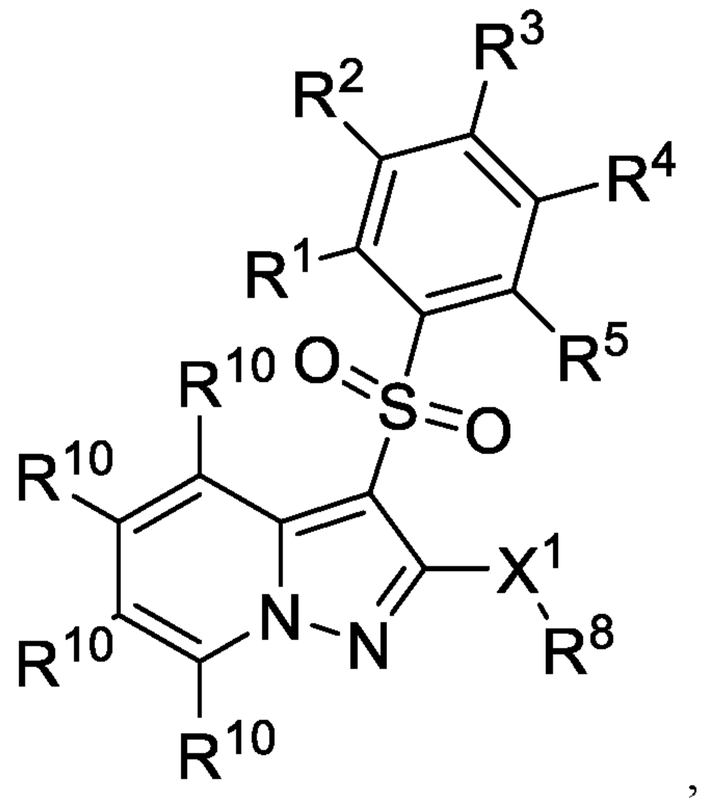
R^6 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments:

R^7 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^6 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

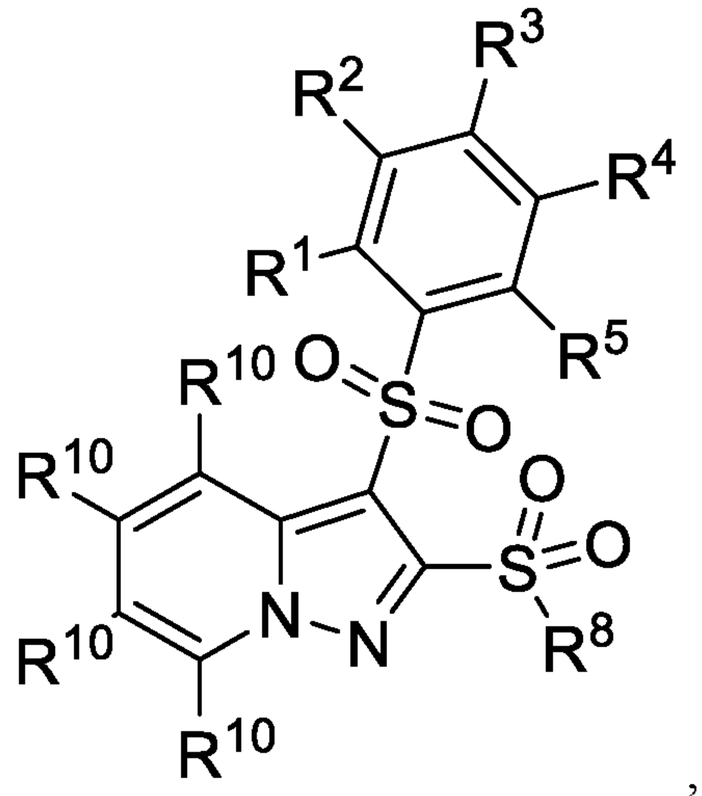
In some embodiments, the compound of Formula (IIIf) has formula:



,

or a pharmaceutically acceptable salt thereof.

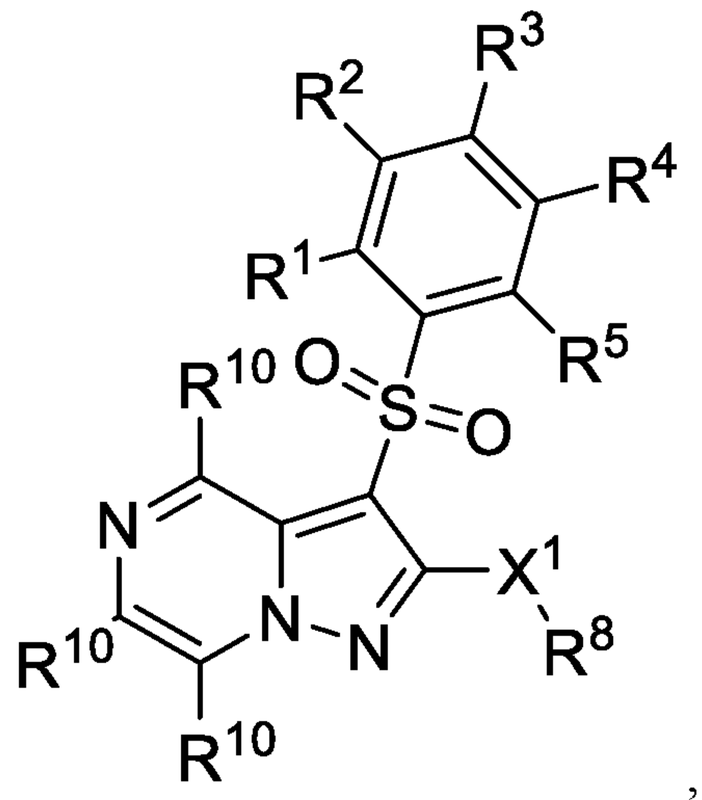
In some embodiments, the compound of Formula (IIIf) has formula:



,

or a pharmaceutically acceptable salt thereof.

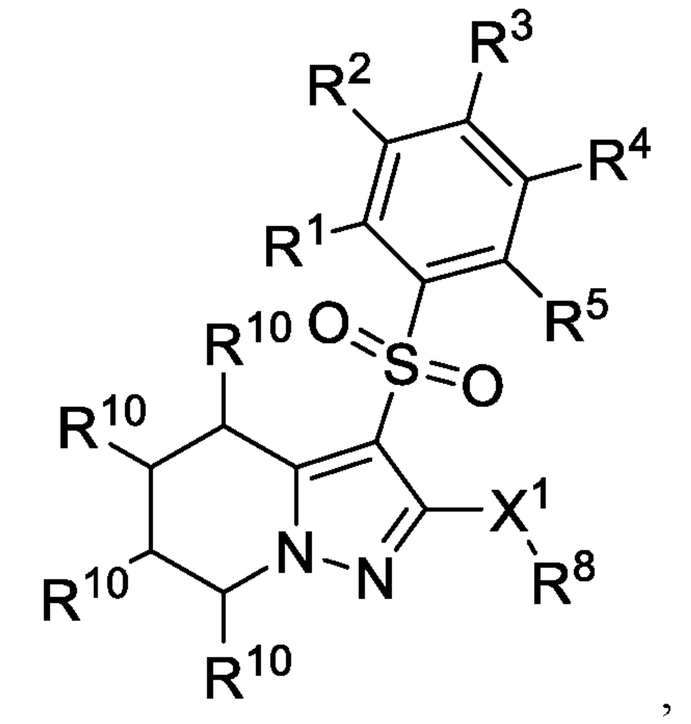
In some embodiments, the compound of Formula (IIIf) has formula:



,

or a pharmaceutically acceptable salt thereof.

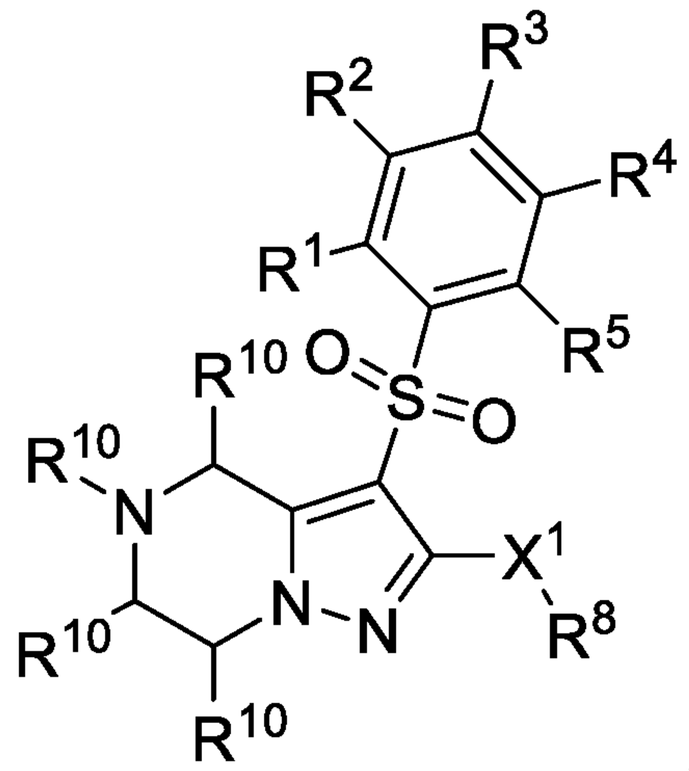
In some embodiments, the compound of Formula (IIIf) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIIf) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, each R^{10} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments of the compound of Formula (IIIf):

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^6 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the compound of Formula (IIIf):

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^6 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^7 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the compound of Formula (IIIf):

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^6 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the compound of Formula (IIIf):

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^6 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the compound of Formula (IVf):

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

each R^{10} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

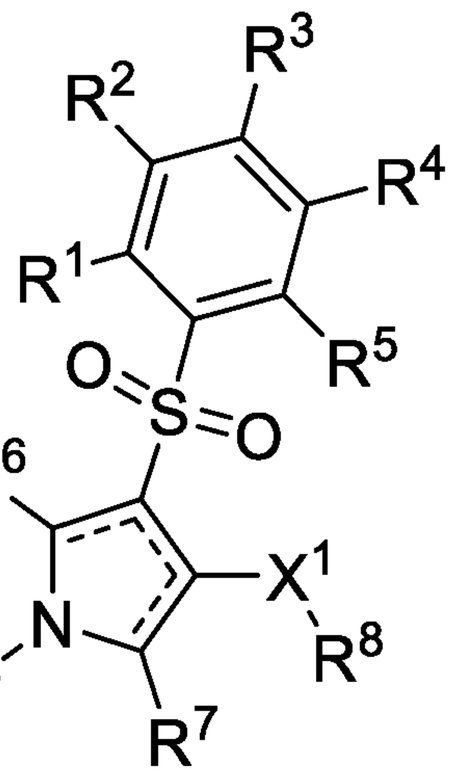
In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

Formula (IIIg-2)

In one general aspect, the present disclosure provides a compound of Formula (IIIg):



(IIIg-2),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

each ⁞‖ represents a single bond or a double bond, provided that not more than two of ⁞‖ are double bonds;

each of R^1, R^2, R^3, R^4, R^5, R^6, and R^7 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered

heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^9 is selected from $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein each of said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}; or

R^7 and R^9, together with the N atom to which R^9 is attached and C atom to which R^7 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}; or

R^6 and R^9, together with the N atom to which R^9 is attached and C atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each R^{10} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

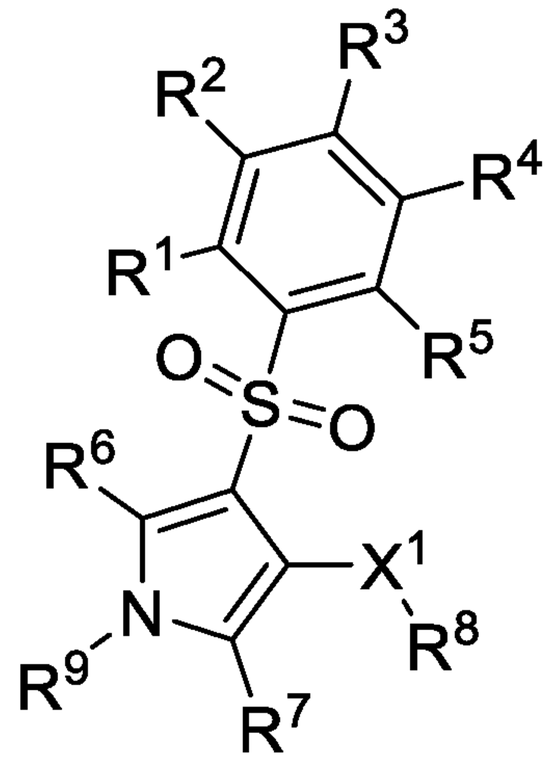
each R^{11} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, the compound of Formula (IIIg-2) has formula (IIIg):



(IIIg),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

each of R^1, R^2, R^3, R^4, R^5, R^6, and R^7 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^9 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}; or

R^7 and R^9, together with the N atom to which R^9 is attached and C atom to which R^7 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}; or

R^6 and R^9, together with the N atom to which R^9 is attached and C atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each R^{10} independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

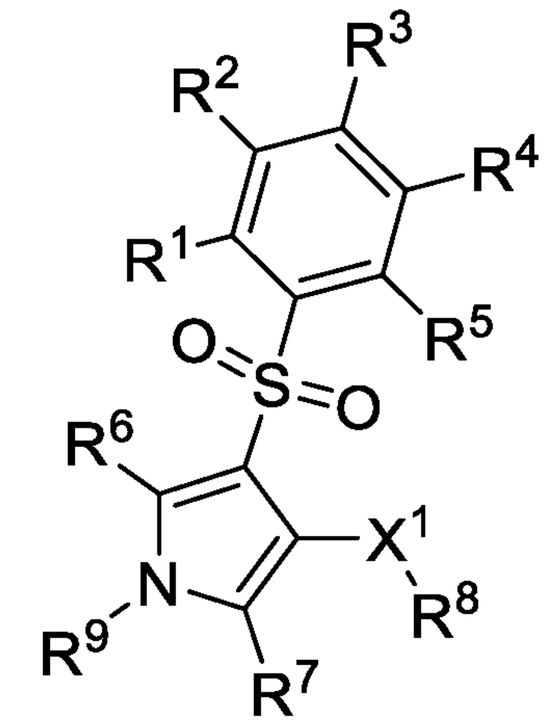
each R^{11} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

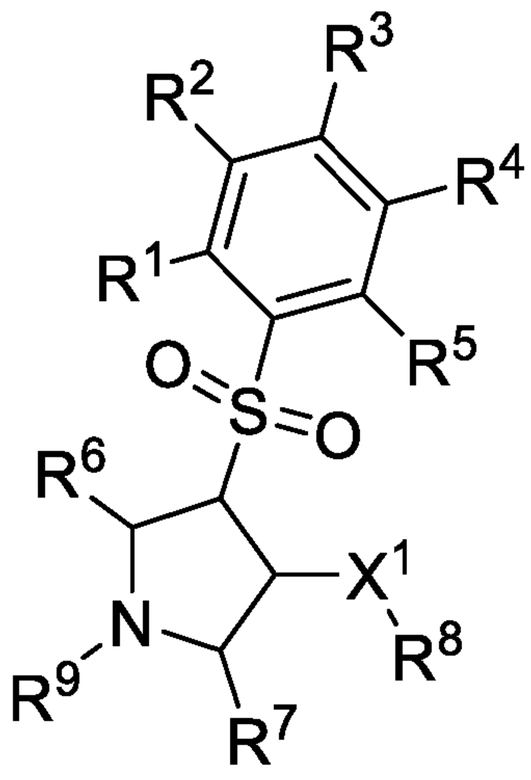
In some embodiments, the compound of Formula (IIIg-2) has formula:



(IIIg),

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIIg-2) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, X^1 is selected from S(O) and $S(O)_2$.

In some embodiments, $X^1$is S(O).

In some embodiments, X^1 is $S(O)_2$.

In some embodiments, X^1 is S.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, at least one of R^1, R^2, R^3, R^4, and R^5 is H.

In some embodiments, R^6 and R^7 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, R^6 and R^7 are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodimetns, R^6 is H or C_{1-6} alkyl, and R^7 is H or C_{1-6} alkyl.

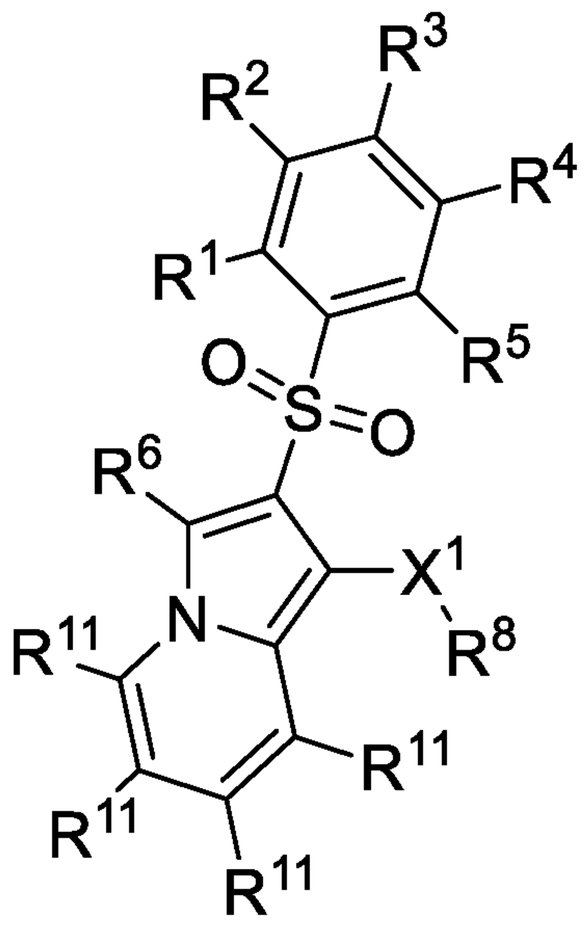
In some embodiments, R^6 and R^7 are each independently selected from H and C_{1-6} alkyl. In some embodiments, R^6 is H. In some embodiments, R^7 is H.

In some embodiments, R^6 is H or C_{1-6} alkyl; and R^7 is selected from halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy. In some aspects of these embodiments, R^6 is H.

In some embodiments, R^7 is H or C_{1-6} alkyl; and R^6 is selected from halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy. In some aspects of these embodiments, R^7 is H.

In some embodiments, R^6 is H or C_{1-6} alkyl; and R^7 and R^9, together with the N atom to which R^9 is attached and C atom to which R^7 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}. In some aspects of these embodiments, R^6 is H.

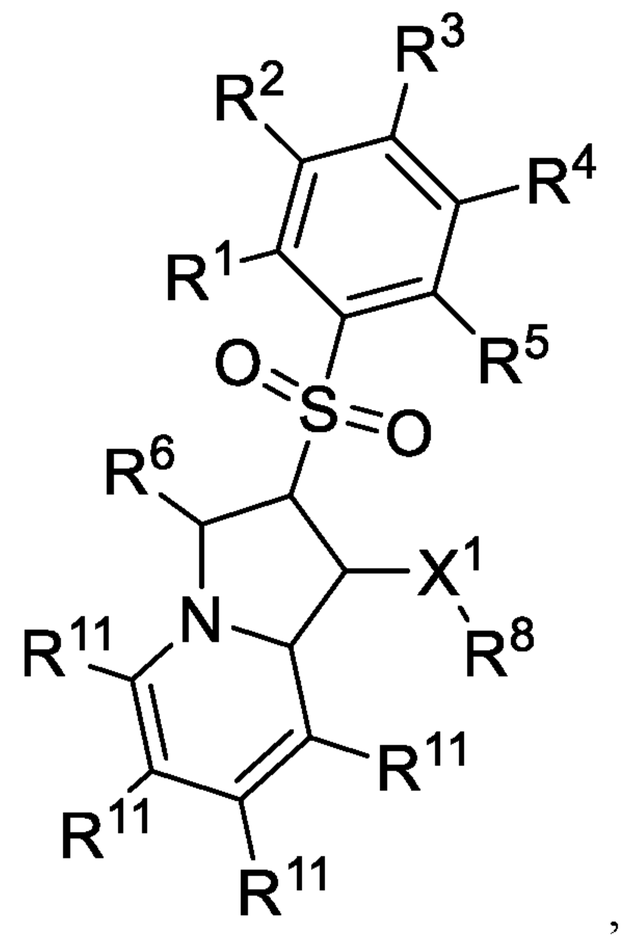
In some embodiments, the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

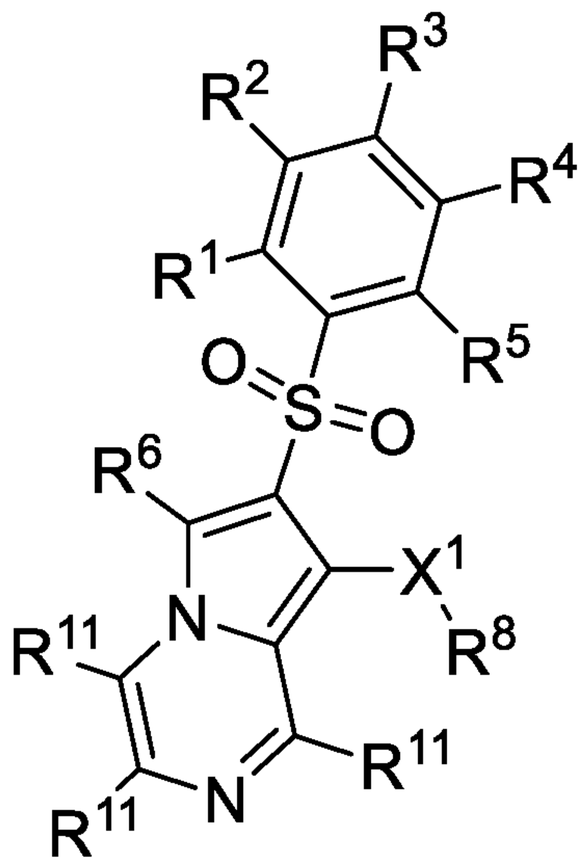
In some embodiments, the compound has formula:



,

or a pharmaceutically acceptable salt thereof.

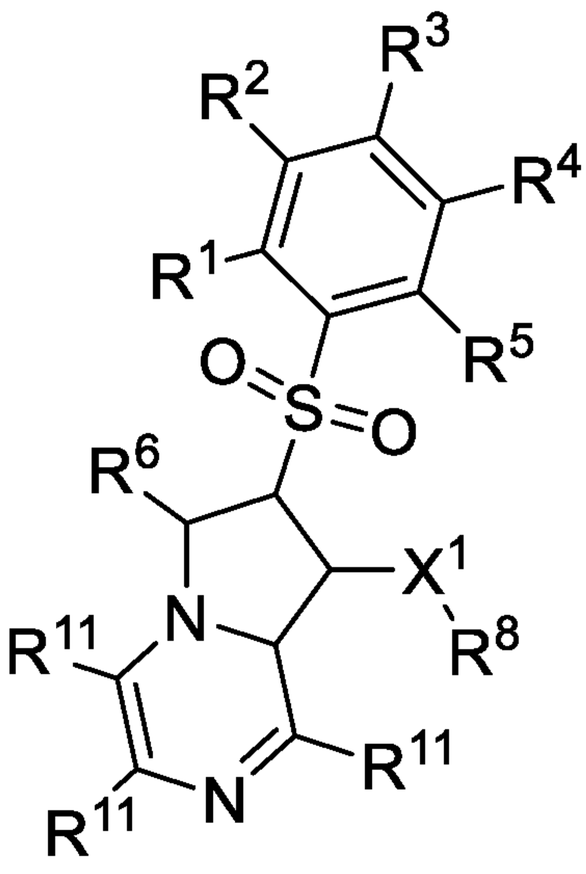
In some embodiments, the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

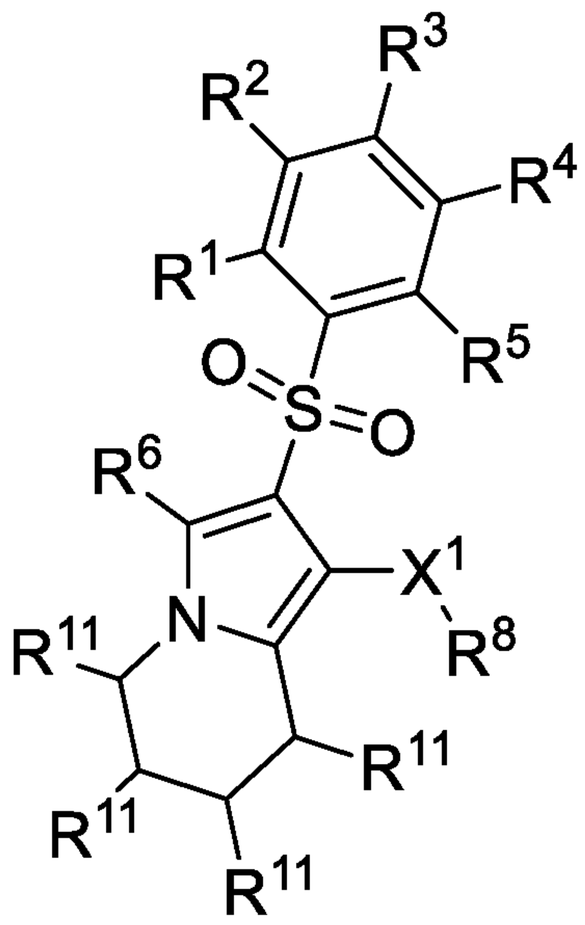
In some embodiments, the compound has formula:



,

or a pharmaceutically acceptable salt thereof.

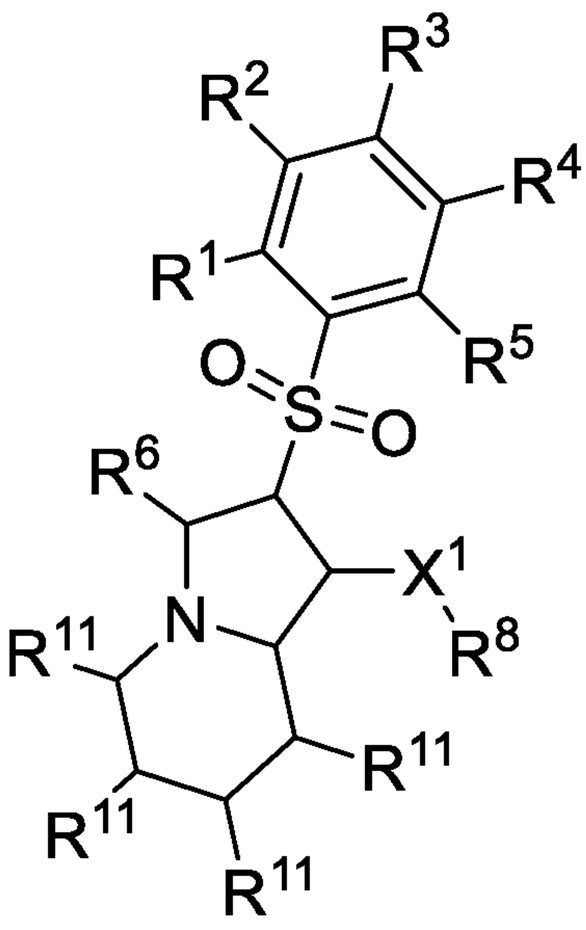
In some embodiments, the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

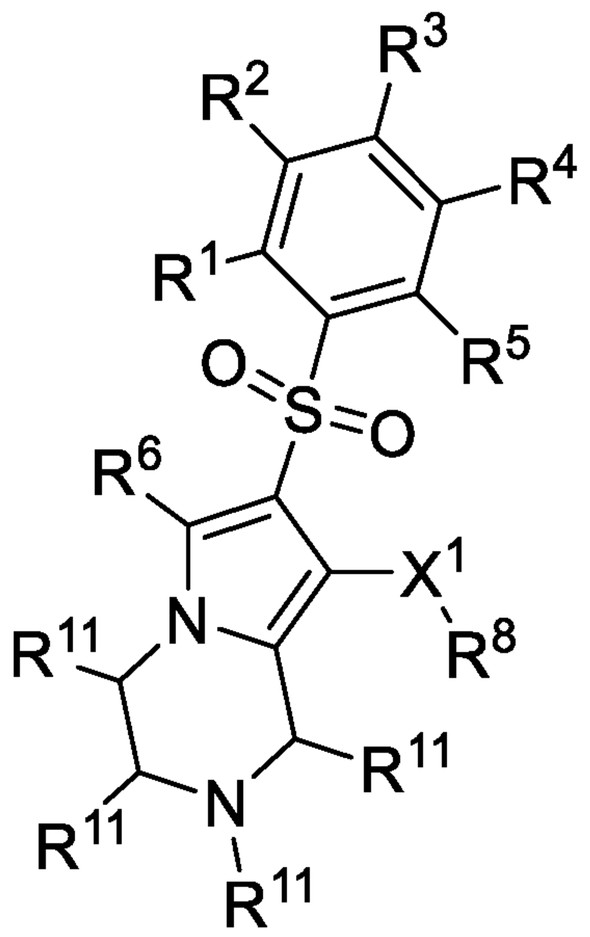
In some embodiments, the compound has formula:



,

or a pharmaceutically acceptable salt thereof.

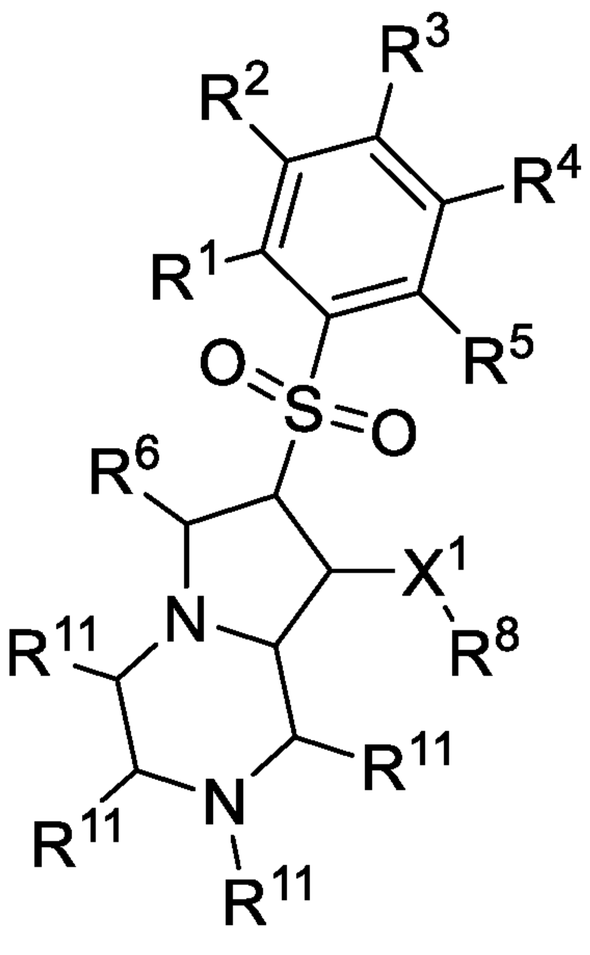
In some embodiments, the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has formula:



,

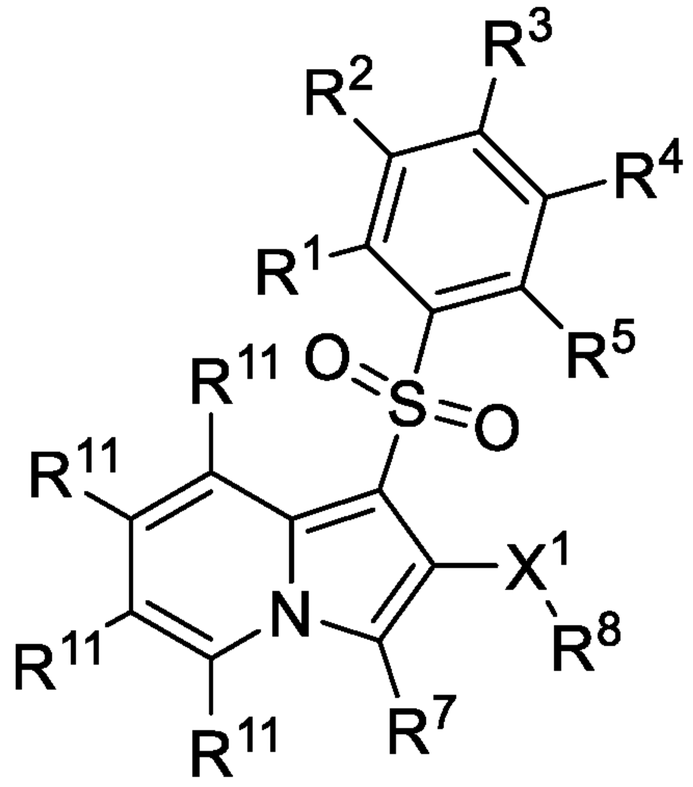
or a pharmaceutically acceptable salt thereof.

In some embodiments:

R^7 is H or C_{1-6} alkyl; and

R^6 and R^9, together with the N atom to which R^9 is attached and C atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}.

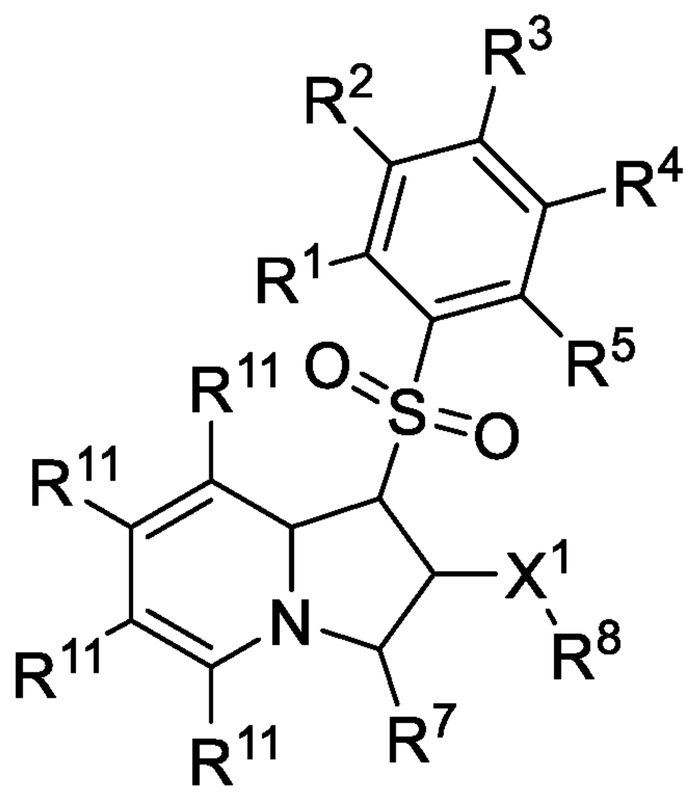
In some embodiments, the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

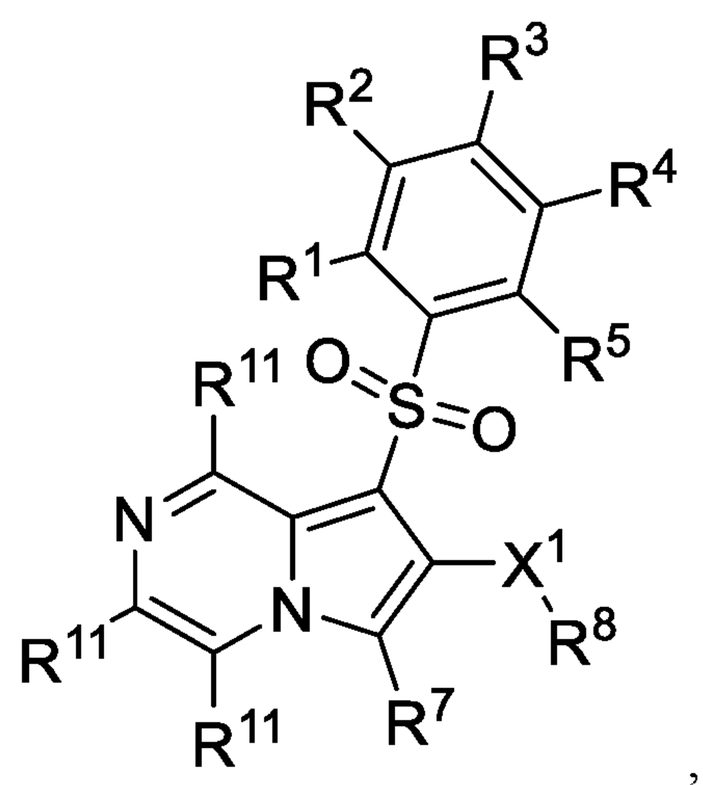
In some embodiments, the compound has formula:



,

or a pharmaceutically acceptable salt thereof.

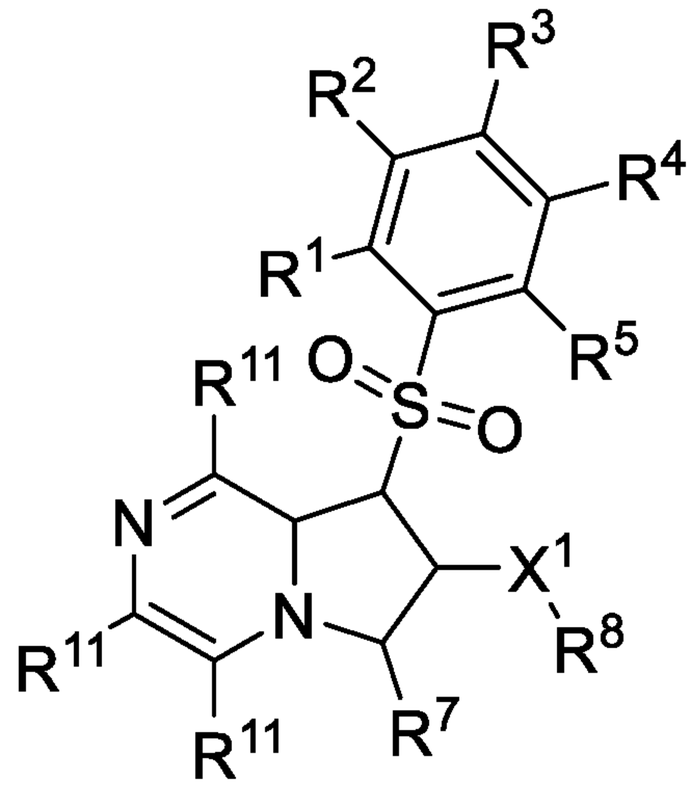
In some embodiments, the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

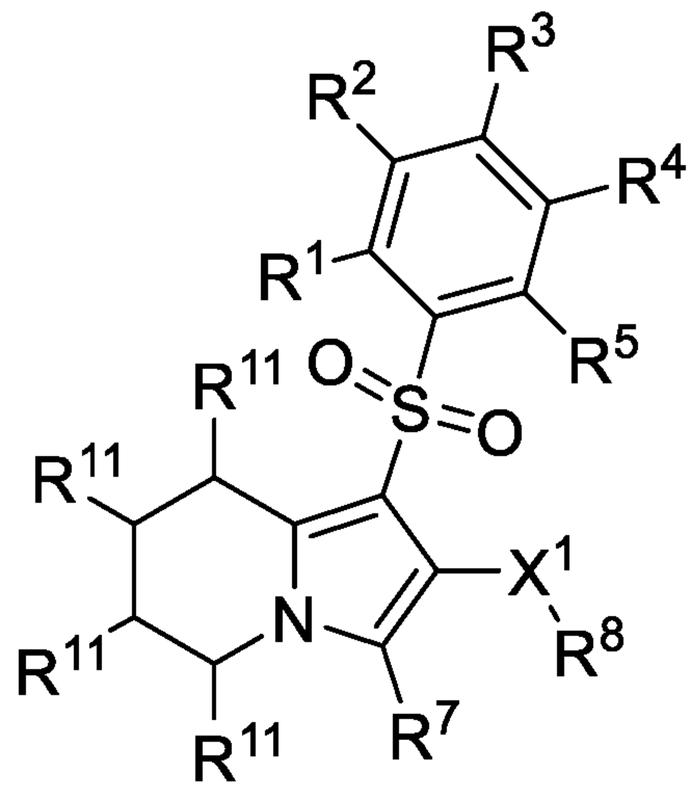
In some embodiments, the compound has formula:



,

or a pharmaceutically acceptable salt thereof.

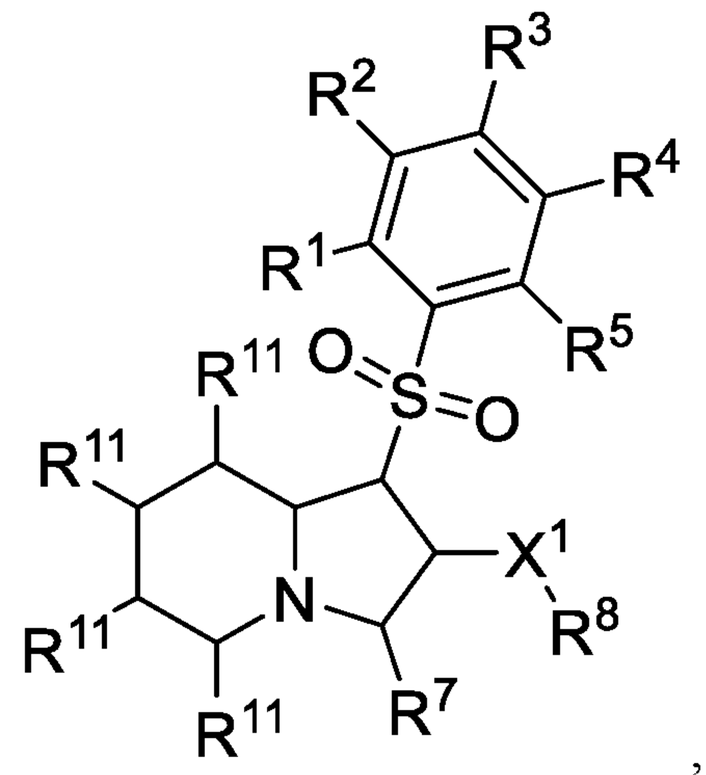
In some embodiments, the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

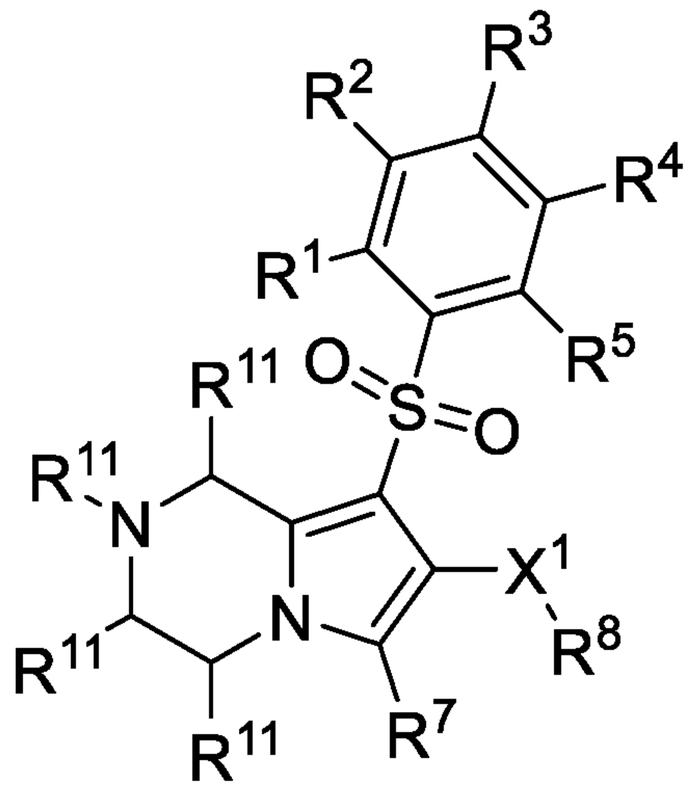
In some embodiments, the compound has formula:



,

or a pharmaceutically acceptable salt thereof.

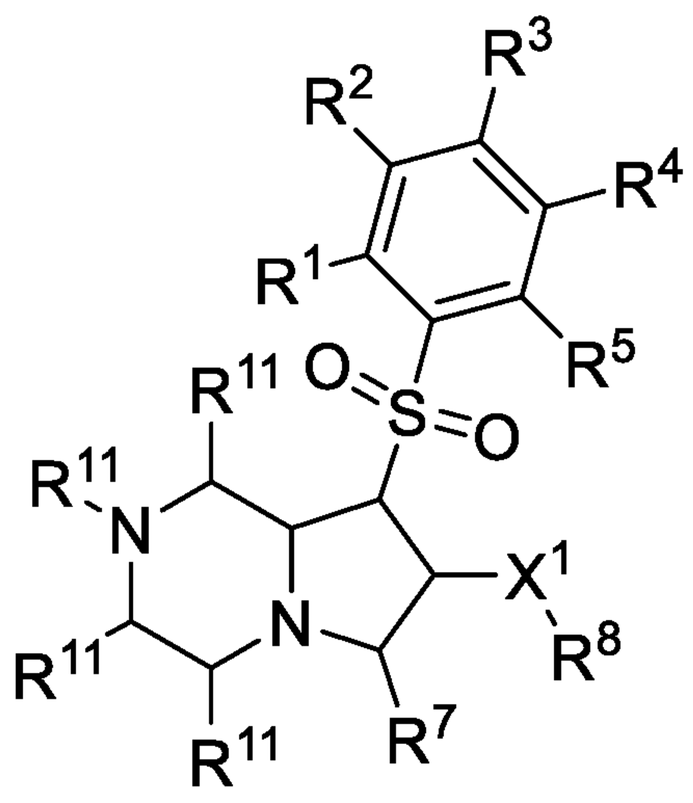
In some embodiments, the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, R^9 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^9 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^9 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^9 is $C(O)R^{b1}$. In some embodiments, R^9 is 4-10 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$.

In some embodiments, R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^{10} is selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, R^{10} is selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, R^{10} is independently selected from C_{6-12} aryl, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, R^{11} is selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, R^{11} is selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^6 and R^7 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^9 is selected from $C(O)R^{b1}$, C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein said C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from C_{6-12} aryl, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the compound of Formula (IIIg):

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^6 and R^7 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the compound of Formula (IIIg):

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^6 is H or C_{1-6} alkyl;

R^7 is selected from halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the compound of Formula (IIIg):

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^7 is H or C_{1-6} alkyl;

R^6 is selected from halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each

of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the compound of Formula (IIIg):

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^6 is H or C_{1-6} alkyl;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the compound of Formula (IIIg):

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^7 is H or C_{1-6} alkyl;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered

heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

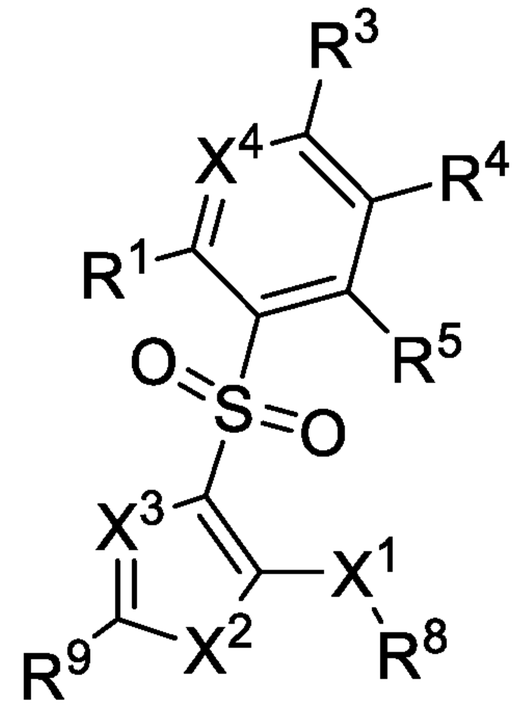
In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound is selected from any one of the compounds of Table 12, or a pharmaceutically acceptable salt thereof.

Formula (IIIh)

In one general aspect, the present disclosure provides a compound of Formula (IIIh)



(IIIh),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

X^4 is selected from N and CR^2;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$,

$S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

X^2 is selected from O, S, and NR^6;

R^6 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

X^3 is selected from N and CR^7;

R^7 is selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^9 is selected from $S(O)_2R^{b1}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}; or

R^9 and R^6, together with the carbon atom to which R^9 is attached and the N atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}; or

R^6 and R^8, together with N atom to which R^6 is attached and S atom to which R^8 is attached, form 4-10 membered heterocycloalkyl substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each R^{10} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

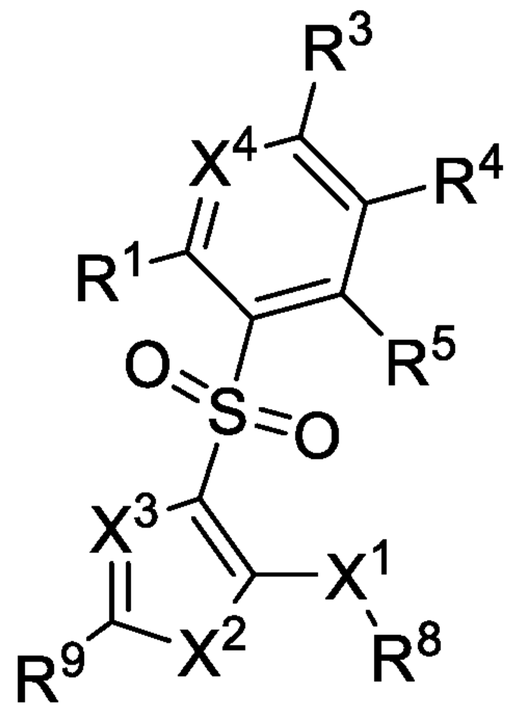
each R^{11} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino. In some embodiments, if X^3 is N and X^2 is O, then R^9 is selected from $S(O)_2R^{b1}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}.

In some embodiments, the present disclosure provides a compound of Formula (IIIh):



(IIIh),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

X^4 is selected from N and CR^2;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

X^2 is selected from O, S, and NR^6;

R^6 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

X^3 is selected from N and CR^7;

R^7 is selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3

substituents independently selected from R^{10};

R^9 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}; or

R^9 and R^6, together with the carbon atom to which R^9 is attached and the N atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}; or

R^6 and R^8, together with N atom to which R^6 is attached and S atom to which R^8 is attached, form 4-10 membered heterocycloalkyl substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each R^{10} independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{11} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-

C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, X^1 is selected from S(O) and $S(O)_2$. In some embodiments, X^1 is S(O). In some embodiments, X^1 is $S(O)_2$. In some embodiments, X^1 is S.

In some embodiments, X^4 is CR^2. In some embodiments, X^4 is N.

In some embodiments, X^1 is $S(O)_2$ and X^4 is CR^2. In some embodiments, X^1 is $S(O)_2$ and X^4 is N.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, at least one of R^1, R^2, R^3, R^4, and R^5 is H.

In some embodiments, R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

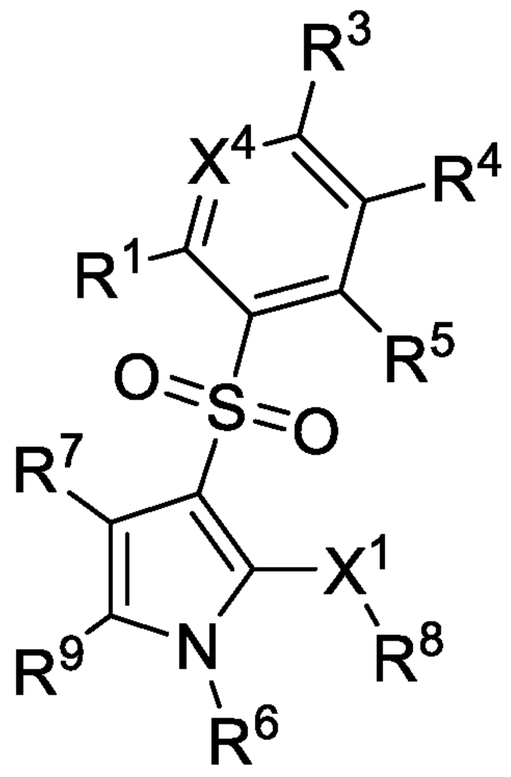
In some embodiments, R^8 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}. In some embodiments, R^8 is C_{3-10} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}. In some embodiments, R^8 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}. In some

embodiments, R^8 is 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}. In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$.

In some embodiments, R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, the compound of Formula (IIIh) has formula:



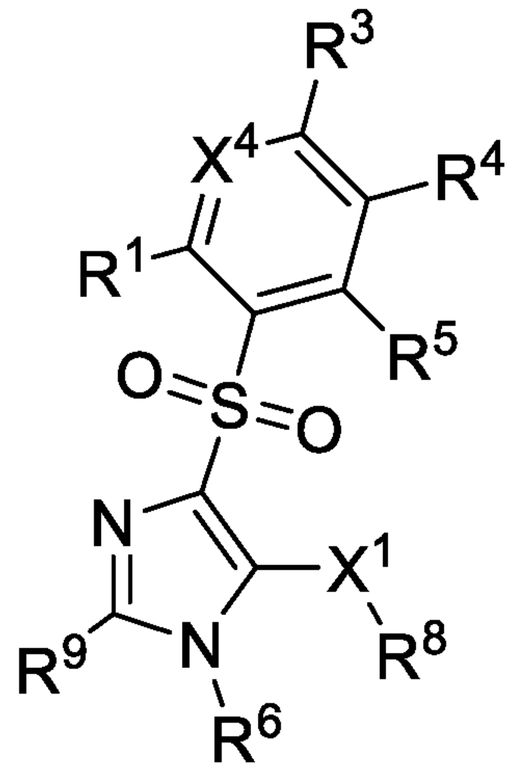
,

or a pharmaceutically acceptable salt thereof.

In some embodiments, R^7 is selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^7 is selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy. In some embodiments, R^7 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

In some embodiments, the compound of Formula (IIIh) has formula:



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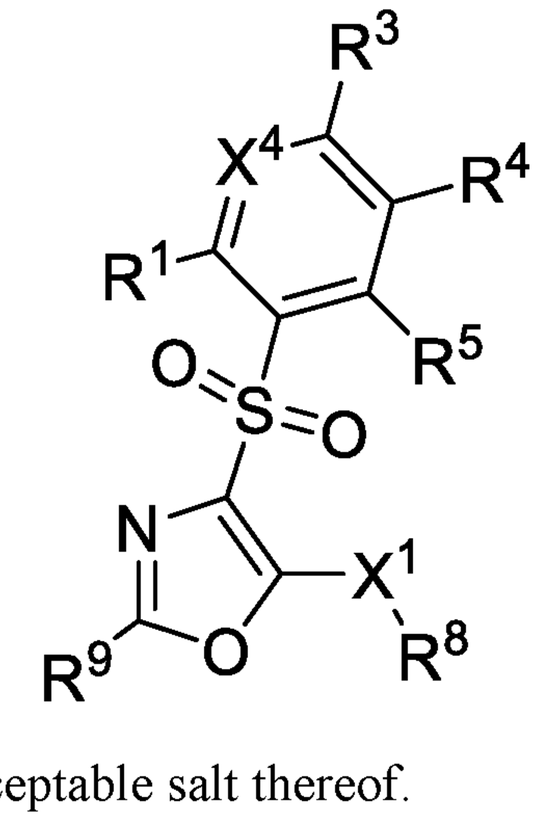
or a pharmaceutically acceptable salt thereof.

In some embodiments, R^6 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}. In some embodiments, R^6 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}. In some embodiments, R^6 is selected from H and C_{1-6} alkyl.

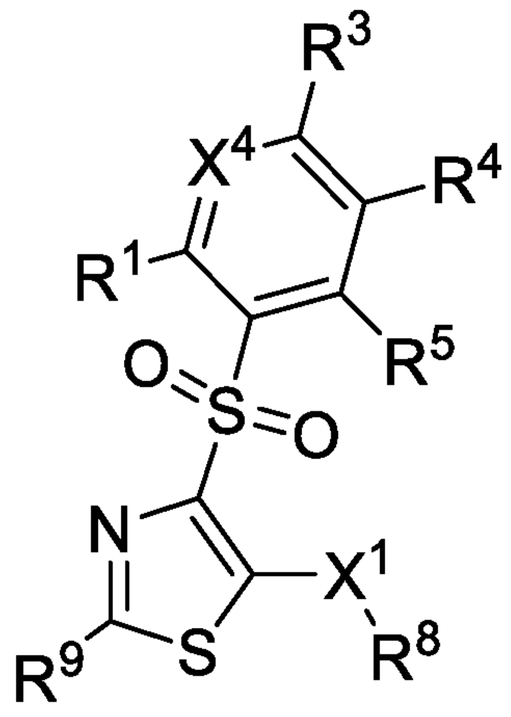
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, R^9 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^9 is $S(O)_2R^{b1}$.

In some embodiments, R^9 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^9 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^9 is selected from C_{3-10} cycloalkyl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^9 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

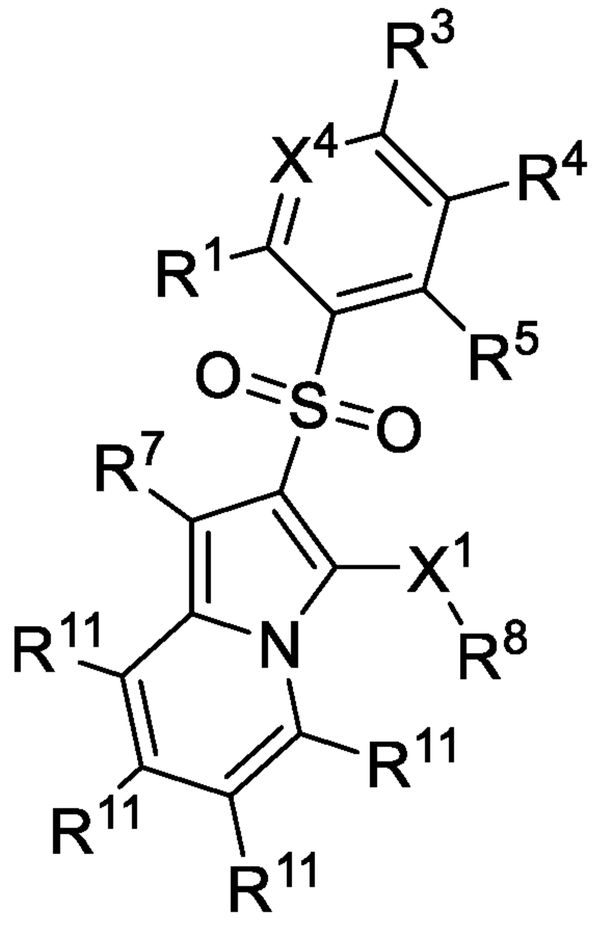
In some embodiments, R^9 is C_{3-10} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^9 is selected from 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^9 is 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^9 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

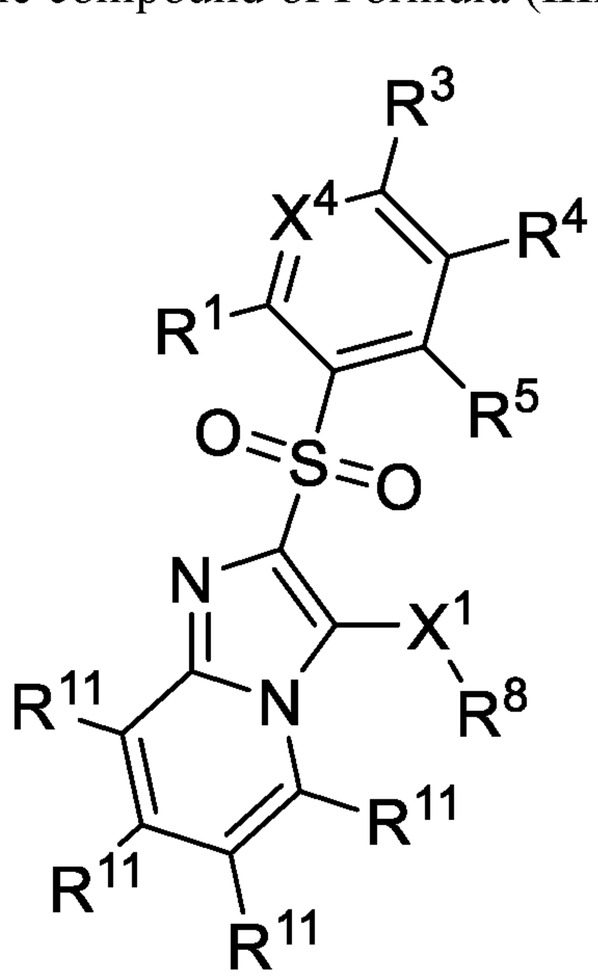
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

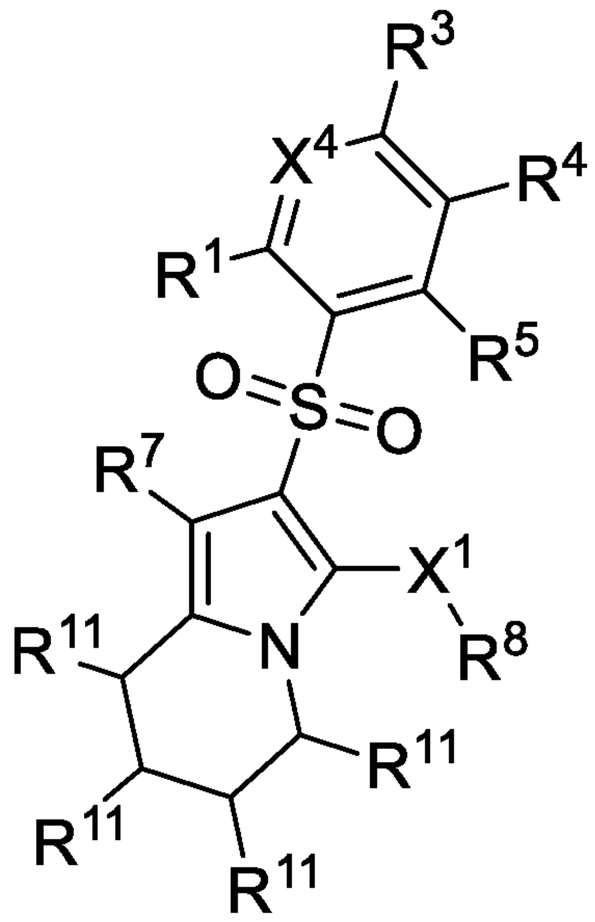
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

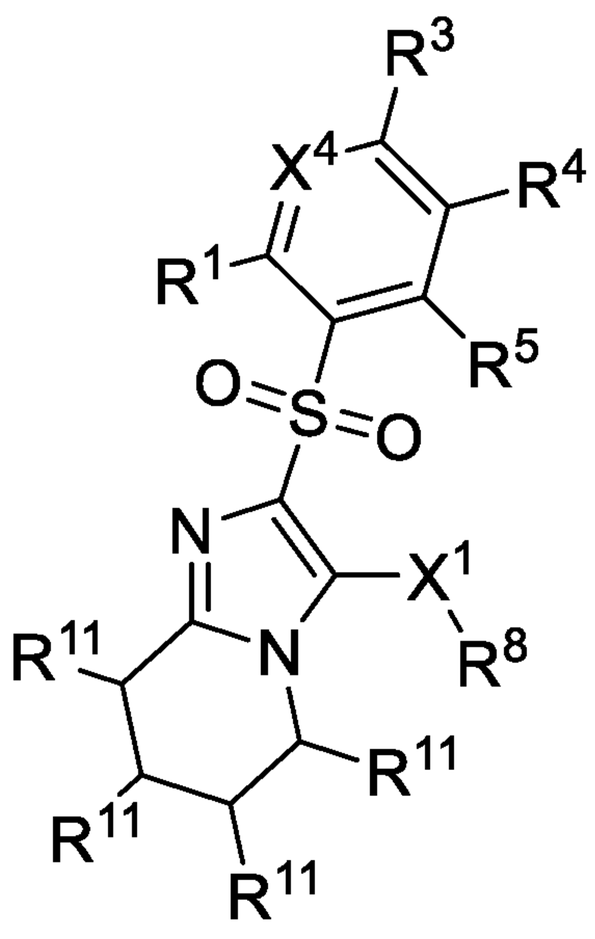
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

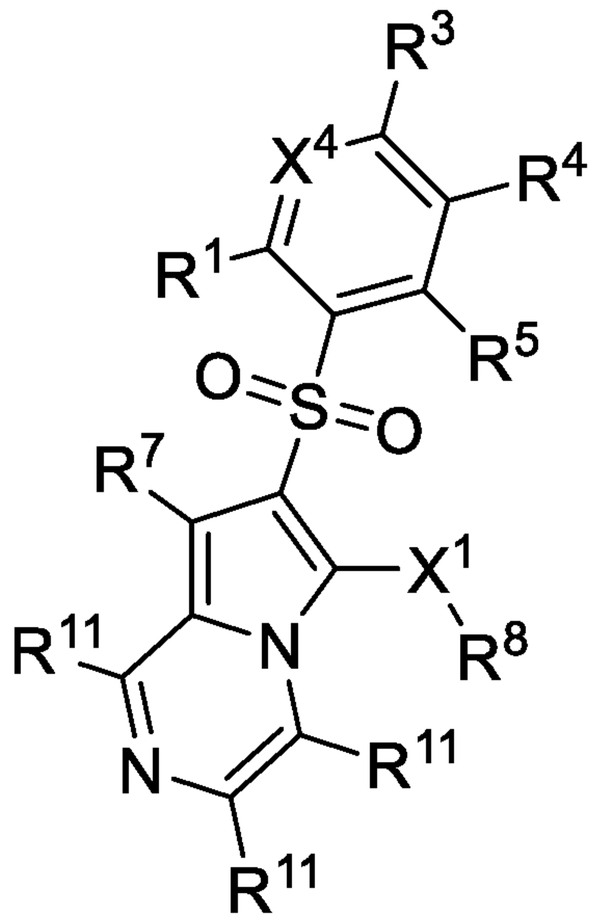
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

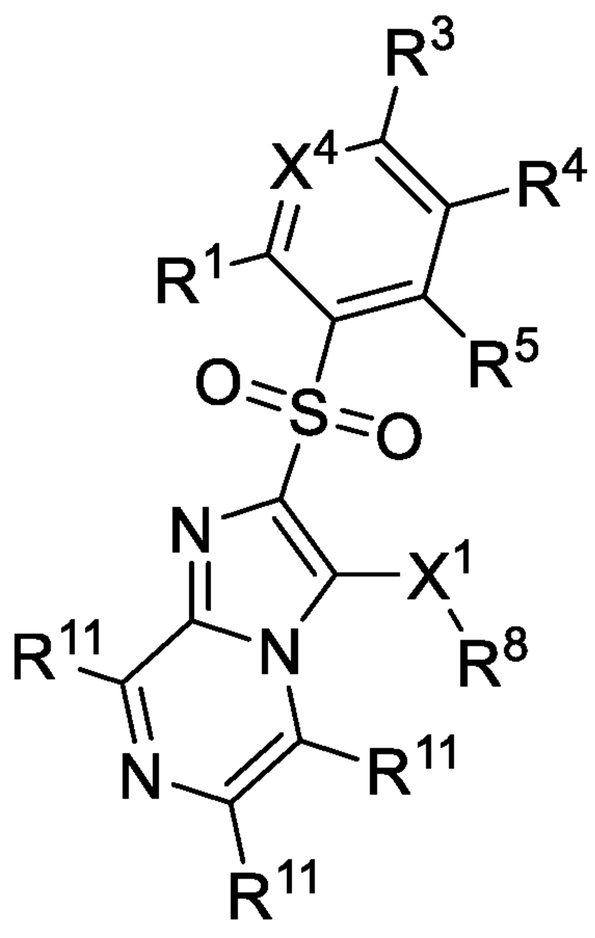
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

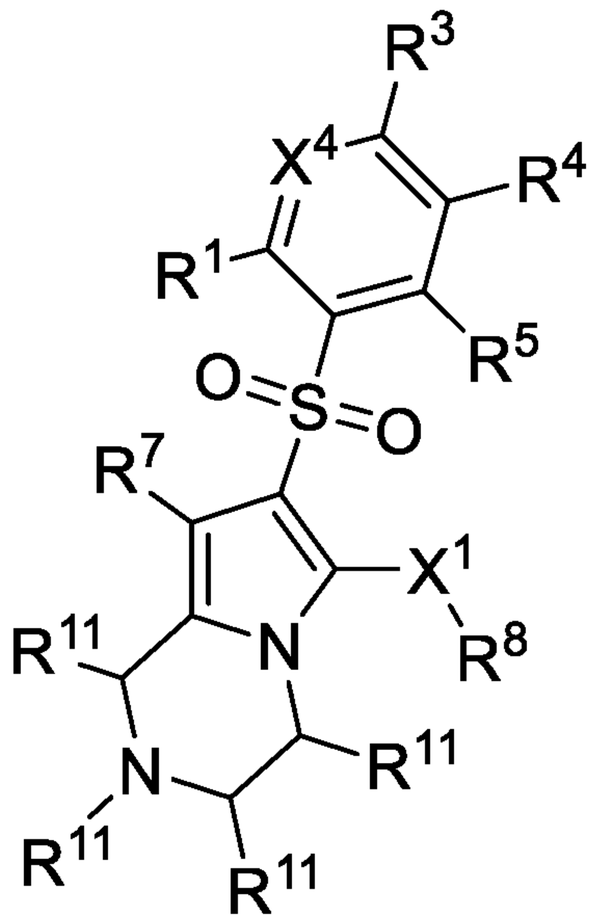
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

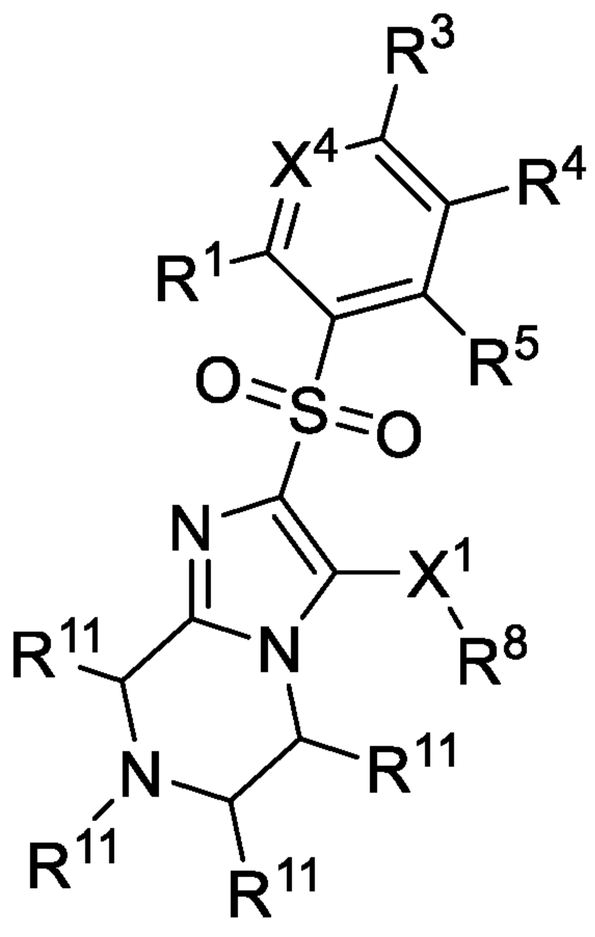
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

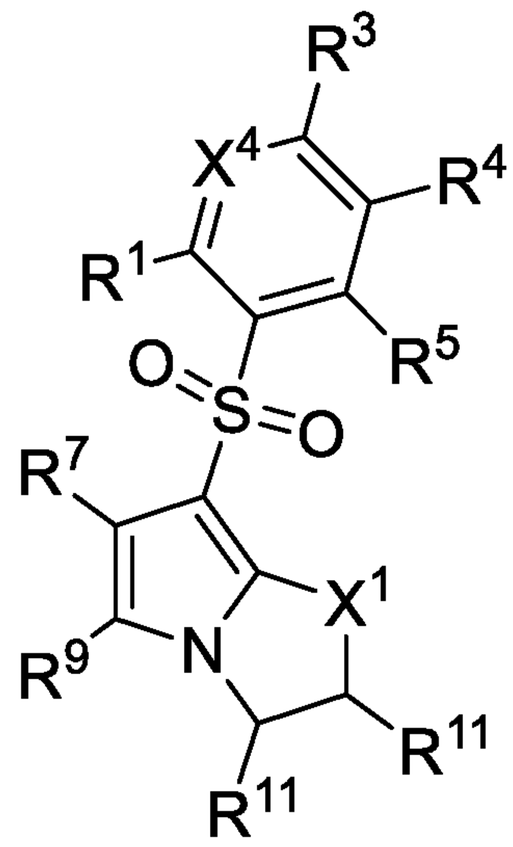
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

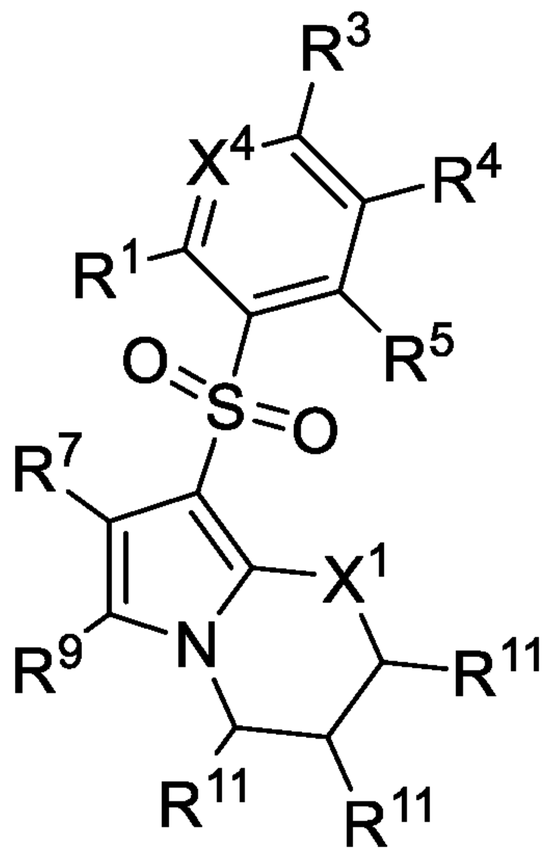
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

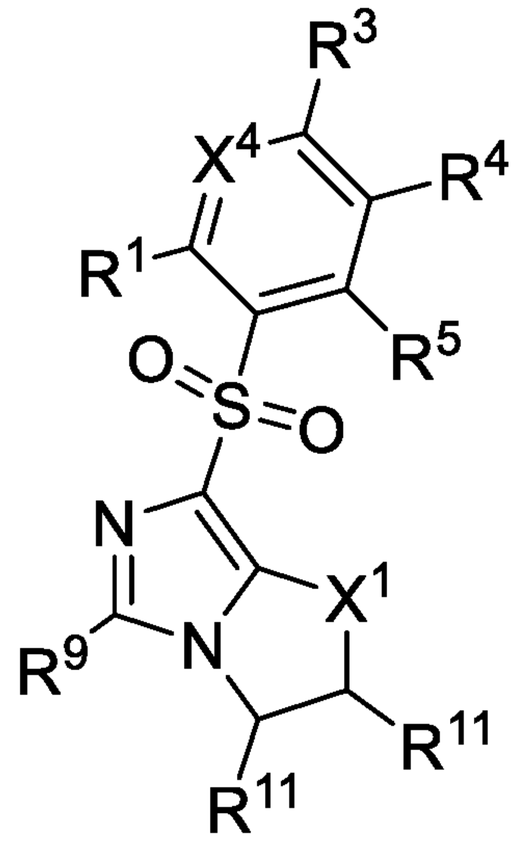
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

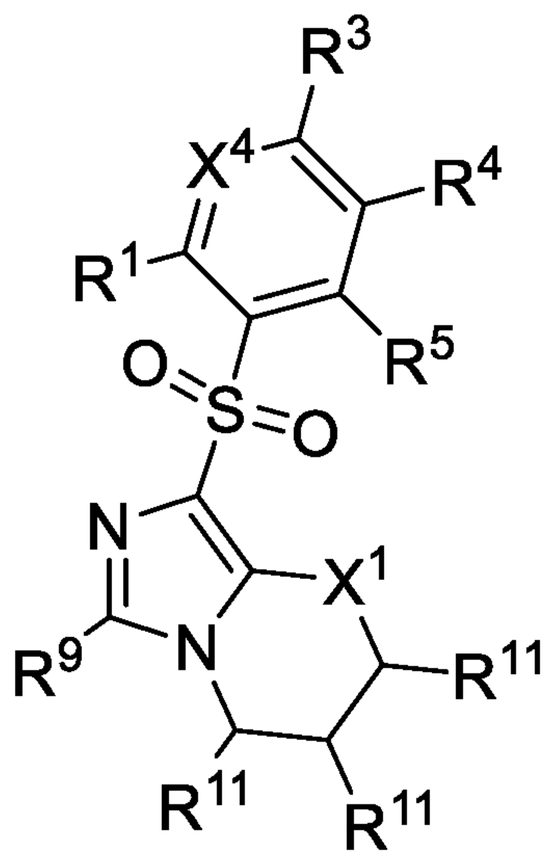
In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, each R^{10} is independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, and $NR^{c1}R^{d1}$.

In some embodiments, Cy^1 is C_{3-10} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

In some embodiments, each R^{10} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, each R^{11} is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, each R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^7 is selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^6 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^9 is selected from $S(O)_2R^{b1}$ and C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; or

R^9 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, and $NR^{c1}R^{d1}$; and

each R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the compound of Formula (IIIh):

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^7 is selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^6 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^9 is selected from R^9 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; or

R^9 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

each R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments of the compound of Formula (IIIh):

X^1 is selected from S(O) and $S(O)_2$;

R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^7 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^6 is selected from H and C_{1-6} alkyl;

R^9 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; or

R^9 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

each R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered

heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

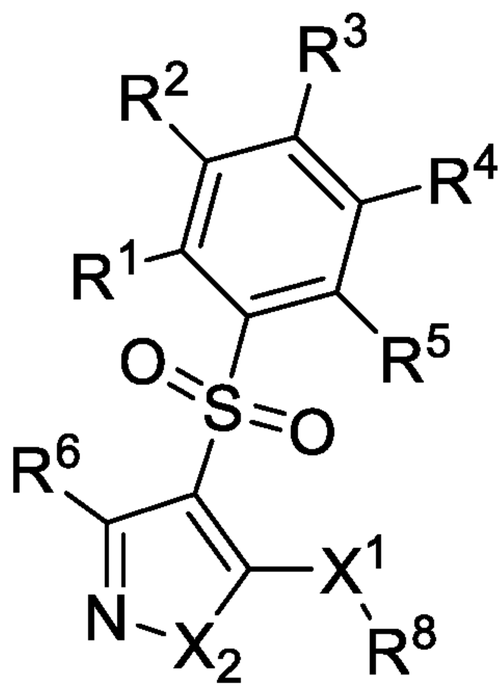
In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (IIIh) is selected from any one of the compounds of Table 8, Table 9, Table 10, and Table 11, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIIh) is selected from any one of the compounds of Table 8, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIIh) is selected from any one of the compounds of Table 9, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIIh) is selected from any one of the compounds of Table 10, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IIIh) is selected from any one of the compounds of Table 11, or a pharmaceutically acceptable salt thereof.

Formula (IIIi)

In one general aspect, the present disclosure provides a compound of Formula (IIIi):



(IIIi),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

X^2 is selected from S and NR^7;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^9;

R^6 and R^7 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

provided that at least one of R^6 and R^7 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

or R^6 and R^7, together with the C atom to which R^6 is attached and N atom to

which R^7 is attached, from a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^9 independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

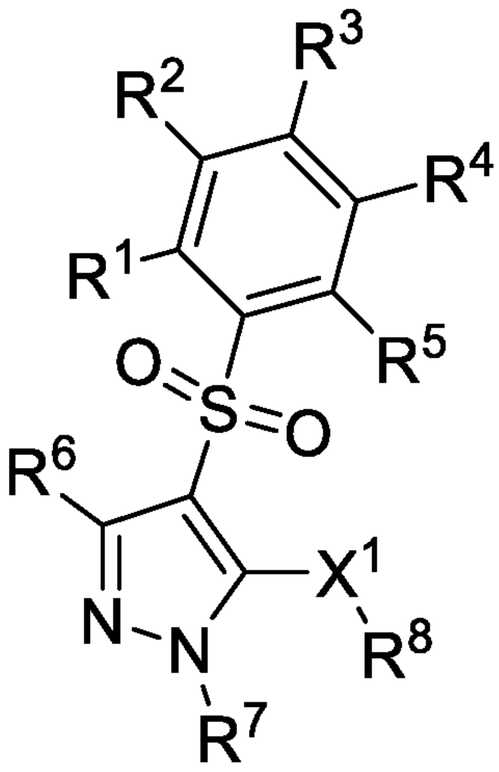
each R^{10} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

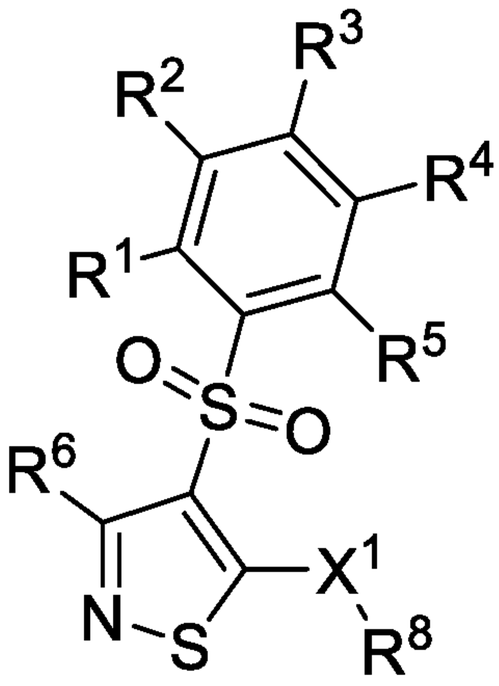
In some embodiments, the compound of Formula (IIIi) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IIIi) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H and halo.

In some embodiments, R^6 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments:

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H and halo;

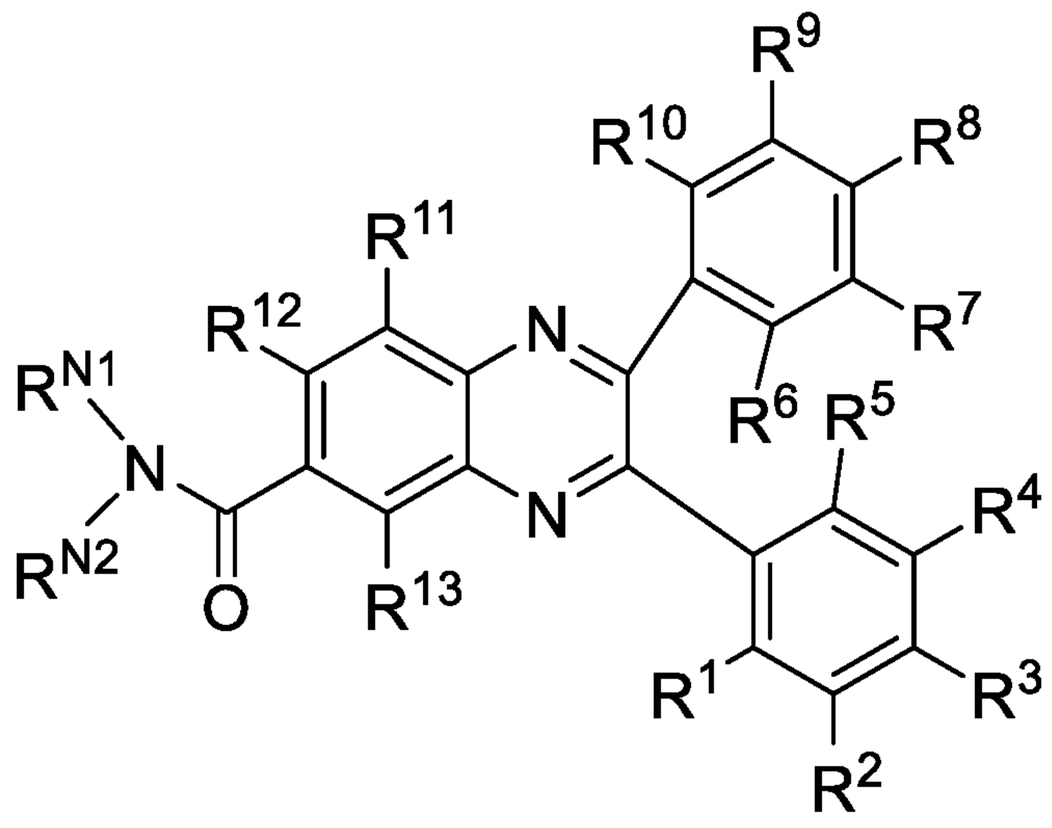
R^6 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

R^8 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, the compound is selected from any one of the compounds of Table 15, or a pharmaceutically acceptable salt thereof.

Formula (IVa)

In one general aspect, the present disclosure provides a compound of Formula (IVa):



(IVa),

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

or R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{14};

each R^{14} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino,

di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy. In some embodiments, at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is H.

In some embodiments, R^{N1} is selected from H, C_{1-6} alkyl, and C_{2-6} alkenyl. In some embodiments, R^{N1} is H. In some embodiments, R^{N1} is C_{1-6} alkyl. In some embodiments, R^{N1} is C_{2-6} alkenyl.

In some embodiments, R^{N2} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, R^{N2} is H.

In some embodiments, R^{N2} is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}. In some embodiments, R^{N2} is C_{2-6} alkenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}. In some embodiments, R^{N2} is C_{3-10} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}. In some aspects of these embodiments, the 4-10 membered heterocycloalkyl is selected from pyrrolidine, piperazine, morpholine, and piperidine.

In some embodiments, each R^{14} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, each R^{14} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$.

In some embodiments, each R^{14} independently selected from Cy^1, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$. In some embodiments, R^{14} is Cy^1. In some embodiments, R^{14} is C_{1-6} alkyl. In some embodiments, R^{14} is OR^{a1}. In some embodiments, R^{14} is $C(O)R^{b1}$. In some embodiments, R^{14} is $C(O)NR^{c1}R^{d1}$. In some embodiments, R^{14} is $C(O)OR^{a1}$. In some embodiments, R^{14} is $NR^{c1}R^{d1}$.

In some embodiments, each Cy^1 is independently selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3, substituents independently selected from R^{Cy1}.

In some embodiments, Cy^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3, substituents independently selected from R^{Cy1}. In some embodiments, Cy^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3, substituents independently selected from R^{Cy1}. In some embodiments, Cy^1 is 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3, substituents independently selected from R^{Cy1}.

In some embodiments, each Cy^1 is independently selected from phenyl, piperidine, thiophene, pyridine, piperazine, morpholine, azepane, pyrrolidone, pyrrolidine, and pyrimidine, each of which is optionally substituted with 1, 2, or 3, substituents independently selected from R^{Cy1}.

In some embodiments, each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{15}.

In some embodiments, each R^{Cy1} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$.

In some embodiments, each R^{Cy1} is independently selected from halo, C_{1-6} alkyl, OR^{a1}, SR^{a1}, and $NR^{c1}R^{d1}$.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-

C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments of the compound of Formula (IVa):

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

R^{N1} is selected from H, C_{1-6} alkyl, and C_{2-6} alkenyl;

R^{N2} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

R^{14} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$;

Cy^1 is independently selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3, substituents independently selected from R^{Cy1};

R^{Cy1} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents

independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments of the compound of Formula (IVa):

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^{N1} is selected from H, C_{1-6} alkyl, and C_{2-6} alkenyl;

R^{N2} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2} together with the N atom to which they are attached from pyrrolidine, piperazine, morpholine, or piperidine, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

each R^{14} independently selected from Cy^1, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$;

each Cy^1 is independently selected from phenyl, piperidine, thiophene, pyridine, piperazine, morpholine, azepane, pyrrolidone, pyrrolidine, and pyrimidine, each of which is optionally substituted with 1, 2, or 3, substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, C_{1-6} alkyl, OR^{a1}, SR^{a1}, and $NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

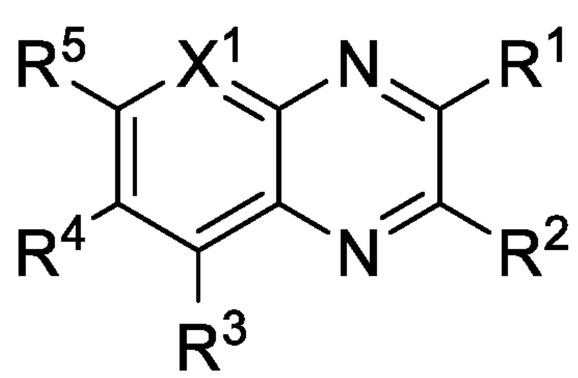
each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, the compound of Formula (IVa) is selected from any one of the compounds of Table 4a or Table 4b, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IVa) is selected from any one of the compounds of Table 4a, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IVa) is selected from any one of the compounds of Table 4b, or a pharmaceutically acceptable salt thereof. In some

embodiments, the present disclosure provides a compound selected from any one of the compounds of Table 4b or Table 4b-2, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a compound selected from any one of the compounds of Table 4b, or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides a compound selected from any one of the compounds of Table 4b-2, or a pharmaceutically acceptable salt thereof.

Formula (IVb)

In one general aspect, the present disclosure provides a compound of Formula (IVb)



(IVb),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^8;

each R^8 is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl ,4-10 membered heterocycloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each

optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

R^1 and R^2 are each independently selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene,

HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, X^1 is CR^6.

In some embodiments, X^1 is N.

In some embodiments, R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^7.

In some embodiments, R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

In some embodiments, R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^8. In some embodiments, R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8.

In some embodiments, each R^8 is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl ,4-10 membered heterocycloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10

membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9. In some embodiments, R^8 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, each R^9 is independently selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^9 is independently selected from C_{1-6} alkyl, halo, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$. In some embodiments, each R^9 is independently selected from C_{1-6} alkyl, halo, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$. In some embodiments, each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$. In some embodiments, R^9 is OR^{a1}. In some embodiments, R^9 is $NR^{c1}R^{d1}$.

In some embodiments, R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^1 is C_{1-6} haloalkyl; and R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and R^2 is C_{1-6} haloalkyl.

In some embodiments, R^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and R^2 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some of the above embodiments, the 5-10 membered heteroaryl is thiophene. In some of the above embodiments, the C_{6-10} aryl is phenyl.

In some embodiments, each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}. In some embodiments, each R^{10} is independently selected from halo and $S(O)_2R^{b1}$. In some embodiments, R^{10} is halo. In some embodiments, R^{10} is $S(O)_2R^{b1}$.

In some embodiments, each R^{11} is independently selected from OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments of the compound of Formula (IVb):

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

In some embodiments, of the compound of Formula (IVb):

R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^2 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

In some embodiments of a compound of Formula (IVb):

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is C_{1-6} haloalkyl;

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

In some embodiments of a compound of Formula (IVb):

R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is trifluoromethyl;

R^2 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

In some embodiments of a compound of Formula (IVb):

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^2 is C_{1-6} haloalkyl;

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

In some embodiments of a compound of Formula (IVb):

R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^2 is trifluoromethyl;

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

In some embodiments of a compound of Formula (IVb):

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

In some embodiments of a compound of Formula (IVb):

R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and

indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is thiophenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^2 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

In some embodiments of a compound of Formula (IVb):

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^2 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

In some embodiments of a compound of Formula (IVb):

R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

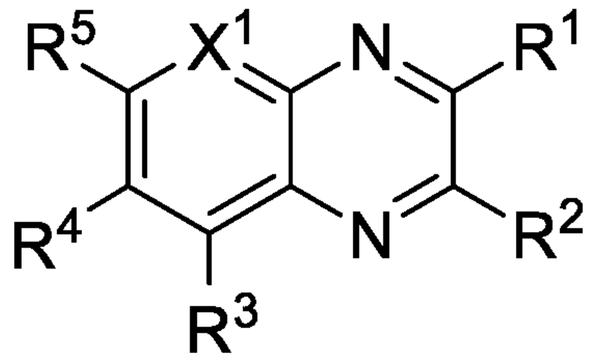
R^2 is thiophenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

In some embodiments, the compound of Formula (IVb) is selected from any one of the compounds of Table 4c, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IVb) is selected from any one of the compounds of Table 4c or Table 4c-2, or a pharmaceutically acceptable salt thereof.

Formula (IVc)

In one general aspect, the present disclosure provides a compound of Formula (IVc)



(IVc),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^4 is selected from $C(O)NR^{N1}R^{N2}$, $C(O)OR^{a1}$, and CN;

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14};

each R^{14} independently selected from H, Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from R^8 and $S(O)_2R^8$;

R^8 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

provided that R^1 and R^2 are not both C_{6-10} aryl;

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, X^1 is CR^6.

In some embodiments, X^1 is N.

In some embodiments, R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^7.

In some embodiments, R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy. In some embodiments, R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

In some embodiments, R^4 is selected from $C(O)NR^{N1}R^{N2}$ and $C(O)OR^{a1}$. In some embodiments, R^4 is selected from $C(O)NR^{N1}R^{N2}$ and CN. In some embodiments, R^4 is selected from $C(O)OR^{a1}$ and CN. In some embodiments, R^4 is $C(O)NR^{N1}R^{N2}$. In some embodiments, R^4 is $C(O)OR^{a1}$. In some embodiments, R^4 is CN.

In some embodiments, each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, R^{N1} is selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, R^{N1} is H. In some embodiments, R^{N1} is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}. In some embodiments, R^{N1} is C_{2-6} alkynyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}. In some embodiments, R^{N1} is 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, R^{N2} is selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

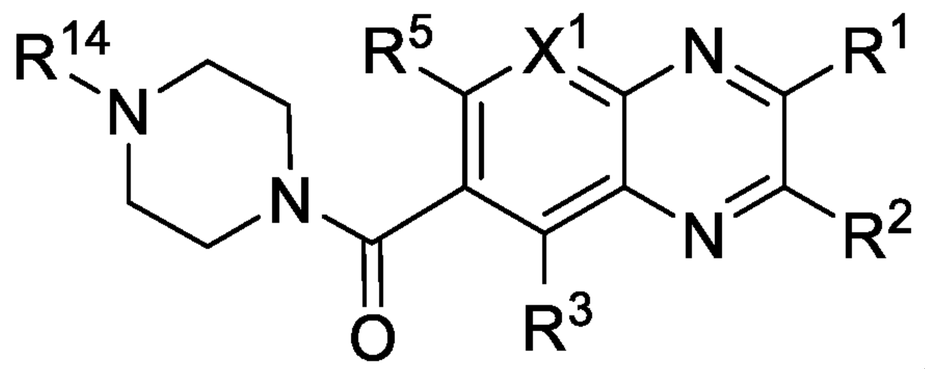
In some embodiments, R^{N2} is H. In some embodiments, R^{N2} is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}. In some embodiments, R^{N2} is C_{2-6} alkynyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}. In some embodiments, R^{N2} is 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, each R^{14} is independently selected from H, Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

In some embodiments, each R^{14} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$. In some embodiments, each R^{14} is independently selected from C_{1-6} alkyl and $NR^{c1}R^{d1}$. In some embodiments, R^{14} is C_{1-6} alkyl. In some embodiments, $NR^{c1}R^{d1}$.

In some embodiments, the compound of Formula (IVc) has formula:



,

or a pharmaceutically acceptable salt thereof.

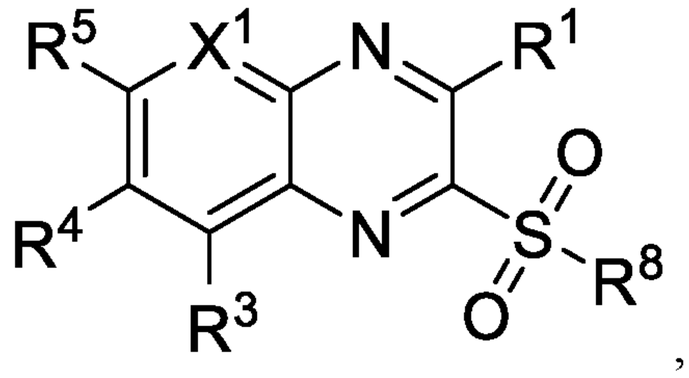
In some embodiments, R^1 is C_{1-6} haloalkyl; and R^2 is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 independently selected R^{10}.

In some embodiments, R^1 is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 independently selected R^{10}; and R^2 is C_{1-6} haloalkyl.

In some embodiments, R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and R^2 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

In some embodiments, R^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

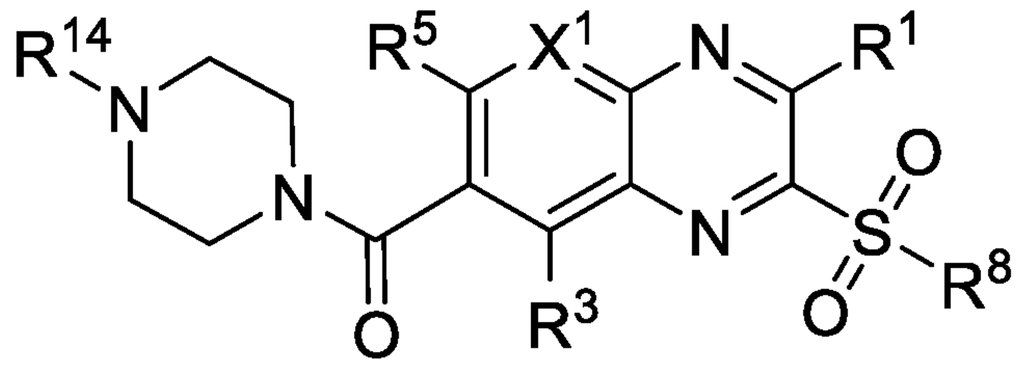
In some embodiments, the compound of Formula (IVc) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IVc) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, R^1 is C_{1-6} haloalkyl; and R^8 is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 independently selected R^{10}.

In some embodiments, R^1 is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 independently selected R^{10}; and R^8 is C_{1-6} haloalkyl.

In some embodiments, R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and R^8 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

In some embodiments, R^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and R^8 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

In some embodiments, R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and R^8 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

In some embodiments, R^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and R^8 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

In some aspects of the above embodiments, the 5-10 membered heteroaryl is selected from thiophenyl and pyridinyl; and the C_{6-10} aryl is phenyl.

In some embodiments, R^1 is C_{1-6} haloalkyl; and R^8 is C_{1-6} haloalkyl.

In some embodiments, each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}. In some embodiments, each R^{10} is independently selected from halo and C_{1-6} alkyl. In some embodiments, R^{10} is halo. In some embodiments, R^{10} is C_{1-6} alkyl.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments of a compound of Formula (IVc):

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14};

each R^{14} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; and

each R^{10} is independently selected from halo and C_{1-6} alkyl.

In some aspects of the above embodiments,

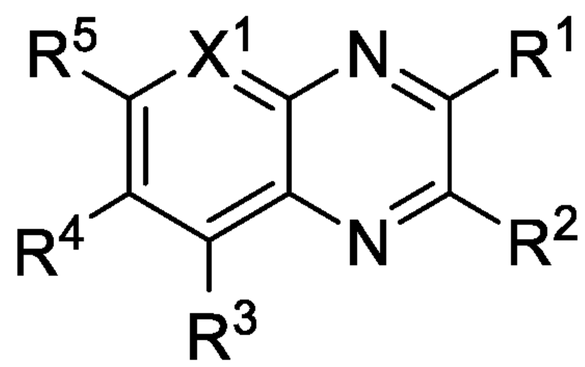
R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R^{14} is independently selected from C_{1-6} alkyl and $NR^{c1}R^{d1}$.

In some embodiments, the compound of Formula (IVc) is selected from any one of the compounds of Table 4d, or a pharmaceutically acceptable salt thereof.

Formula (IVd)

In one general aspect, the present disclosure provides a compound of Formula (IVd):



(IVd),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^3 is selected from $C(O)NR^{N1}R^{N2}$ and $C(O)OR^{a1}$;

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14};

each R^{14} independently selected from H, Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from R^8 and $S(O)_2R^8$;

R^8 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered

heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, X^1 is CR^6.

In some embodiments, X^1 is N.

In some embodiments, R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7.

In some embodiments, R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy. In some embodiments, R^4, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

In some embodiments, R^3 is $C(O)NR^{N1}R^{N2}$.

In some embodiments, R^3 is $C(O)OR^{a1}$.

In some embodiments, each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, R^{N1} is selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

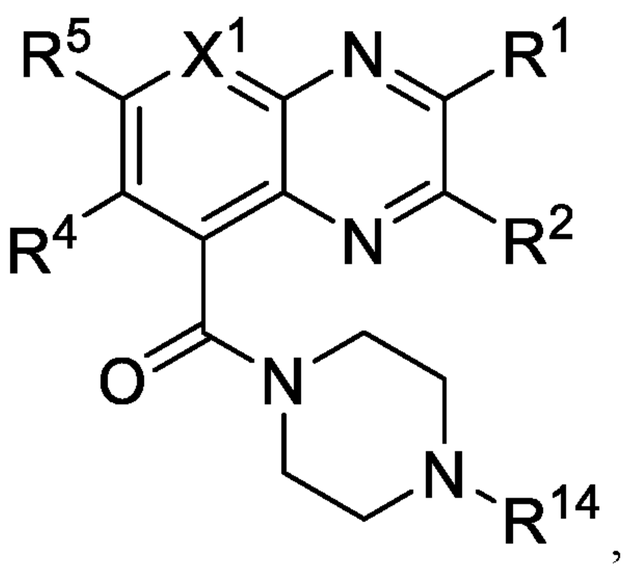
In some embodiments, R^{N1} is H. In some embodiments, R^{N1} is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}. In some embodiments, R^{N1} is C_{2-6} alkynyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}. In some embodiments, R^{N1} is 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, R^{N2} is selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, R^{N2} is H. In some embodiments, R^{N2} is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}. In some embodiments, R^{N2} is C_{2-6} alkynyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}. In some embodiments, R^{N2} is 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14}.

In some embodiments, the compound of Formula (IVd) has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, each R^{14} is independently selected from H, Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$. In some embodiments, each R^{14} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$. In some embodiments, each R^{14} is independently selected from C_{1-6} alkyl and $NR^{c1}R^{d1}$. In some embodiments, R^{14} is C_{1-6} alkyl. In some embodiments, R^{14} is $NR^{c1}R^{d1}$.

In some embodiments, R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

In some embodiments, each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}. In some embodiments, each R^{10} is independently selected from halo and C_{1-6} alkyl.

In some embodiments, each R^{11} is independently selected from OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments of a compound of Formula (IVd):

R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14};

wherein each R^{14} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; and

each R^{10} is independently selected from halo and C_{1-6} alkyl.

In some aspects of the above embodiments:

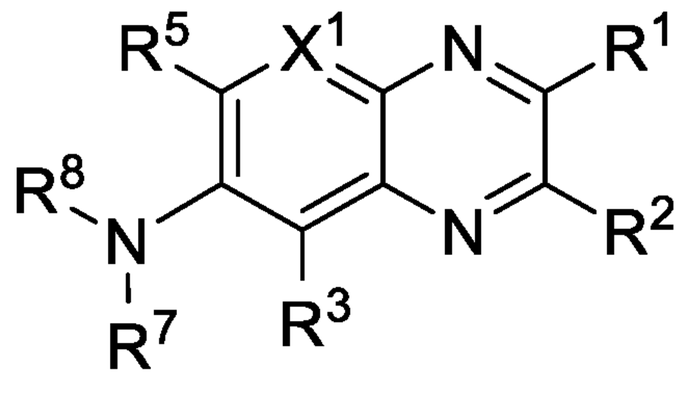
R^4, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each R^{14} is independently selected from C_{1-6} alkyl and $NR^{c1}R^{d1}$.

In some embodiments, the compound of Formula (IVd) is selected from any one of the compound of Table 4e, or a pharmaceutically acceptable salt thereof.

Formula (IVe)

In one general aspect, the present disclosure provides a compound of Formula (IVe)



(IVe),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and

$S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

or R^7 and R^8 together with the N atom to which they are attached form a 4-10 membered heterocycloalkyl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from R^8 and $S(O)_2R^8$;

R^8 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino; and any C_{1-6} alkyl, C_{1-6} alkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$,

$NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from R^{8a} and $S(O)_2R^{8a}$;

R^{8a} is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6}

alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

In some embodiments, X^1 is CR^6.

In some embodiments, X^1 is N.

In some embodiments, R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy. In some embodiments, R^4, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

In some embodimetns, R^7 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodimetns, R^8 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

In some embodiments, each R^9 is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$.

In some embodiments, R^7 is selected from H and C_{1-6} alkyl; and R^8 is selected from $C(O)R^{b1}$ and $C(O)OR^{a1}$. In some embodiments, R^7 is selected from H and C_{1-6} alkyl; and R^8 is $C(O)NR^{c1}R^{d1}$.

In some embodiments, each R^{c1} and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl and C_{3-10} cycloalkyl are each optionally substituted with 1 or 2 independently selected R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^{a1} and R^{b1} is independently selected from C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

In some embodiments, each R^g is independently selected from OH, halo, C_{1-6} alkyl, C_{1-6} alkoxy, 4-10 membered heterocycloalkyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkylsulfonyl, C_{1-6} alkylcarbamyl, and C_{1-6} alkylcarbonyl, and any C_{1-6} alkyl, C_{1-6} alkoxy, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1 or 2 substituents independently selected from C_{1-6} alkyl and C_{1-6} alkoxy.

In some embodiments, each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

In some embodiments, each R^g is independently selected from halo, C_{1-6} alkyl, 4-10 membered heterocycloalkyl, amino, C_{1-6} alkylsulfonyl, C_{1-6} alkylcarbamyl, and C_{1-6} alkylcarbonyl.

In some embodiments, R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

In some embodiments, each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$,

$NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}. In some embodiments, each R^{10} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}. In some embodiments, each R^{10} is independently selected from halo and C_{1-6} alkyl.

In some embodiments of a compound of Formula (IVe):

R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^7 is selected from H and C_{1-6} alkyl;

R^8 is selected from $C(O)R^{b1}$ and $C(O)OR^{a1}$;

each R^{a1} and R^{b1} is independently selected from C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

each R^g is independently selected from halo, C_{1-6} alkyl, 4-10 membered heterocycloalkyl, amino, C_{1-6} alkylsulfonyl, C_{1-6} alkylcarbamyl, and C_{1-6} alkylcarbonyl;

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10};

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

each R^{10} is independently selected from halo and C_{1-6} alkyl.

In some embodiments:

R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^7 is selected from H and C_{1-6} alkyl;

R^8 is $C(O)NR^{c1}R^{d1}$;

each R^{c1} and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl and C_{3-10} cycloalkyl are each optionally substituted with 1 or 2 independently selected R^g;

each R^g is independently selected from OH, halo, C_{1-6} alkyl, C_{1-6} alkoxy, 4-10 membered heterocycloalkyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkylsulfonyl, C_{1-6} alkylcarbamyl, and C_{1-6} alkylcarbonyl, and any C_{1-6} alkyl, C_{1-6}

alkoxy, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1 or 2 substituents independently selected from C_{1-6} alkyl and C_{1-6} alkoxy;

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10};

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

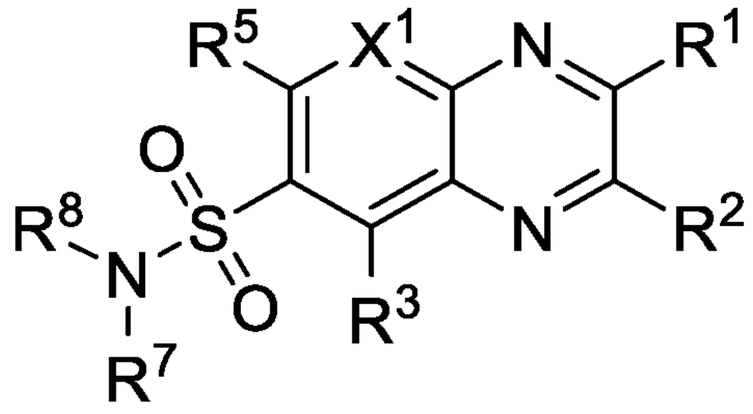
each R^{10} is independently selected from halo and C_{1-6} alkyl.

In some embodiments, the compound of Formula (IVe) is selected from any one of the compounds of Table 4f, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IVe) is selected from any one of the compounds of Table 4f or Table 4f-2, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula (IVe) is selected from any one of the compounds of Table 4f-2, or a pharmaceutically acceptable salt thereof.

Formula (IVf)

In one general aspect, the present disclosure provides a compound of Formula (IVf)



(IVf),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10}

cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

or R^7 and R^8 together with the N atom to which they are attached form a 4-10 membered heterocycloalkyl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino, and any C_{1-6} alkyl, C_{1-6} alkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

In some embodiments, X is N.

In some embodiments, X is CR^6.

In some embodiments, R^3, R^5, and R^6 are each independently selected from H, halo, OH, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

In some embodiments, R^3, R^5, and R^6 are each H.

In some embodiments:

R^7 is H; and

R^8 is selected from C_{1-6} alkyl and C_{3-10} cycloalkyl, each of which is independently selected from 1 or 2 substituents independently selected from R^9.

In some embodiments, R^9 is independently selected from C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$; wherein said C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{10}.

In some embodiments:

R^1 is C_{6-10} aryl, optionally substituted with 1 or 2 independently selected R^{10}; and

R^2 is C_{6-10} aryl, optionally substituted with 1 or 2 independently selected R^{10}.

In some embodiments, each R^{10} is independently selected from halo, OH, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

In some embodiments:

R^1 is C_{6-10} aryl, optionally substituted with 1 or 2 independently selected R^{10};

R^2 is C_{6-10} aryl, optionally substituted with 1 or 2 independently selected R^{10};

X is CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, OH, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino;

R^7 is H;

R^8 is selected from C_{1-6} alkyl and C_{3-10} cycloalkyl, each of which is independently selected from 1 or 2 substituents independently selected from R^9;

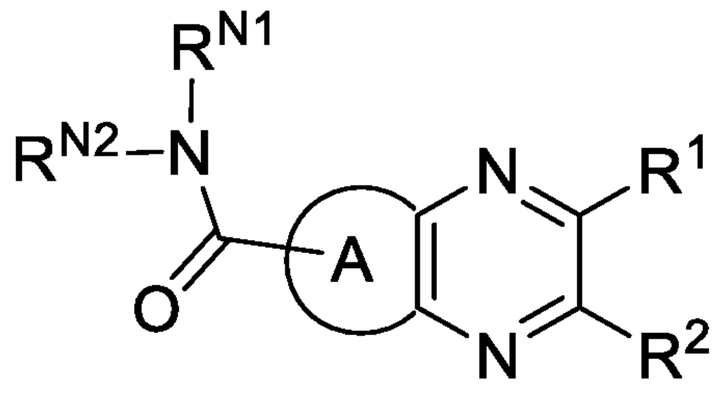
each R^9 is independently selected from C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$; wherein said C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo, OH, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

In some embodiments, the compound is selected from any one of the compounds of Table 4g, or a pharmaceutically acceptable salt thereof.

Formula (IVg)

In one general aspect, the present disclosure provides a compound of Formula (IVg):



(IVg),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{3-8} cycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

or R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{14};

each R^{14} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

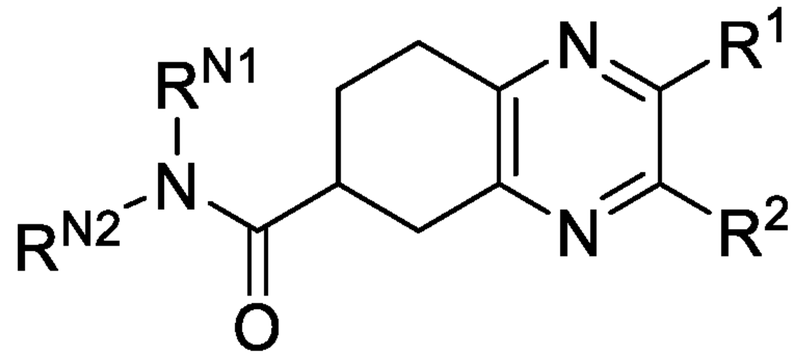
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl,

C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino, and any C_{1-6} alkyl, C_{1-6} alkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

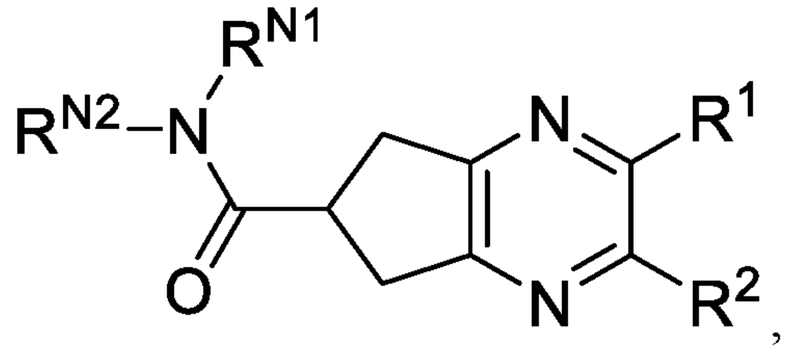
In some embodiments, the compound of Formula (IVg) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (IVg) has formula:



,

or a pharmaceutically acceptable salt thereof.

In some embodiments:

R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

In some embodiments, the compound is selected from any one of the compounds of Table 17, or a pharmaceutically acceptable salt thereof.

In some embodiments, a salt of any one of the compounds disclosed herein is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl

functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

In some embodiments, acids commonly employed to form pharmaceutically acceptable salts of the compounds disclosed herein include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-l,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid.

In some embodiments, bases commonly employed to form pharmaceutically acceptable salts of the compounds disclosed herein include hydroxides of alkali metals, including sodium, potassium, and lithium; hydroxides of alkaline earth metals such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, organic amines such as unsubstituted or hydroxyl-substituted mono-, di-, or tri-alkylamines, dicyclohexylamine; tributyl amine; pyridine; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-OH-(C1-C6)-alkylamine), such as N,N-dimethyl-N-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; morpholine; thiomorpholine; piperidine; pyrrolidine; and amino acids such as arginine, lysine, and the like.

In some embodiments, any one of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, is substantially isolated.

Methods of making therapeutic compounds

Compounds as set forth in any one of the Formulae disclosed herein, including salts thereof, can be prepared using organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes. A person skilled in the art knows how to select and implement appropriate synthetic protocols, and appreciates that a broad repertoire of synthetic organic reactions is available to be potentially employed in synthesizing compounds provided herein.

Suitable synthetic methods of starting materials, intermediates, and products can be identified by reference to the literature, including reference sources such as: *Advances in Heterocyclic Chemistry*, Vols. 1-107 (Elsevier, 1963-2012); *Journal of Heterocyclic Chemistry* Vols. 1-49 (*J. Heterocyclic Chemistry*, 1964-2012); Carreira *et al.*, (Ed.) *Science of Synthesis*, Vols. 1-48 (2001-2010) and Knowledge Updates KU2010/1-4; 2011/1-4; 2012/1-2 (Thieme, 2001-2012); Katritzky *et al.*, (Ed.) *Comprehensive Organic Functional Group Transformations*, (Pergamon Press, 1996); Katritzky *et al.*, (Ed.) *Comprehensive Organic Functional Group Transformations II* (Elsevier, 2nd Edition, 2004); Katritzky *et al.*, (Ed.) *Comprehensive Heterocyclic Chemistry* (Pergamon Press, 1984); Katritzky *et al.*, *Comprehensive Heterocyclic Chemistry II*, (Pergamon Press, 1996); Smith *et al.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th Ed. (Wiley, 2007); Trost *et al.* (Ed.) *Comprehensive Organic Synthesis* (Pergamon Press, 1991).

The reactions for preparing the compounds provided herein can be carried out in suitable solvents that can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures that can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of the compounds provided herein can involve the protection and deprotection of various chemical groups. The need for protection and deprotection,

and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in P. G. M. Wuts and T. W. Greene, *Protective Groups in Organic Synthesis*, 4th Ed., Wiley & Sons, Inc., New York (2006).

Pharmaceutical compositions and formulations

This document also provides pharmaceutical compositions comprising an effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier. The pharmaceutical composition also can comprise any one of the additional therapeutic agents and/or therapeutic molecules described herein. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

Pharmaceutically acceptable carriers, adjuvants, and vehicles that can be used in the pharmaceutical compositions provided herein include, without limitation, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (e.g., human serum albumin), buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol, and wool fat.

The compositions or dosage forms can contain any one or more of the compounds or therapeutic agents described herein in the range of 0.005 percent to 100 percent with the balance made up from the suitable pharmaceutically acceptable carriers or excipients. The contemplated compositions can contain from about 0.001 percent to about 100 percent (e.g., from about 0.1 percent to about 95 percent, from about 75 percent to about 85 percent, or from about 20 percent to about 80 percent) of any one or more of the compounds or therapeutic agents provided herein, wherein the balance can be made up of any pharmaceutically acceptable carrier or excipient described herein, or any combination of these carriers or excipients.

Routes of administration and dosage forms

The therapeutic compounds and/or pharmaceutical compositions provided herein (e.g., a composition containing one or more compounds disclosed herein, or a pharmaceutically acceptable salt thereof) can include those suitable for any acceptable route of administration. Acceptable routes of administration include, without limitation, buccal, cutaneous, endocervical, endosinusial, endotracheal, enteral, epidural, interstitial, intra-abdominal, intra-arterial, intrabronchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intragingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intranasal, intraovarian, intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal, nasogastric, oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral, vaginal, intravitreal, subretinal or other intraocular routes of administrations.

Compositions and formulations described herein can conveniently be presented in a unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and can be prepared by any methods well known in the art of pharmacy. See, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, MD (20th ed. 2000). Such preparative methods include, without limitation, the step of bringing into association with the molecule to be administered ingredients such as a carrier that constitutes one or more accessory ingredients. In general, the compositions can be prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

In some embodiments, any one or more of the compounds or therapeutic agents described herein can be administered orally. Compositions described herein that are suitable for oral administration can be presented as discrete units such as capsules, sachets, granules, or tablets each containing a predetermined amount (e.g., effective amount) of the active ingredient(s); a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus. Soft gelatin capsules can be useful for containing such suspensions, which can beneficially

increase the rate of compound absorption. In the case of tablets for oral use, carriers that are commonly used include, without limitation, lactose, sucrose, glucose, mannitol, silicic acid, and starches. Other acceptable excipients can include, without limitation, (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. For oral administration in a capsule form, useful diluents include, without limitation, lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient(s) can be combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents can be added. Compositions suitable for oral administration include, without limitation, lozenges comprising ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient(s) in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Compositions suitable for parenteral administration include, without limitation, aqueous and non-aqueous sterile injection solutions or infusion solutions that may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions that may include suspending agents and thickening agents. The formulations can be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for injections, saline (e.g., 0.9% saline solution), or 5% dextrose solution, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets. The injection solutions can be in the form of, for example, a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. A sterile injectable preparation

also can be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils can be used as a solvent or suspending medium. For this purpose, any bland fixed oil can be used including, without limitation, synthetic mono- or diglycerides. Fatty acids such as oleic acid and its glyceride derivatives can be used to prepare injectables. In some cases, natural pharmaceutically acceptable oils such as olive oil or castor oil, especially in their polyoxyethylated versions, can be used to prepare injectables. These oil solutions or suspensions also can contain a long-chain alcohol diluent or dispersant.

In some cases, a therapeutic compound and/or pharmaceutical composition provided herein can be administered in the form of suppository for rectal administration. These compositions can be prepared by mixing a compound described herein (e.g., any one of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof) with a suitable non-irritating excipient that is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active component(s). Such materials include, without limitation, cocoa butter, beeswax, and polyethylene glycols.

In some cases, a therapeutic compounds and/or pharmaceutical composition provided herein can be administered by nasal aerosol or inhalation. Such compositions can be prepared according to techniques well known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, for example, U.S. Patent No. 6,803,031. Additional formulations and methods for intranasal administration are found in Ilium, L., *J. Pharm. Pharmacol.*, 56:3-17 (2004); and Ilium, L., *Eur. J. Pharm. Sci.*, 11:1-18 (2000).

In some cases, a therapeutic compounds and/or pharmaceutical composition provided herein can be prepared as a topical composition and used in the form of an aerosol spray, cream, emulsion, solid, liquid, dispersion, foam, oil, gel, hydrogel, lotion, mousse, ointment, powder, patch, pomade, solution, pump spray, stick, towelette, soap, or other forms commonly employed in the art of topical administration and/or cosmetic and skin care formulation. The topical compositions

can be in an emulsion form. Topical administration of a therapeutic compounds and/or pharmaceutical composition provided herein can be useful when the desired treatment involves areas or organs readily accessible by topical application. In some cases, a topical composition can include a combination of any one or more of the compounds or therapeutic agents described herein (e.g., a compound set forth in any one of Formulae (I)-(IV), or a pharmaceutically acceptable salt thereof), and one or more additional ingredients, carriers, excipients, or diluents including, without limitation, absorbents, anti-irritants, anti-acne agents, preservatives, antioxidants, coloring agents/pigments, emollients (moisturizers), emulsifiers, film-forming/holding agents, fragrances, leave-on exfoliants, prescription drugs, preservatives, scrub agents, silicones, skin-identical/repairing agents, slip agents, sunscreen actives, surfactants/detergent cleansing agents, penetration enhancers, and thickeners.

In some cases, one or more compounds or therapeutic agent described herein (e.g., any one of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof) can be incorporated into a composition for coating an implantable medical device such as a prosthesis, artificial valve, vascular graft, stent, or catheter. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in U.S. Patent Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings can be biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, or mixture thereof. In some cases, the coating can optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

In some cases, this document provides an implantable drug release device impregnated with or containing one or more compounds or therapeutic agents described herein (e.g., any one of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof) such that the compound(s) or therapeutic agent(s) are released from the device and are therapeutically active.

Dosages and regimens

A composition (e.g., pharmaceutical compositions provided herein) containing a compound provided herein, or a pharmaceutically acceptable salt thereof, can include that compound in an effective amount (e.g., a therapeutically effective

amount).

Effective doses can vary, depending on the diseases being treated, the severity of the disease, the route of administration, the sex, age and general health condition of the subject, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents, and the judgment of the treating physician.

In some embodiments, an effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, can range, for example, from about 0.1 mg to about 1000 mg. In some cases, the effective amount can be from about 0.5 mg to about 500 mg of a compound disclosed herein, or any amount in between these two values, for example, one of about 0.5 mg, about 1 mg, about 2 mg, about 5 mg, about 10 mg, about 20 mg, about 50 mg, about 100 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, or about 500 mg. The effective amount can be an amount sufficient to alleviate or reduce one or more of the symptoms associated with a disease, disorder, or condition being treated as described herein.

In some cases, an effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, can range, for example, from about 0.001 mg/kg to about 500 mg/kg (e.g., from about 0.001 mg/kg to about 200 mg/kg; from about 0.01 mg/kg to about 200 mg/kg; from about 0.01 mg/kg to about 150 mg/kg; from about 0.01 mg/kg to about 100 mg/kg; from about 0.01 mg/kg to about 50 mg/kg; from about 0.01 mg/kg to about 10 mg/kg; from about 0.01 mg/kg to about 5 mg/kg; from about 0.01 mg/kg to about 1 mg/kg; from about 0.01 mg/kg to about 0.5 mg/kg; from about 0.01 mg/kg to about 0.1 mg/kg; from about 0. 1 mg/kg to about 200 mg/kg; from about 0.1 mg/kg to about 150 mg/kg; from about 0. 1 mg/kg to about 100 mg/kg; from about 0.1 mg/kg to about 50 mg/kg; from about 0. 1 mg/kg to about 10 mg/kg; from about 0.1 mg/kg to about 5 mg/kg; from about 0.1 mg/kg to about 2 mg/kg; from about 0.1 mg/kg to about 1 mg/kg; from about 0.1 mg/kg to about 0.5 mg/kg, or from about 0.5 mg/kg to about 500 mg/kg).

In some cases, an effective amount of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, can be about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, or about 5 mg/kg.

The foregoing dosages can be administered on a daily basis (e.g., as a single dose or as two or more divided doses, e.g., once daily, twice daily, thrice daily) or on a non-daily basis (e.g., every other day, every two days, every three days, once weekly, twice weekly, once every two weeks, or once a month). In some cases, the

dosages can be administered every 4 hours, 6 hours, 8 hours, 12 hours, or 24 hours.

Kits

This document also provides pharmaceutical kits useful, for example, to inhibit NF-κB within cells within a mammal (e.g., a human). In some cases, this document provides pharmaceutical kits useful, for example, to treat diseases, disorders, and conditions referred to herein. Such pharmaceutical kits can include one or more containers containing a pharmaceutical composition that includes a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable salt thereof. In some cases, such kits can further include, if desired, one or more of various conventional pharmaceutical kit components such as containers with one or more pharmaceutically acceptable carriers. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components also can be included in a kit provided herein.

Combination therapies

In some cases, one or more compounds provided herein, or a pharmaceutically acceptable salt thereof, can be combined with one or more therapeutic molecules. Examples of therapeutic molecules that can be used in combination with one or more compounds provided herein, or a pharmaceutically acceptable salt thereof, include, without limitation, anti-inflammatory agents (e.g., steroids and antibodies against IL-6 or TNF-alpha), antimicrobial agents (e.g., antibiotics, anti-mycobacterial drugs, and anti-viral agents), anti-cancer agents (e.g., chemotherapeutic agents and cellular products such as engineered T cells), therapies for atherosclerosis (e.g., lipid-lowering agents, platelet inhibitors), agents to treat polycystic kidney disease (e.g. tolvaptan), therapies used for metabolic syndrome (e.g., insulin, glucose-lowering therapies), therapies for polycystic ovarian syndrome (e.g., metformin), treatment for muscular dystrophies (e.g., steroids, gene therapy approaches) and therapies for pain relief (e.g., non-steroidal anti-inflammatory medicines, opioids, regional nerve blocks).

One or more compounds provided herein, or a pharmaceutically acceptable salt thereof, and the one or more therapeutic molecules can be administered in any order or simultaneously. If simultaneously administered, they can be provided in a single, unified, form or in multiple forms (e.g., either as a single pill or as two

separate pills). One of the items can be given in multiple doses, or both can be given as multiple doses. If not simultaneous, the timing between the multiple doses can vary from more than zero weeks to less than four weeks.

Definitions

As used herein, the term "about" means "approximately" (e.g., plus or minus approximately 10% of the indicated value).

At various places in this document, substituents of compounds provided herein are disclosed in groups or in ranges. It is specifically intended that these groups and ranges include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl.

At various places in this document various aryl, heteroaryl, cycloalkyl, and heterocycloalkyl rings are described. Unless otherwise specified, these rings can be attached to the rest of the molecule at any ring member as permitted by valency. For example, the term "a pyridine ring" or "pyridinyl" may refer to a pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl ring.

It is further appreciated that certain features described herein, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features described herein which are, for brevity, described in the context of a single embodiment, also can be provided separately or in any suitable subcombination.

The term "aromatic" refers to a carbocycle or heterocycle having one or more polyunsaturated rings having aromatic character (i.e., having (4n + 2) delocalized π (pi) electrons where n is an integer).

The term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

As used herein, the phrase "optionally substituted" means unsubstituted or substituted. The substituents are independently selected, and substitution can be at any chemically accessible position. As used herein, the term "substituted" means that

a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, *e.g.*, oxo, can replace two hydrogen atoms. It is to be understood that substitution at a given atom is limited by valency.

Throughout the definitions, the term "C_{n-m}" indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C_{1-4}, C_{1-6}, and the like.

As used herein, the term "C_{n-m} alkyl", employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched, having n to m carbons. Examples of alkyl moieties include, without limitation, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as 2-methyl-1-butyl, *n*-pentyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl, and the like. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms.

As used herein, the term "C_{n-m} haloalkyl", employed alone or in combination with other terms, refers to an alkyl group having from one halogen atom to 2s+1 halogen atoms that may be the same or different, where "s" is the number of carbon atoms in the alkyl group, wherein the alkyl group has n to m carbon atoms. In some embodiments, the haloalkyl group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, "C_{n-m} alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds and having n to m carbons. Example alkenyl groups include, without limitation, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, *sec*-butenyl, and the like. In some embodiments, the alkenyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

As used herein, "C_{n-m} alkynyl" refers to an alkyl group having one or more triple carbon-carbon bonds and having n to m carbons. Example alkynyl groups include, without limitation, ethynyl, propyn-1-yl, propyn-2-yl, and the like. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

As used herein, the term "C_{n-m} alkylene", employed alone or in combination with other terms, refers to a divalent alkyl-linking group having n to m carbons. Examples of alkylene groups include, without limitation, ethan-1,1-diyl, ethan-1,2-diyl, propan-1,1-diyl, propan-1,3-diyl, propan-1,2-diyl, butan-1,4-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl, and the like. In some embodiments, the

alkylene moiety contains 2 to 6, 2 to 4, 2 to 3, 1 to 6, 1 to 4, or 1 to 2 carbon atoms.

As used herein, the term "C_{n-m} alkoxy", employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group has n to m carbons. Example alkoxy groups include, without limitation, methoxy, ethoxy, propoxy (e.g., *n*-propoxy and isopropoxy), butoxy (e.g., *n*-butoxy and *tert*-butoxy), and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, "C_{n-m} haloalkoxy" refers to a group of formula –O-haloalkyl having n to m carbon atoms. An example haloalkoxy group is OCF_3. In some embodiments, the haloalkoxy group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "amino" refers to a group of formula $–NH_2$.

As used herein, the term "C_{n-m} alkylamino" refers to a group of formula -NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Examples of alkylamino groups include, without limitation, N-methylamino, N-ethylamino, N-propylamino (e.g., N-(*n*-propyl)amino and N-isopropylamino), N-butylamino (e.g., N-(*n*-butyl)amino and N-(*tert*-butyl)amino), and the like.

As used herein, the term "di(C_{n-m}-alkyl)amino" refers to a group of formula -$N(alkyl)_2$, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "C_{n-m} alkoxycarbonyl" refers to a group of formula -C(O)O-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Examples of alkoxycarbonyl groups include, without limitation, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl (e.g., *n*-propoxycarbonyl and isopropoxycarbonyl), butoxycarbonyl (e.g., *n*-butoxycarbonyl and *tert*-butoxycarbonyl), and the like.

As used herein, the term "C_{n-m} alkylcarbonyl" refers to a group of formula -C(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Examples of alkylcarbonyl groups include, without limitation, methylcarbonyl, ethylcarbonyl, propylcarbonyl (e.g., *n*-propylcarbonyl and isopropylcarbonyl), butylcarbonyl (e.g., *n*-butylcarbonyl and *tert*-butylcarbonyl), and the like.

As used herein, the term "C_{n-m} alkylcarbonylamino" refers to a group of formula -NHC(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "C_{n-m} alkylsulfonylamino" refers to a group of formula -$NHS(O)_2$-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "aminosulfonyl" refers to a group of formula -$S(O)_2NH_2$.

As used herein, the term "C_{n-m} alkylaminosulfonyl" refers to a group of formula -$S(O)_2NH$(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "di(C_{n-m} alkyl)aminosulfonyl" refers to a group of formula -$S(O)_2N$(alkyl)$_2$, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "aminosulfonylamino" refers to a group of formula -$NHS(O)_2NH_2$.

As used herein, the term "C_{n-m} alkylaminosulfonylamino" refers to a group of formula -$NHS(O)_2NH$(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "di(C_{n-m} alkyl)aminosulfonylamino" refers to a group of formula -$NHS(O)_2N$(alkyl)$_2$, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "aminocarbonylamino", employed alone or in combination with other terms, refers to a group of formula -$NHC(O)NH_2$.

As used herein, the term "C_{n-m} alkylaminocarbonylamino" refers to a group of formula -NHC(O)NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "di(C_{n-m} alkyl)aminocarbonylamino" refers to a group of formula -$NHC(O)N$(alkyl)$_2$, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "carbamyl" to a group of formula –$C(O)NH_2$.

As used herein, the term "C_{n-m} alkylcarbamyl" refers to a group of formula -C(O)-NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "di(C_{n-m}-alkyl)carbamyl" refers to a group of formula –C(O)N(alkyl)$_2$, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "thio" refers to a group of formula -SH.

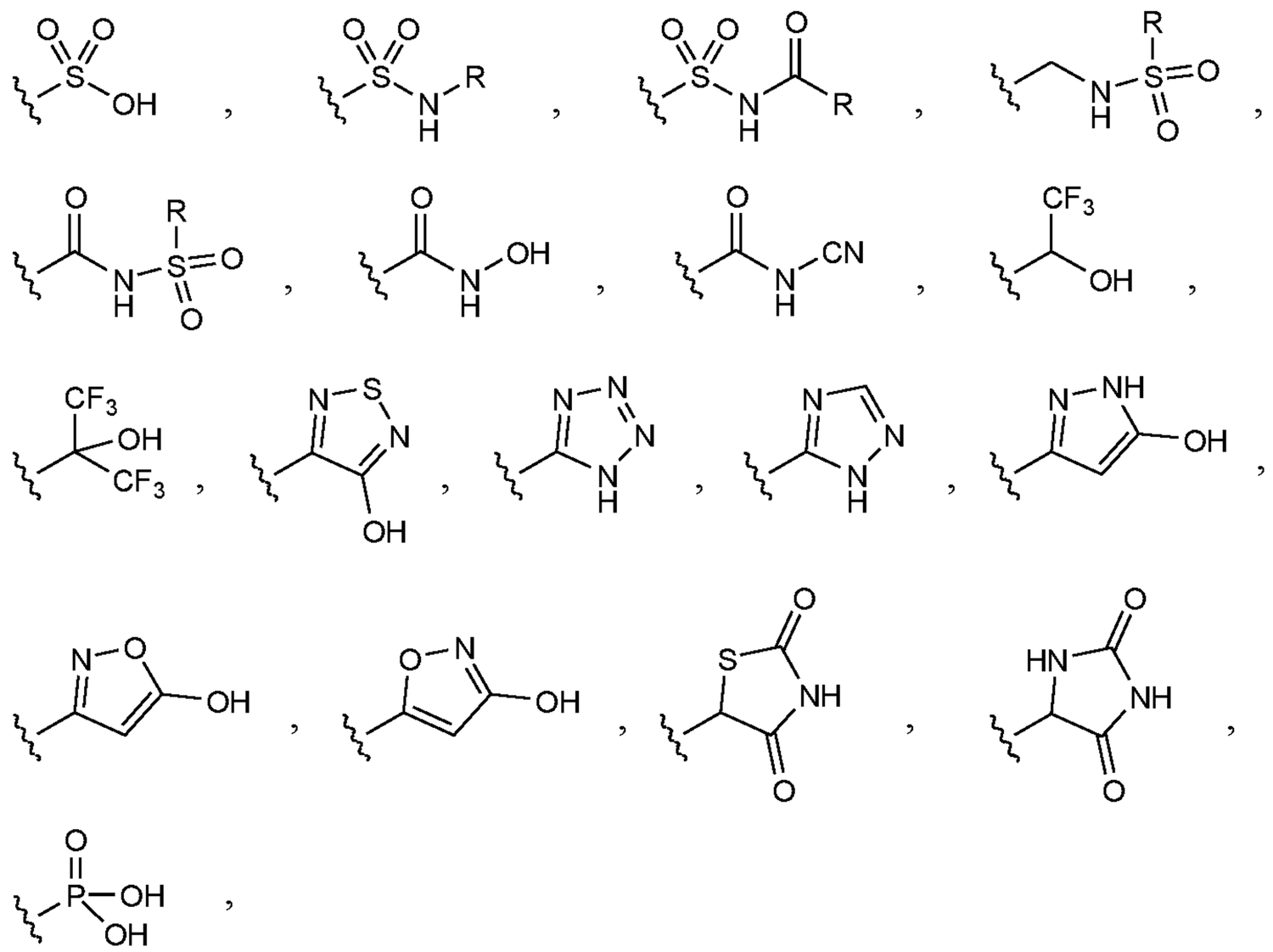
As used herein, the term "C_{n-m} alkylthio" refers to a group of formula -S-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "C_{n-m} alkylsulfinyl" refers to a group of formula -S(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "C_{n-m} alkylsulfonyl" refers to a group of formula -S(O)$_2$-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term "carbonyl", employed alone or in combination with other terms, refers to a -C(=O)- group, which may also be written as C(O).

As used herein, the term "carboxy" refers to a -C(O)OH group. In some embodiments, the "carboxy" group also refers to a bioisostere replacement group selected from the group consisting of:



and the like, where R refers to a hydrogen, (C_1-C_8) alkyl, or C_6 aryl.

As used herein, the term "cyano-C_{1-3} alkyl" refers to a group of formula -(C_{1-3} alkylene)-CN.

As used herein, the term "HO-C_{1-3} alkyl" refers to a group of formula -(C_{1-3} alkylene)-OH.

As used herein, "halo" refers to F, Cl, Br, or I. In some embodiments, a halo is F, Cl, or Br.

As used herein, the term "aryl," employed alone or in combination with other terms, refers to an aromatic hydrocarbon group, which can be monocyclic or polycyclic (e.g., having 2, 3, or 4 fused rings). The term "C_{n-m} aryl" refers to an aryl group having from n to m ring carbon atoms. Aryl groups include, e.g., phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups can have from 6 to 10 carbon atoms. In some embodiments, the aryl group is phenyl or naphthyl.

As used herein, "cycloalkyl" refers to non-aromatic cyclic hydrocarbons including cyclized alkyl and/or alkenyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3, or 4 fused rings) groups and spirocycles. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by 1 or 2 independently selected oxo or sulfide groups (e.g., C(O) or C(S)). Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or

thienyl derivatives of cyclopentane, cyclohexane, and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Cycloalkyl groups can have 3, 4, 5, 6, 7, 8, 9, or 10 ring-forming carbons (C_{3-10}). In some embodiments, the cycloalkyl is a C_{3-10} monocyclic or bicyclic cycloalkyl. In some embodiments, the cycloalkyl is a C_{3-7} monocyclic cycloalkyl. Example cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl, and the like. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, "heteroaryl" refers to a monocyclic or polycyclic aromatic heterocycle having at least one heteroatom ring member selected from sulfur, oxygen, and nitrogen. In some embodiments, the heteroaryl ring has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur, and oxygen. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide. In some embodiments, the heteroaryl is a 5-10 membered monocyclic or bicyclic heteroaryl having 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur, and oxygen. In some embodiments, the heteroaryl is a 5-6 monocyclic heteroaryl having 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur, and oxygen. In some embodiments, the heteroaryl is a five-membered or six-membered heteroaryl ring. A five-membered heteroaryl ring is a heteroaryl with a ring having five ring atoms wherein one or more (e.g., 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary five-membered ring heteroaryls include, without limitation, thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl. A six-membered heteroaryl ring is a heteroaryl with a ring having six ring atoms wherein one or more (e.g., 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary six-membered ring heteroaryls include, without limitation, pyridyl, pyrazinyl, pyrimidinyl, triazinyl, and pyridazinyl. Ring-forming carbon atoms of a heteroaryl group can be optionally substituted by 1 or 2 independently selected oxo or sulfide groups (e.g., C(O) or C(S)).

As used herein, "heterocycloalkyl" refers to non-aromatic monocyclic or polycyclic heterocycles having one or more ring-forming heteroatoms selected from O, N, or S. Included in heterocycloalkyl are monocyclic 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl groups. Heterocycloalkyl groups can also include spirocycles. Example heterocycloalkyl groups include, without limitation, pyrrolidin-2-one, 1,3-isoxazolidin-2-one, pyranyl, tetrahydropyran, oxetanyl, azetidinyl, morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, azepanyl, benzazapene, and the like. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by 1 or 2 independently selected oxo or sulfido groups (e.g., C(O), S(O), C(S), or $S(O)_2$, etc.). The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of piperidine, morpholine, azepine, etc. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl is a monocyclic 4-6 membered heterocycloalkyl having 1 or 2 heteroatoms independently selected from nitrogen, oxygen, or sulfur and having one or more oxidized ring members. In some embodiments, the heterocycloalkyl is a monocyclic or bicyclic 4-10 membered heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur and having one or more oxidized ring members.

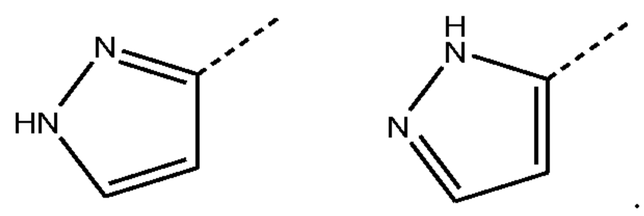
At certain places, the definitions or embodiments refer to specific rings (e.g., an azetidine ring, a pyridine ring, etc.). Unless otherwise indicated, these rings can be attached to any ring member provided that the valency of the atom is not exceeded. For example, an azetidine ring can be attached at any position of the ring, whereas a pyridin-3-yl ring is attached at the 3-position.

As used herein, the term "oxo" refers to an oxygen atom as a divalent substituent, forming a carbonyl group when attached to a carbon (e.g., C=O), or attached to a heteroatom forming a sulfoxide or sulfone group.

The term "compound" as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

The compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds provided herein that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Any appropriate method can be used to prepare optically active forms from, for example, optically inactive starting materials. For example, techniques such as resolution of racemic mixtures or stereoselective synthesis can be used to prepare optically active forms of a compound provided herein. Many geometric isomers of olefins, C=N double bonds, N=N double bonds, and the like also can be present in a compound described herein, and all such stable isomers are contemplated herein. *Cis* and *trans* geometric isomers of the compounds provided herein are described and can be isolated as a mixture of isomers or as separated isomeric forms. In some embodiments, a compound provided herein has the *(R)*-configuration. In some embodiments, a compound provided herein has the *(S)*-configuration.

Compounds provided herein also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers that are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include, without limitation, ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H-, and 4H-1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. For example, in aqueous solution, pyrazoles can exhibit the following isomeric forms, which are referred to as tautomers of each other:



As readily understood by one skilled in the art, a wide variety of functional groups and other structures can exhibit tautomerism, and all tautomers of compounds as described herein are within the scope provided herein.

As used herein, the term "cell" is meant to refer to a cell that is *in vitro*, *ex vivo*, or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal (e.g., a human). In some embodiments, an *in vitro* cell can be a cell in cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal (e.g., a human).

As used herein, the term "contacting" refers to the bringing together of indicated moieties or items in an *in vitro* system, an *ex vivo* system, or an *in vivo* system. For example, "contacting" a cell with a compound provided herein includes the act of administering that compound to a mammal (e.g., a human) containing that cell as well as, for example, introducing that compound into a cell culture containing that cell.

As used herein, the term "mammal" includes, without limitation, mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, elephants, deer, non-human primates (e.g., monkeys and apes), house pets, and humans.

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

As used herein, the term "treating" or "treatment" refers to (a) inhibiting a disease, disorder, or condition, for example, inhibiting a disease, disorder, or condition in a mammal (e.g., human) that is experiencing or displaying the pathology or symptomatology of the disease, disorder, or condition (e.g., arresting further development of the pathology and/or symptomatology), or (b) ameliorating the disease, disorder, or condition, for example, ameliorating a disease, disorder, or condition in a mammal (e.g., a human) that is experiencing or displaying the pathology or symptomatology of the disease, disorder, or condition (e.g., reversing the pathology and/or symptomatology).

As used herein, the term "preventing" or "prevention" of a disease, disorder, or condition refers to decreasing the risk of occurrence of the disease, disorder, or condition in a mammal or group of mammals (e.g., a mammal or group of mammals predisposed to or susceptible to the disease, disorder, or condition). In some

embodiments, preventing a disease, disorder, or condition refers to decreasing the possibility of acquiring the disease, disorder, or condition and/or its associated symptoms. In some embodiments, preventing a disease, disorder, or condition refers to completely or almost completely stopping the disease, disorder, or condition from occurring.

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EXAMPLES

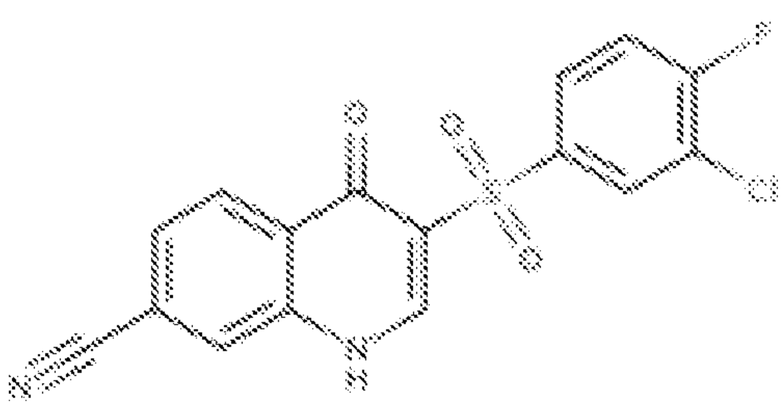
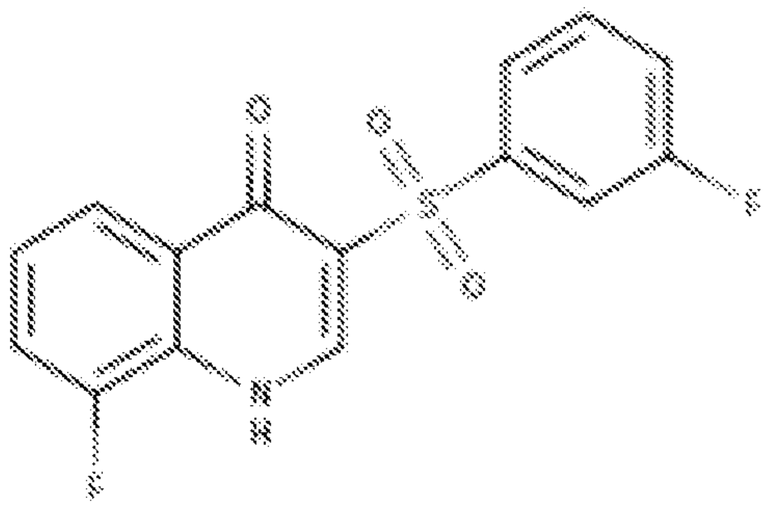
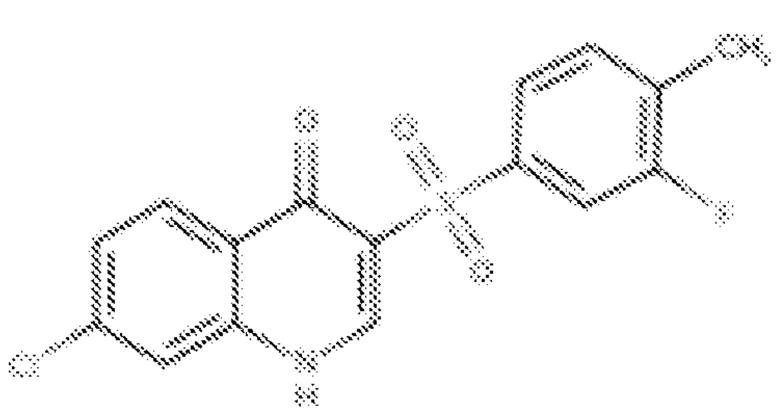
Methods

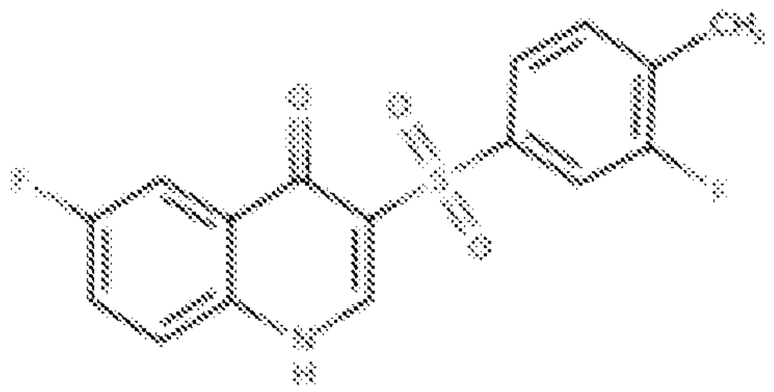
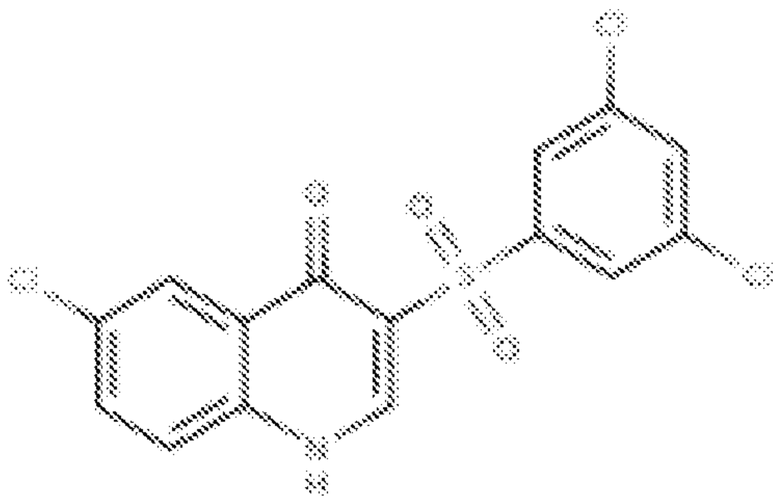
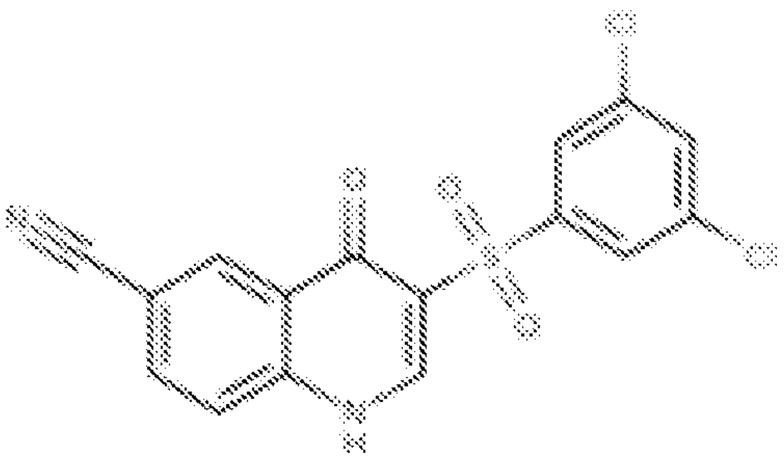
25k THP1-NF-κB-LUC cells were dispensed into 384 well plate (per well). Cells were treated with compounds with various concentrations for 2 hours before addition of LPS (10 ng/mL) for 18 hours. Secreted luciferase activity were measured using quant-luc reagents (1 bag of luc reagent dilute to 40 mL, use 10 μL per well). Data were normalized to vehicle control and graphed. Compound IC_{50} towards inhibiting NF-κB were determined through Prism. Similarly, 10k human PBMCs cells were cultured in 384 well plate (per well). Cells were treated with compounds with various concentrations for 2 hours before addition of LPS (10 ng/mL) for 18 hours, and supernatants were collected and assayed for TNF ELISA. Compound IC_{50} towards inhibiting TNF release were determined through Prism.

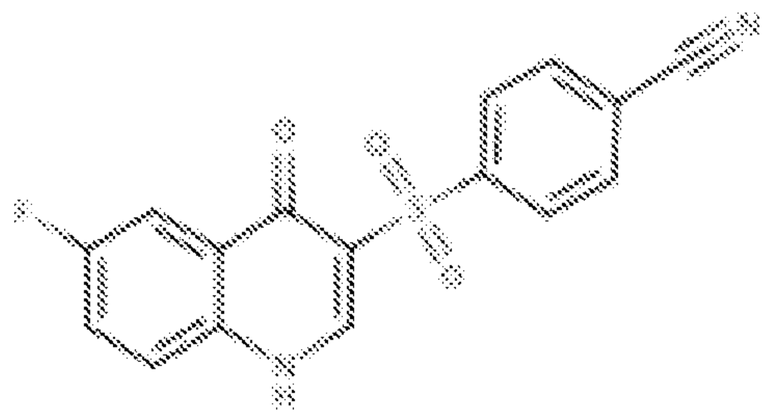
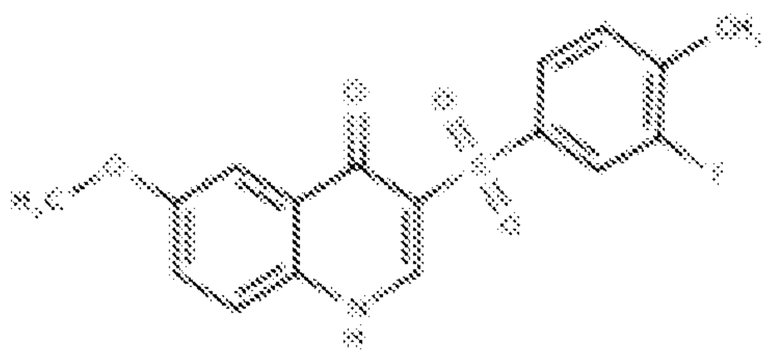
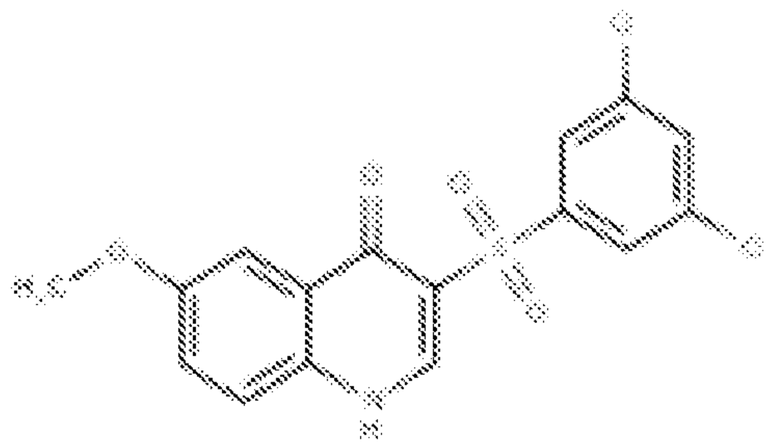
Activity: "+" >10 μM, "++" >1 μM and < 10 μM, "+++" > 0.1 μM and < 1 μM, "++++" <0.1 μM.

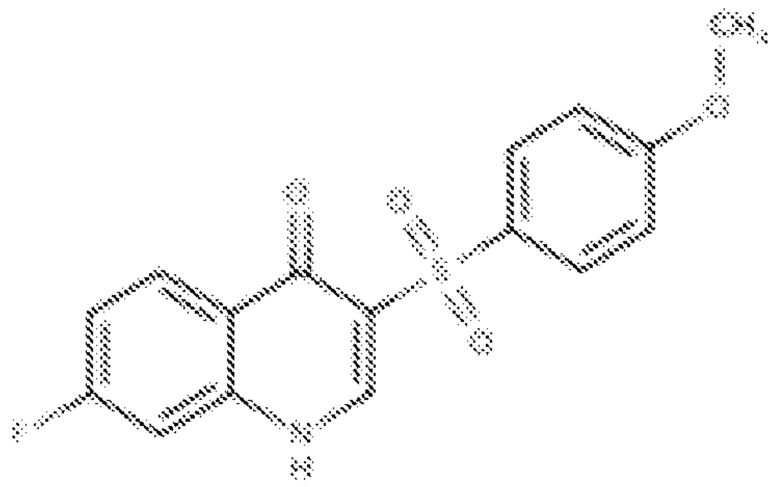
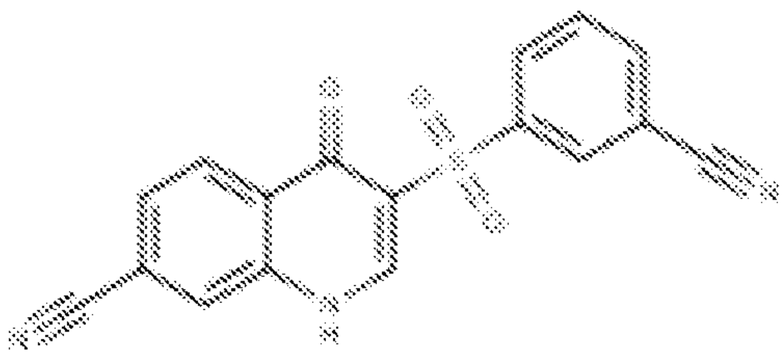
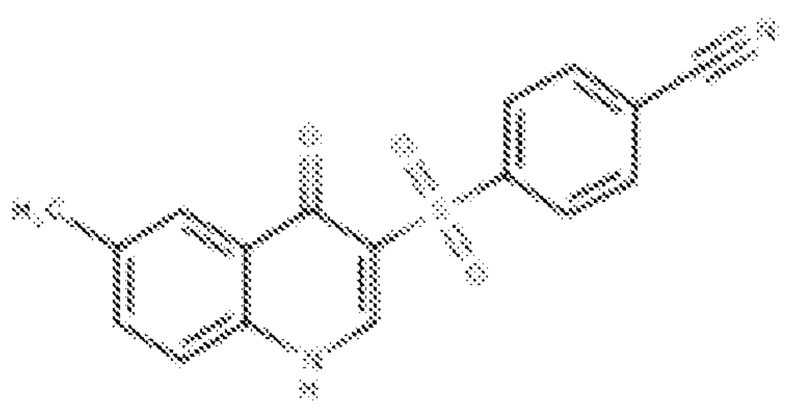
Example 1 – Bioassay results for tested compounds

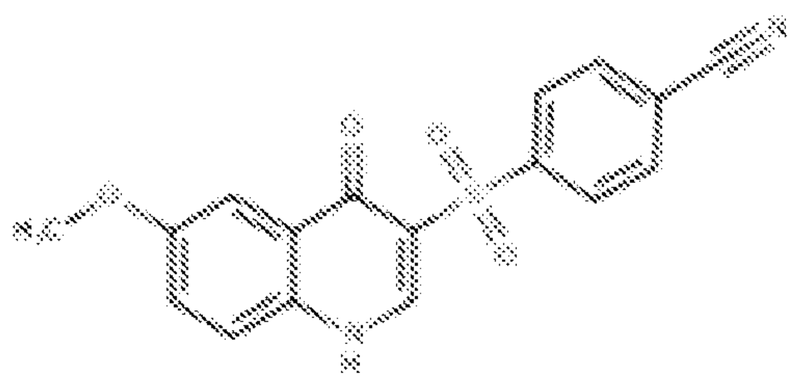
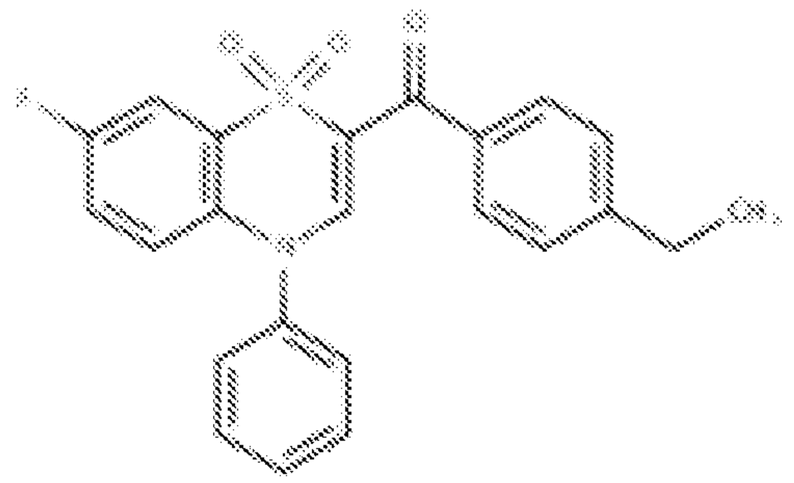
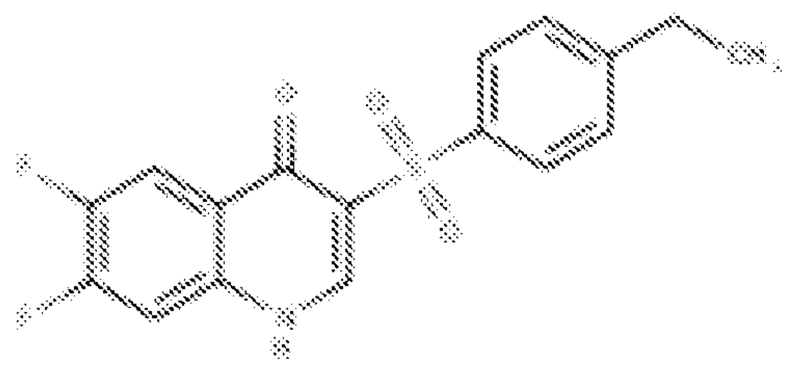
Table 1a

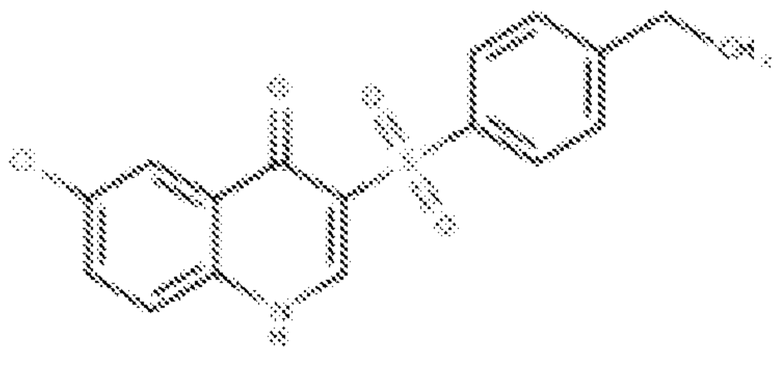
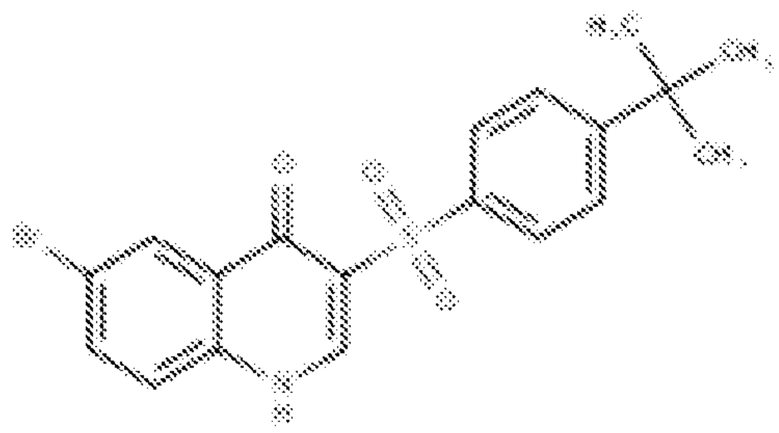
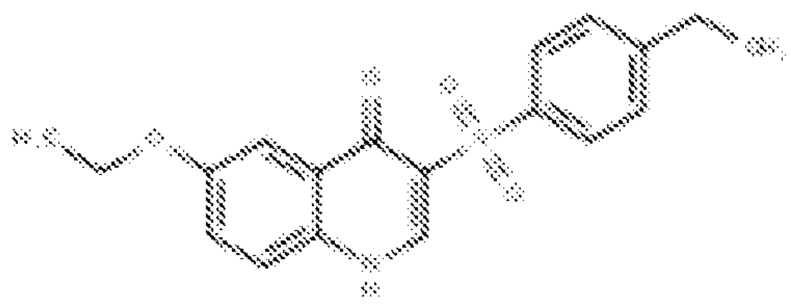
No.	Compound	IC_{50} (NF-κB assay)
BC18300		+++
BC18301		++
BC18302		++++

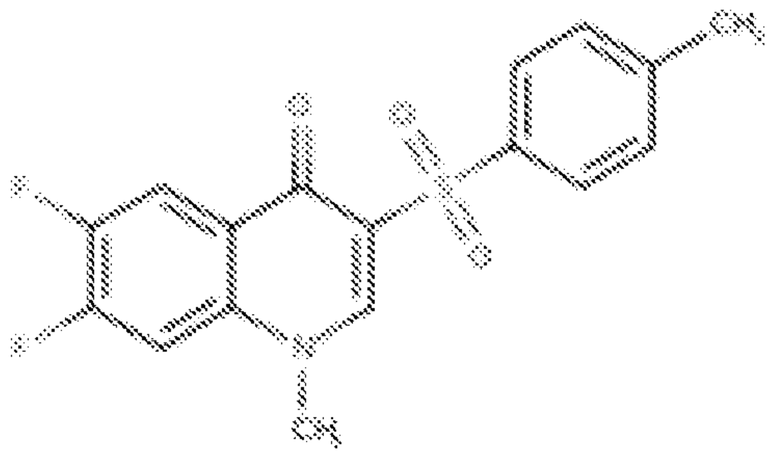
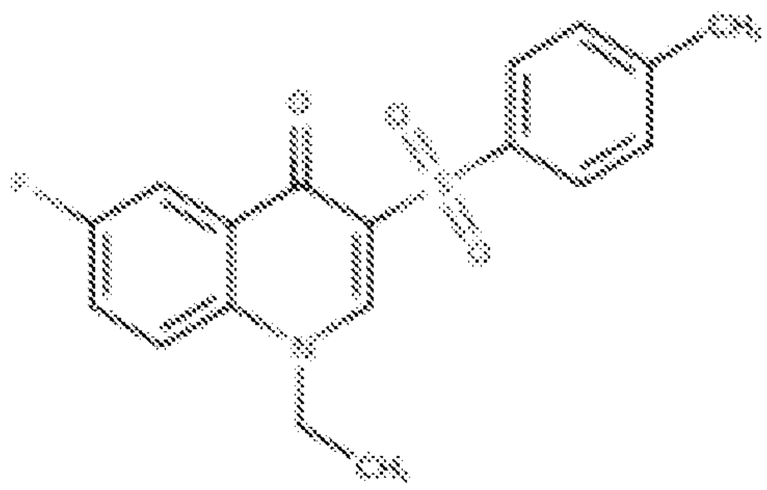
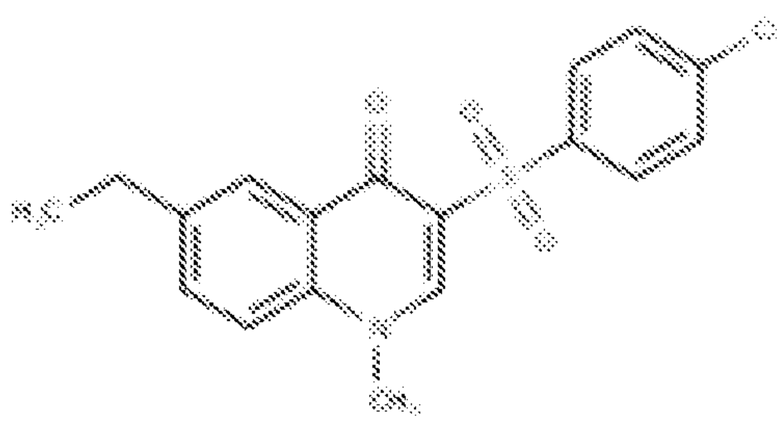
BC18303		++++
BC18304		++
BC18305		+++

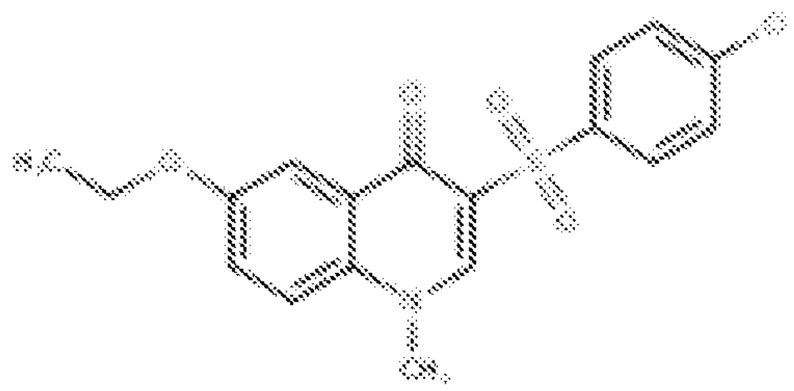
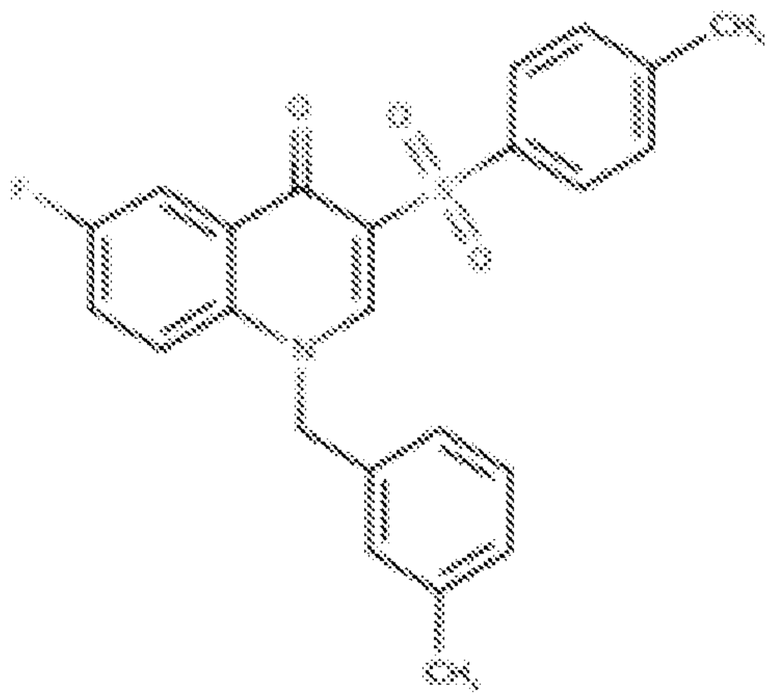
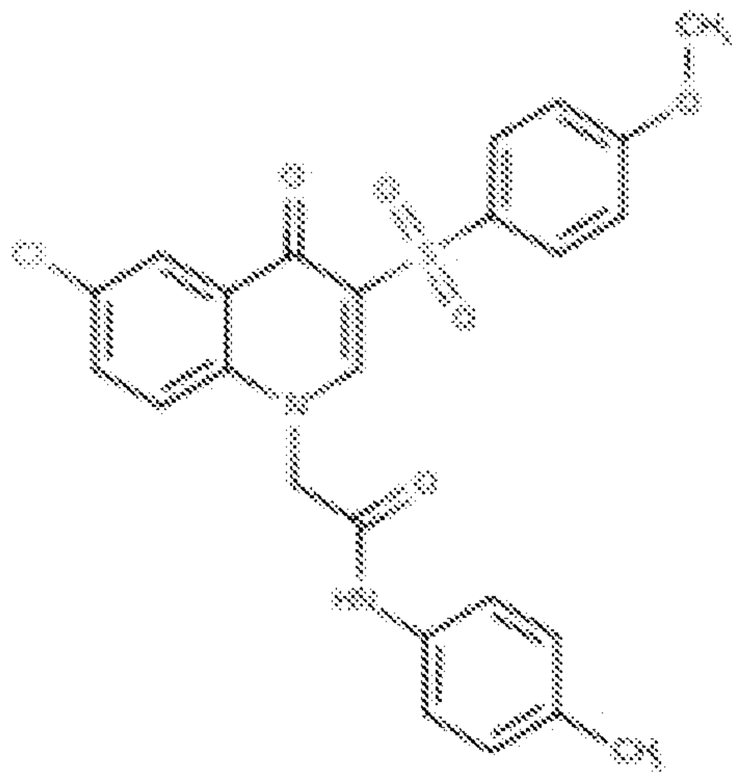
BC18306		+
BC18307		+++
BC18308		+

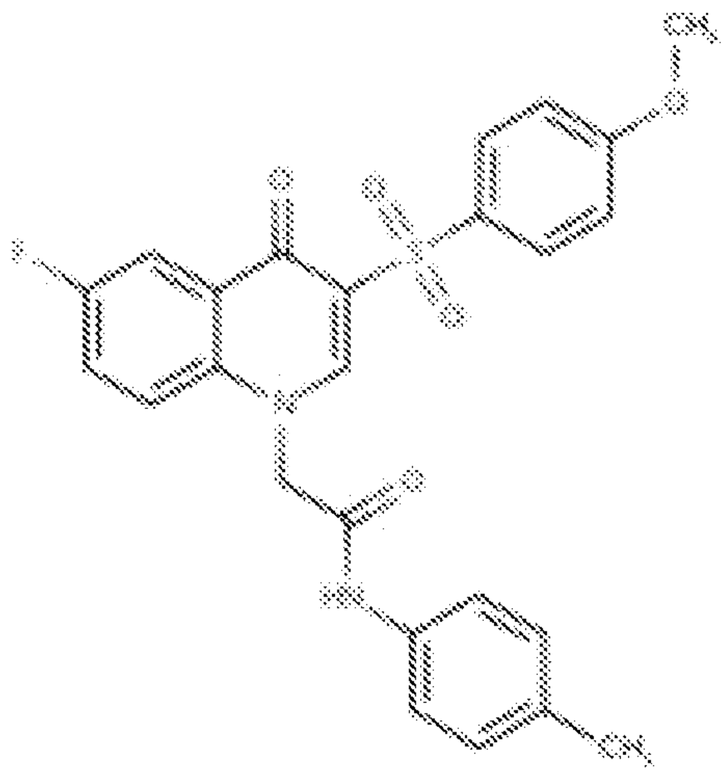
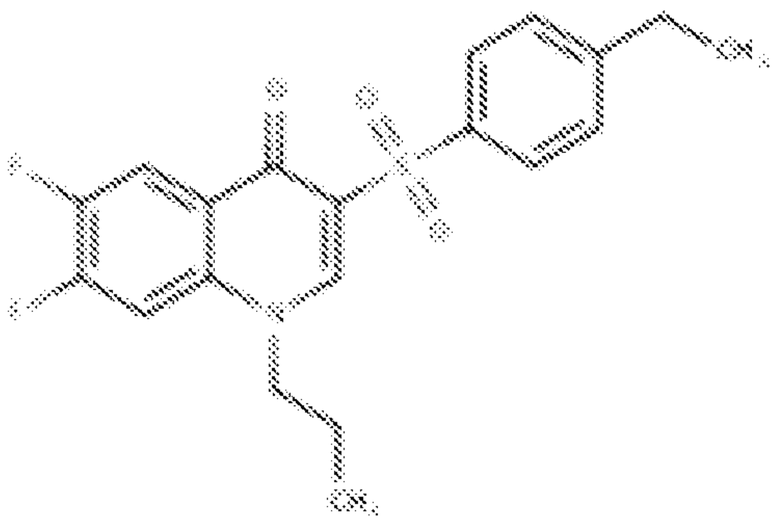
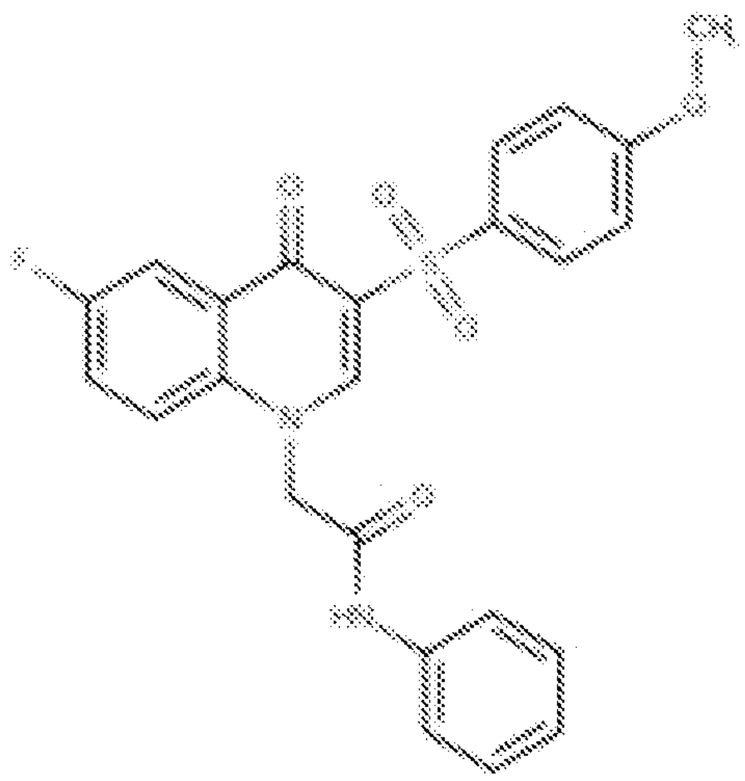
BC18309		++
BC18310		++++
BC18311		+

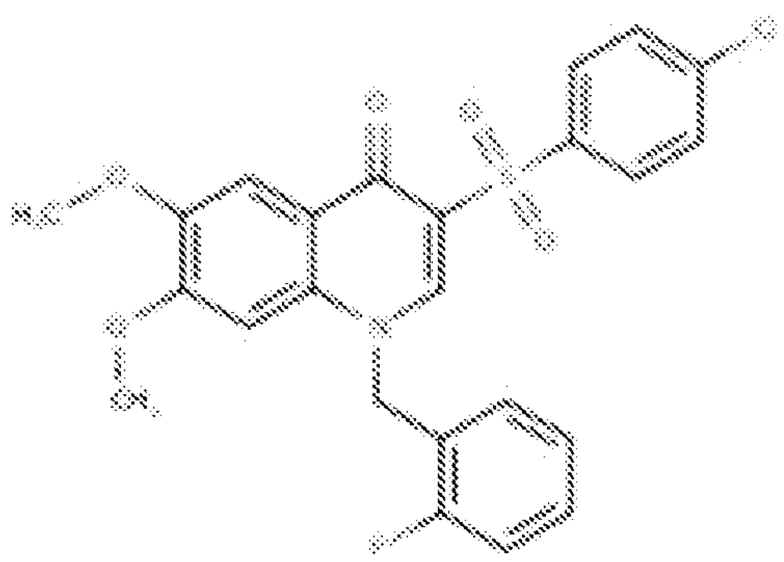
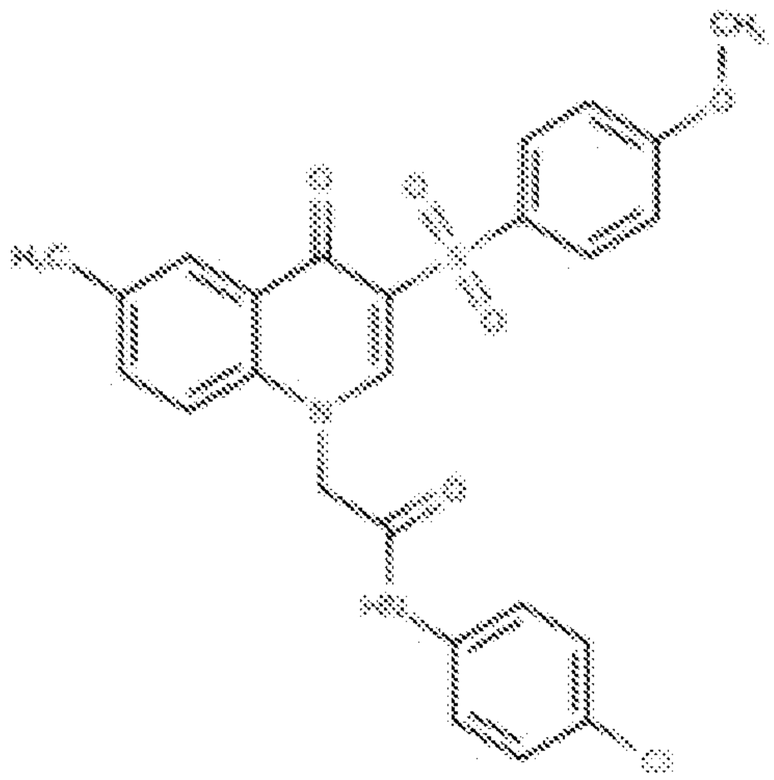
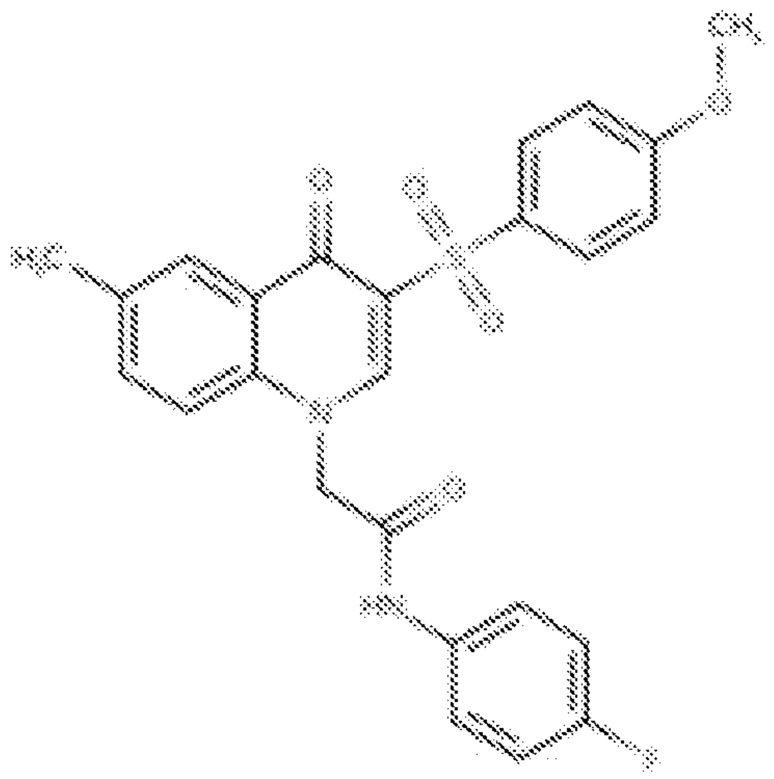
BC18312		+
BC18318		+
BC18320		++++

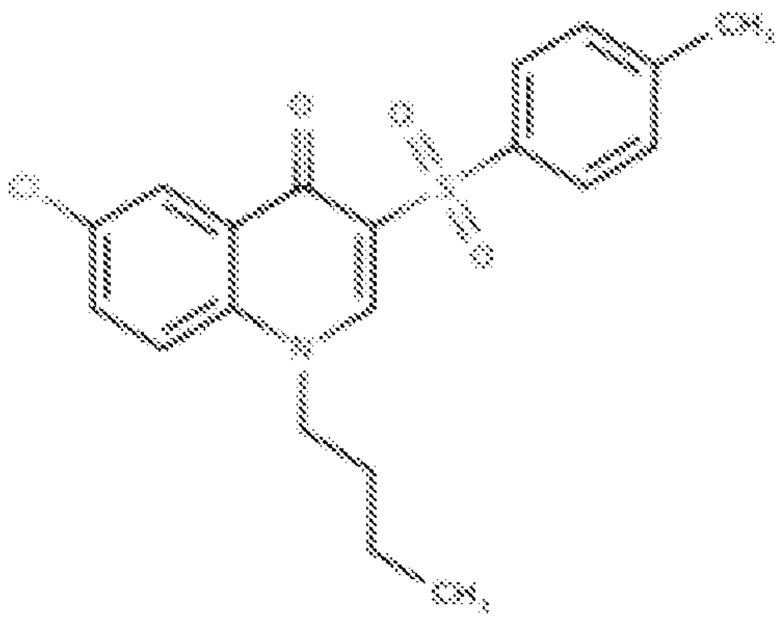
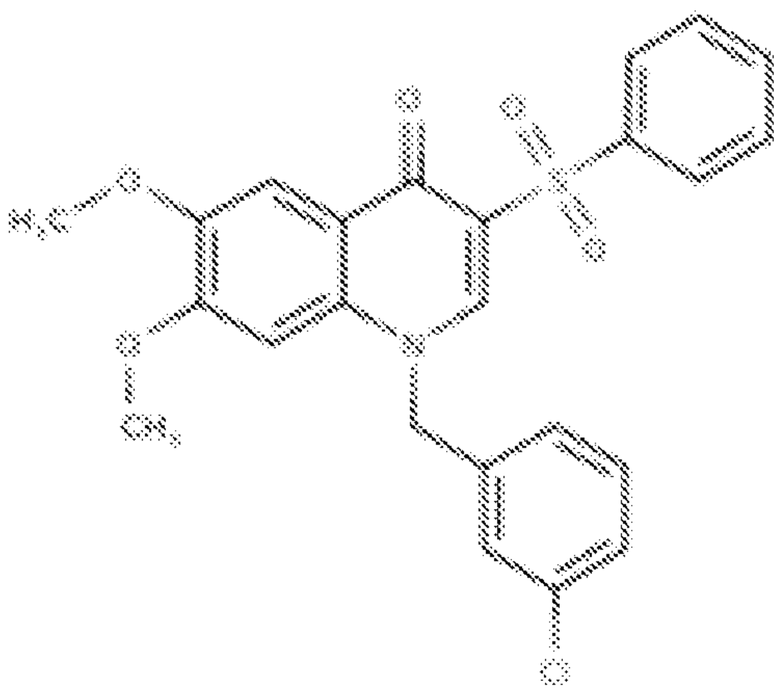
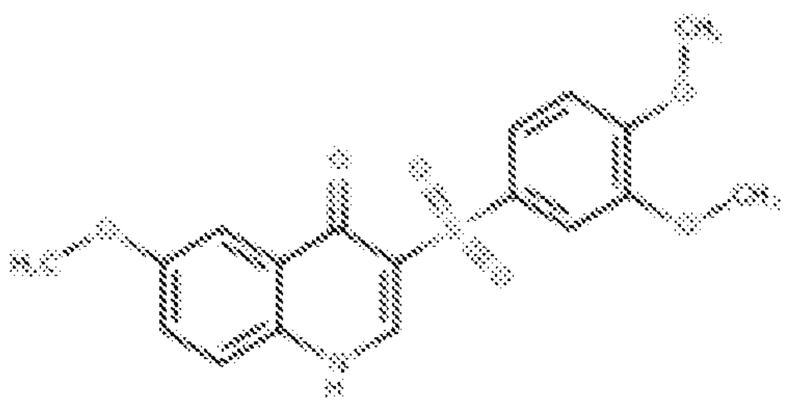
BC18321		+++
BC18322		++
BC18323		+++

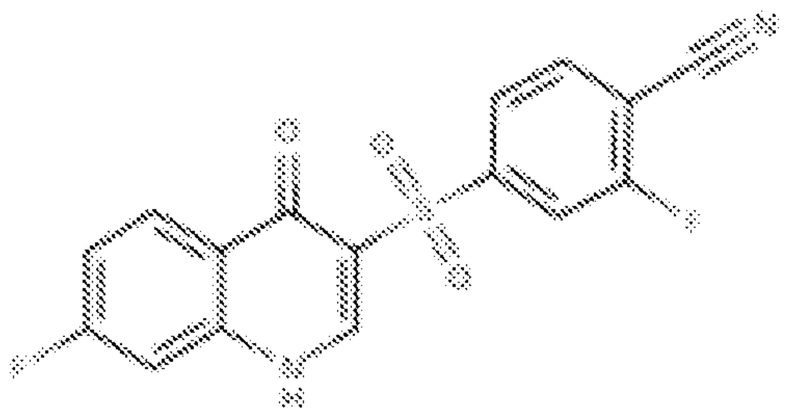
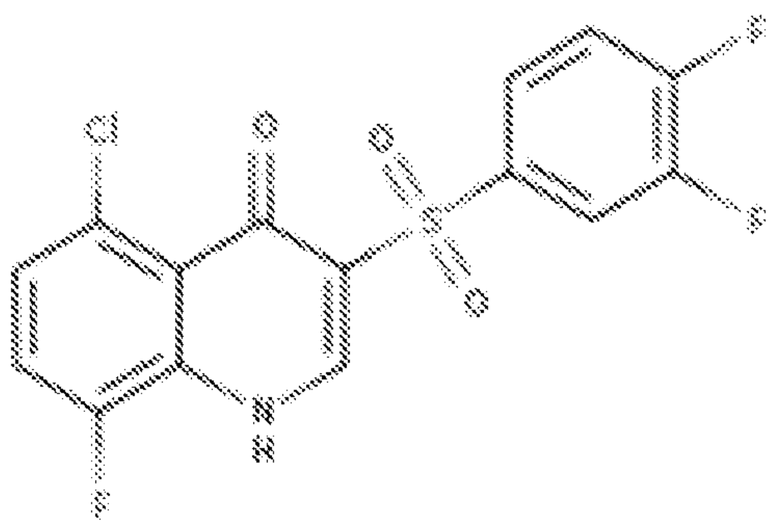
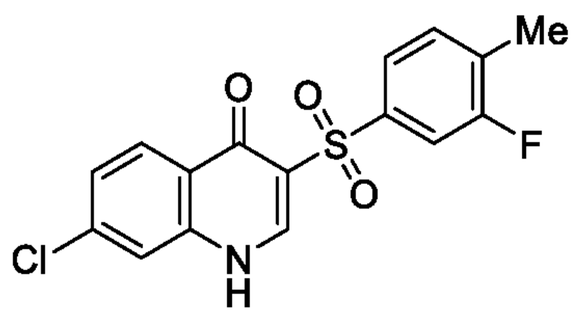
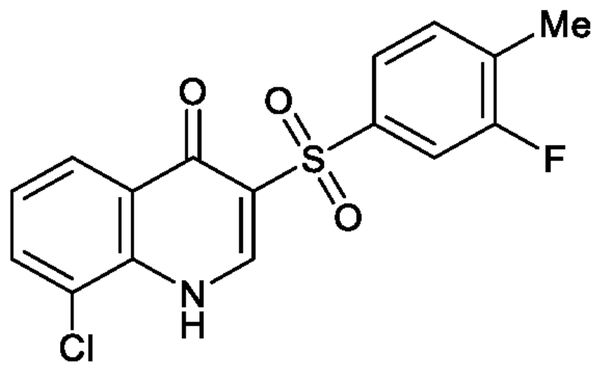
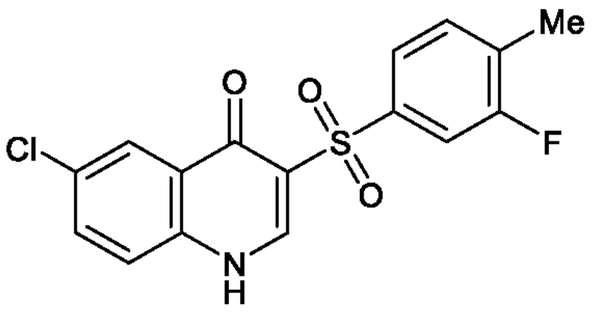
BC18324		+
BC18325		+
BC18326		+

BC18327		+
BC18328		++
BC18329		+

BC18330		+
BC18331		+
BC18332		+

BC18333		+
BC18334		+
BC18335		+

BC18336		+
BC18337		+
BC18338		+

BC18339		+++
BC18340		++++
BC19001		
BC19003		
BC19004		

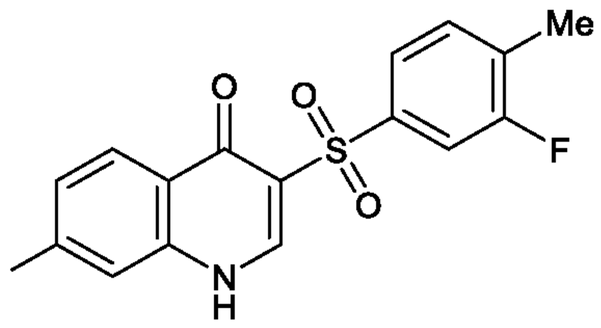
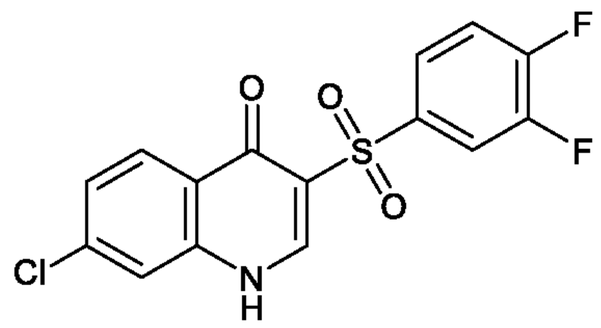
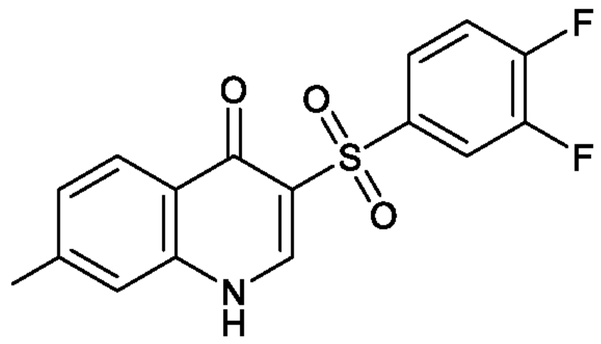
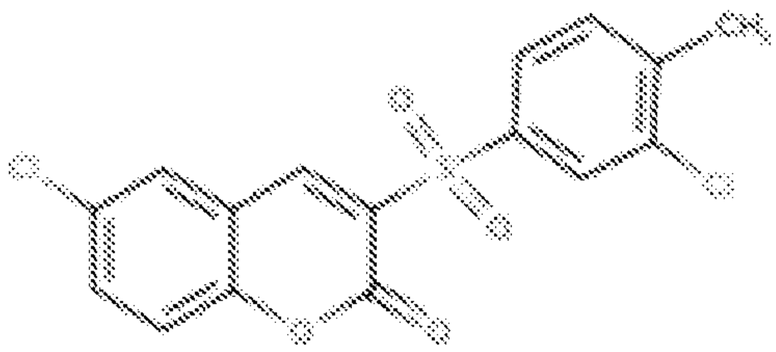
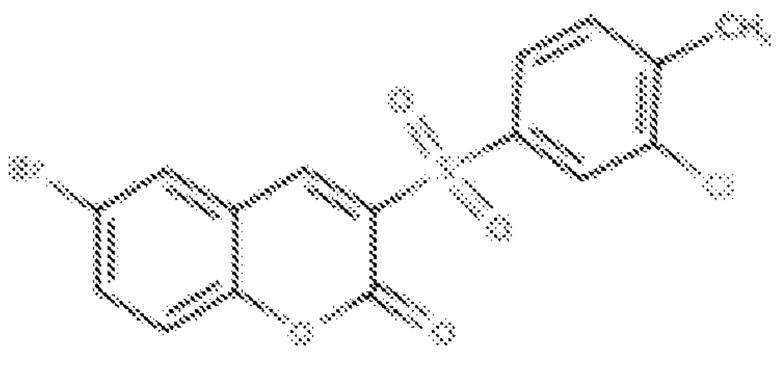
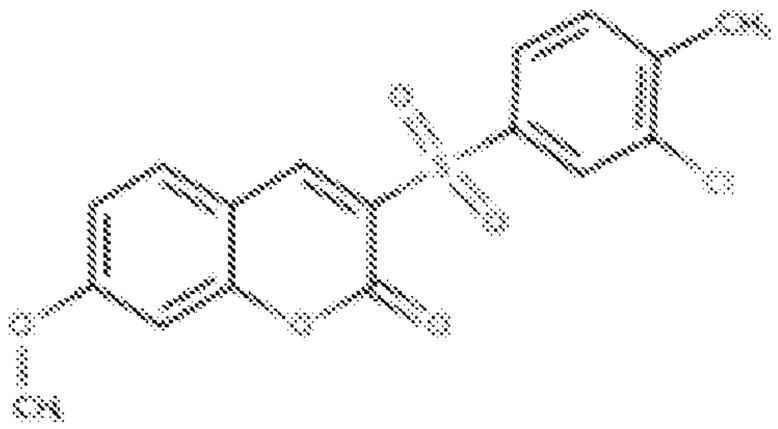
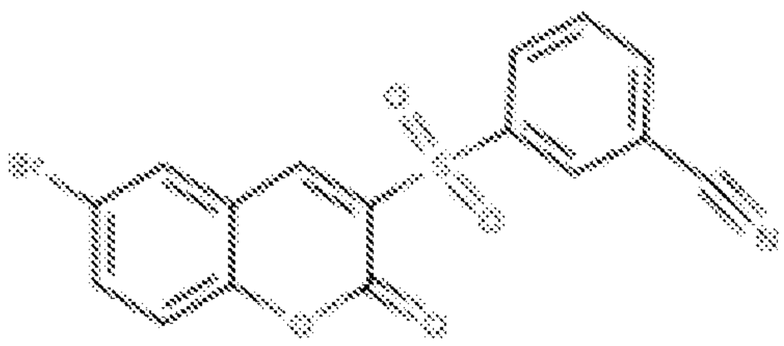
BC19005		
BC19006		
BC19007		

Table 1b

No.	Compound	IC_{50} (NF-κB assay)
BC18313		+

BC18314		+
BC18316		+
BC18317		+

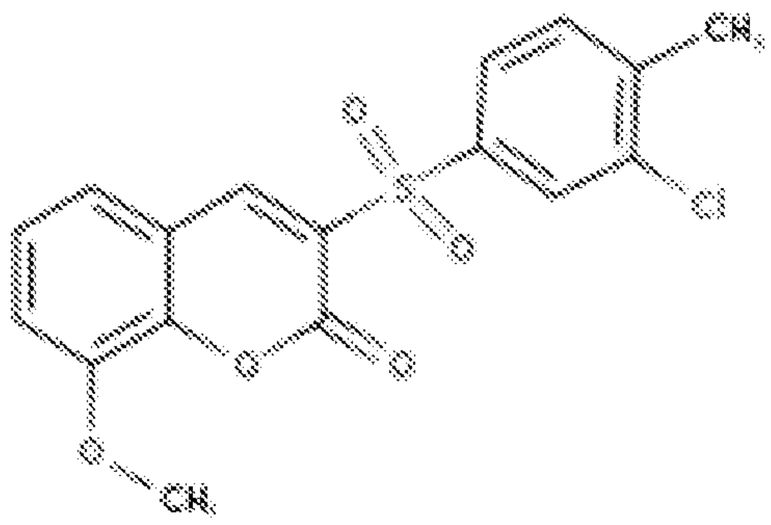
BC18319		+

Table 1c

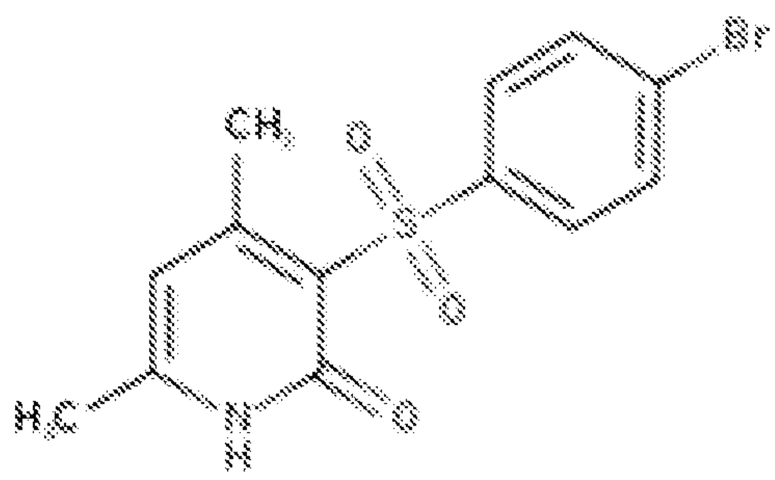
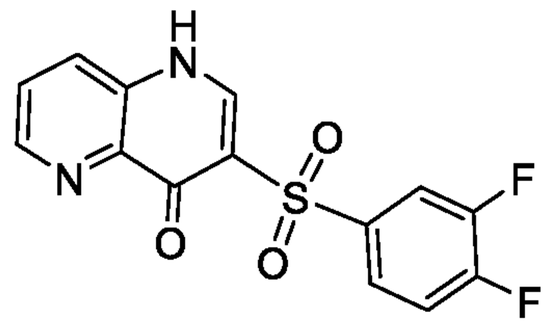
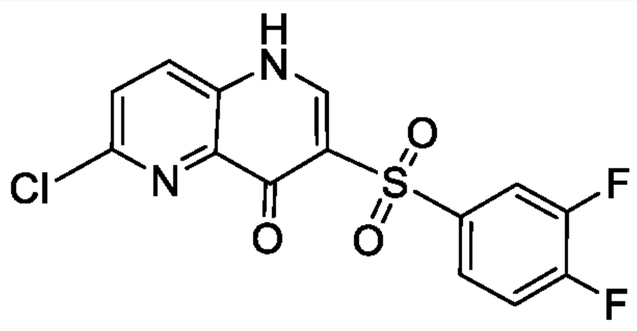
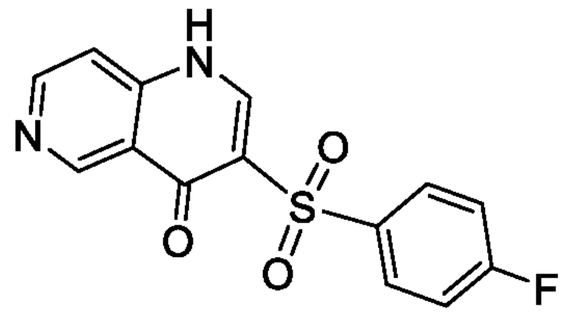
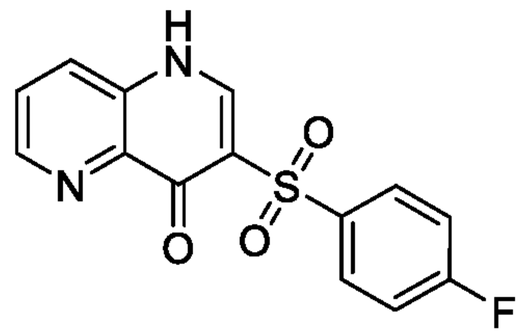
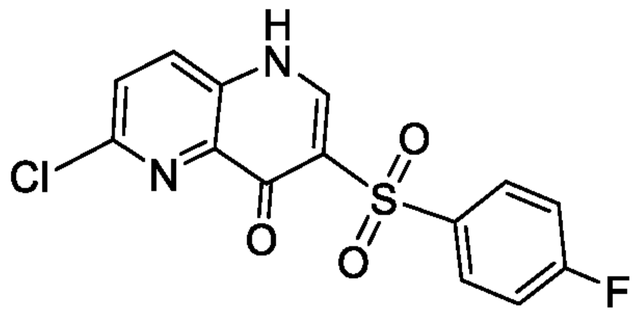
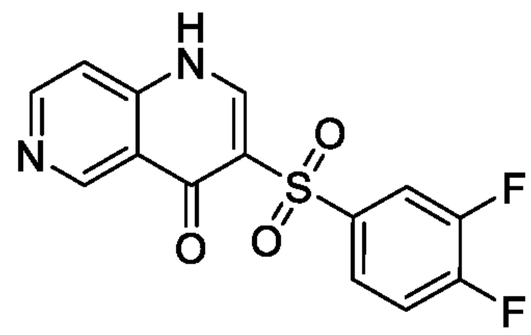
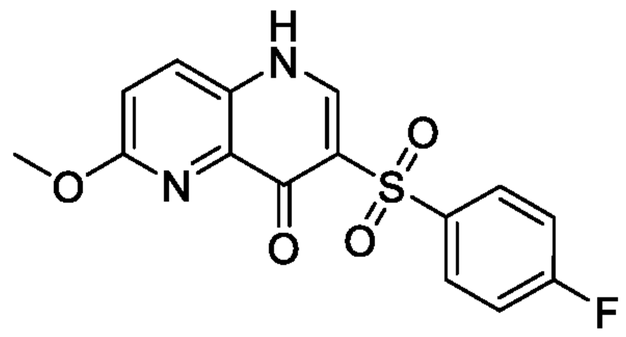
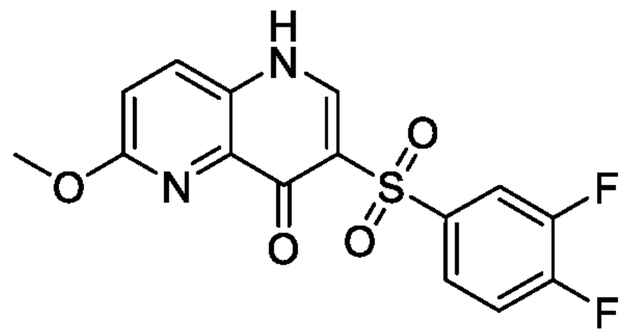
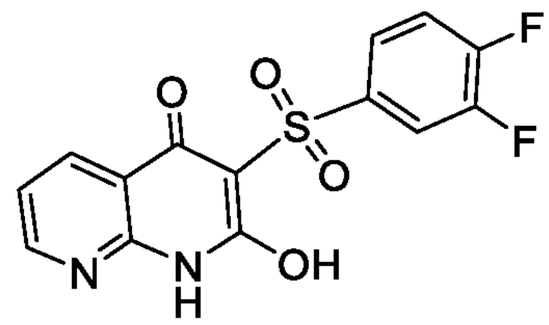
No.	Compound	IC_{50} (NF-κB assay)
BC18315		+

Table 1d

BC No.	ZE No.	Compound	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19121	ZE22-0017		+	+

BC19122	ZE22-0018		+	+
BC19123	ZE22-0021		++	+
BC19124	ZE22-0024		+	+
BC19160	ZE22-0019		+	+
BC19201	ZE22-0020		+	+
BC19202	ZE22-0022		+	+
BC19203	ZE22-0023		++	+
BC19256	ZE22-0016		++	+

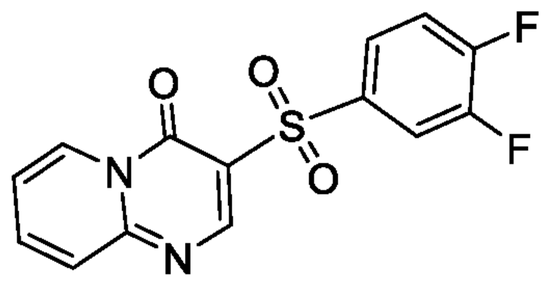
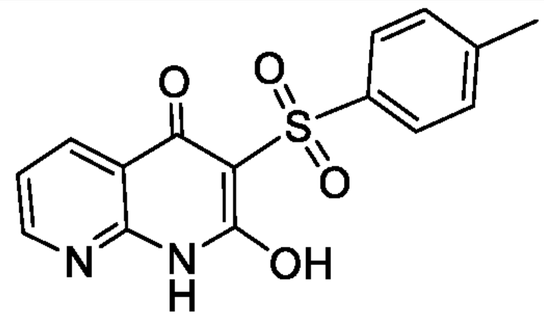
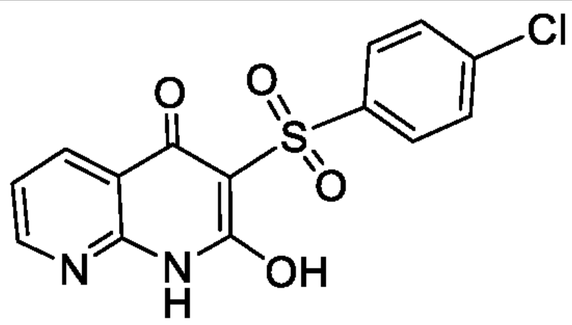
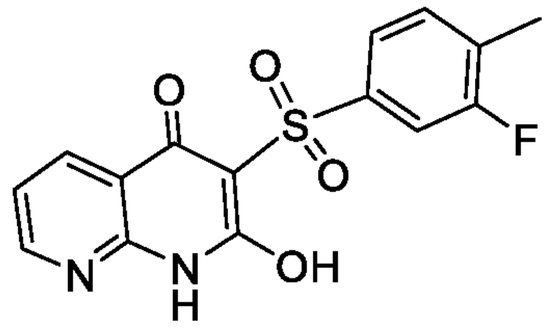
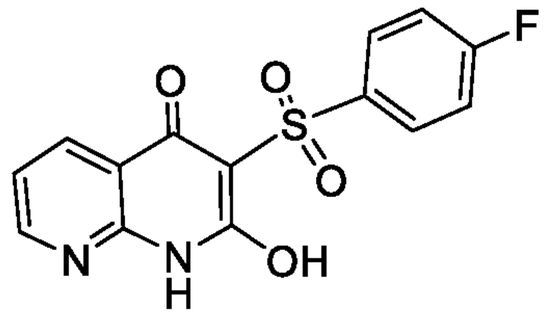
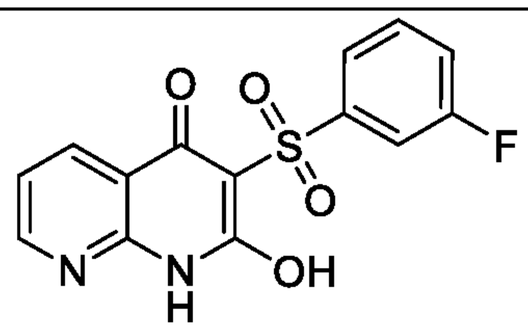
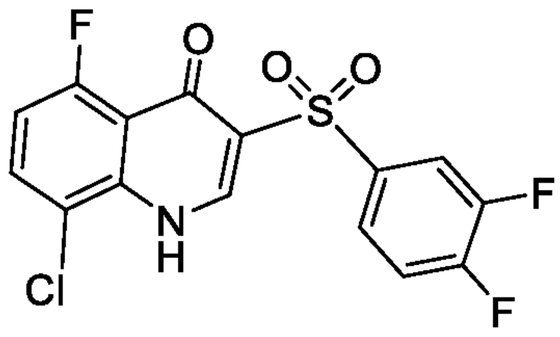
BC19257	ZE22-0025		+	+
BC19258	ZE22-0027		++	+
BC19259	ZE22-0029		++	+
BC19322	ZE22-0015		++	+
BC19323	ZE22-0028		+	+
BC19409	ZE22-0013		+	+

Table 1e

BC No.	ZE No.	Compound	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19196	ZE22-0004		+++	+

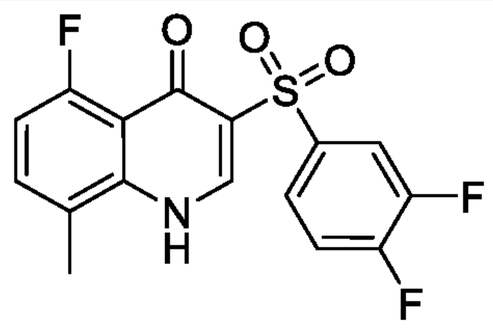
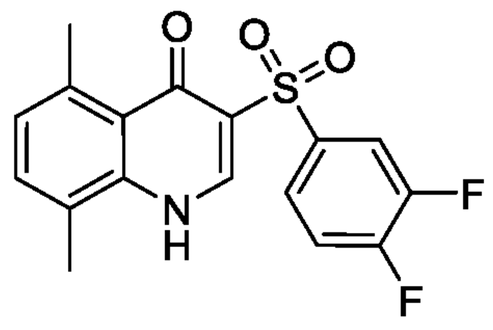
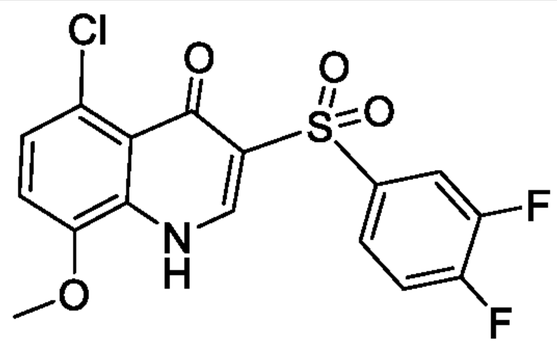
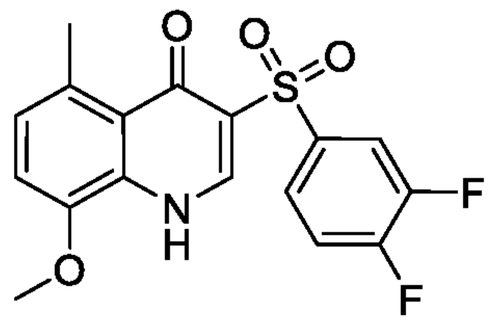
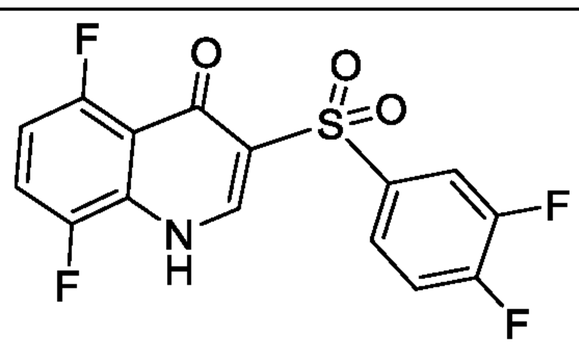
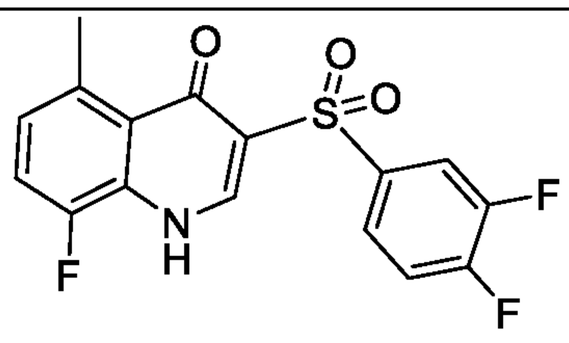
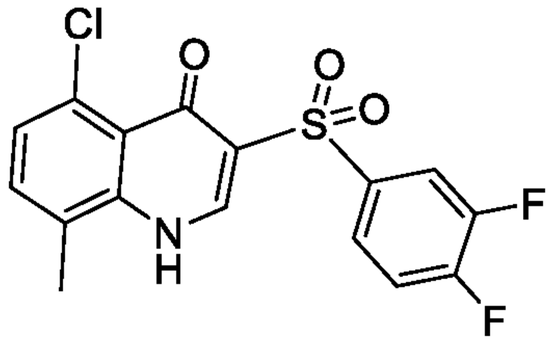
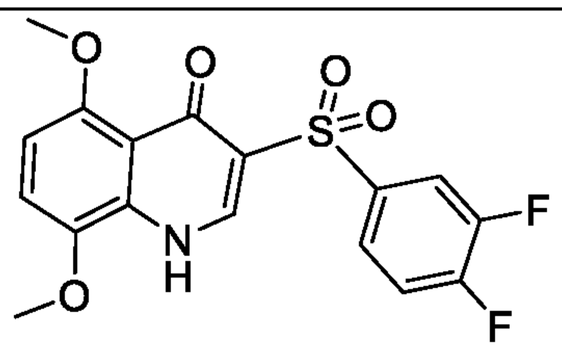
BC19197	ZE22-0007		+++	+
BC19198	ZE22-0009		++	+
BC19199	ZE22-0010		+++	+
BC19200	ZE22-0011		++	+
BC19252	ZE22-0001		++++	+
BC19253	ZE22-0002		++++	+
BC19254	ZE22-0008		++++	+
BC19255	ZE22-0012		++	+

Table 1f

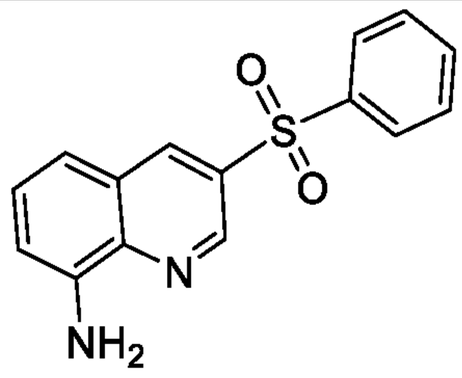
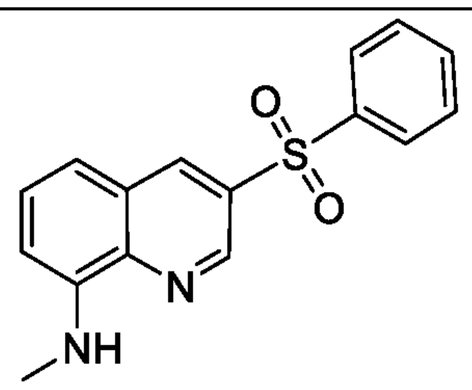
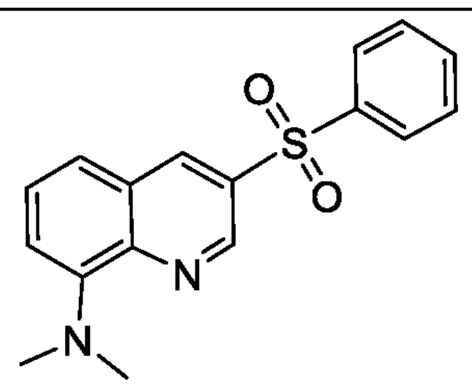
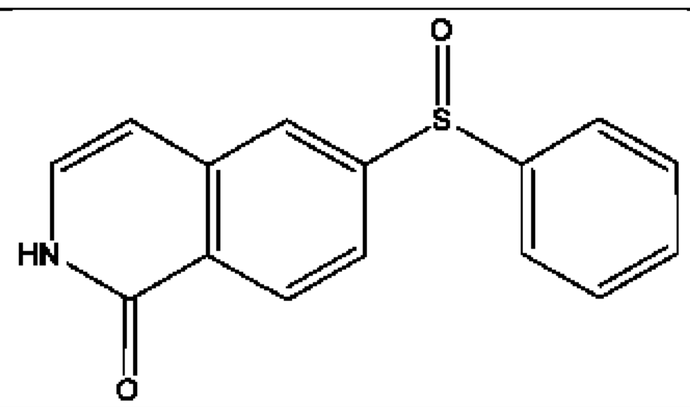
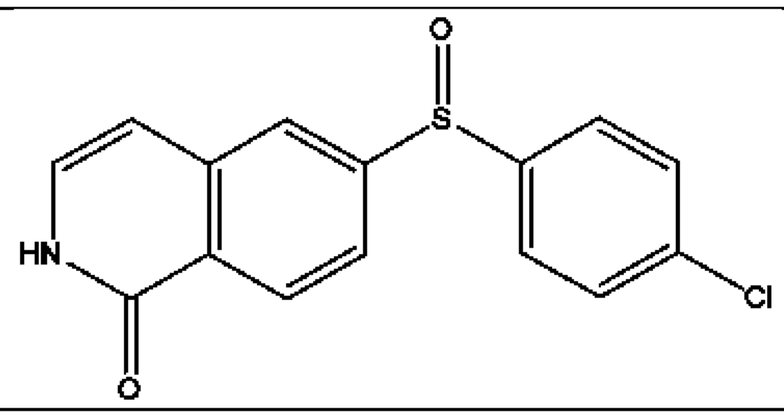
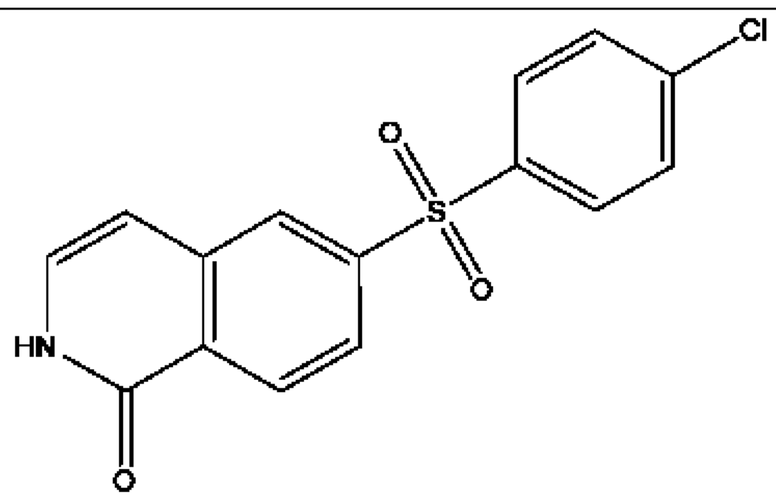
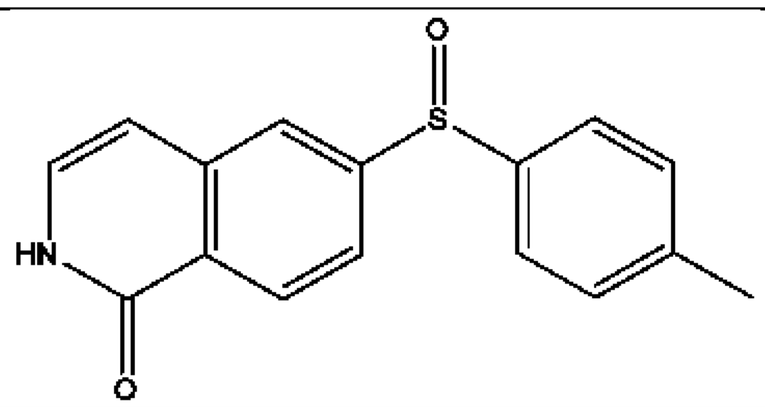
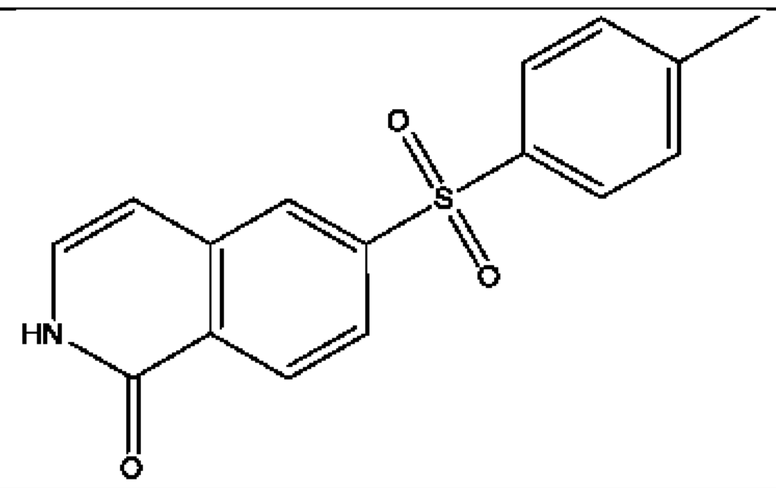
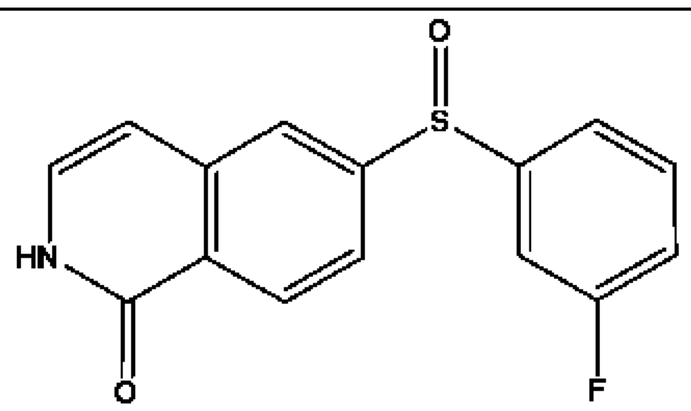
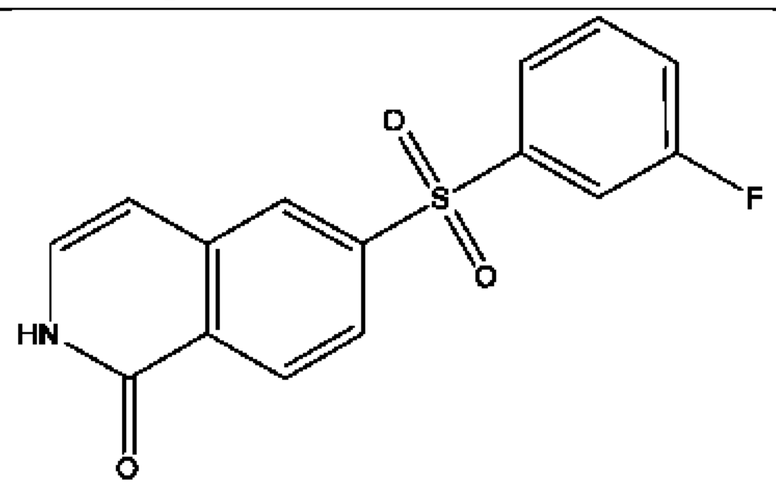
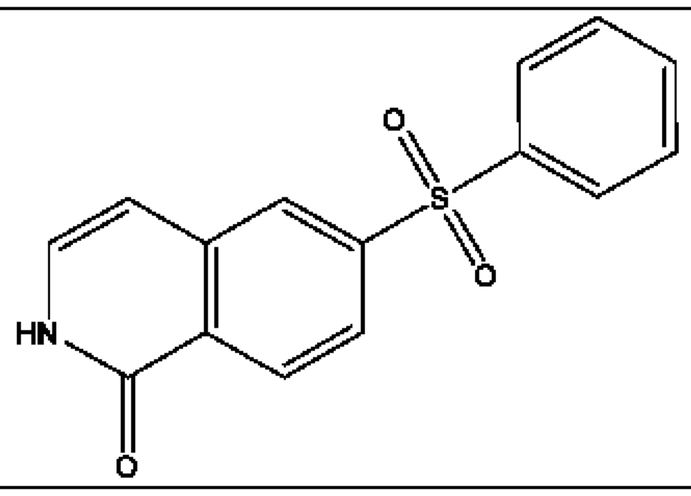
BC No.	ZE No.	Compound	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19324	ZE22-0030		+	+++
BC19325	ZE22-0032		+	++
BC19326	ZE22-0034		+	++

Table 1g

BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19454		+	+
BC19515		+	+

BC19516		+	+
BC19517		+	+
BC19518		+	+
BC19519		+	+
BC19520		+	+
BC19579		+	+

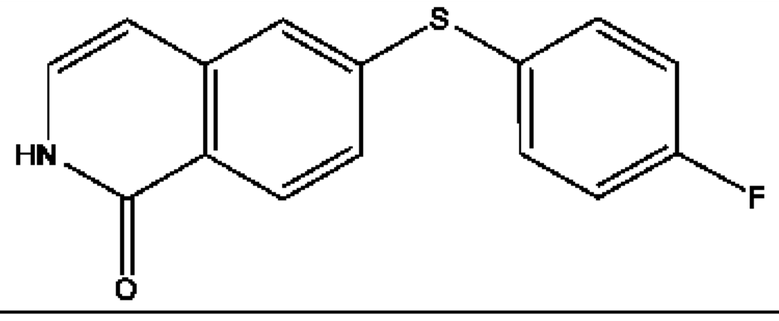
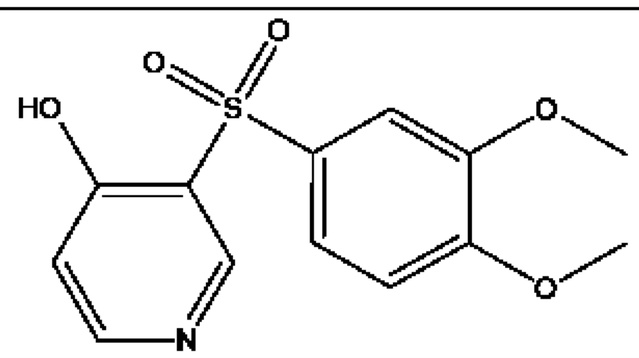
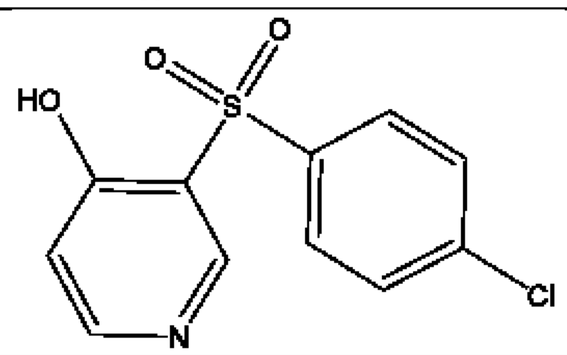
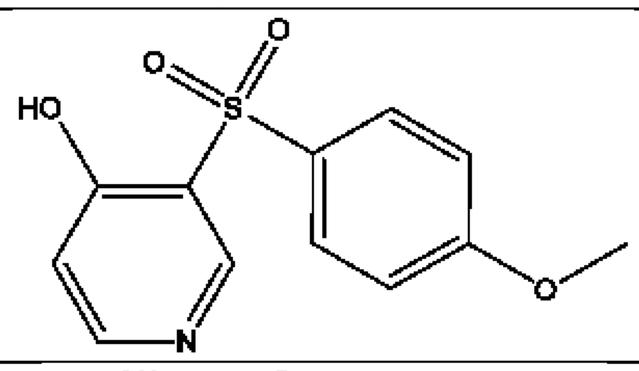
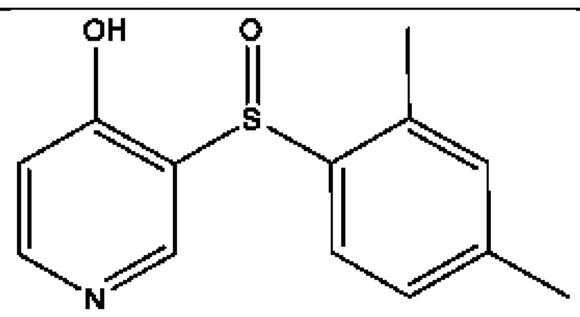
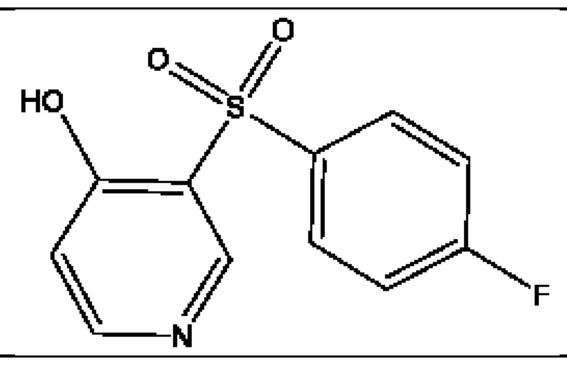
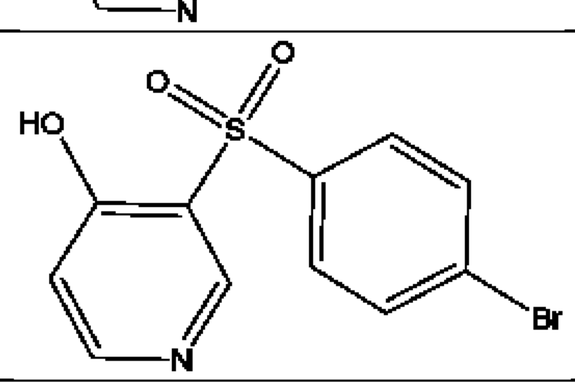
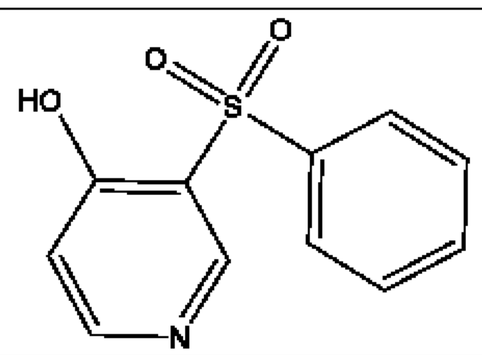
BC19580		+	+

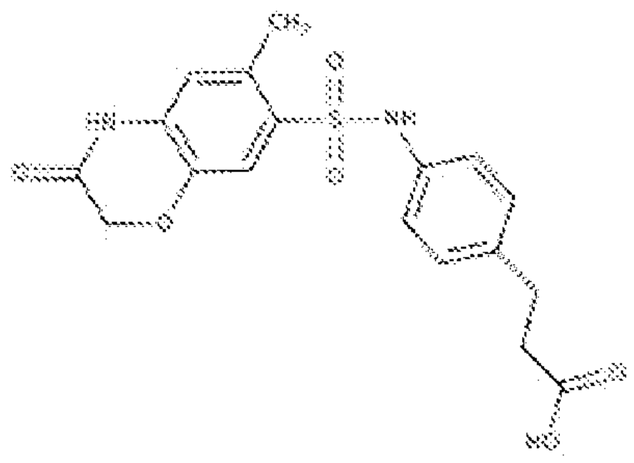
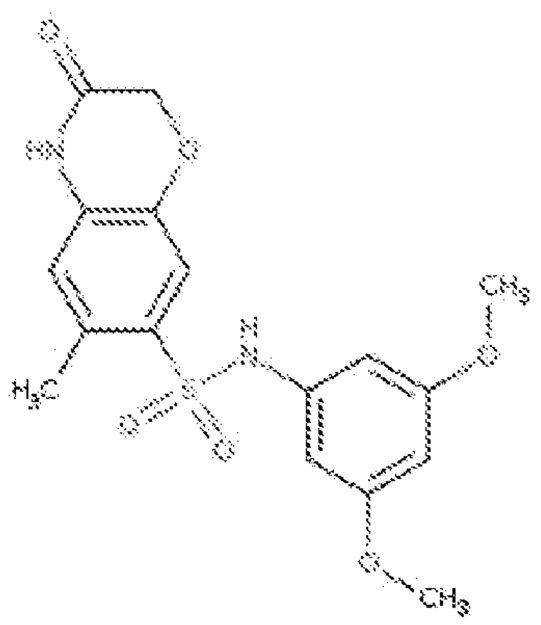
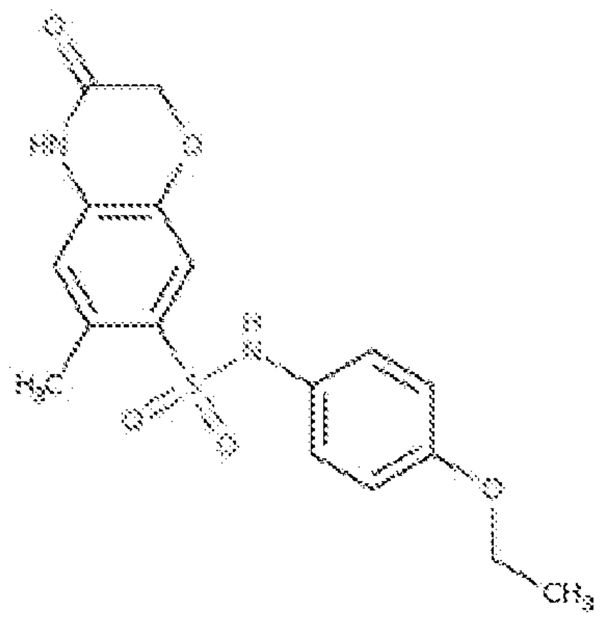
Table 1h

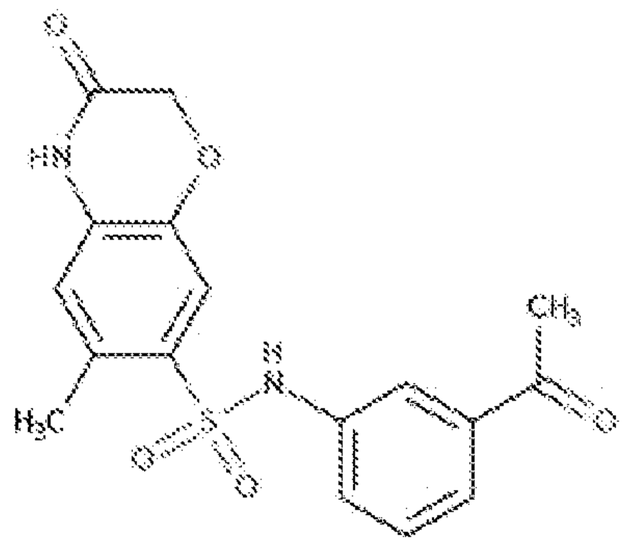
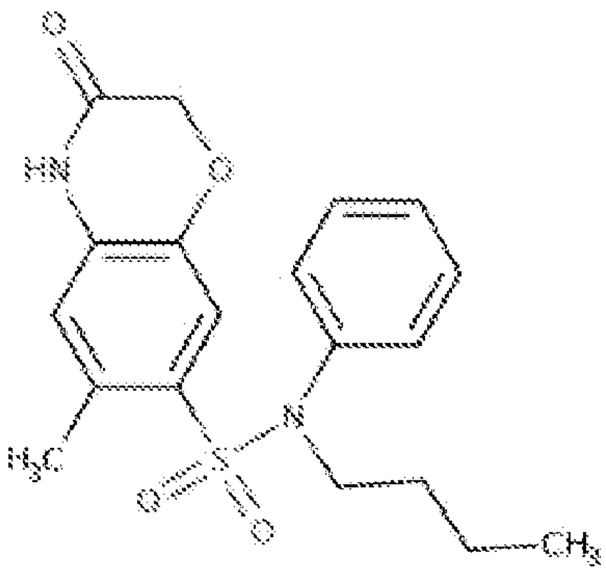
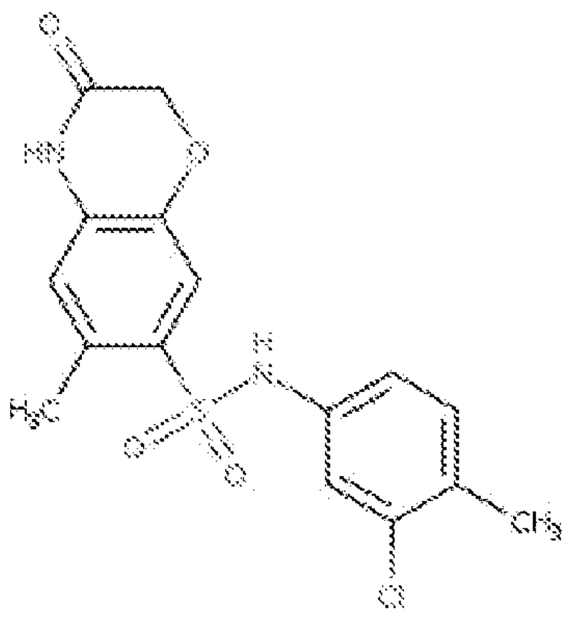
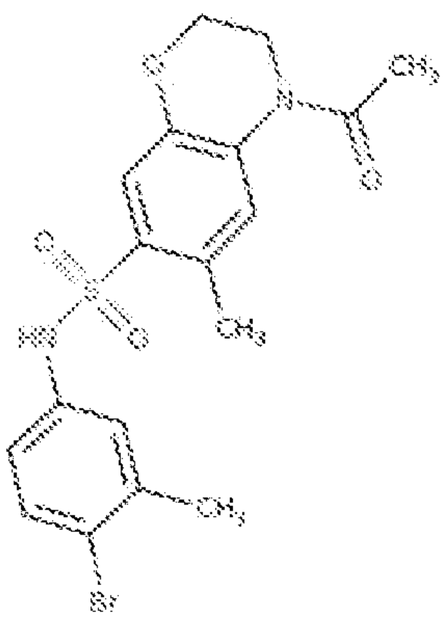
BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19455		+	+
BC19456		+	+
BC19457		+	+
BC19458		+	+
BC19459		+	+
BC19460		+	+

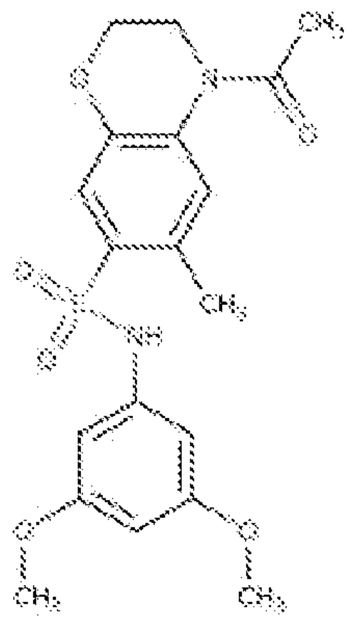
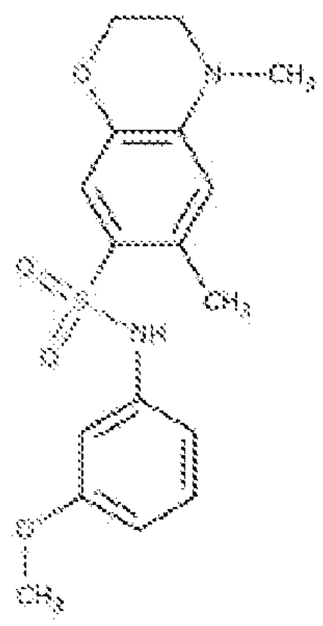
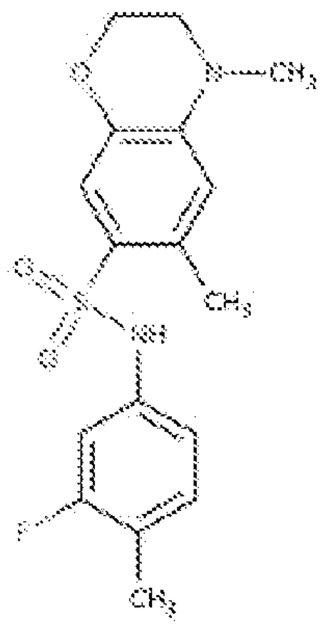
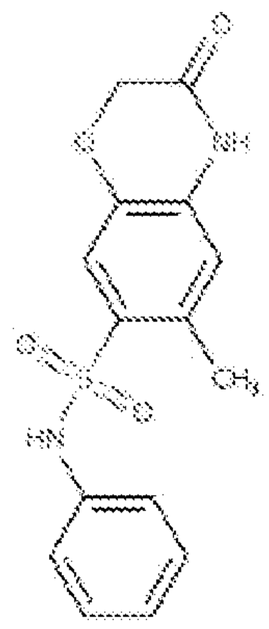
BC19461		+	+

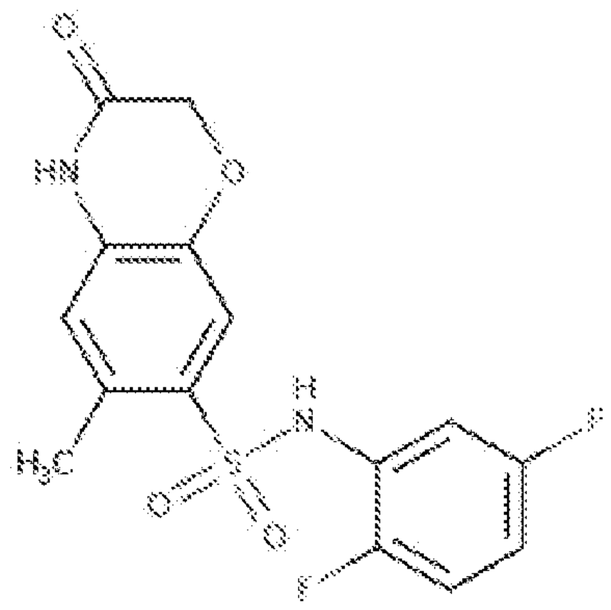
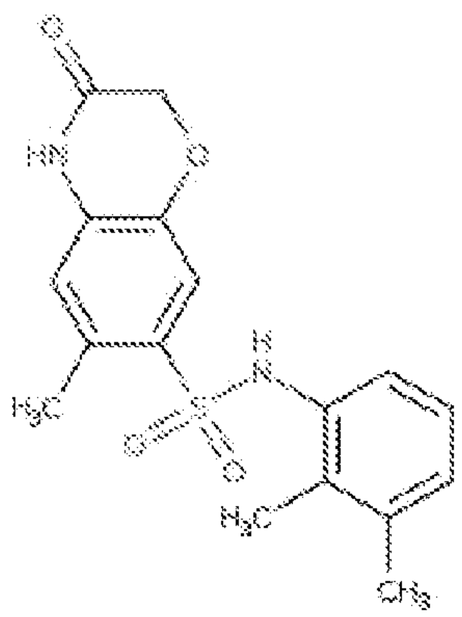
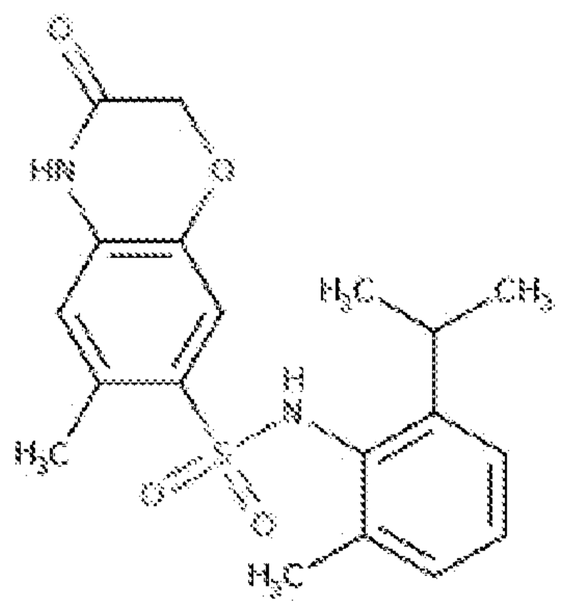
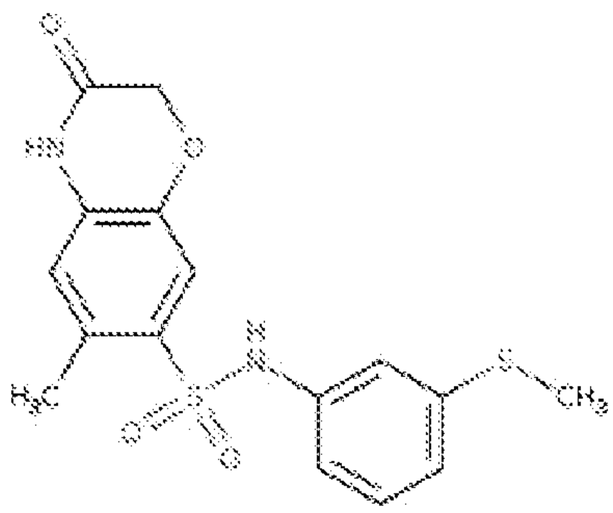
Example 2 – Bioassay results for tested compounds

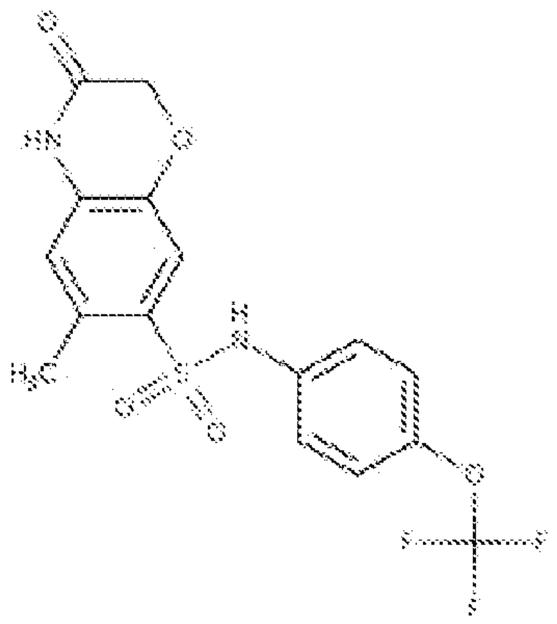
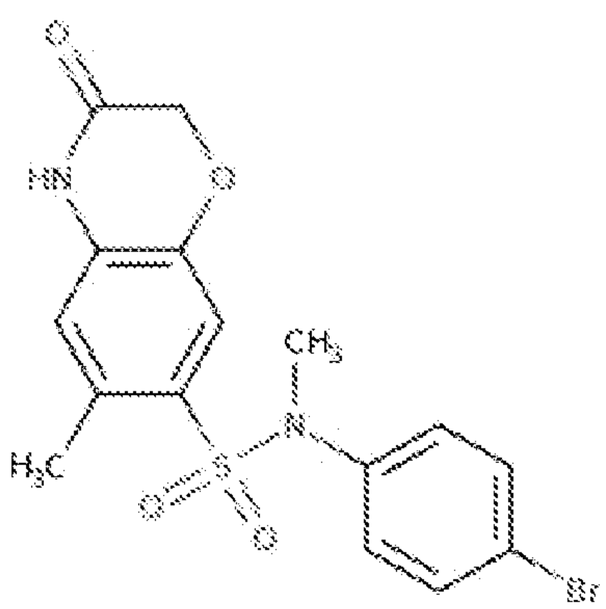
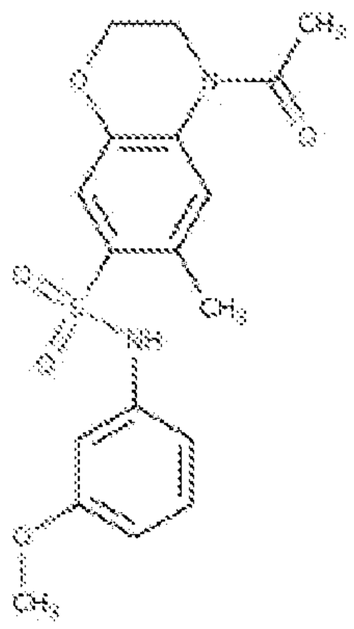
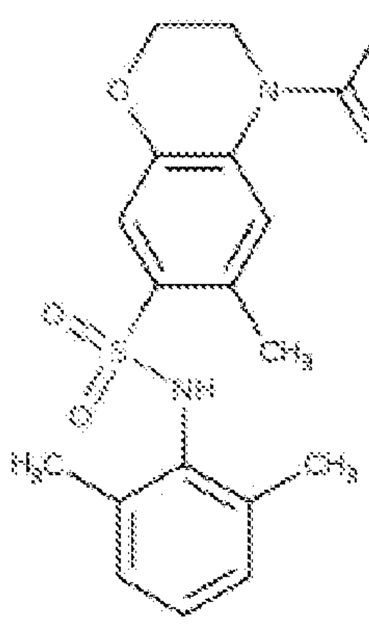
Table 2a

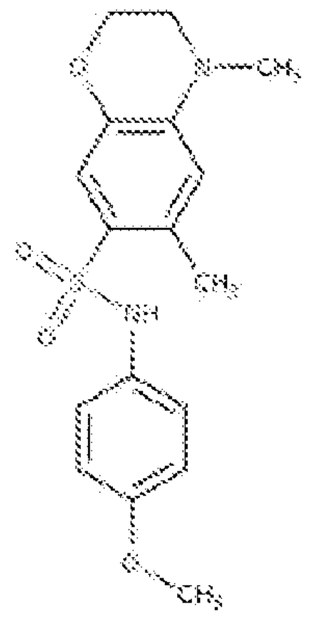
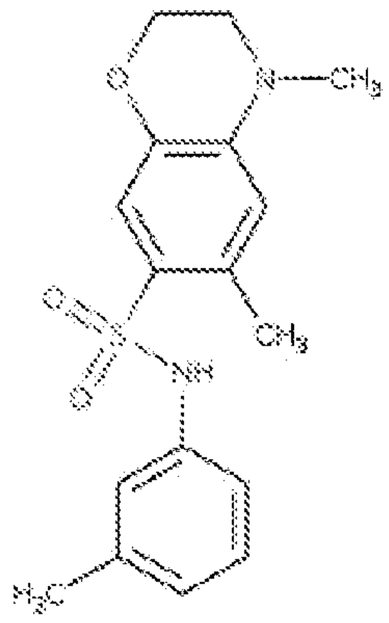
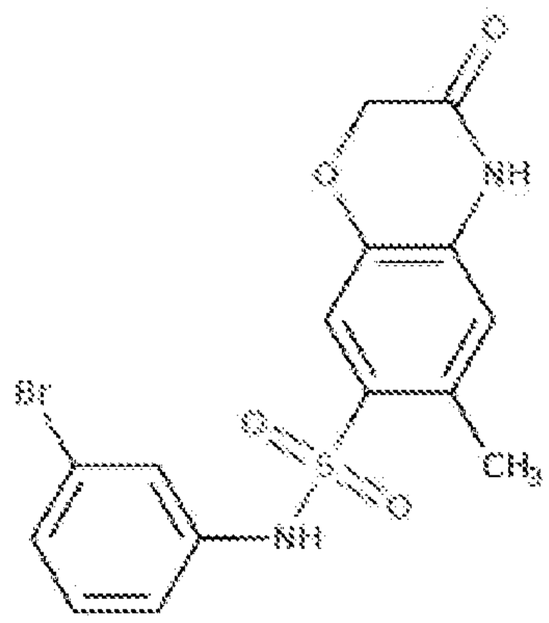
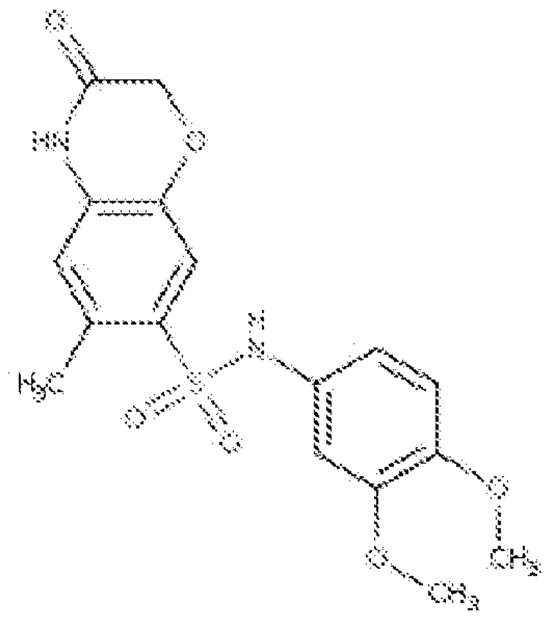
BC No.	Compound	IC_{50} NF-κB assay
BC181300		+
BC181301		+
BC181302		++++

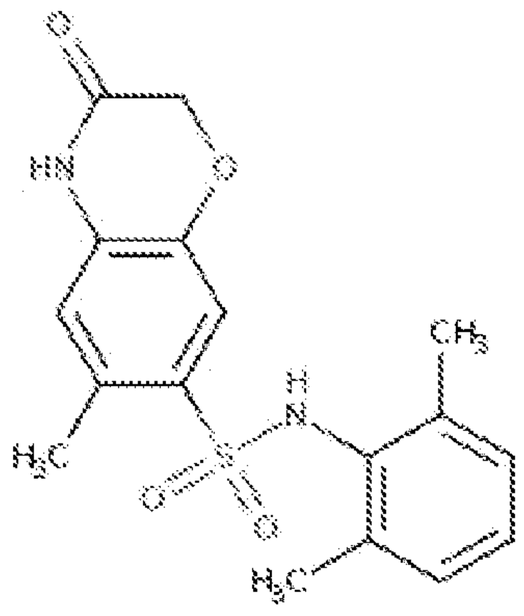
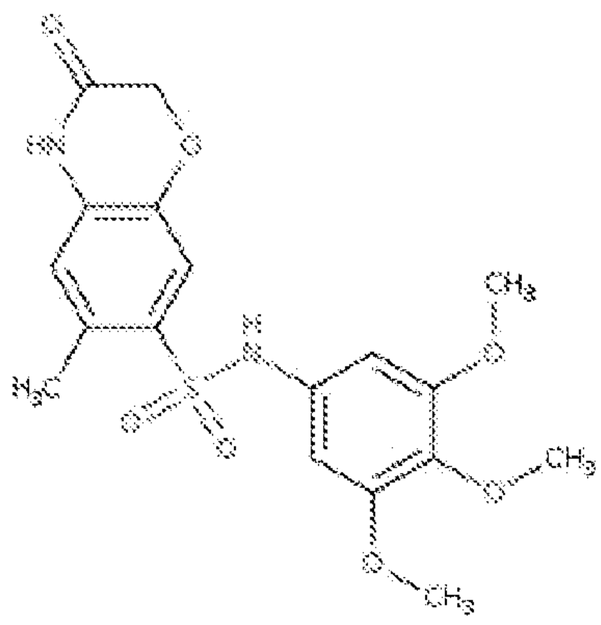
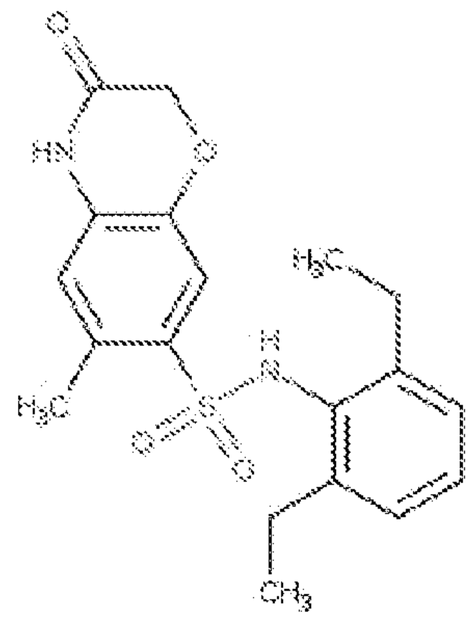
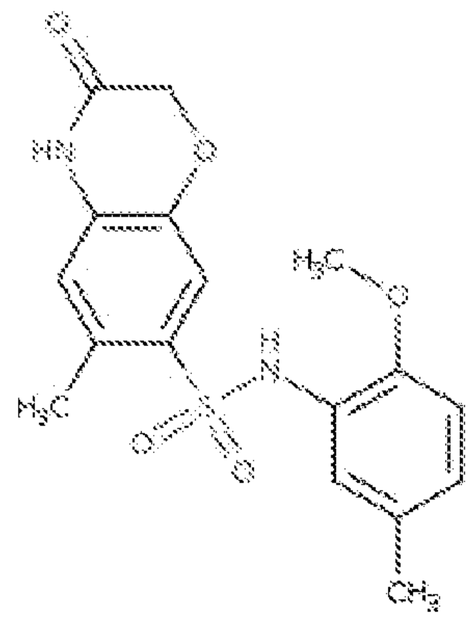
BC181303		++++
BC181304		+
BC181305		++++
BC181306		++

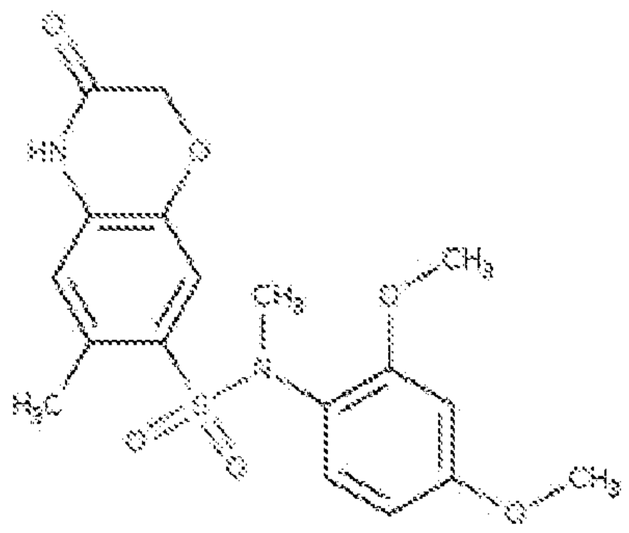
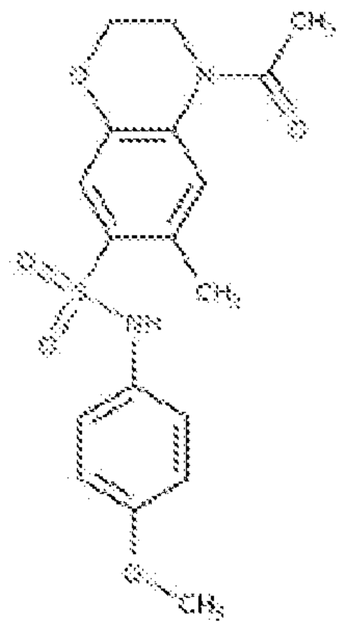
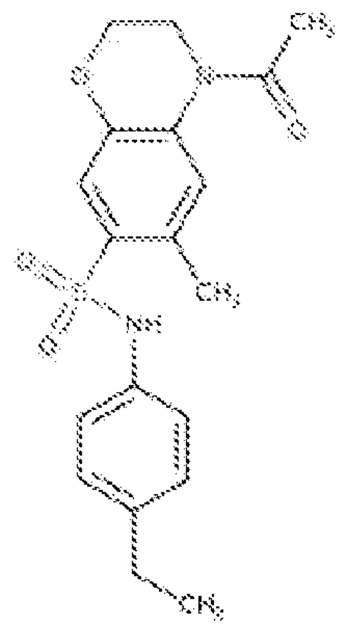
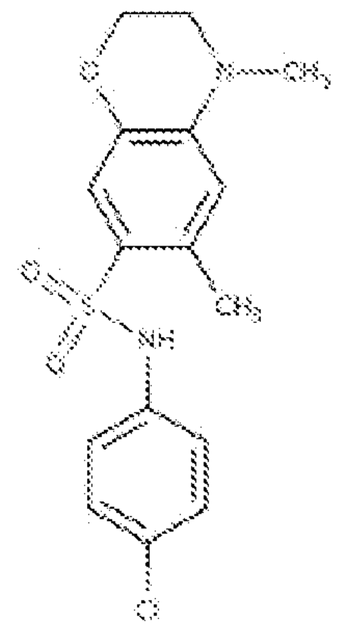
BC181307		+
BC181308		+
BC181309		+
BC181310		++++

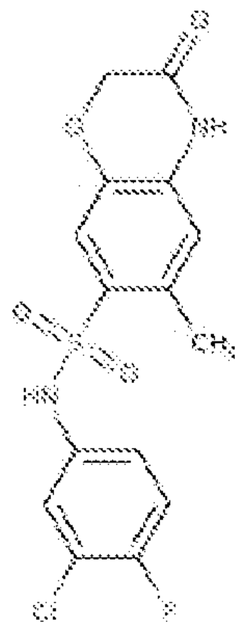
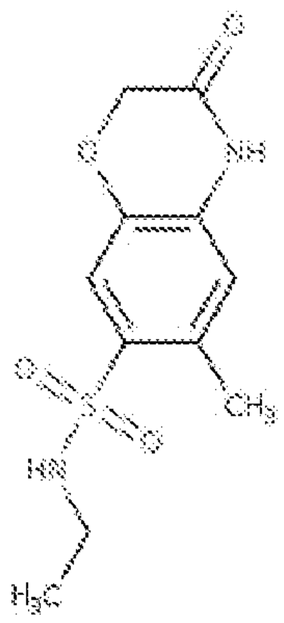
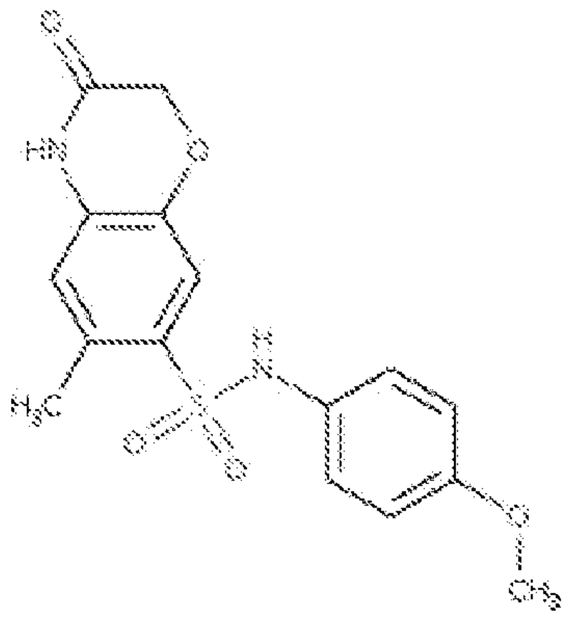
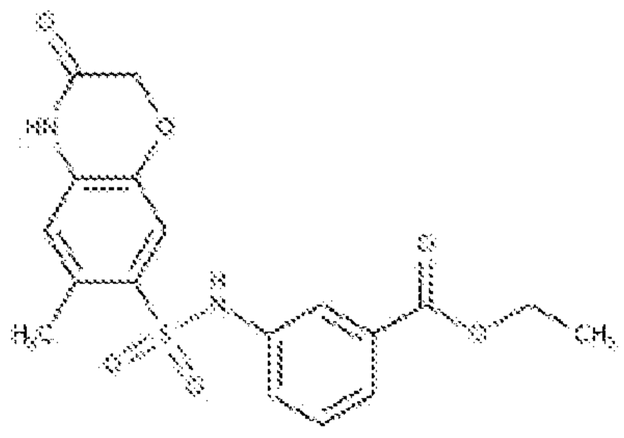
BC181311		++++
BC181312		++
BC181313		+
BC181314		++++

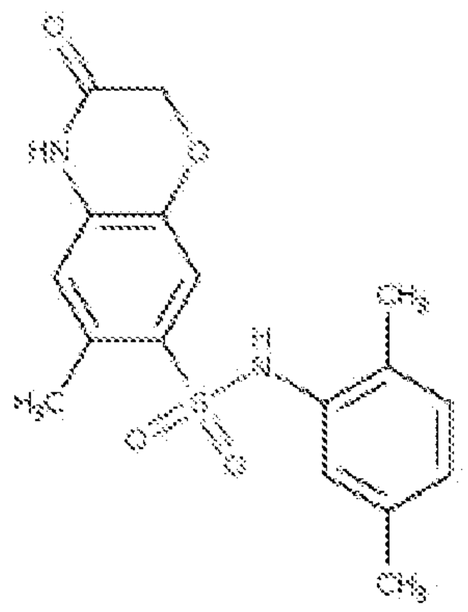
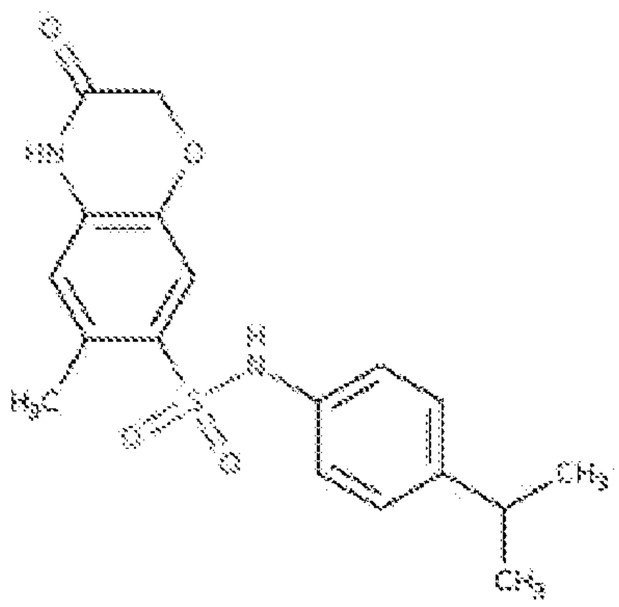
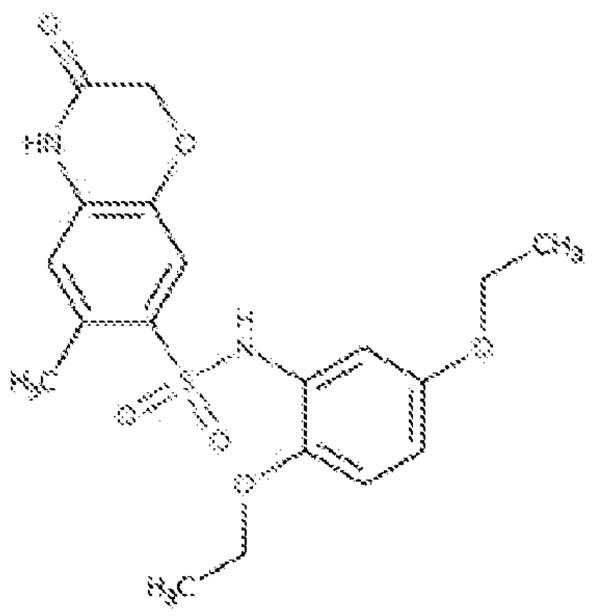
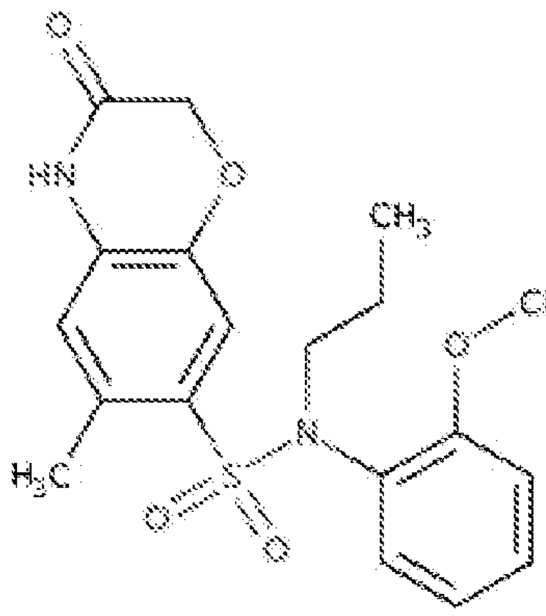
BC181315		++++
BC181316		+
BC181317		+
BC181318		+

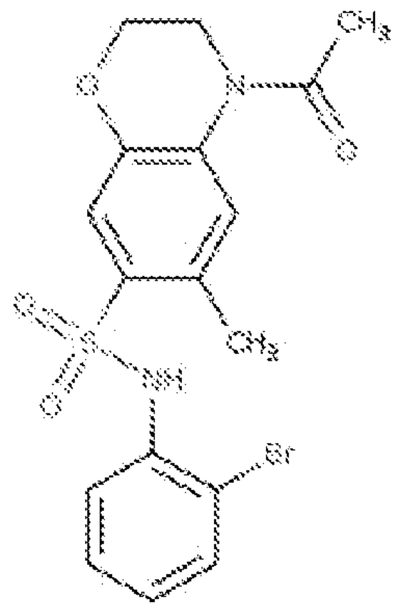
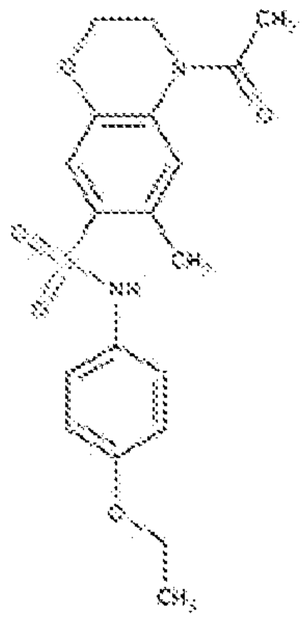
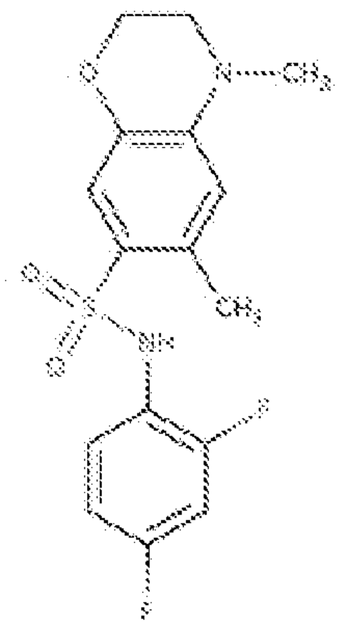
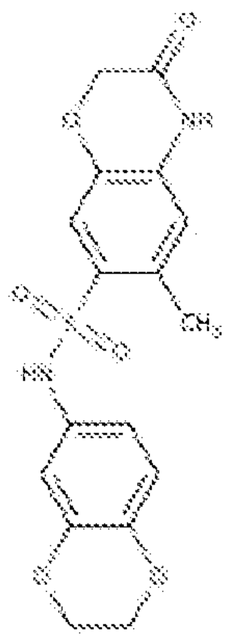
BC181319		+
BC181320		+
BC181321		++++
BC181322		+

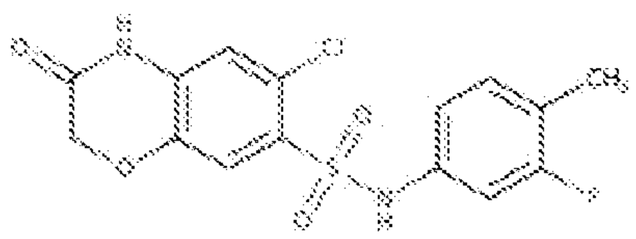
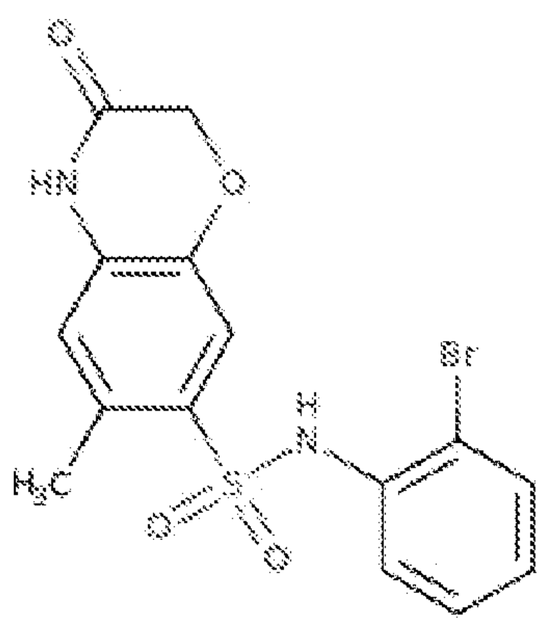
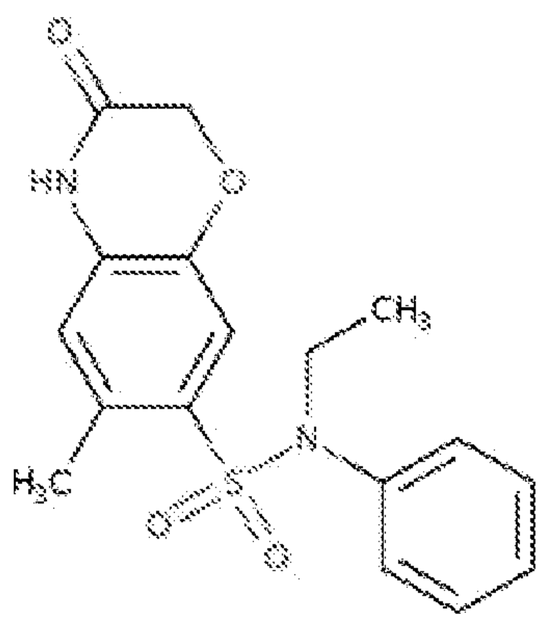
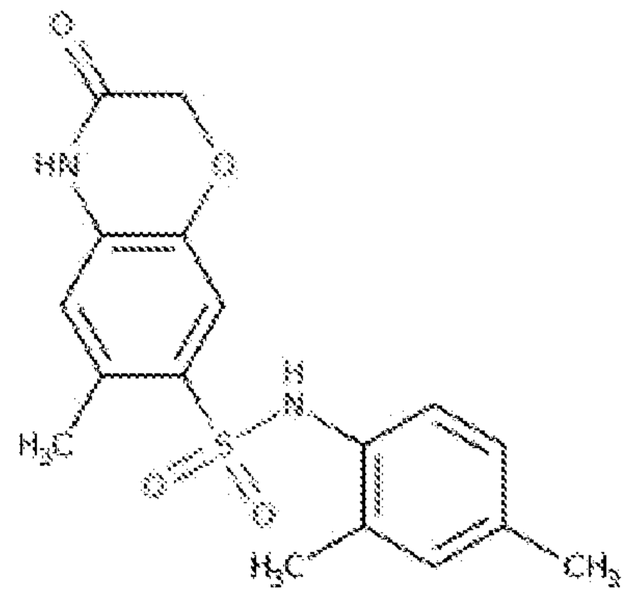
BC181323		+
BC181324		+
BC181325		+
BC181326		+

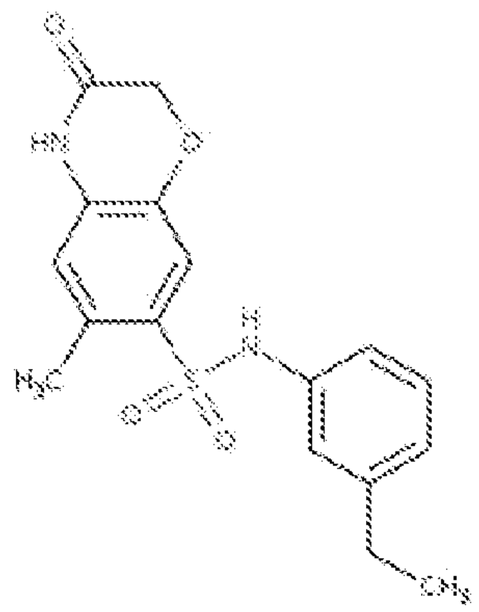
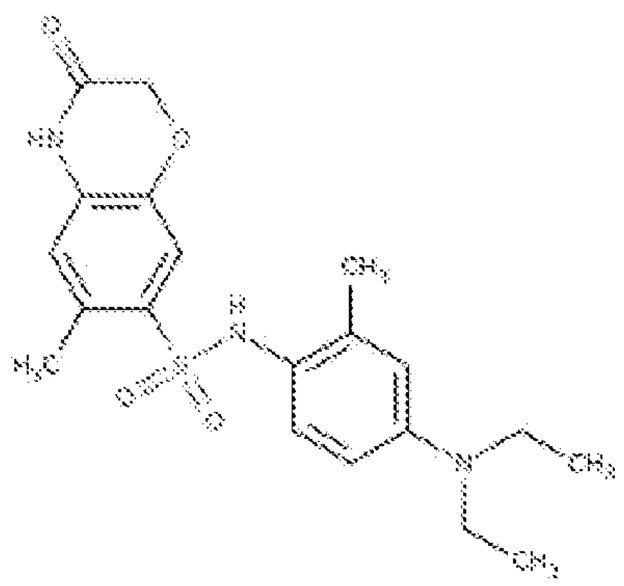
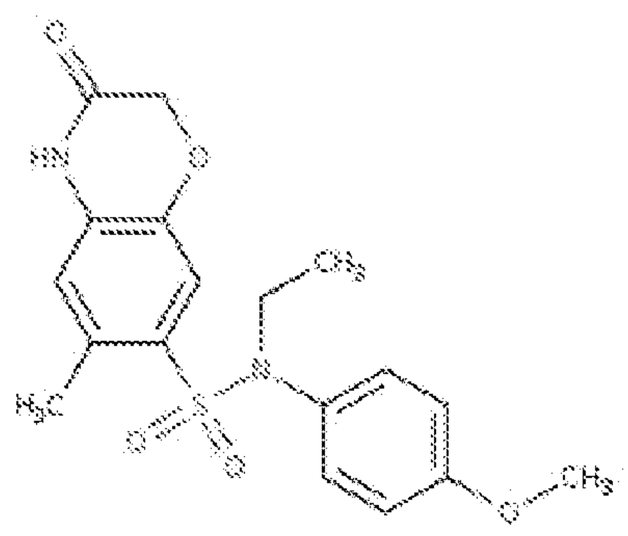
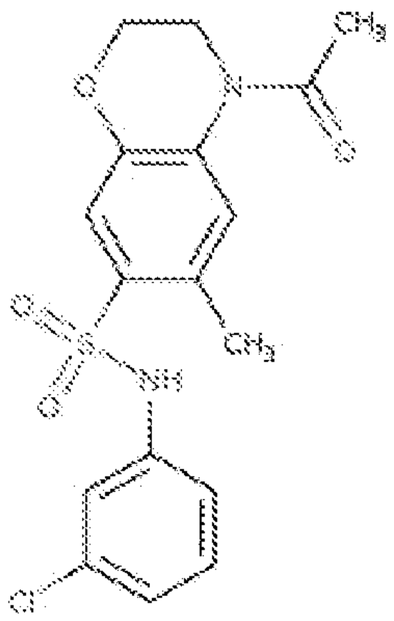
BC181327		+
BC181328		+
BC181329		++
BC181330		++

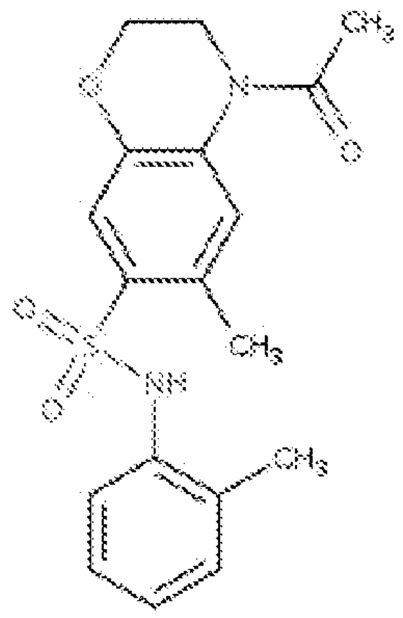
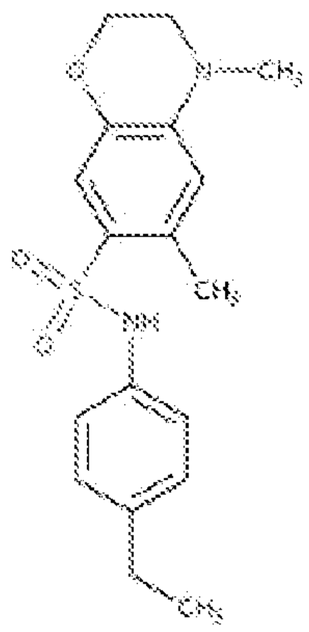
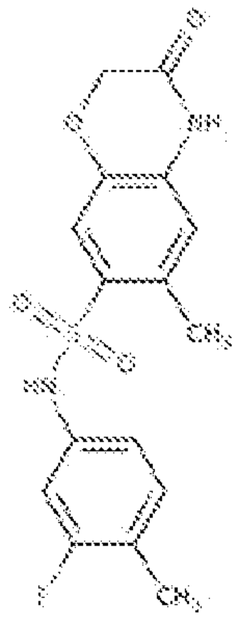
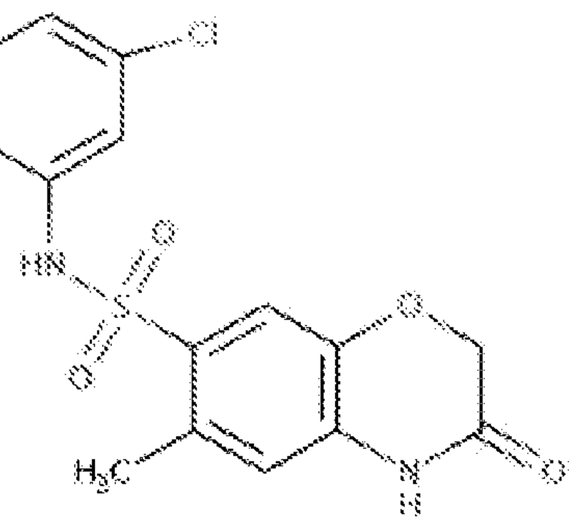
BC181331		++++
BC181332		+
BC181333		++
BC181334		++

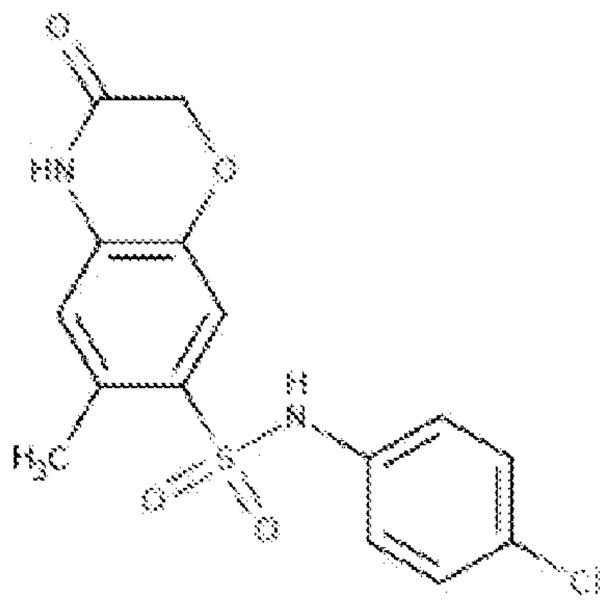
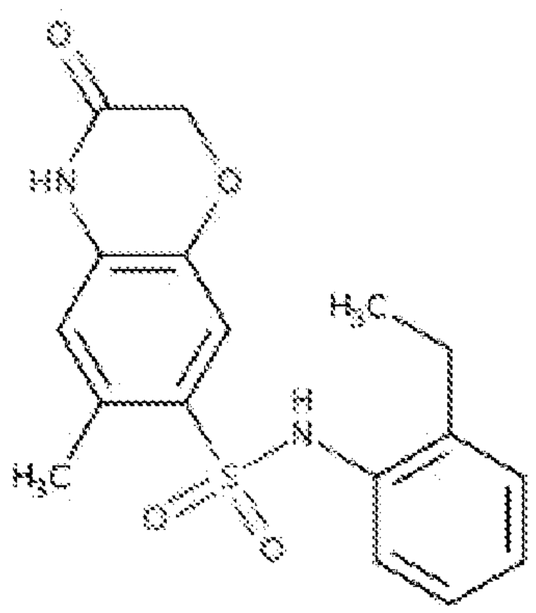
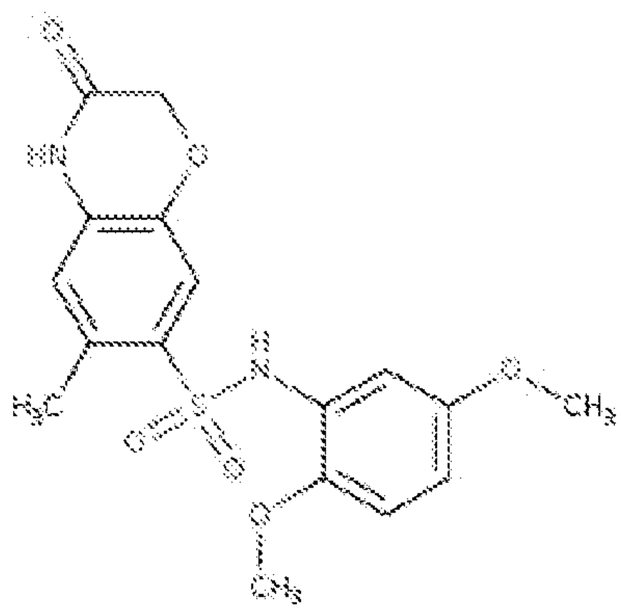
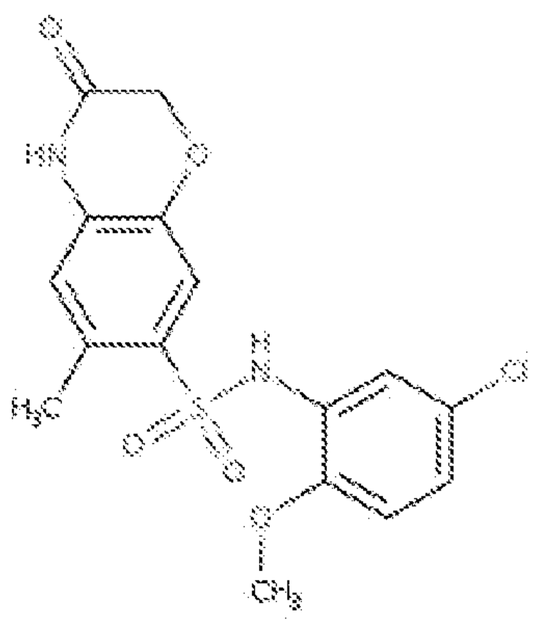
BC181335		+
BC181336		++++
BC181337		+
BC181338		++

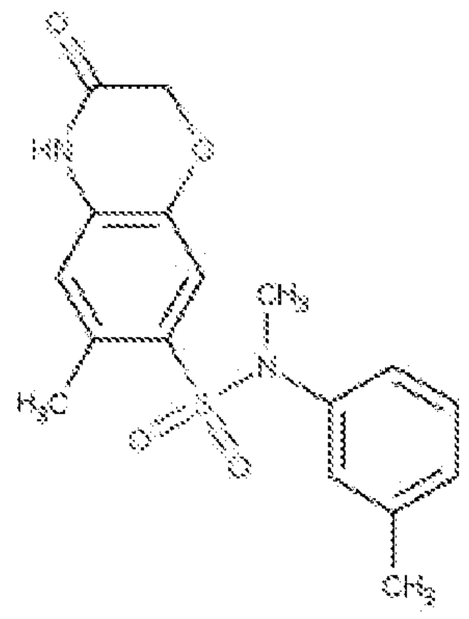
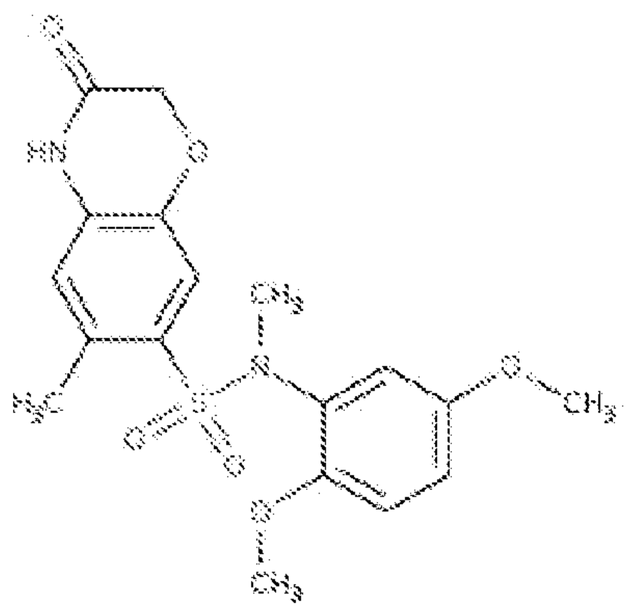
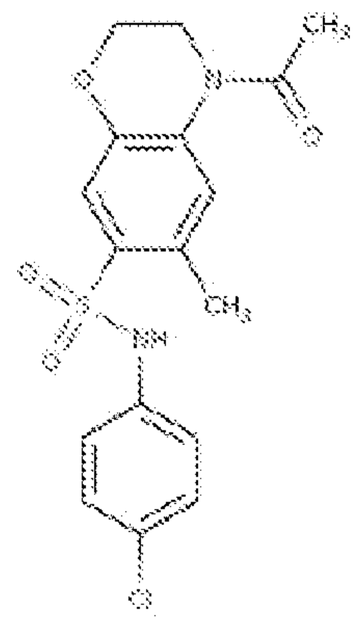
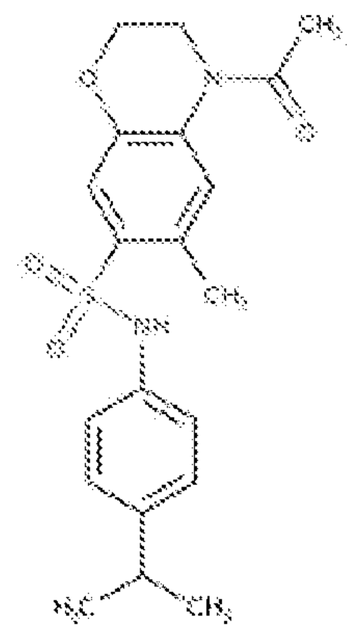
BC181339		+
BC181340		+
BC181341		++
BC181342		+++

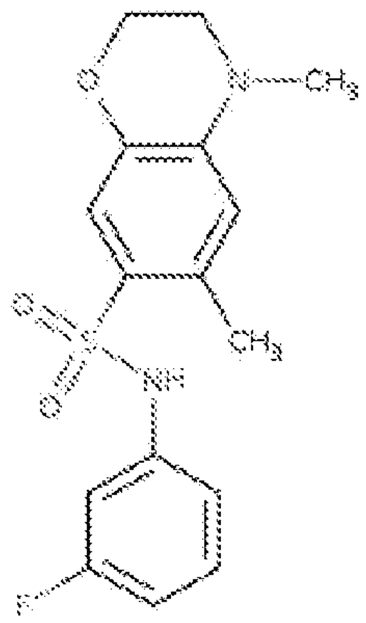
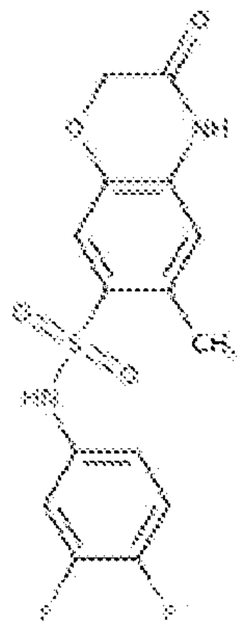
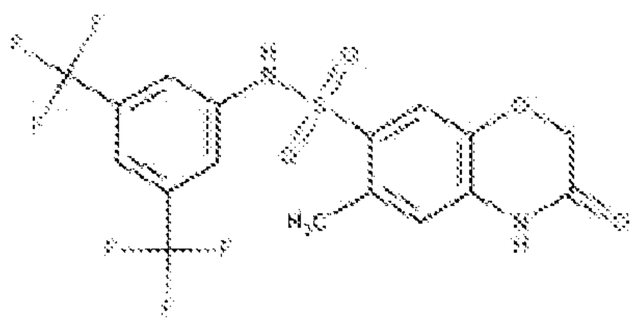
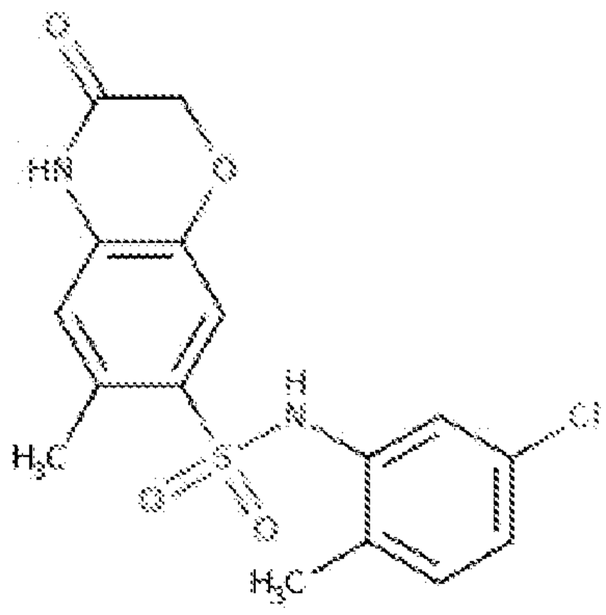
BC181343		++++
BC181344		+++
BC181345		+
BC181346		+

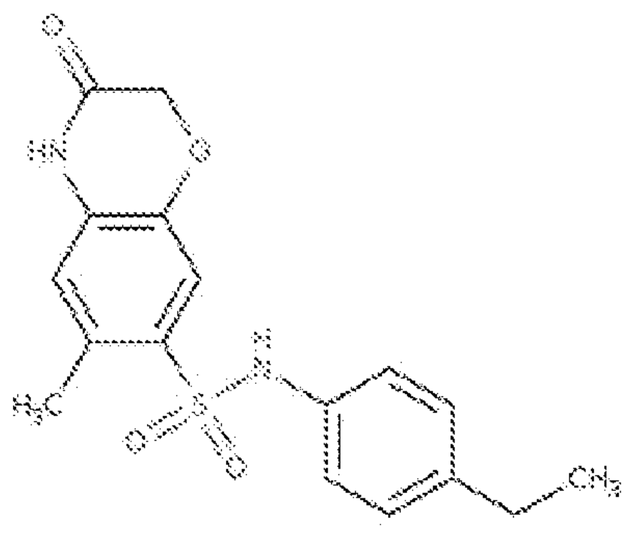
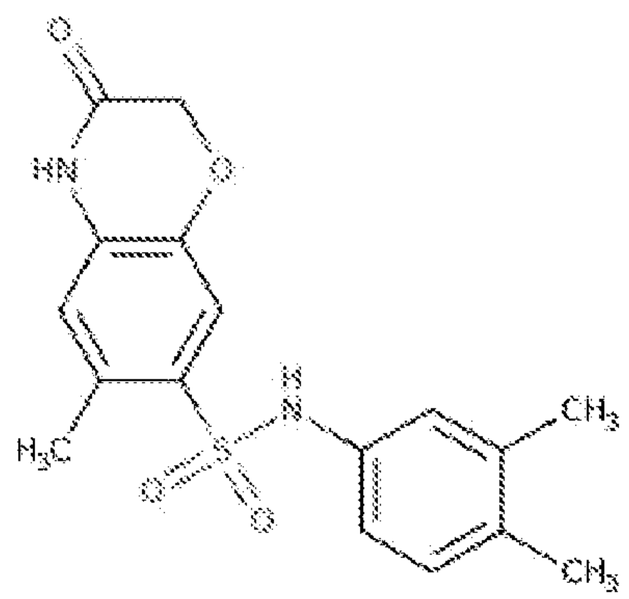
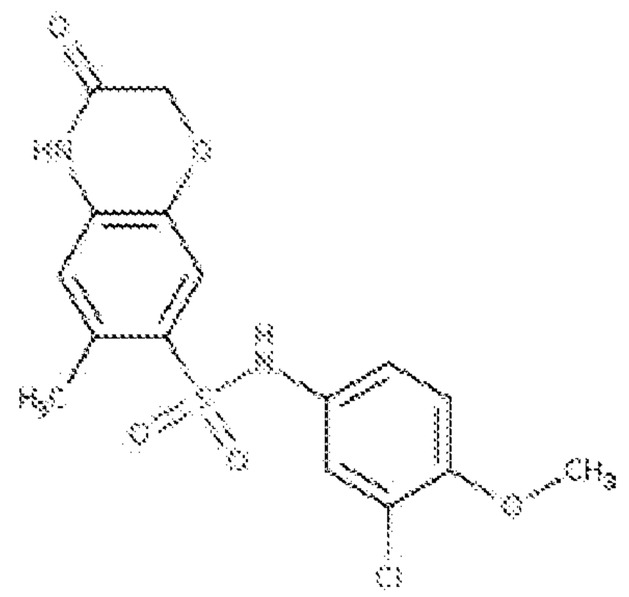
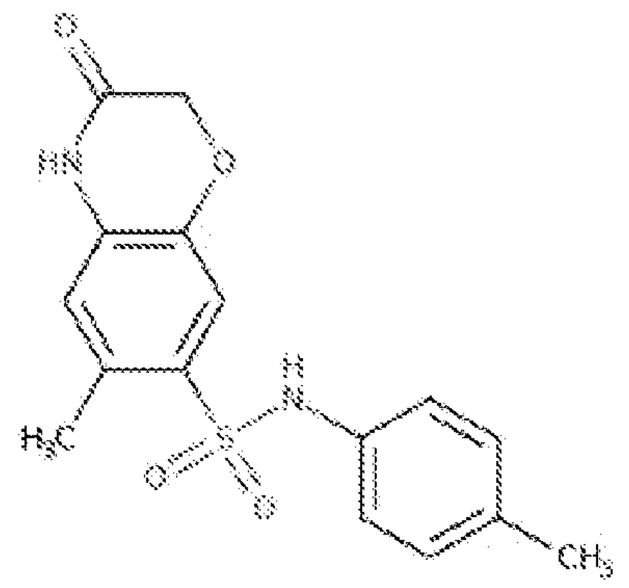
BC181347		++
BC181348		+
BC181349		+
BC181350		++

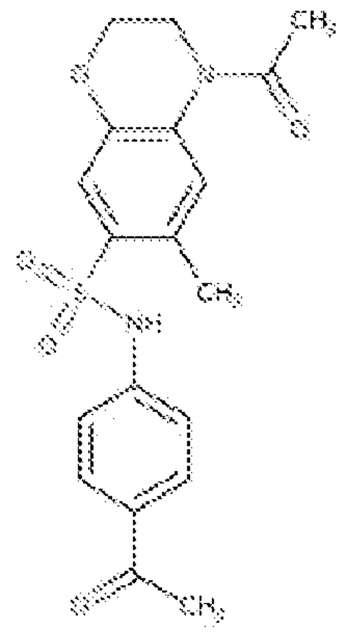
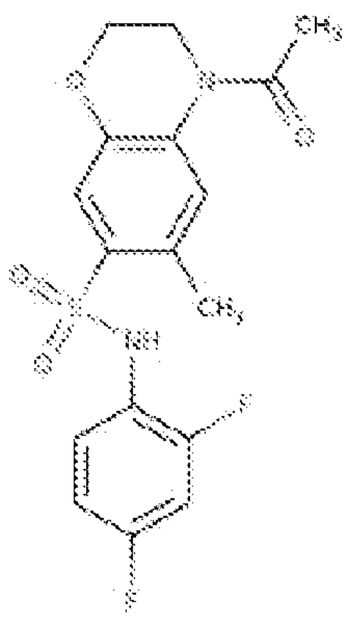
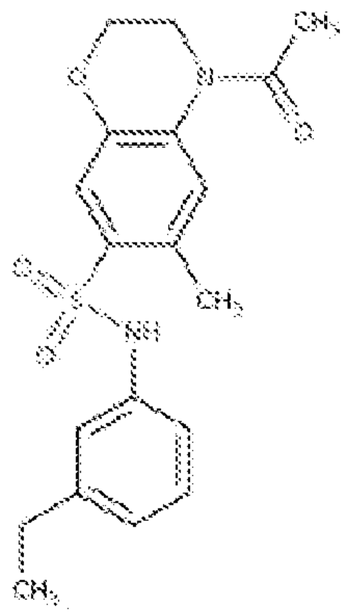
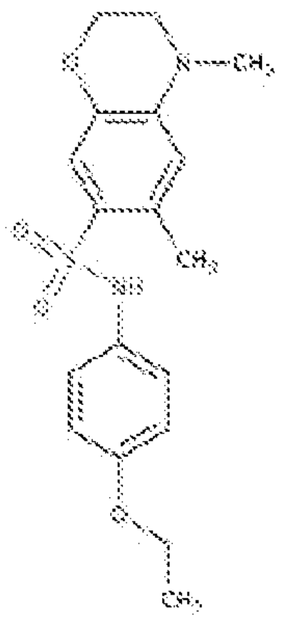
BC181351		+
BC181352		+
BC181353		++++
BC181354		++++

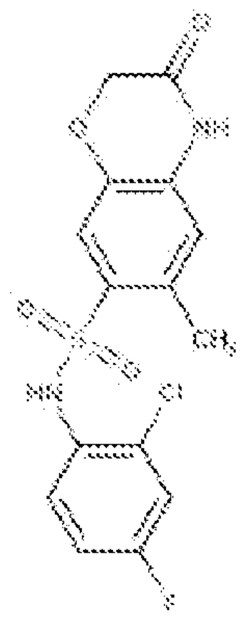
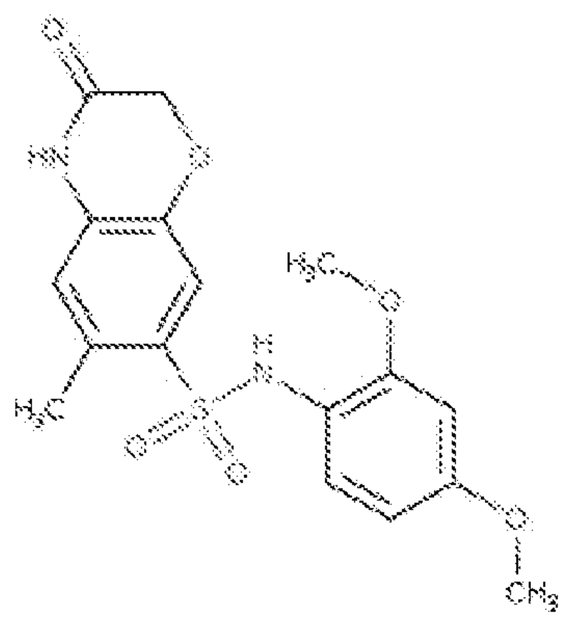
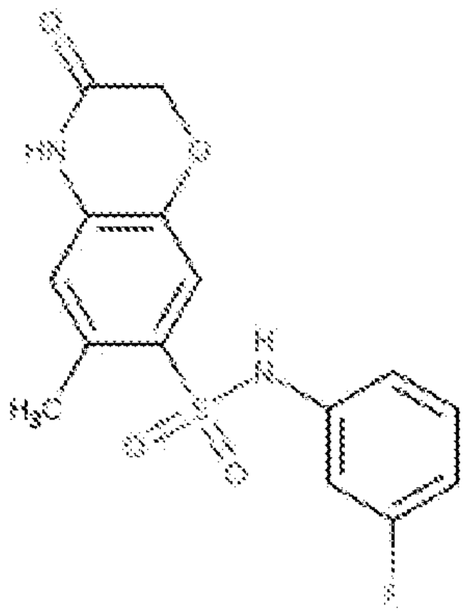
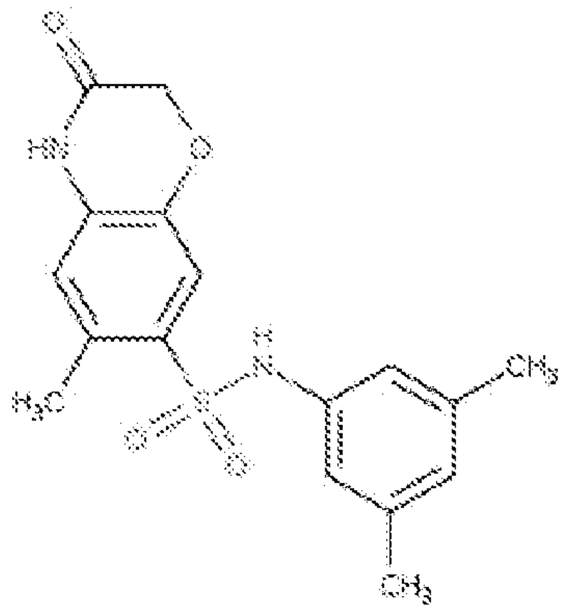
BC181355		++++
BC181356		+
BC181357		+
BC181358		+

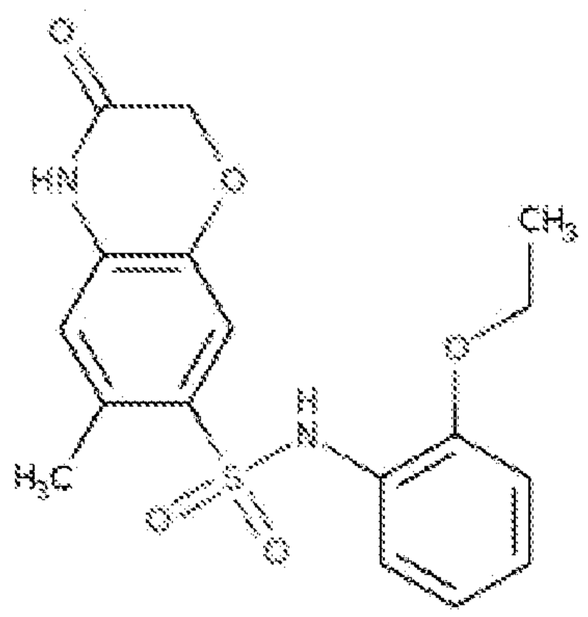
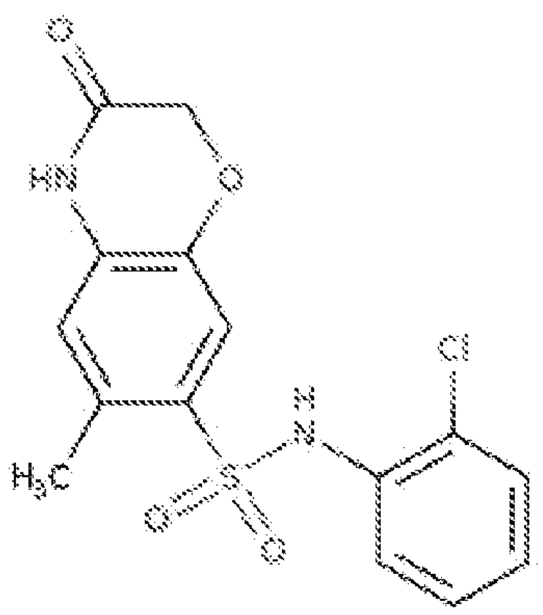
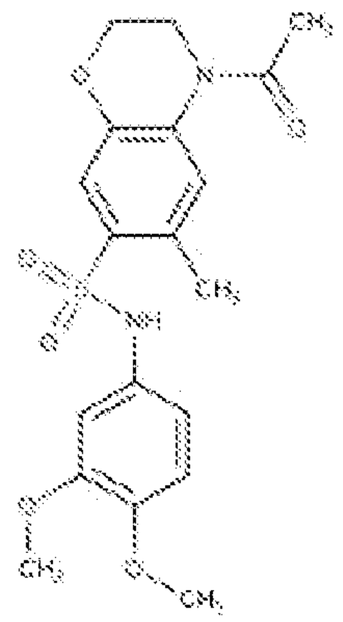
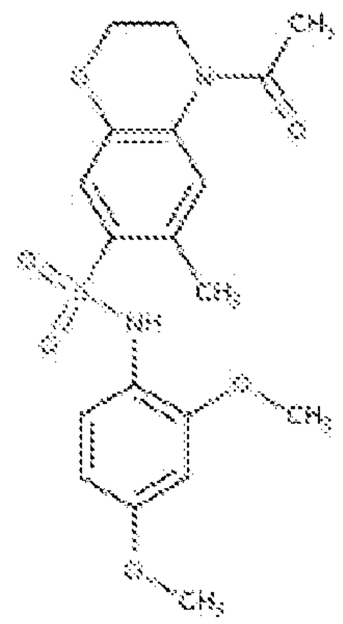
BC181359		+
BC181360		+
BC181361		+++
BC181362		++

BC181363		+
BC181364		+++
BC181365		++
BC181366		++

BC181367		++++
BC181368		++
BC181369		++
BC181370		++++

BC181371		+
BC181372		++
BC181373		+
BC181374		+

BC181375		+++
BC181376		+
BC181377		++++
BC181378		++

BC181379		+
BC181380		+++
BC181381		+
BC181382		+

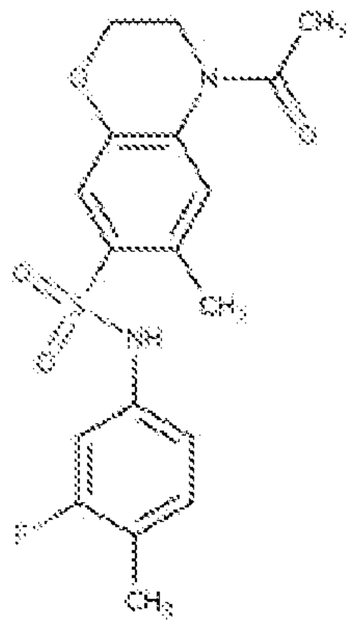
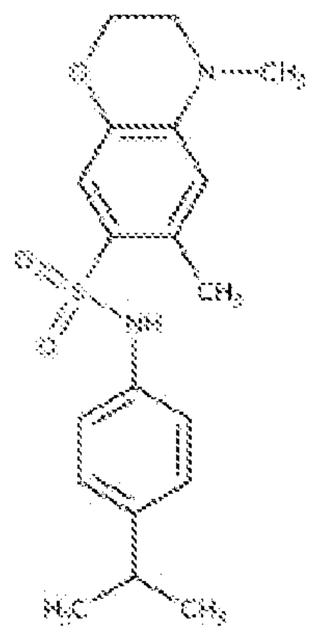
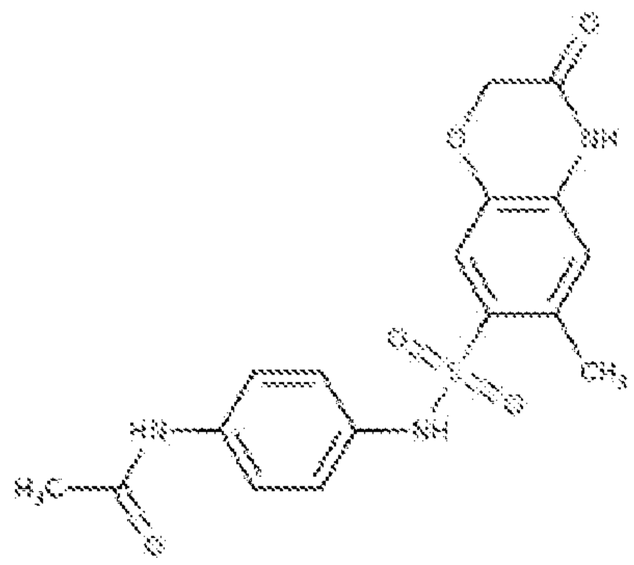
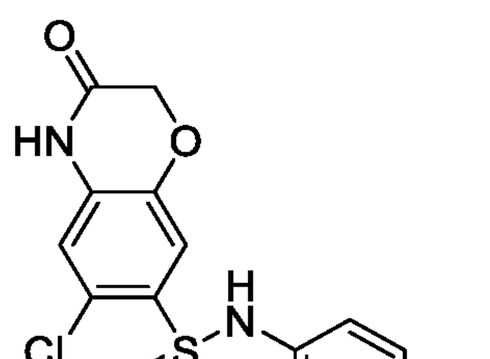
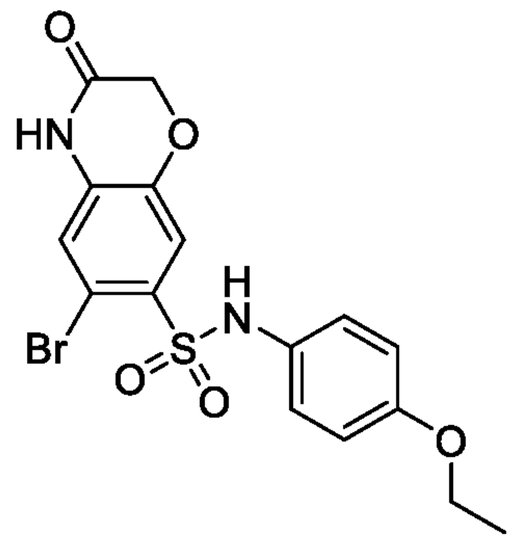
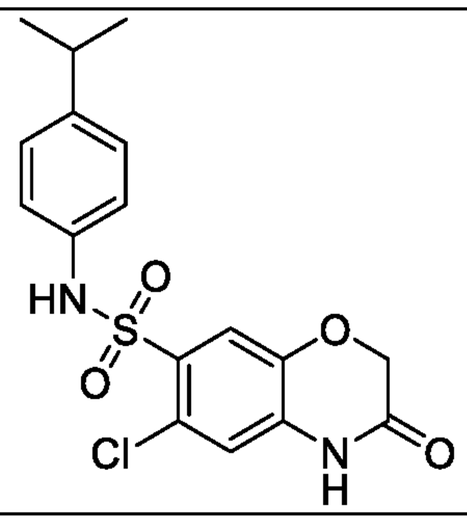
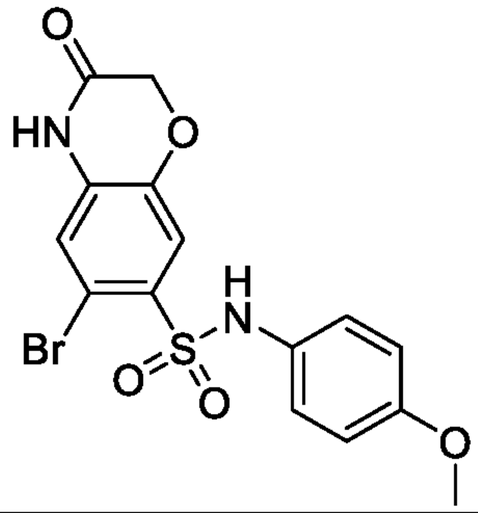
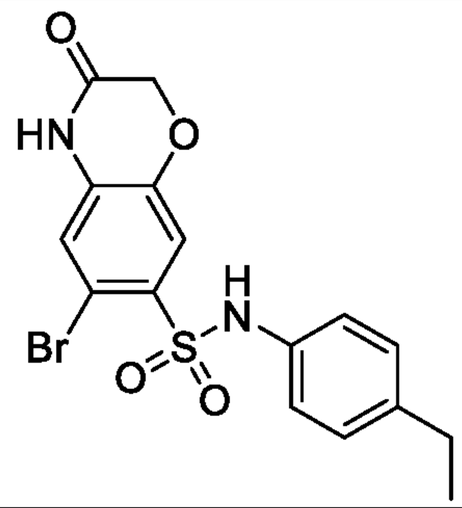
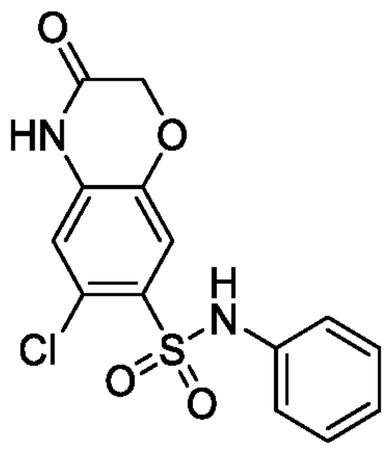
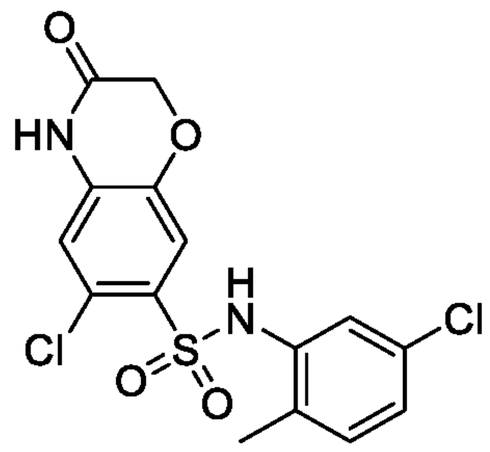
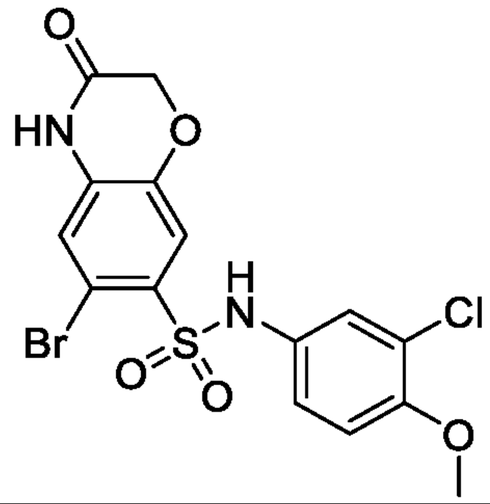
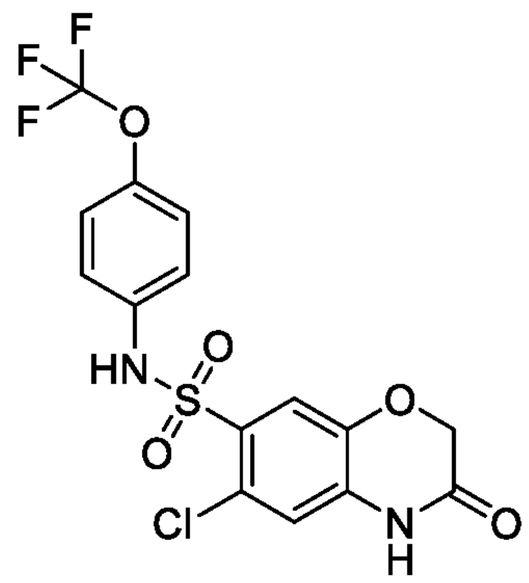
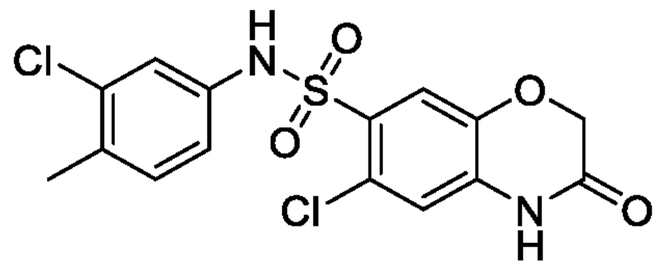
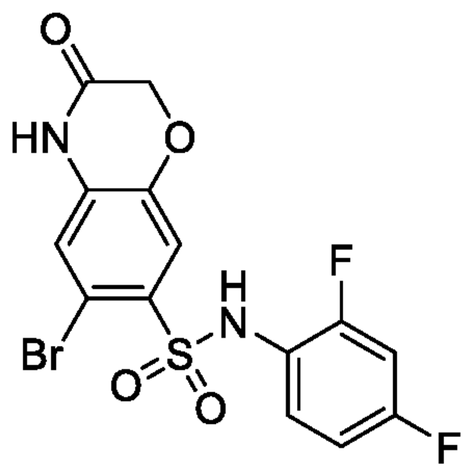
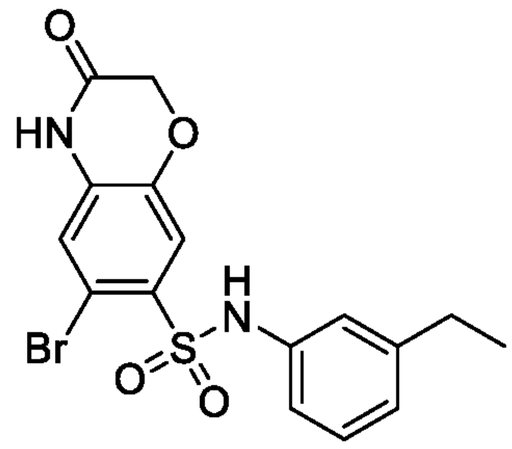
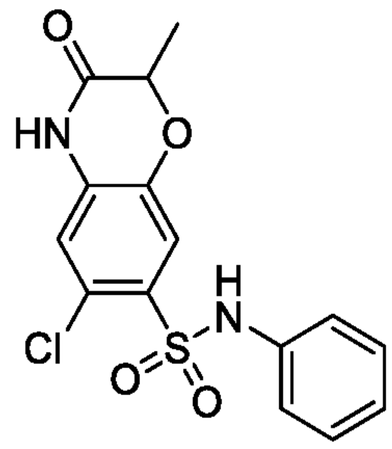
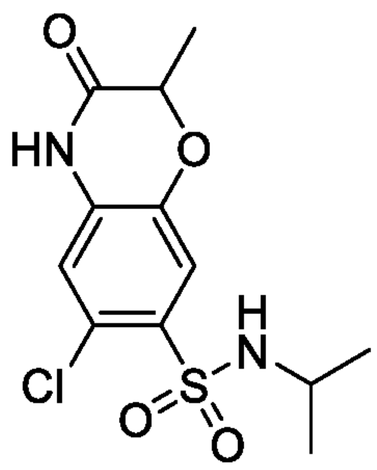
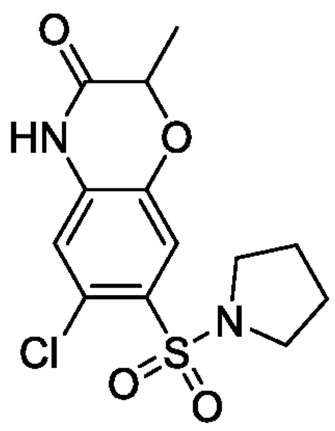
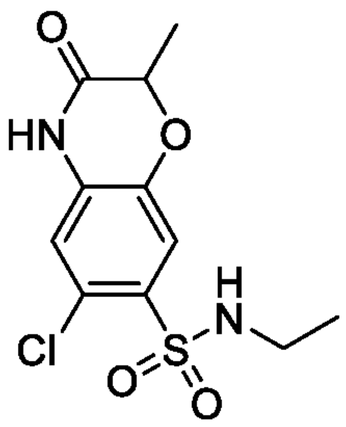
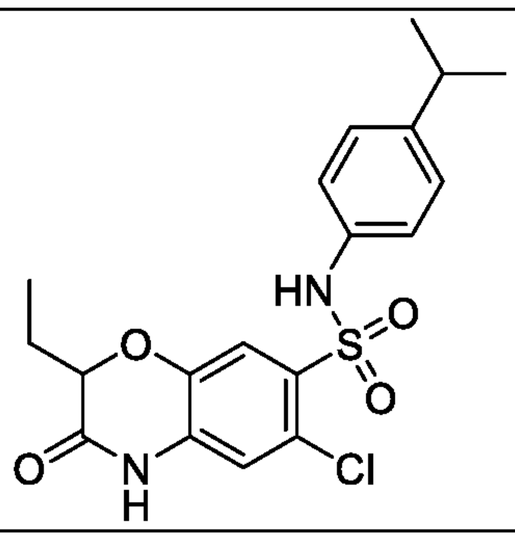
BC181383		+++
BC181384		++
BC181385		+

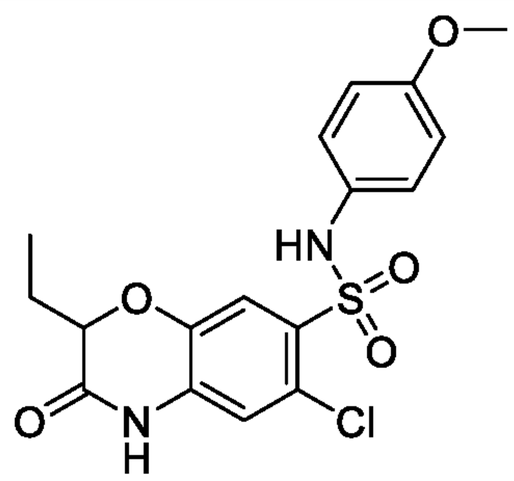
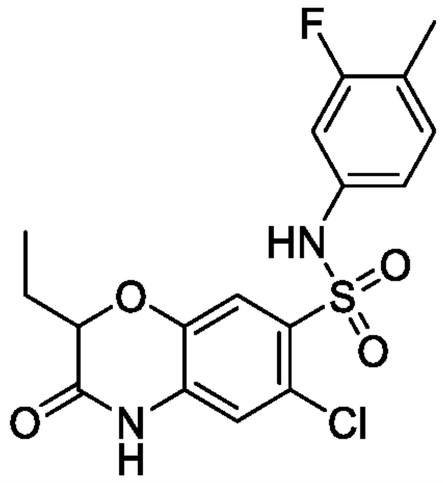
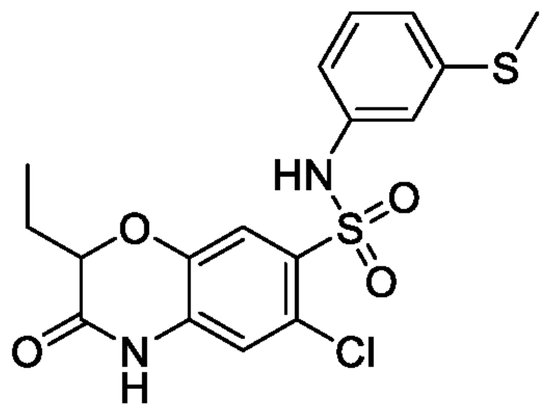
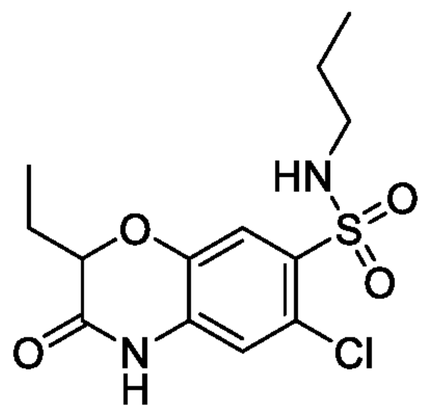
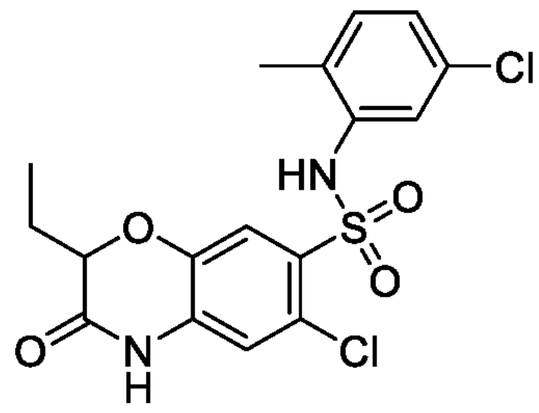
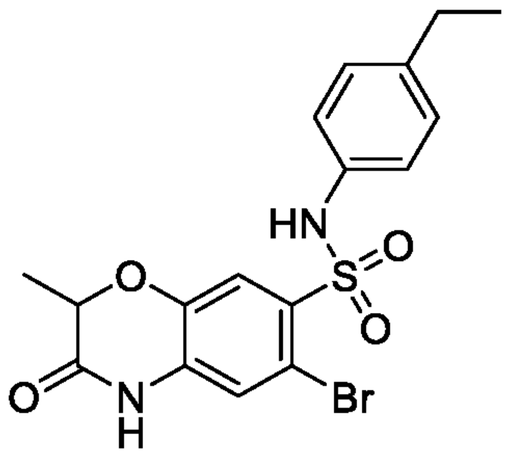
Table 2c

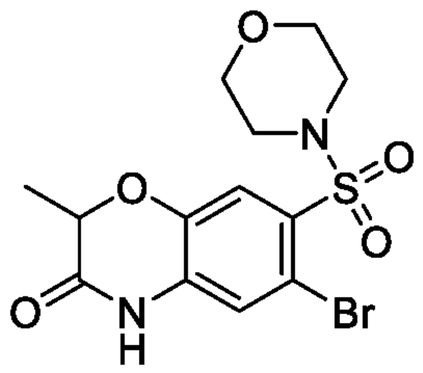
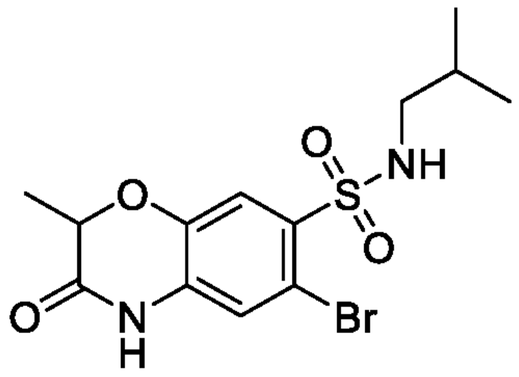
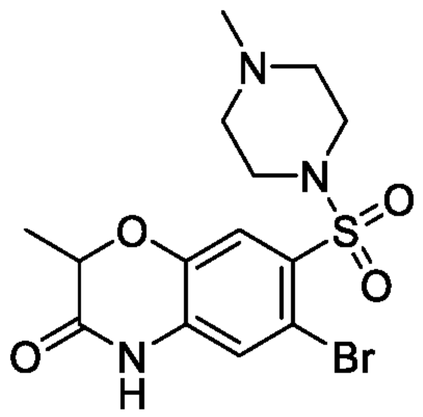
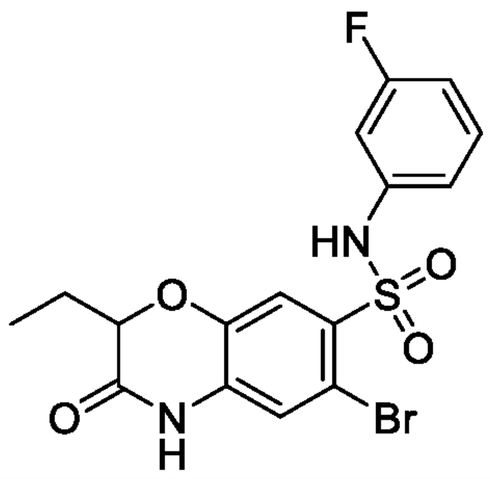
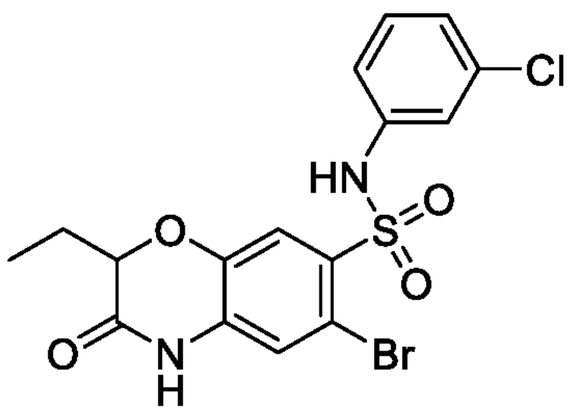
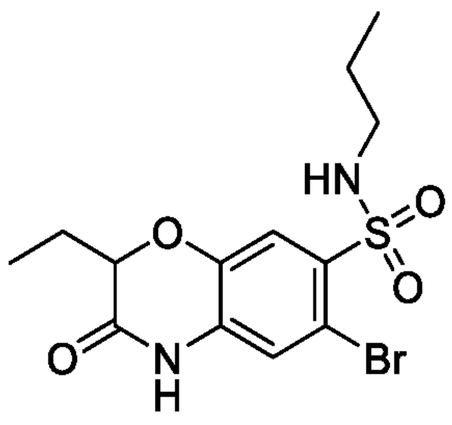
BC No.	ZE No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19133	ZE24-0004		++++	+

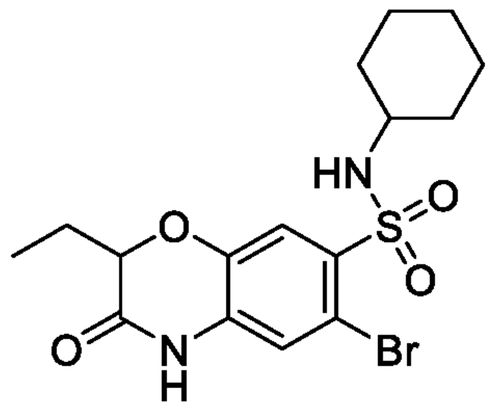
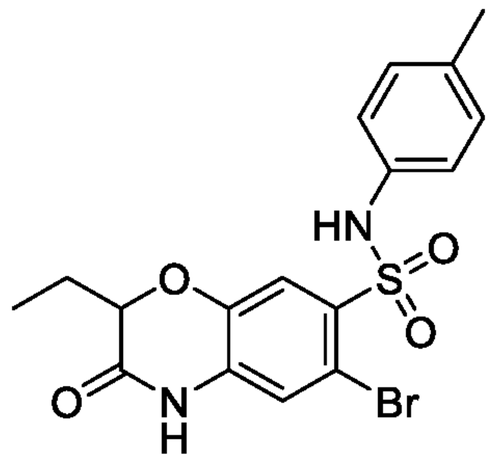
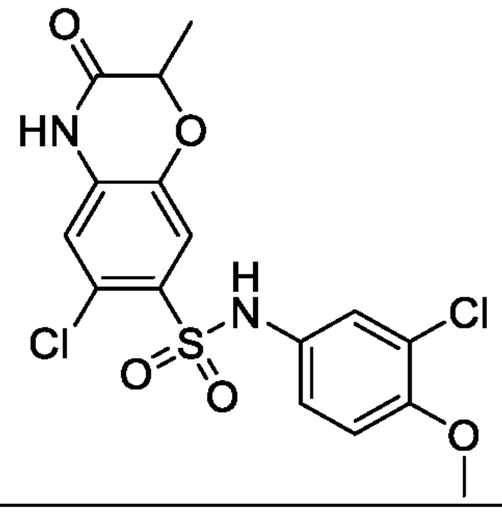
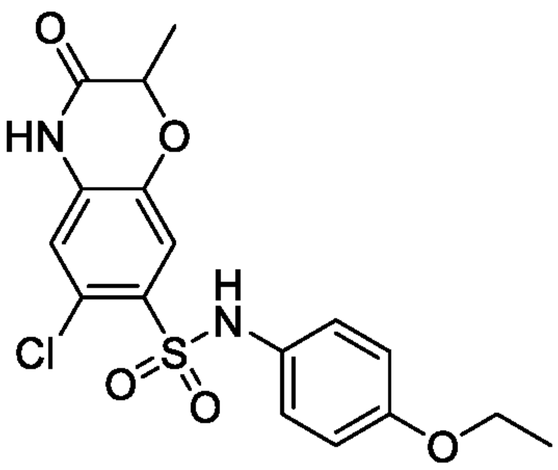
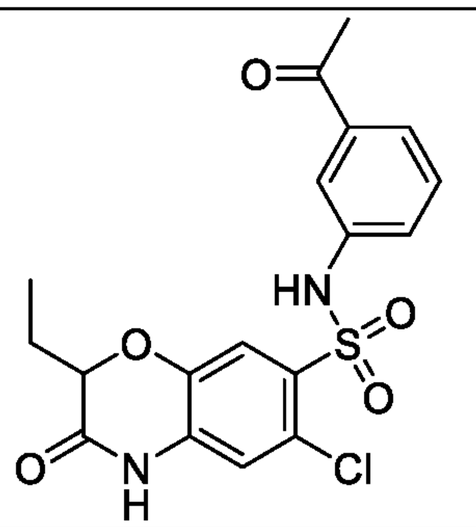
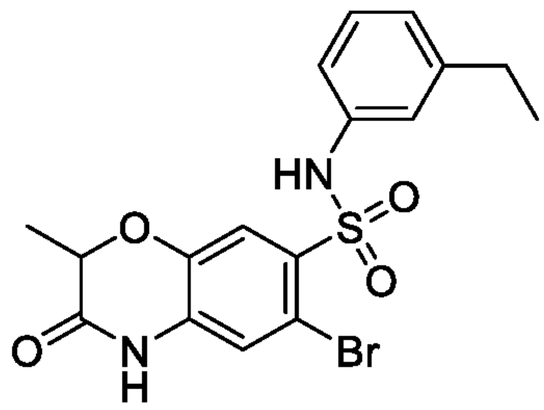
BC19135	ZE24-0009		+	+
BC19136	ZE24-0010		+	+
BC19137	ZE24-0011		+++	+
BC19138	ZE24-0015		++++	+
BC19161	ZE24-0003		++	+

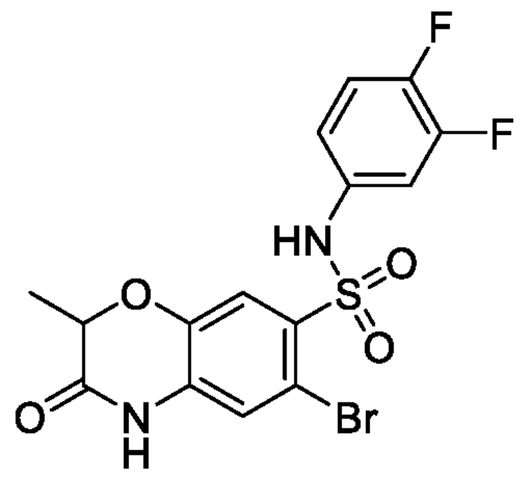
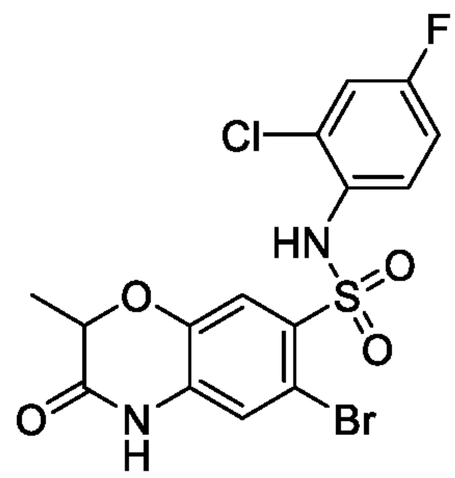
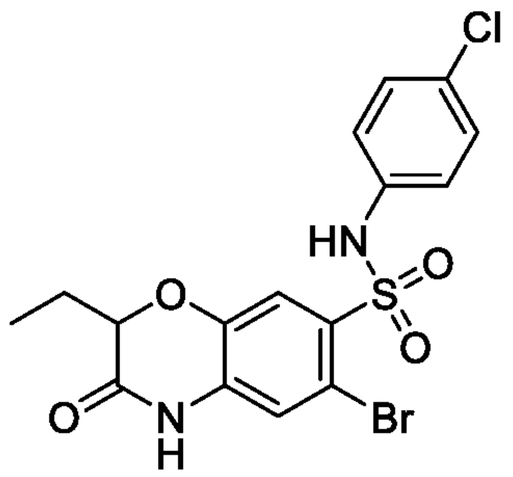
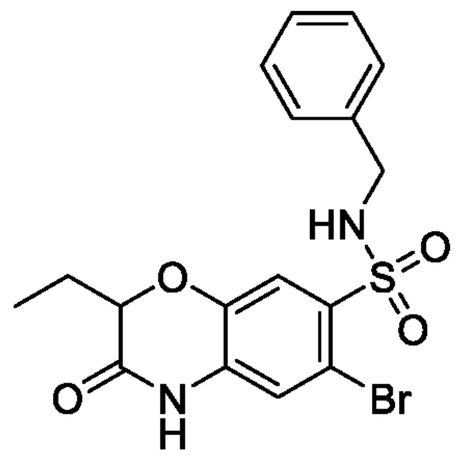
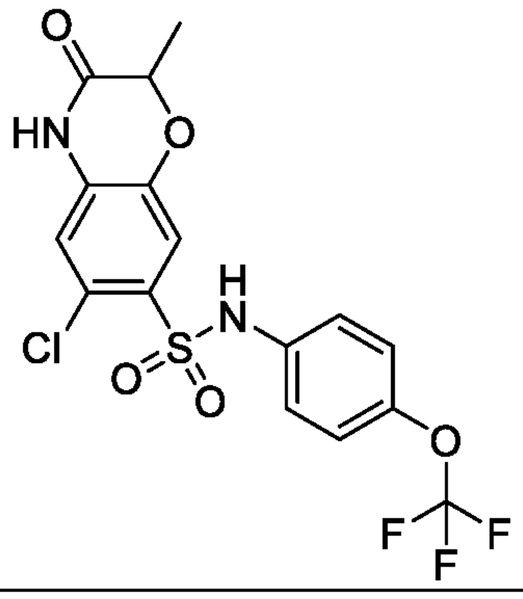
BC19162	ZE24-0005		+	+
BC19163	ZE24-0007		+	+
BC19164	ZE24-0008		++++	+
BC19165	ZE24-0012		+++	+
BC19166	ZE24-0014		++++	+

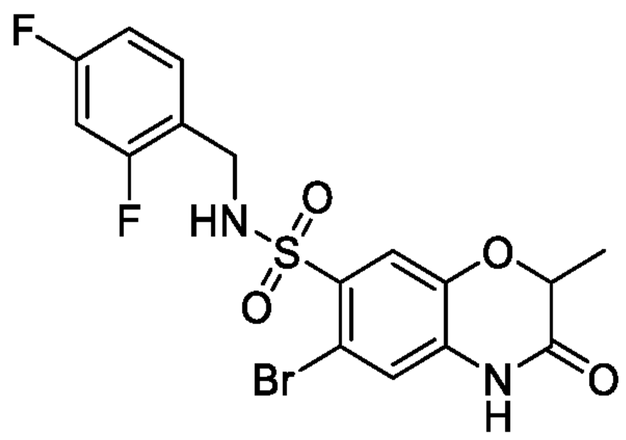
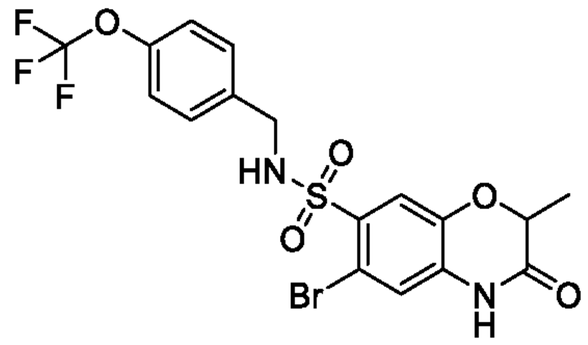
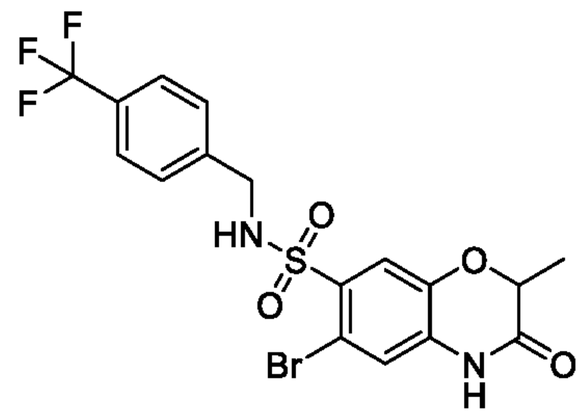
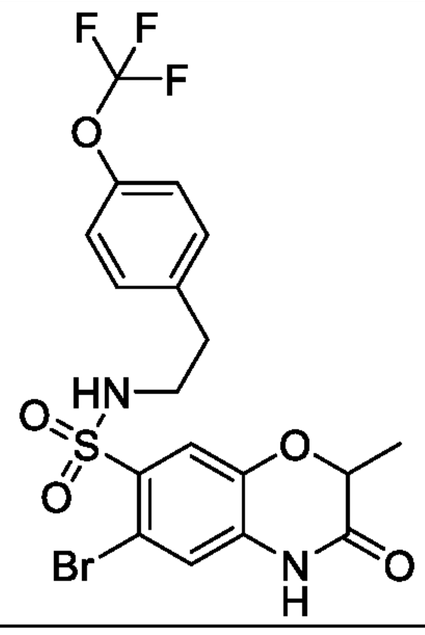
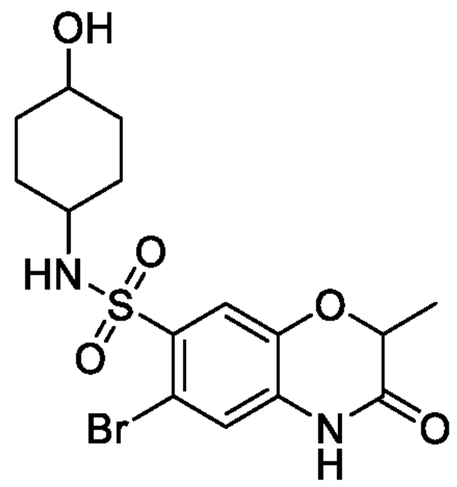
BC19167	ZE24-0016		+++	+
BC19206	ZE24-0018		++	+
BC19207	ZE24-0023		+	+
BC19208	ZE24-0024		+	+
BC19209	ZE24-0025		++	+
BC19210	ZE24-0028		++++	+

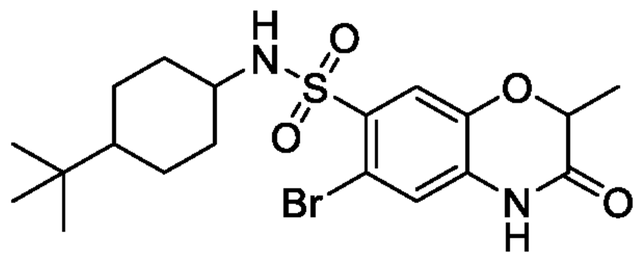
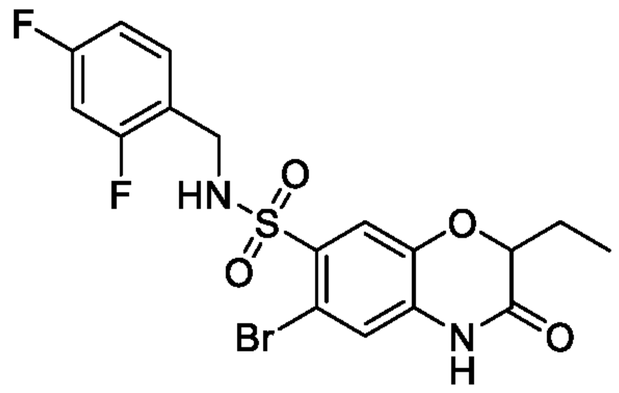
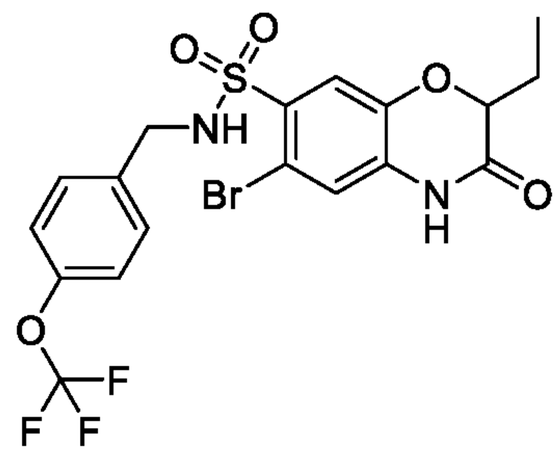
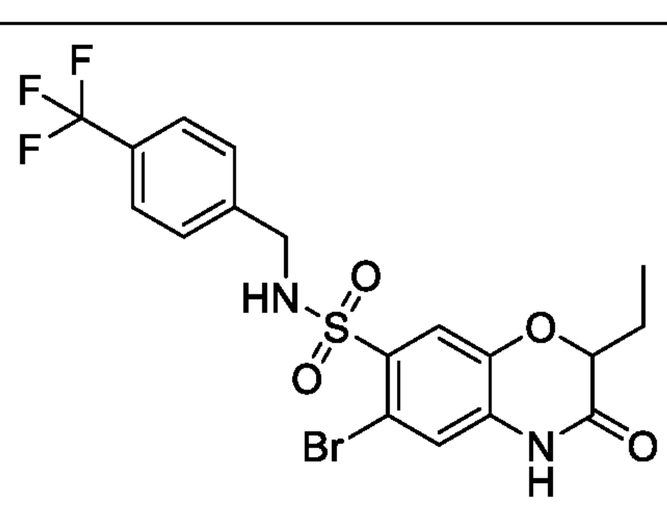
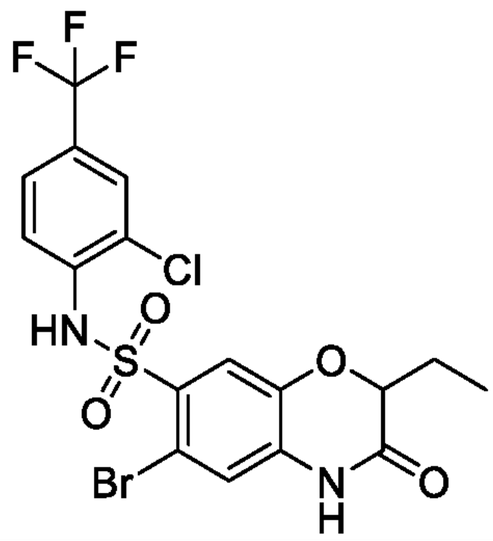
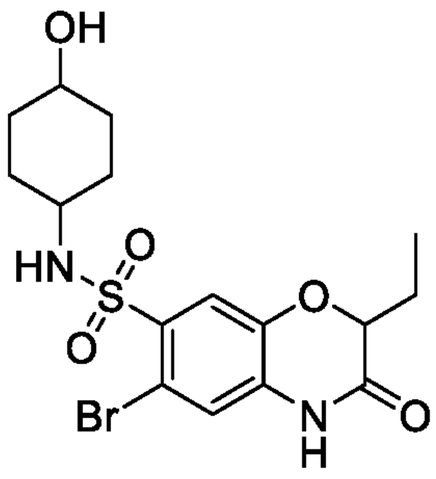
BC19211	ZE24-0029		+++	+
BC19212	ZE24-0030		++++	+
BC19213	ZE24-0031		+++	+
BC19214	ZE24-0032		+	+
BC19215	ZE24-0033		++	+
BC19216	ZE24-0034		++++	+

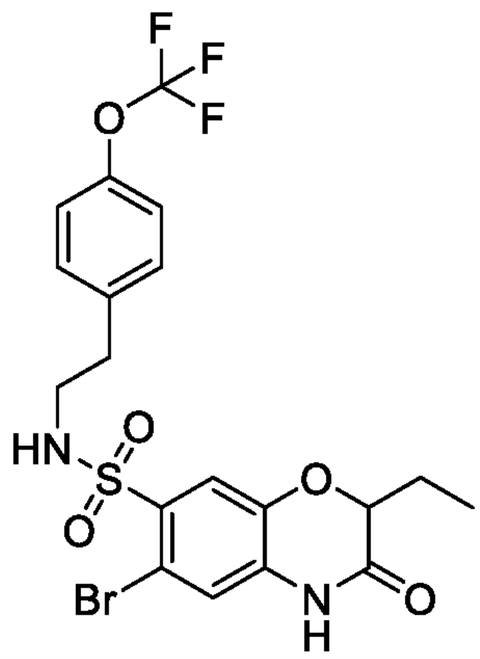
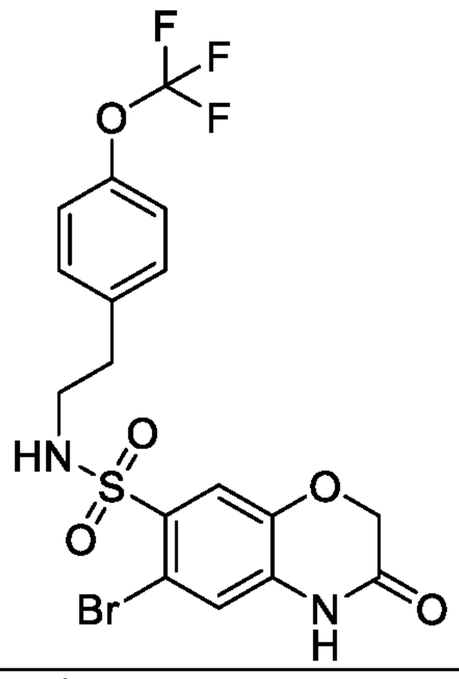
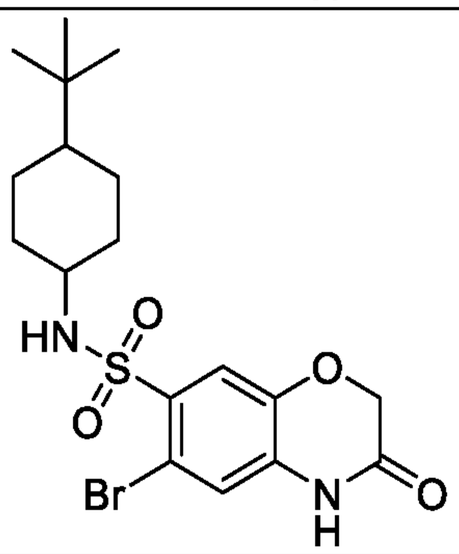
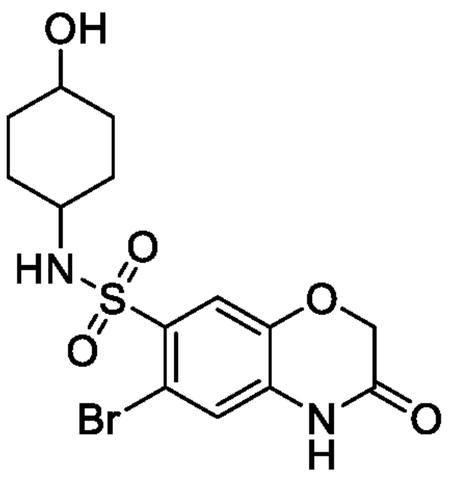
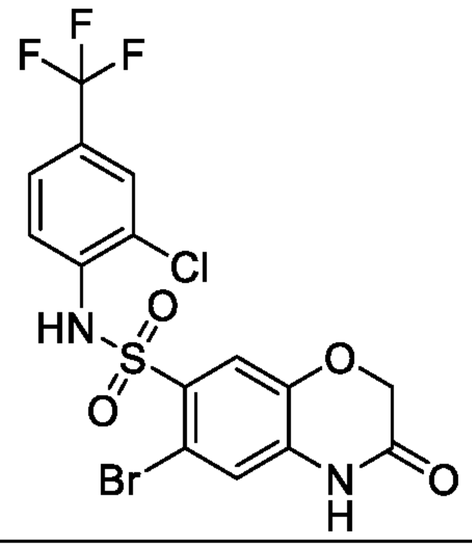
BC19217	ZE24-0039		+	+
BC19218	ZE24-0040		+	+
BC19219	ZE24-0041		+	+
BC19220	ZE24-0043		+++	+
BC19221	ZE24-0044		+++	+
BC19222	ZE24-0045		+	+

BC19223	ZE24-0047		+	+
BC19224	ZE24-0048		+++	+
BC19280	ZE24-0020		++	+
BC19281	ZE24-0021		+++	+
BC19282	ZE24-0027		+++	+
BC19283	ZE24-0036		+++	+

BC19284	ZE24-0037		++++	+
BC19285	ZE24-0038		++	+
BC19286	ZE24-0042		++++	+
BC19287	ZE24-0046		++	+
BC19354	ZE24-0019		++++	+

BC19356	ZE24-0082		++	+
BC19357	ZE24-0083		+	+
BC19358	ZE24-0084		+	+
BC19359	ZE24-0086		+	+
BC19360	ZE24-0087		+	+

BC19361	ZE24-0088		+	+
BC19368	ZE24-0096		+	+
BC19369	ZE24-0097		+	+
BC19370	ZE24-0098		+	+
BC19371	ZE24-0099		++	+
BC19372	ZE24-0100		+	+

BC19373	ZE24-0102		+	+
BC19387	ZE24-0117		+	+
BC19388	ZE24-0118		+	+
BC19389	ZE24-0119		+	+
BC19390	ZE24-0120		++	+

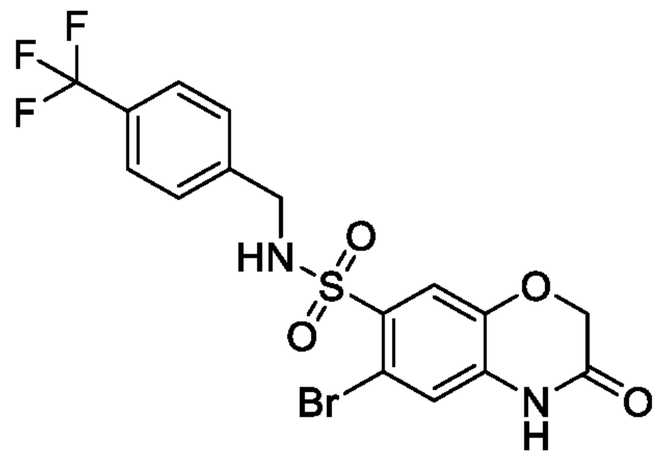
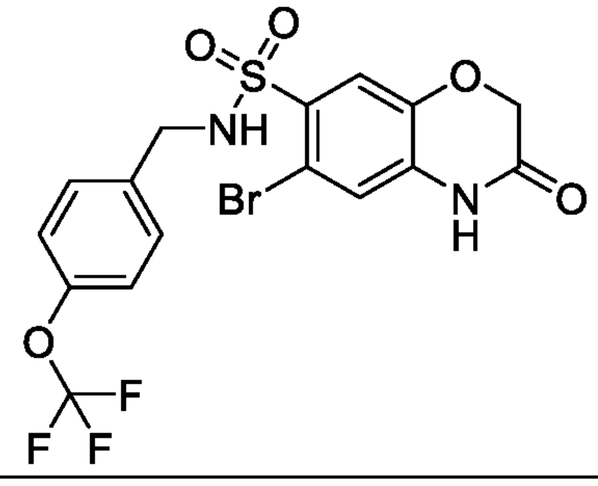
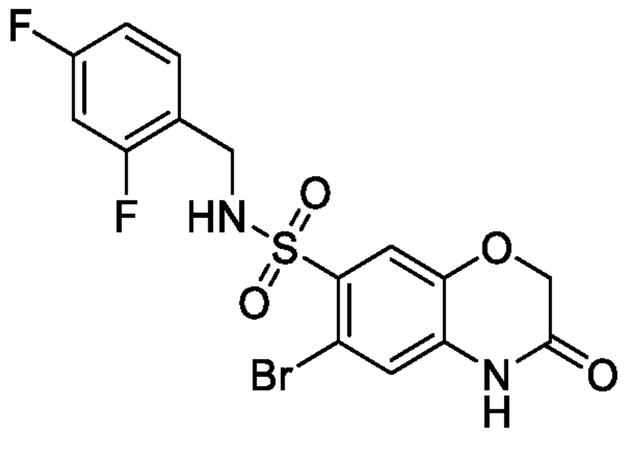
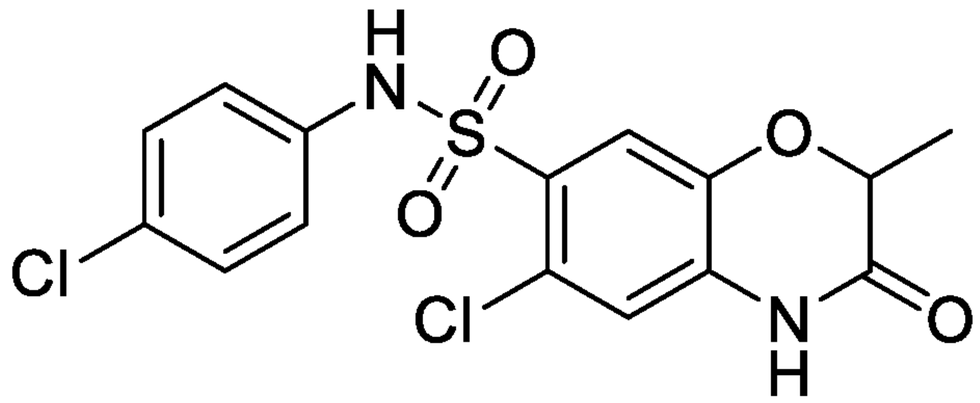
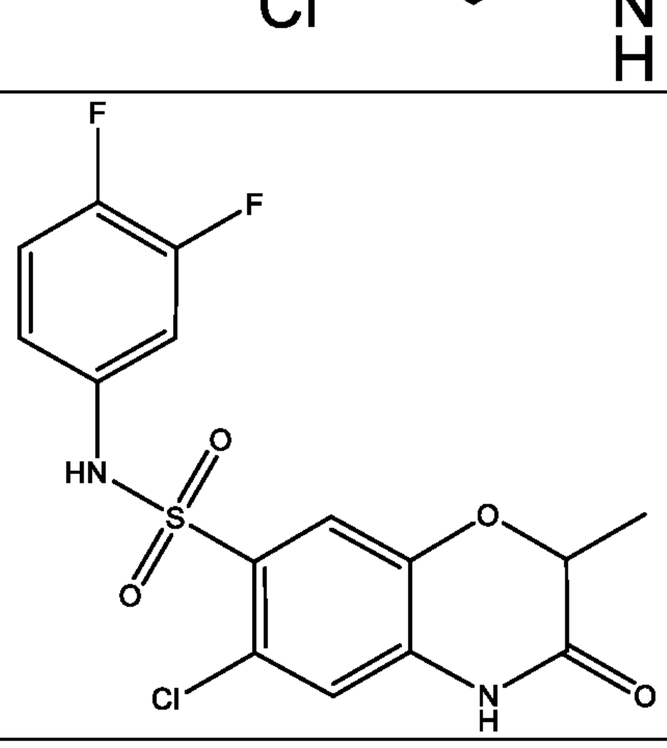
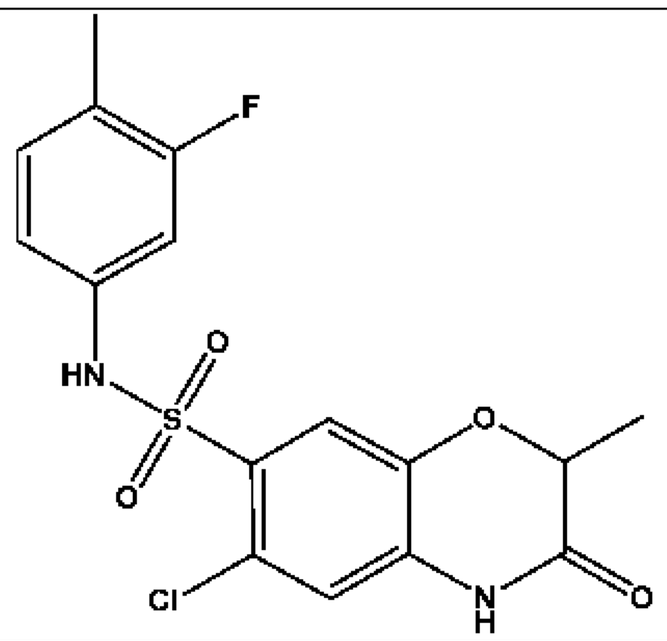
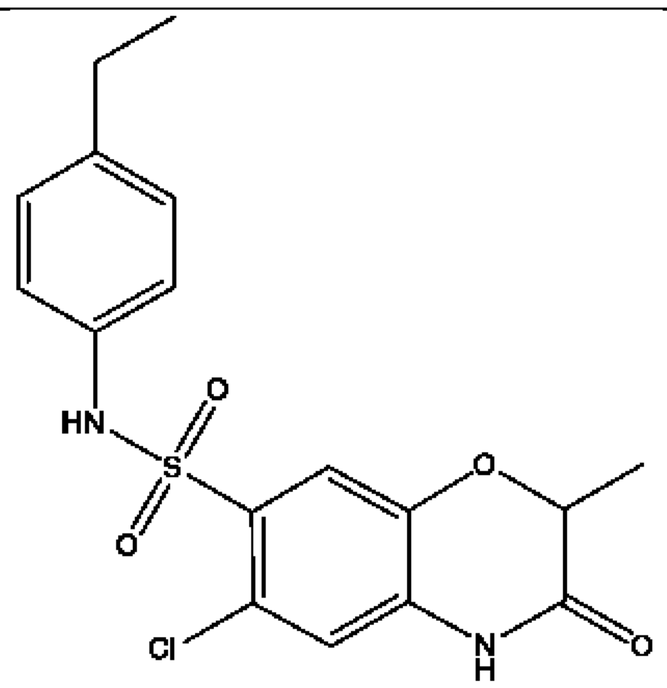
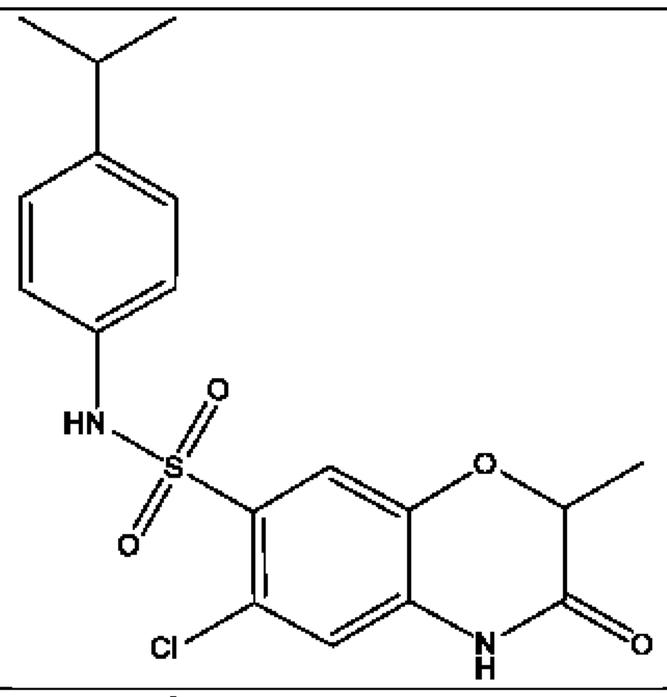
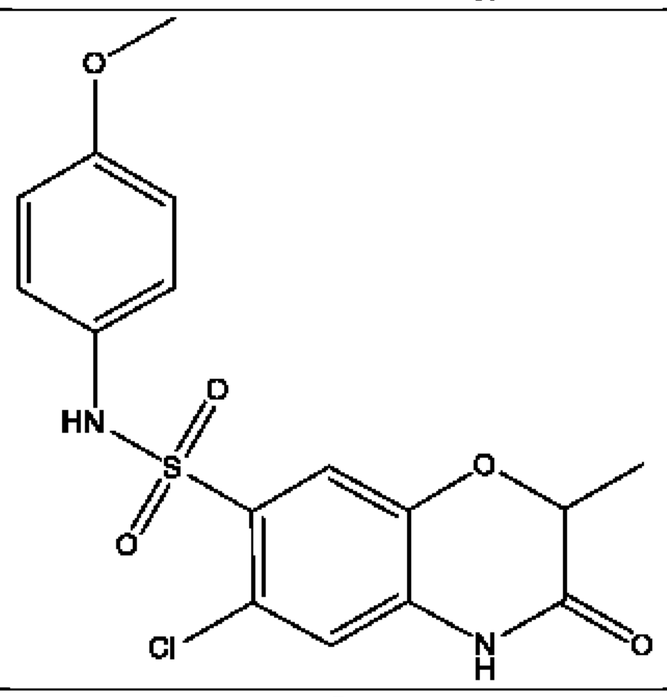
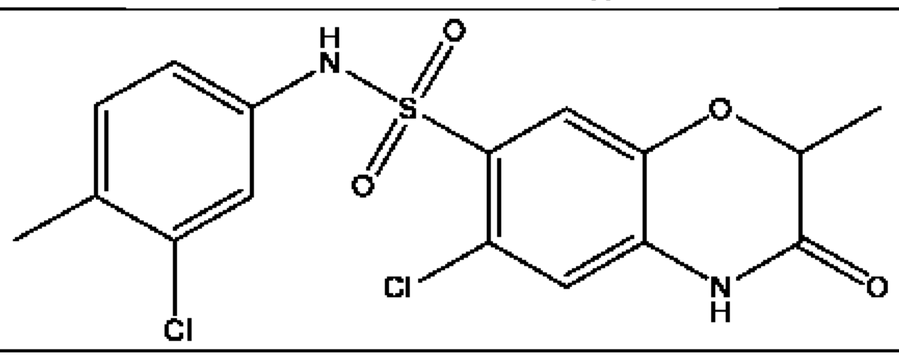
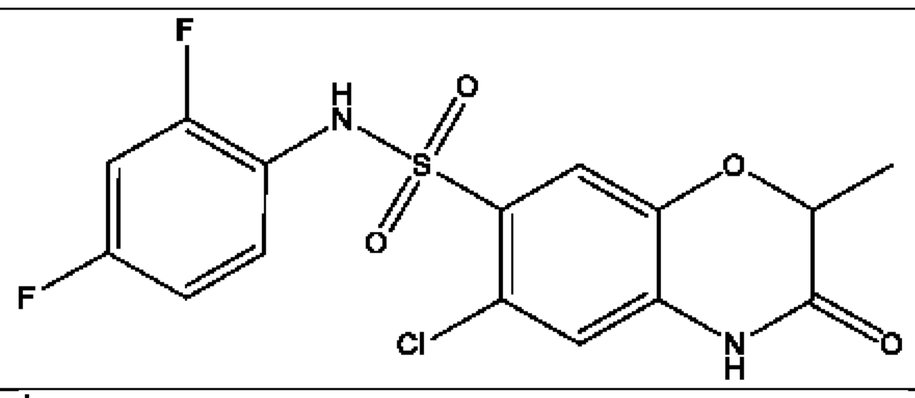
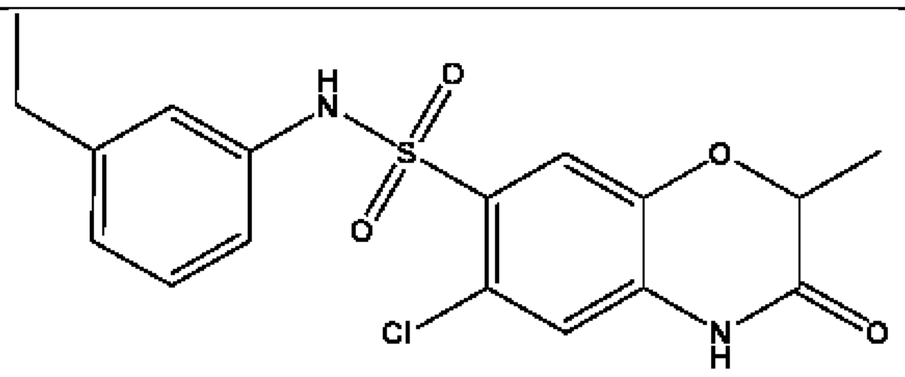
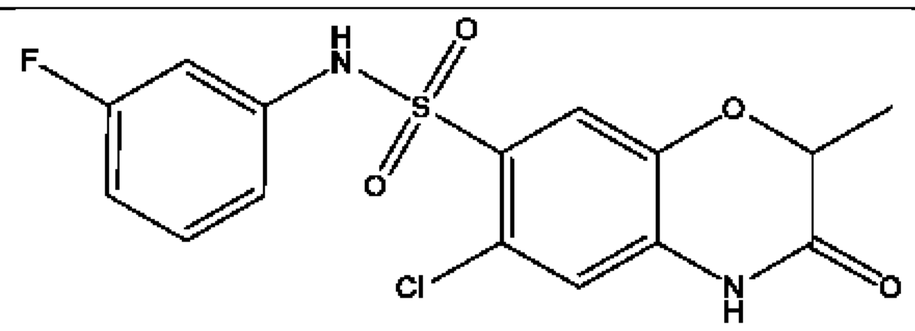
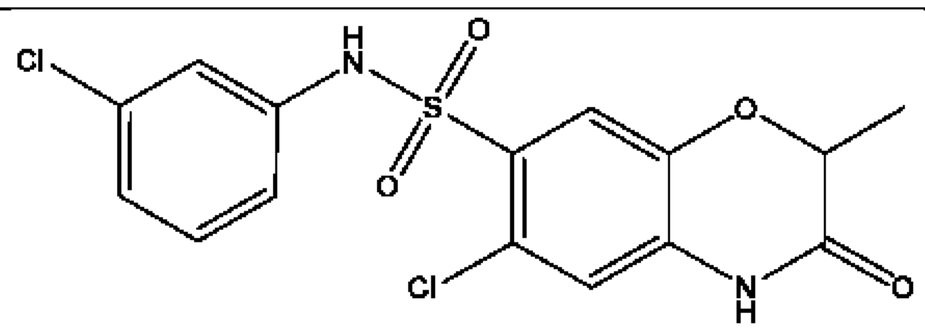
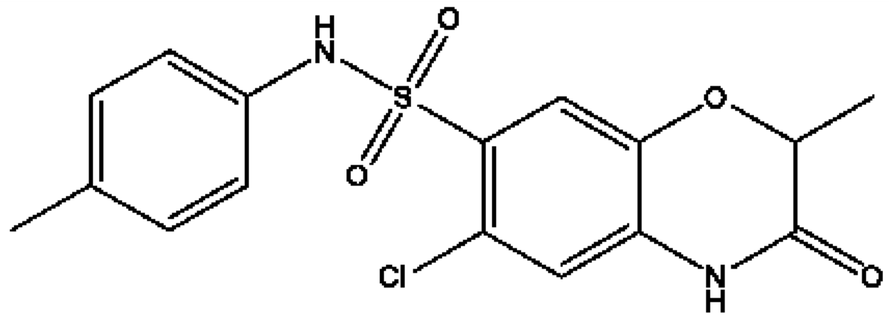
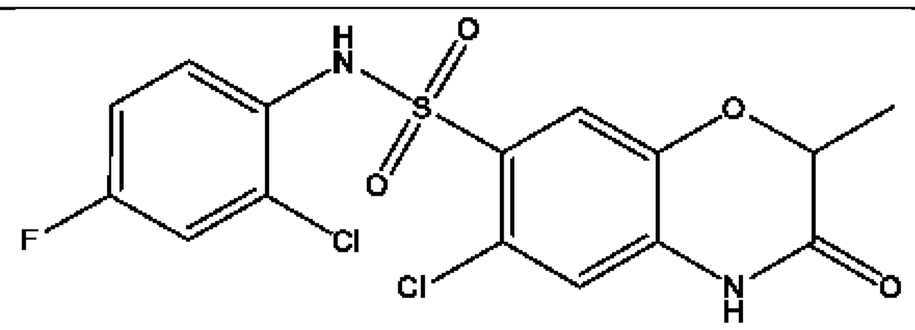
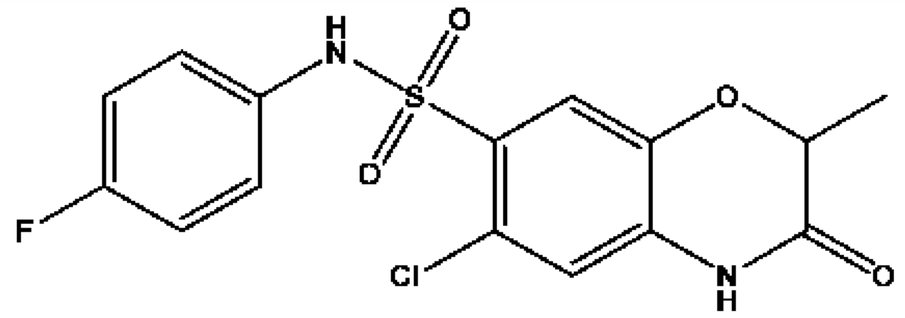
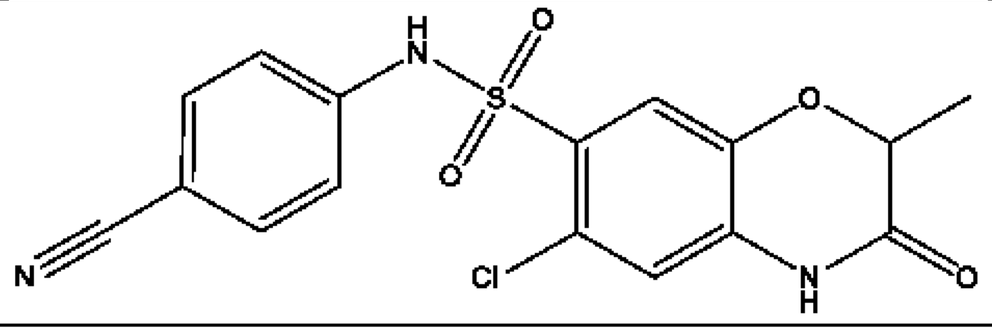
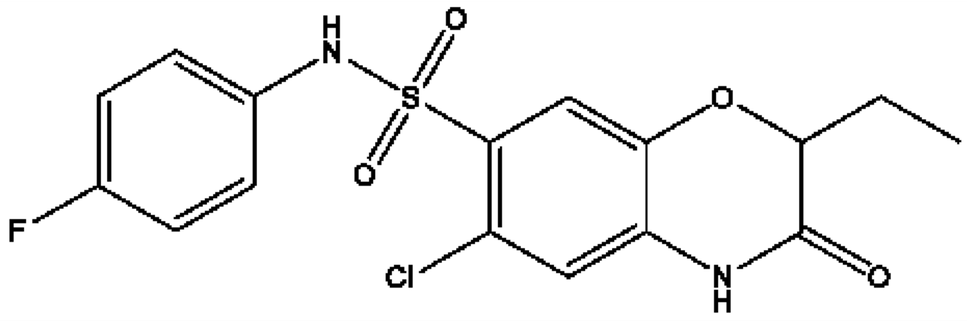
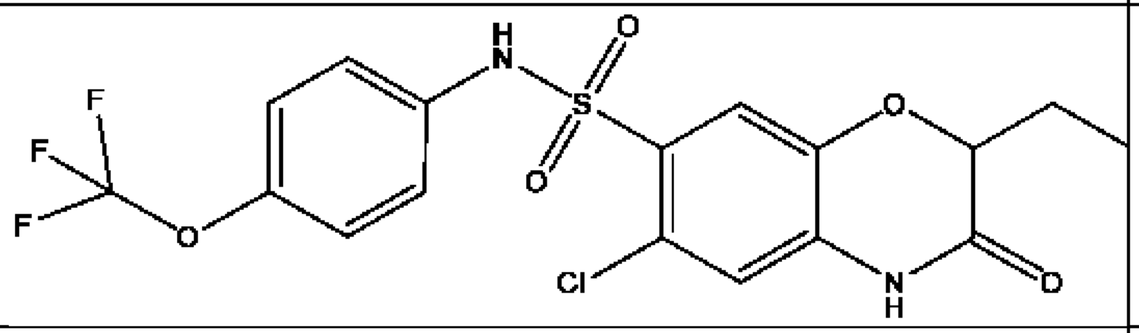
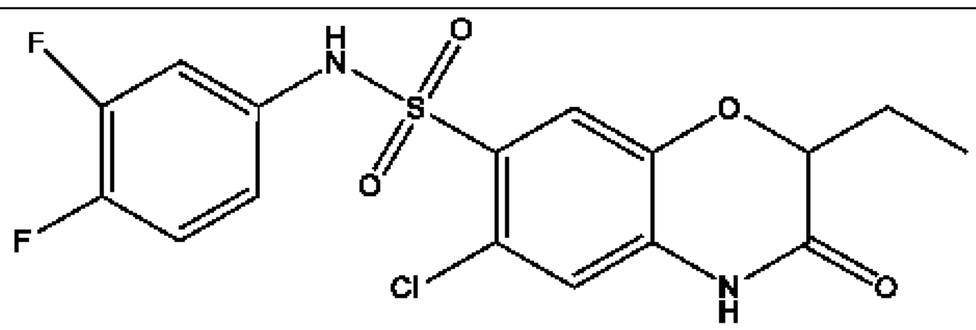
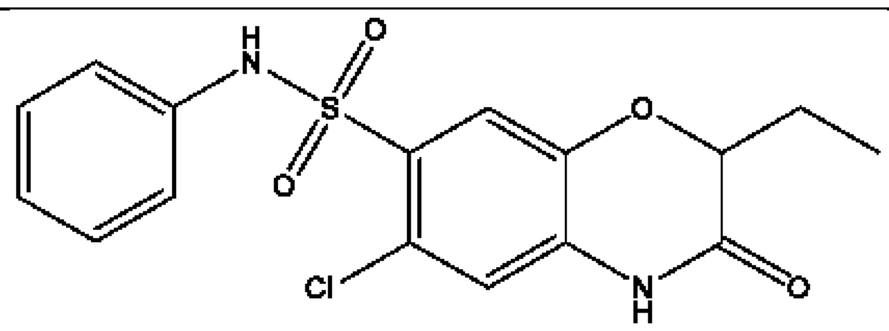
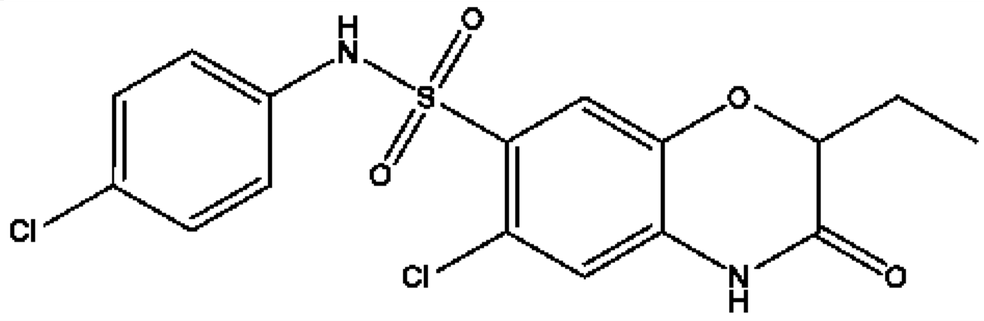
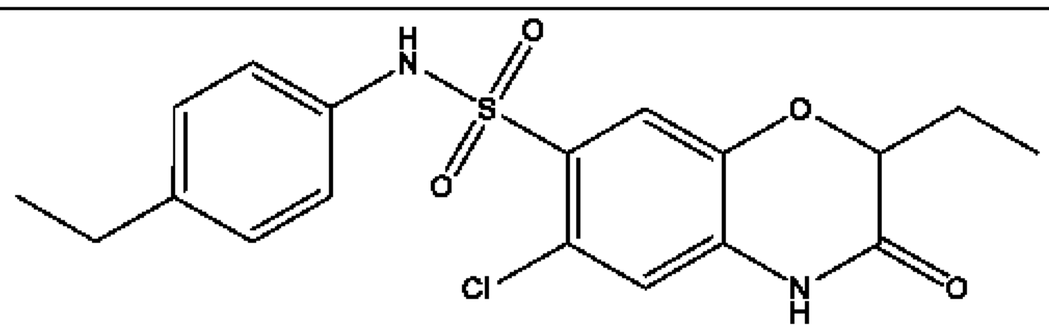
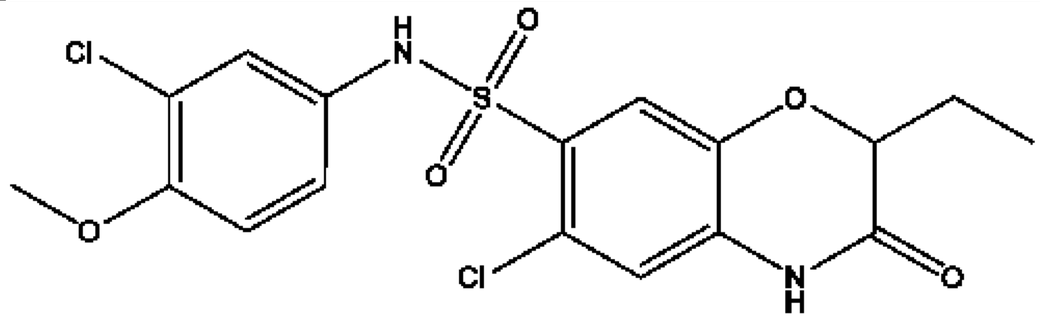
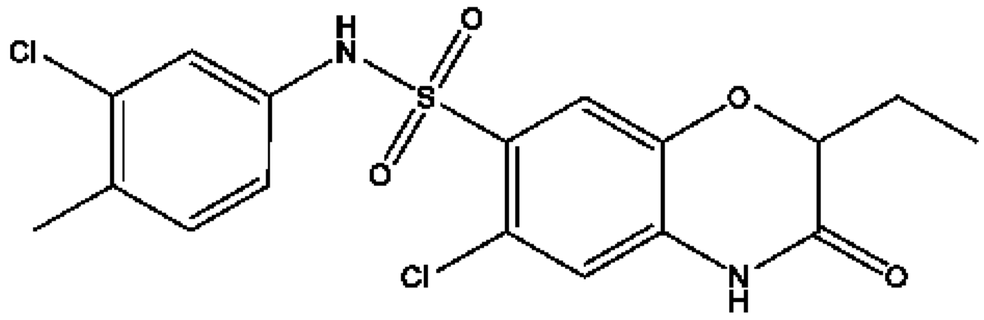
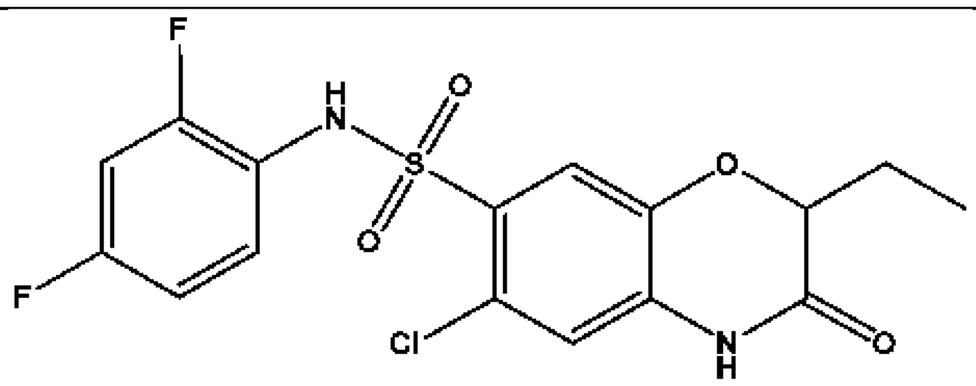
BC19391	ZE24-0121		+	+
BC19392	ZE24-0122		+	+
BC19393	ZE24-0123		+	+

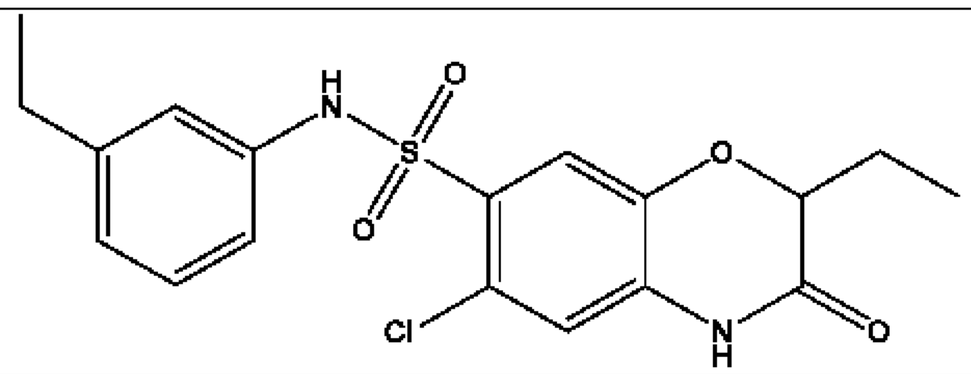
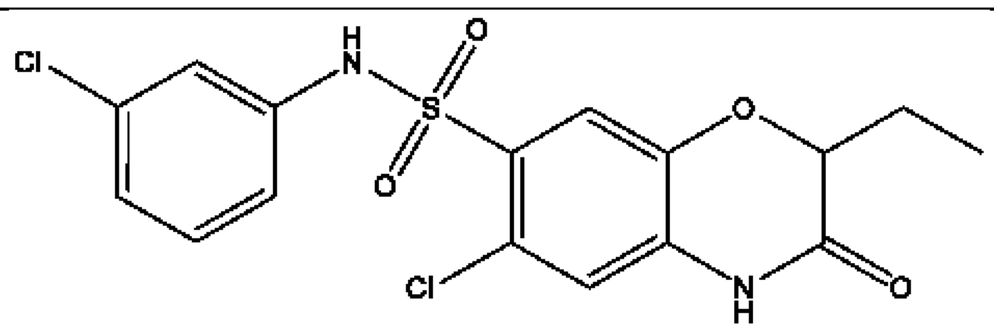
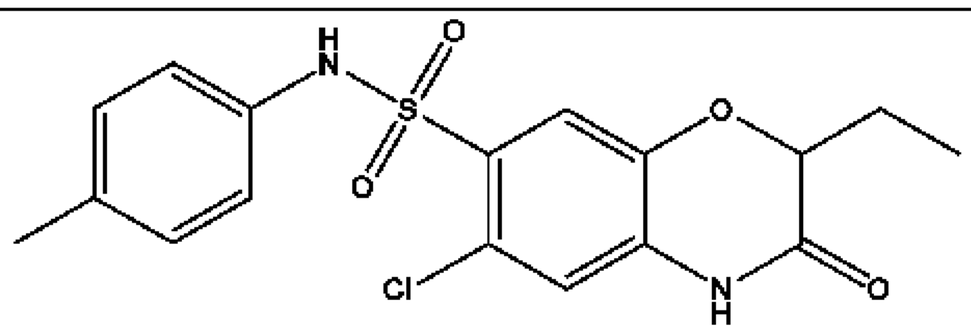
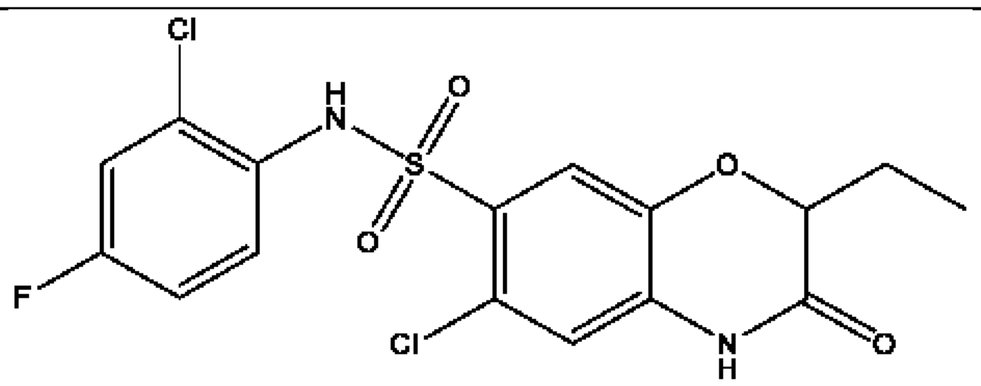
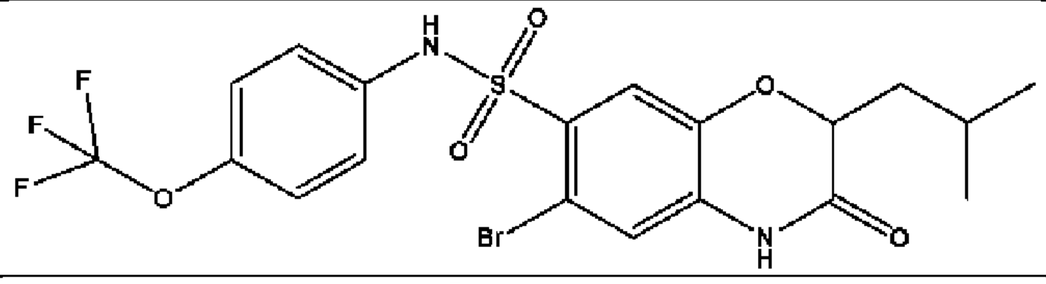
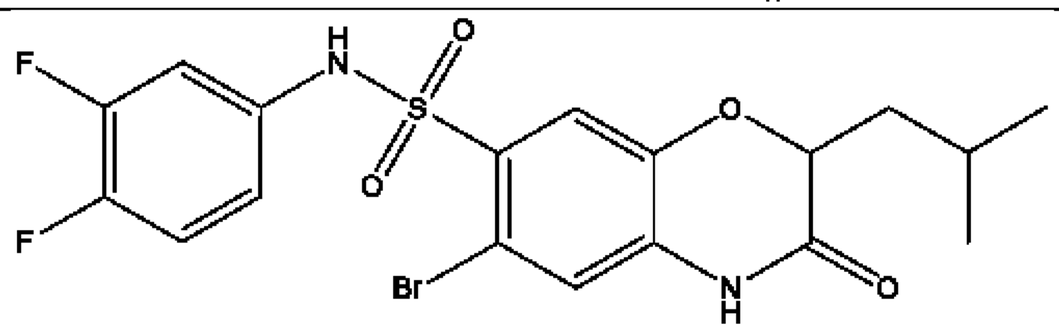
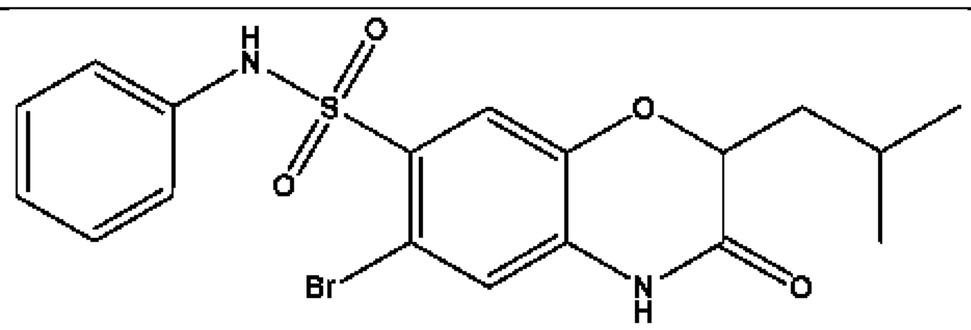
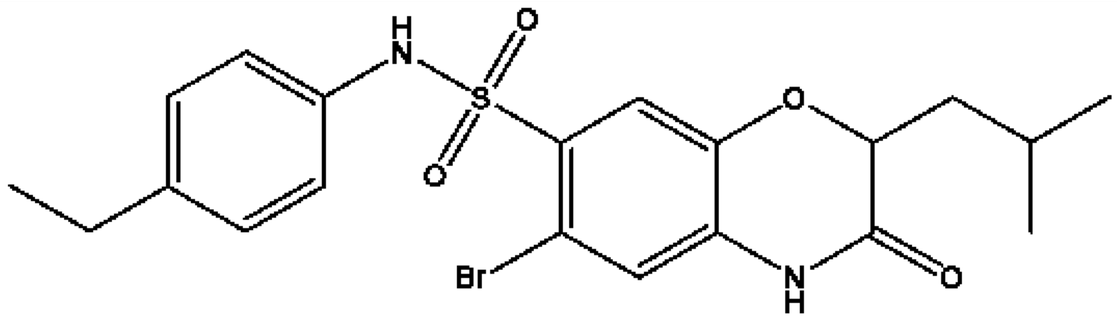
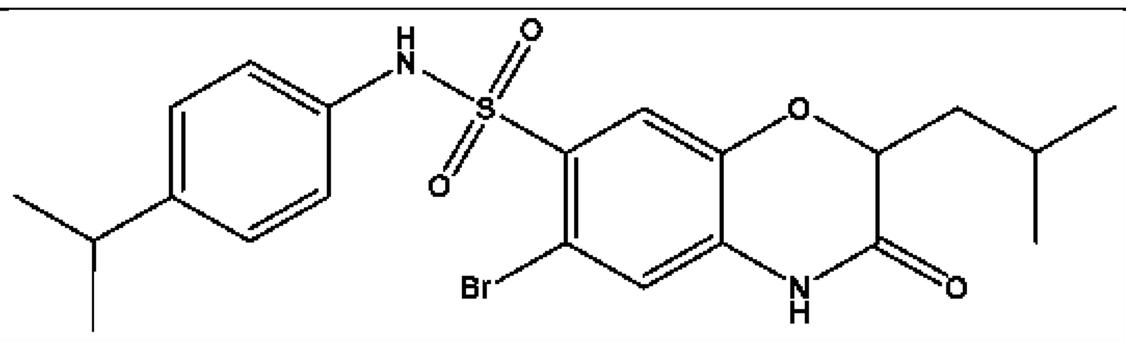
Table 2c-2

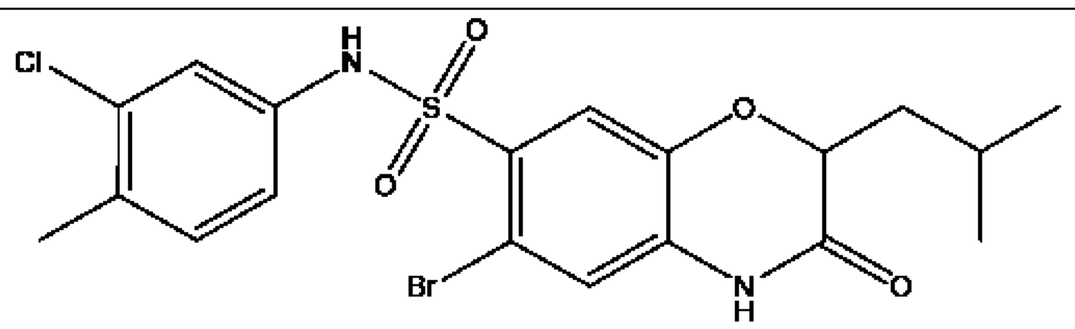
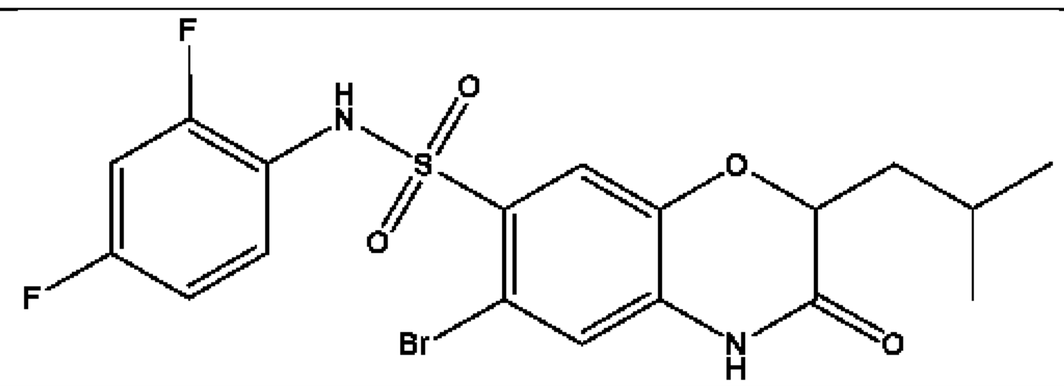
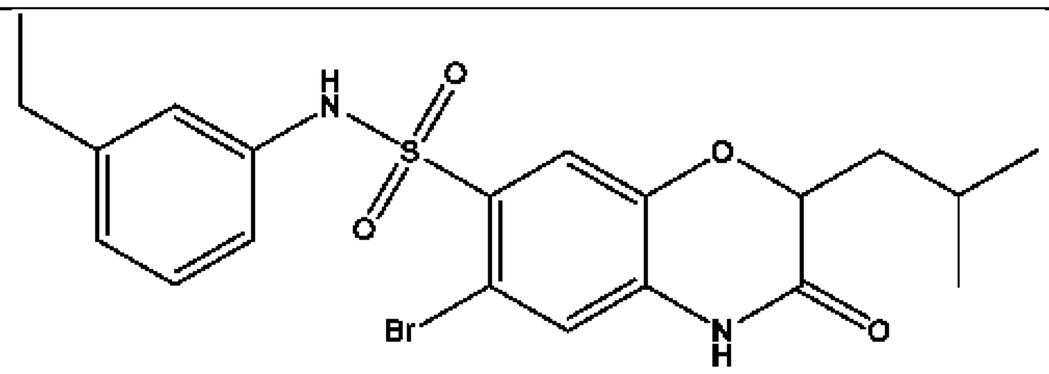
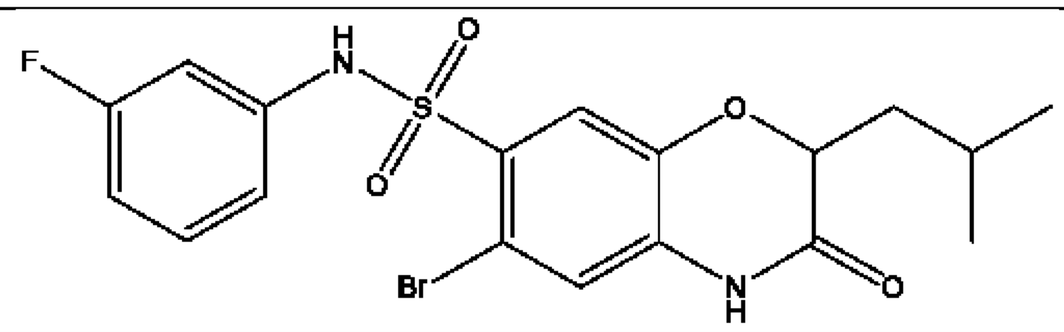
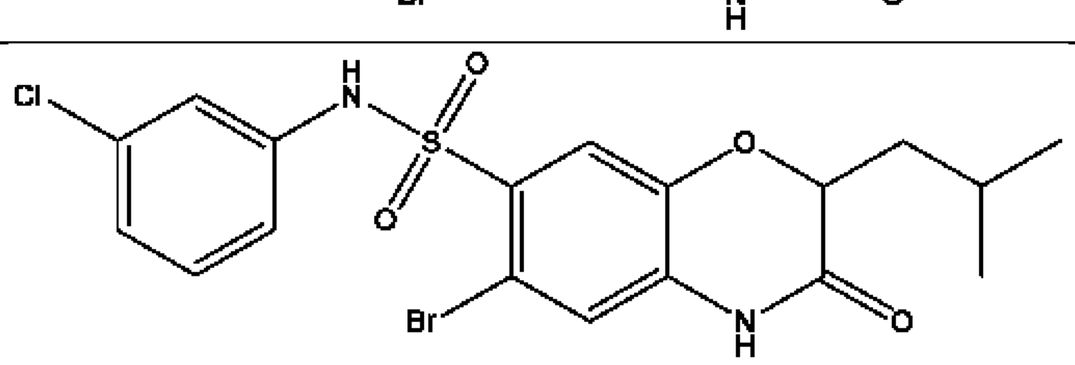
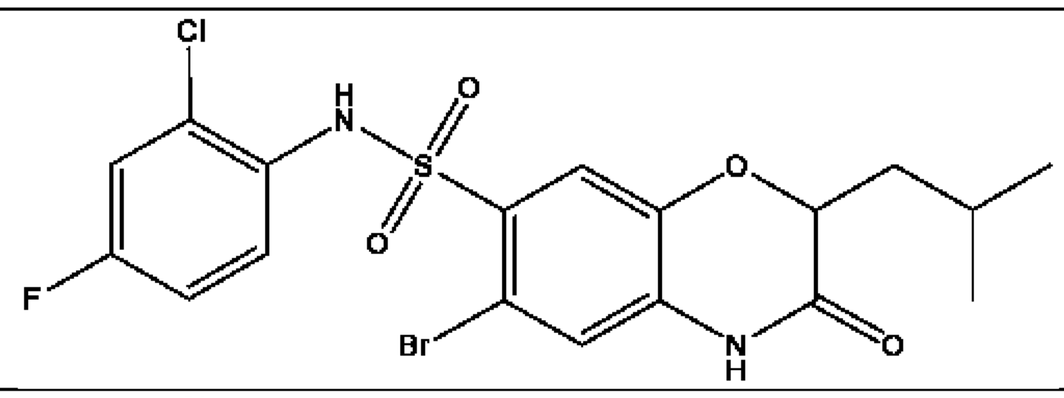
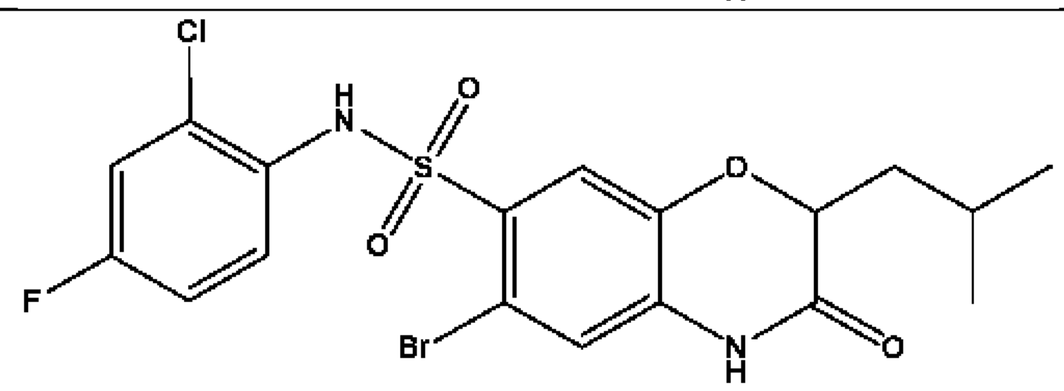
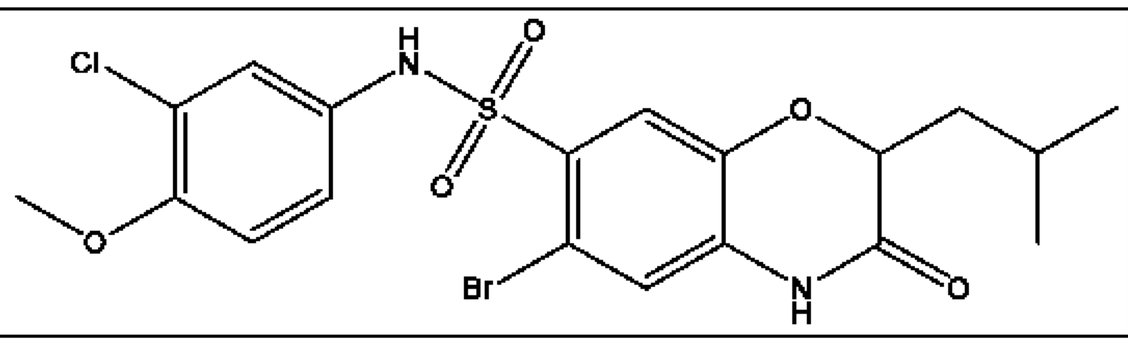
BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19696		+++	+
BC19698		++++	+

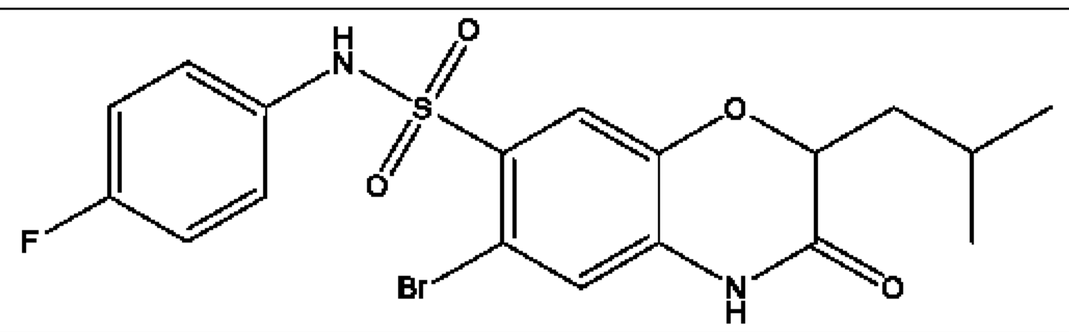
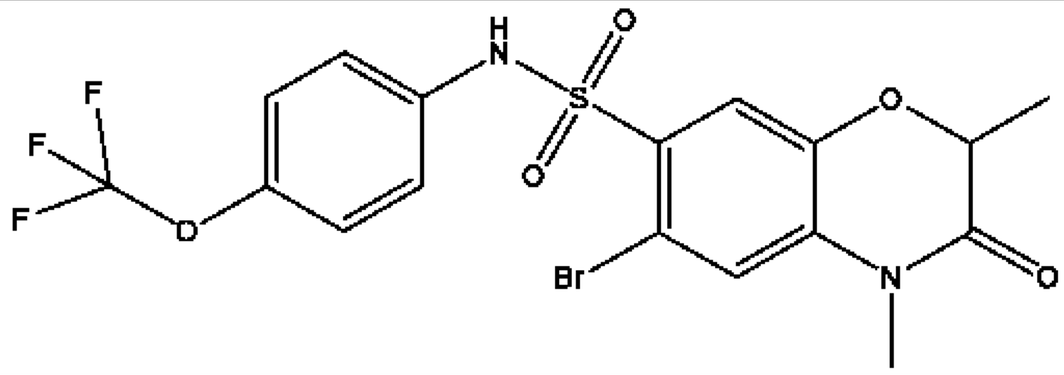
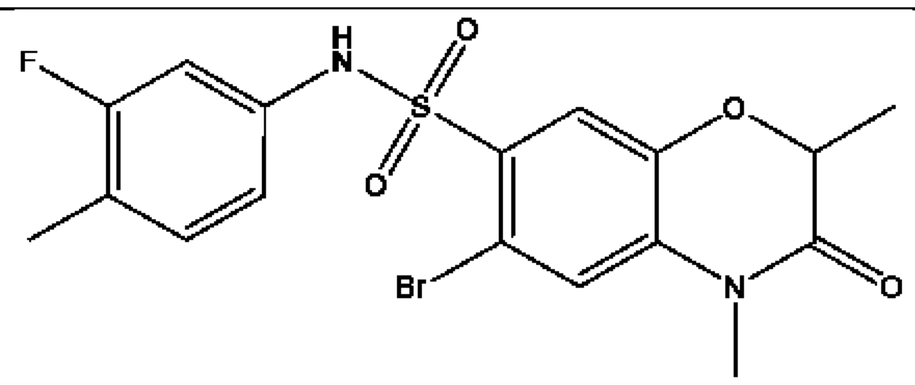
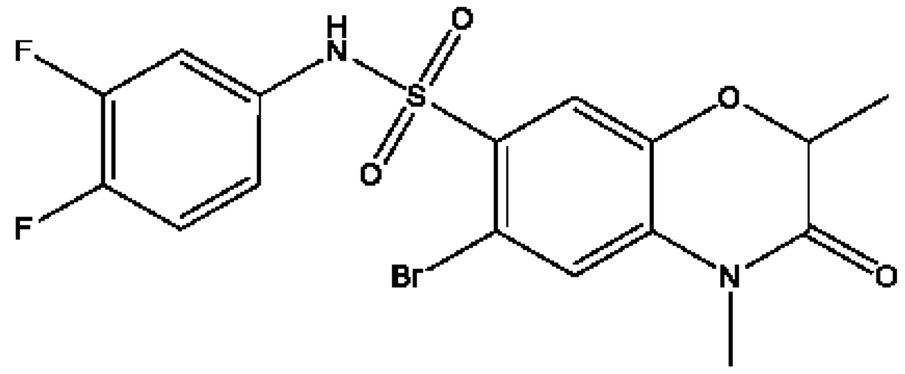
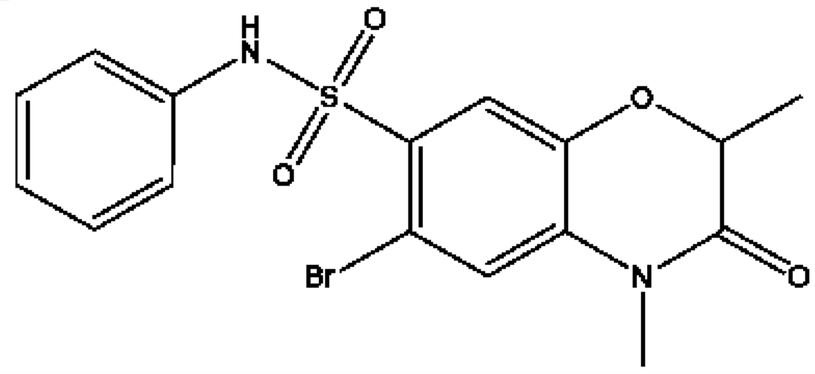
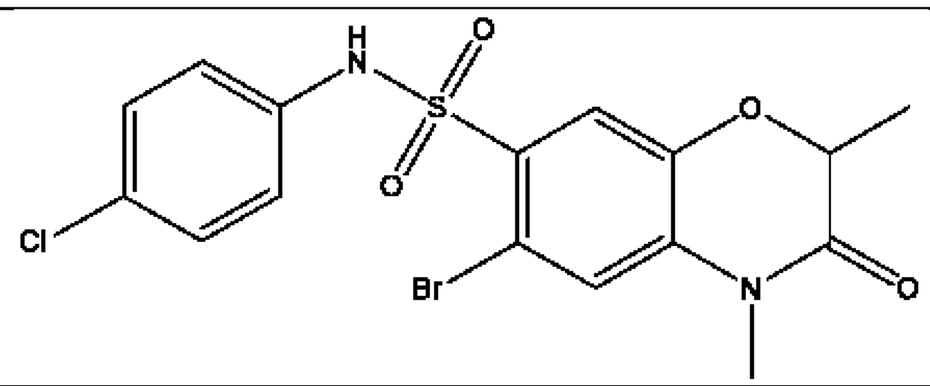
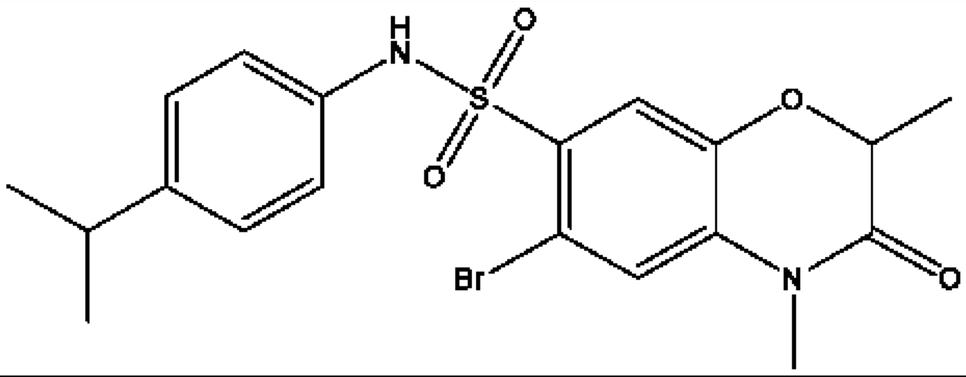
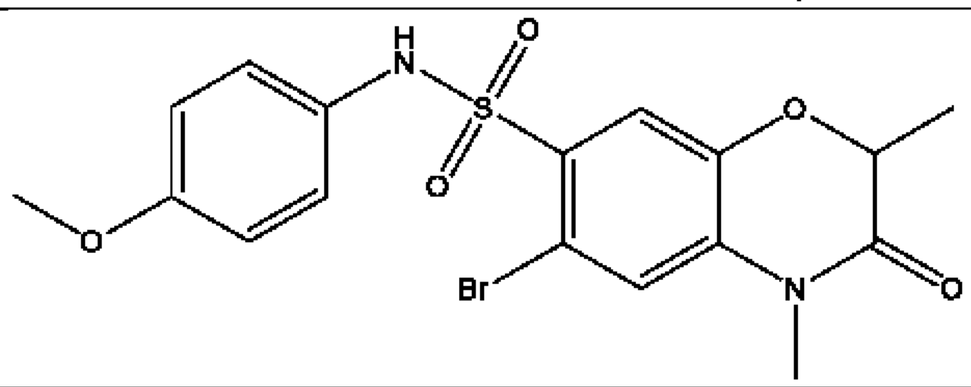
BC19700		++++	+
BC19702		++++	+
BC19704		+	+
BC19706		++++	+
BC19708		++++	+

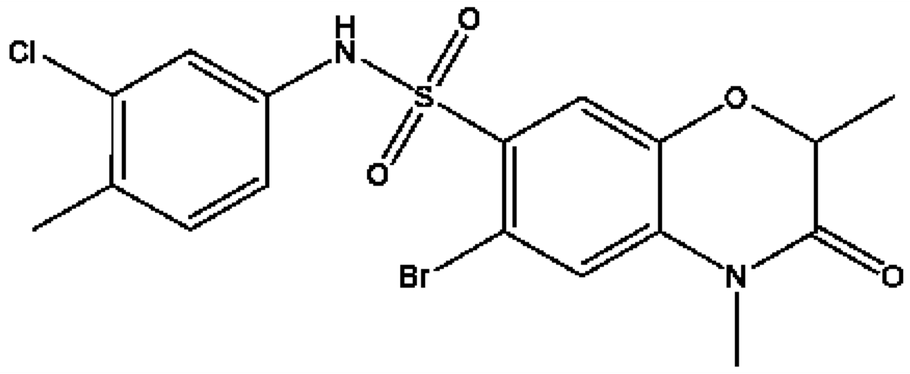
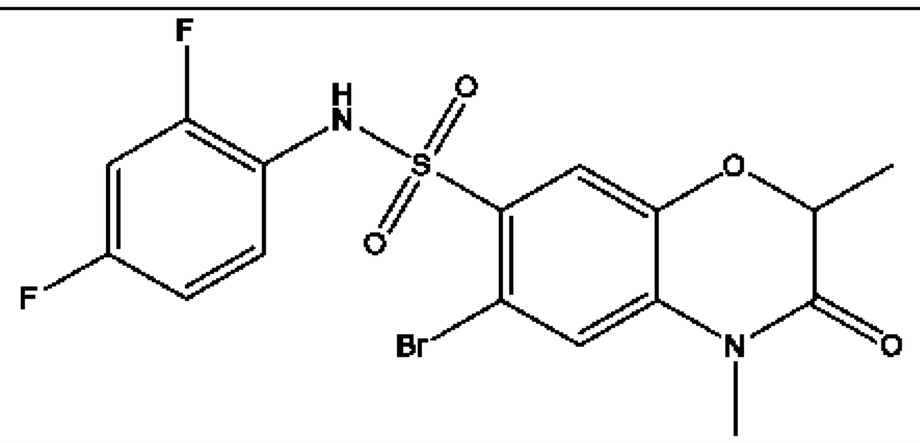
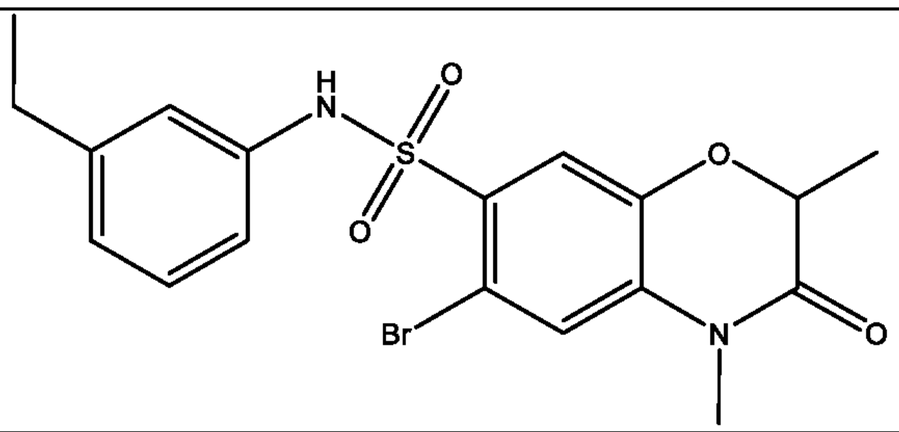
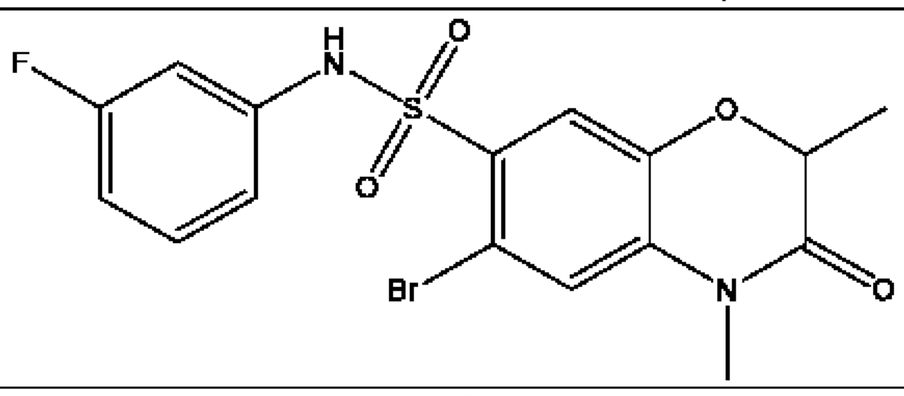
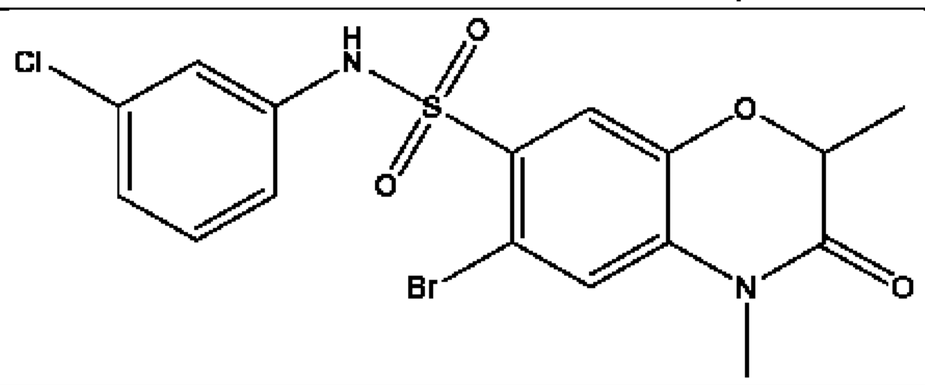
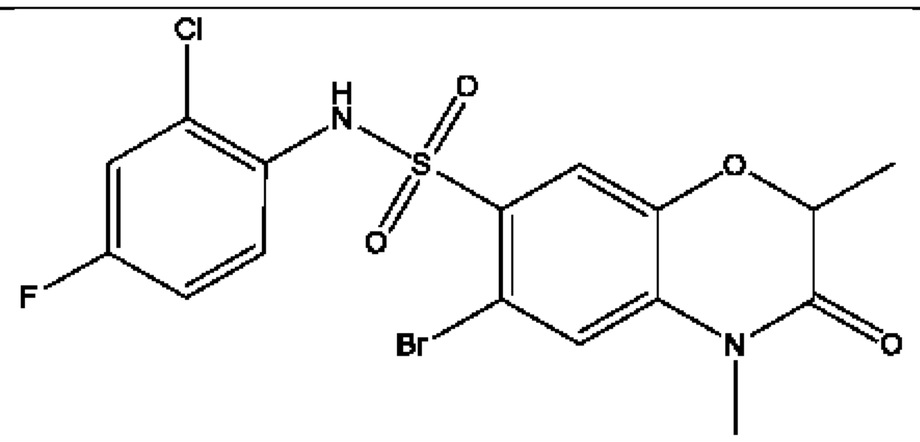
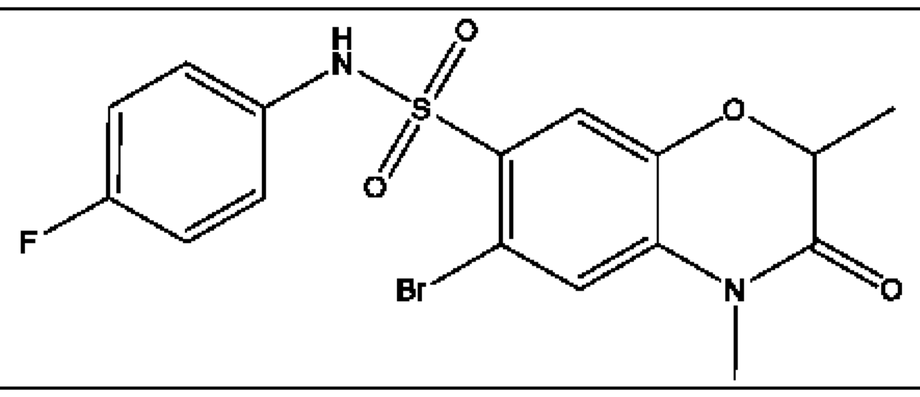
BC19709		++++	+
BC19711		++++	+
BC19713		+++	++
BC19715		++++	++
BC19717		++++	+
BC19719		+++	+
BC19721		++++	++
BC19729		+++	+

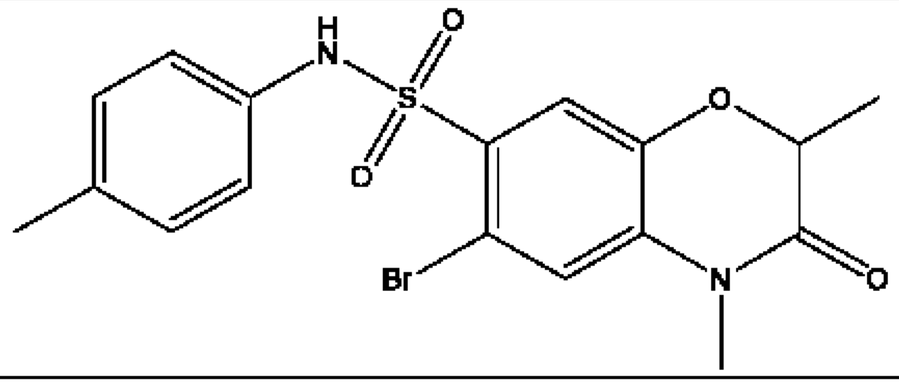
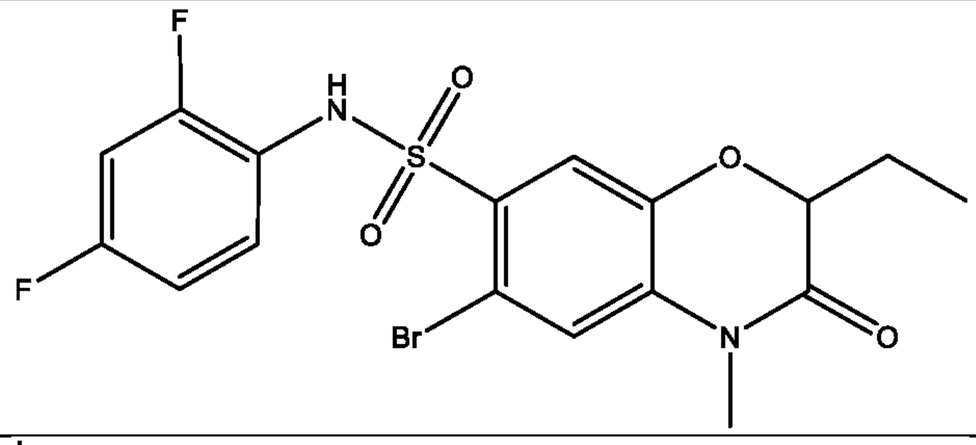
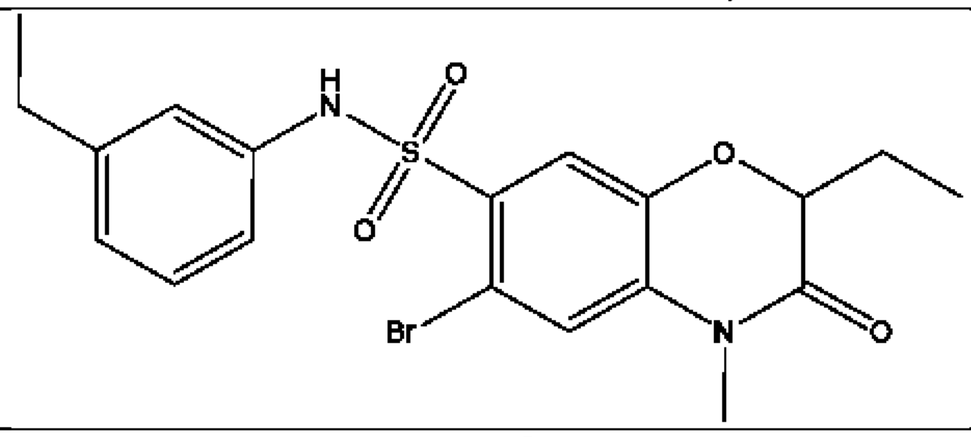
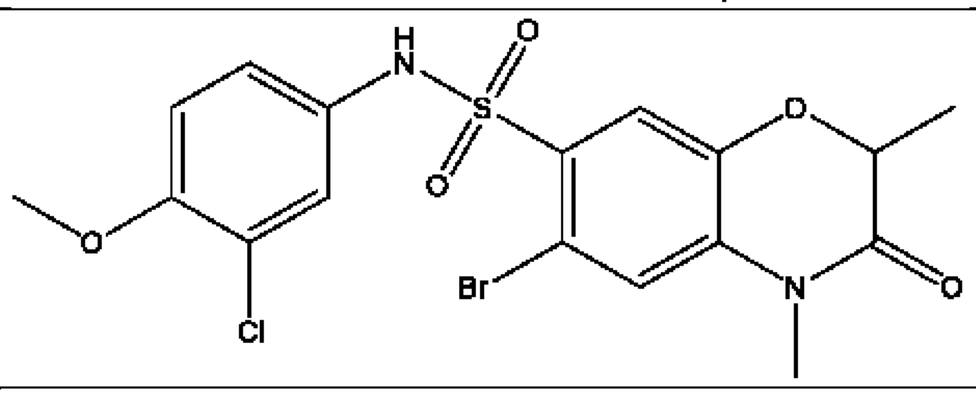
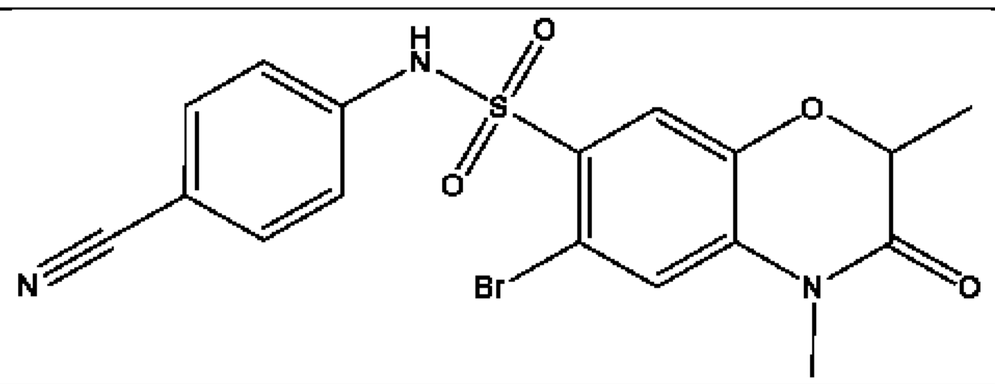
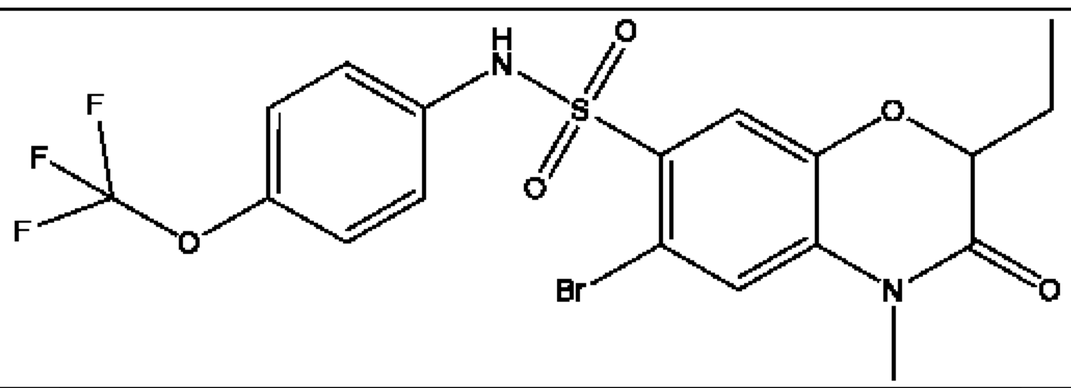
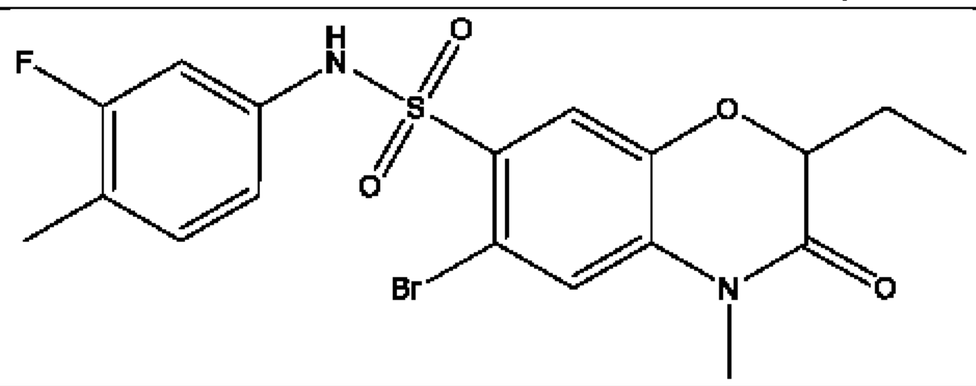
BC19731		+++	+
BC19733		++++	+
BC19735		++++	+
BC19737		+++	+
BC19739		++++	+
BC19741		++++	+
BC19743		++	+
BC19745		++	+
BC19747		+++	+

BC19749		+++	+
BC19751		+++	+
BC19753		++++	+
BC19755		++	+
BC19758		+++	+
BC19760		++++	+
BC19762		+++	+
BC19764		++	+
BC19766		++	++

BC19768		++	+
BC19770		+++	+
BC19772		+++	+
BC19774		+++	+
BC19776		+++	+
BC19778		+	+
BC19778		+	+
BC19780		++	+

BC19782		++	+
BC19784		++	+
BC19786		++	+
BC19788		++++	+
BC19790		++	+
BC19792		++	+
BC19794		++	+
BC19795		+	++

BC19797		++	++
BC19799		+++	++
BC19901		++	+
BC19903		+++	+
BC19905		++	+
BC19907		+	+
BC19910		++	+

BC19912		+	+
BC19914		+++	+
BC19916		++	+
BC19919		+	+
BC19920		+++	+
BC19922		++++	+
BC19924		++++	++

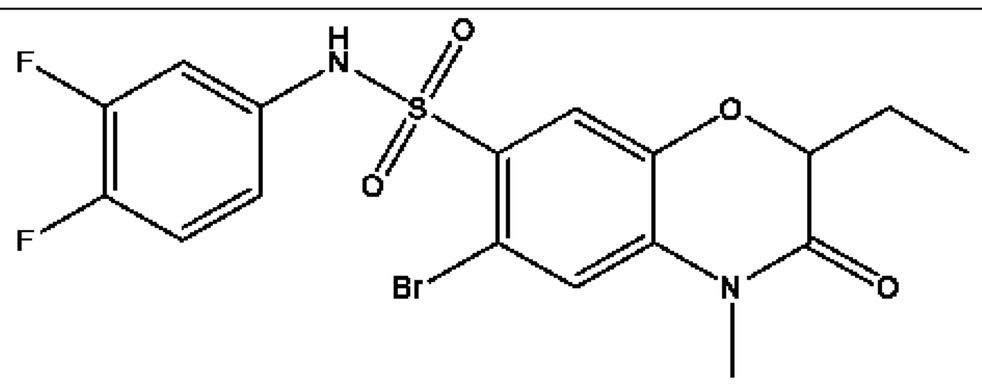
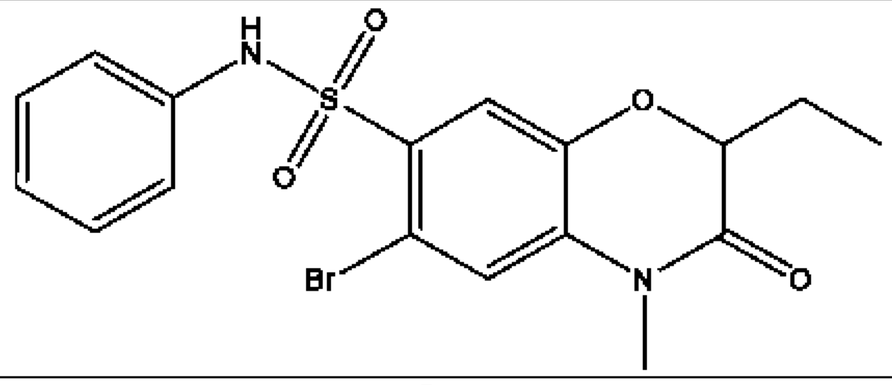
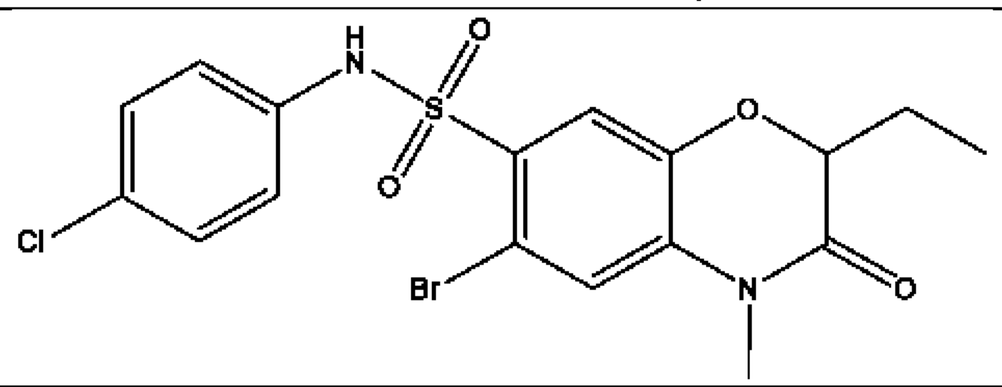
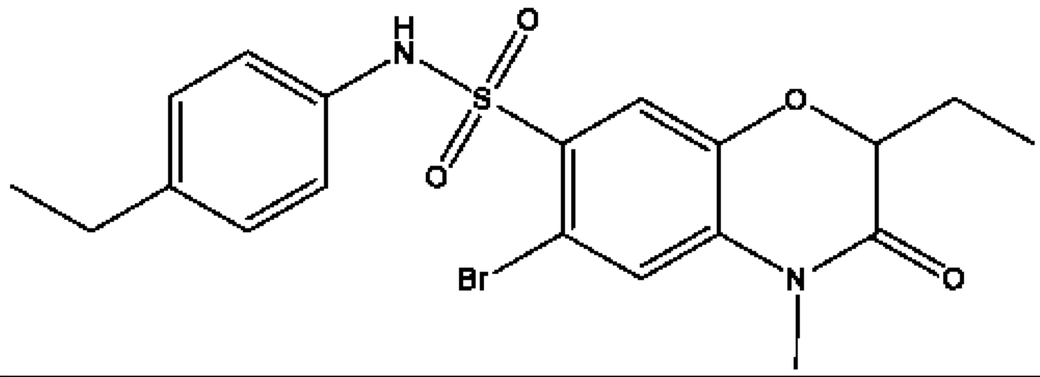
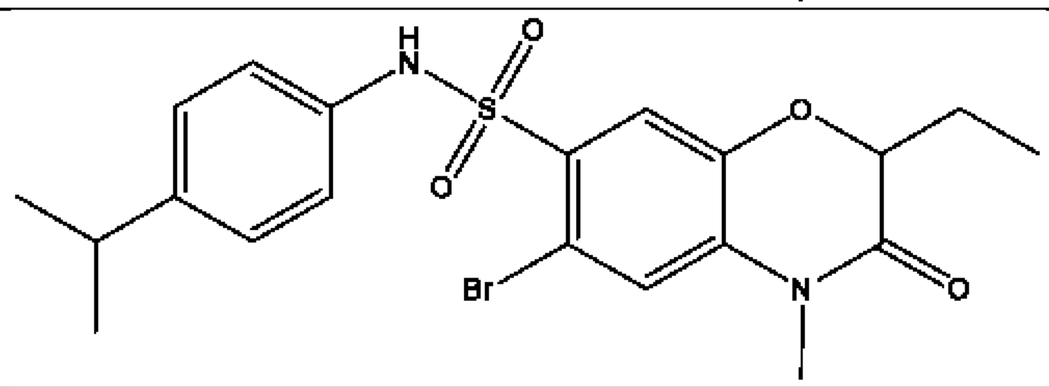
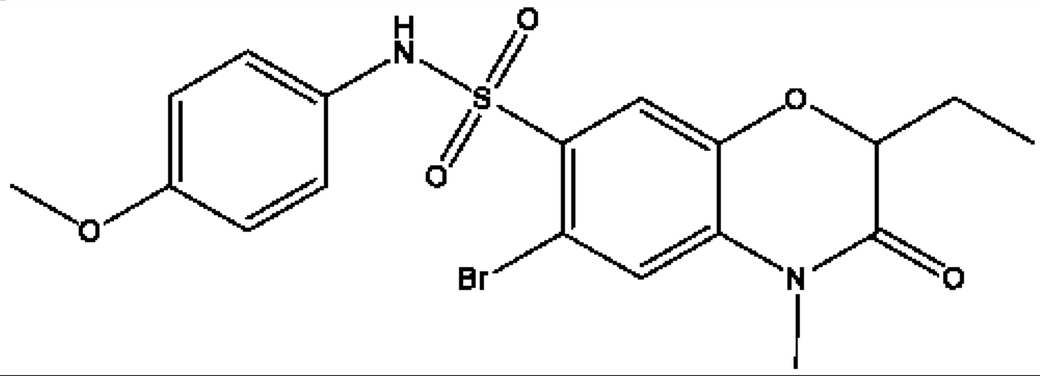
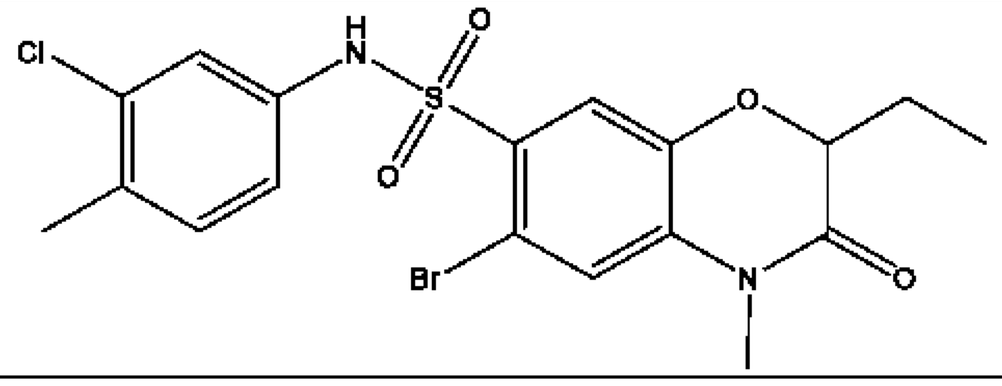
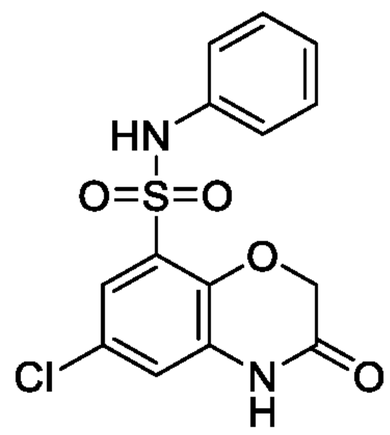
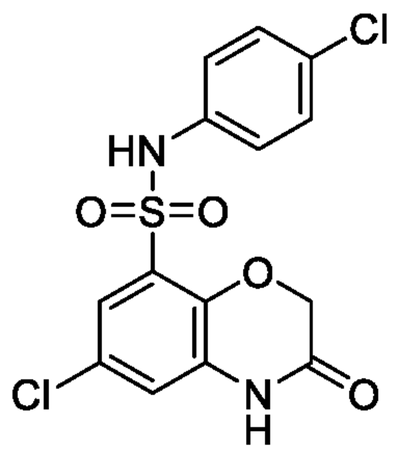
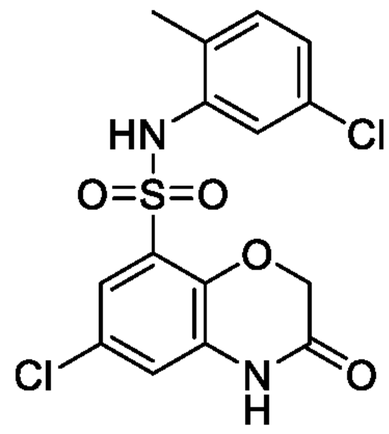
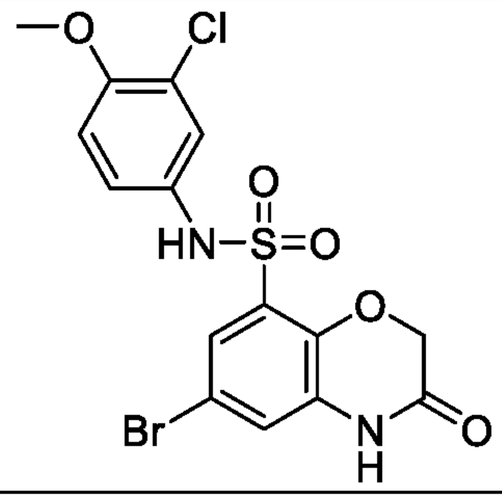
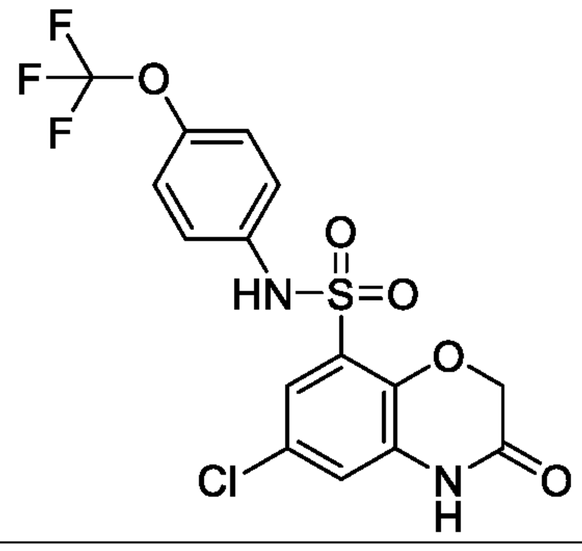
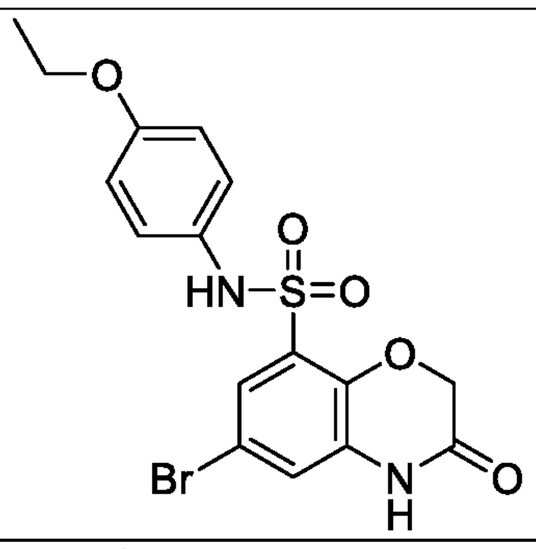
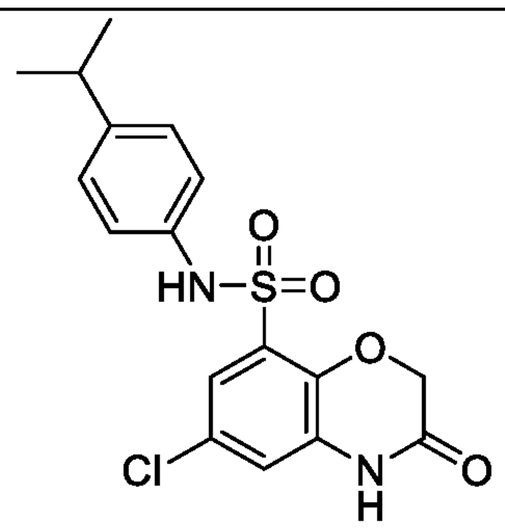
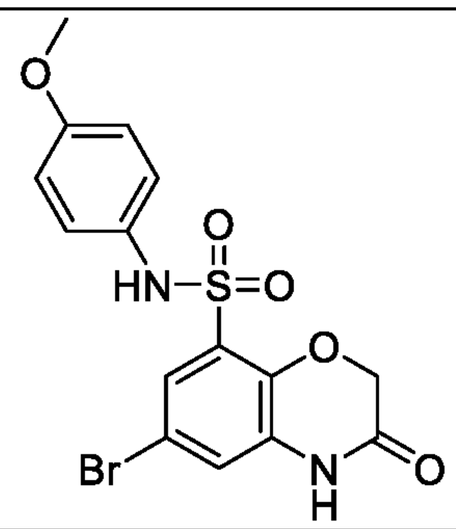
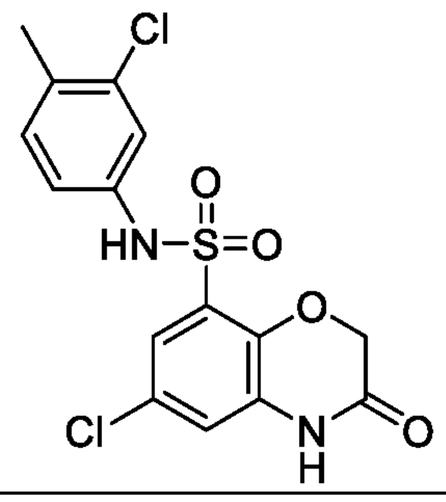
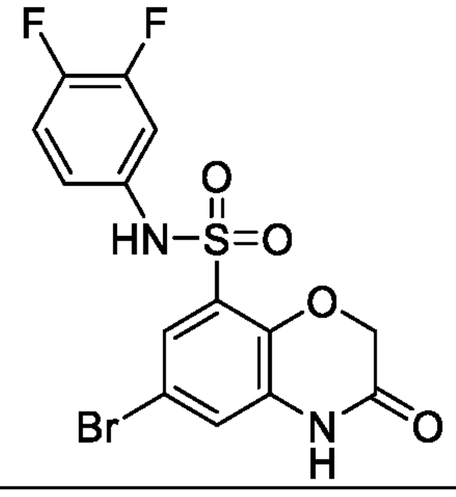
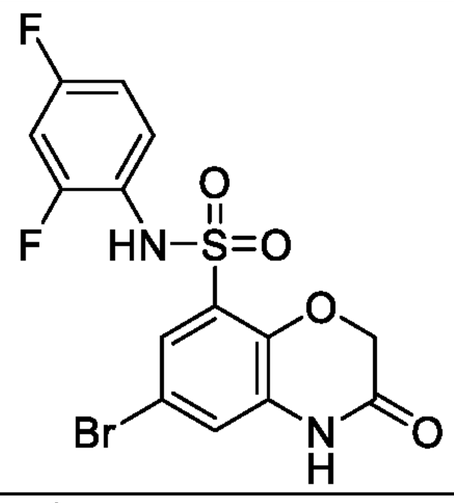
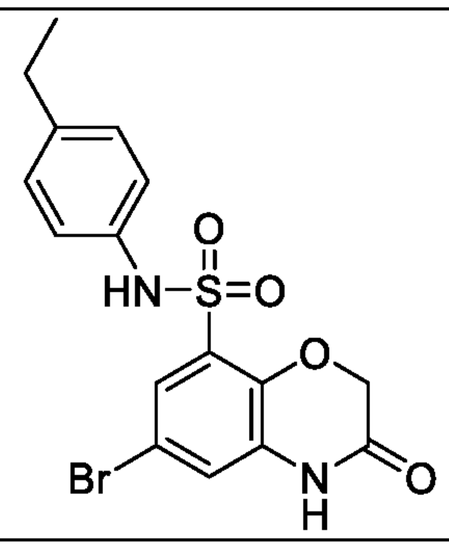
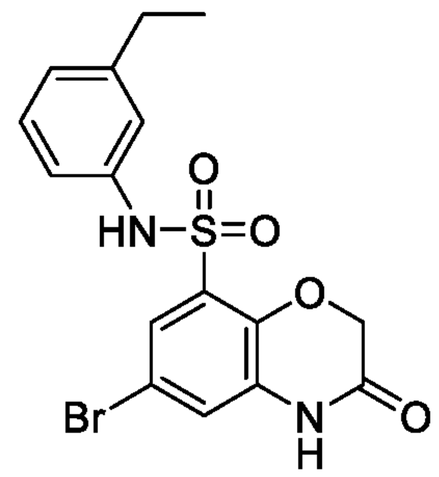
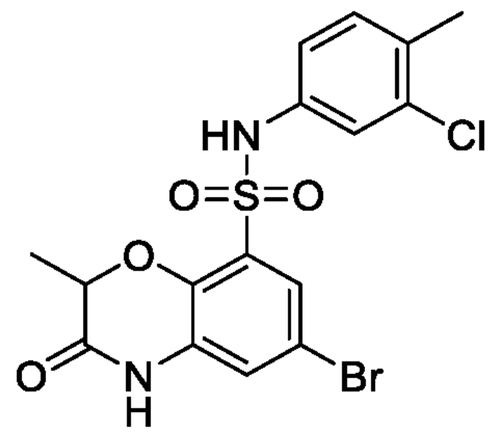
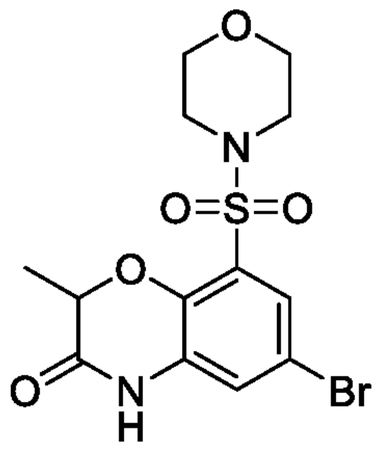
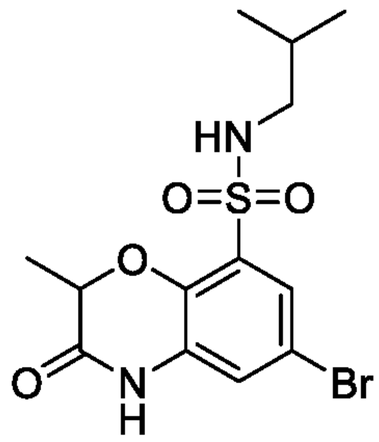
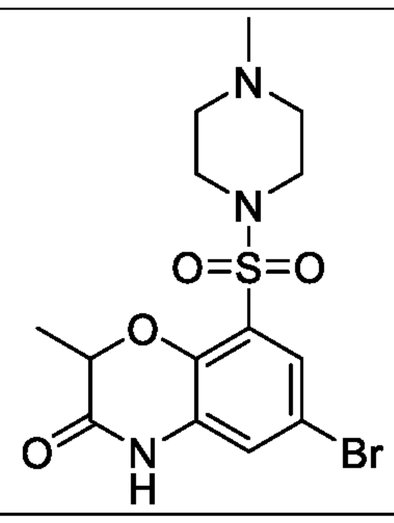
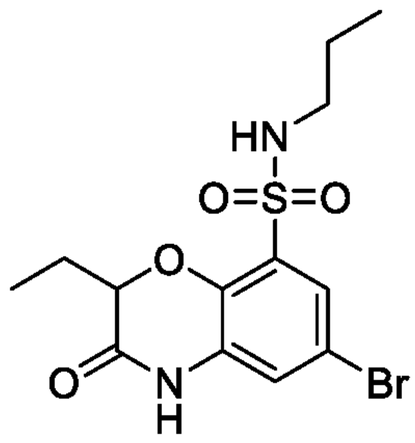
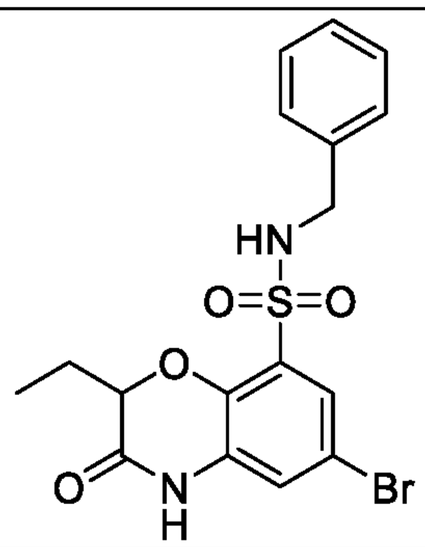
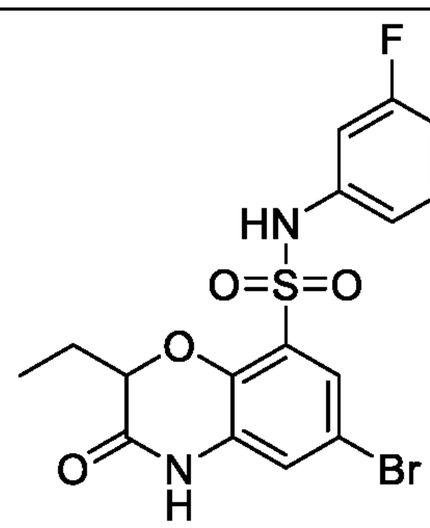
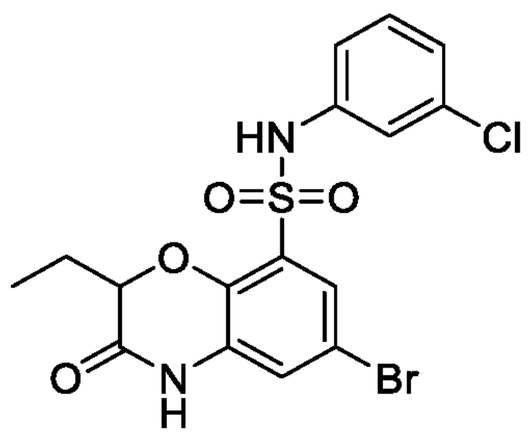
BC19926		++++	+
BC19928		+++	++
BC19930		+++	+
BC19932		++++	++
BC19934		+++	++
BC19936		++++	+
BC19938		+++	++

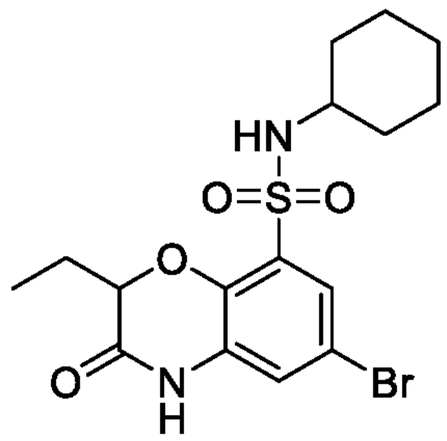
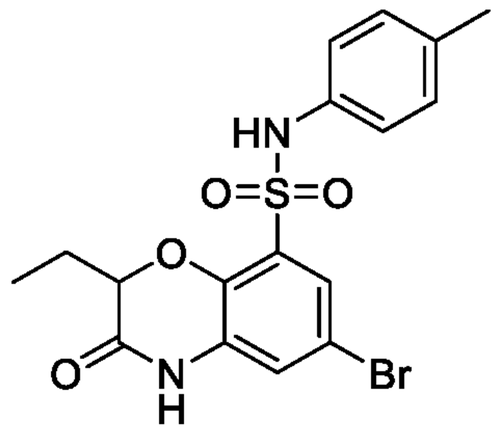
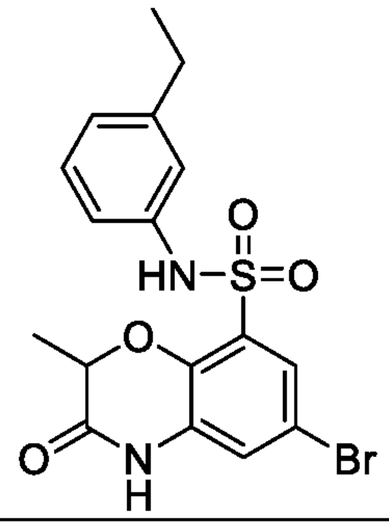
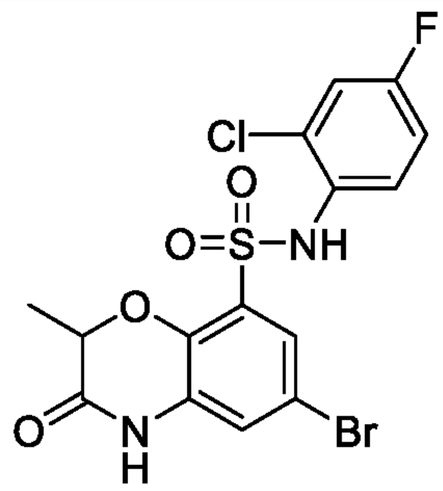
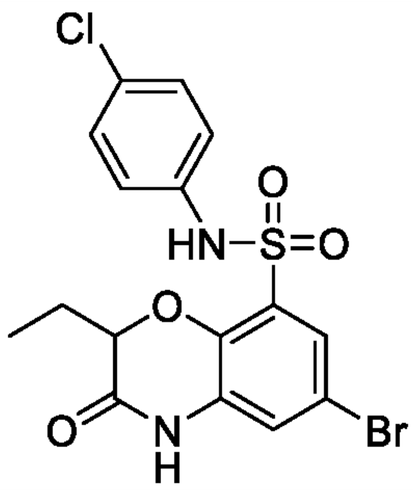
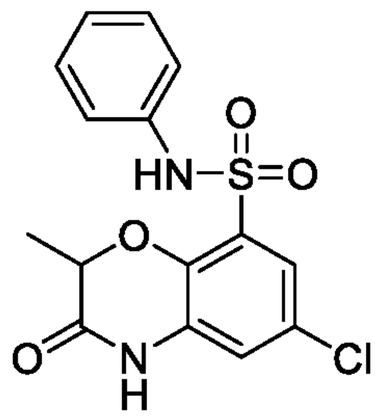
Table 2d

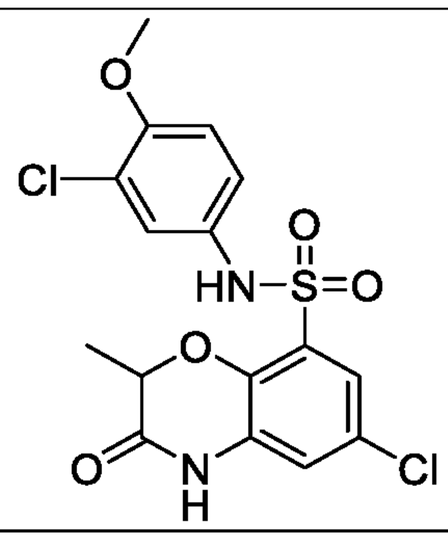
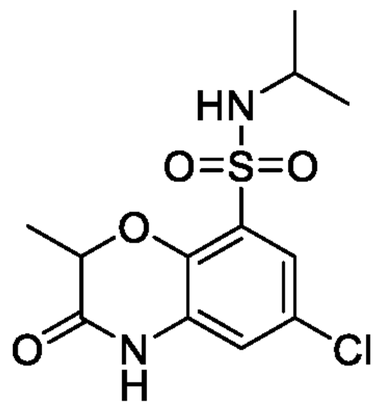
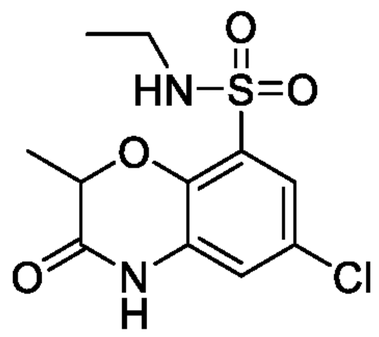
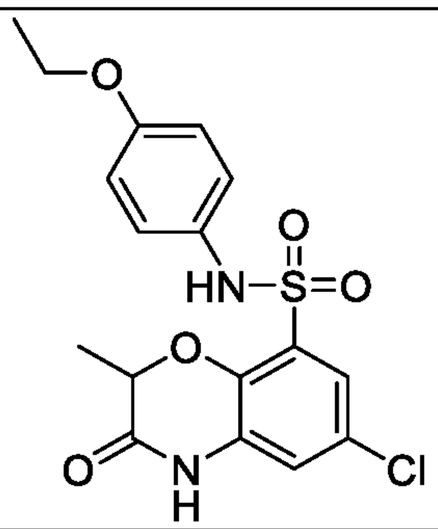
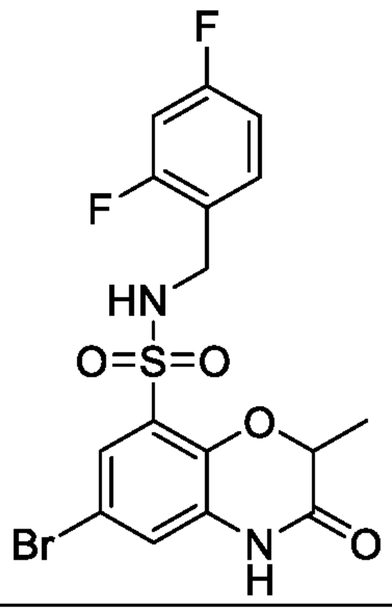
BC No.	ZE No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19168	ZE24-0050		++++	+
BC19169	ZE24-0051		++++	+
BC19170	ZE24-0052		++	+
BC19171	ZE24-0053		++++	+
BC19172	ZE24-0054		++++	+

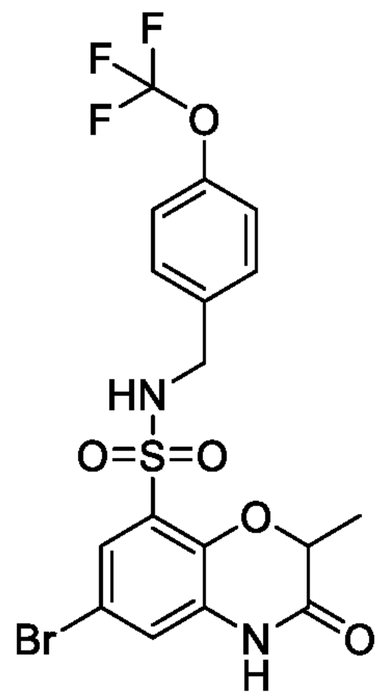
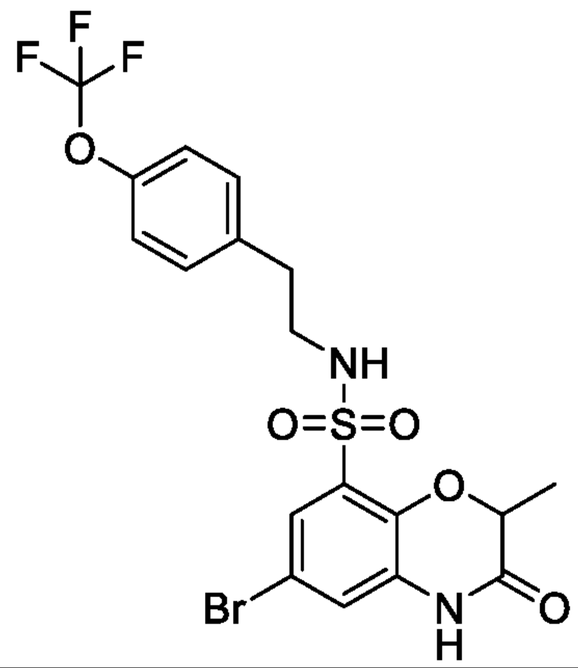
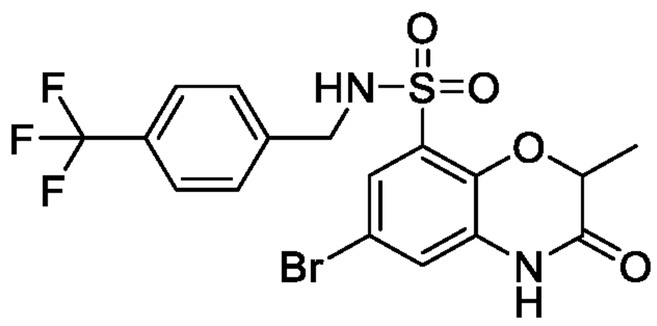
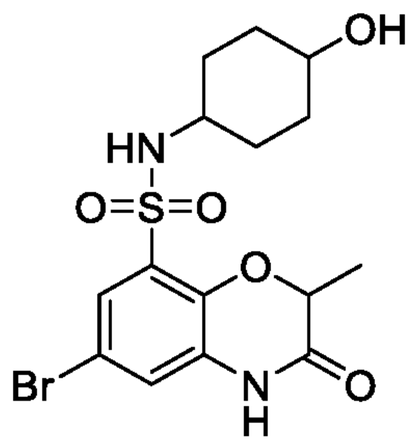
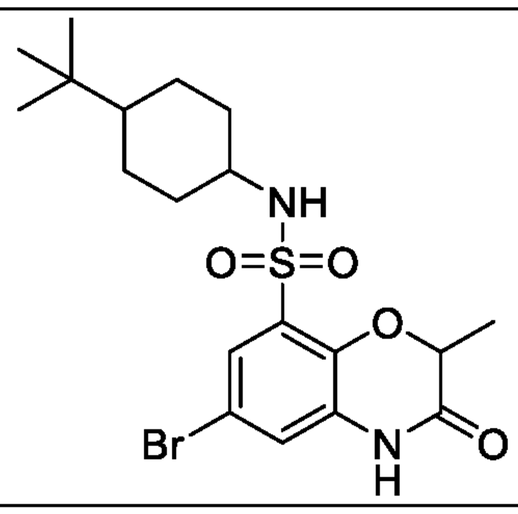
BC19173	ZE24-0055		++++	+
BC19174	ZE24-0056		++++	+
BC19175	ZE24-0057		++++	+
BC19176	ZE24-0058		++++	+
BC19177	ZE24-0059		++++	+

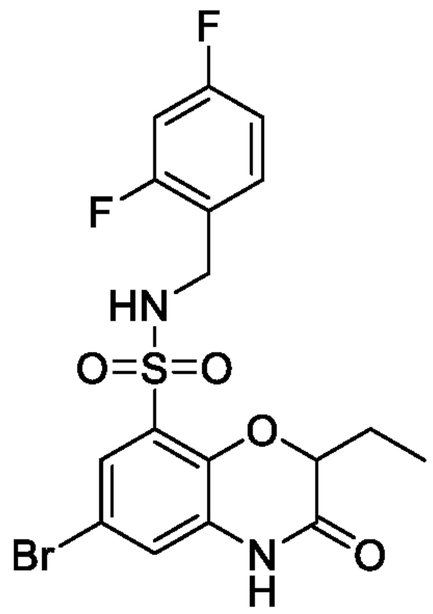
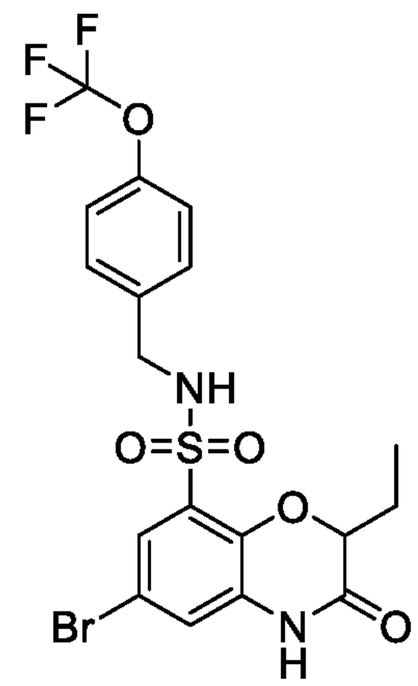
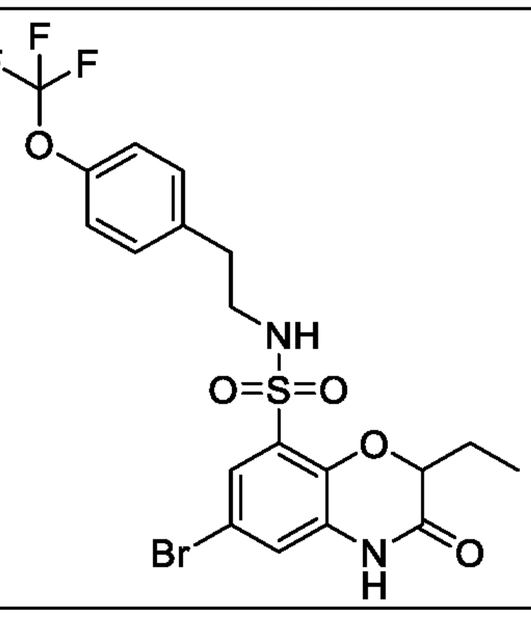
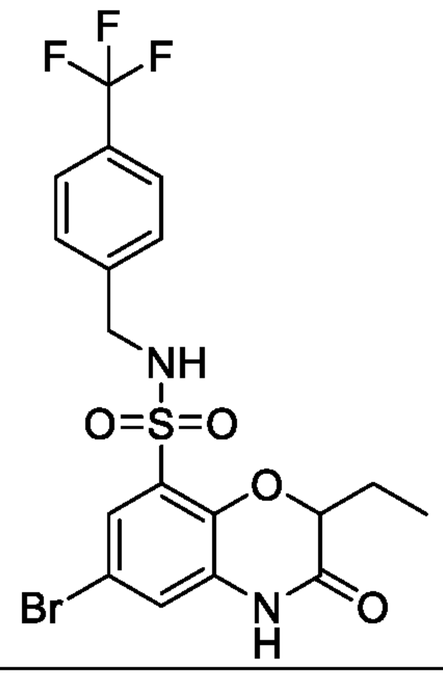
BC19178	ZE24-0060		++++	++
BC19179	ZE24-0061		++++	+
BC19180	ZE24-0062		++++	+
BC19225	ZE24-0064		+++	+
BC19226	ZE24-0065		++	+
BC19227	ZE24-0066		+	+

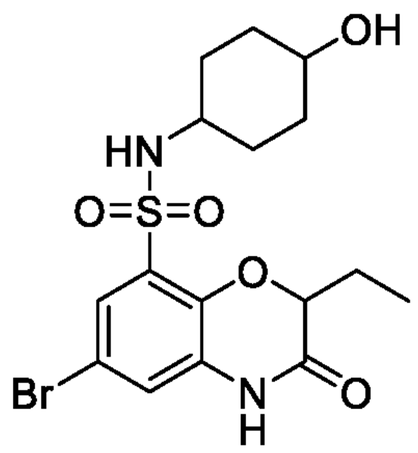
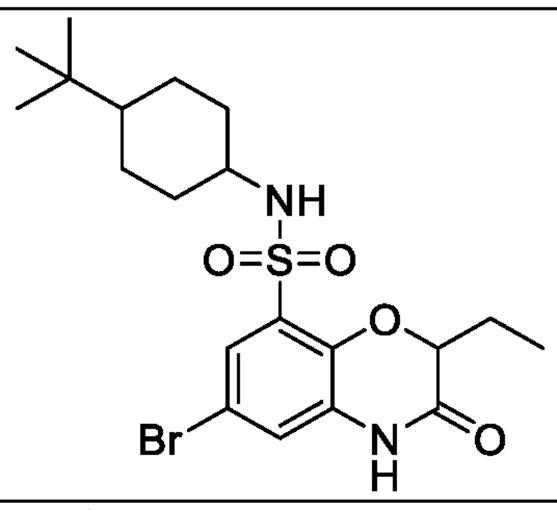
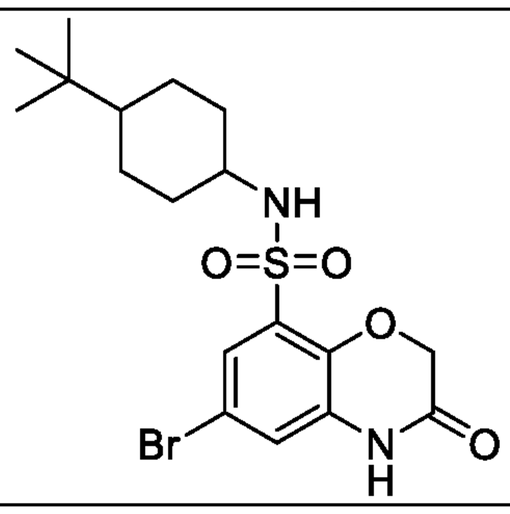
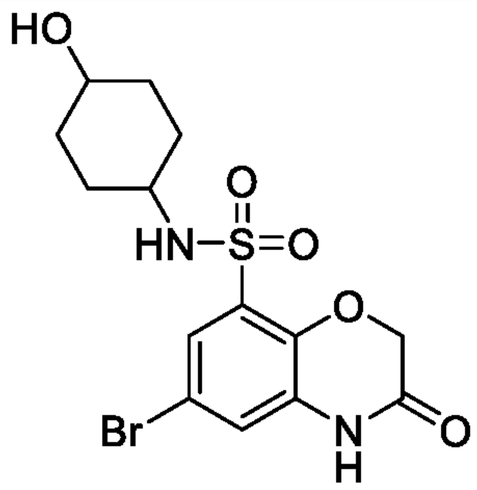
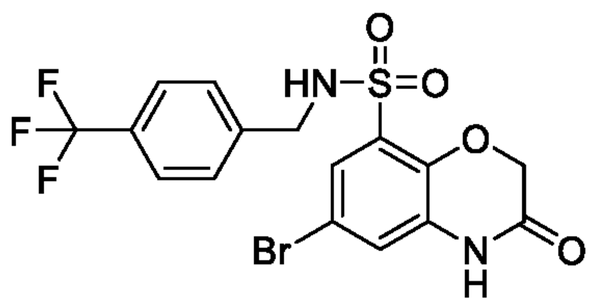
BC19228	ZE24-0067		+	+
BC19229	ZE24-0068		++	+
BC19230	ZE24-0069		++++	+
BC19231	ZE24-0070		++++	+
BC19232	ZE24-0071		++++	+

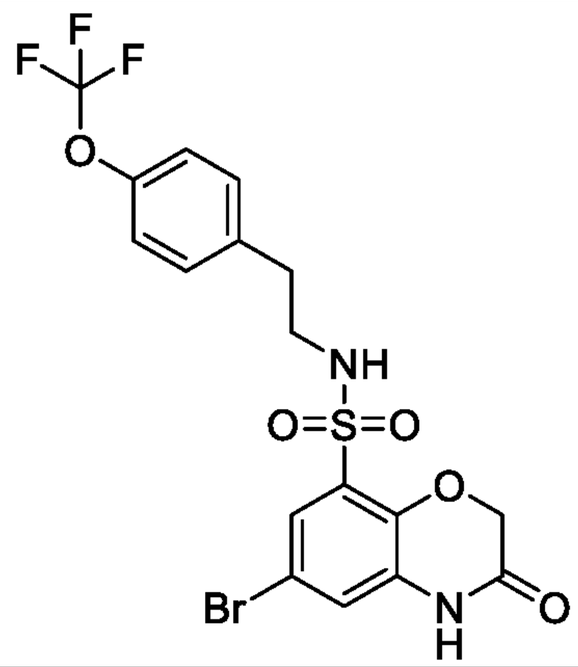
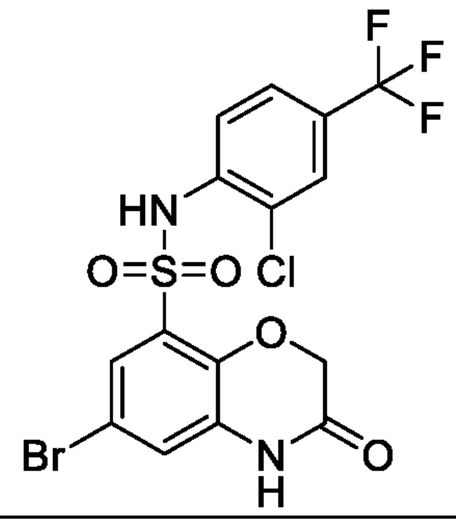
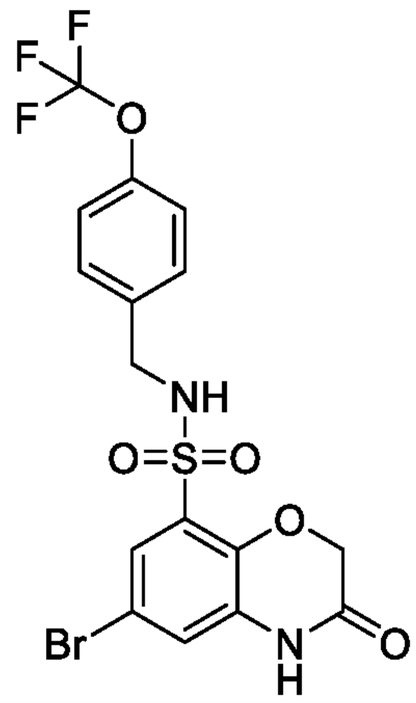
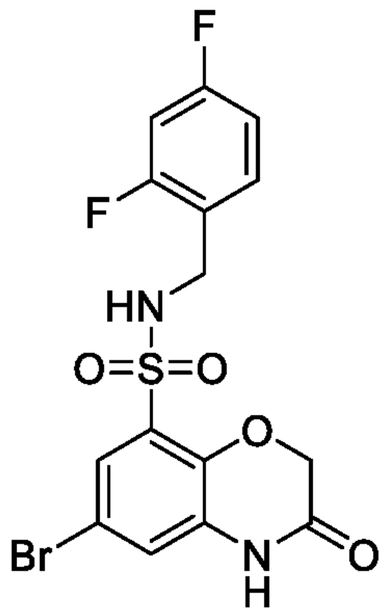
BC19233	ZE24-0072		++	++
BC19234	ZE24-0073		++++	++
BC19288	ZE24-0074		++++	+
BC19289	ZE24-0075		++++	+
BC19290	ZE24-0076		++++	+
BC19291	ZE24-0077		++++	+

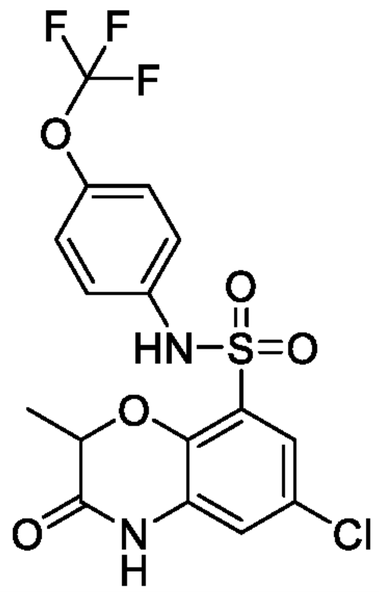
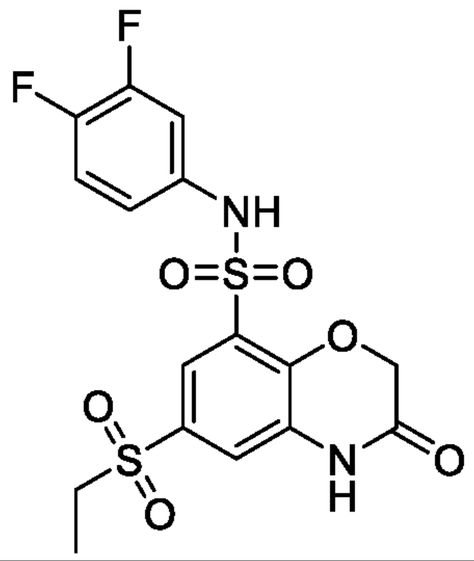
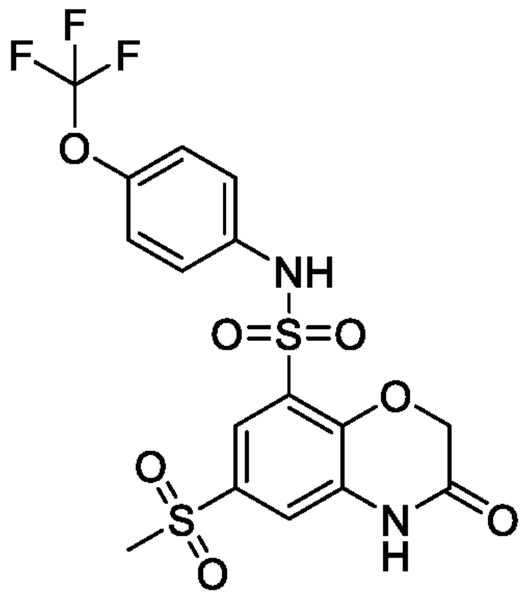
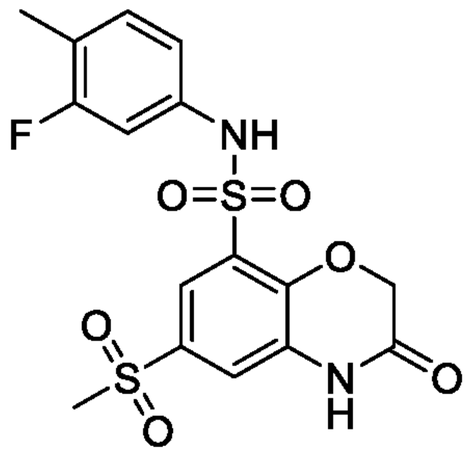
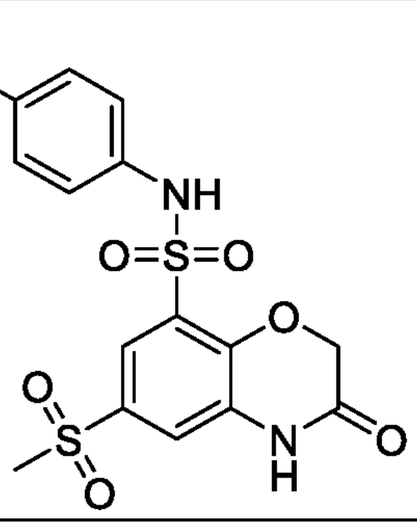
BC19292	ZE24-0078		++++	+
BC19293	ZE24-0080		+++	+
BC19294	ZE24-0081		++	+
BC19355	ZE24-0079		++++	+
BC19362	ZE24-0089		+++	+

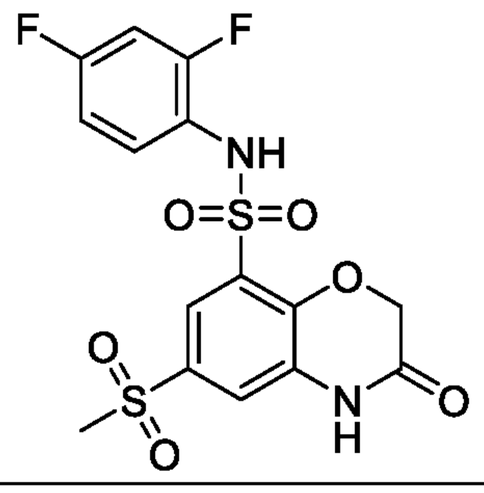
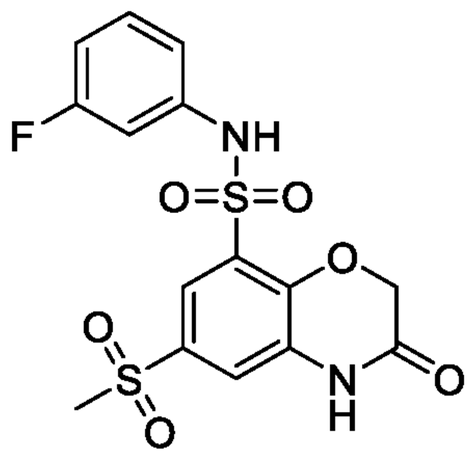
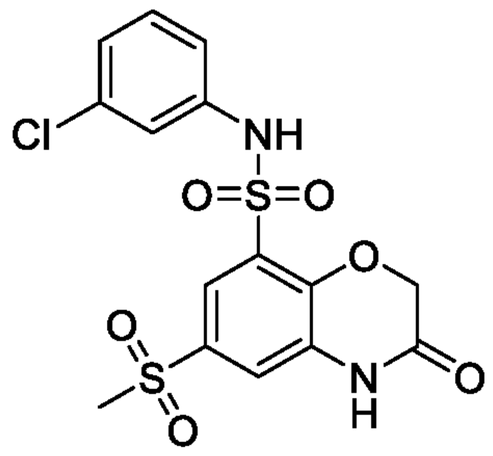
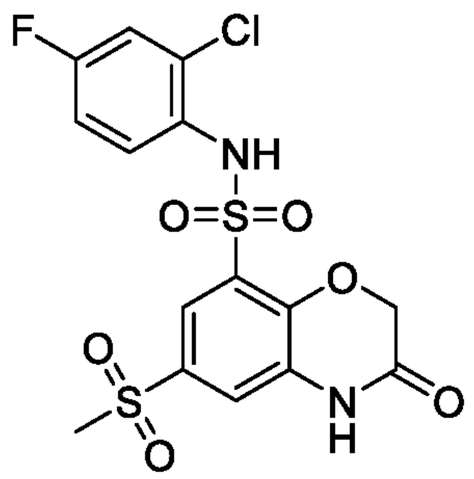
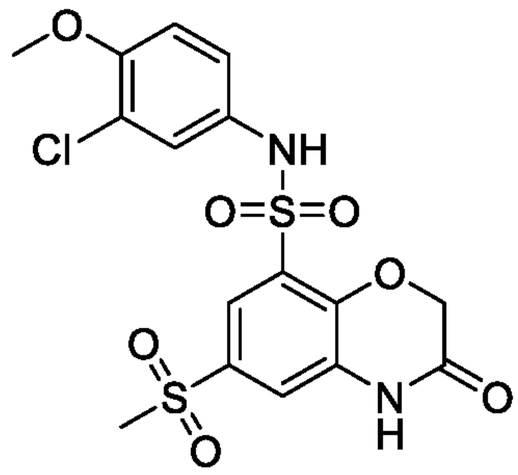
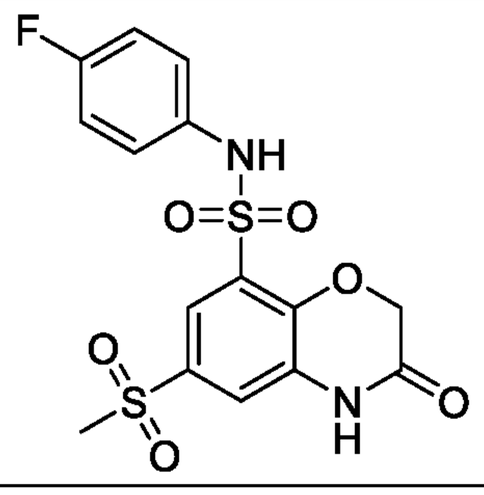
BC19363	ZE24-0090		++++	+
BC19364	ZE24-0092		+	+
BC19365	ZE24-0093		++	+
BC19366	ZE24-0094		+	+
BC19367	ZE24-0095		+	+

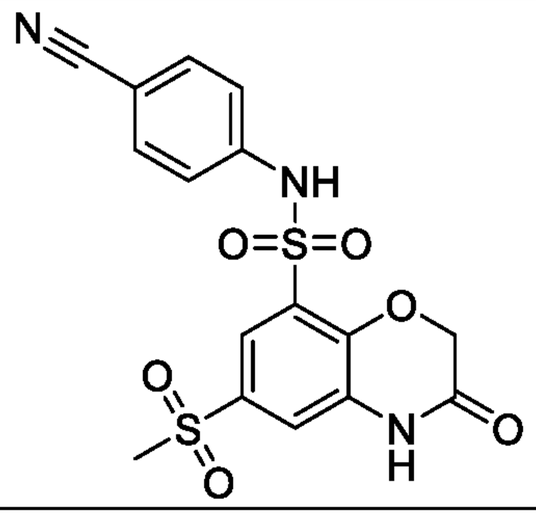
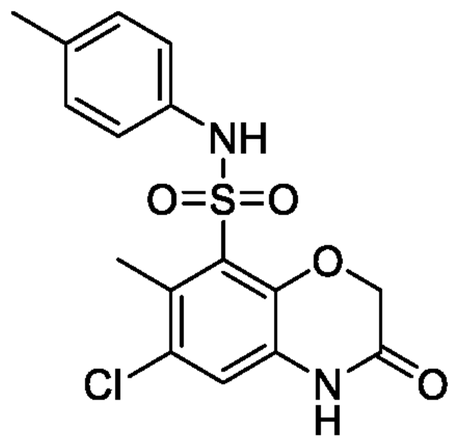
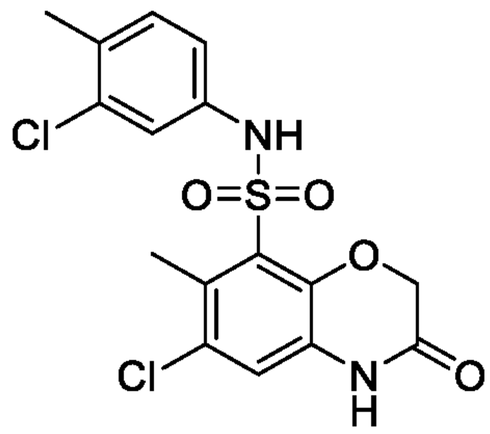
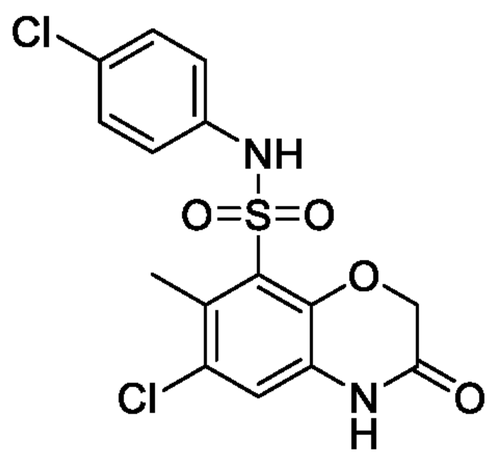
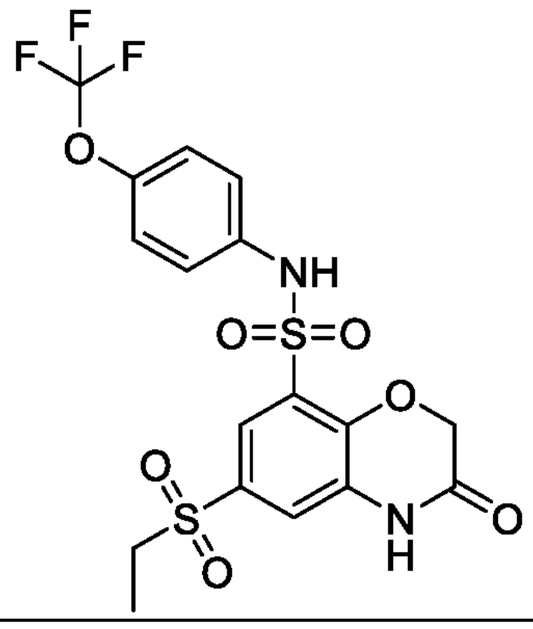
BC19374	ZE24-0103		++++	++
BC19375	ZE24-0104		++++	+
BC19376	ZE24-0106		++	+
BC19377	ZE24-0107		++++	+

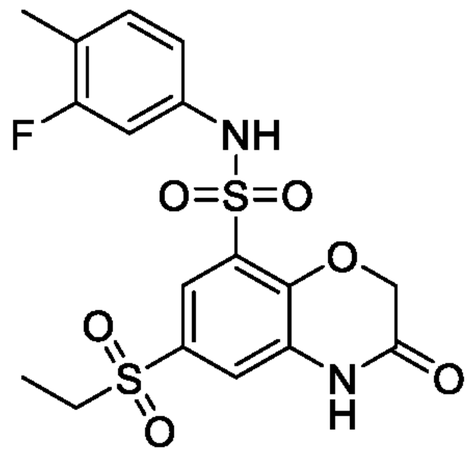
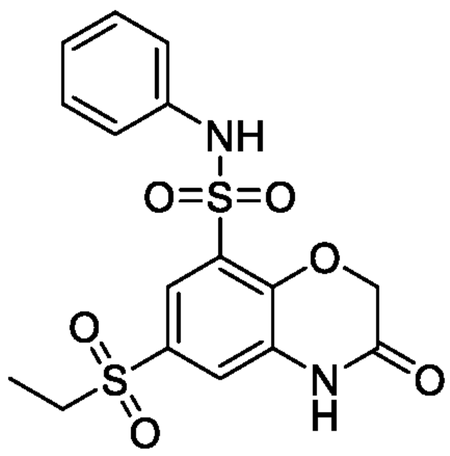
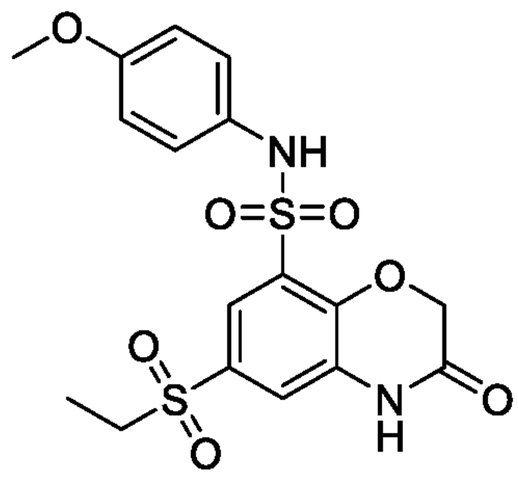
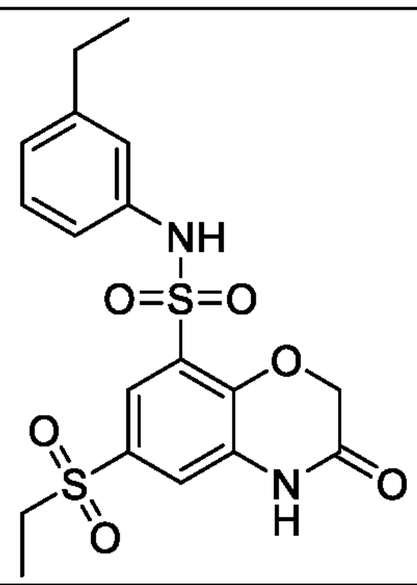
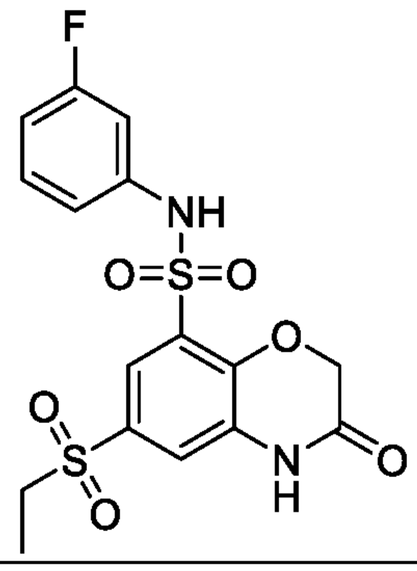
BC19378	ZE24-0108		+	+
BC19379	ZE24-0109		+	+
BC19380	ZE24-0110		+	+
BC19381	ZE24-0111		+	+
BC19382	ZE24-0112		+	+

BC19383	ZE24-0113		+	+
BC19384	ZE24-0114		++++	+
BC19385	ZE24-0115		+	+
BC19386	ZE24-0116		+	+

BC19394	ZE24-0124		++++	+
BC19421	ZE24-0125		++++	+
BC19422	ZE24-0127		++++	+
BC19423	ZE24-0128		++++	+
BC19424	ZE24-0132		++++	+

BC19425	ZE24-0135		++++	+
BC19426	ZE24-0137		++++	+
BC19427	ZE24-0138		++++	+
BC19428	ZE24-0140		+++	+
BC19429	ZE24-0141		+	+
BC19430	ZE24-0142		++++	+

BC19431	ZE24-0144		++++	+
BC19432	ZE24-0147		+++	+
BC19433	ZE24-0150		++++	+
BC19434	ZE24-0151		++++	+
BC19435	ZE24-0152		++++	+

BC19436	ZE24-0153		++++	+
BC19437	ZE24-0154		++++	+
BC19438	ZE24-0158		++++	+
BC19439	ZE24-0161		++++	+
BC19440	ZE24-0162		++++	+

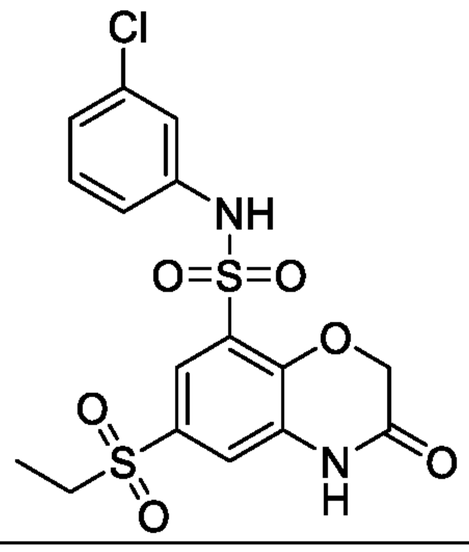
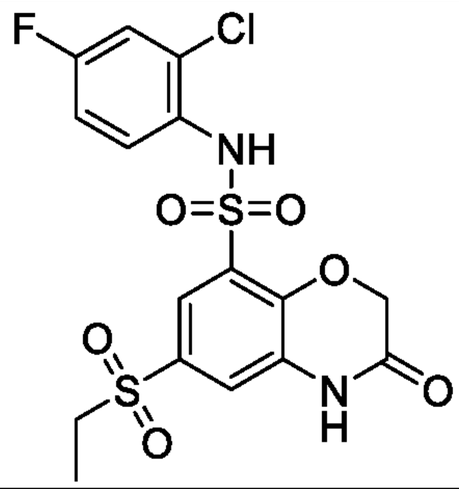
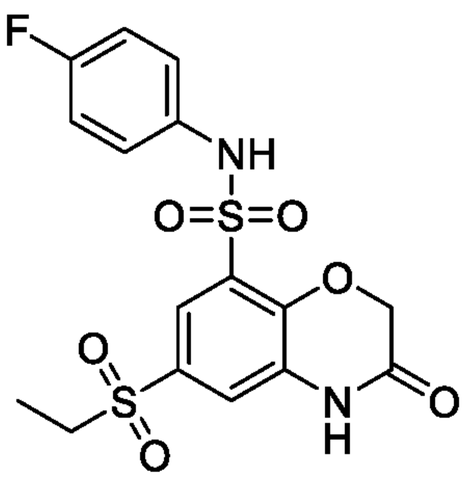
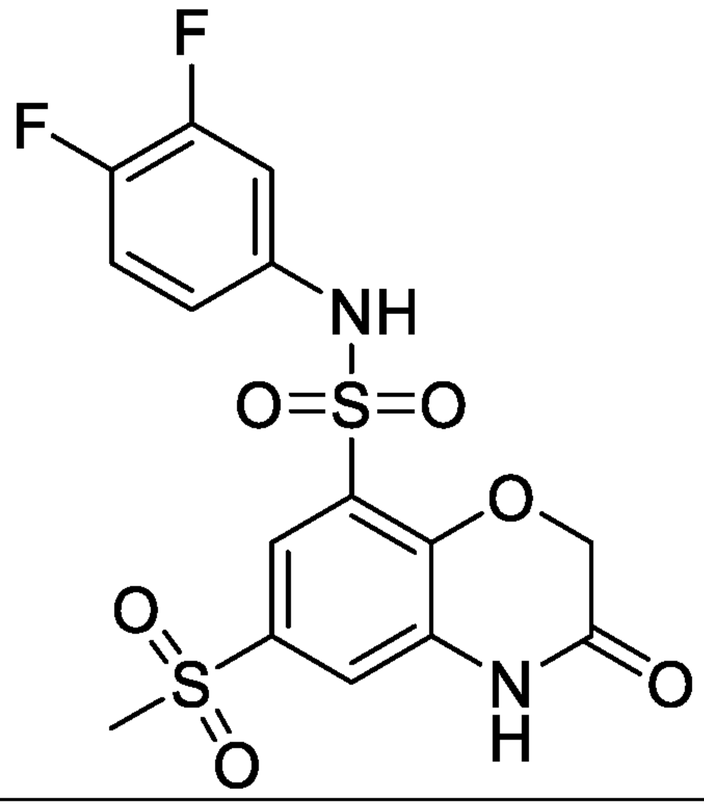
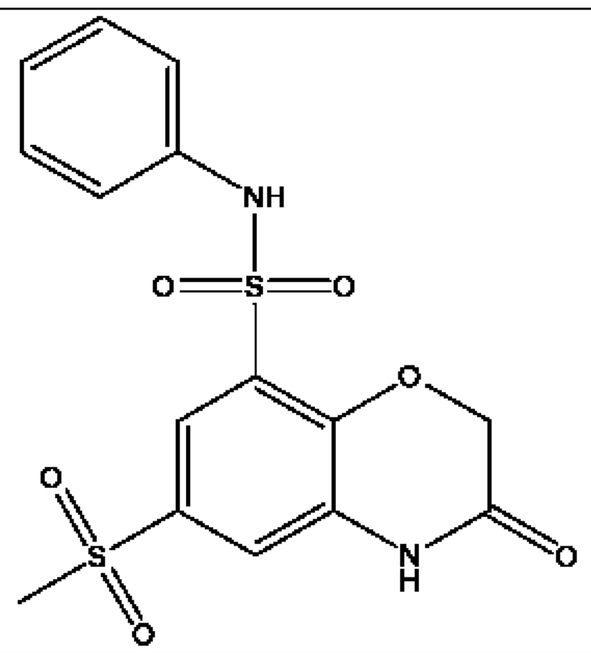
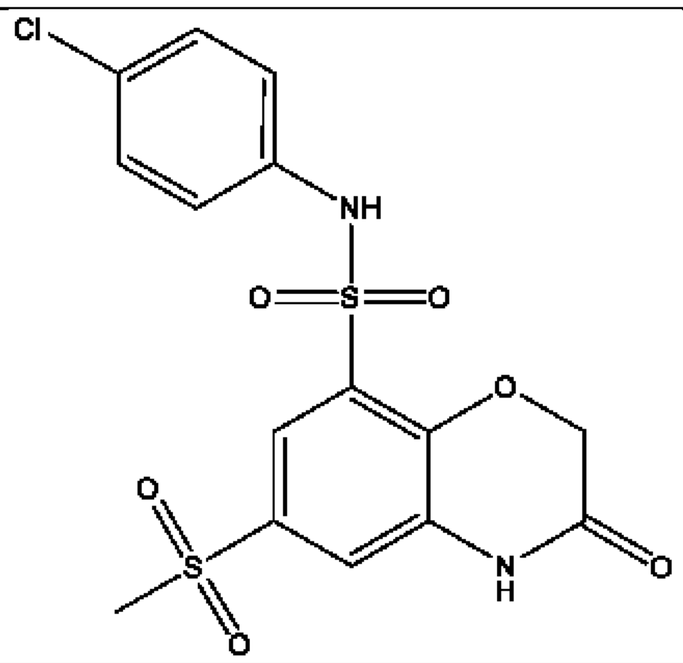
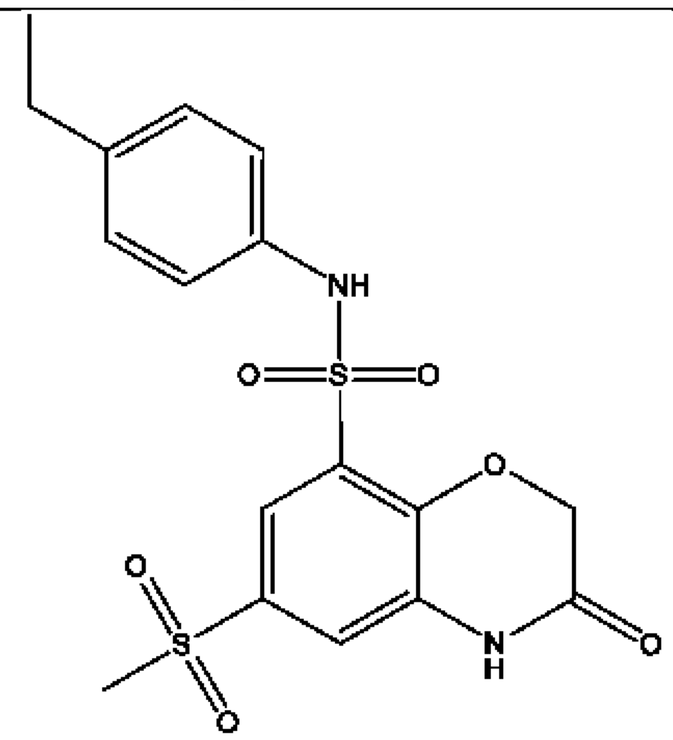
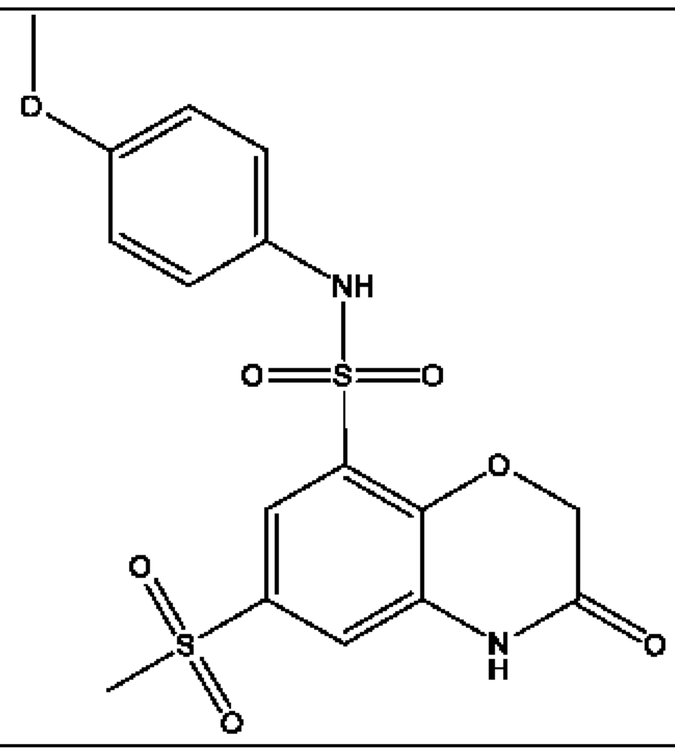
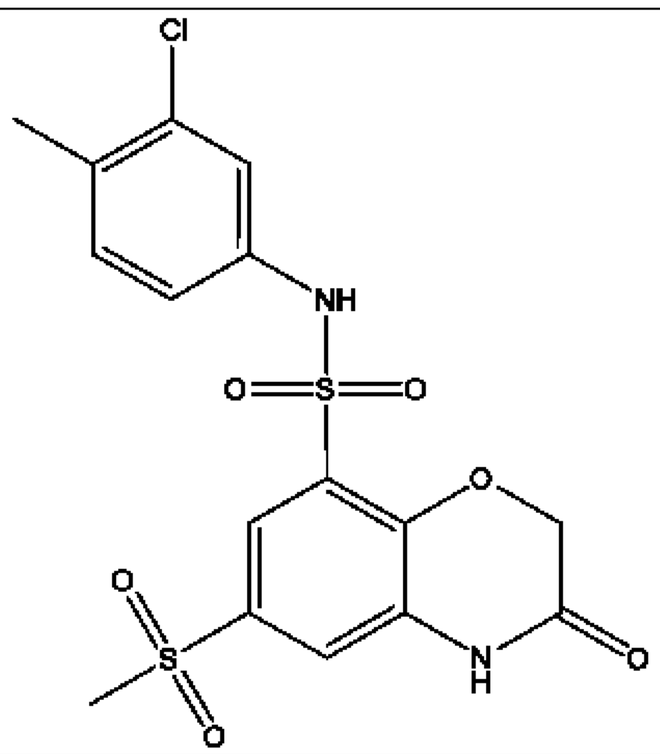
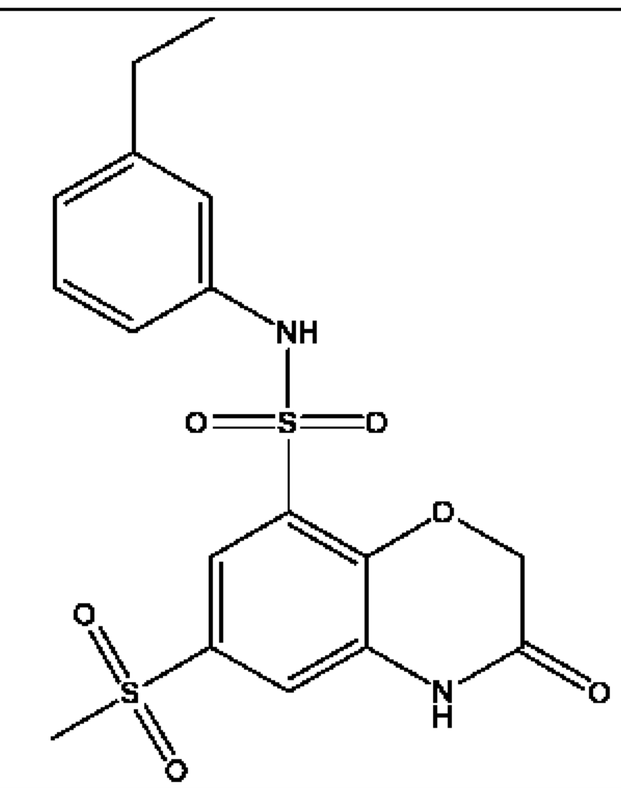
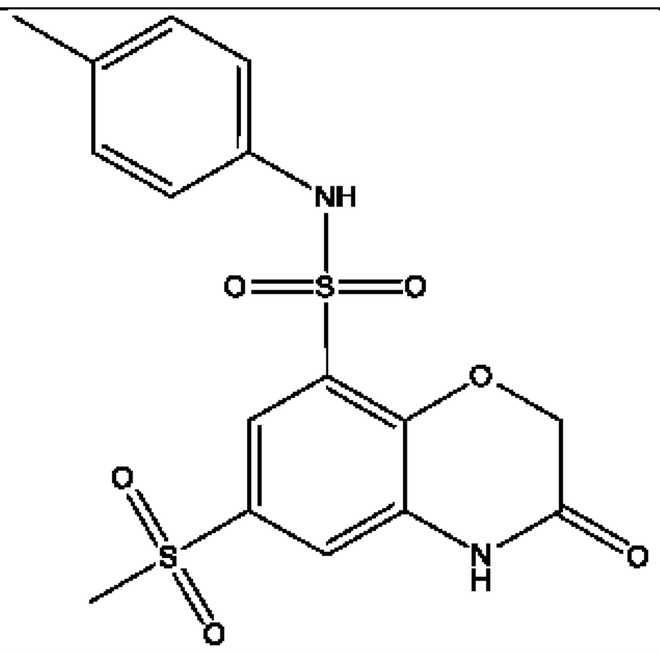
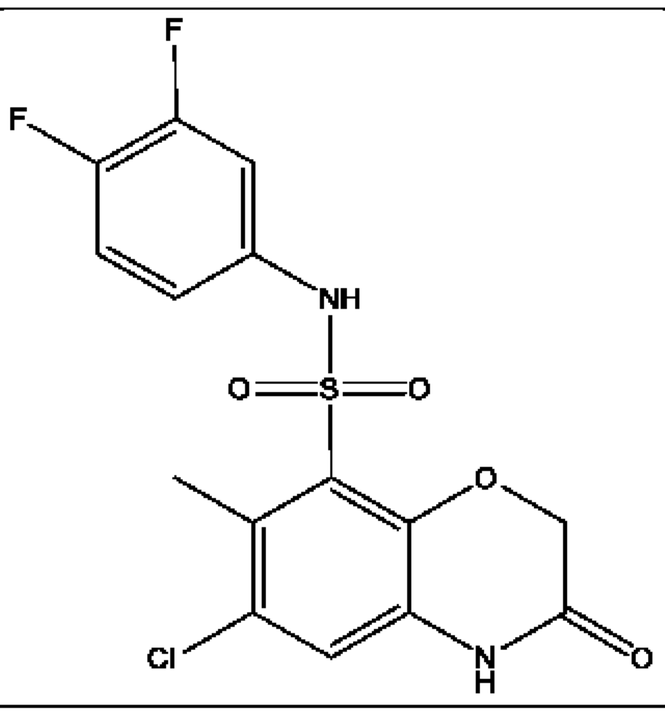
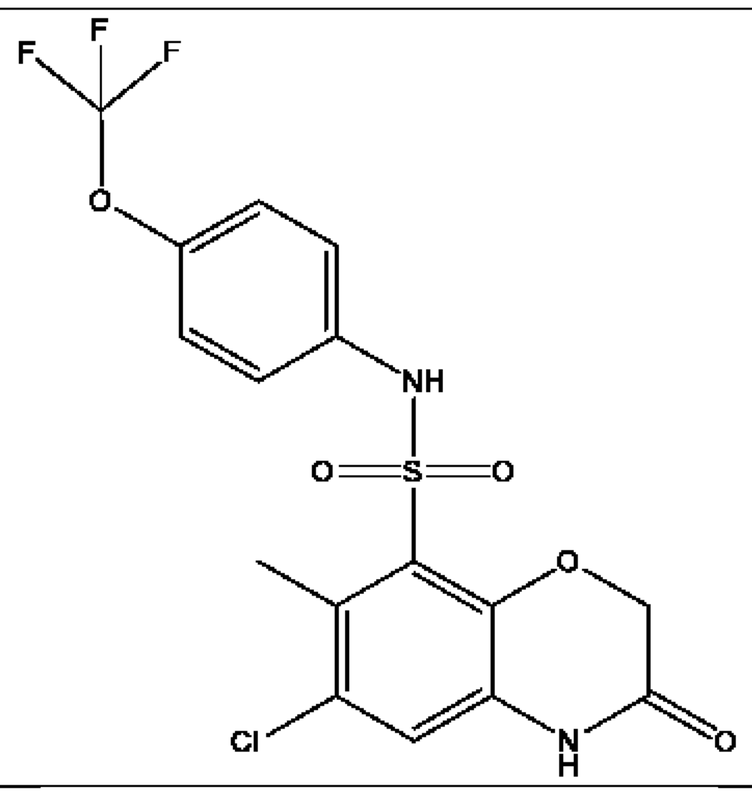
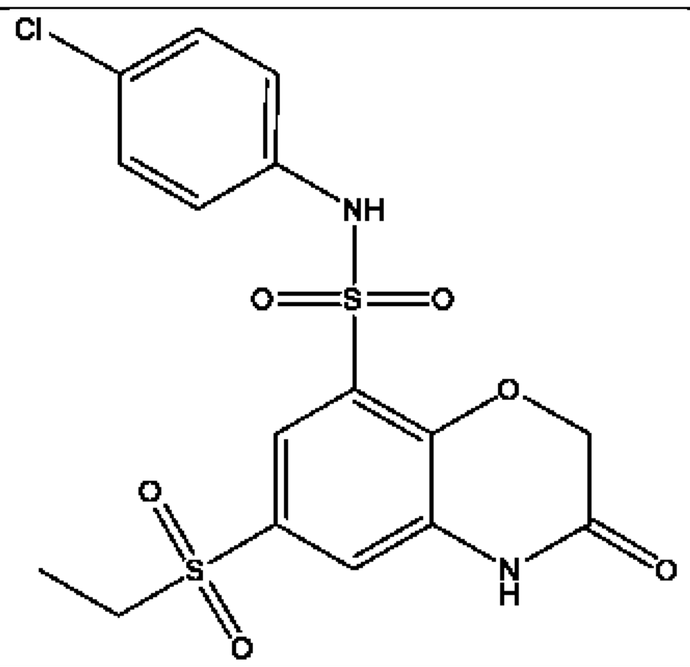
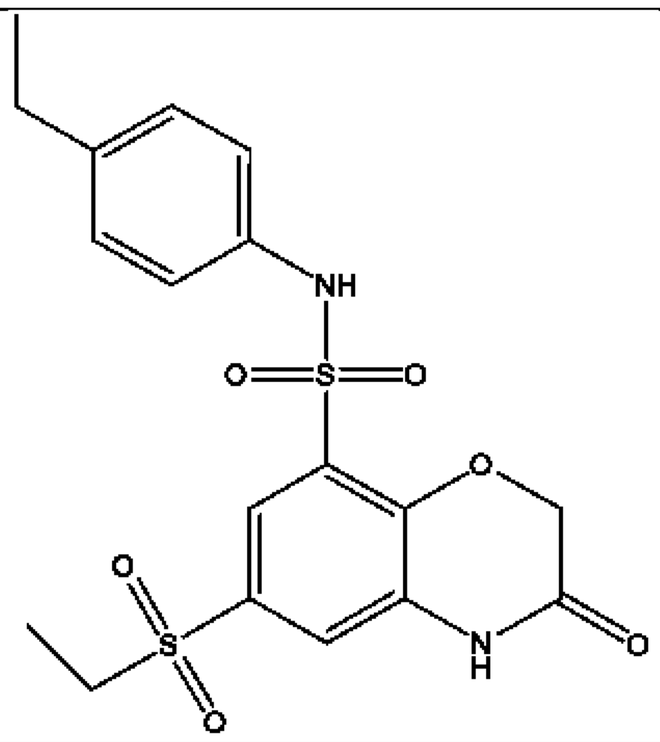
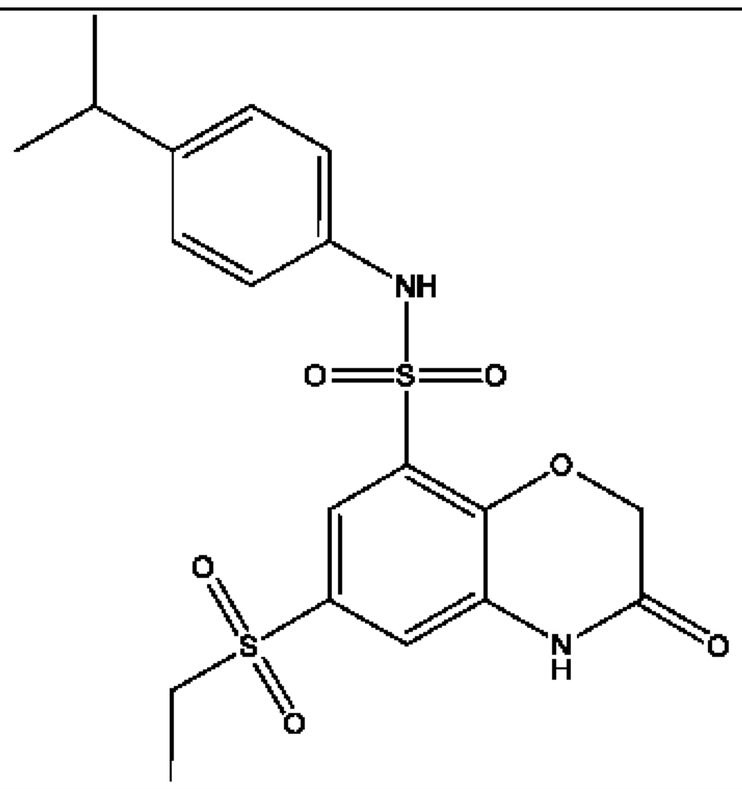
BC19441	ZE24-0163		++++	+
BC19442	ZE24-0165		+++	+
BC19443	ZE24-0167		++++	+

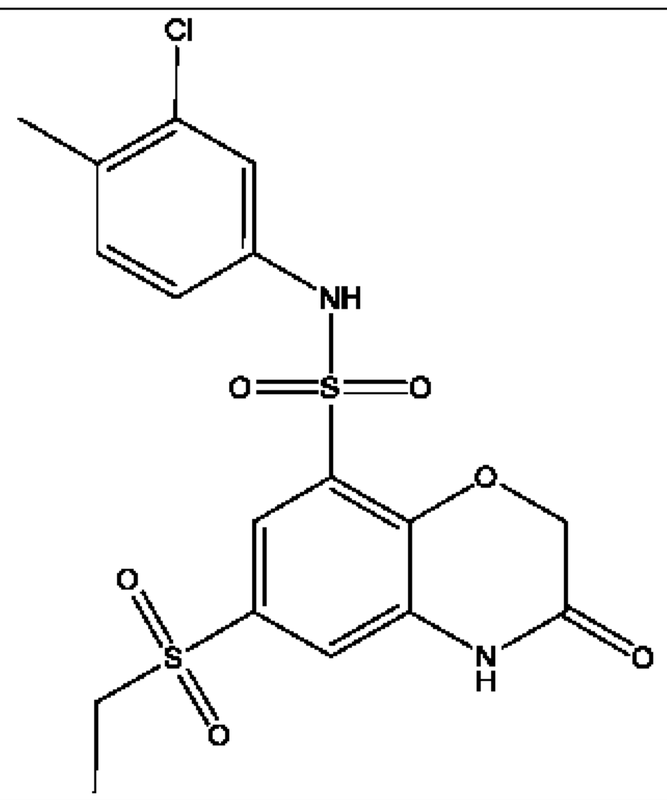
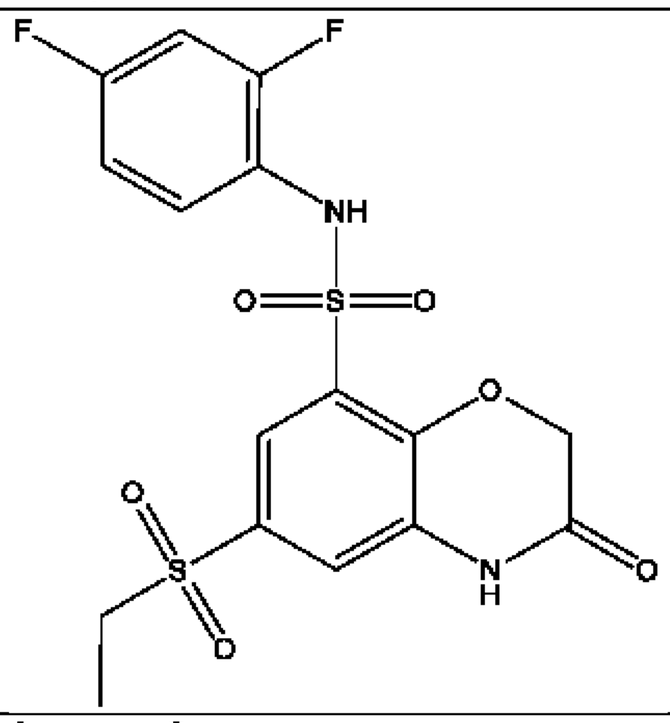
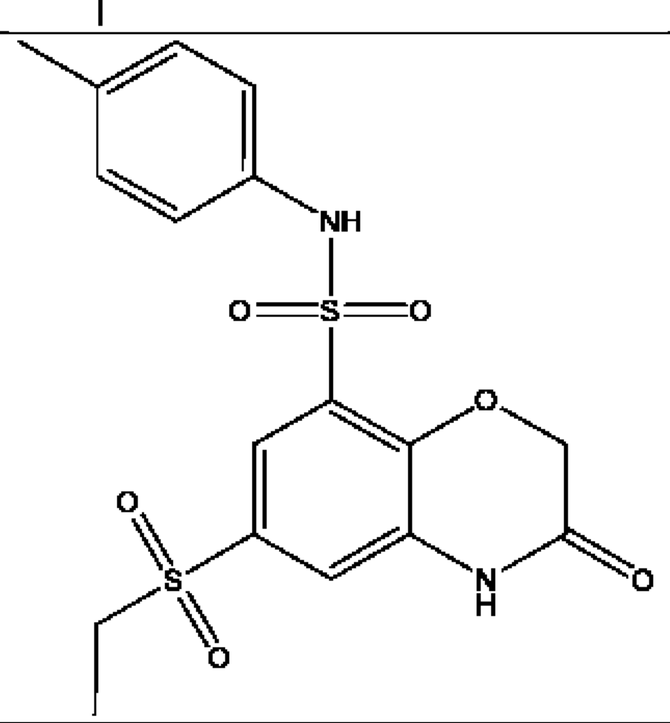
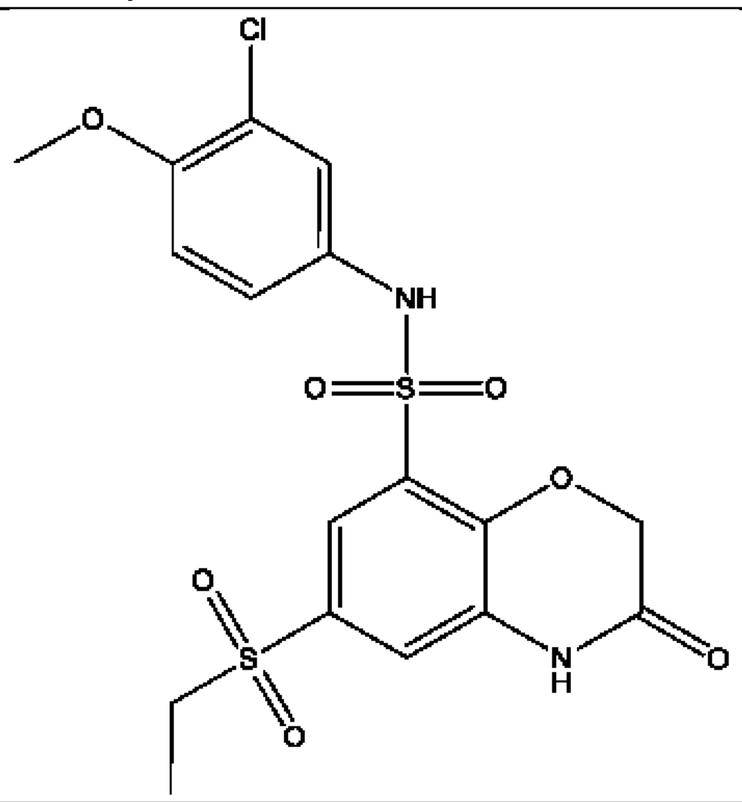
Table 2d-2

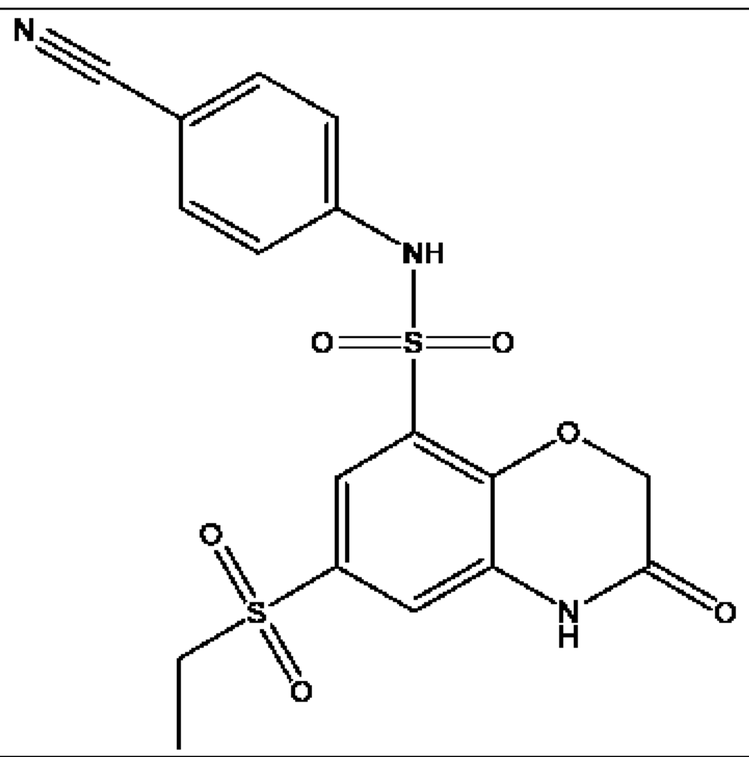
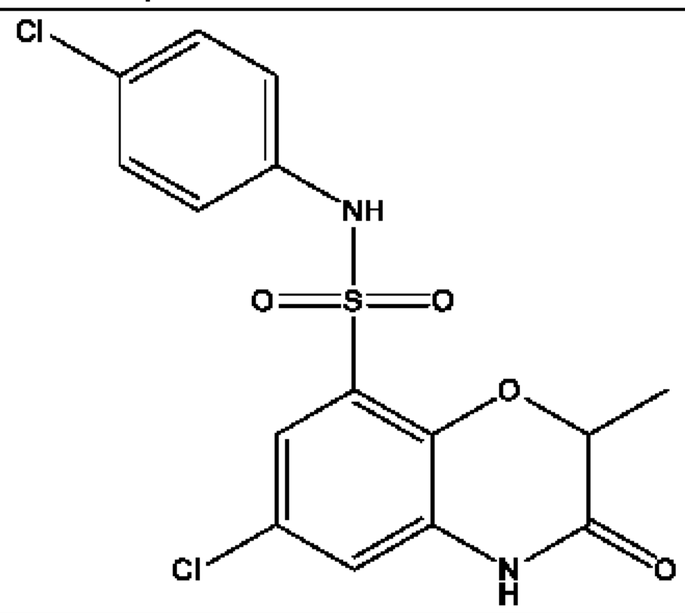
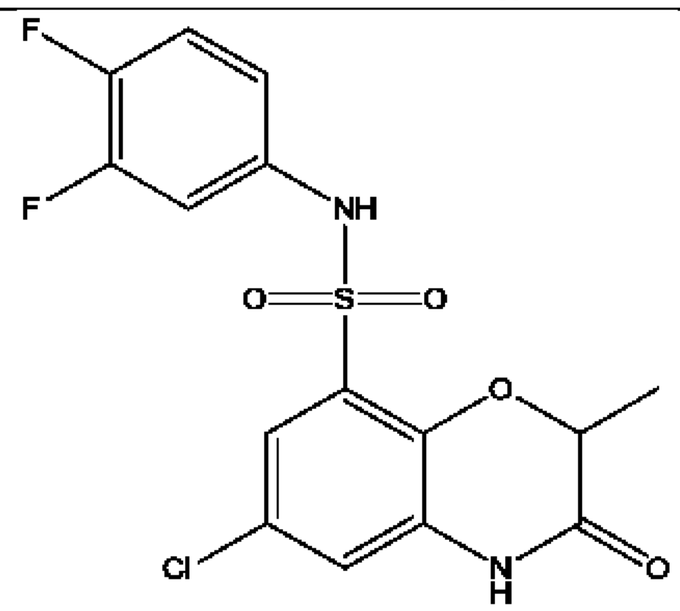
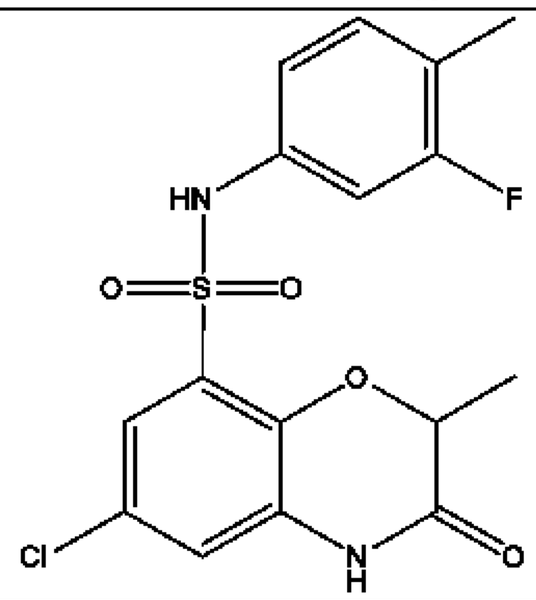
BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19481		++++	+

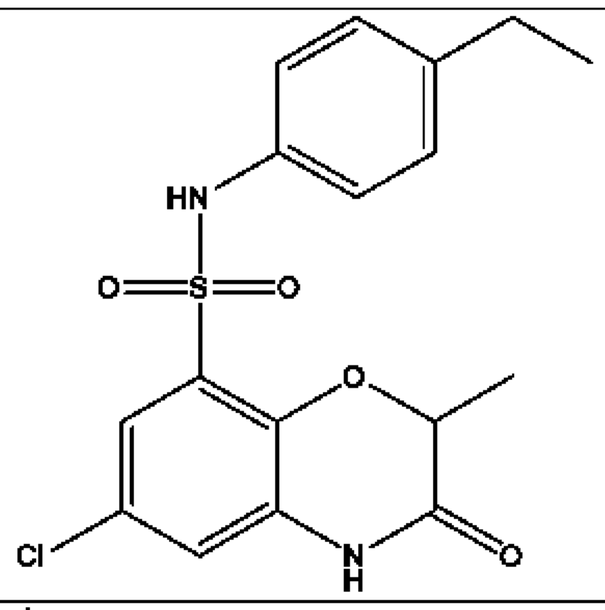
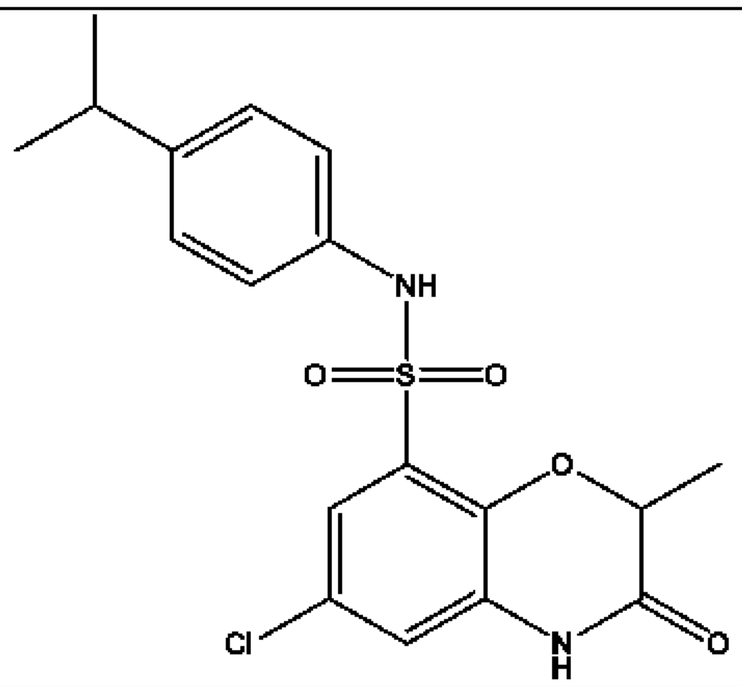
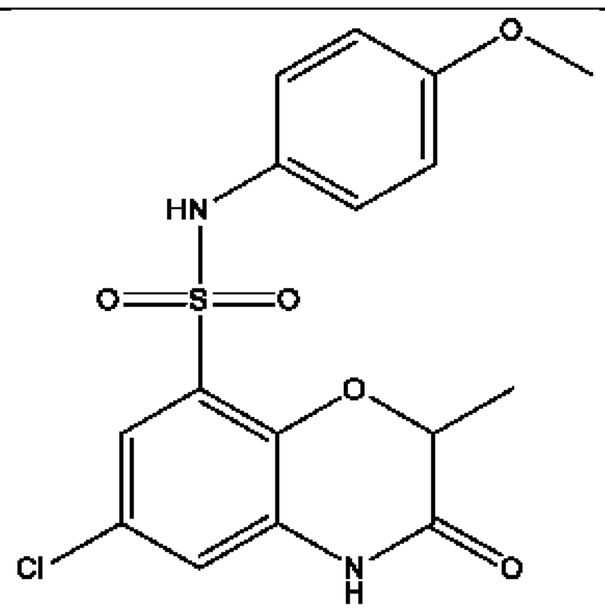
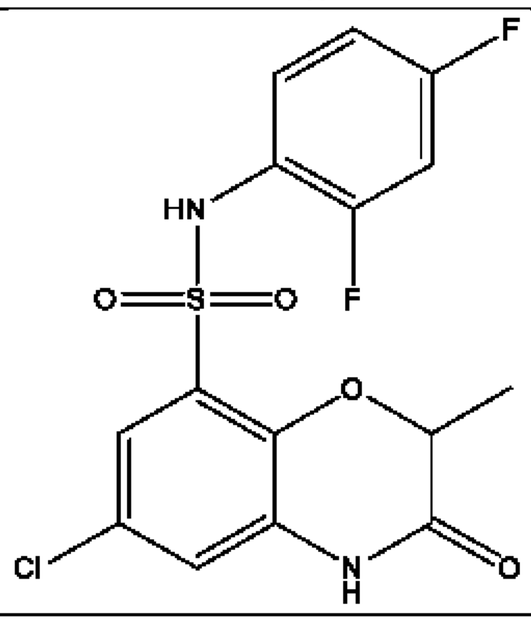
BC19482		+++	+
BC19483		++++	+
BC19484		++++	+
BC19485		++++	+

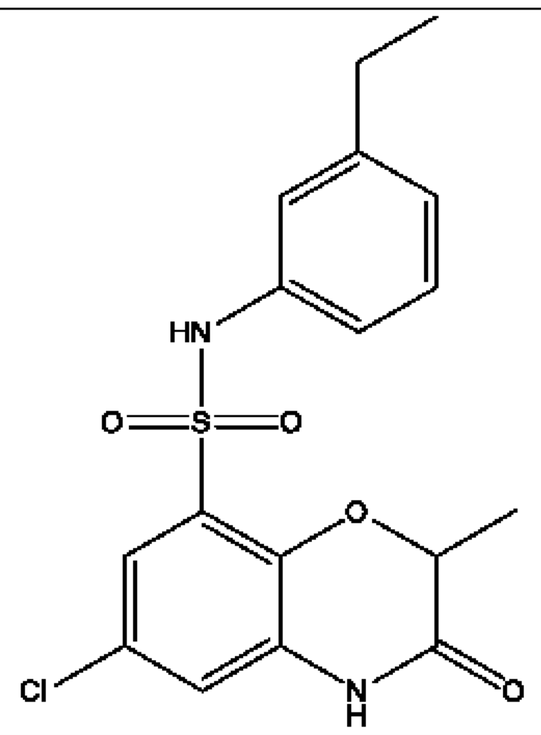
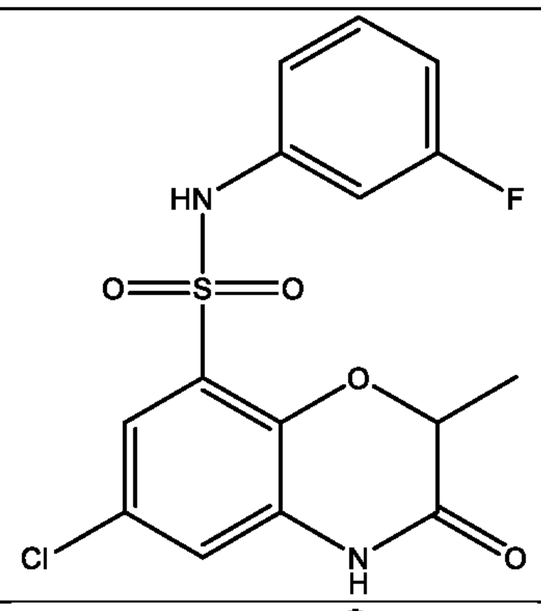
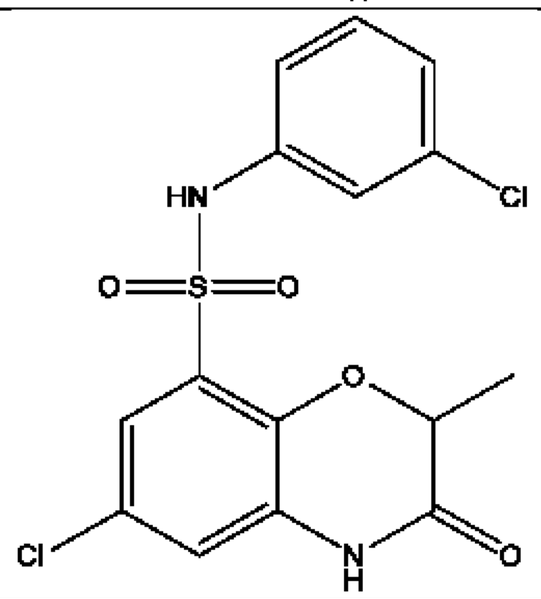
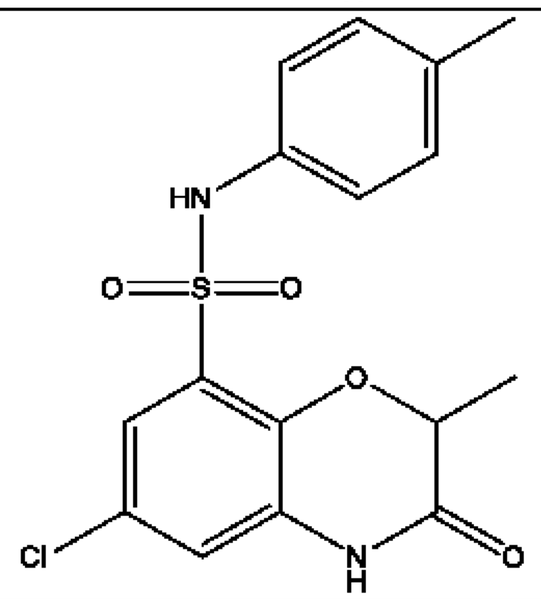
BC19486		++++	+
BC19487		+++	+
BC19488		++++	+
BC19489		++++	+

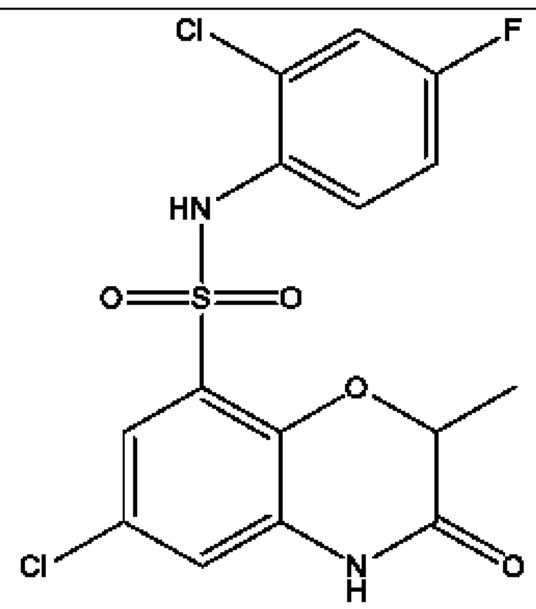
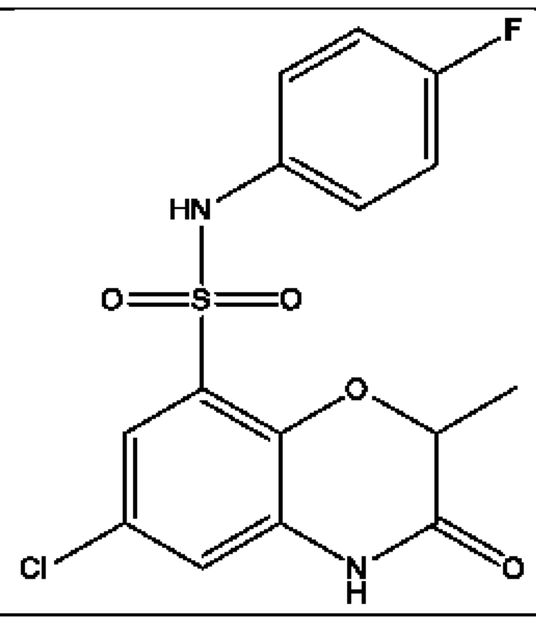
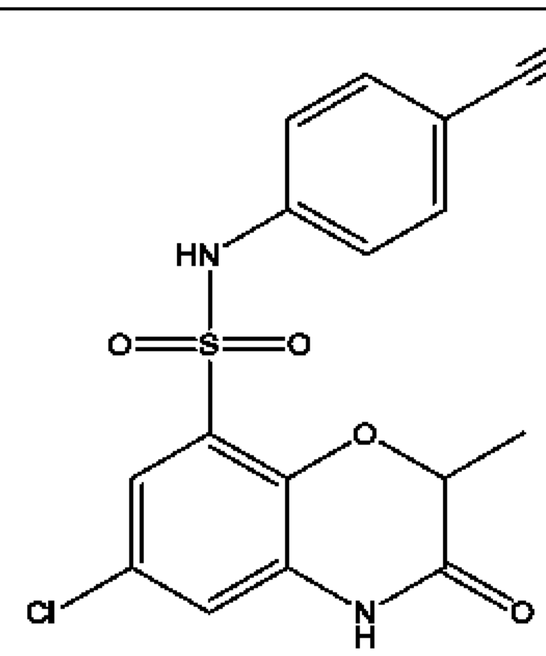
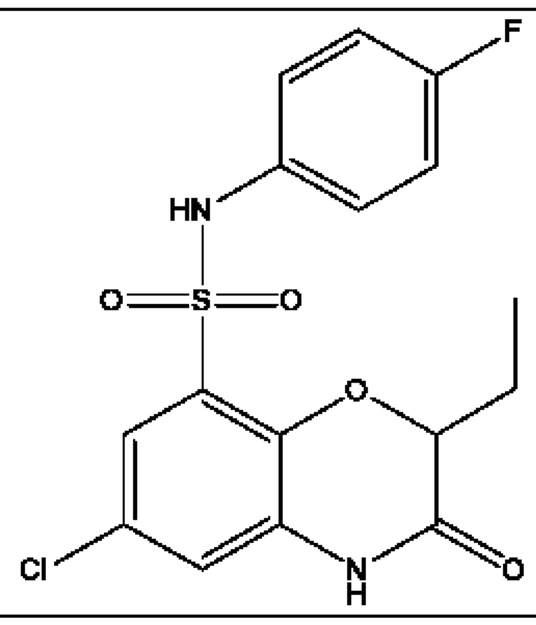
BC19490		++++	+
BC19491		++++	+
BC19492		++++	+
BC19493		++++	+

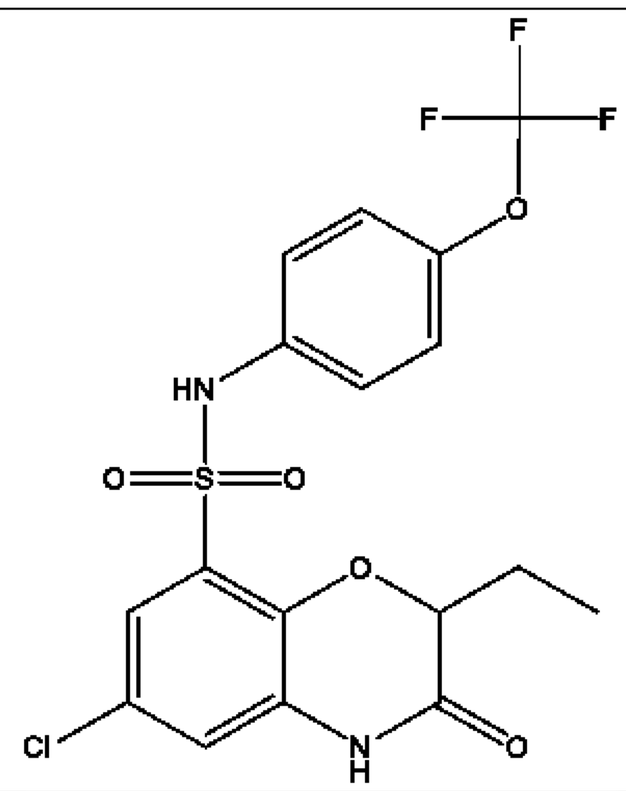
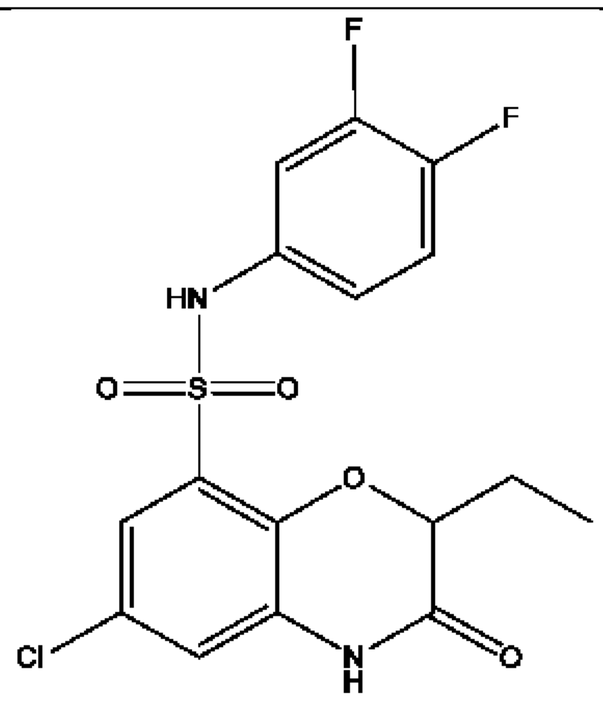
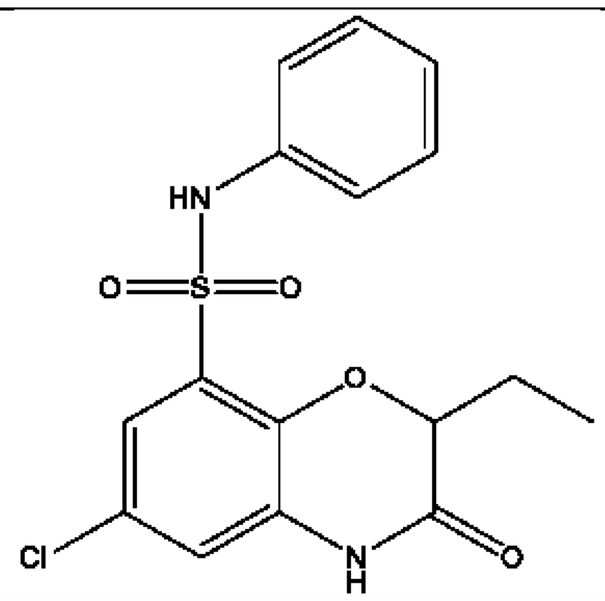
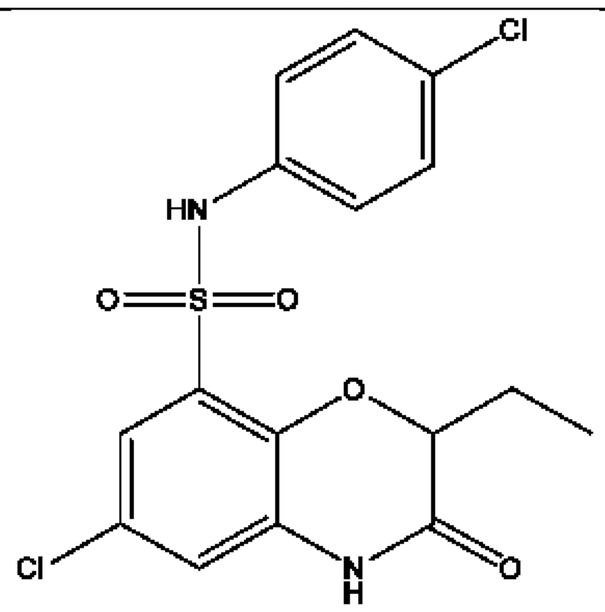
BC19544		++++	+
BC19545		++++	+
BC19546		++++	+
BC19547		+++	+

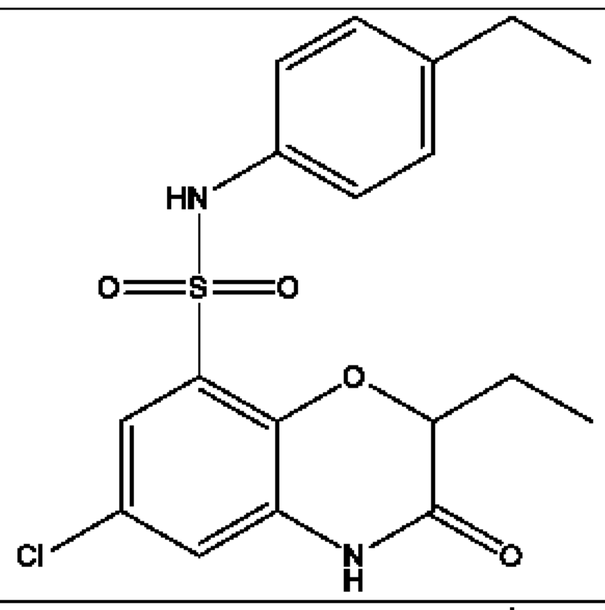
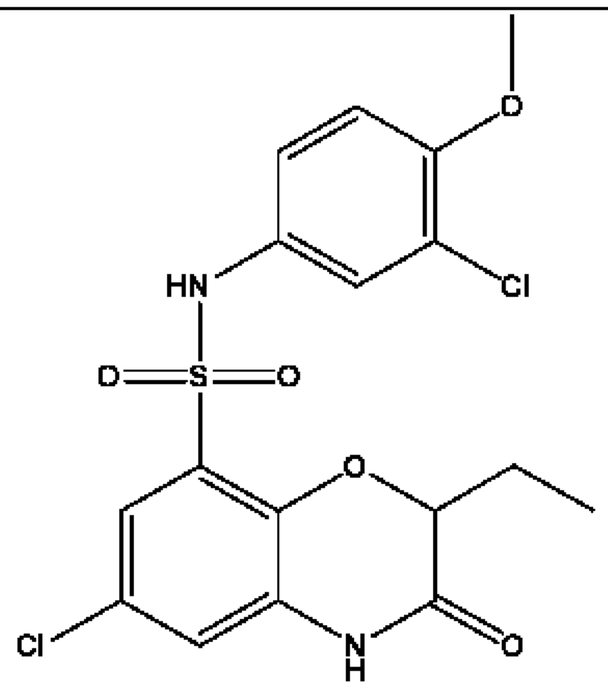
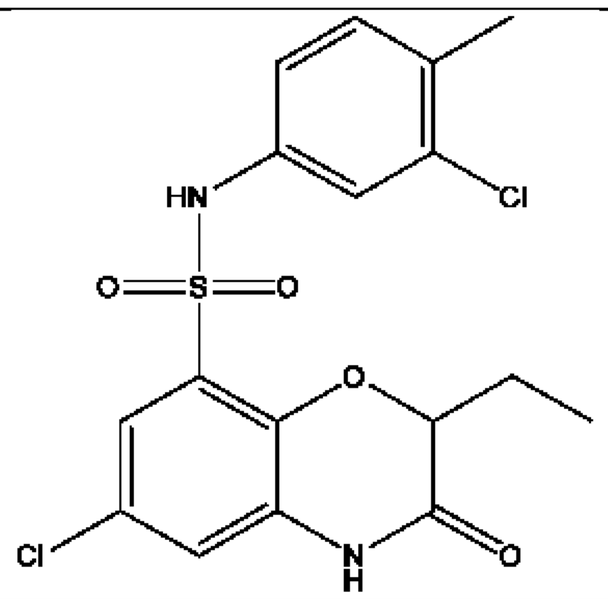
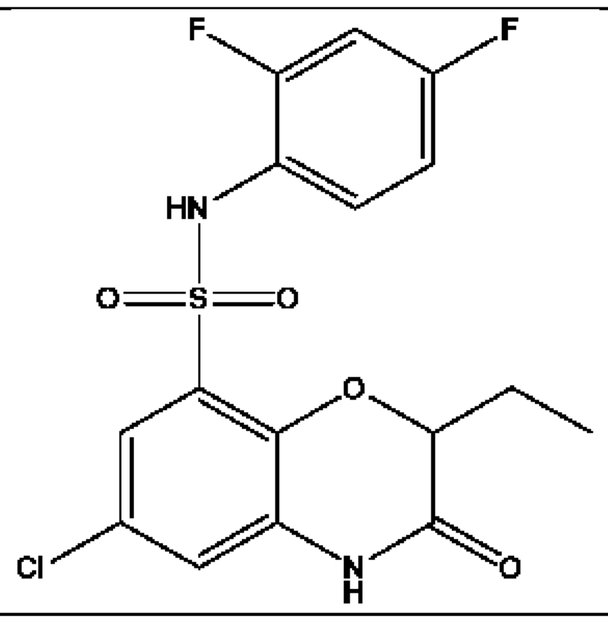
BC19548		++++	+
BC19697		++++	+
BC19699		++++	+
BC19701		++++	+

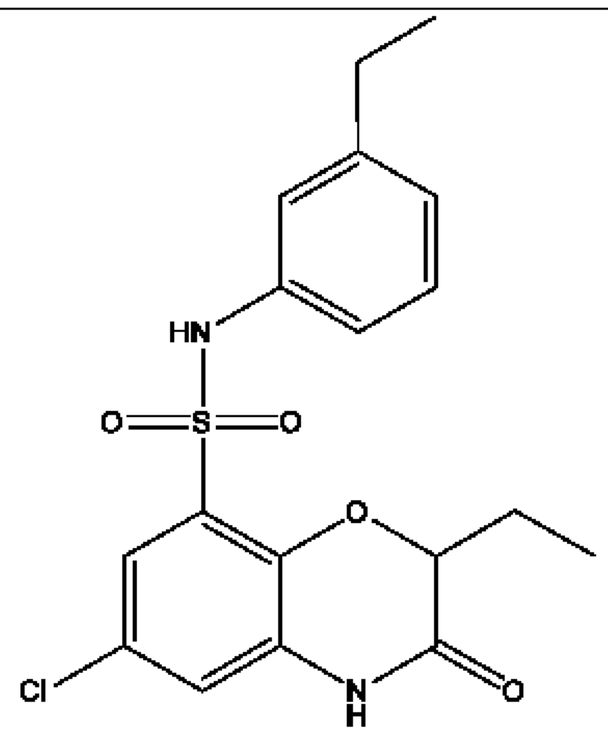
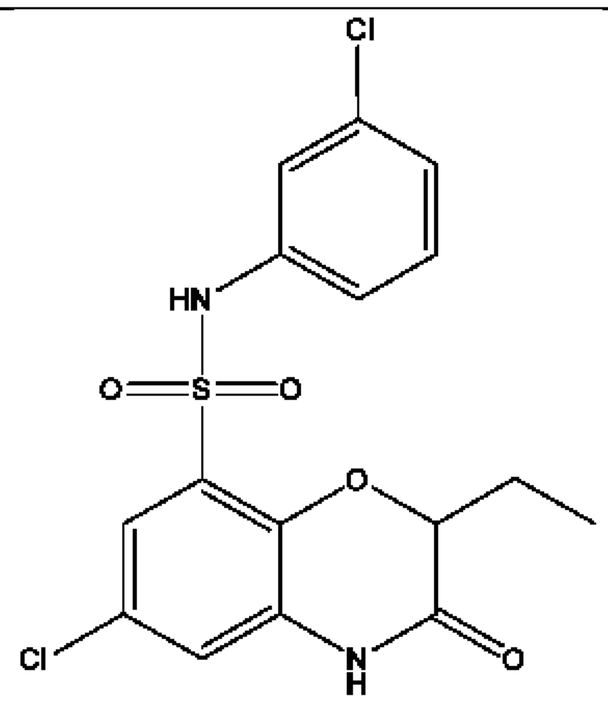
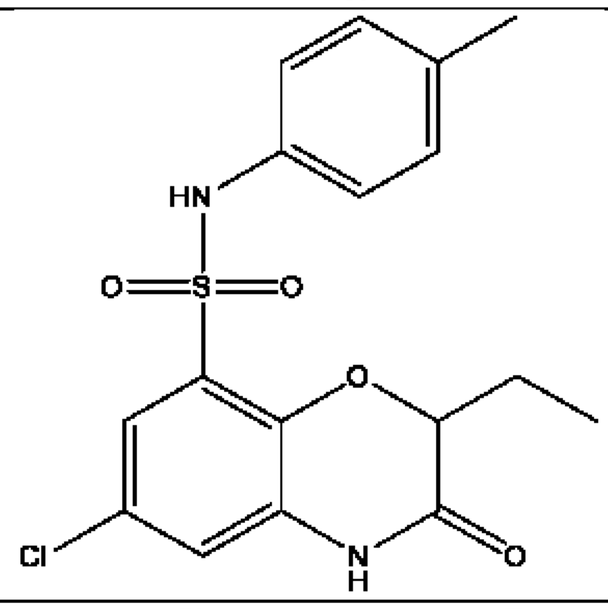
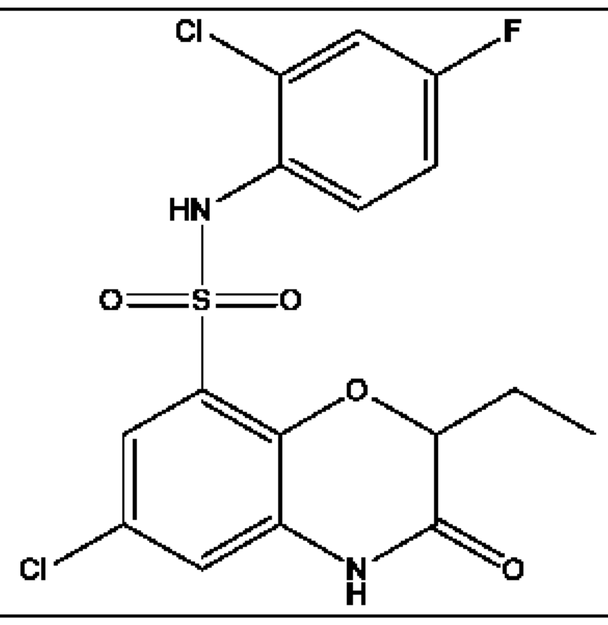
BC19703		++++	+
BC19705		++++	+
BC19707		++++	+
BC19710		++++	+

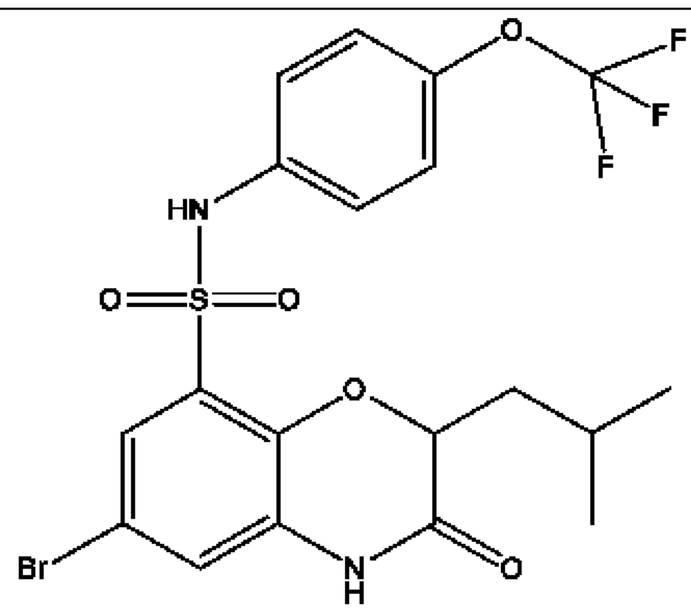
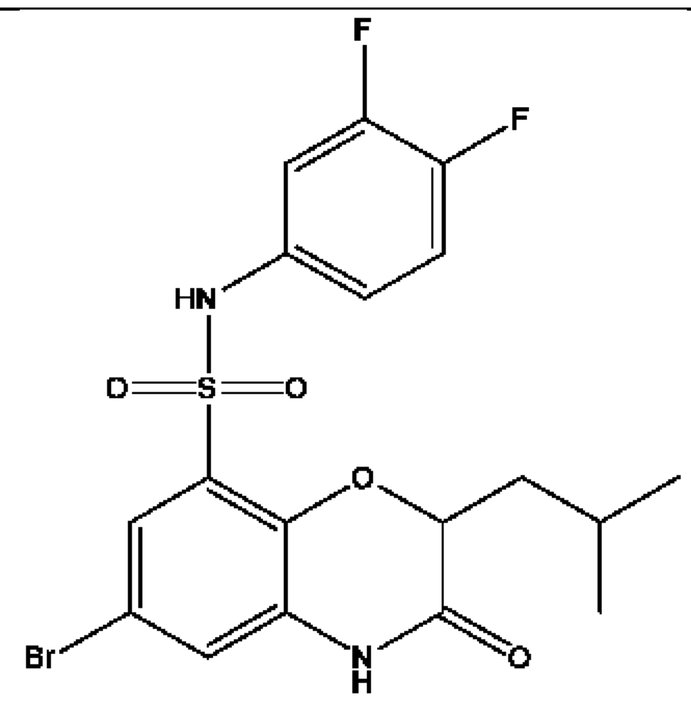
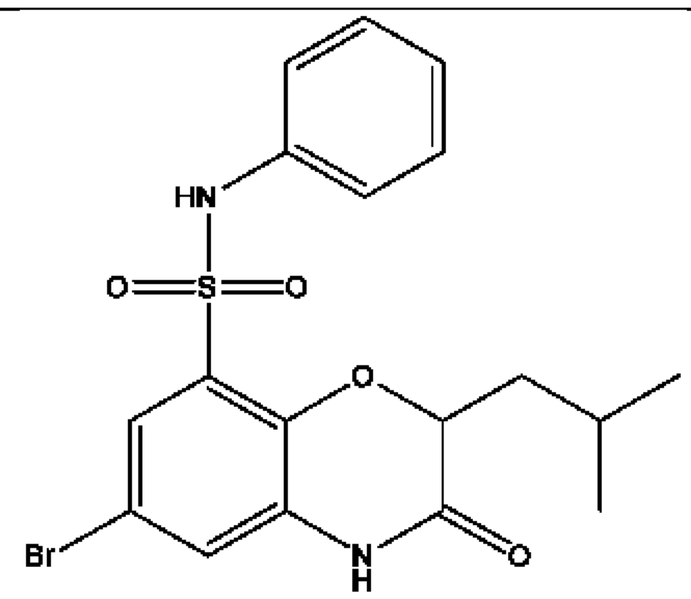
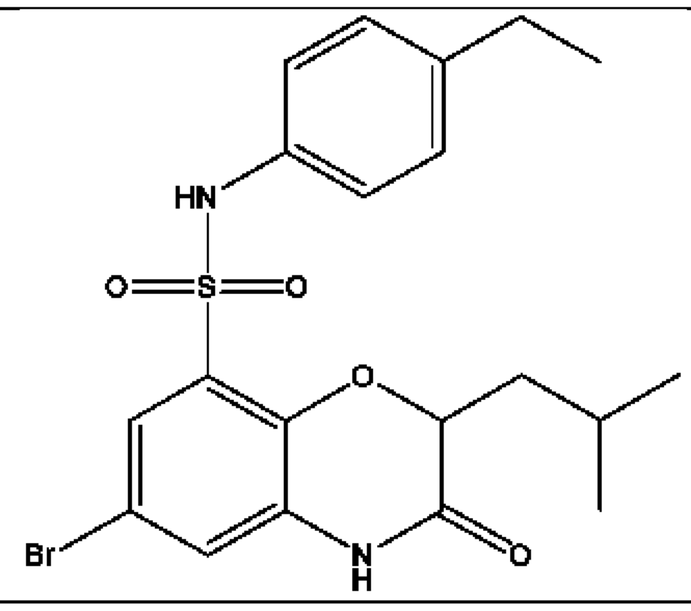
BC19712		++++	+
BC19714		++++	++
BC19716		++++	++
BC19718		++++	++

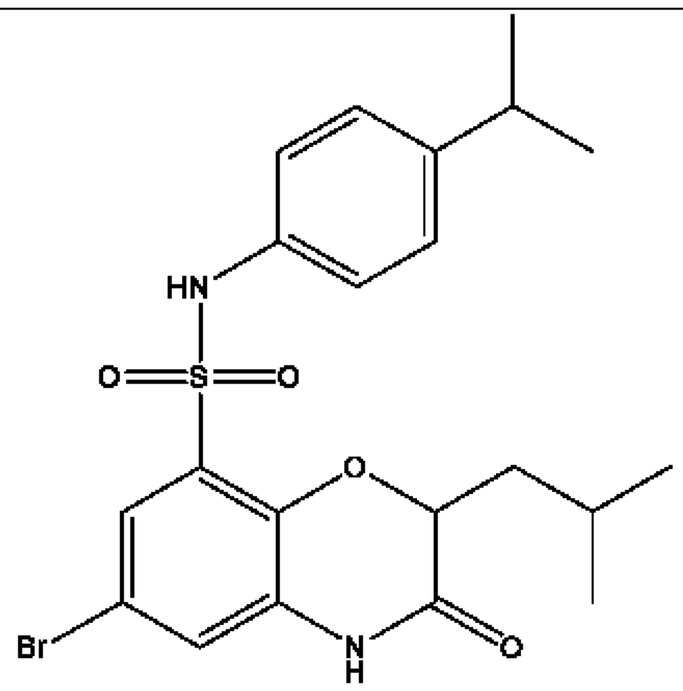
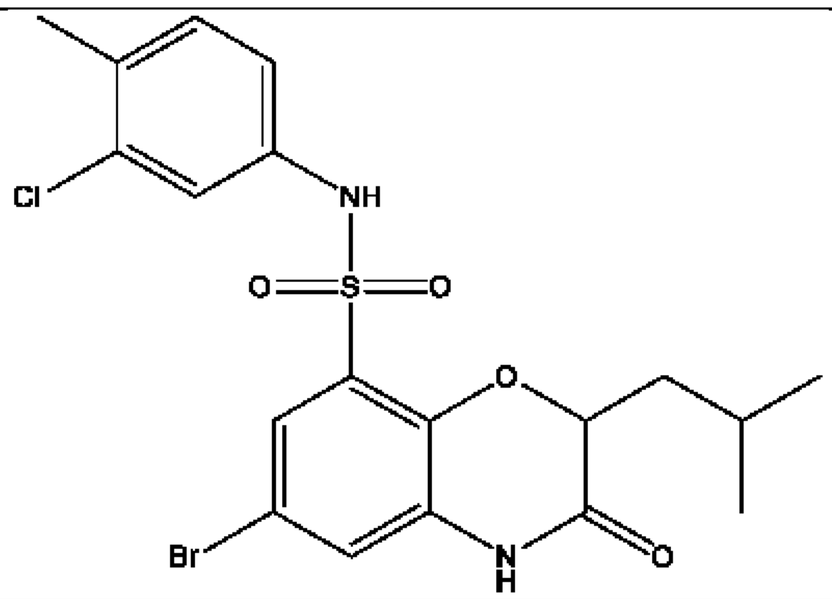
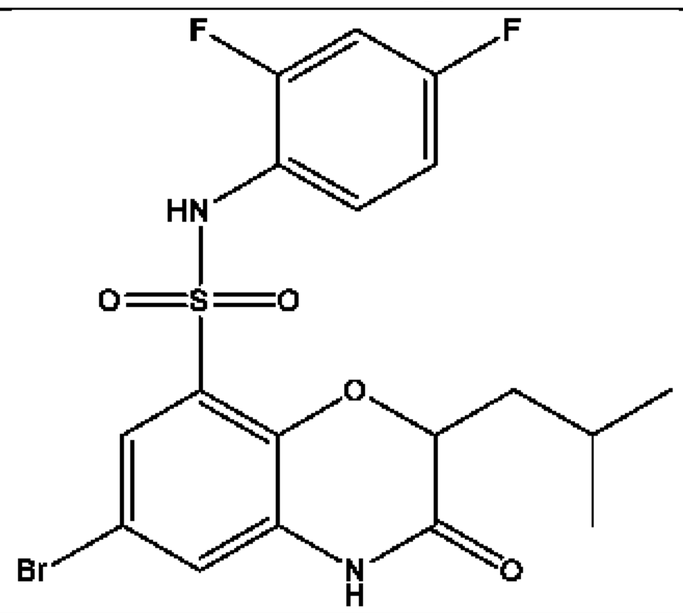
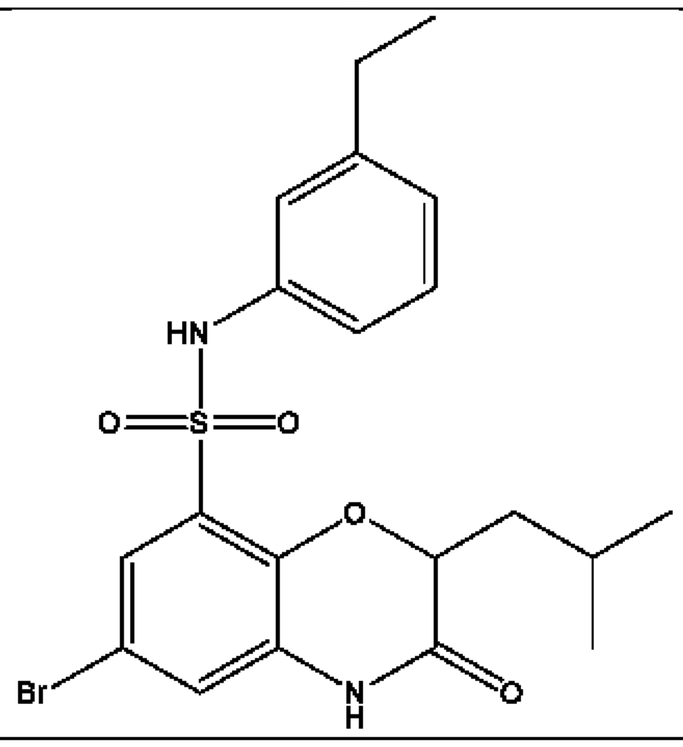
BC19720		++++	+
BC19722		++++	++
BC19730		++++	+
BC19732		++++	++

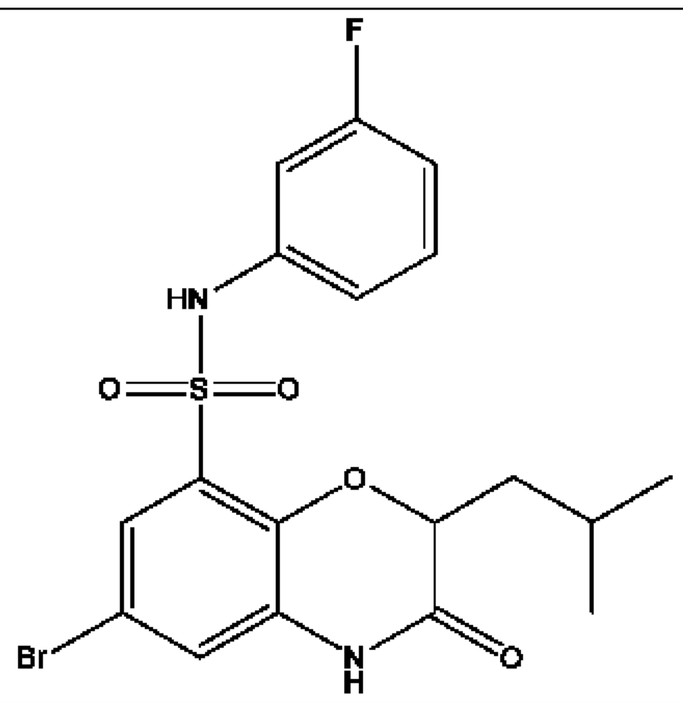
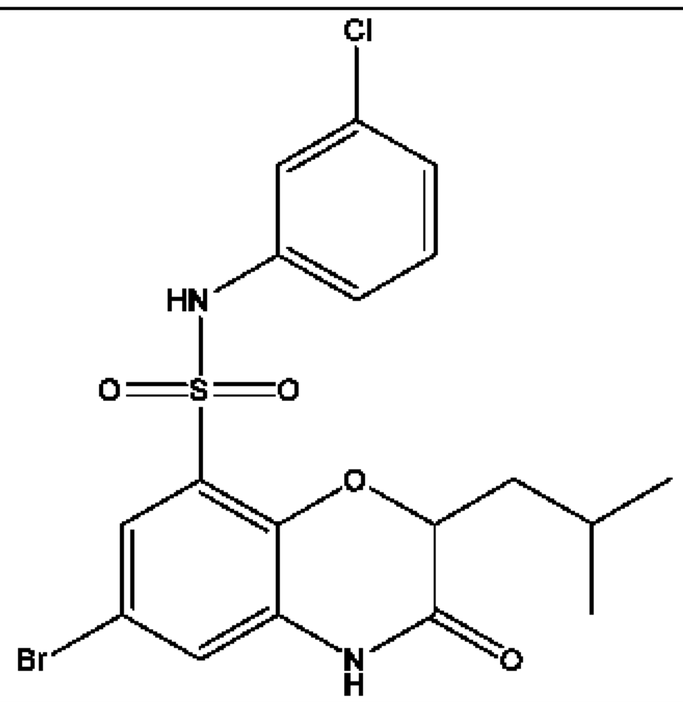
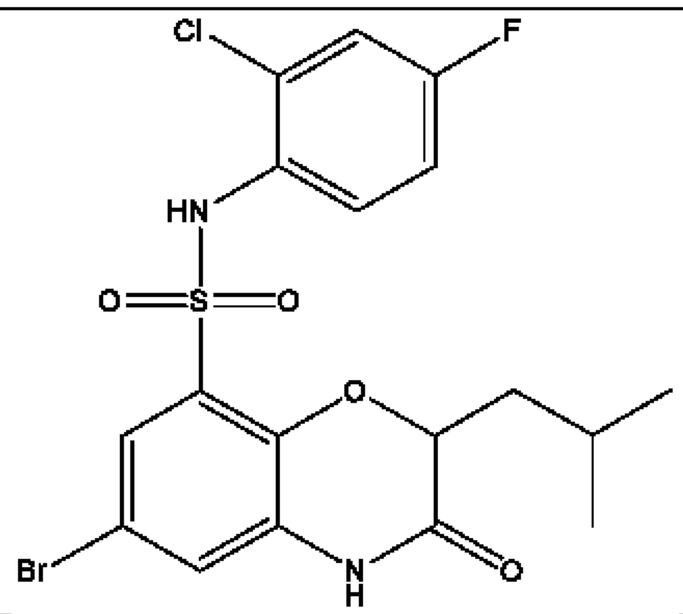
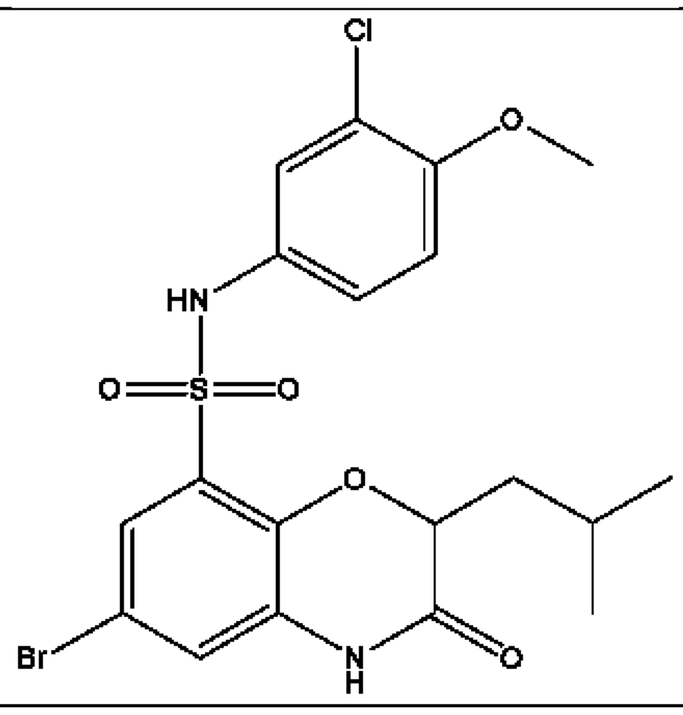
BC19734		++++	+
BC19736		++++	+
BC19738		++++	+
BC19740		++++	+

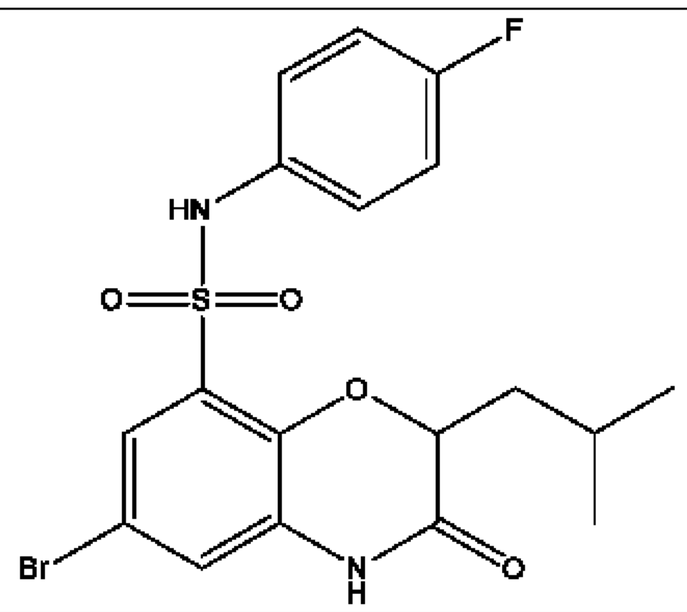
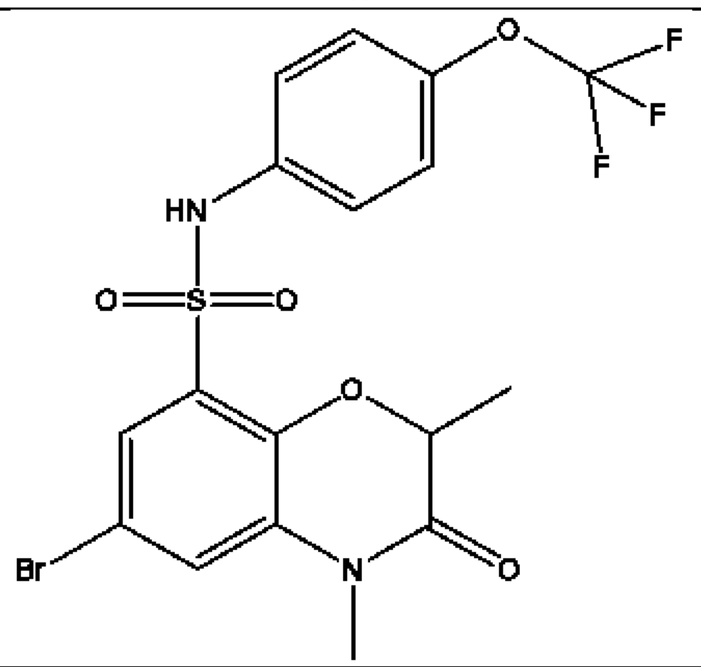
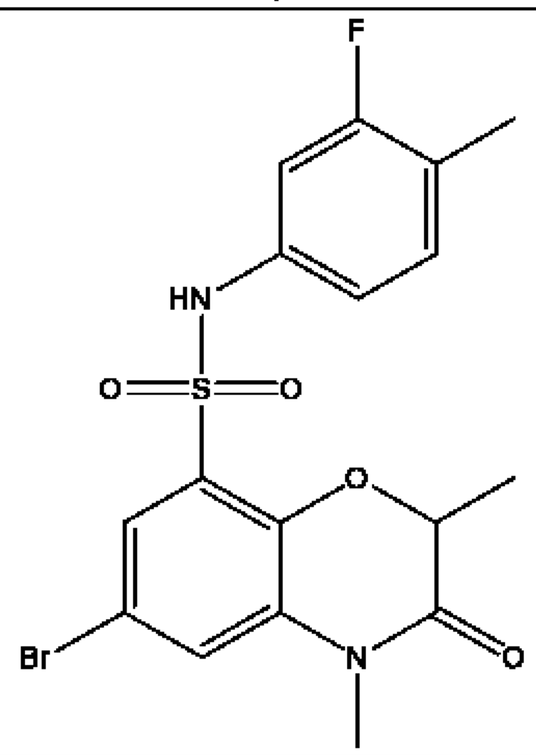
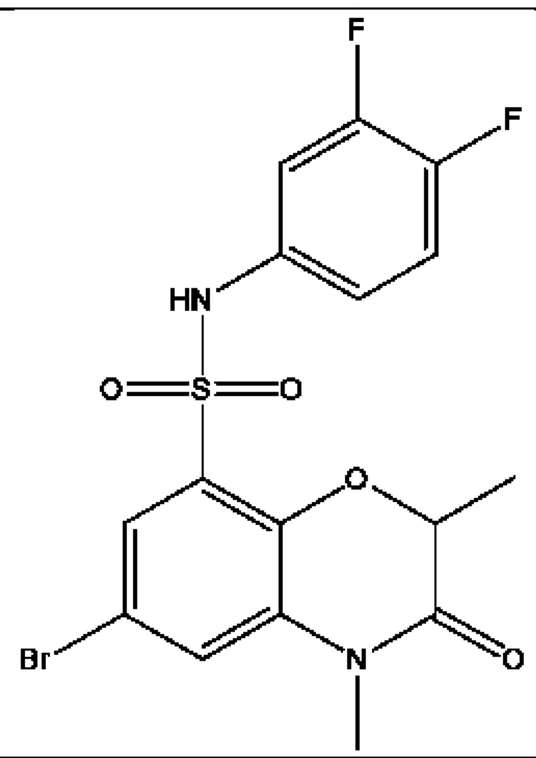
BC19742		++++	++
BC19744		++++	++
BC19746		++++	+
BC19748		++++	+

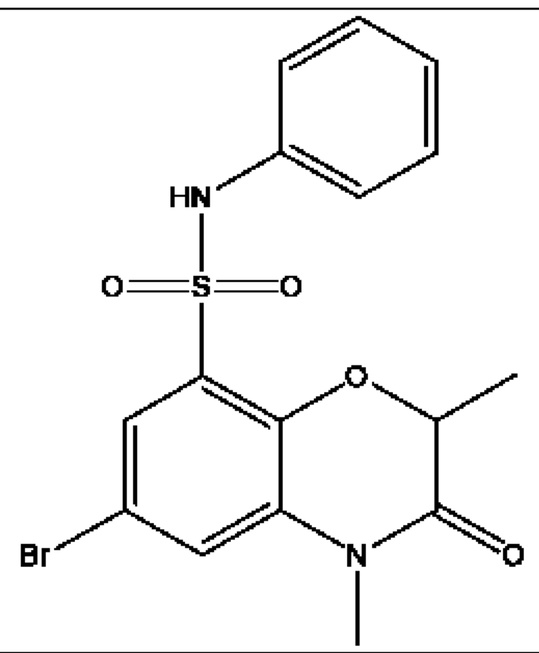
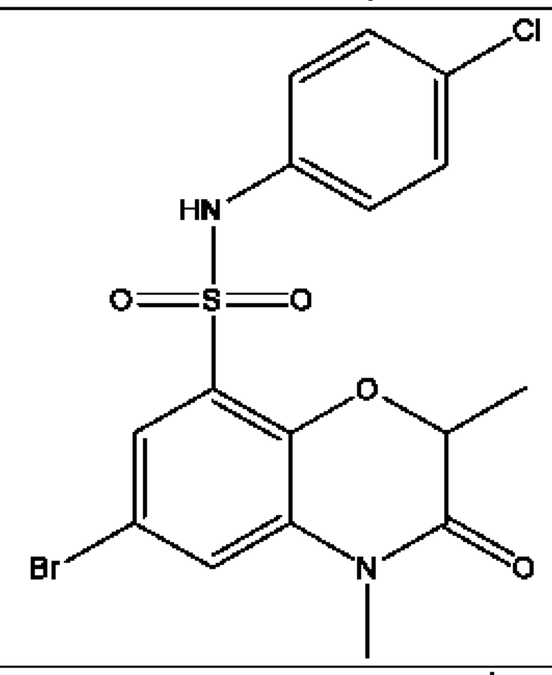
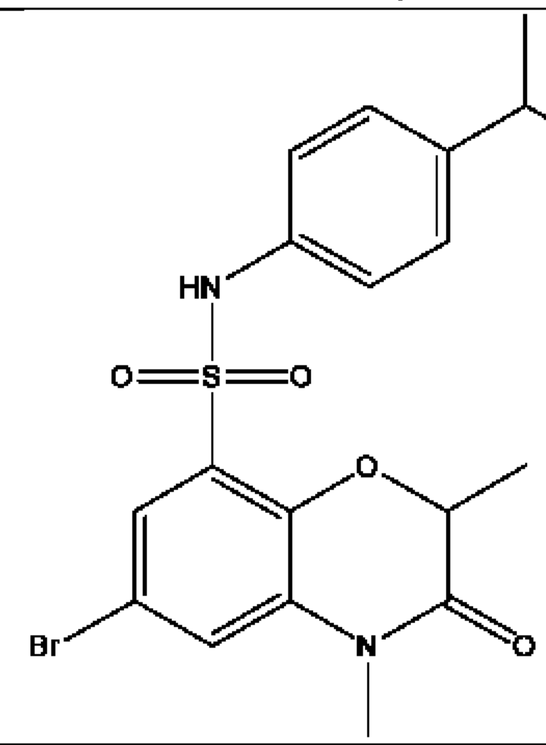
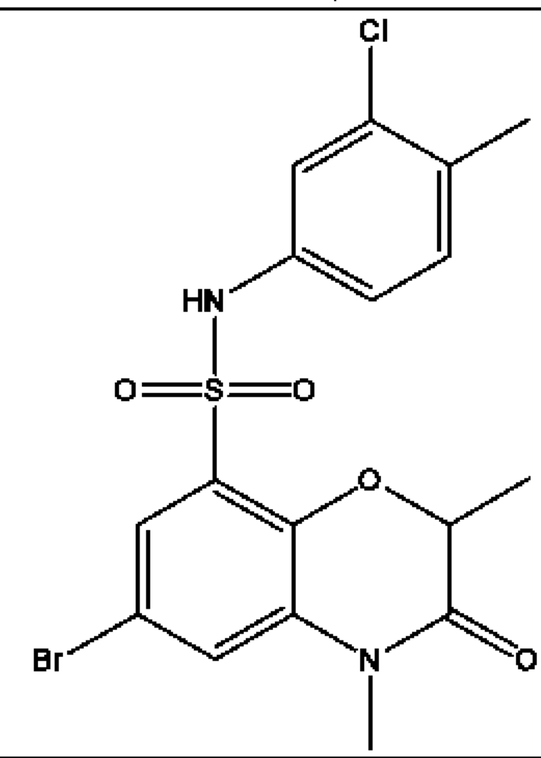
BC19750		++++	+
BC19752		++++	+
BC19754		++++	++
BC19756		++++	+

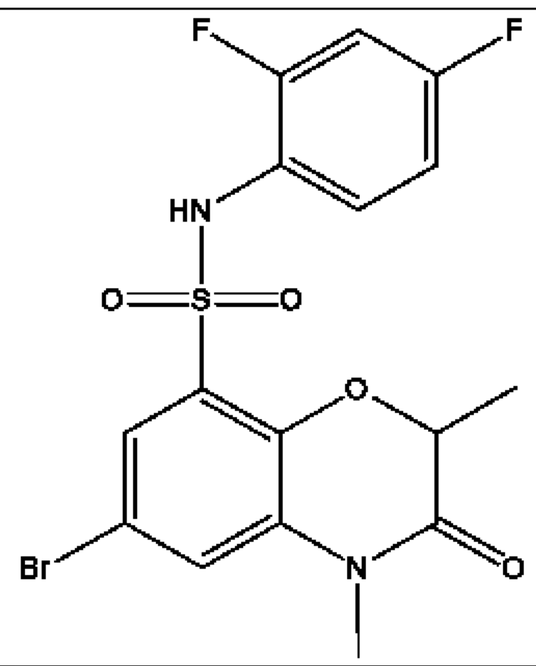
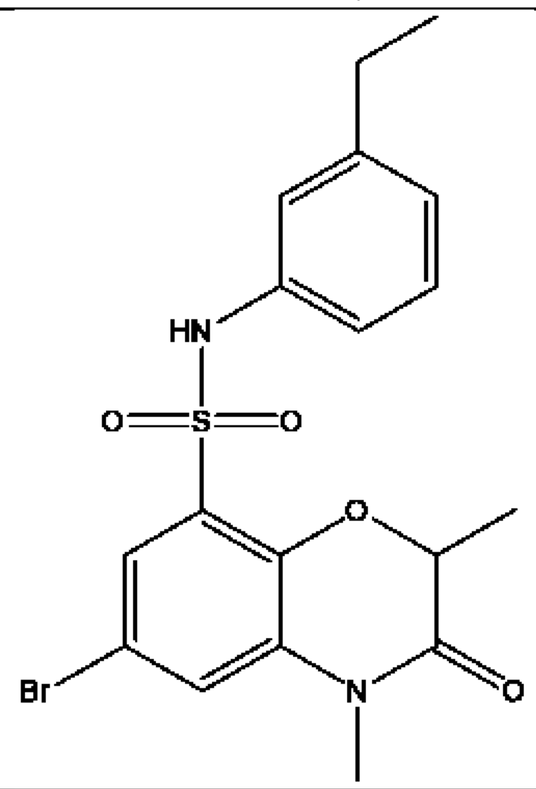
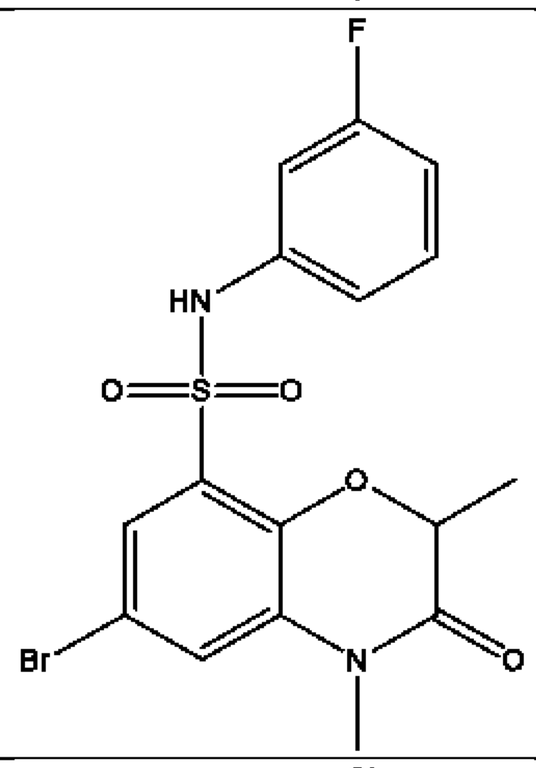
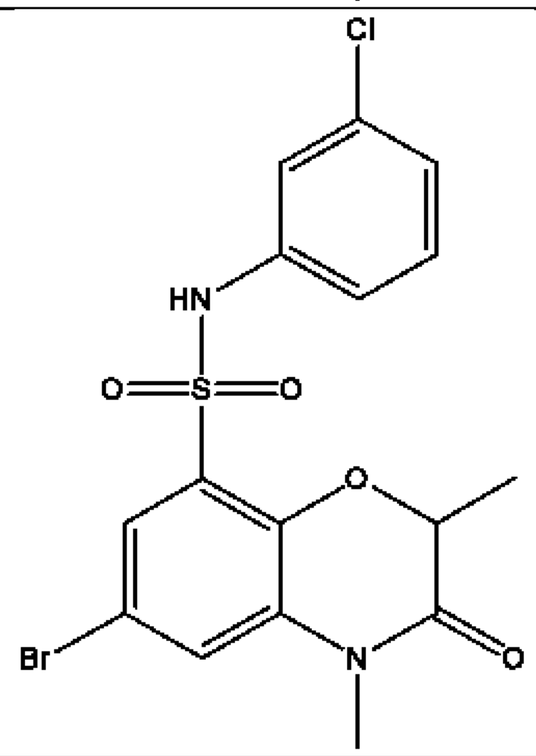
BC19757		++++	+
BC19759		++++	+
BC19761		+++	+
BC19763		+++	++

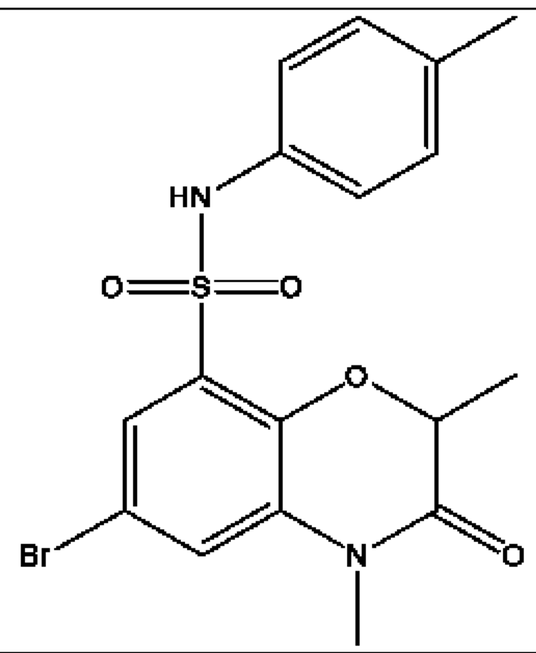
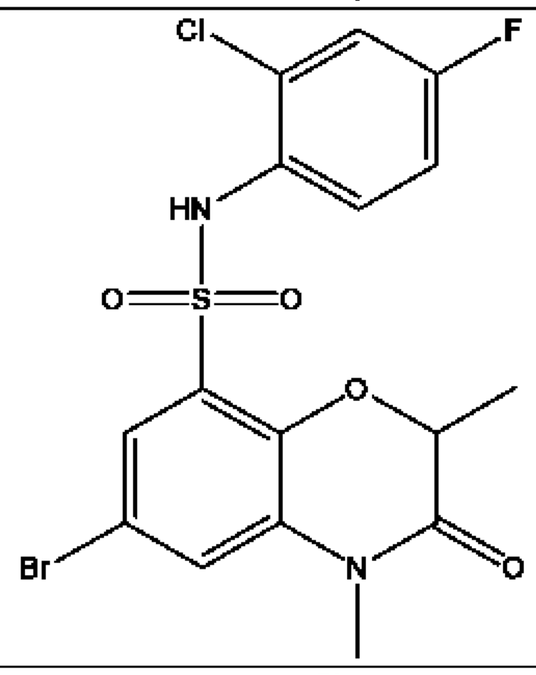
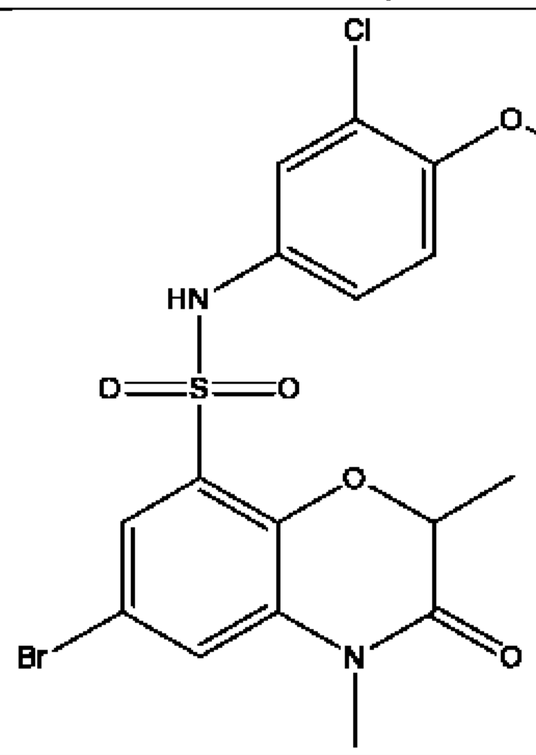
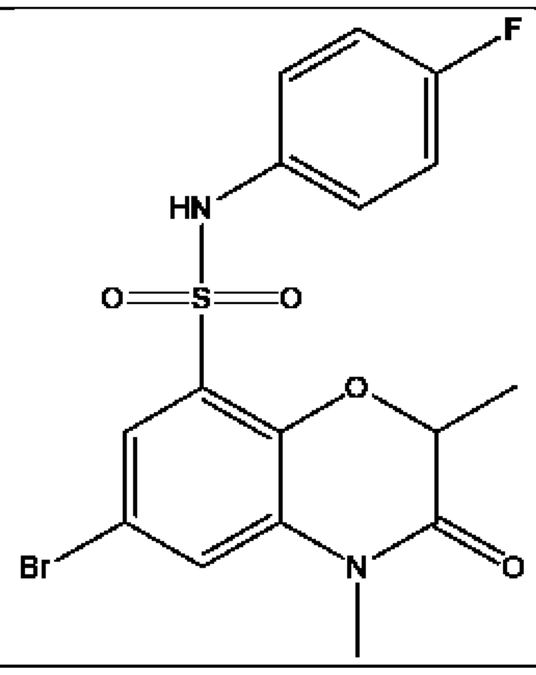
BC19765		++++	+
BC19767		++++	+
BC19769		++++	+
BC19771		++++	+

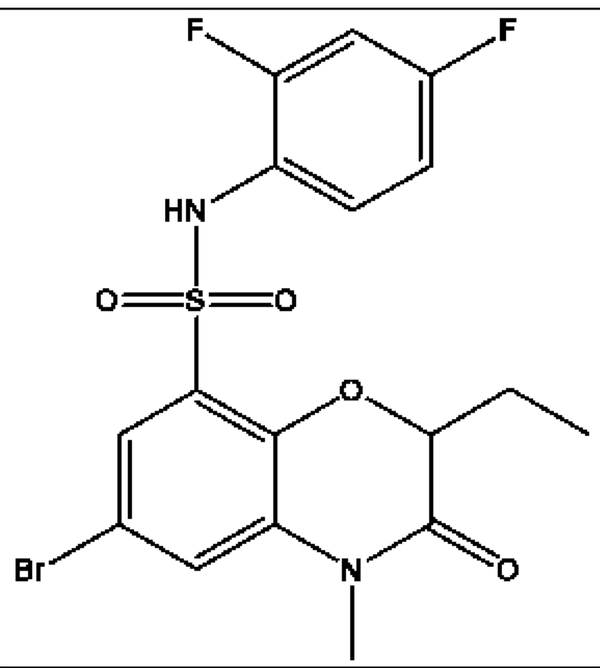
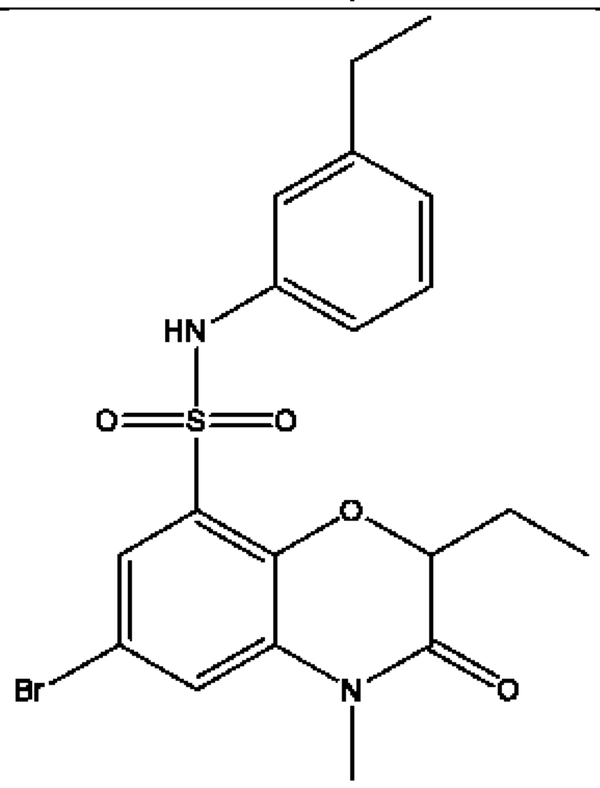
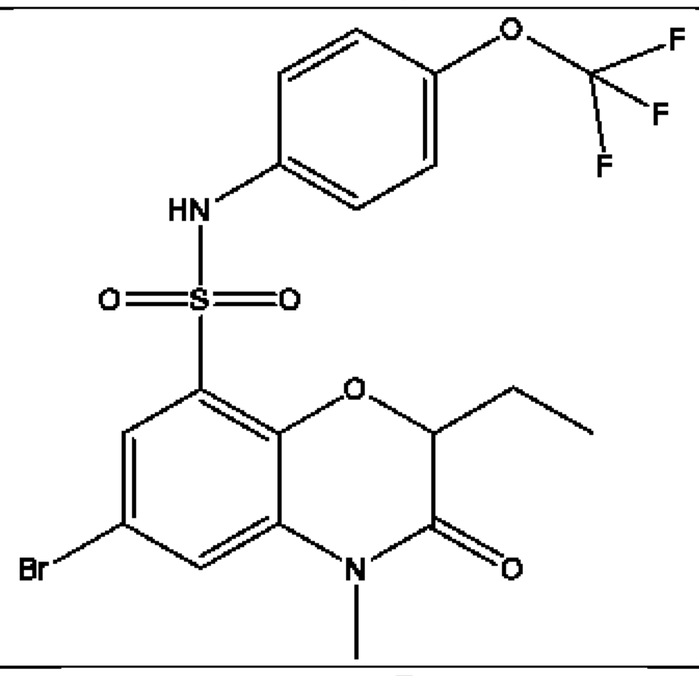
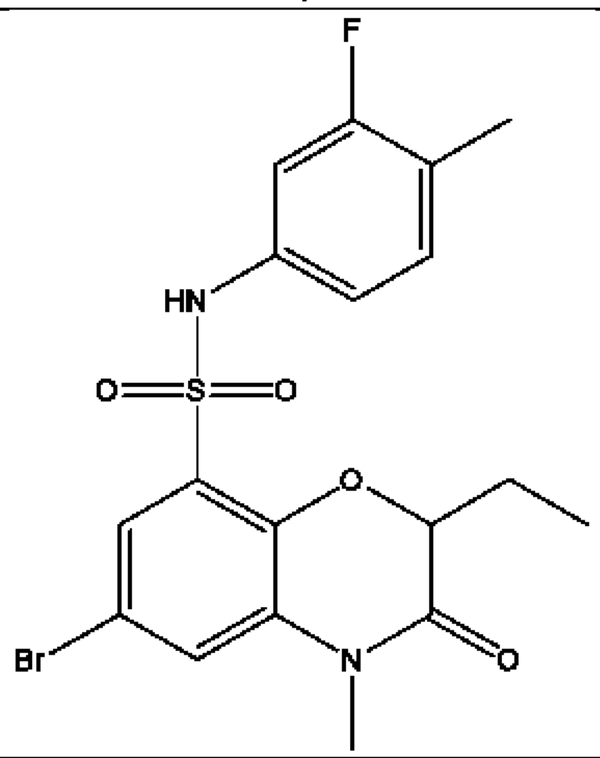
BC19773		++++	+
BC19775		++++	+
BC19777		++++	+
BC19779		+++	++

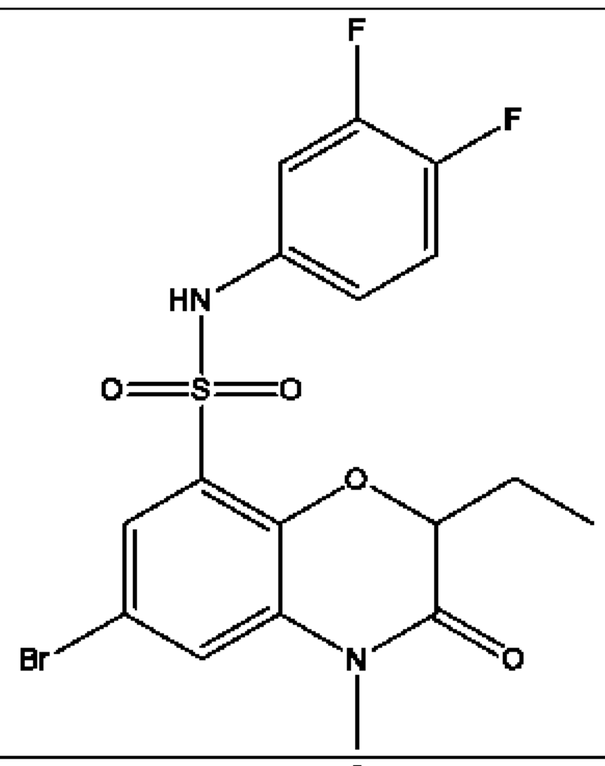
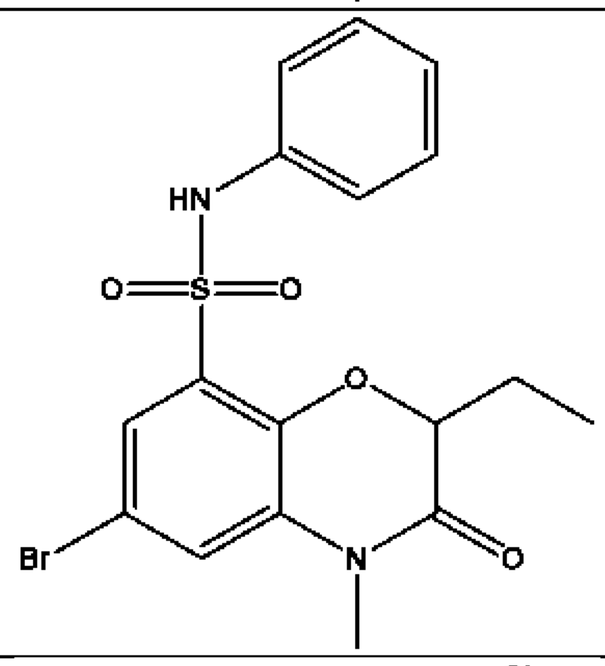
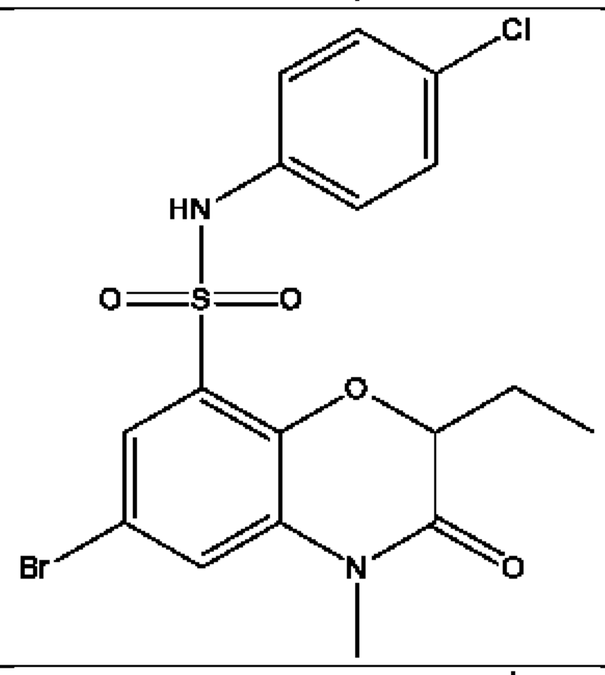
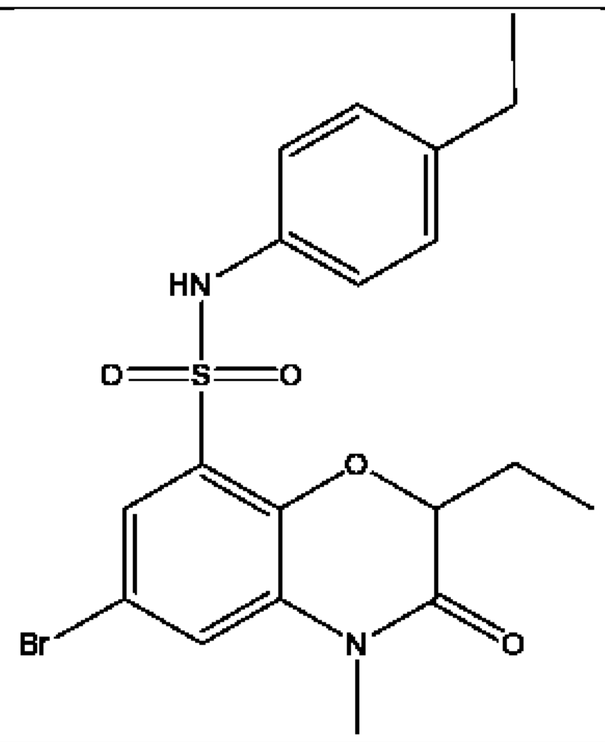
BC19781		++++	++
BC19783		++++	+
BC19785		++++	+
BC19787		++++	+

BC19789		++++	++
BC19791		++++	+
BC19793		++++	+
BC19796		++++	++

BC19798		++++	++
BC19900		+++	+
BC19902		++++	+
BC19904		++++	+

BC19906		++++	++
BC19908		++++	+
BC19909		+	+
BC19911		++++	+

BC19913		++++	+
BC19915		++++	+
BC19921		++++	++
BC19923		++++	++

BC19925		++++	++
BC19927		++++	++
BC19929		++++	++
BC19931		++++	++

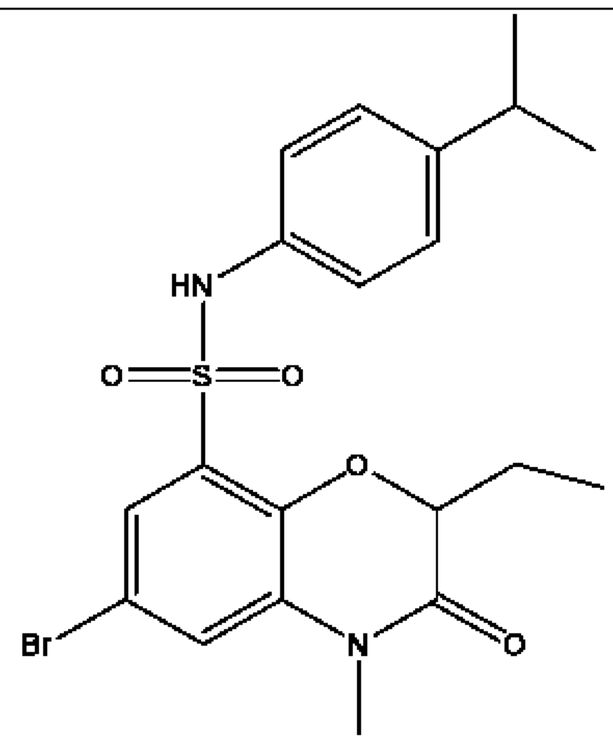
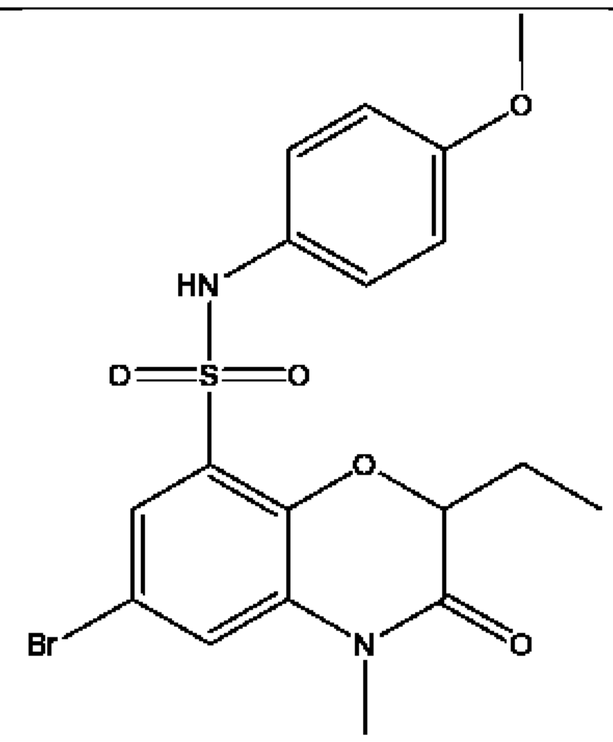
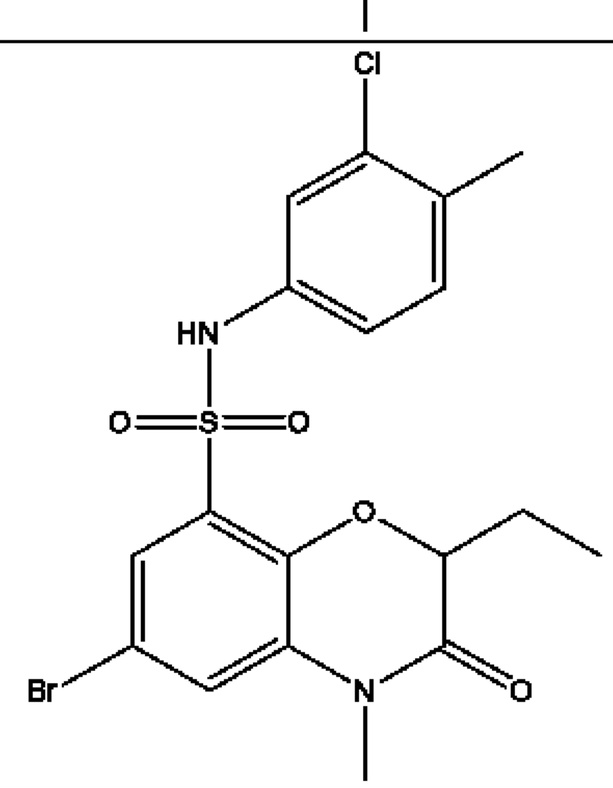
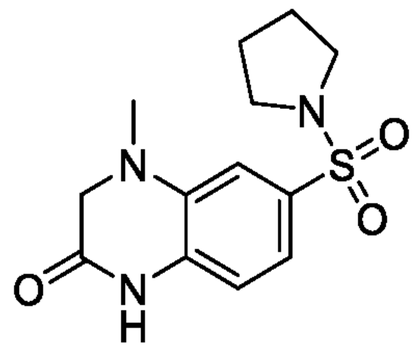
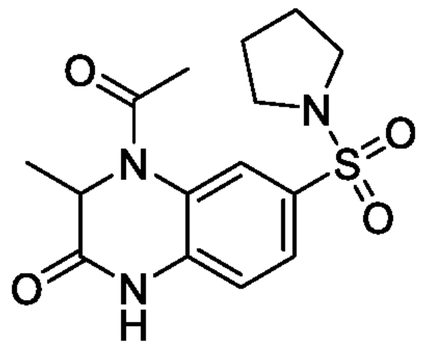
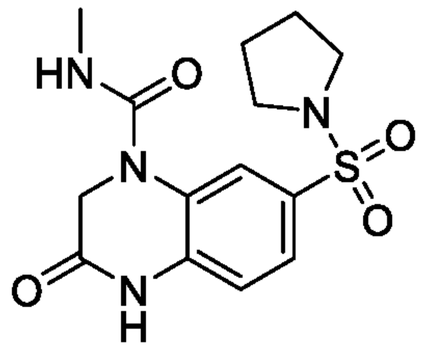
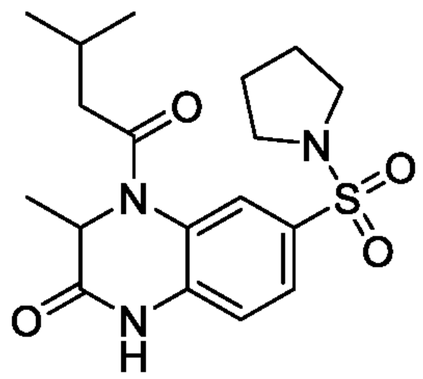
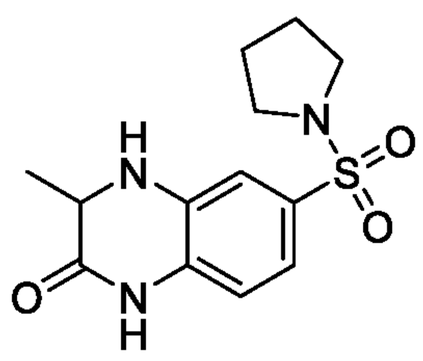
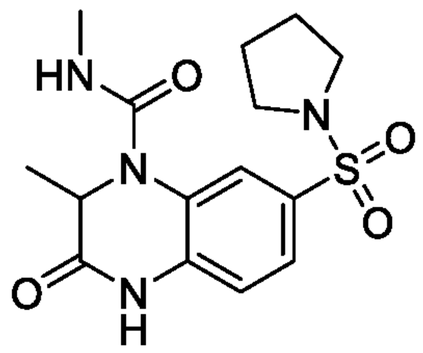
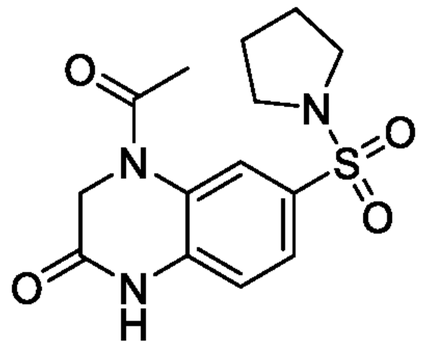
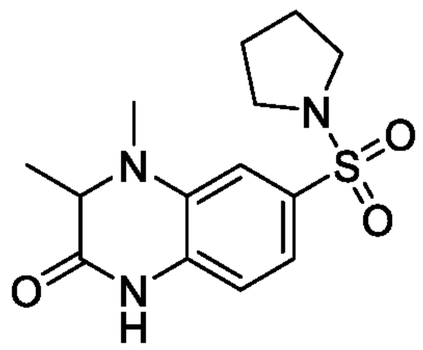
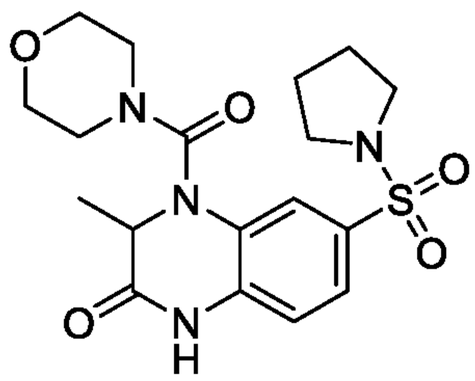
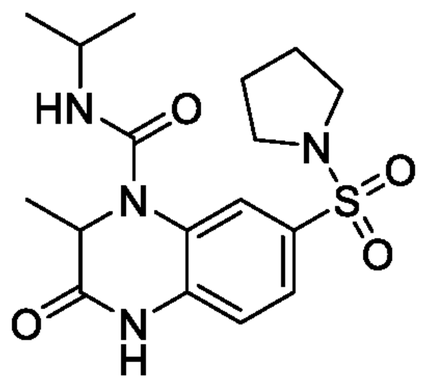
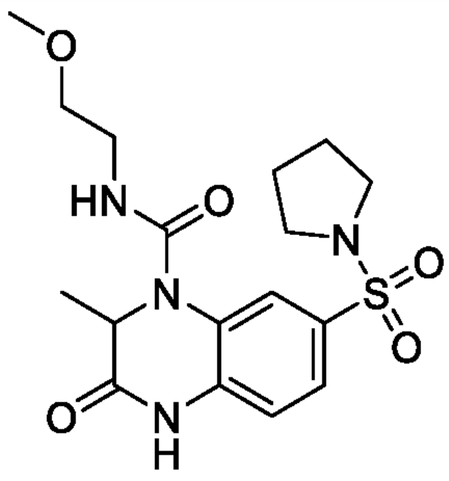
BC19933		++++	++
BC19935		++++	++
BC19937		++++	++

Table 2e

BC No.	ZE No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19181	ZE25-0002		+	+
BC19182	ZE25-0005		+	+
BC19183	ZE25-0017		+	+
BC19184	ZE25-0026		+	+
BC19235	ZE25-0015		+	+

BC19236	ZE25-0028		+	+
BC19295	ZE25-0001		++++	+
BC19296	ZE25-0007		++	+
BC19297	ZE25-0030		++	+
BC19298	ZE25-0032		++++	+
BC19299	ZE25-0033		++	+

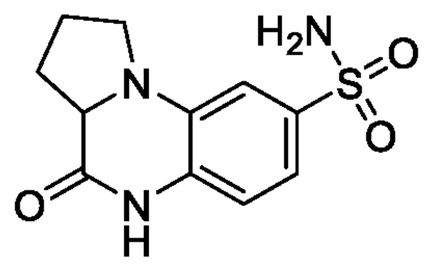
BC19300	ZE25-0039		+++	+

Table 16

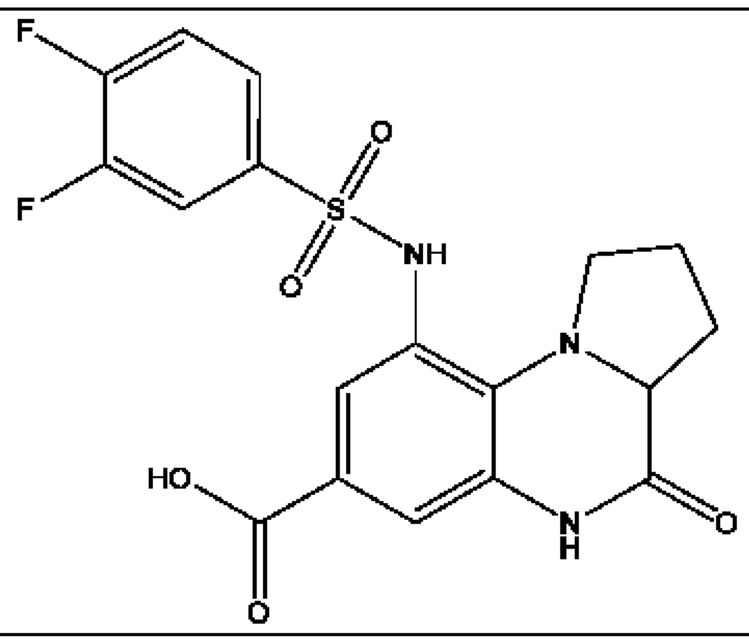
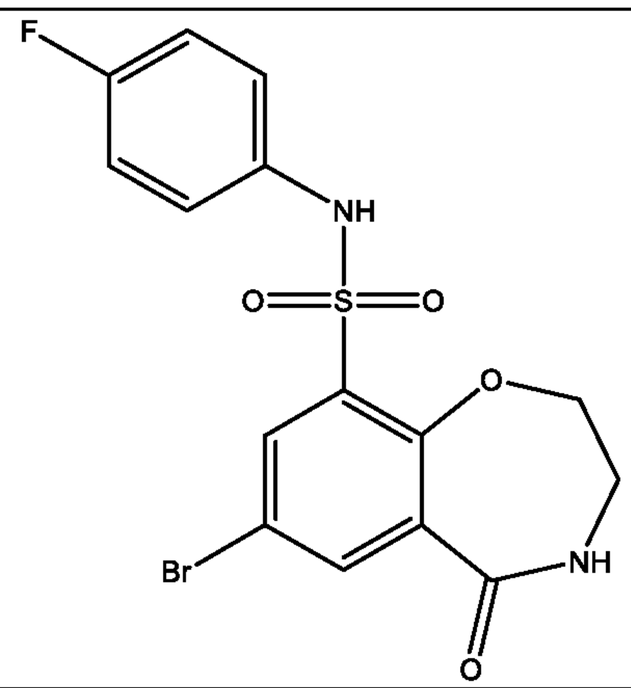
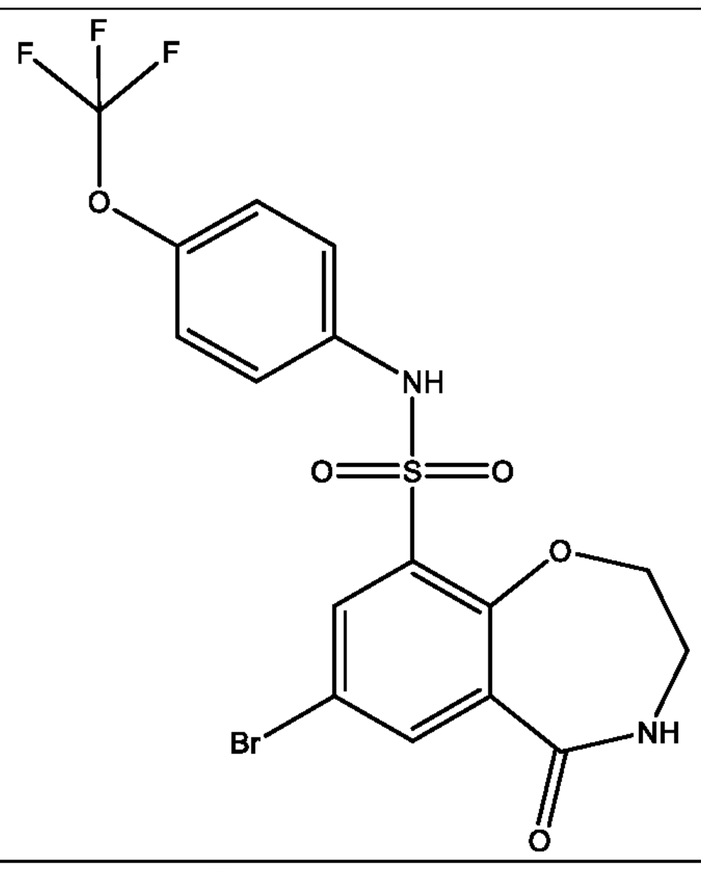
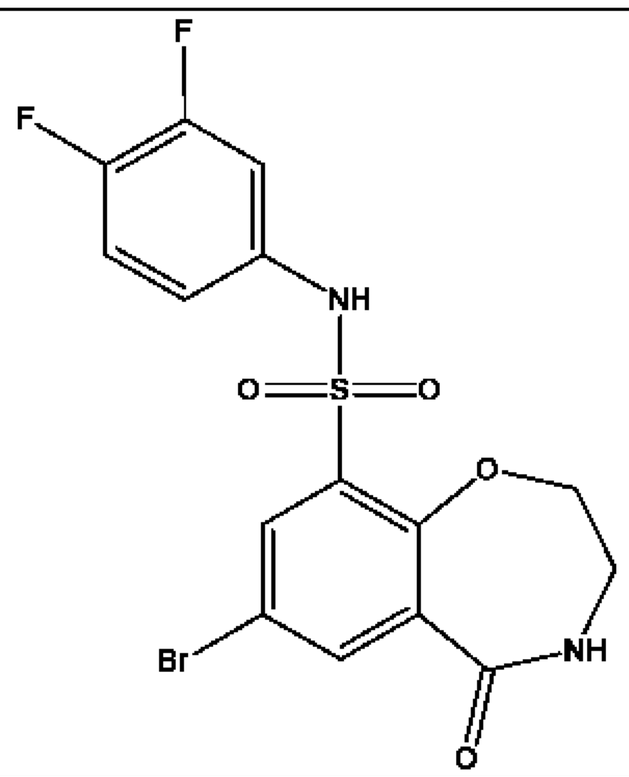
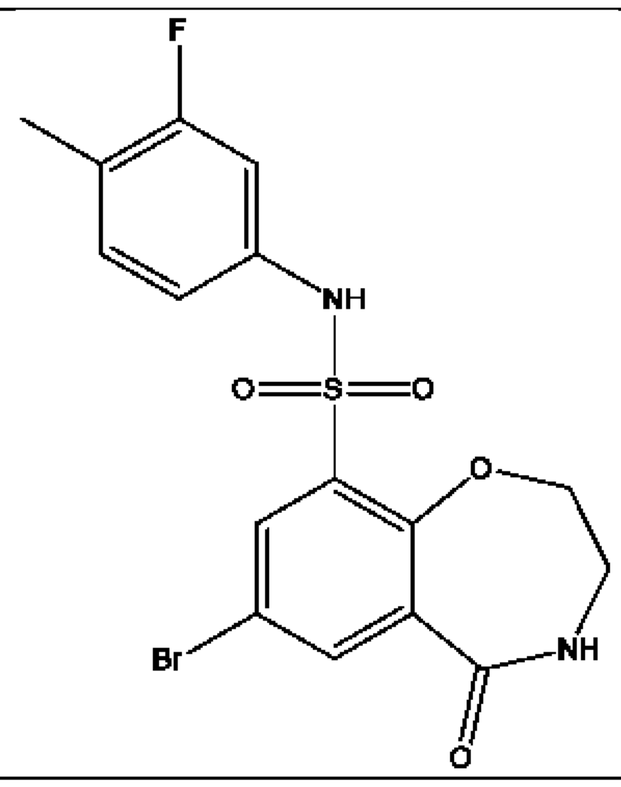
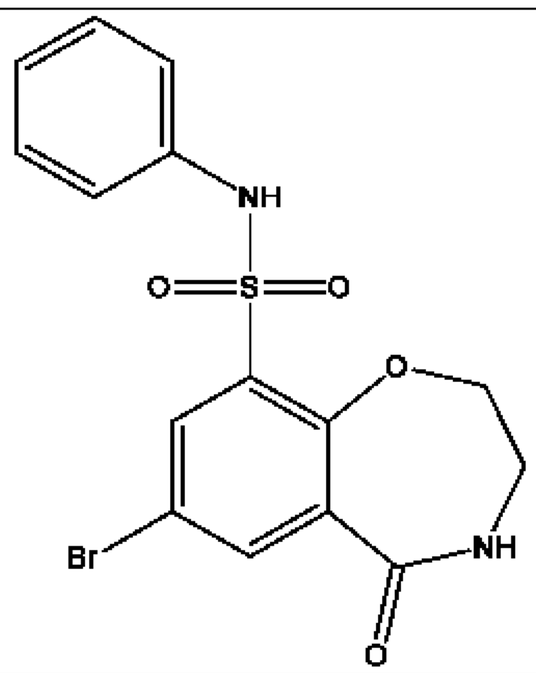
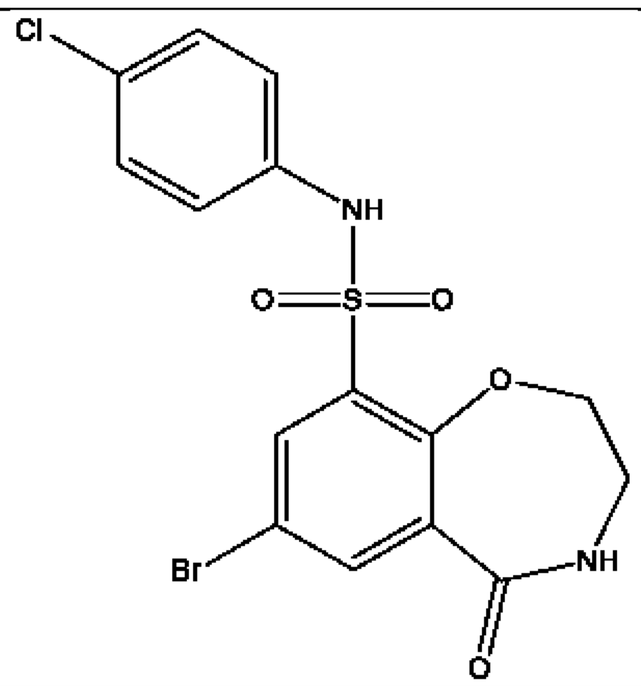
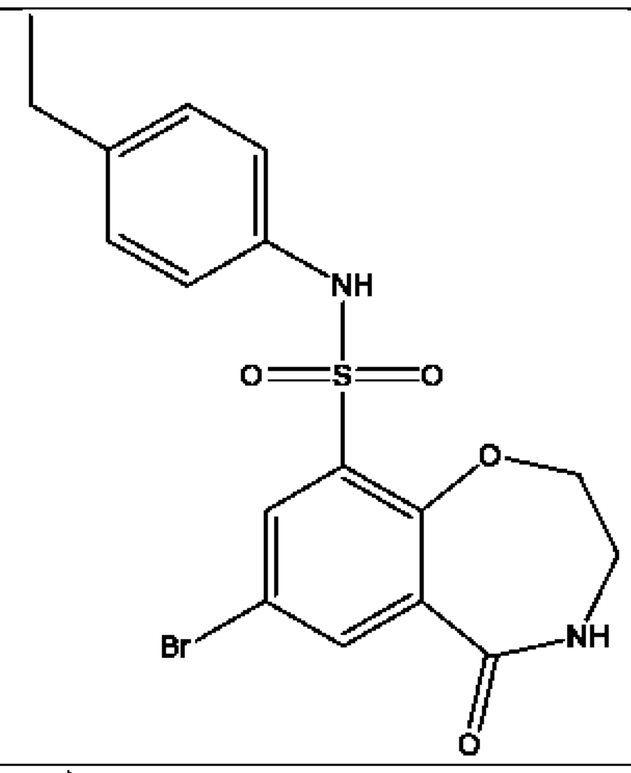
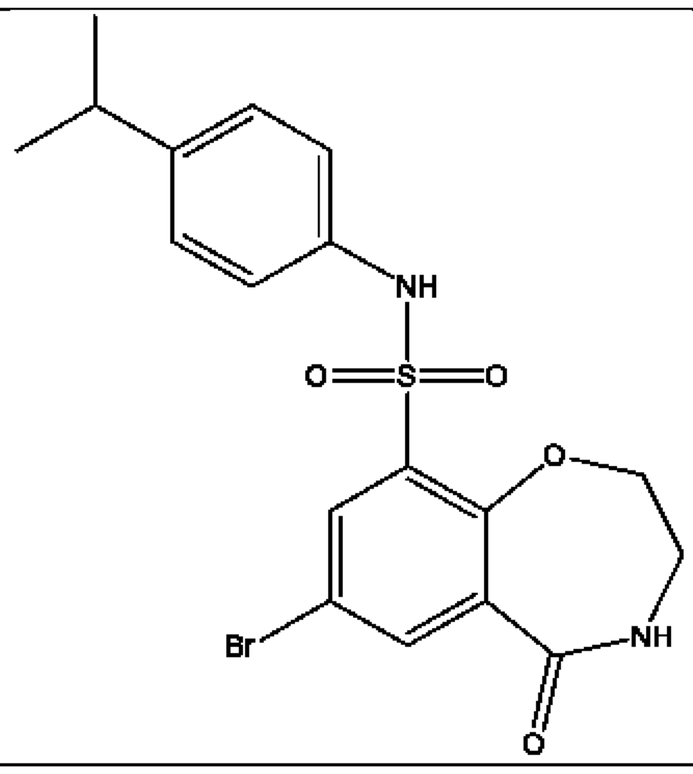
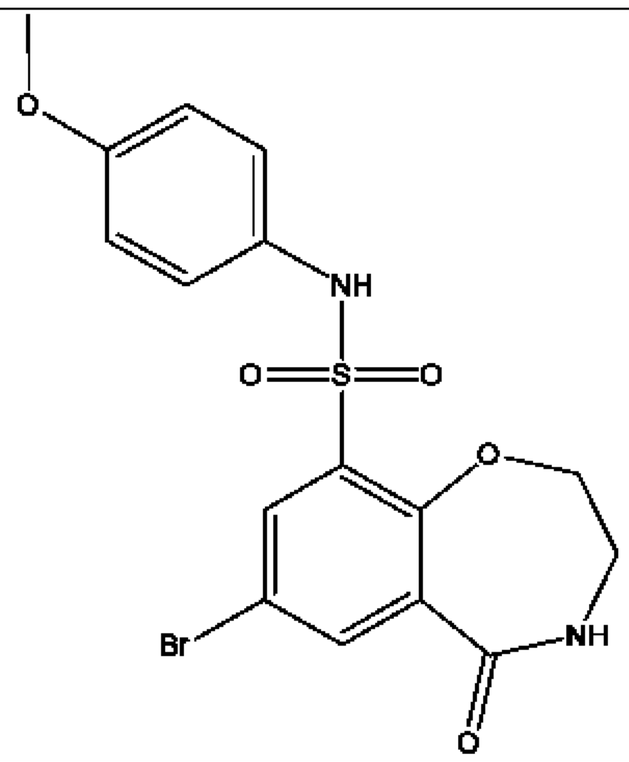
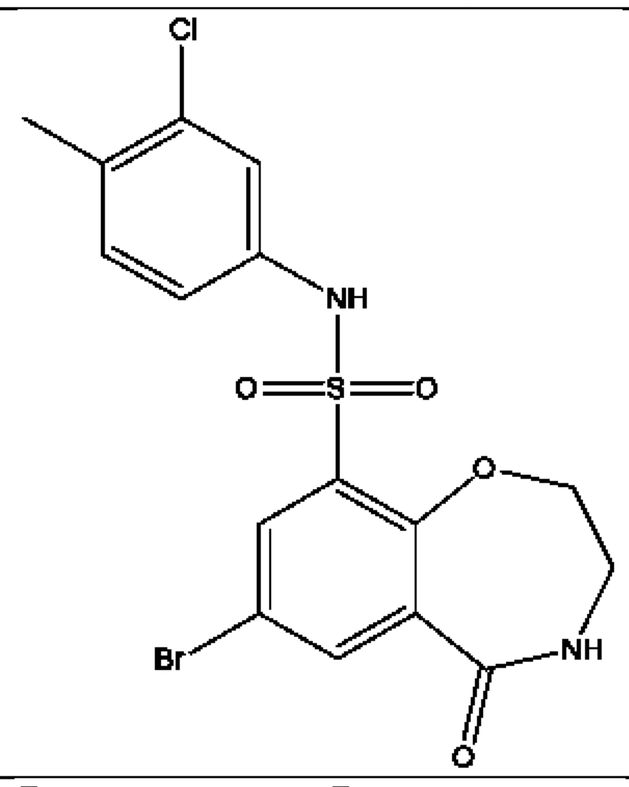
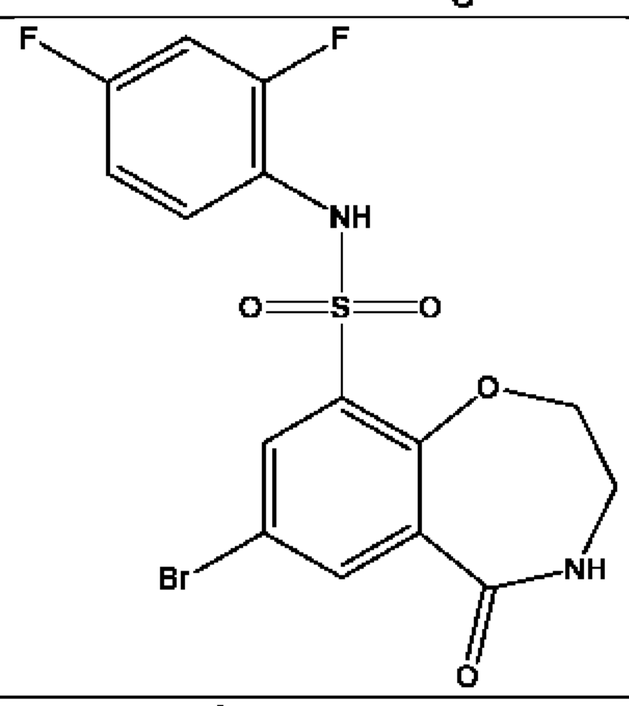
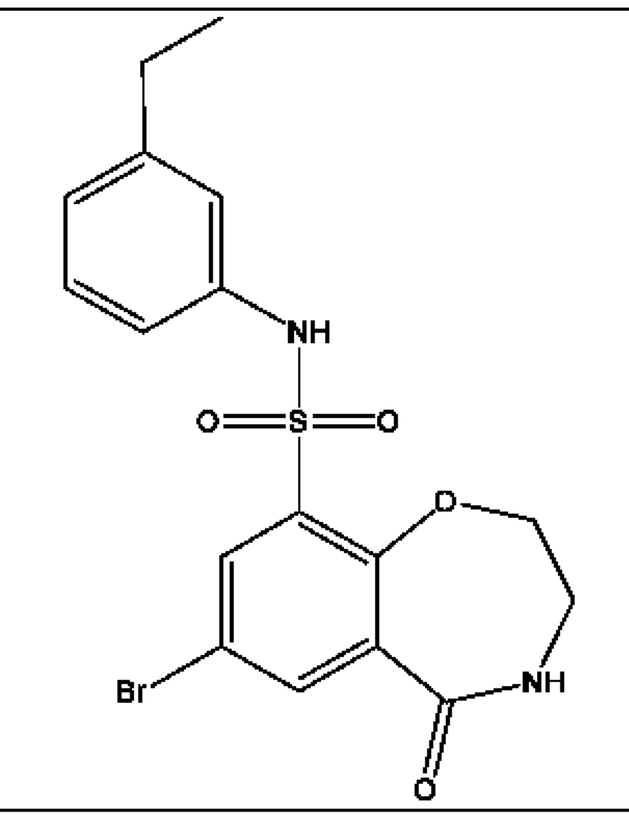
BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19917		+	+

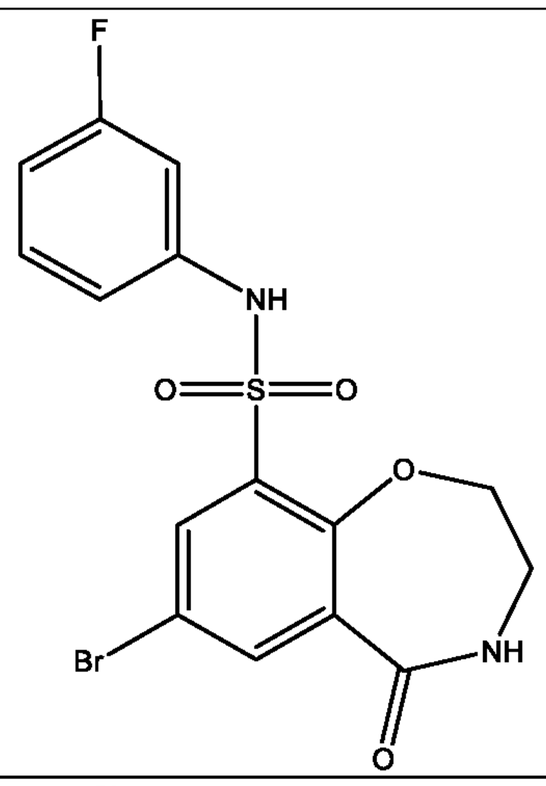
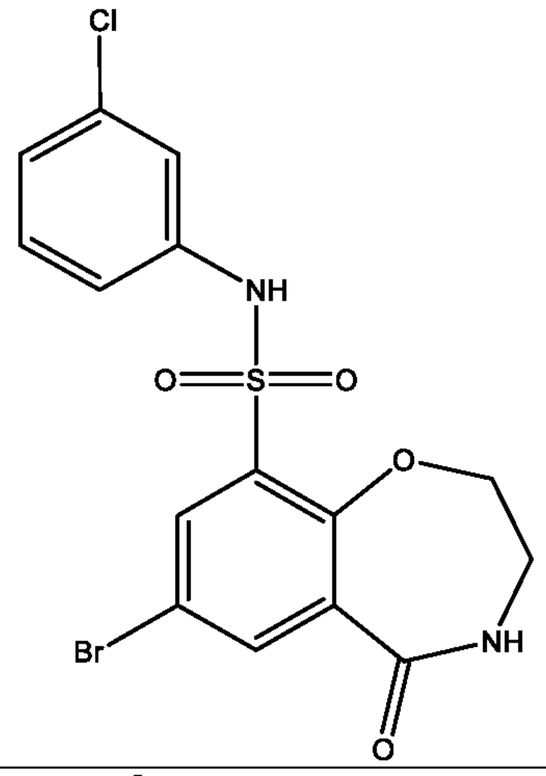
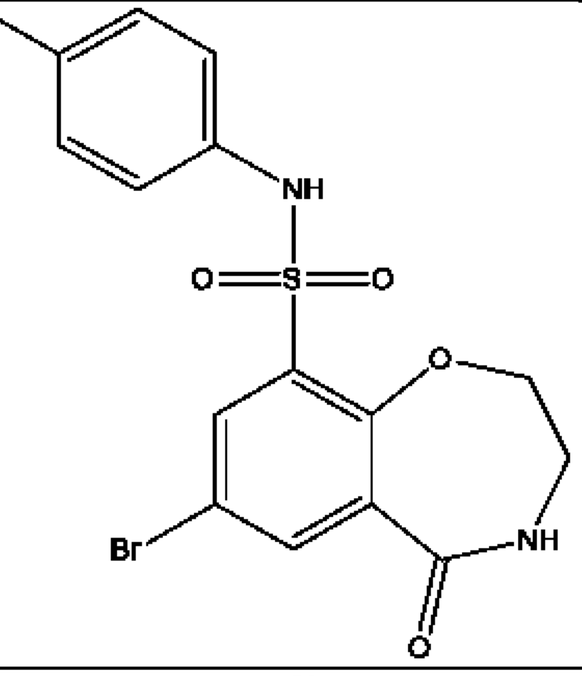
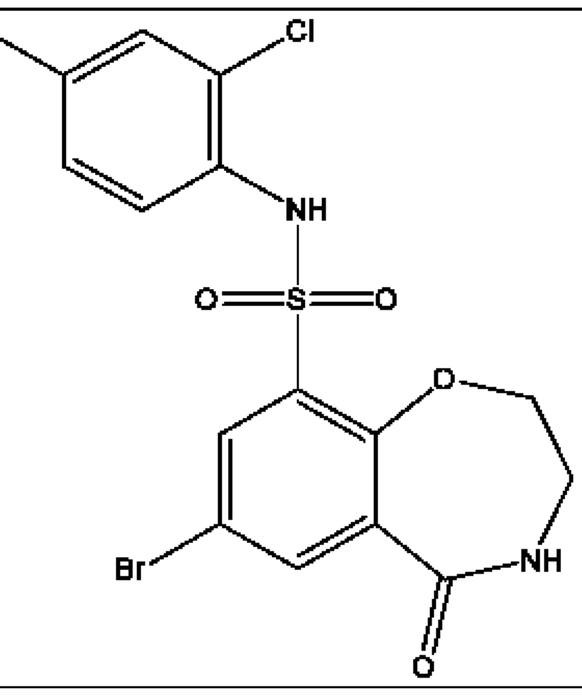
Table 2f

BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19549		++	+

BC19550		++++	+
BC19551		+++	+
BC19552		+++	+

BC19553		++	+
BC19603		+++	+
BC19604		++	+
BC19605		+	+

BC19606		++	+
BC19607		+++	+
BC19608		++	+
BC19609		++	+

BC19610		+++	+
BC19611		++++	+
BC19612		++	+
BC19613		+	+

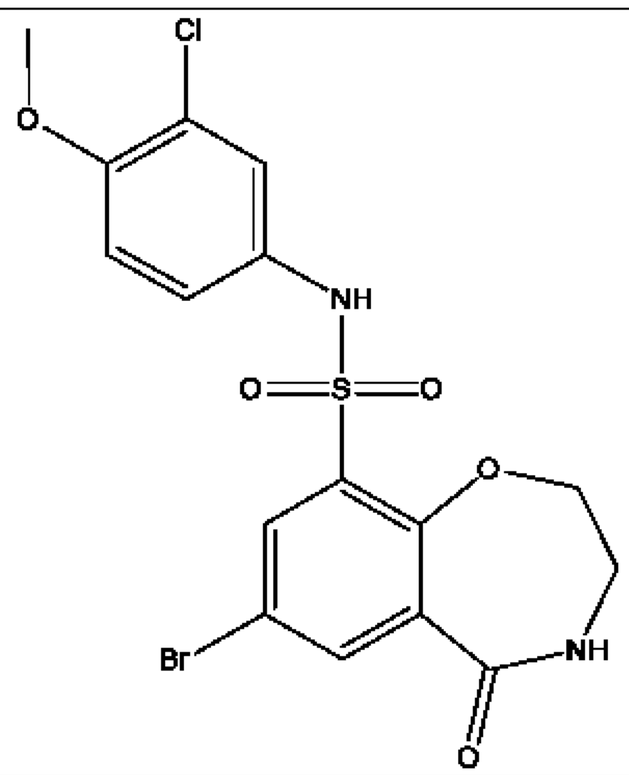
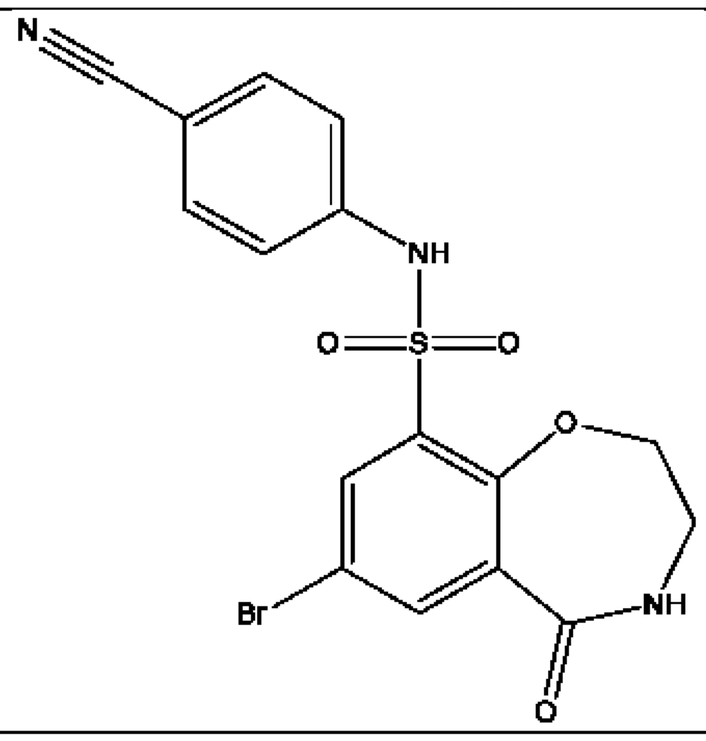
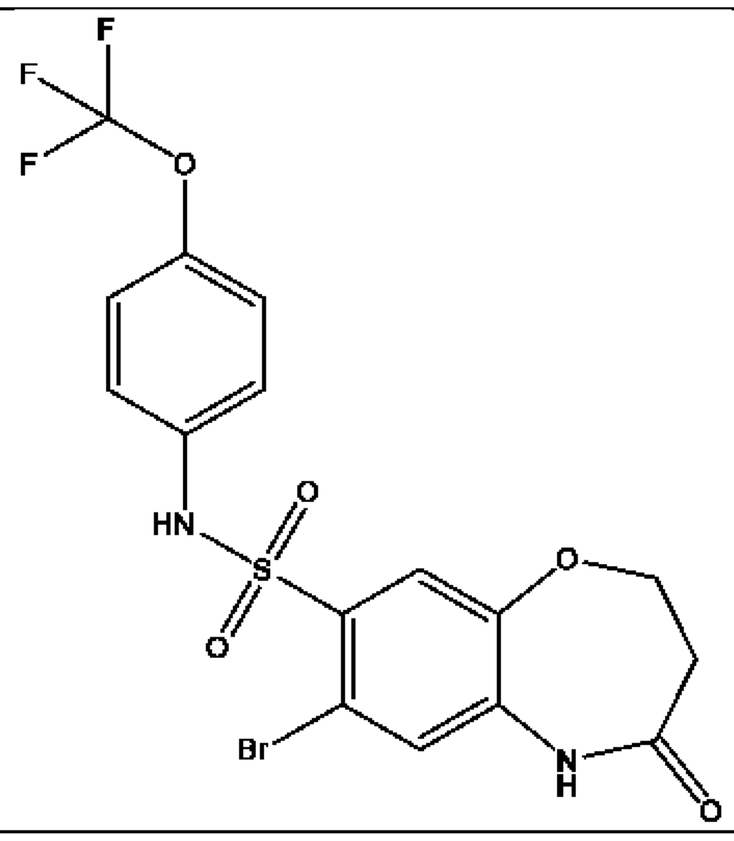
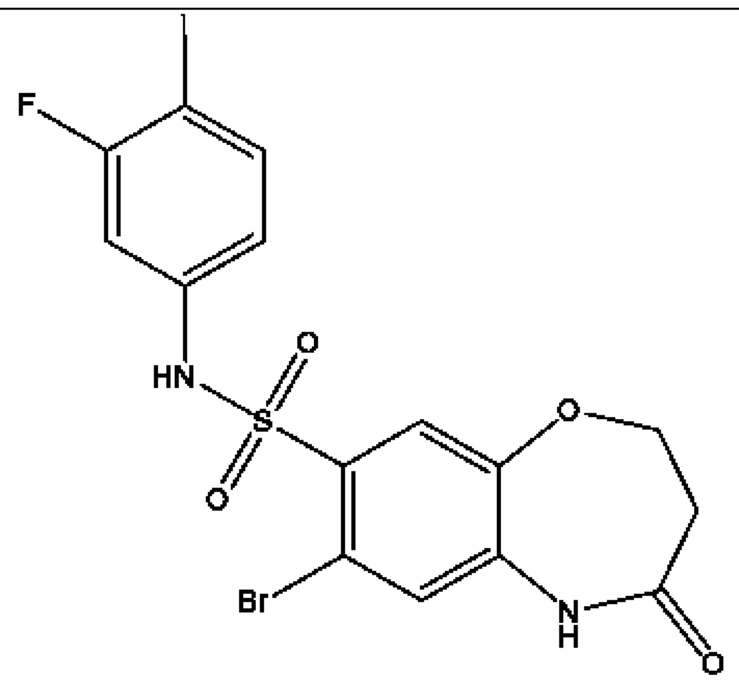
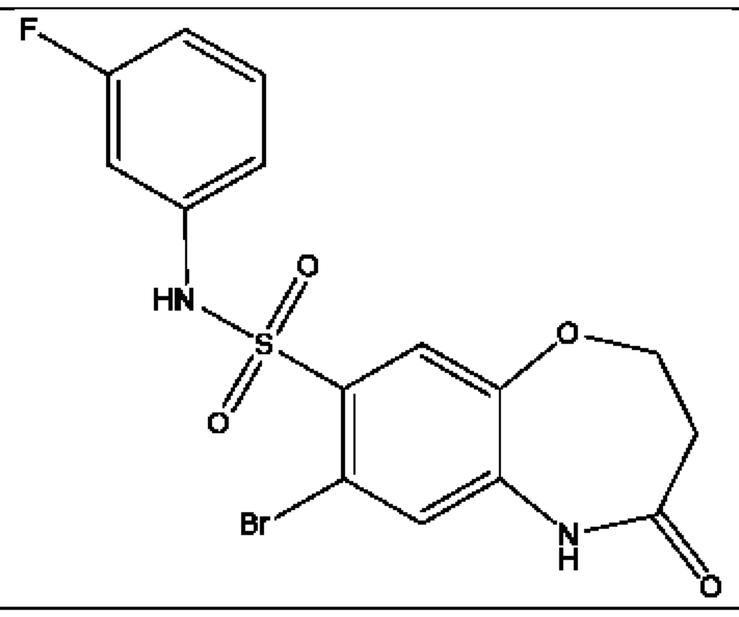
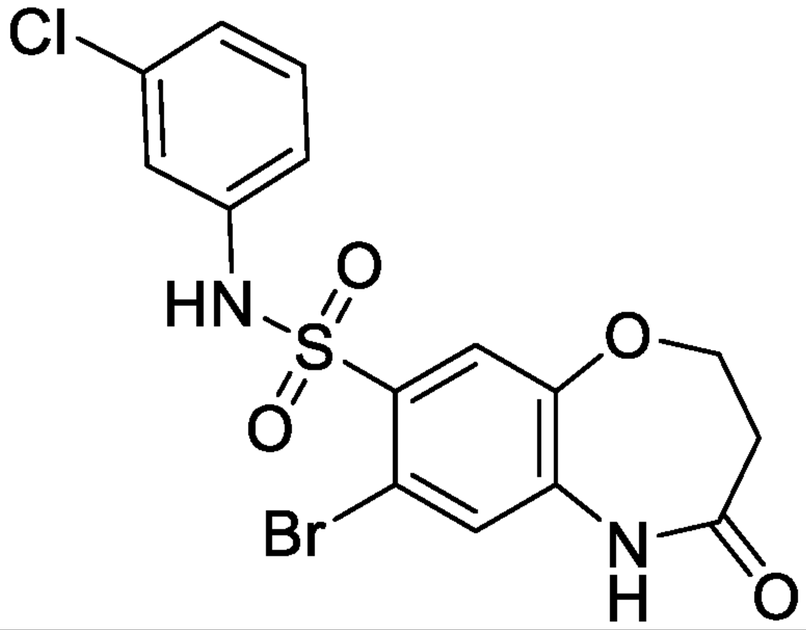
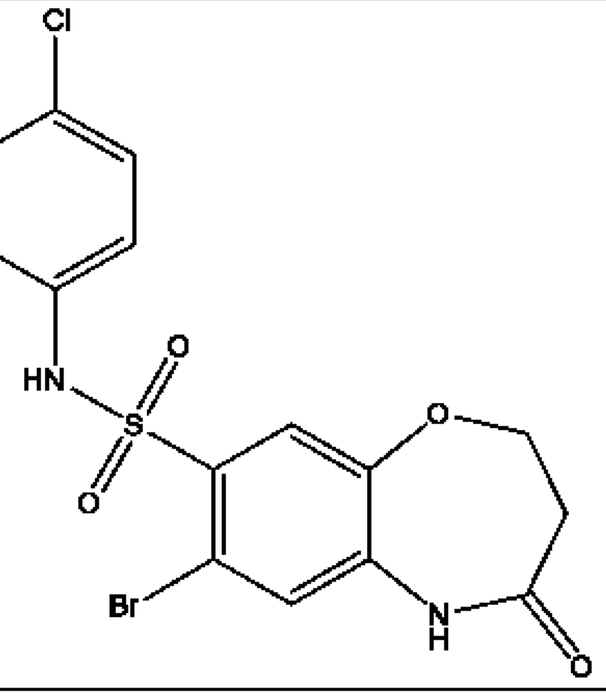
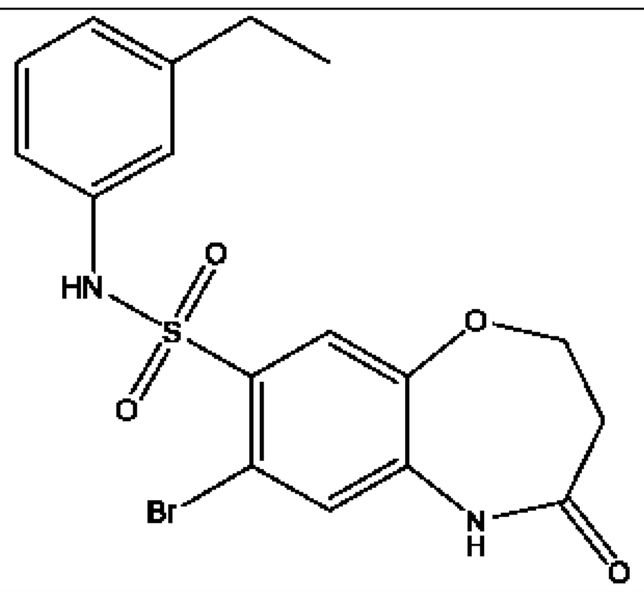
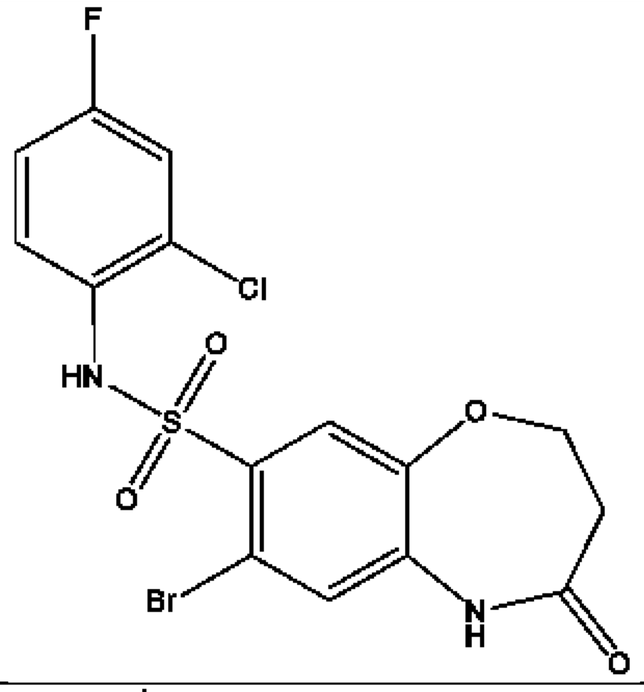
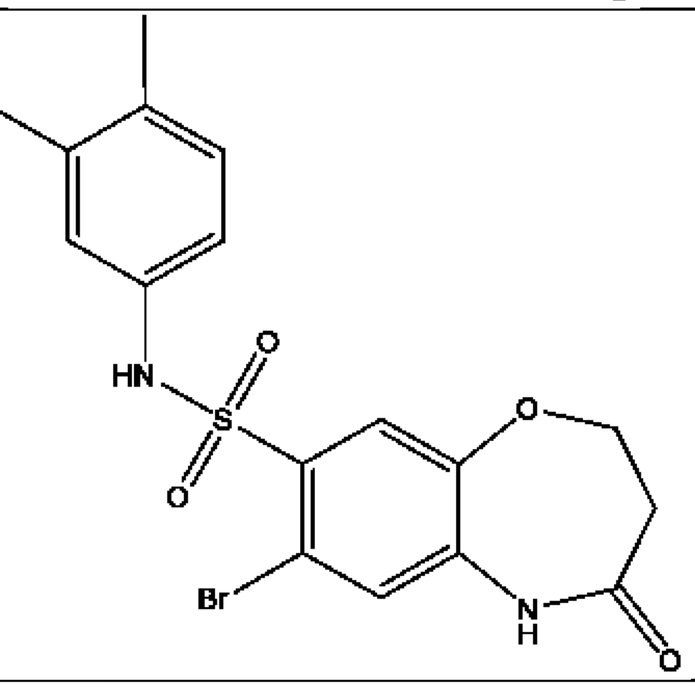
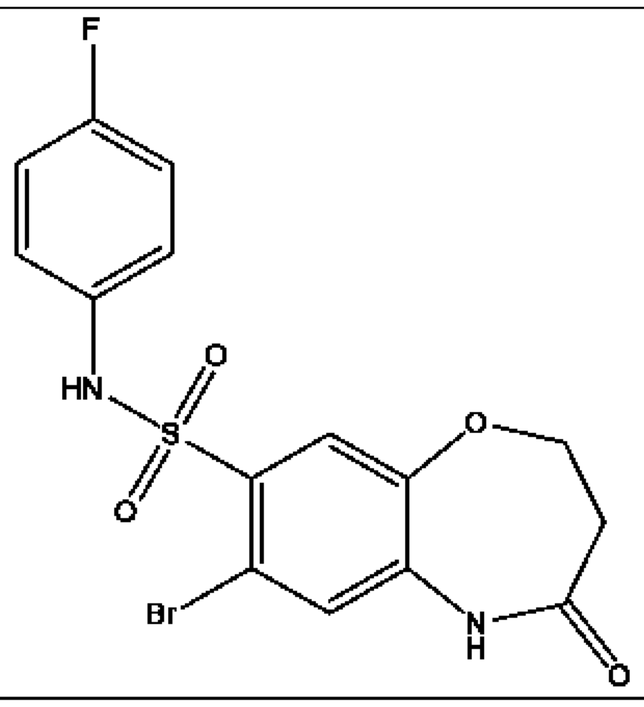
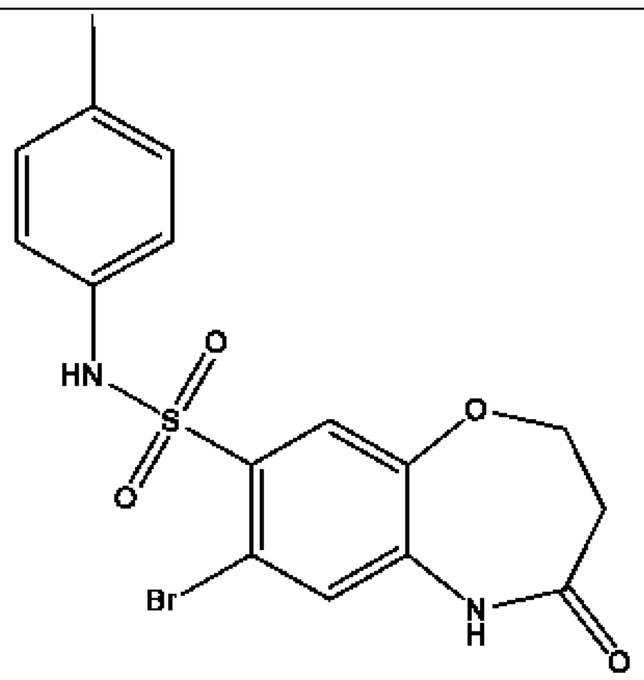
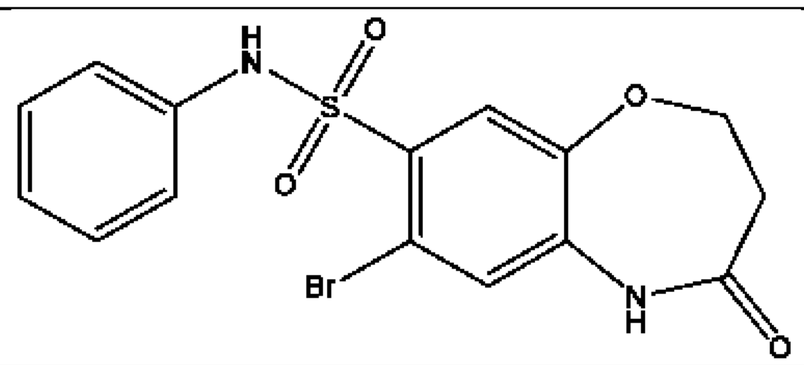
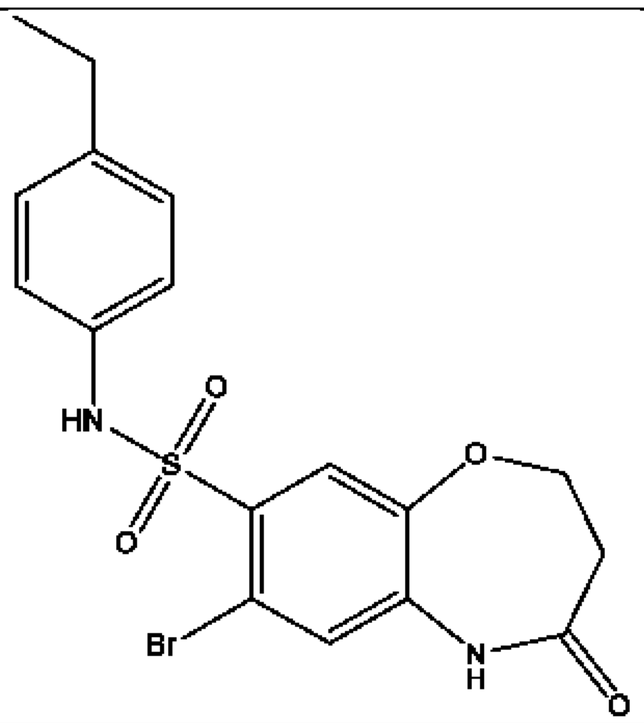
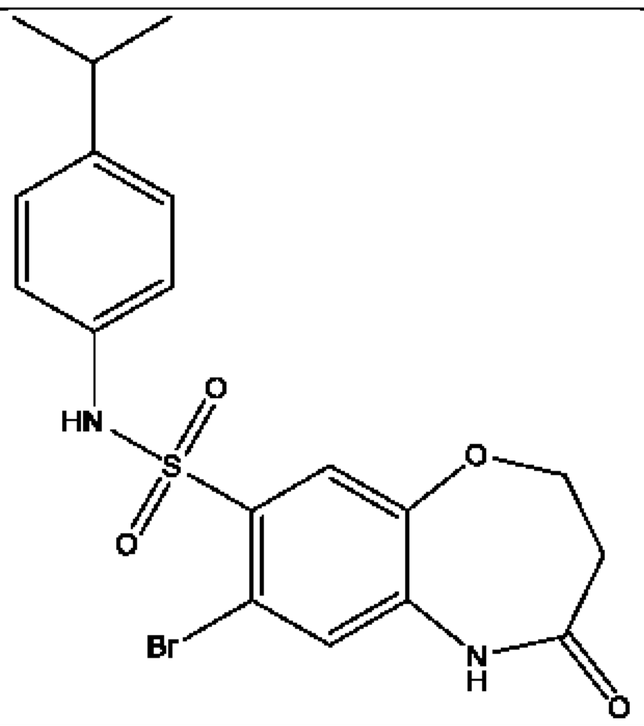
BC19614		+	+
BC19615		+++	+

Table 2g

BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19652		++	+

BC19653		+	+
BC19654		+	+
BC19655		+	+
BC19656		++	+

BC19657		++	+
BC19658		+	+
BC19659		+	+
BC19660		+	+

BC19661		+	+
BC19689		+	++
BC19690		+	+
BC19691		+	++

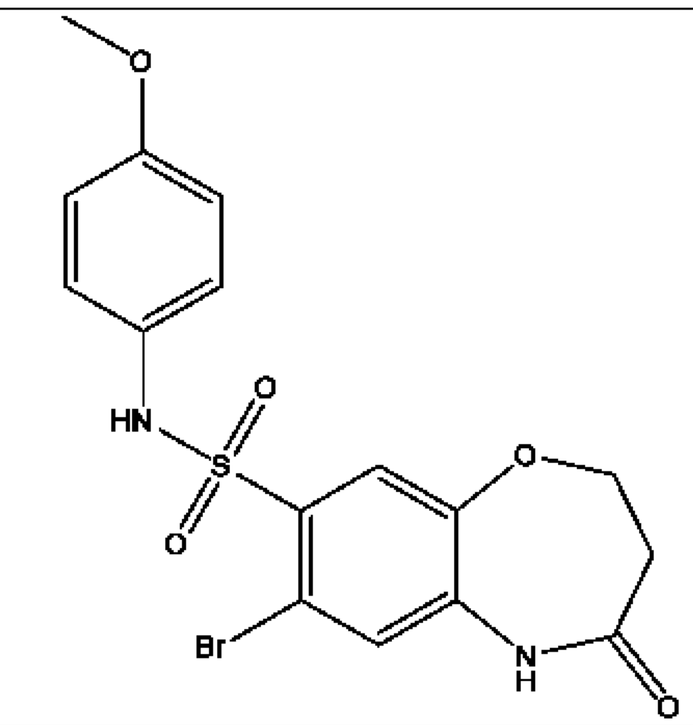
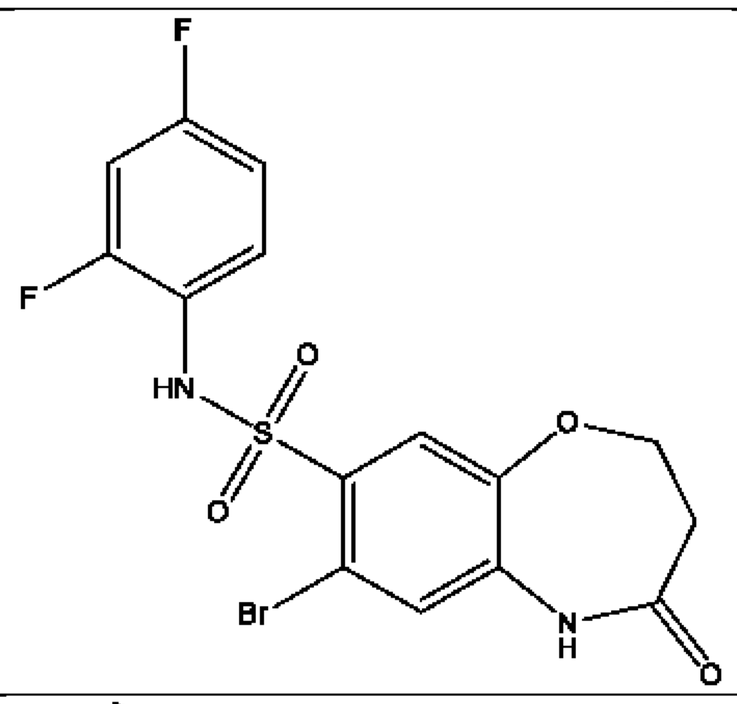
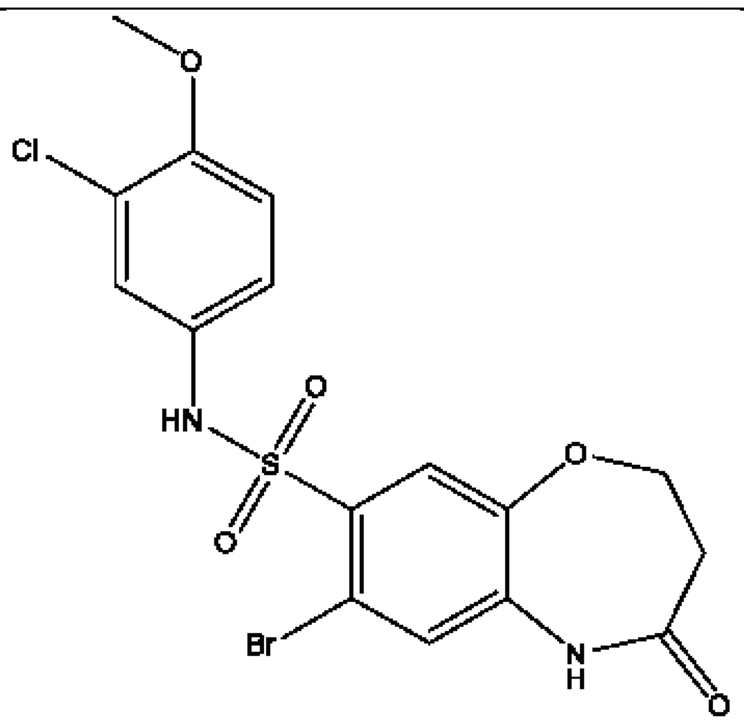
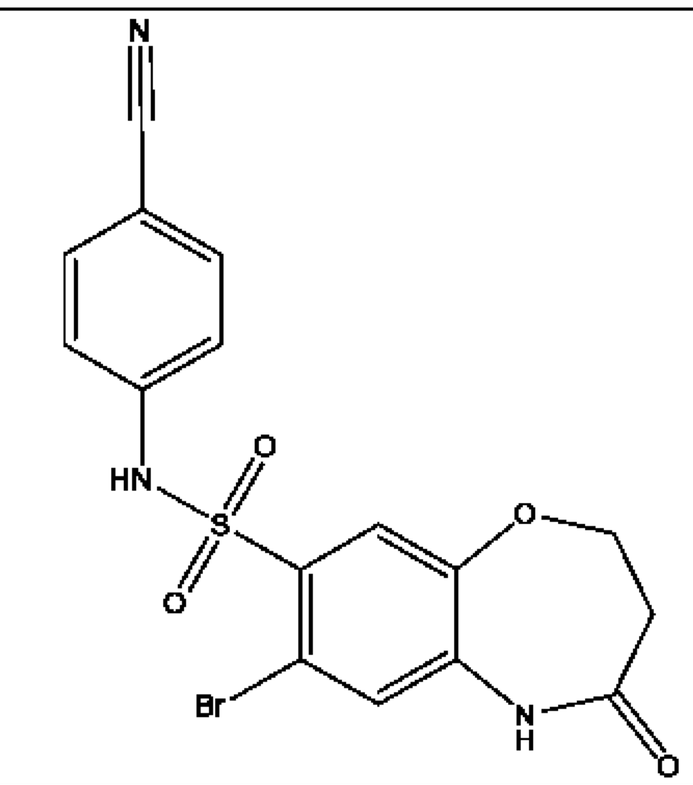
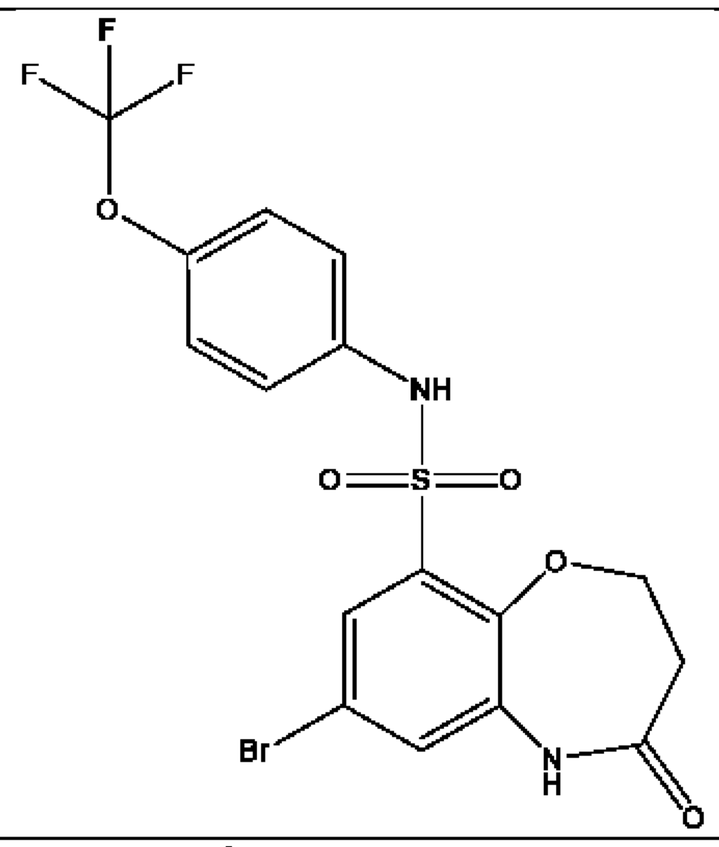
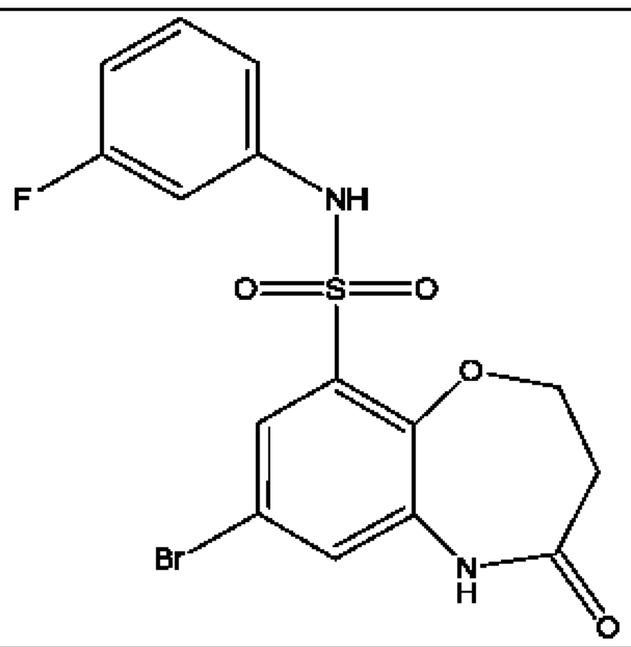
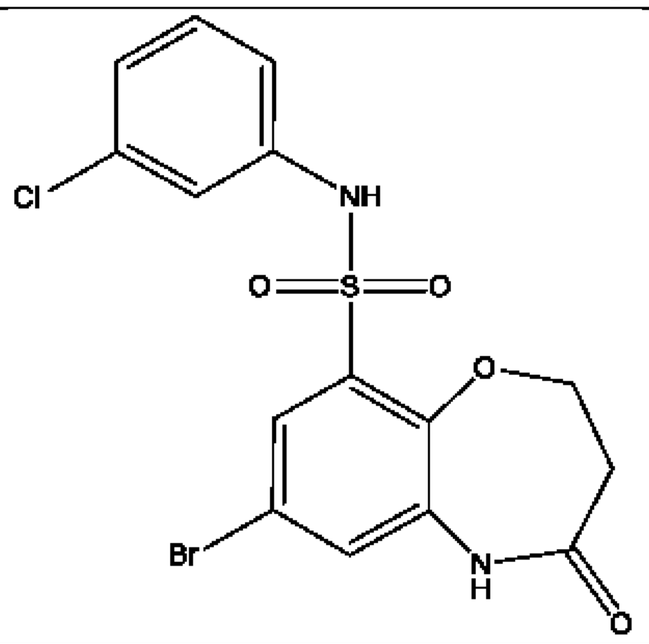
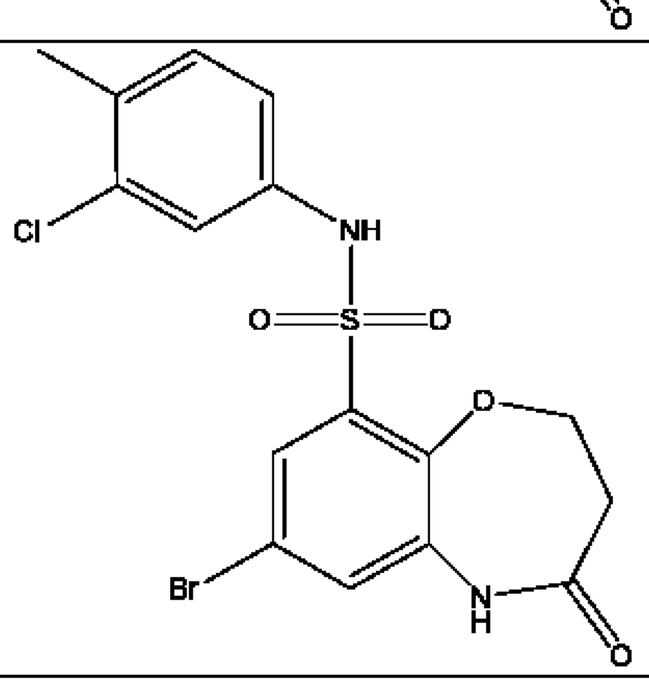
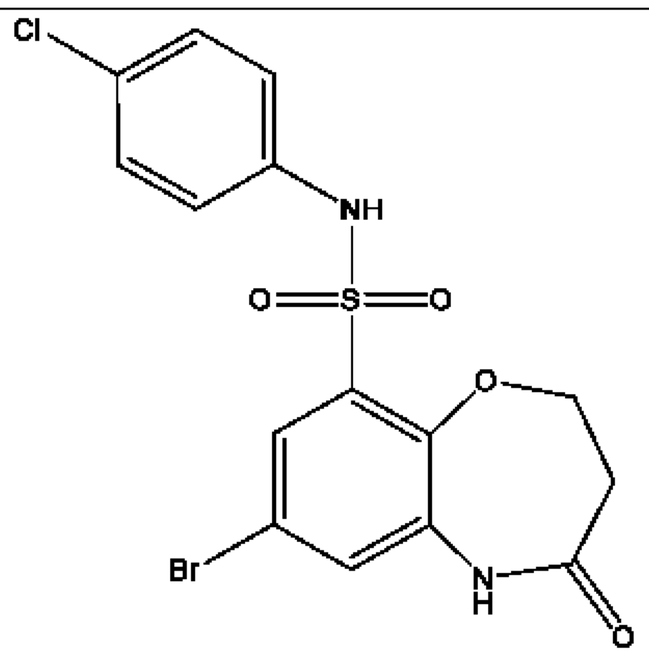
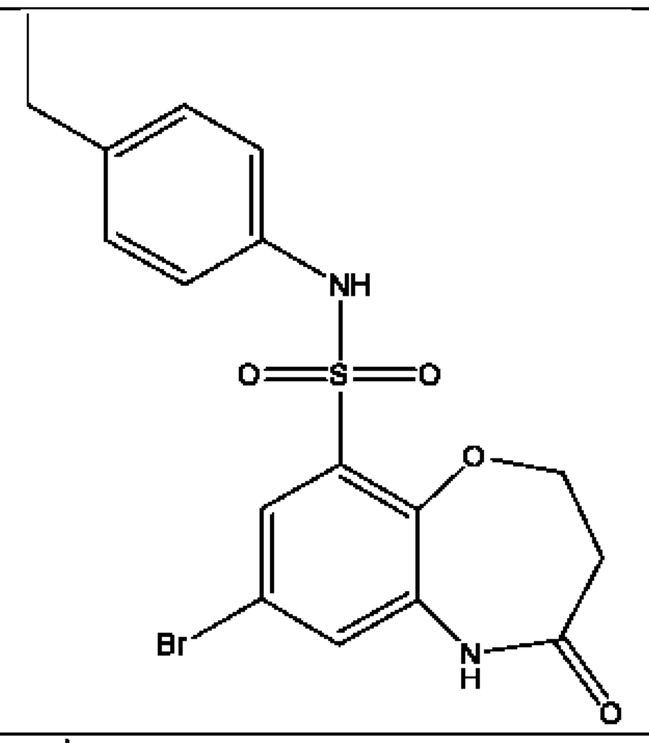
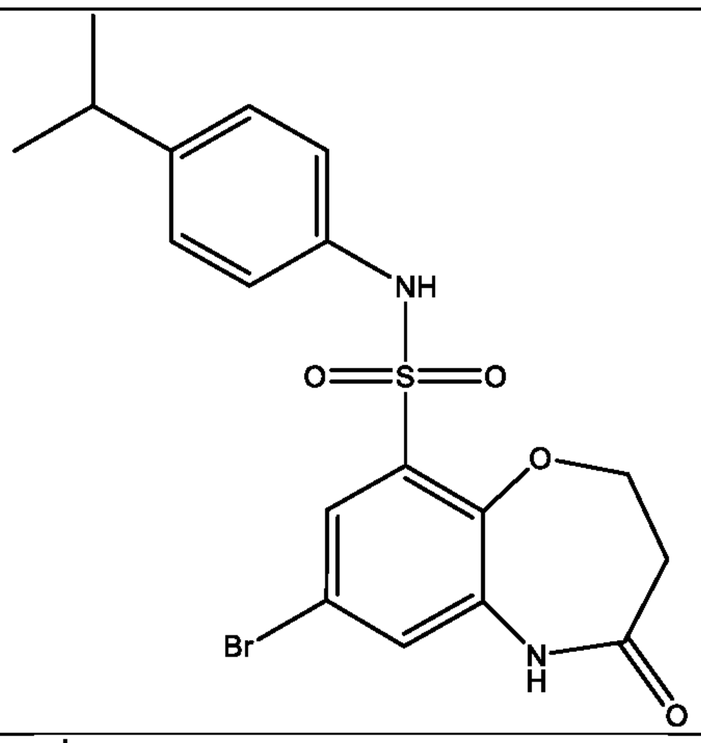
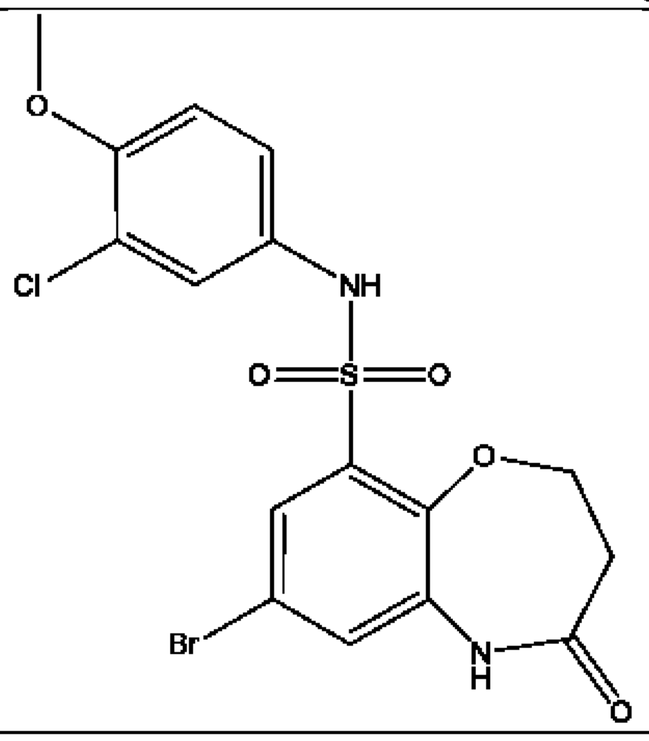
BC19692		+	+
BC19693		+	+
BC19694		+	+
BC19695		+	++

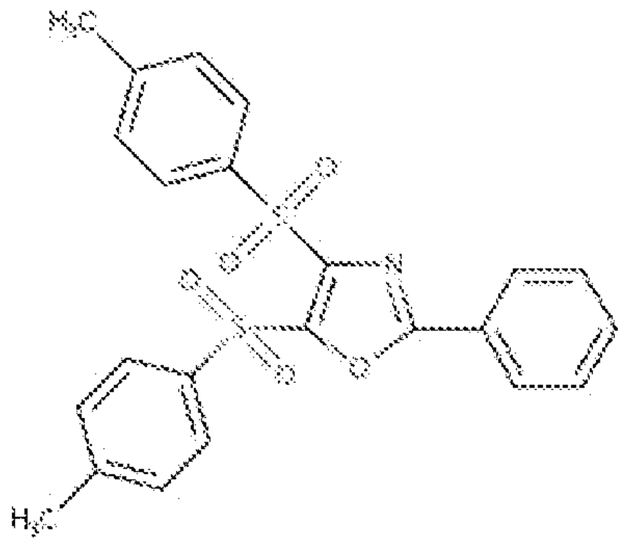
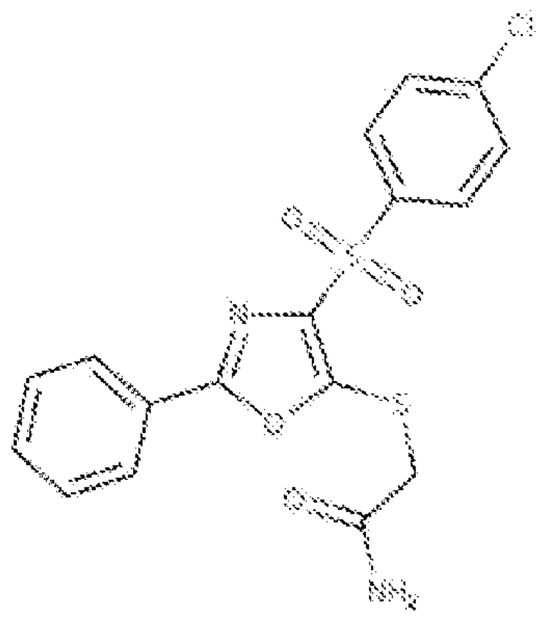
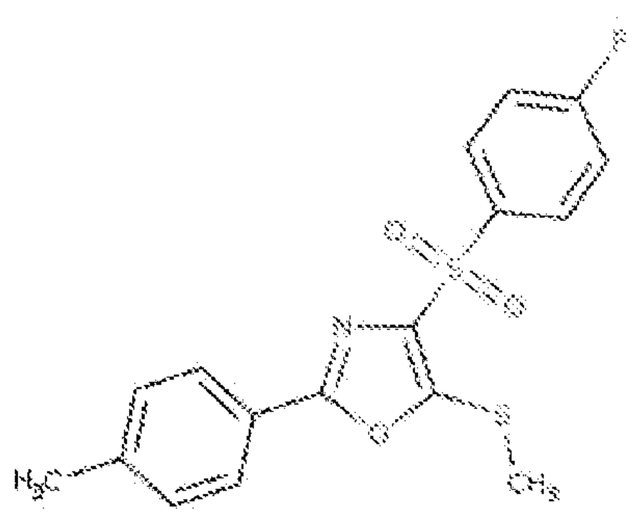
Table 2h

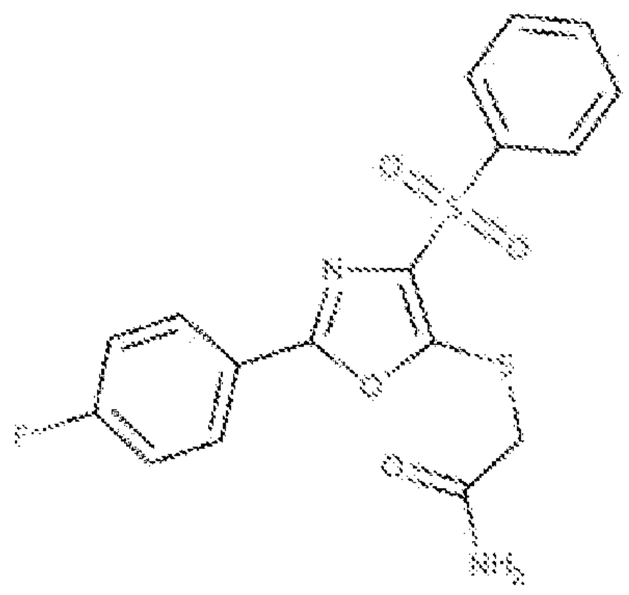
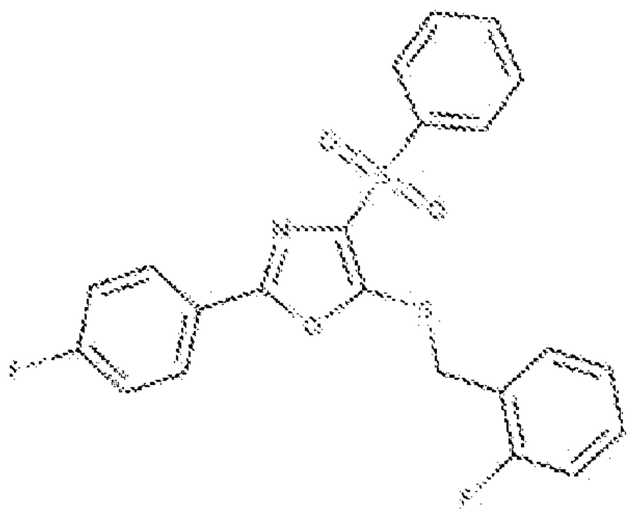
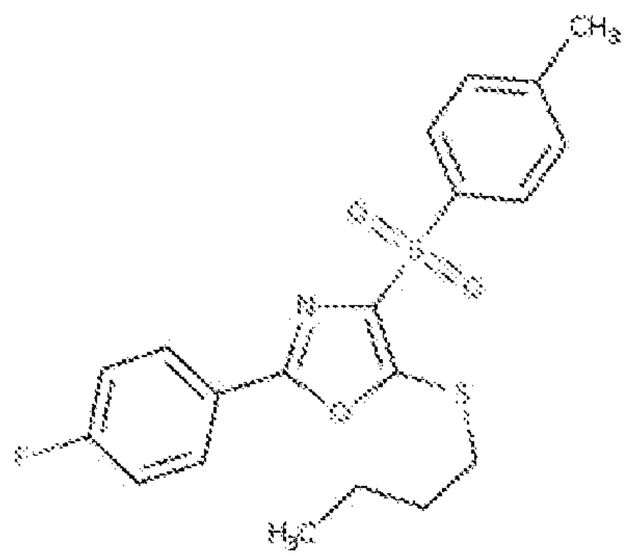
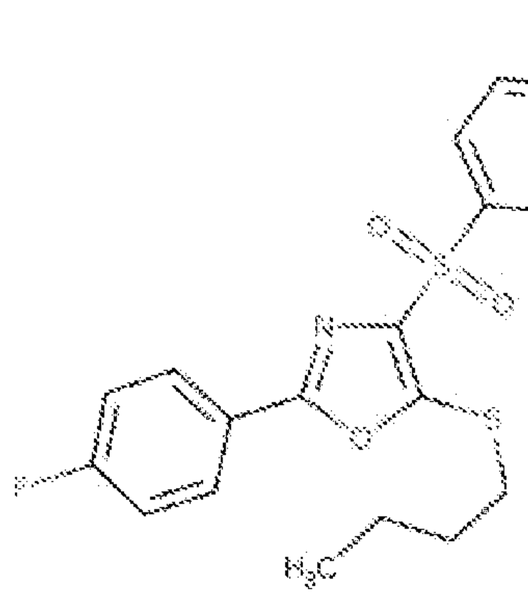
BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19648		++++	+
BC19649		++++	+
BC19650		++++	+
BC19651		+++	+

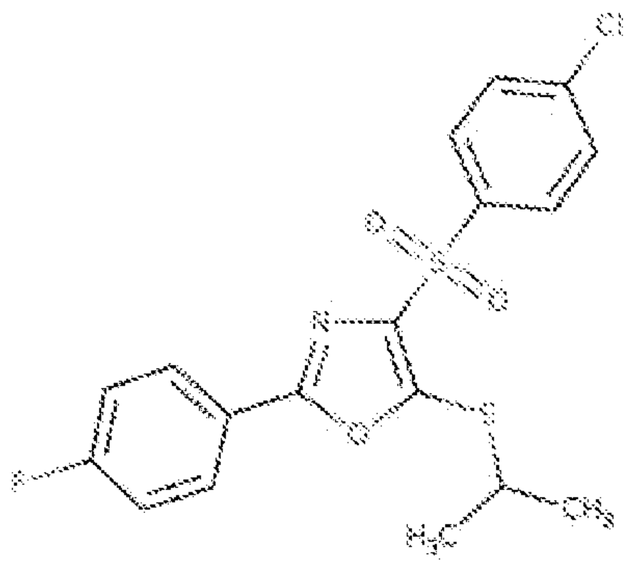
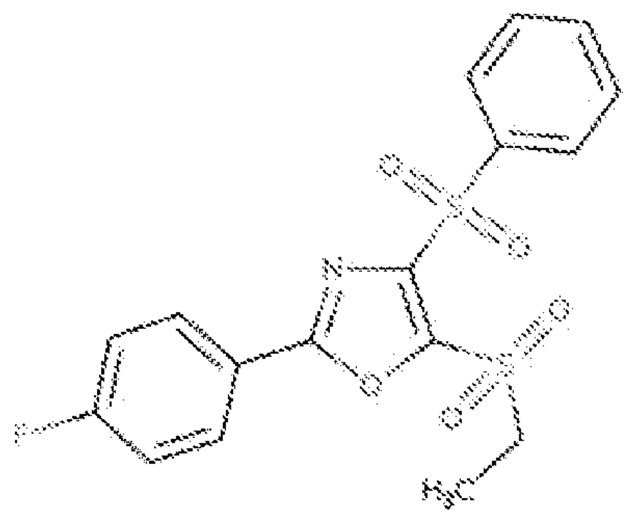
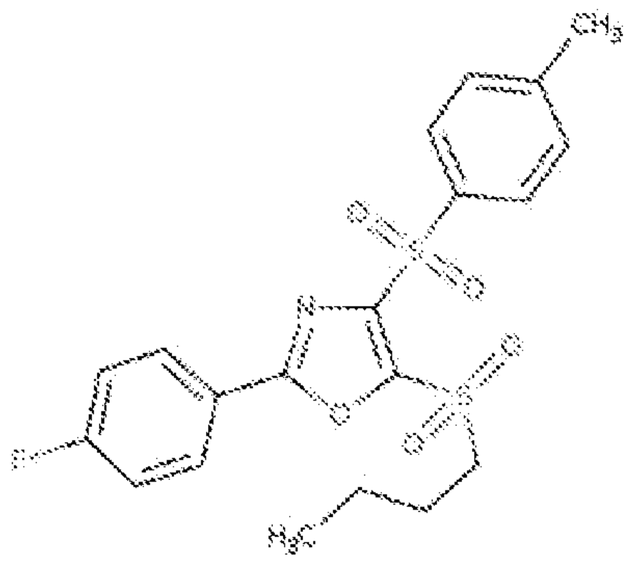
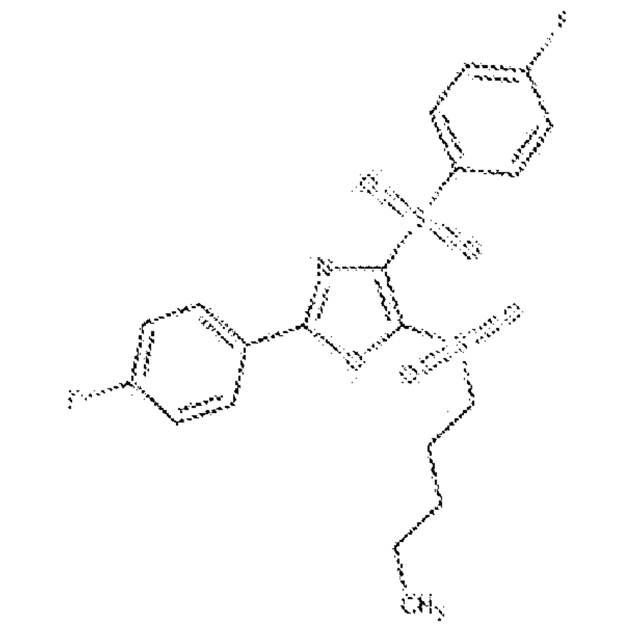
BC19685		++++	++
BC19686		++++	+
BC19687		++++	+
BC19688		+	+

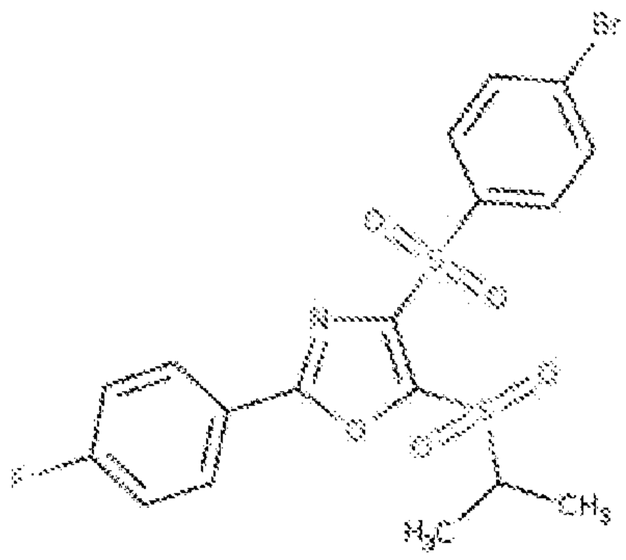
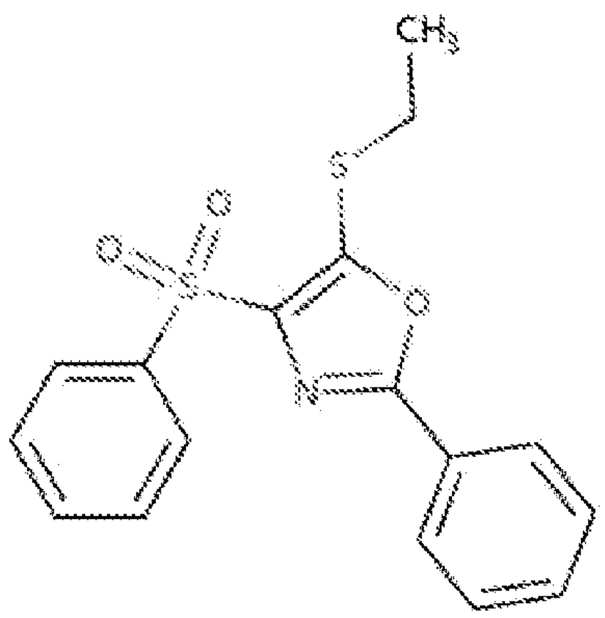
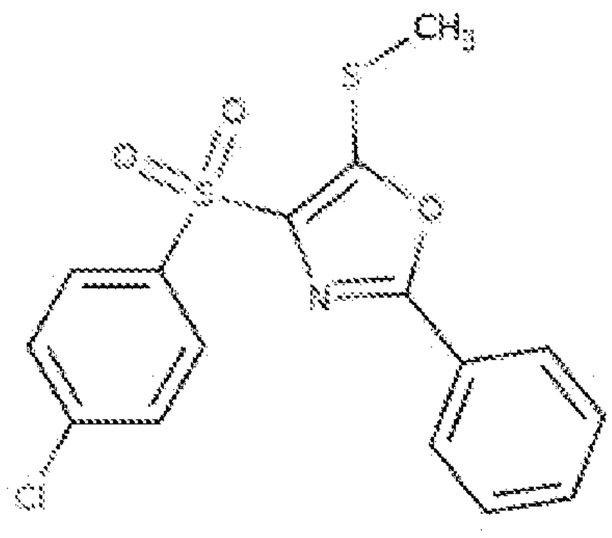
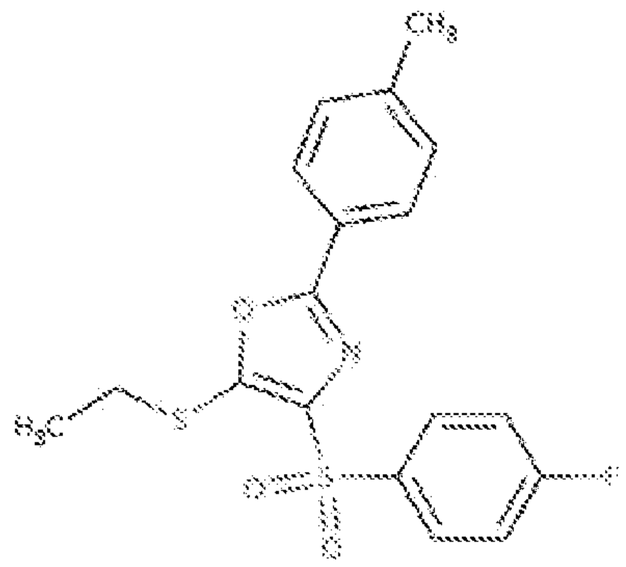
Example 3 – bioassay results for tested compounds

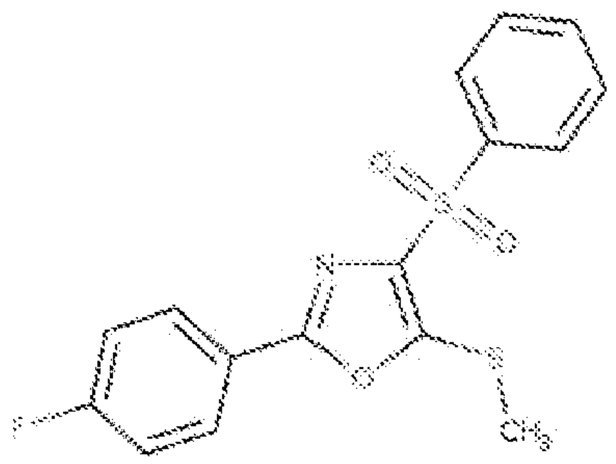
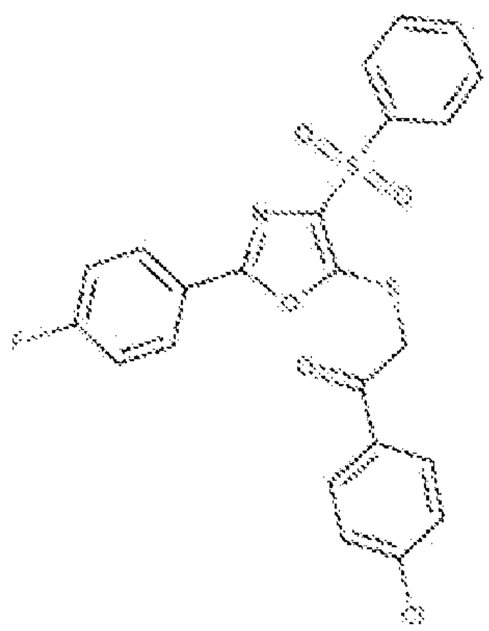
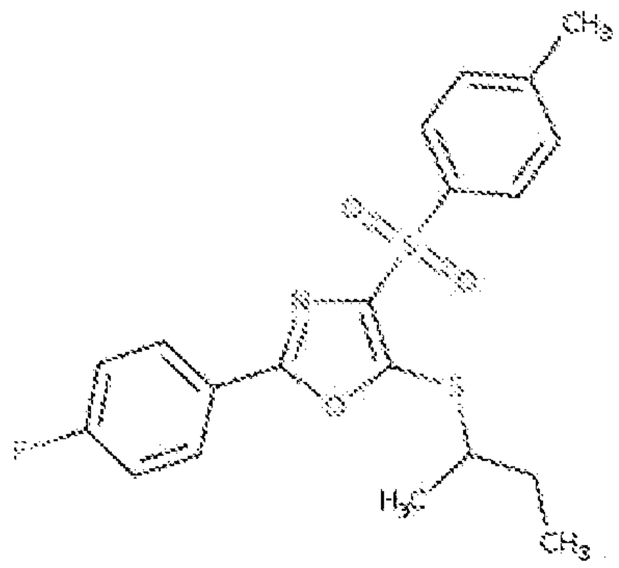
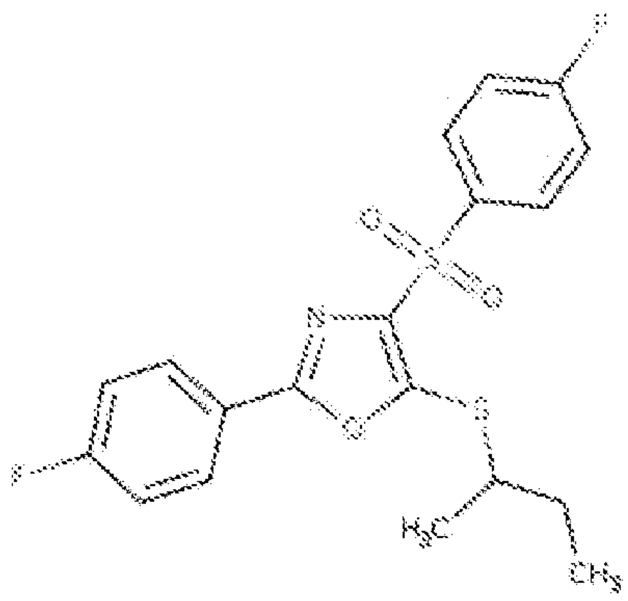
Table 3a

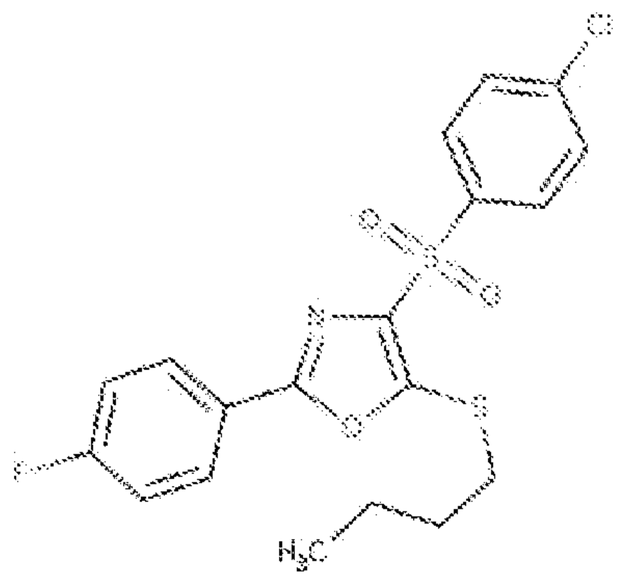
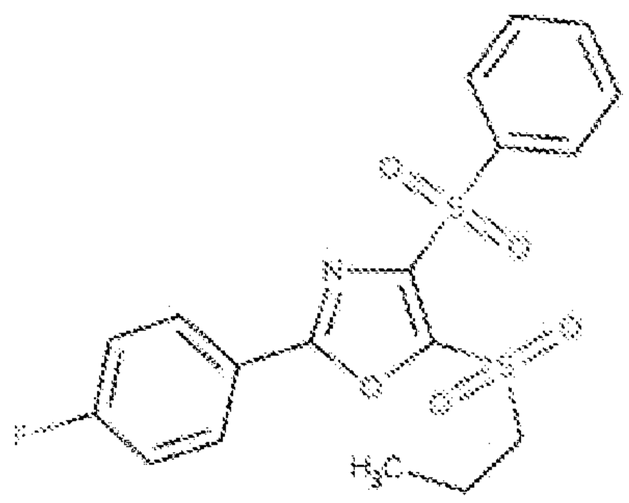
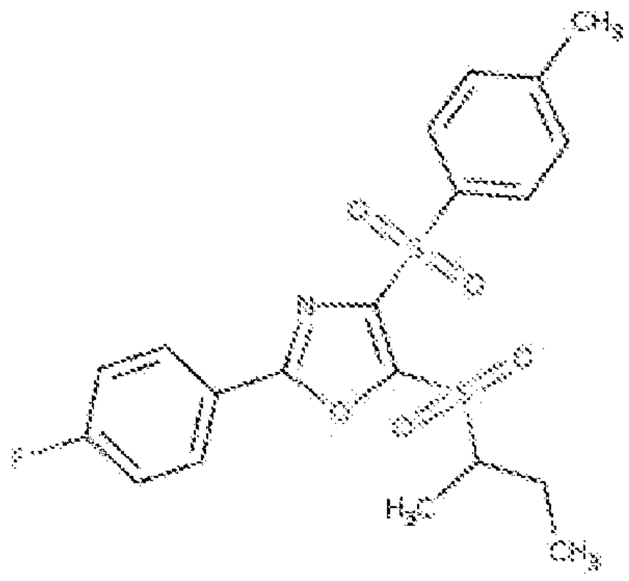
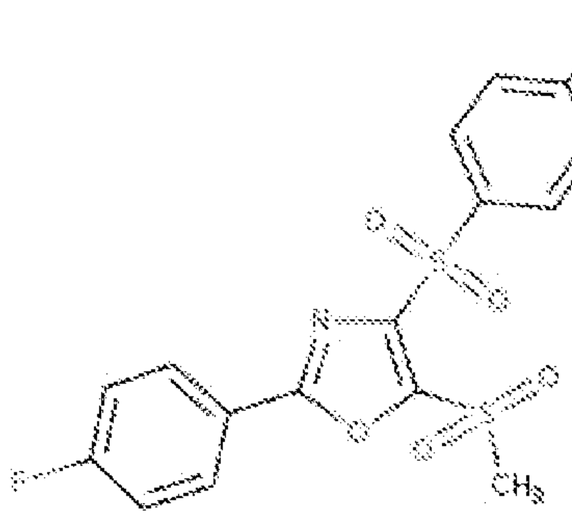
BC No.	Compound	IC_{50} (NF-κB assay)
BC18500		++++
BC18501		+
BC18502		+

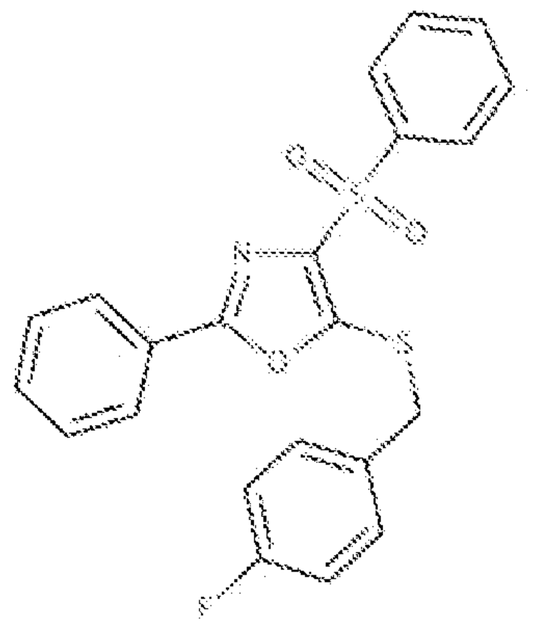
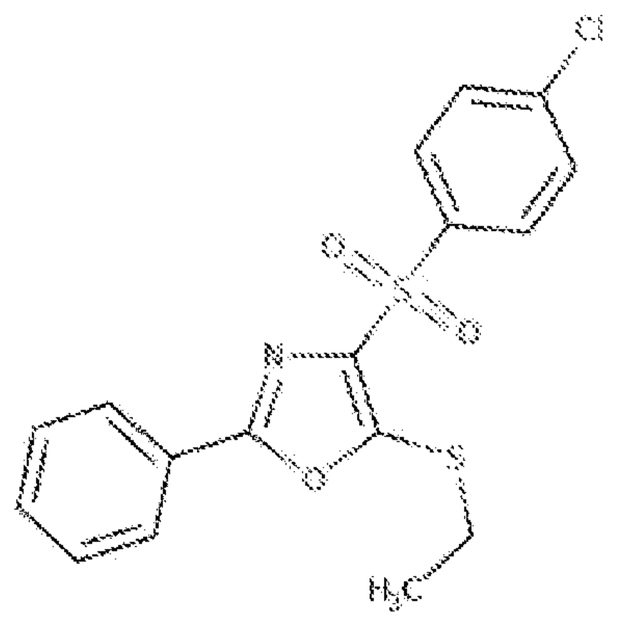
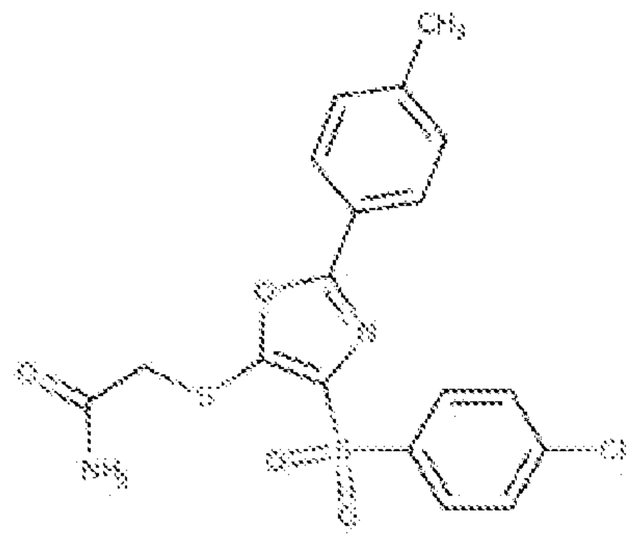
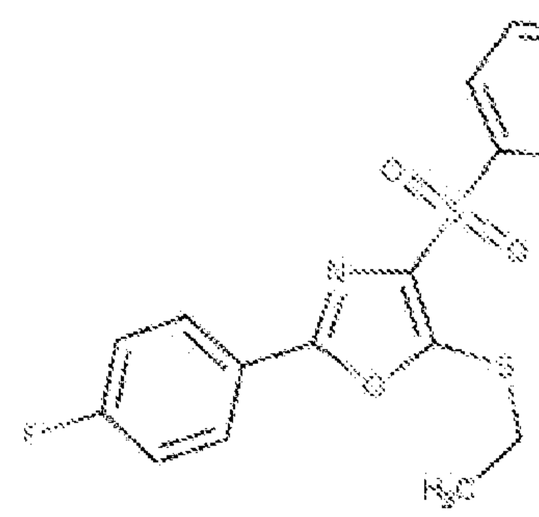
BC18503		++
BC18504		++
BC18505		++
BC18506		+

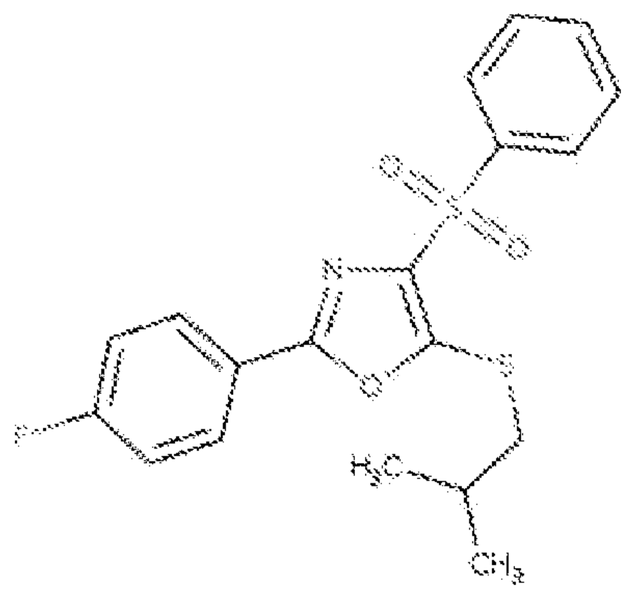
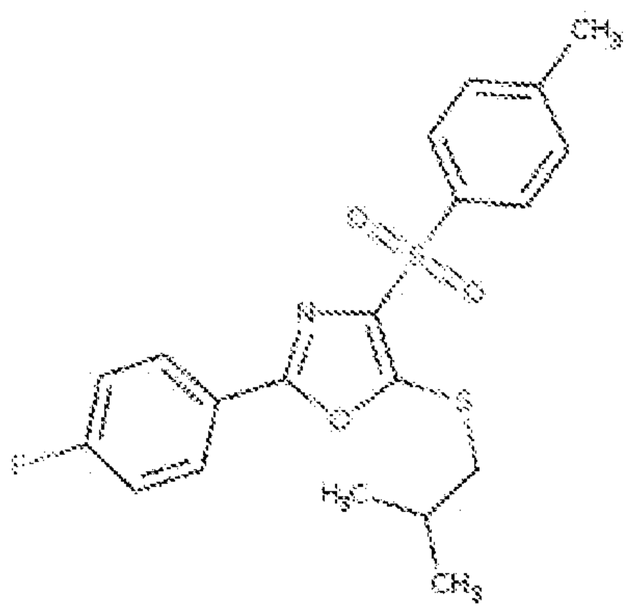
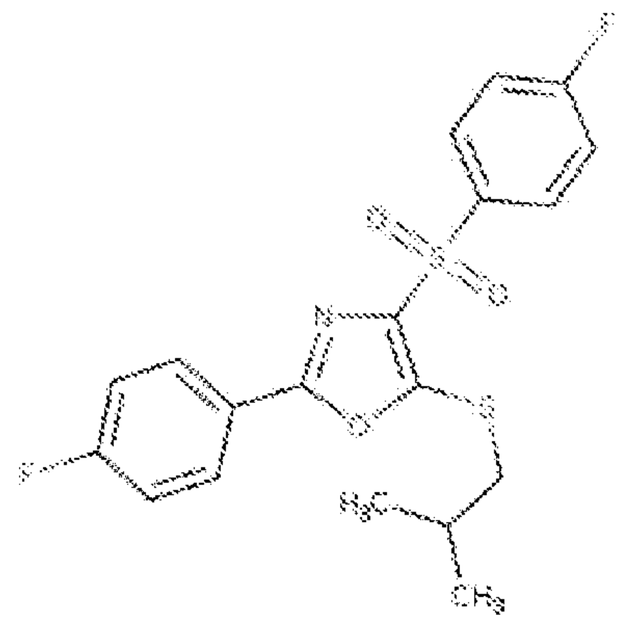
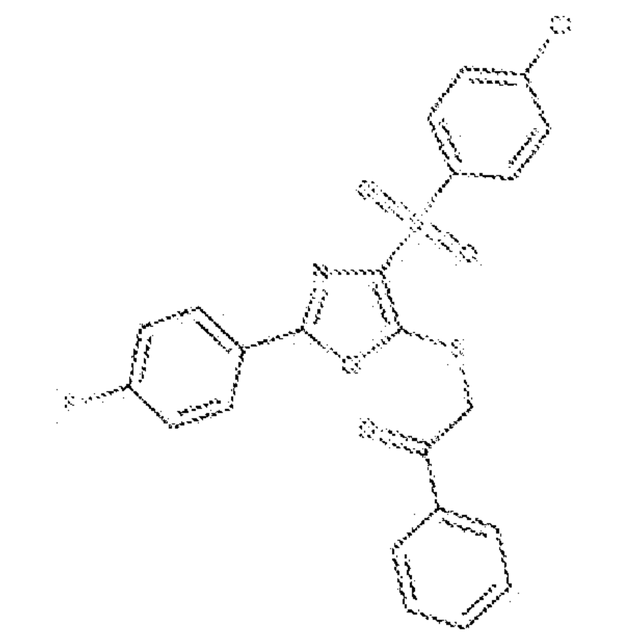
BC18507		++
BC18508		++++
BC18509		++++
BC18510		+++

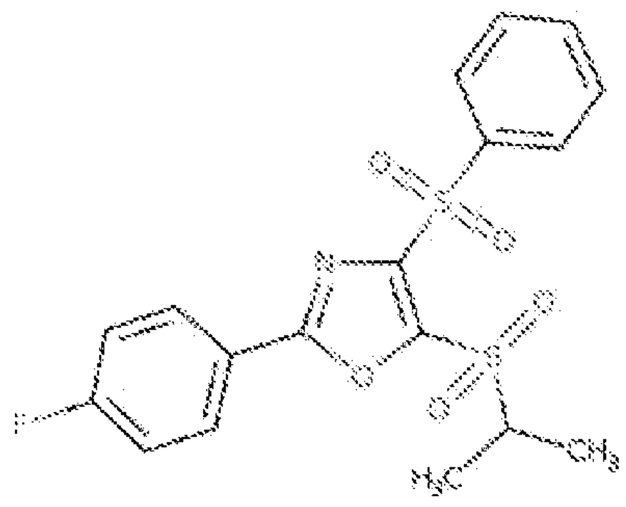
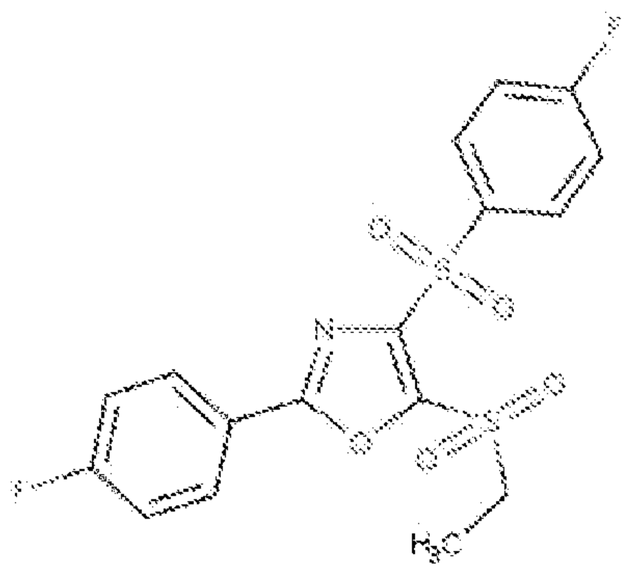
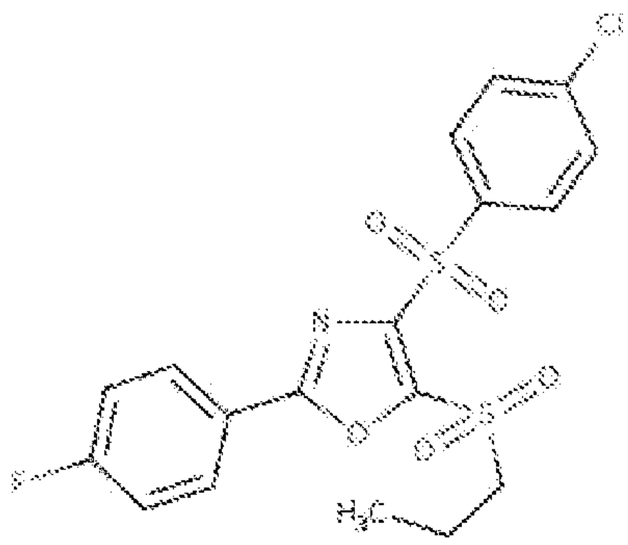
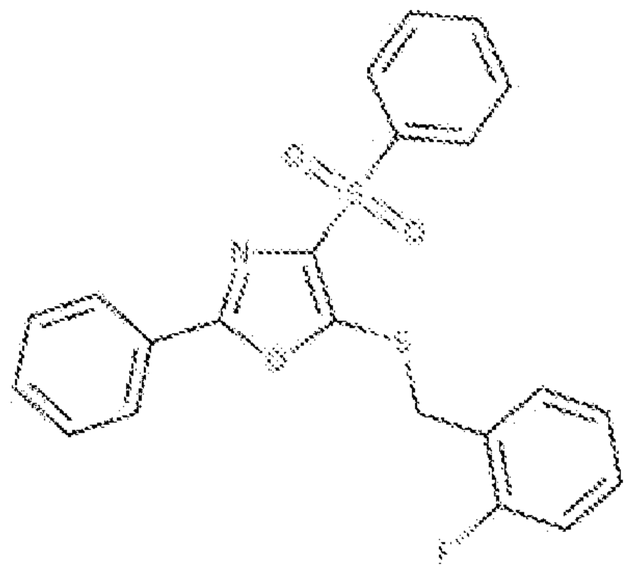
BC18511		++++
BC18512		++
BC18513		+
BC18514		++

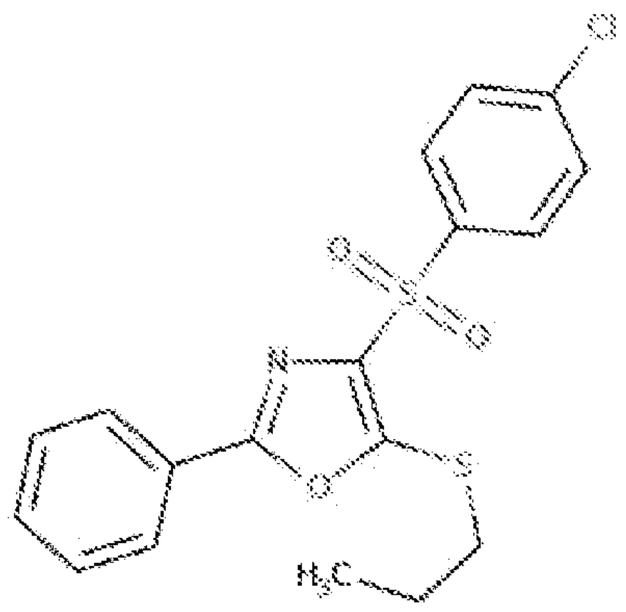
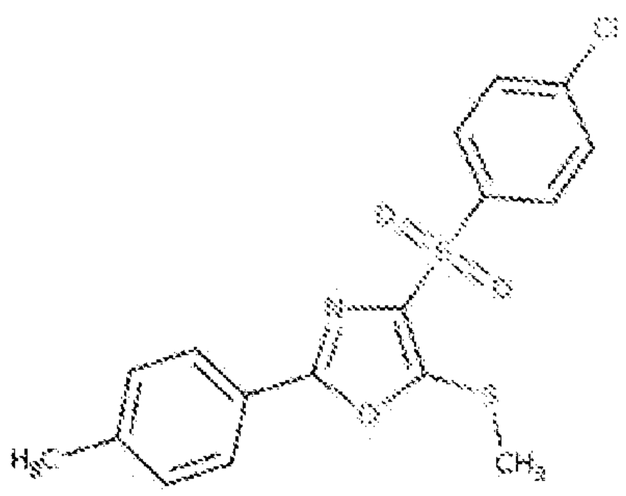
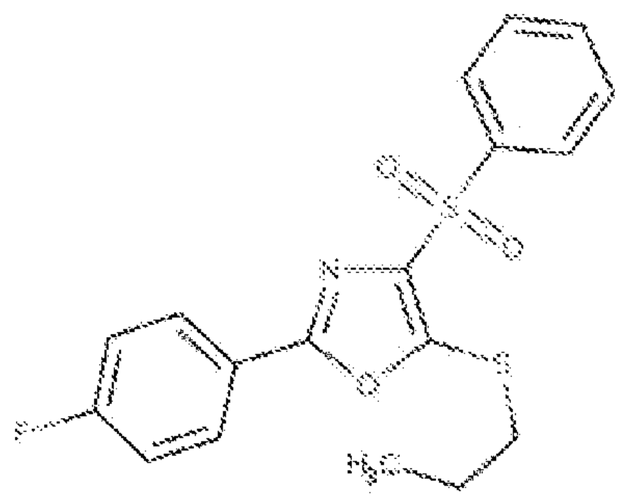
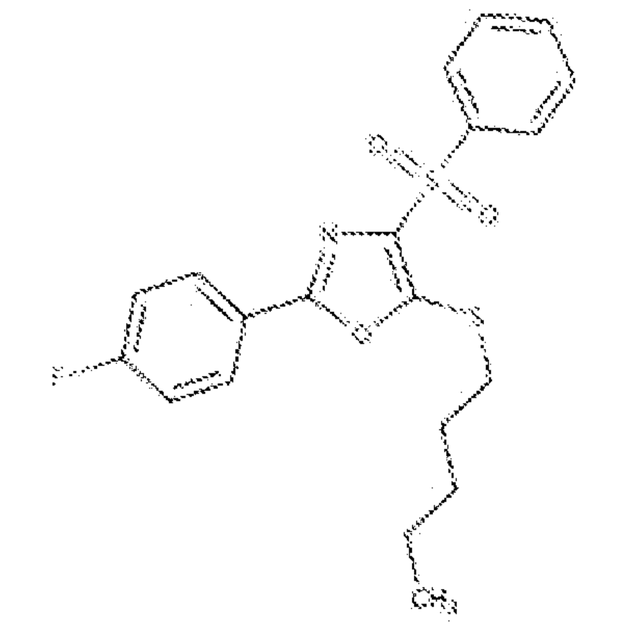
BC18515		+
BC18516		++
BC18517		++
BC18518		++

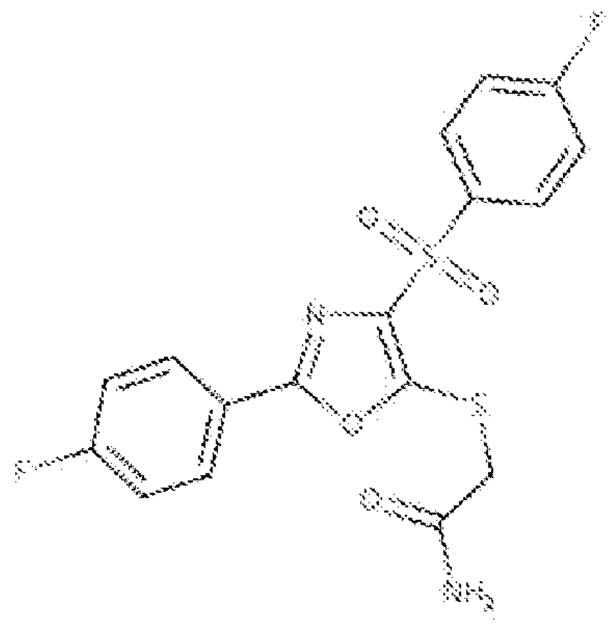
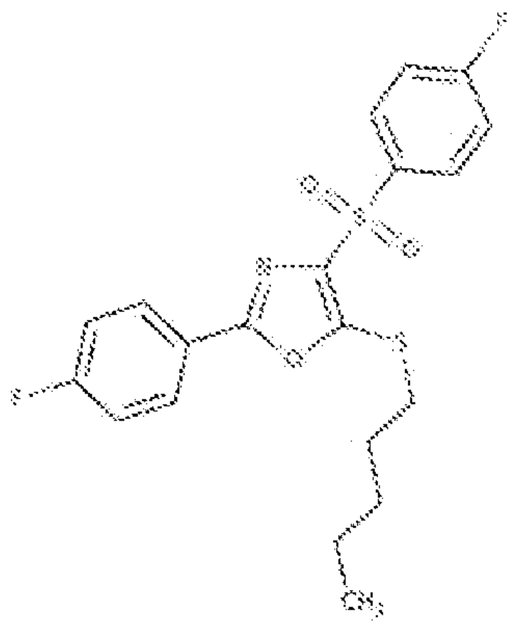
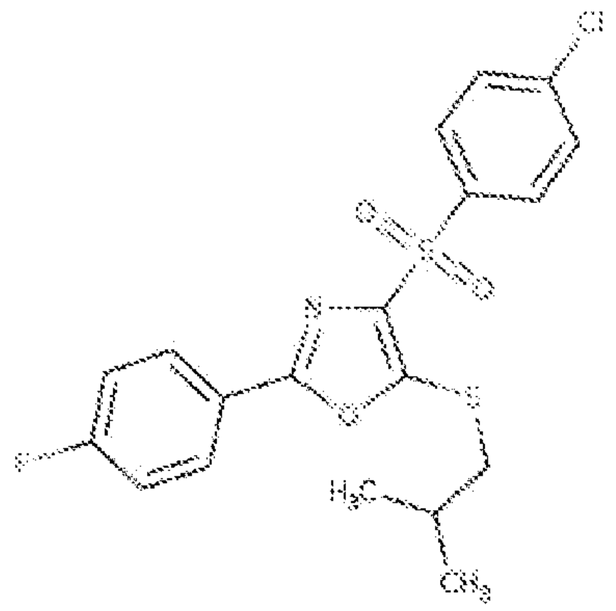
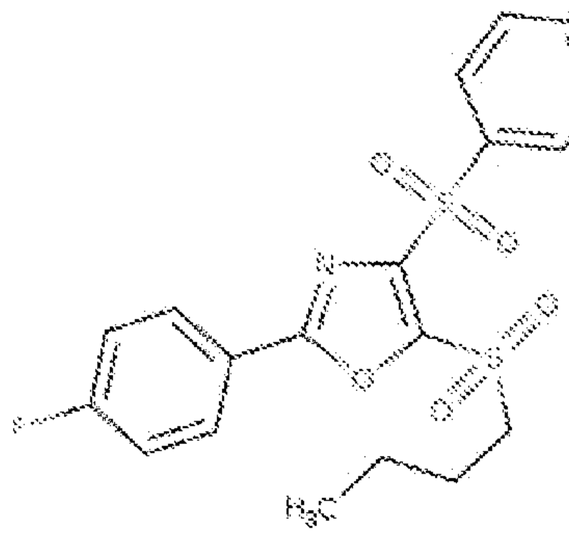
BC18519		+
BC18520		++++
BC18521		++++
BC18522		++++

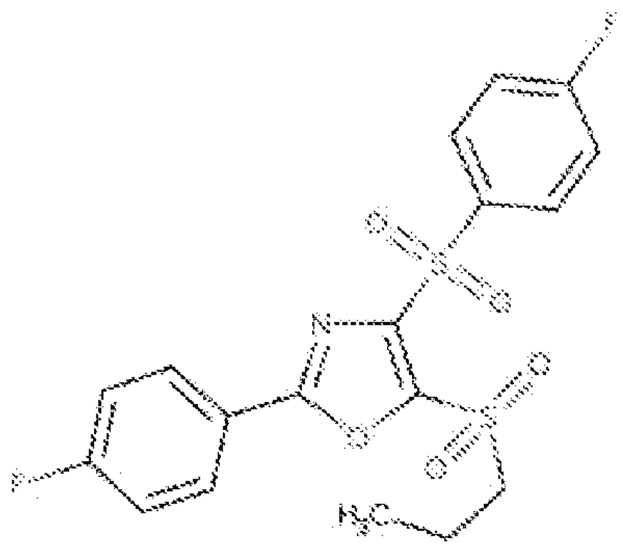
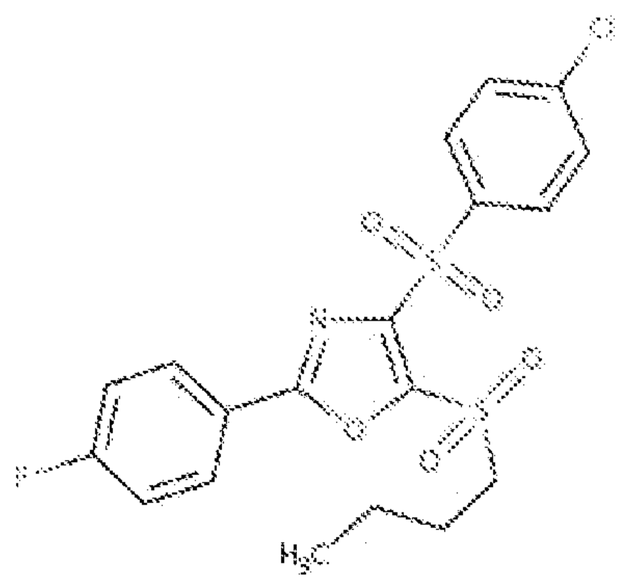
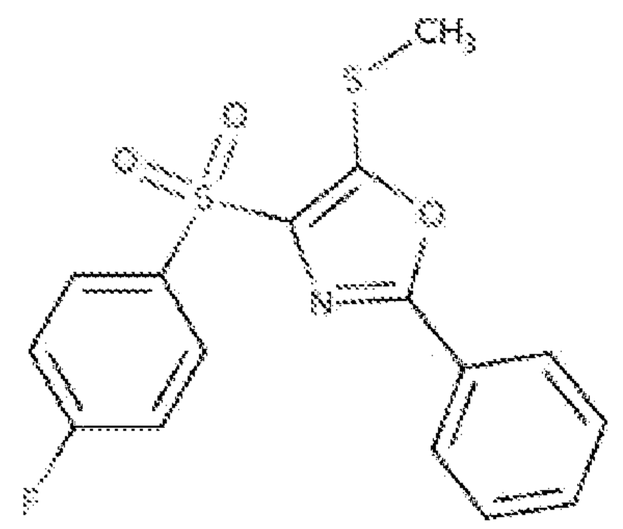
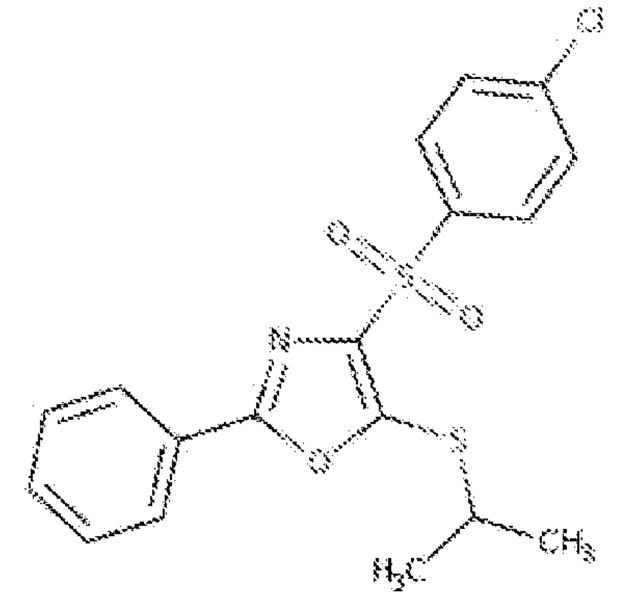
BC18523		+
BC18524		++
BC18525		+
BC18526		++

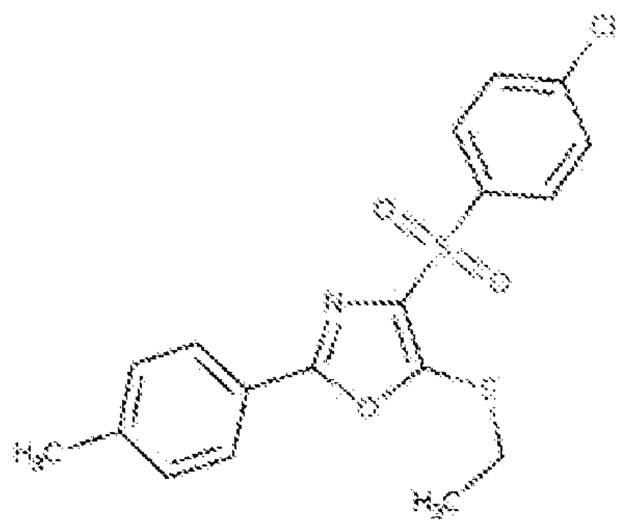
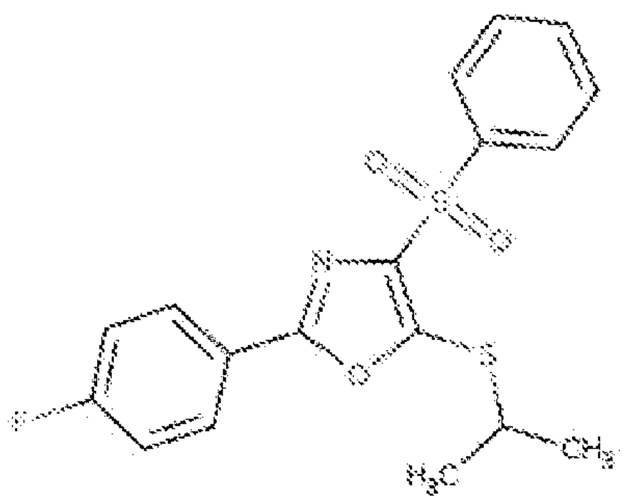
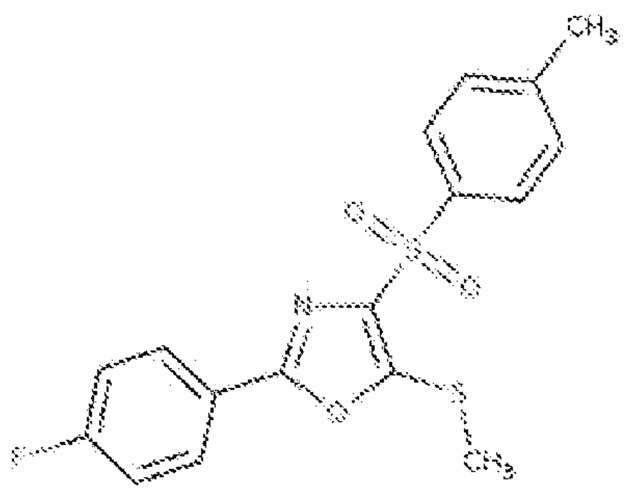
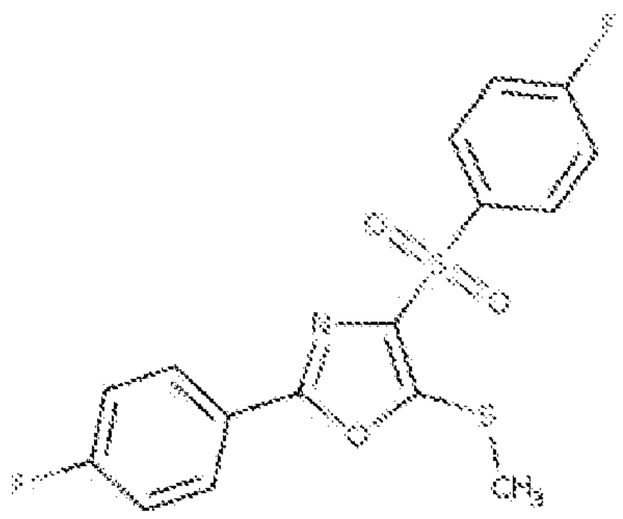
BC18527		++
BC18528		+
BC18529		++
BC18530		++

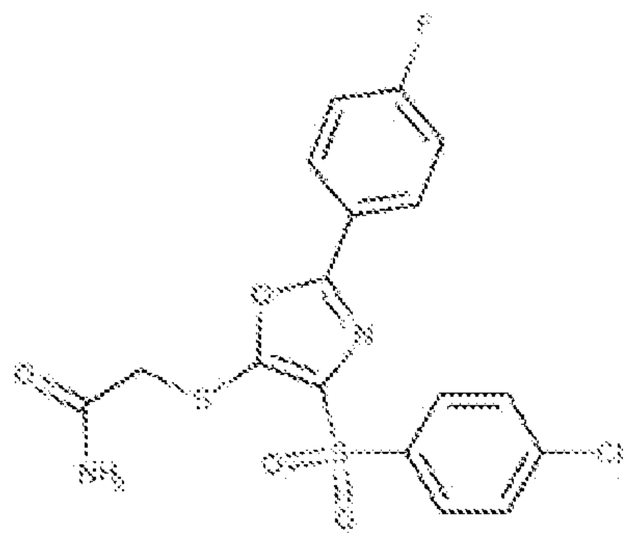
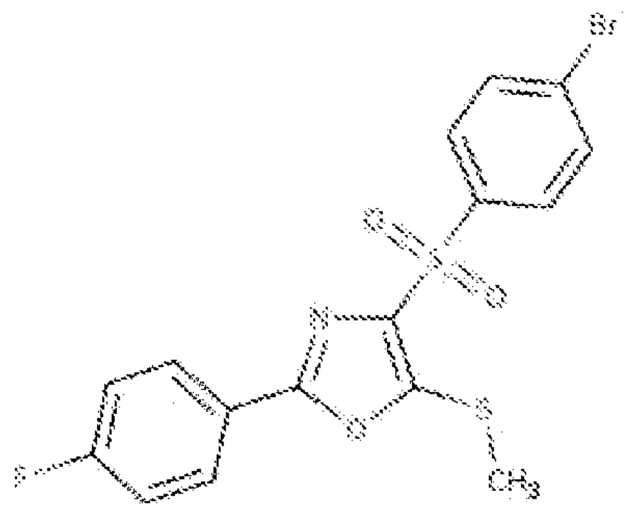
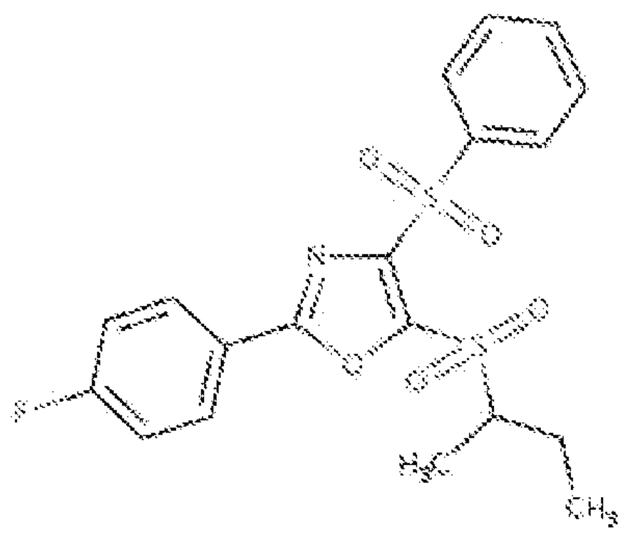
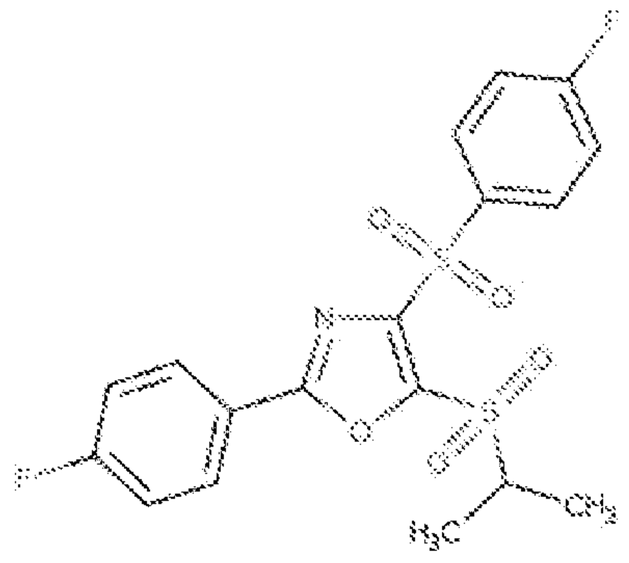
BC18531		++++
BC18532		++++
BC18533		++++
BC18534		+

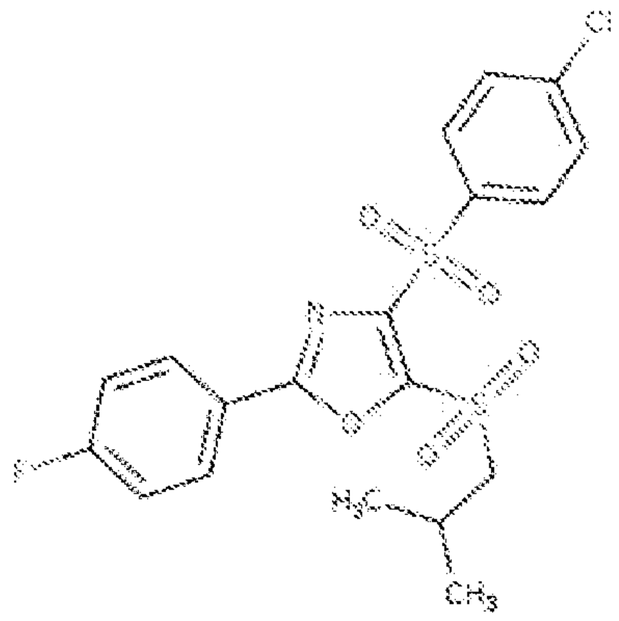
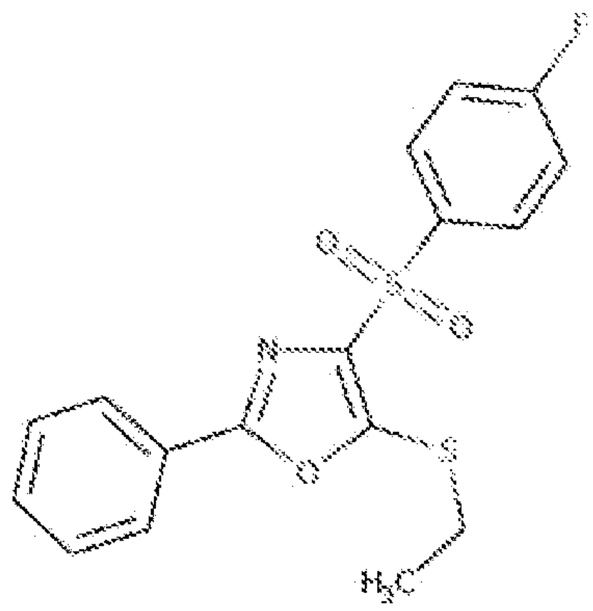
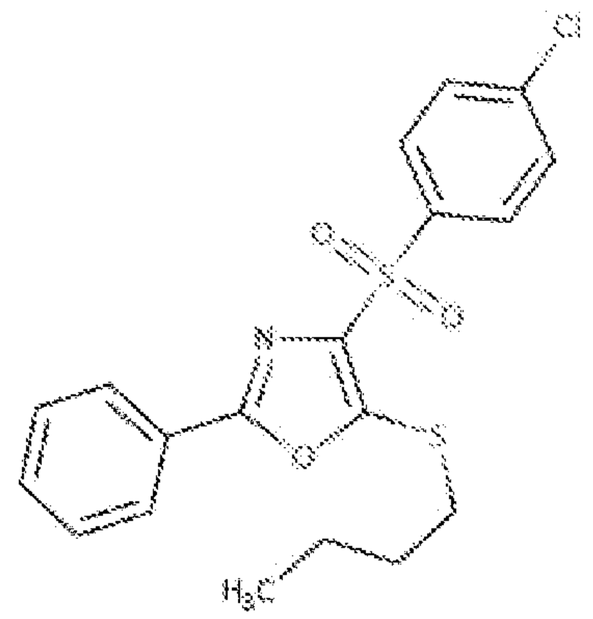
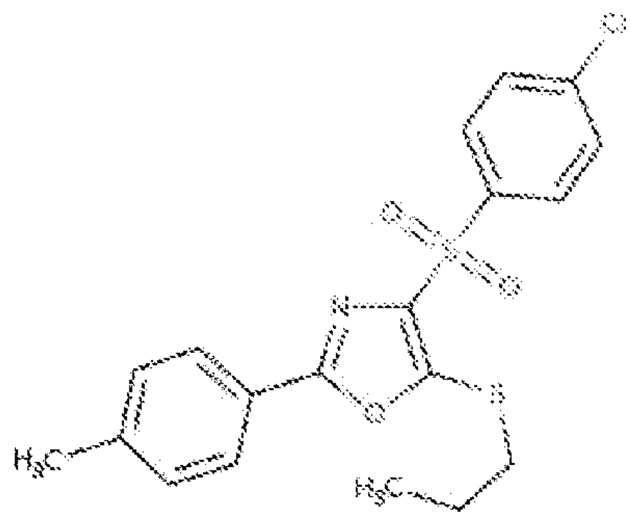
BC18535		++
BC18536		+
BC18537		++
BC18538		+

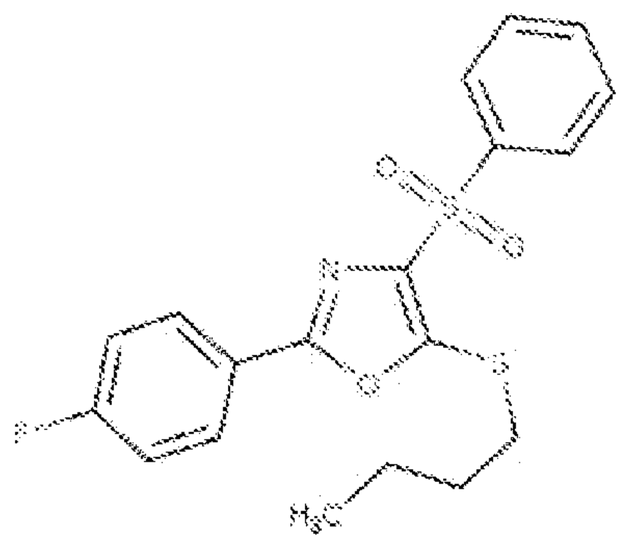
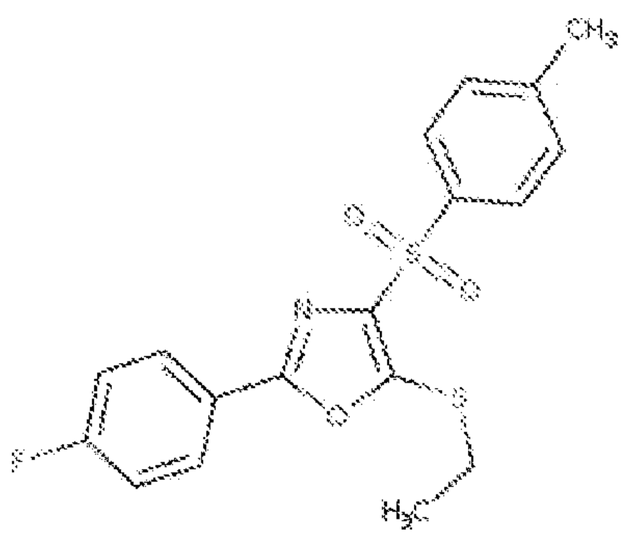
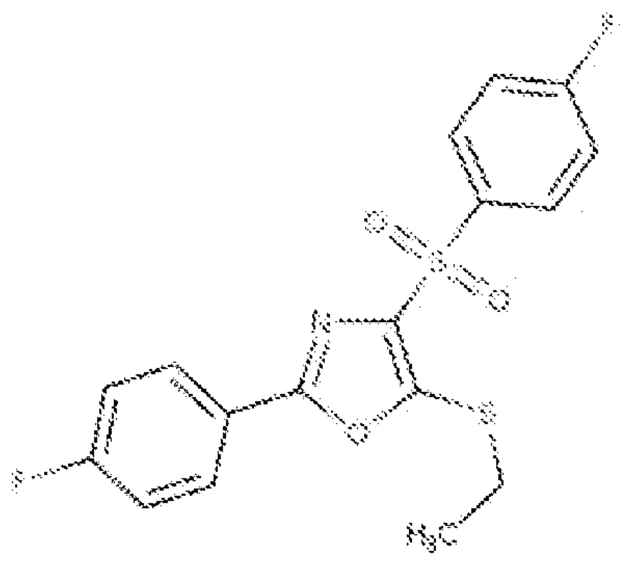
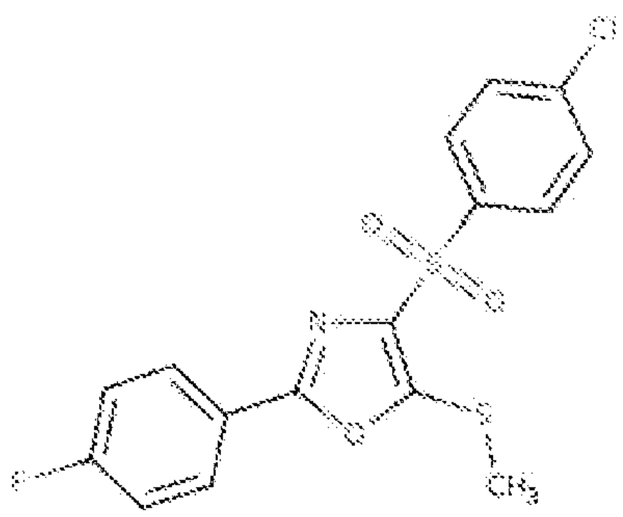
BC18539		+
BC18540		+
BC18541		+
BC18542		++++

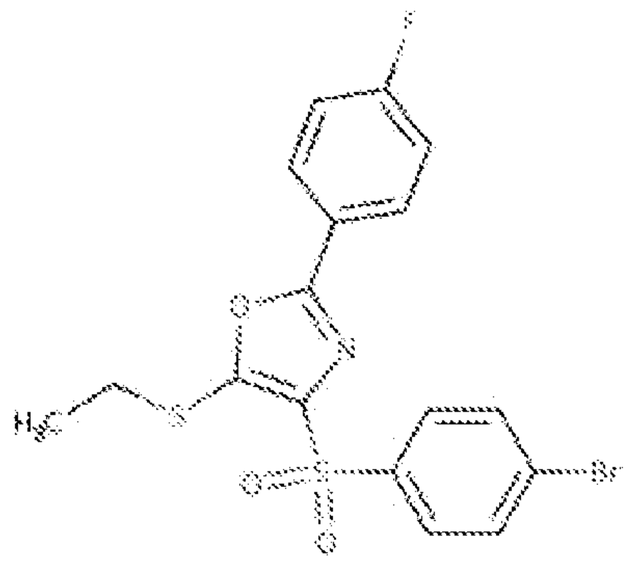
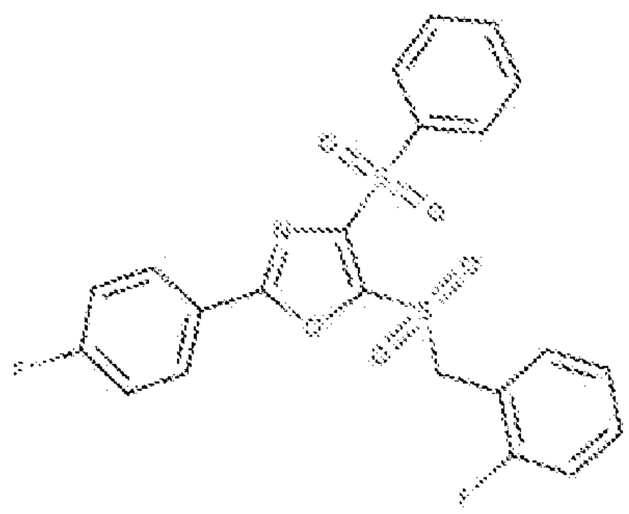
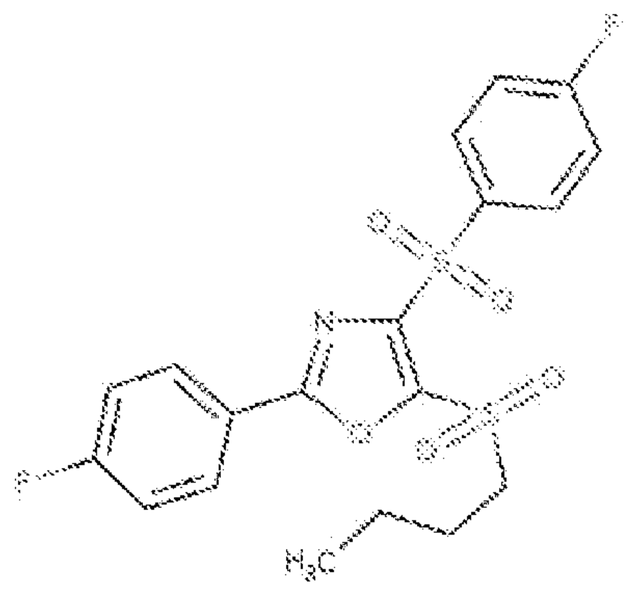
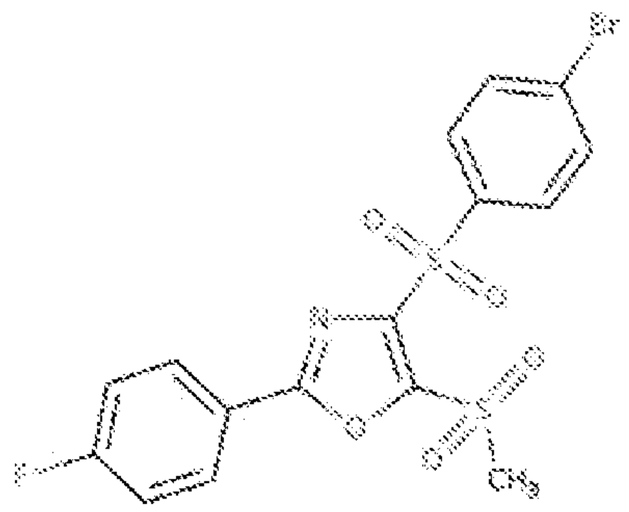
BC18543		++++
BC18544		+++
BC18545		++
BC18546		++

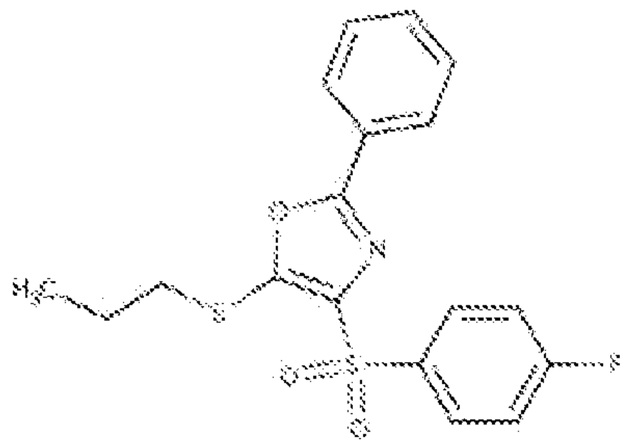
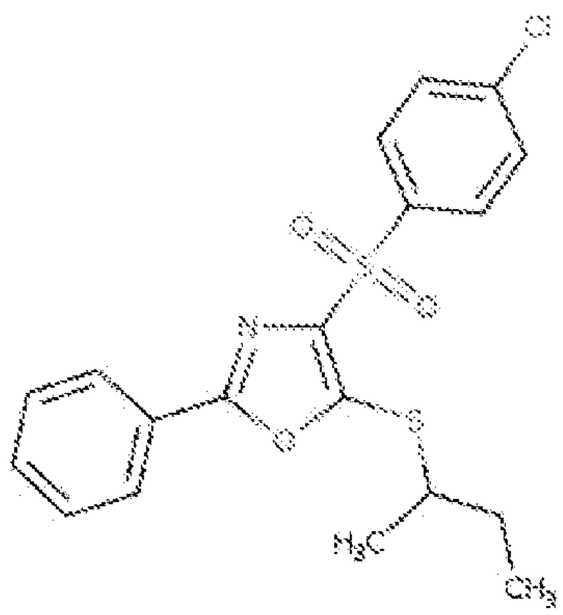
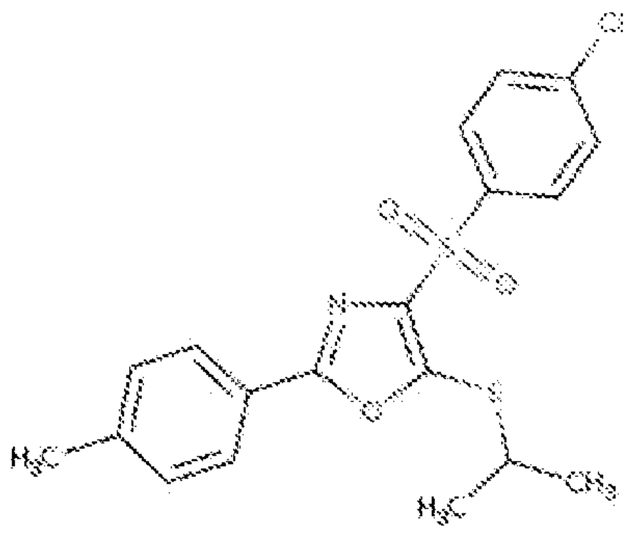
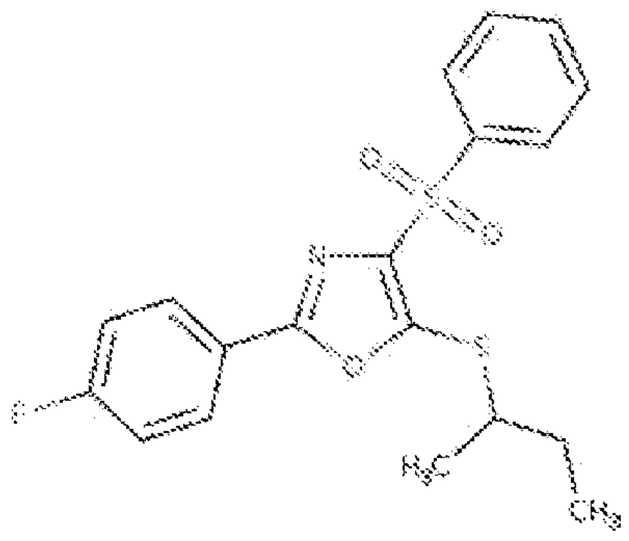
BC18547		+
BC18548		++
BC18549		+
BC18550		+

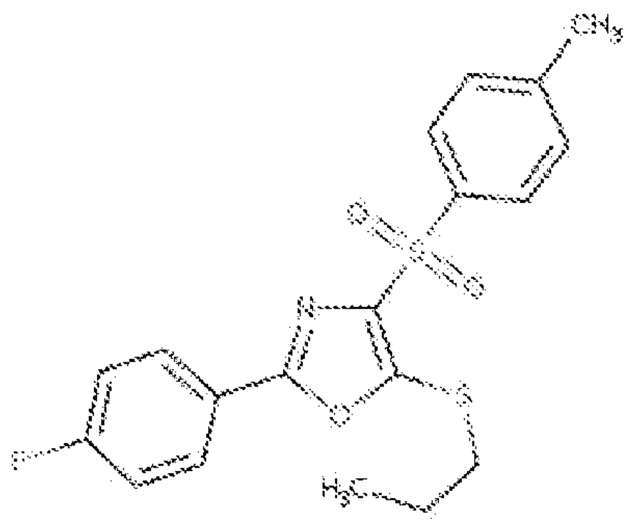
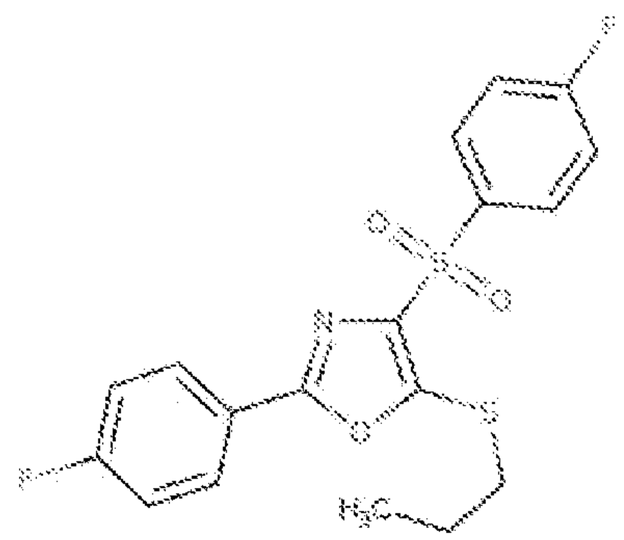
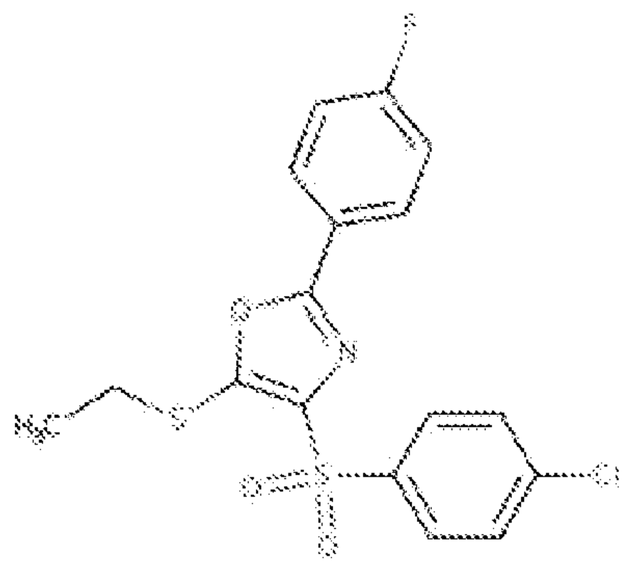
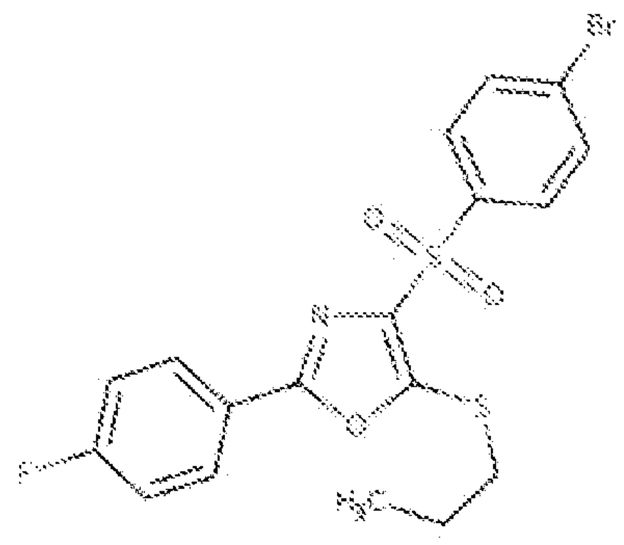
BC18551		+
BC18552		+
BC18553		++++
BC18554		++++

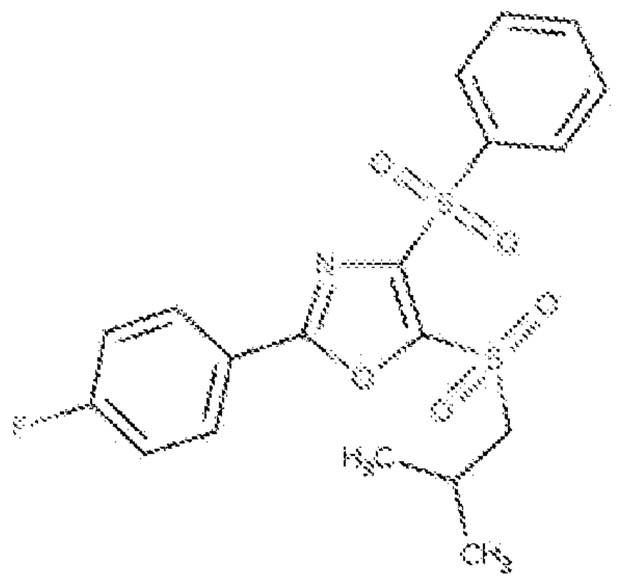
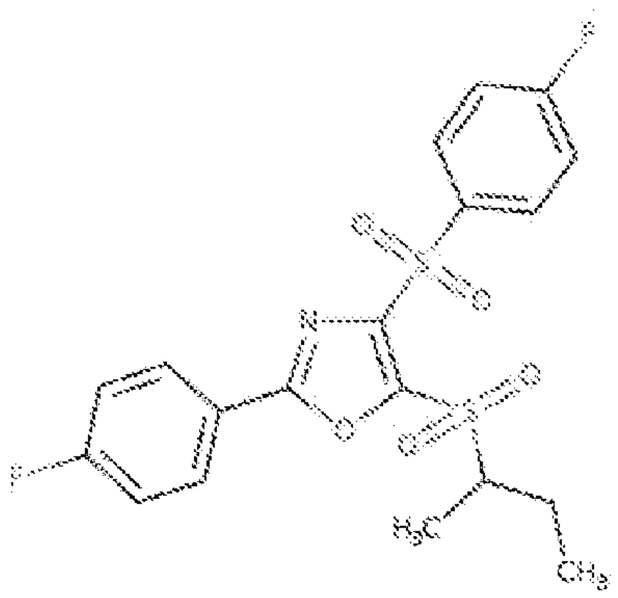
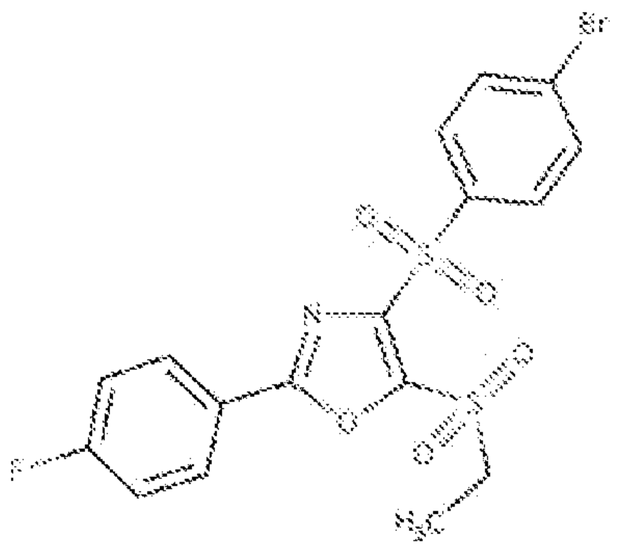
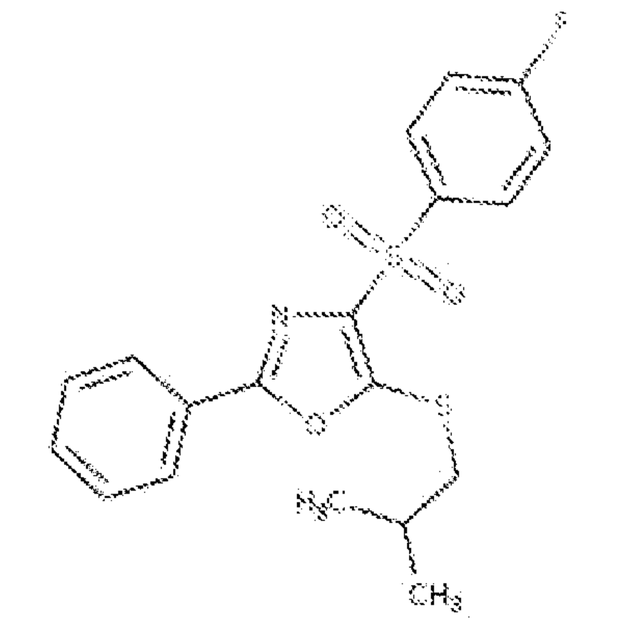
BC18555		++++
BC18556		++
BC18557		++
BC18558		+

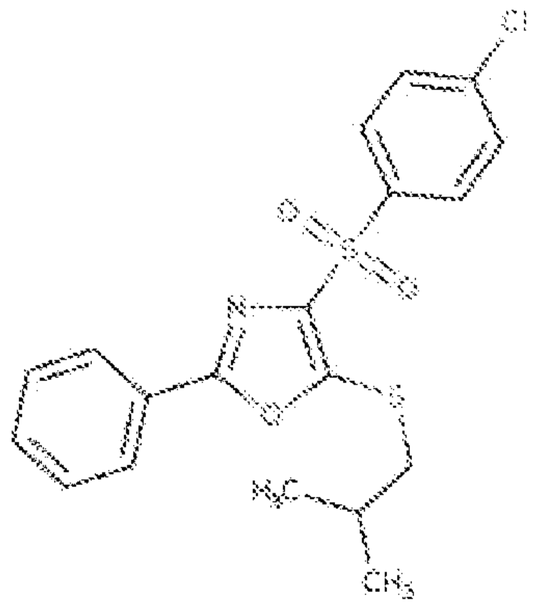
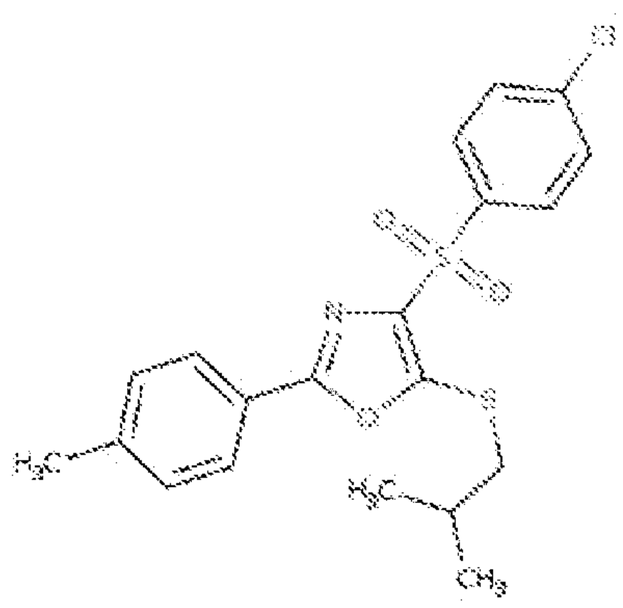
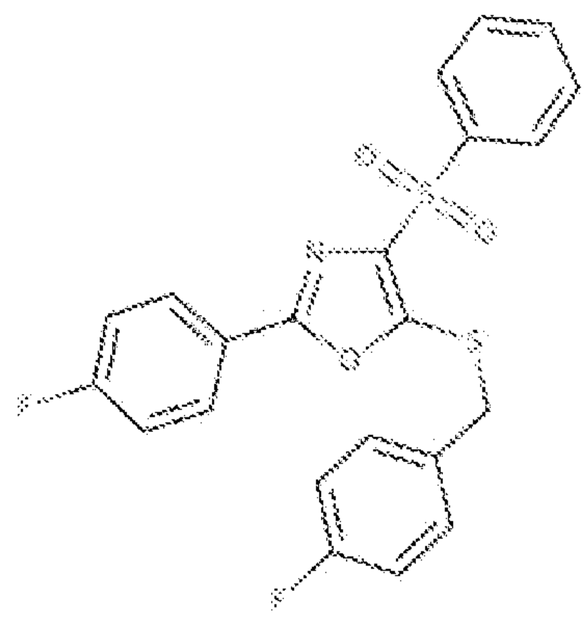
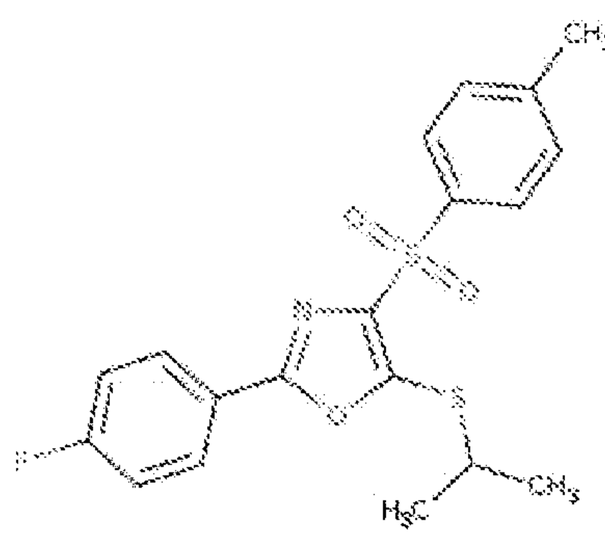
BC18559		++
BC18560		++
BC18561		++
BC18562		+

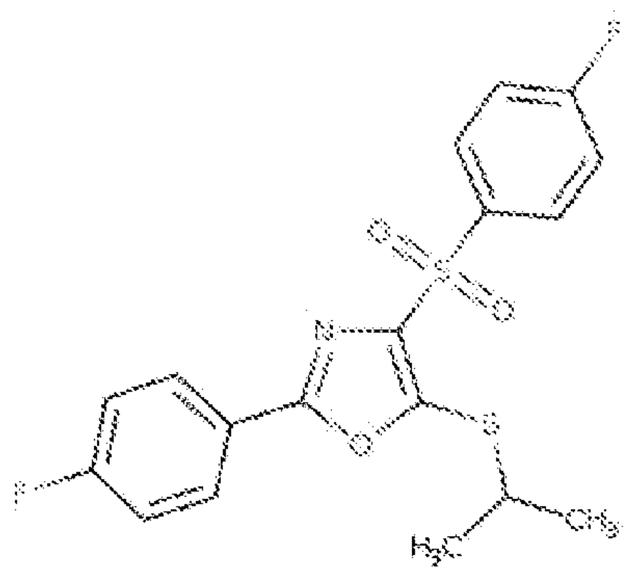
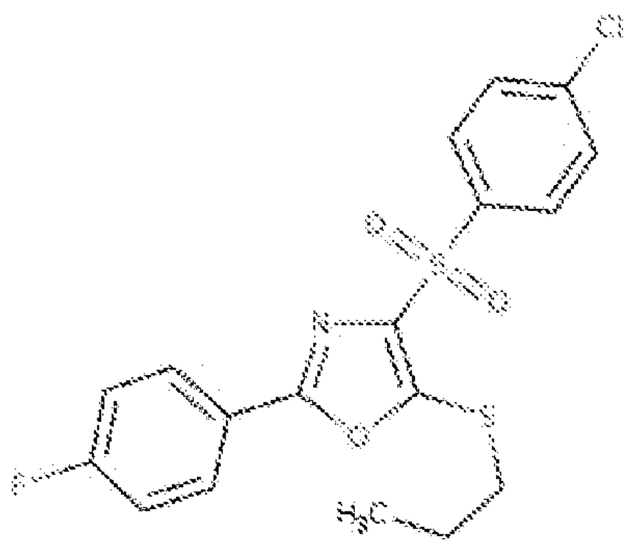
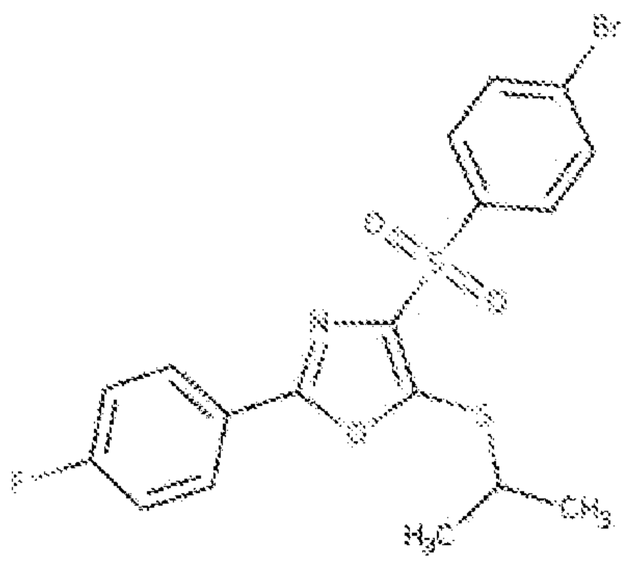
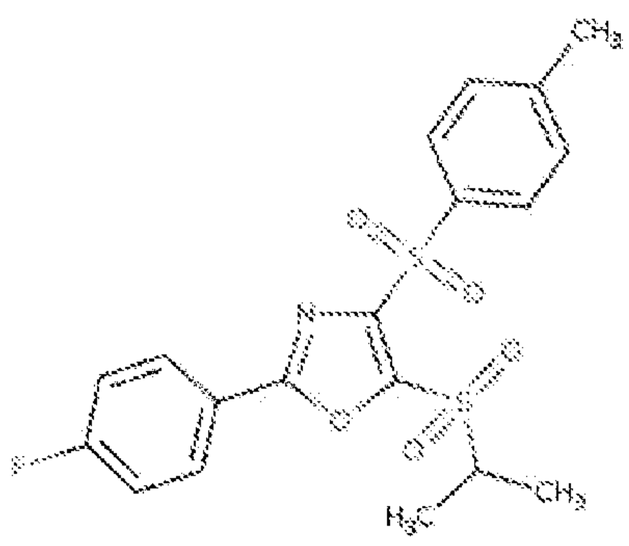
BC18563		+
BC18564		++++
BC18565		++++
BC18566		++++

BC18567		+
BC18568		++
BC18569		++
BC18570		++

BC18571		++
BC18572		+
BC18573		++
BC18574		+

BC18575		++++
BC18576		++++
BC18577		++++
BC18578		++

BC18579		++
BC18580		+
BC18581		++
BC18582		++

BC18583		++
BC18584		+
BC18585		++
BC18586		++++

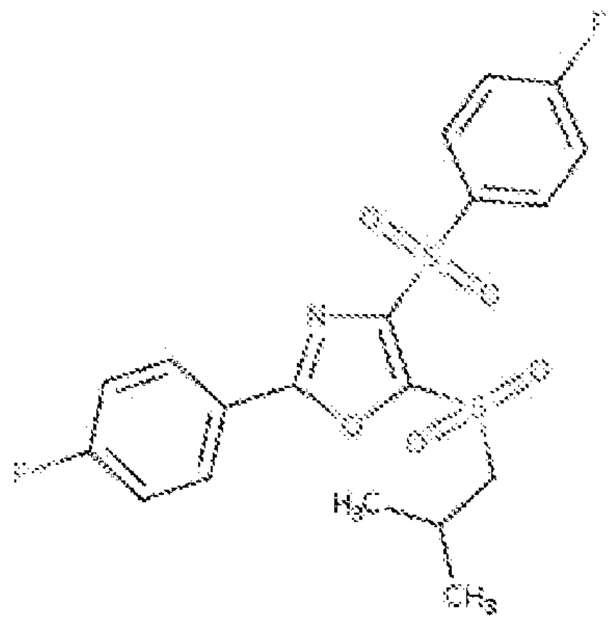
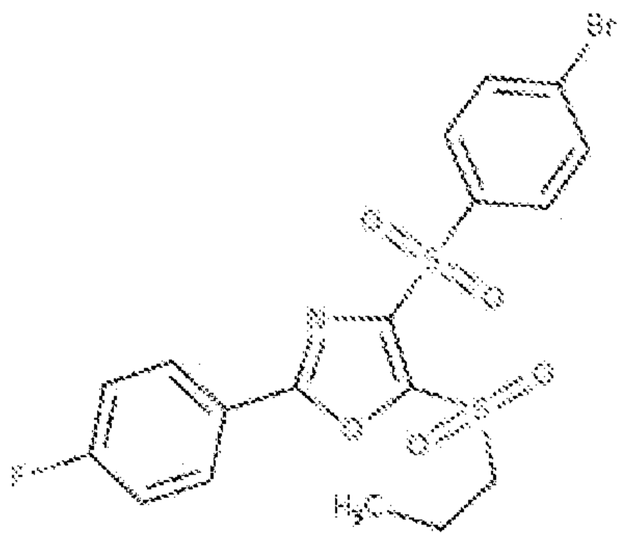
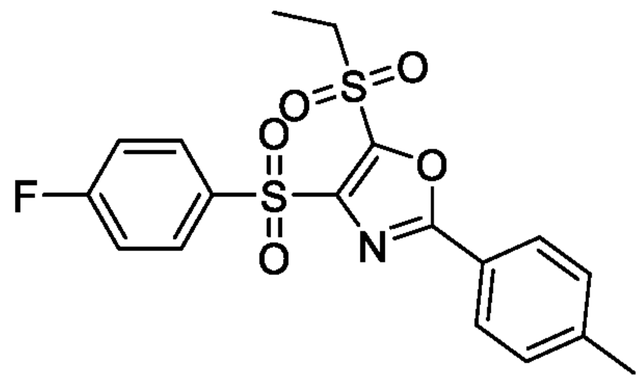
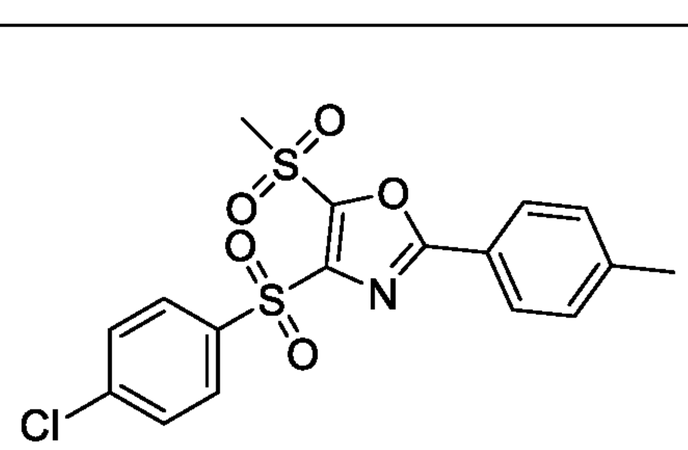
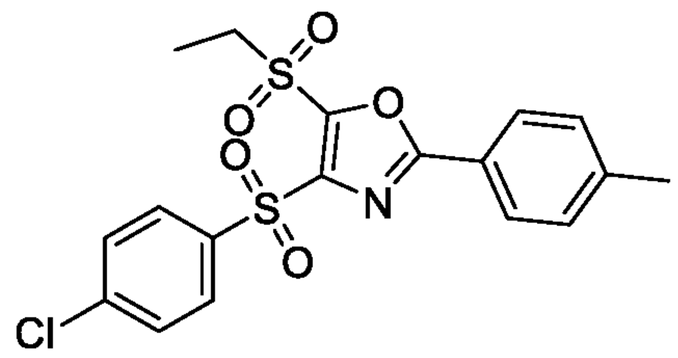
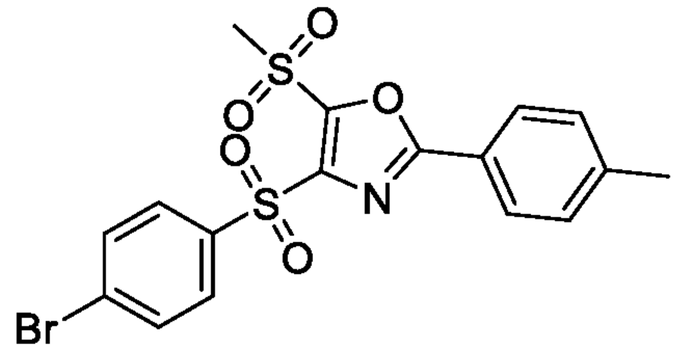
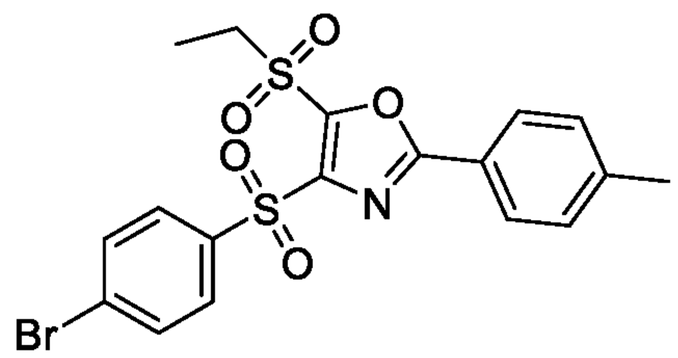
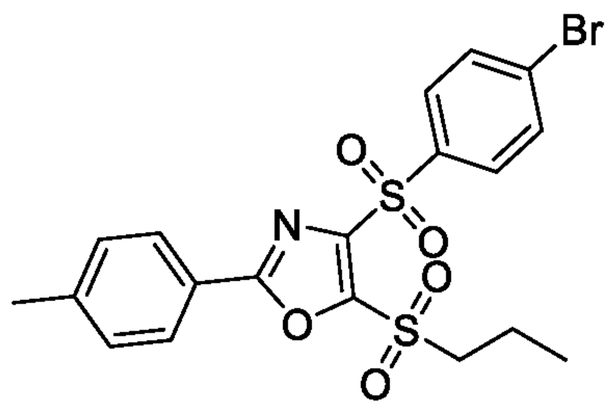
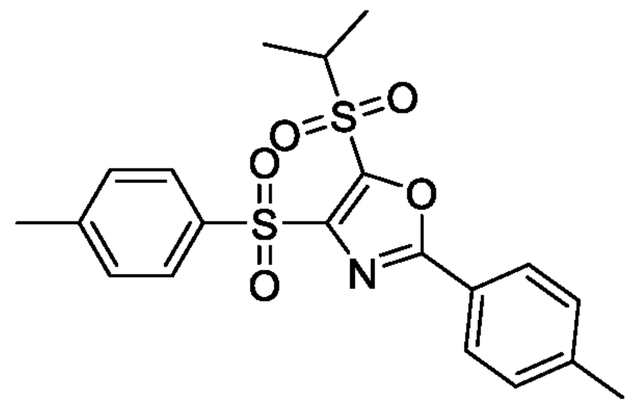
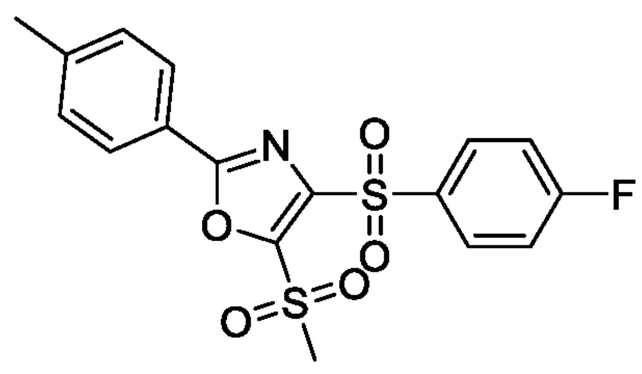
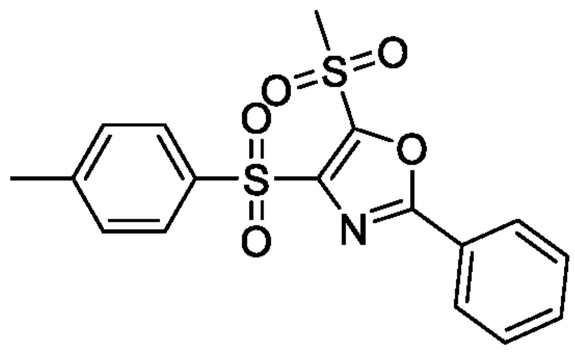
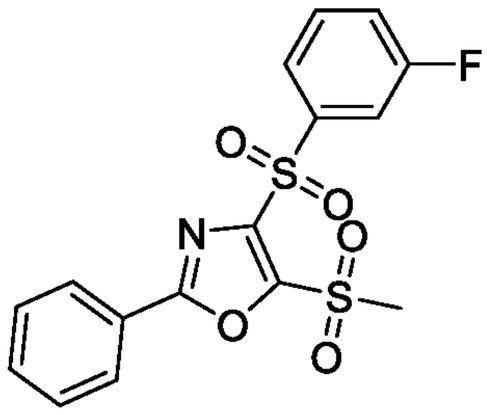
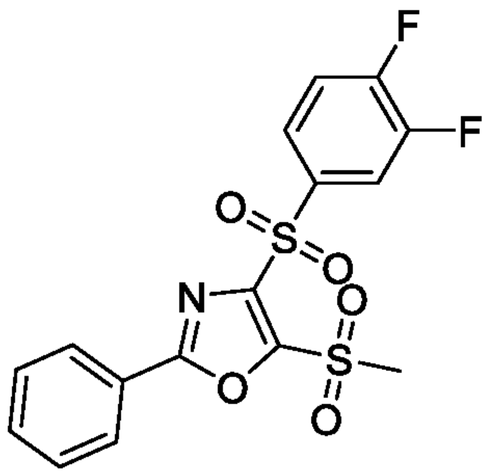
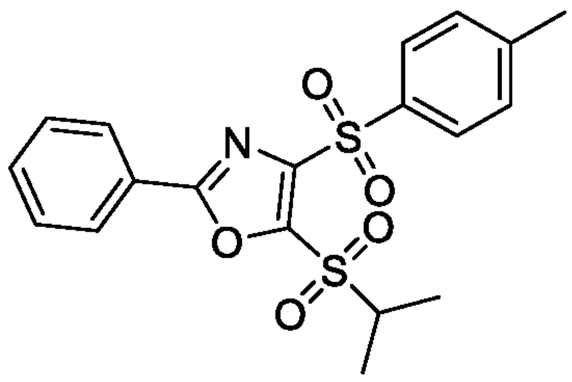
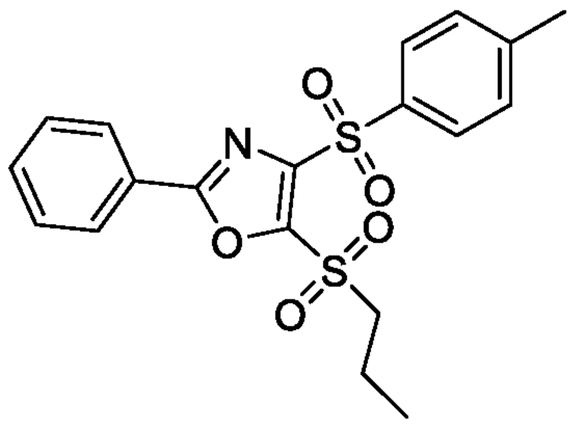
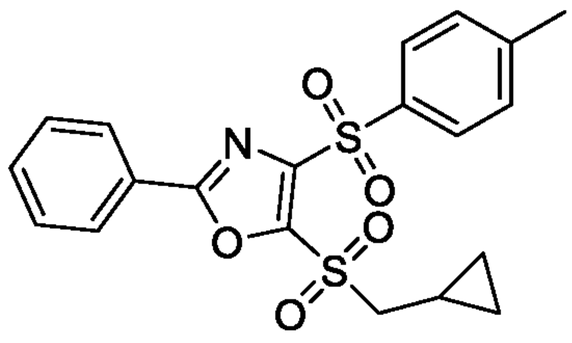
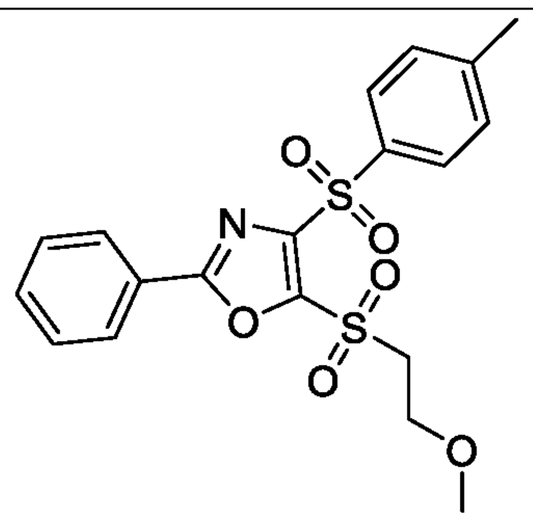
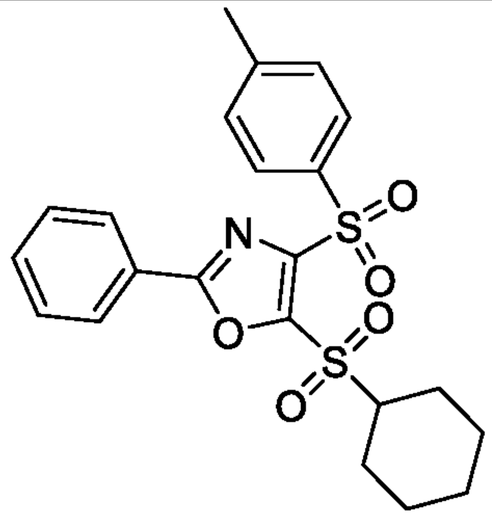
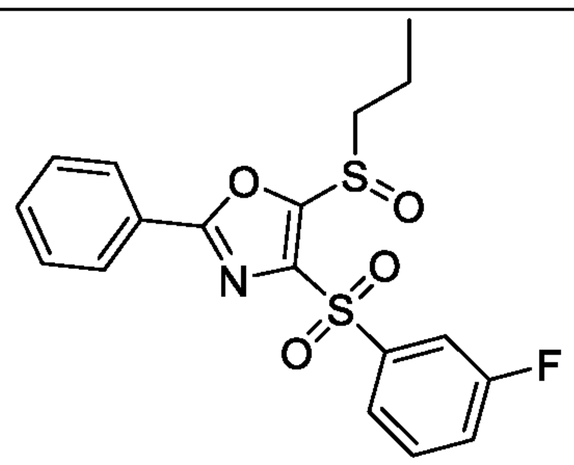
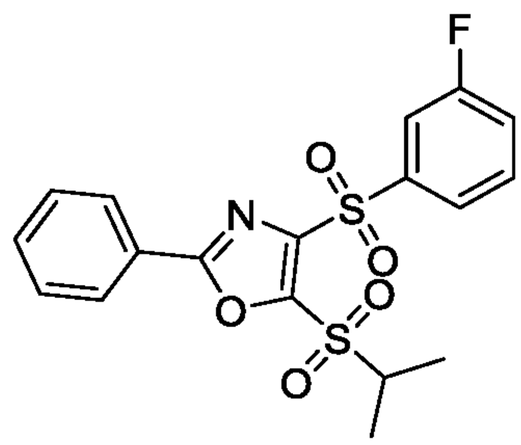
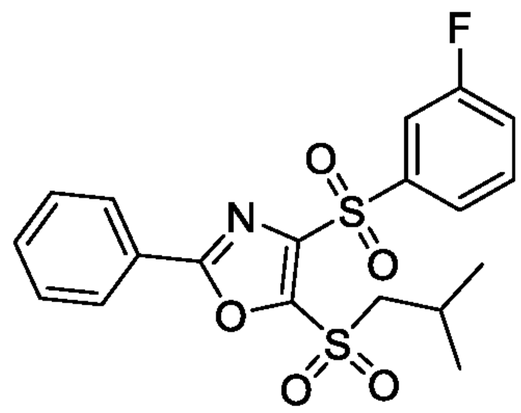
BC18587		++++
BC18588		++++

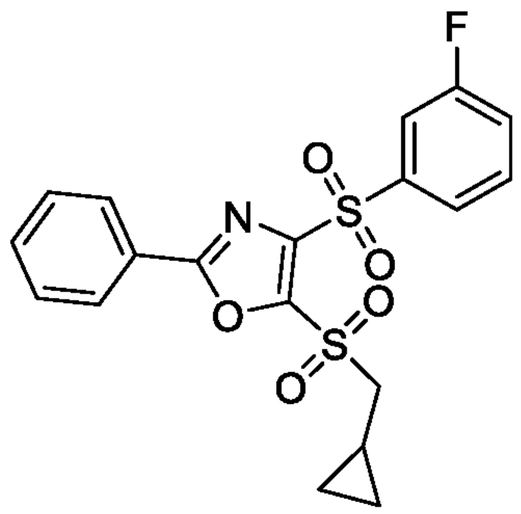
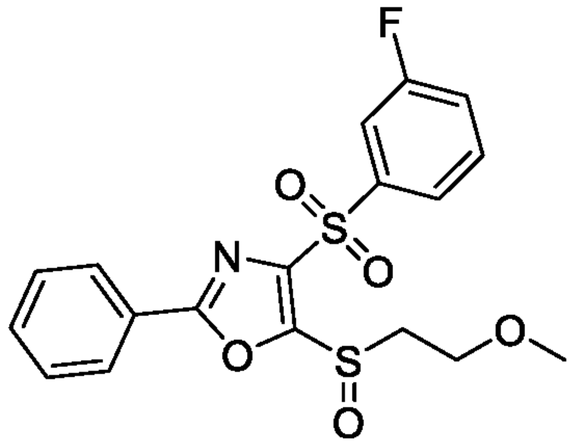
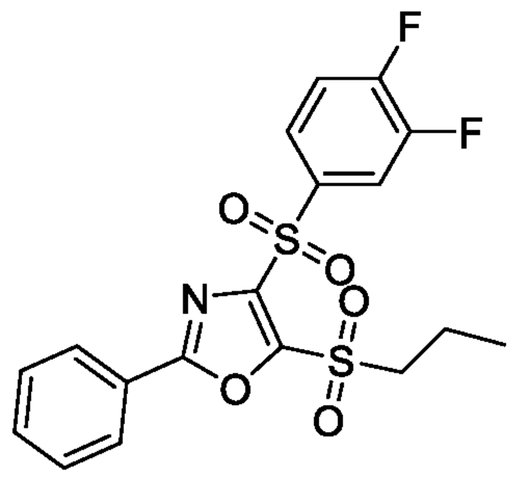
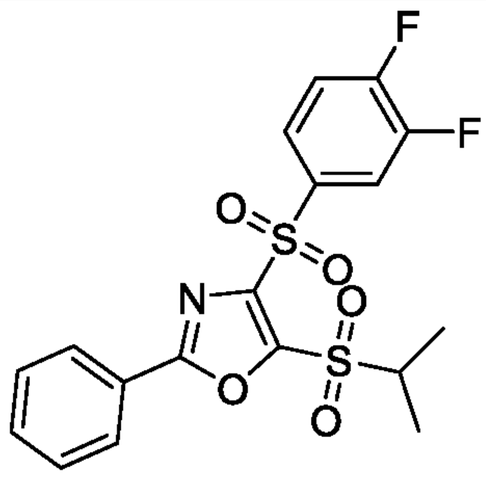
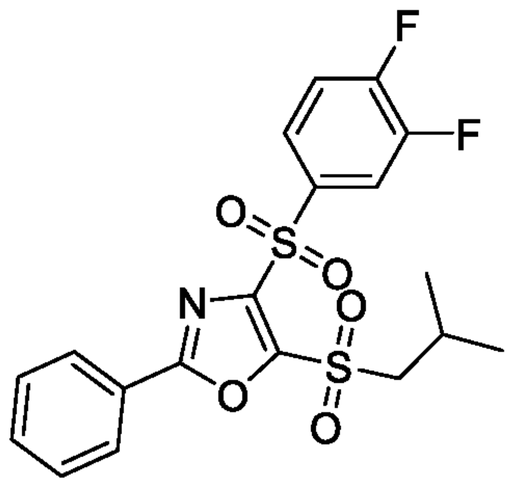
Table 3b

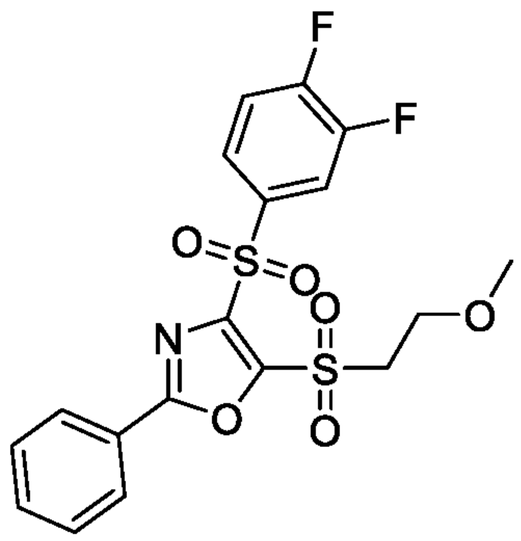
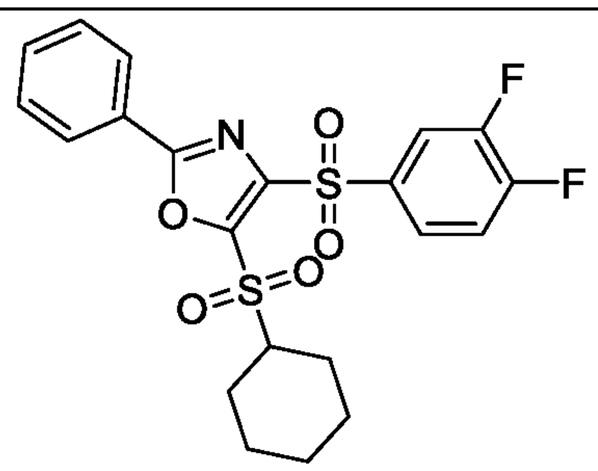
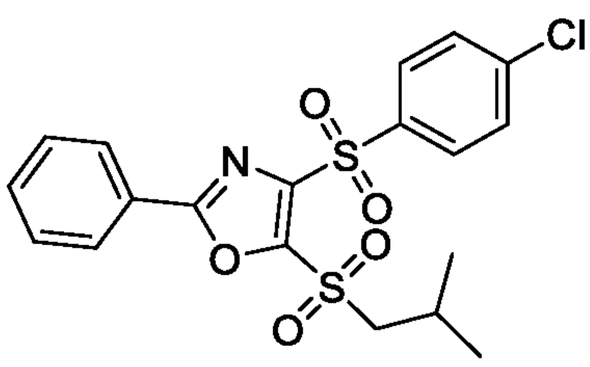
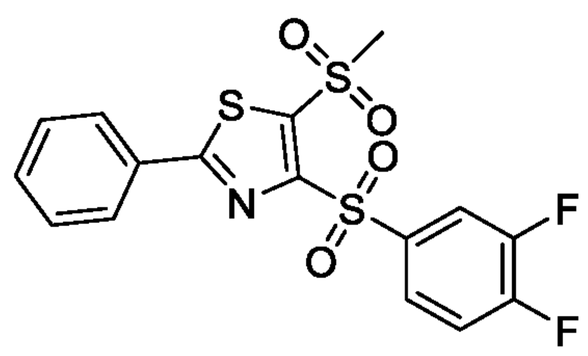
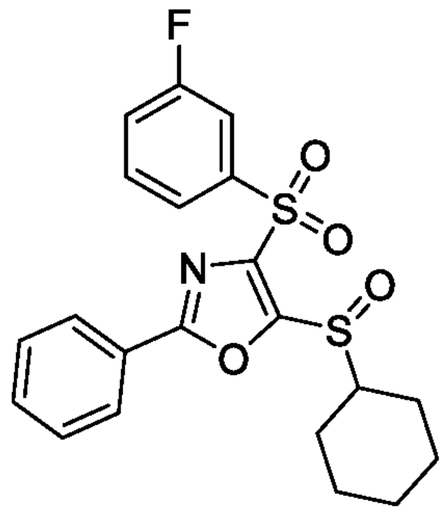
BC No.	ZE No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19125	ZE23-0008		++++	++++
BC19126	ZE23-0009		++	+++

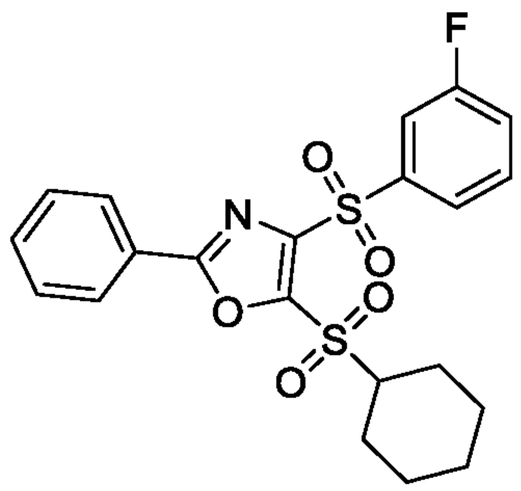
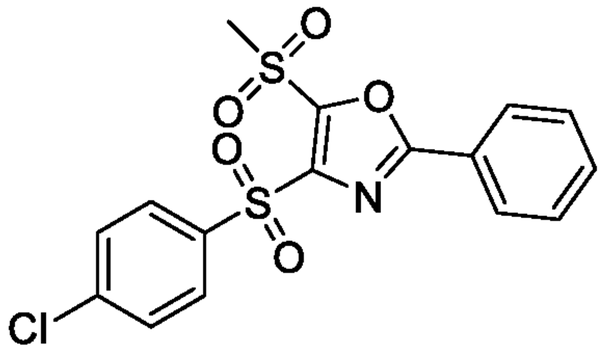
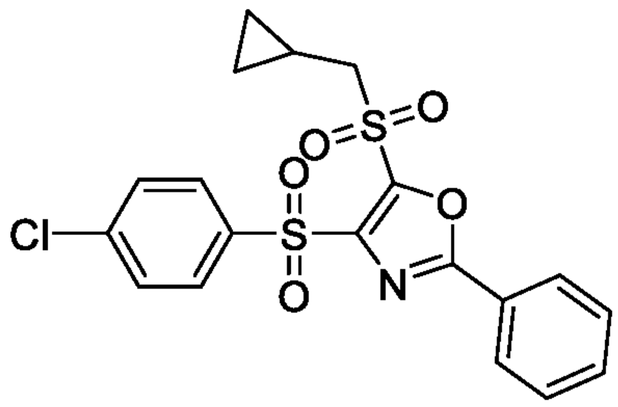
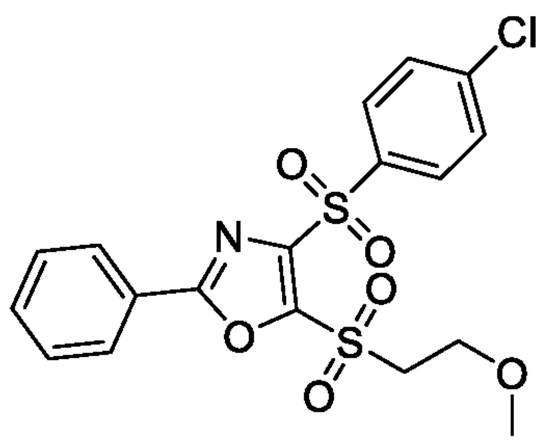
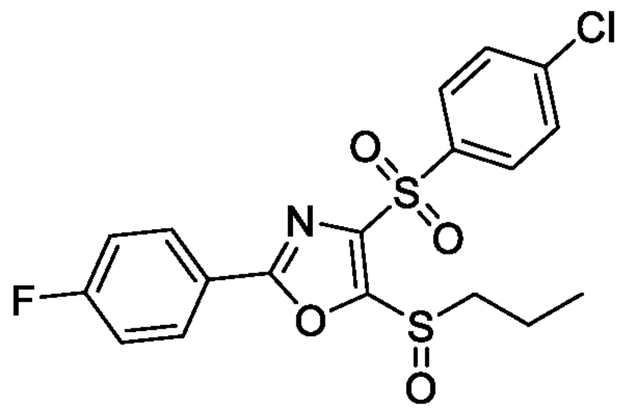
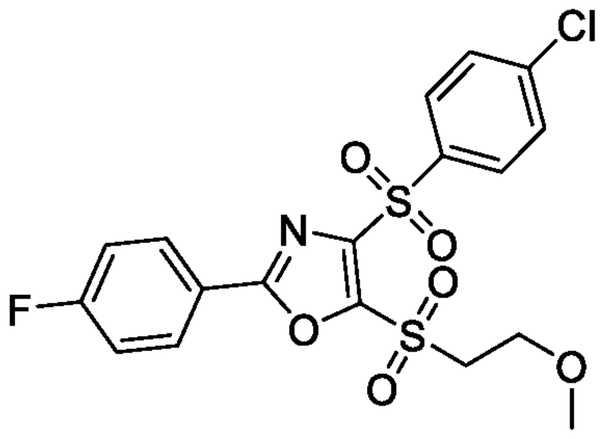
BC19127	ZE23-0010		++++	++
BC19128	ZE23-0012		++	+++
BC19129	ZE23-0013		++++	+++
BC19130	ZE23-0014		+++	+++
BC19146	ZE23-0004		++++	+++
BC19147	ZE23-0007		+++	+++

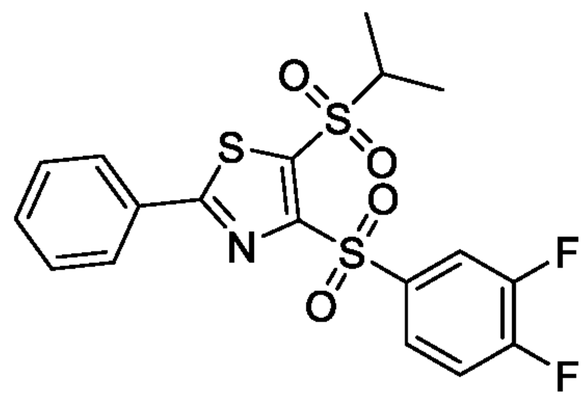
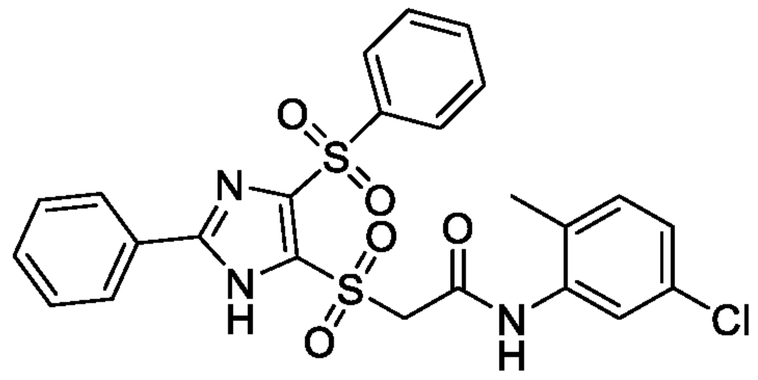
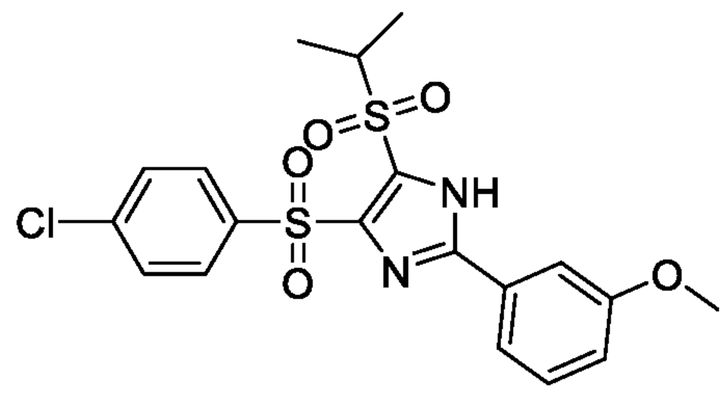
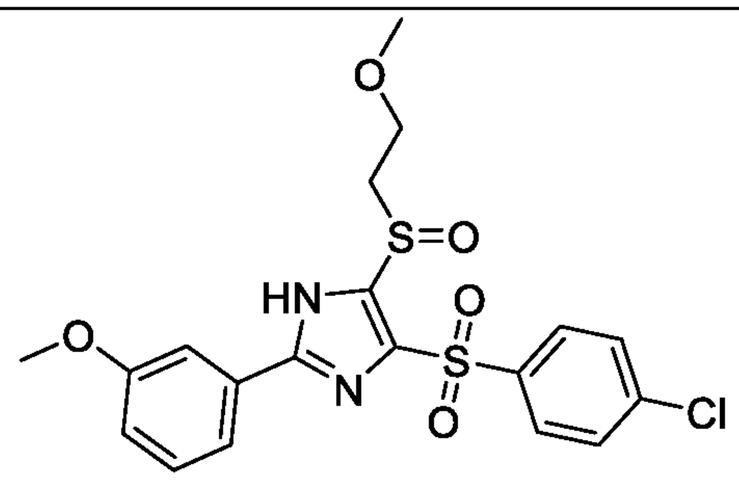
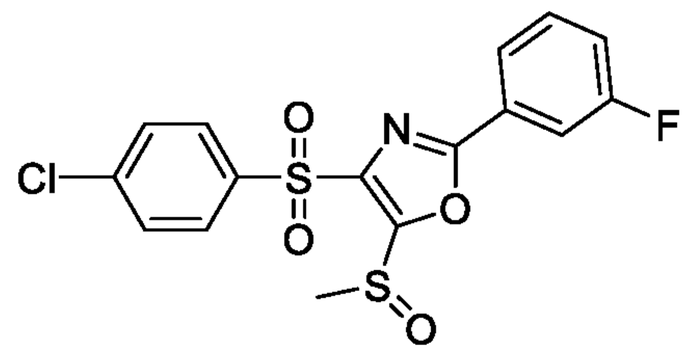
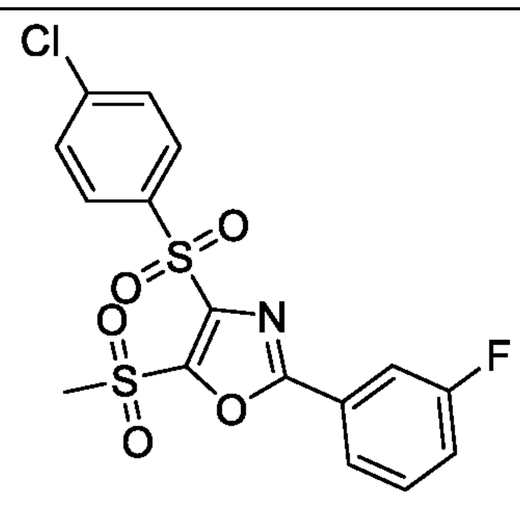
BC19260	ZE23-0016		++++	++++
BC19261	ZE23-0018		++++	+
BC19262	ZE23-0019		+++	++++
BC19263	ZE23-0022		+++	+++
BC19264	ZE23-0023		++++	+++
BC19265	ZE23-0024		++++	+++

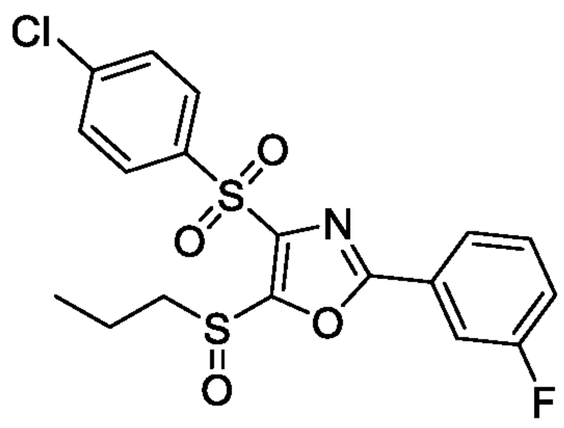
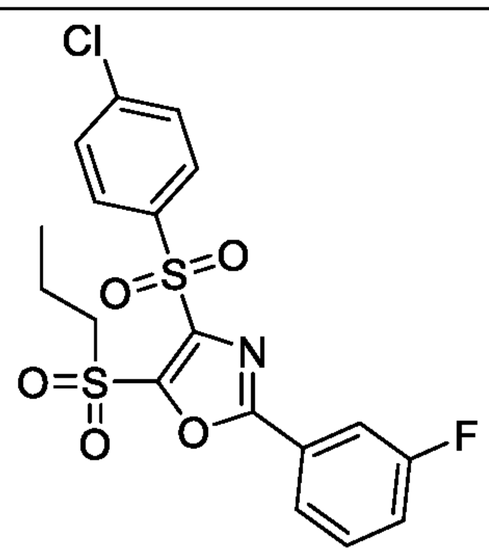
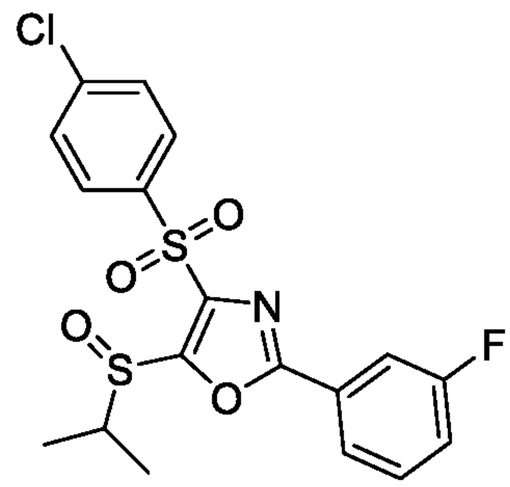
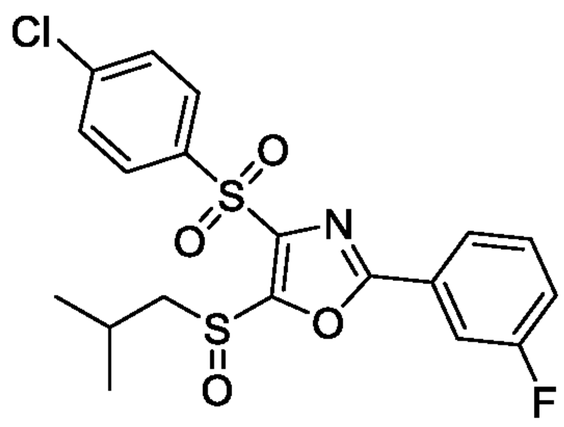
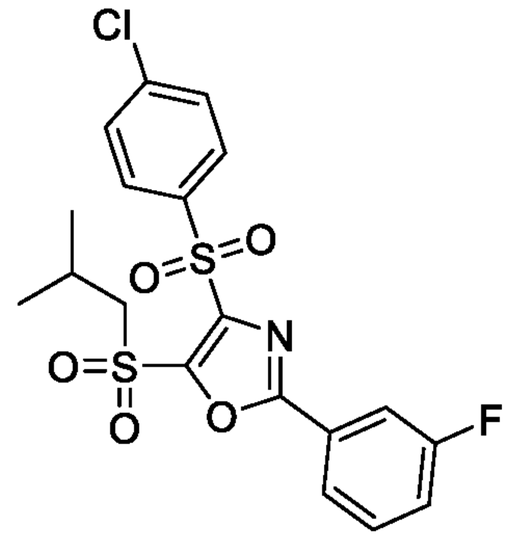
BC19266	ZE23-0025		++++	++++
BC19267	ZE23-0026		++++	+++
BC19268	ZE23-0028		+++	++++
BC19269	ZE23-0030		+++	++++
BC19270	ZE23-0031		++++	++++

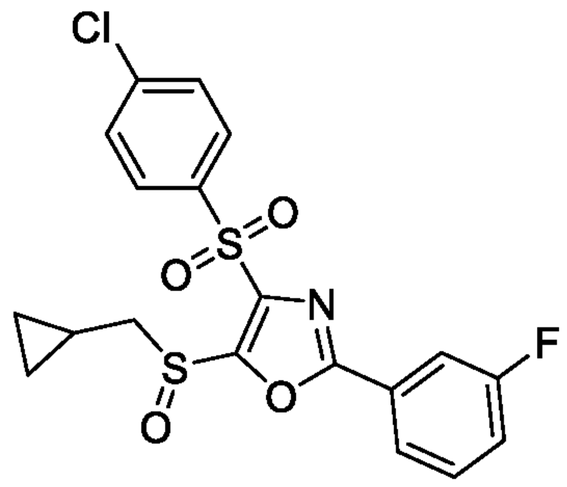
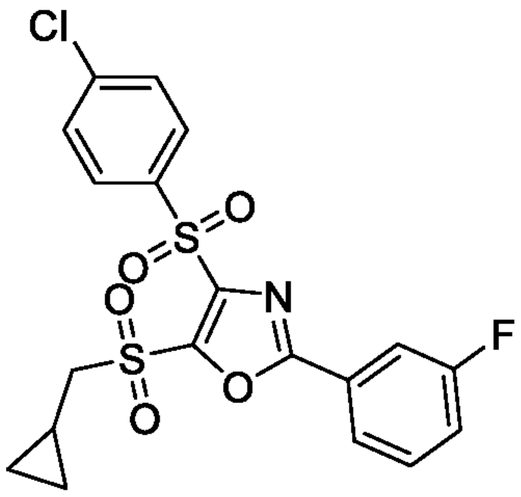
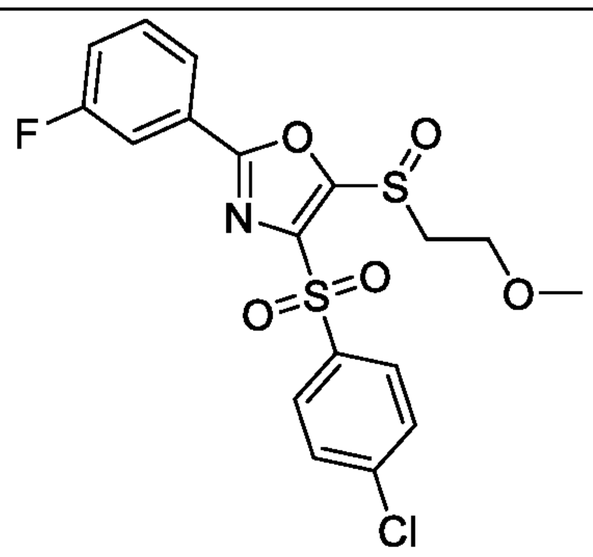
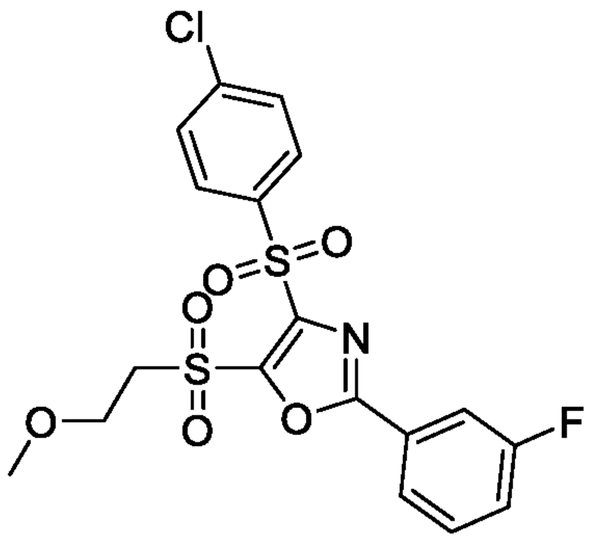
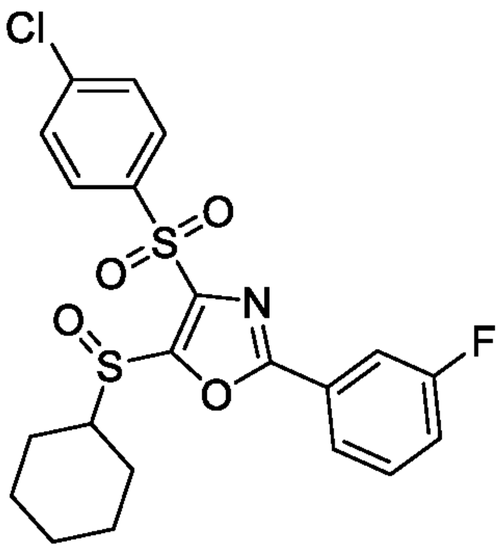
BC19271	ZE23-0032		+++	++++
BC19272	ZE23-0033		++++	++++
BC19273	ZE23-0039		+++	+++
BC19274	ZE23-0040		++++	+++
BC19275	ZE23-0041		++++	++++

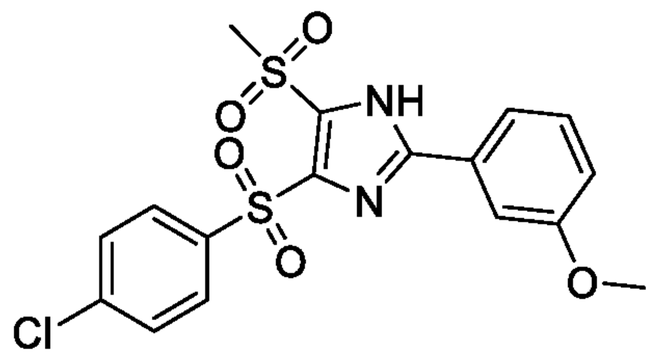
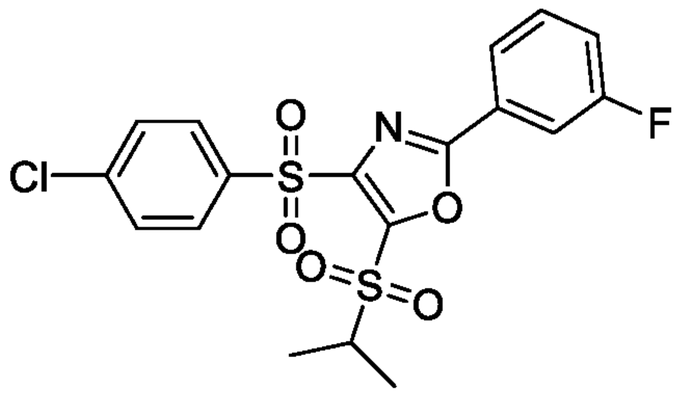
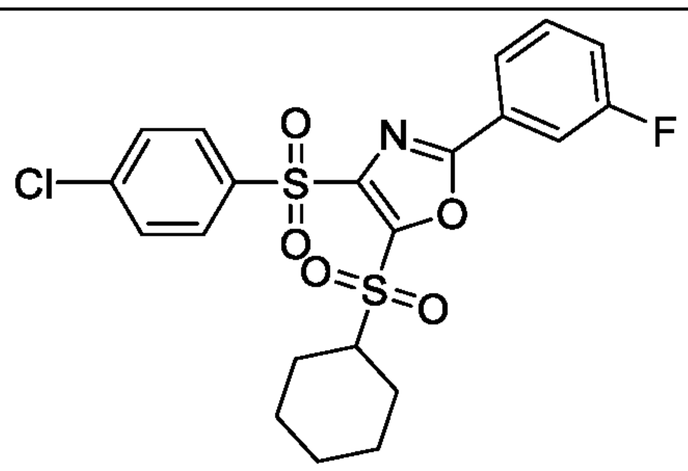
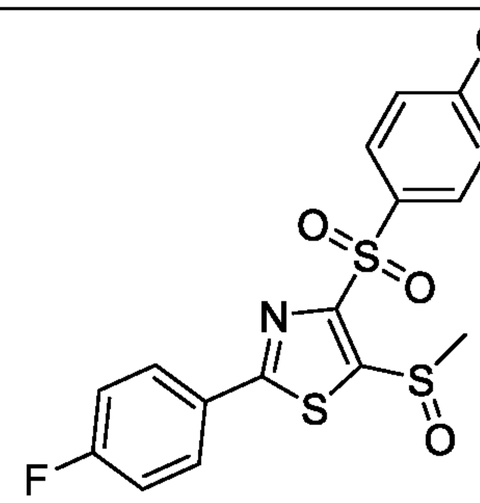
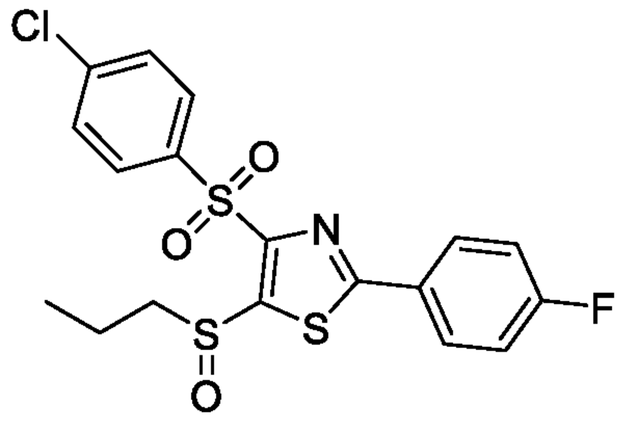
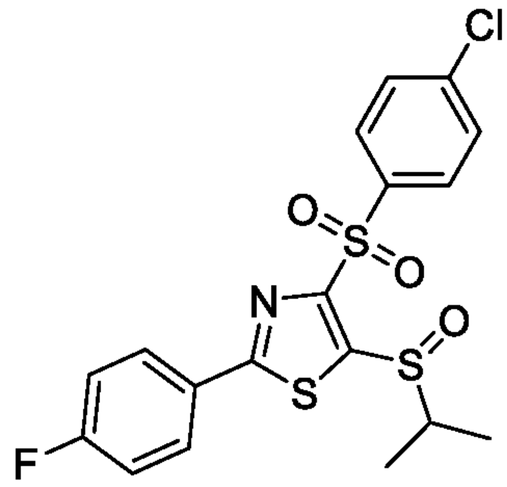
BC19276	ZE23-0044		+++	++++
BC19277	ZE23-0045		++++	+++
BC19278	ZE23-0051		++++	++++
BC19279	ZE23-0065		+++	+++
BC19327	ZE23-0037		++	++

BC19328	ZE23-0038		++++	+++
BC19329	ZE23-0047		++++	++++
BC19330	ZE23-0052		+++	+++
BC19331	ZE23-0055		++++	++++
BC19332	ZE23-0057		+++	++++
BC19333	ZE23-0058		++++	++++

BC19334	ZE23-0064		+	++
BC19335	ZE23-0066		+	+
BC19336	ZE23-0083		+	+
BC19337	ZE23-0087		+	+
BC19342	ZE23-0102		++++	++++
BC19343	ZE23-0103		++	++++

BC19344	ZE23-0104		+++	+++
BC19345	ZE23-0105		+++	+++
BC19346	ZE23-0106		++++	++++
BC19347	ZE23-0108		++++	++++
BC19348	ZE23-0109		++++	+++

BC19349	ZE23-0110		+++	++++
BC19350	ZE23-0111		++	++
BC19351	ZE23-0112		+++	++++
BC19352	ZE23-0113		+++	++++
BC19353	ZE23-0116		+++	+++

BC19410	ZE23-0082		+++	+
BC19411	ZE23-0107		++++	++++
BC19412	ZE23-0117		+++	+++
BC19413	ZE23-0127		+	++
BC19414	ZE23-0128		+	+
BC19415	ZE23-0129		+	++

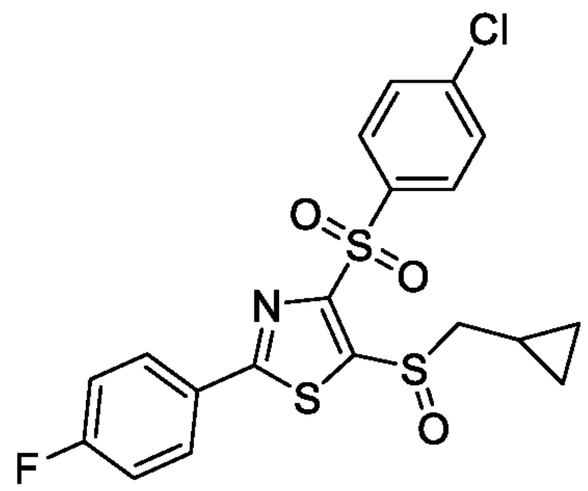
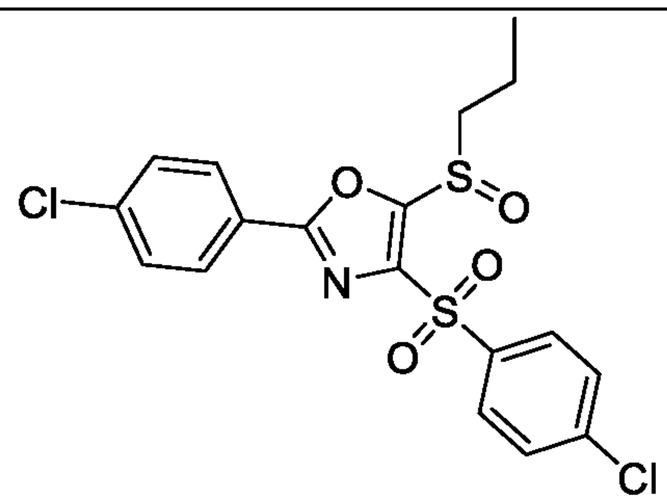
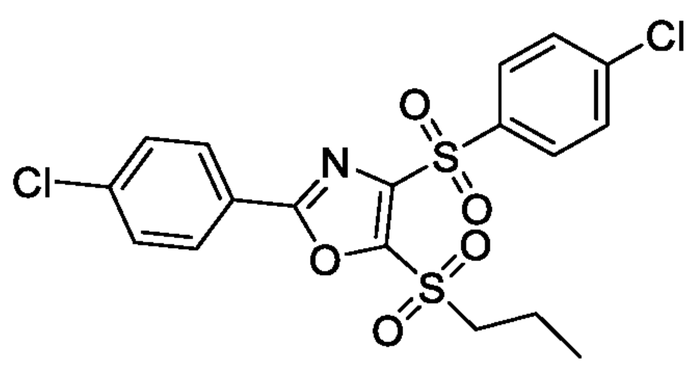
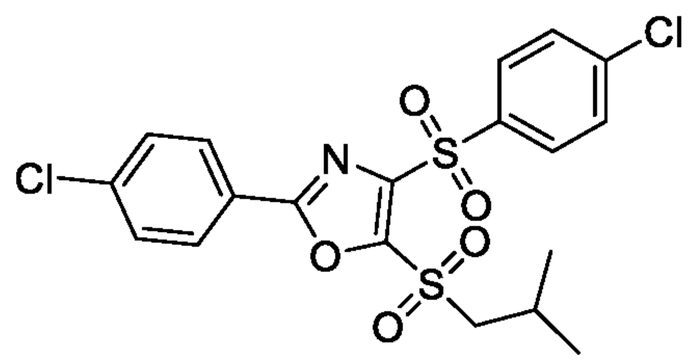
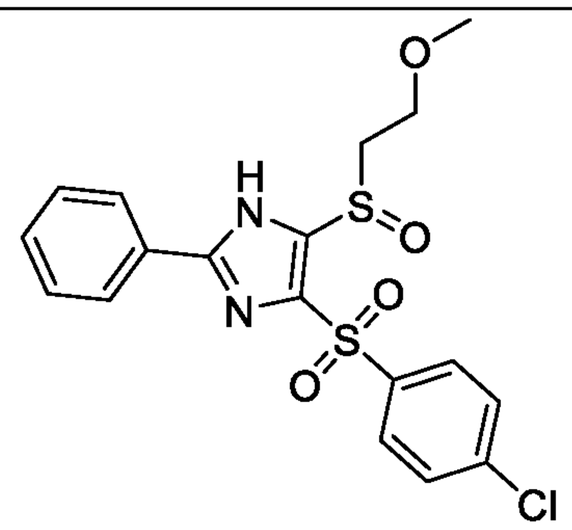
BC19416	ZE23-0131		+	+
BC19417	ZE23-0133		+++	++
BC19418	ZE23-0134		++	++
BC19419	ZE23-0136		++	+++
BC19420	ZE23-0145		+	+

Table 3b-2

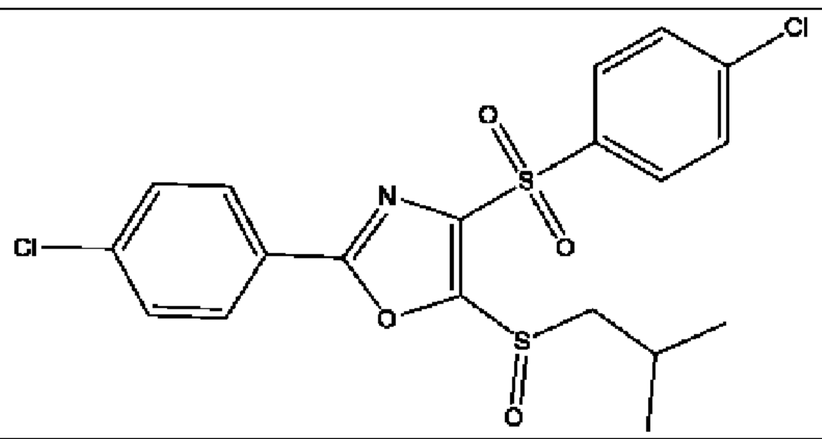
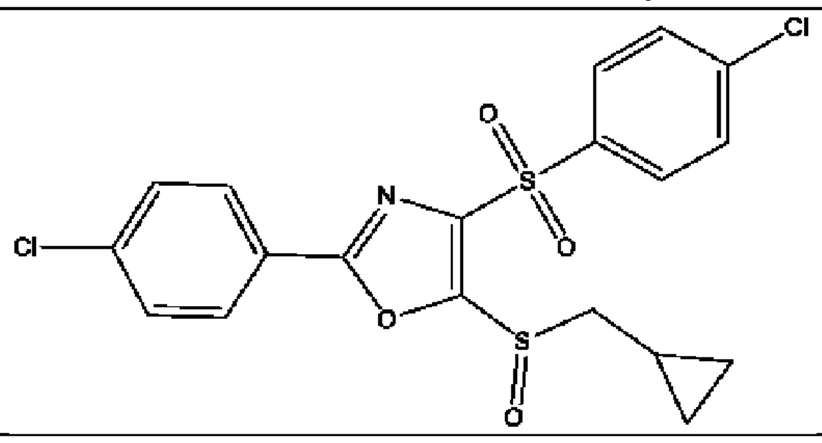
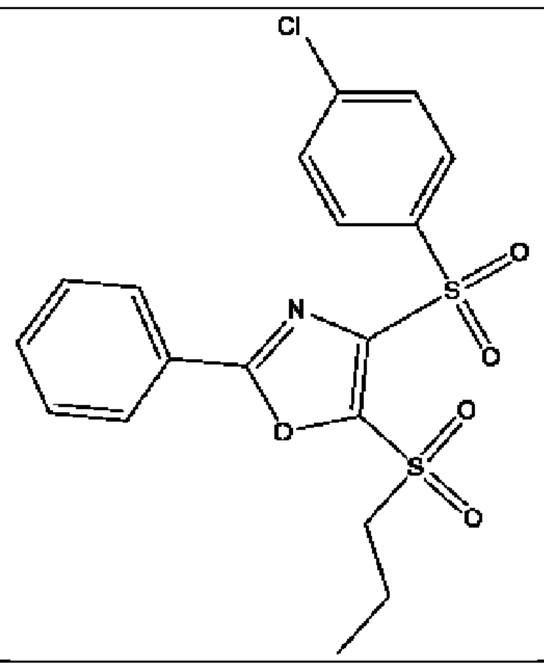
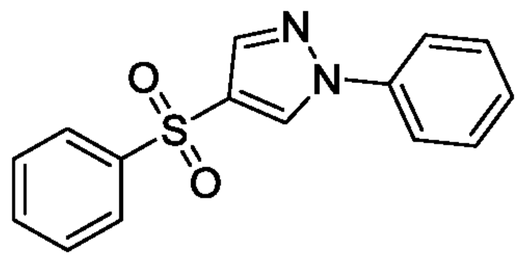
BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19463		++++	+++
BC19464		+++	++++
BC19521		++++	+++

Table 3c

BC No.	ZE No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19204	ZE23-0020		+	+

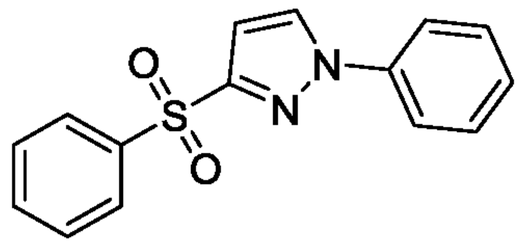
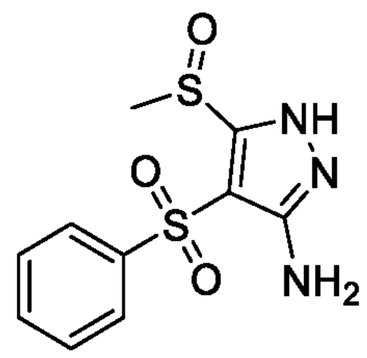
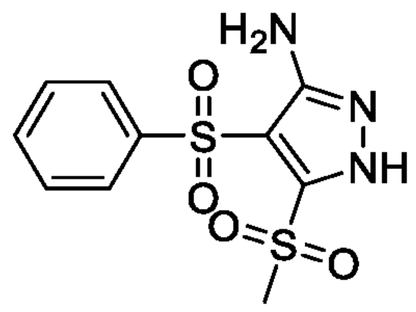
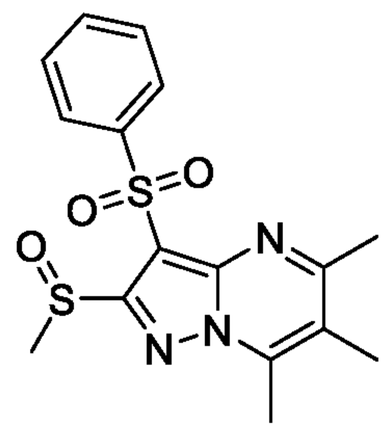
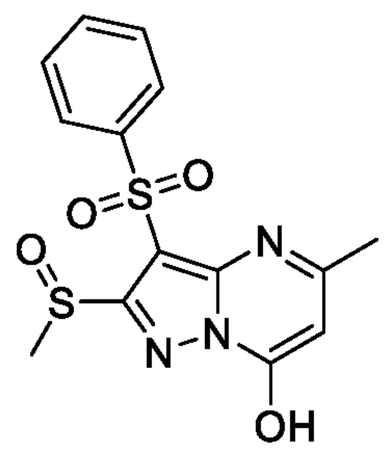
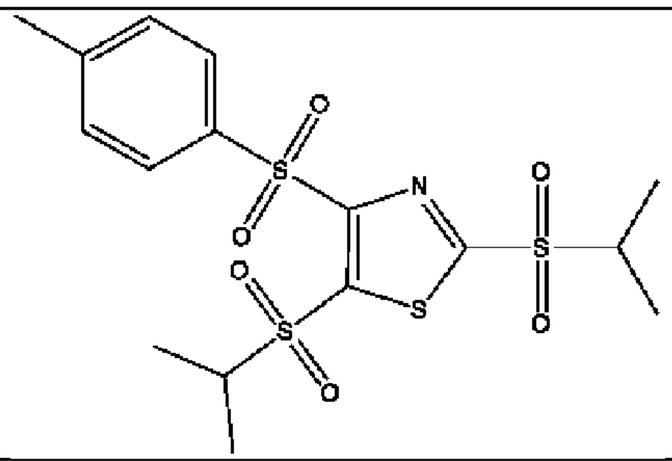
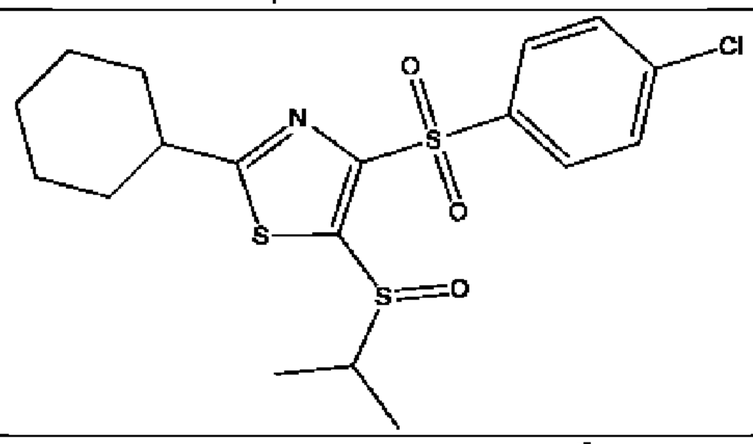
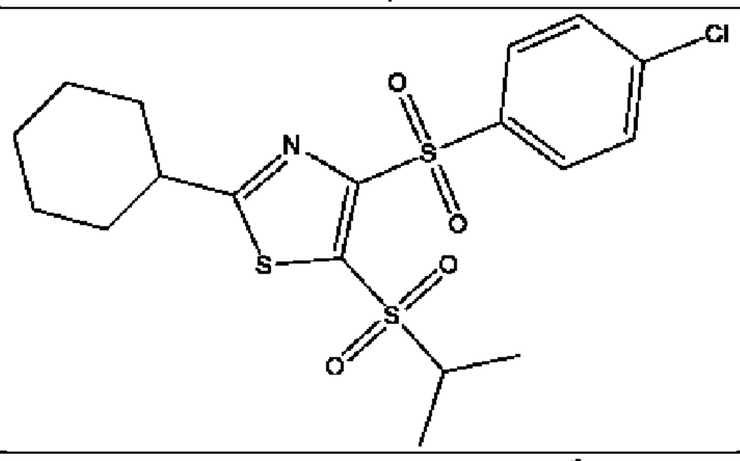
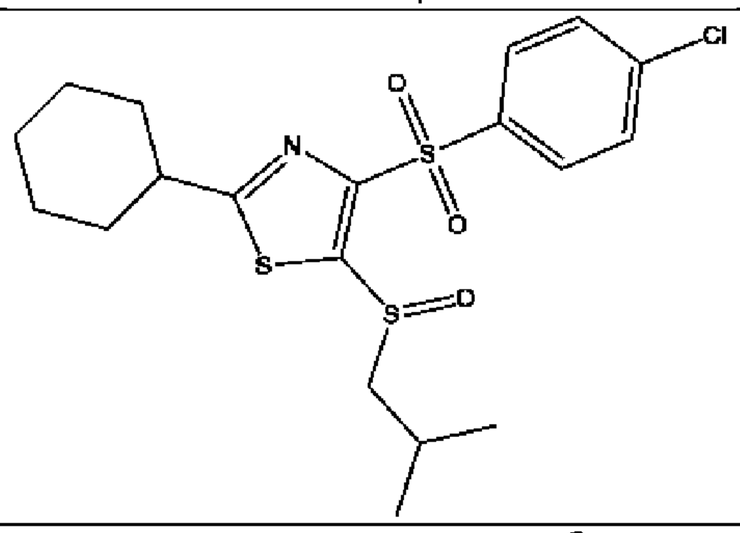
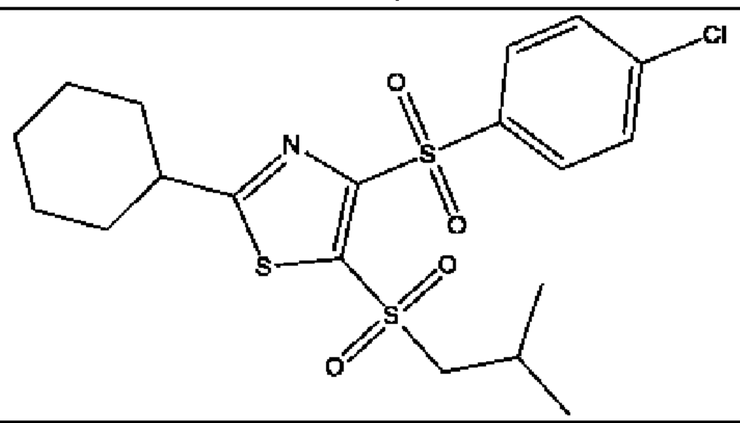
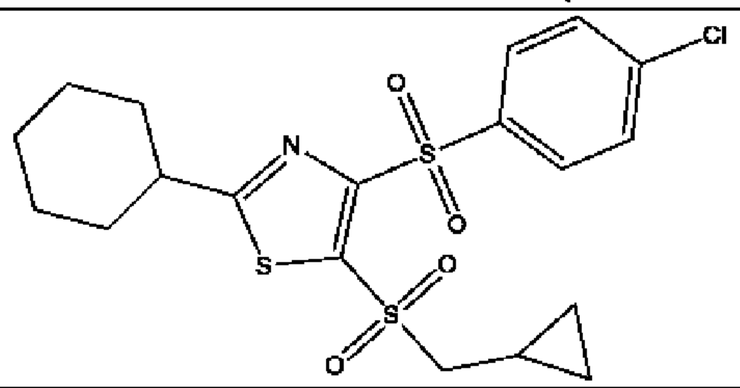
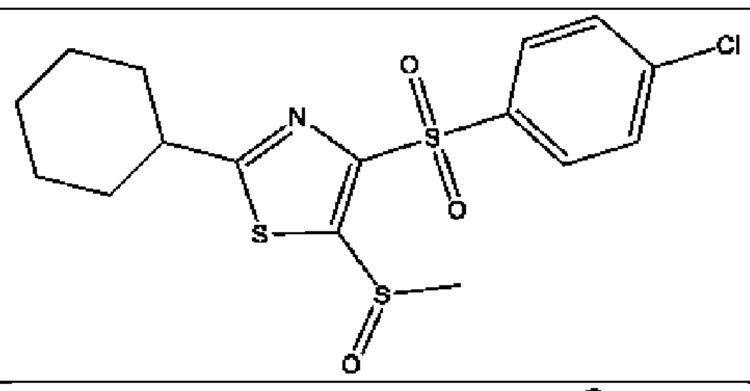
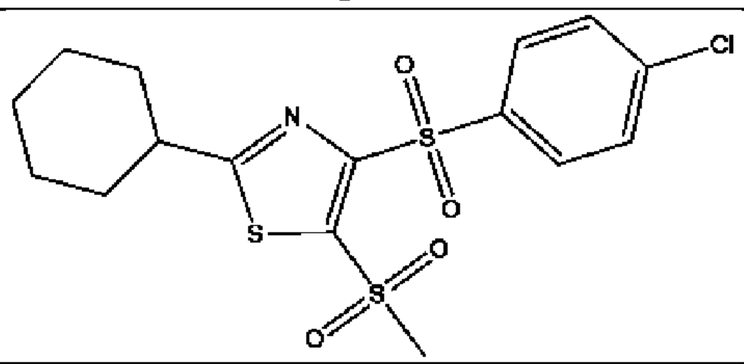
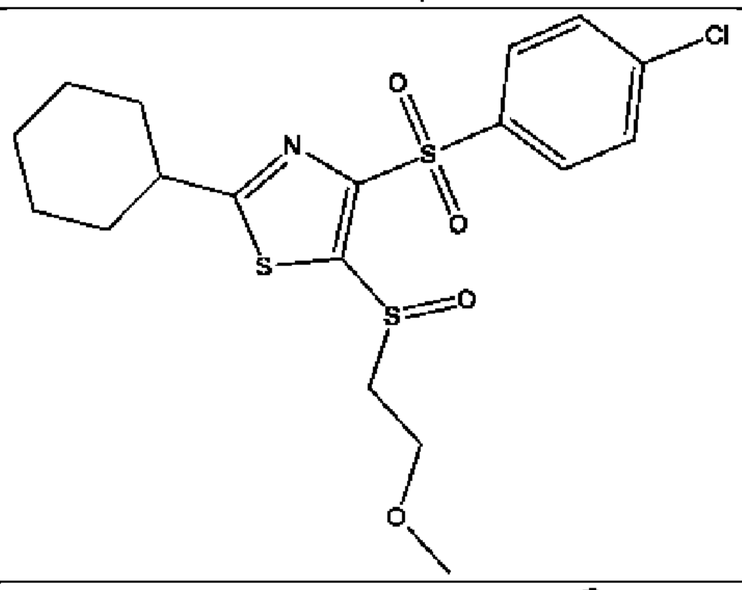
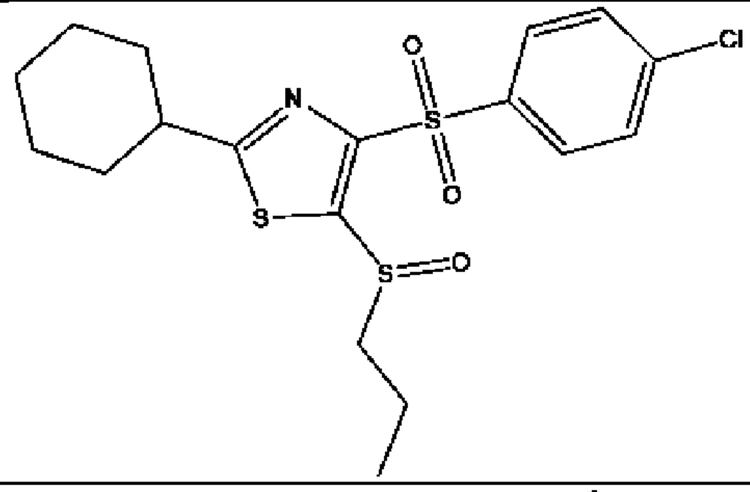
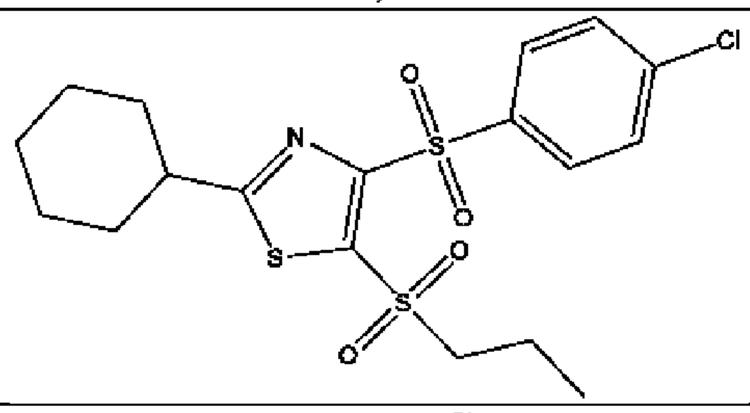
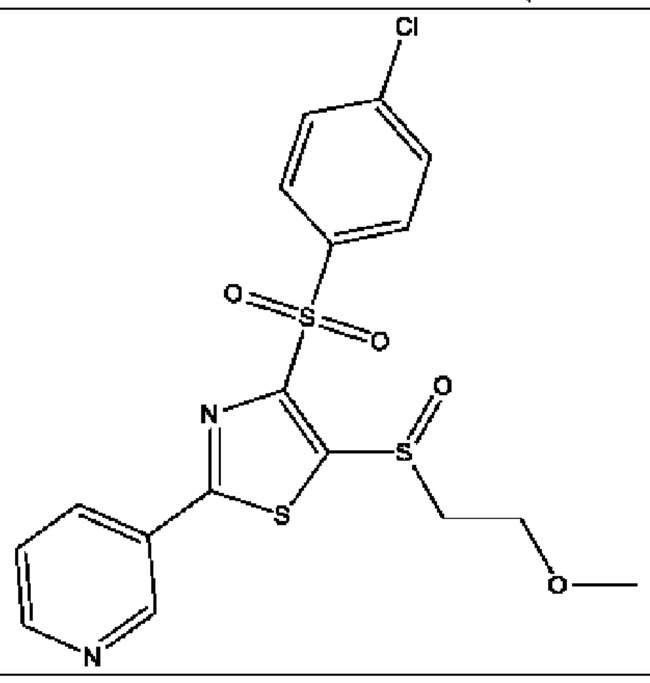
BC19205	ZE23-0021		++	+
BC19338	ZE23-0091		+	+
BC19339	ZE23-0092		+	+
BC19340	ZE23-0096		+	+
BC19341	ZE23-0098		+	+

Table 8

BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19543		+++	++++
BC19635		+	+
BC19636		+	+
BC19637		+	+
BC19638		+	+
BC19639		+	+

BC19640		+	+
BC19641		+	+
BC19642		+	+
BC19645		+	+
BC19646		+	+
BC19679		++	+++

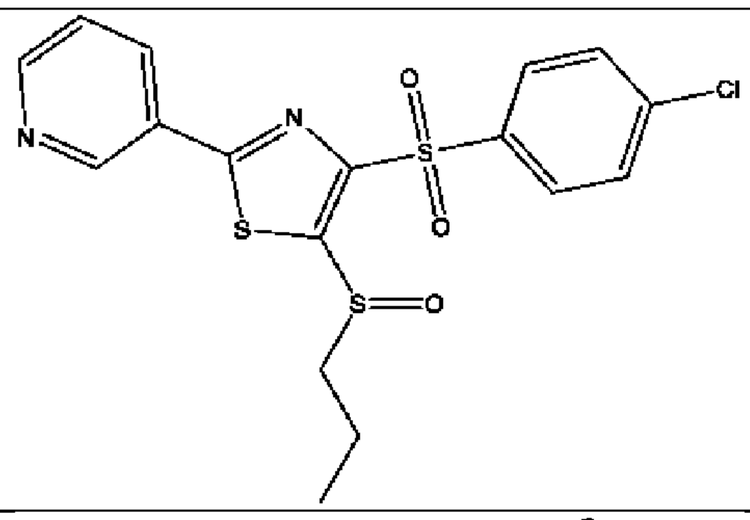
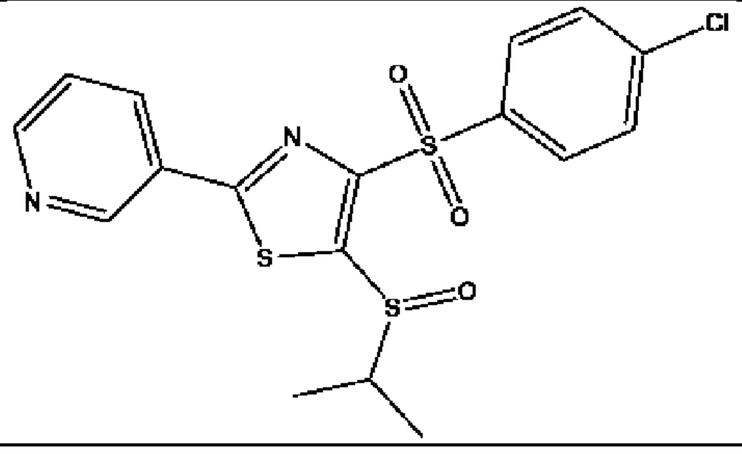
BC19724		++	++
BC19725		+	+

Table 9

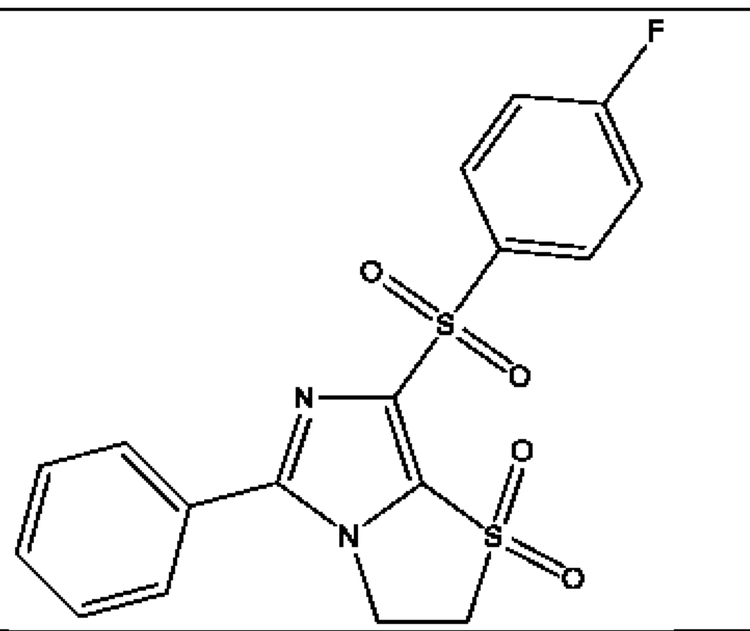
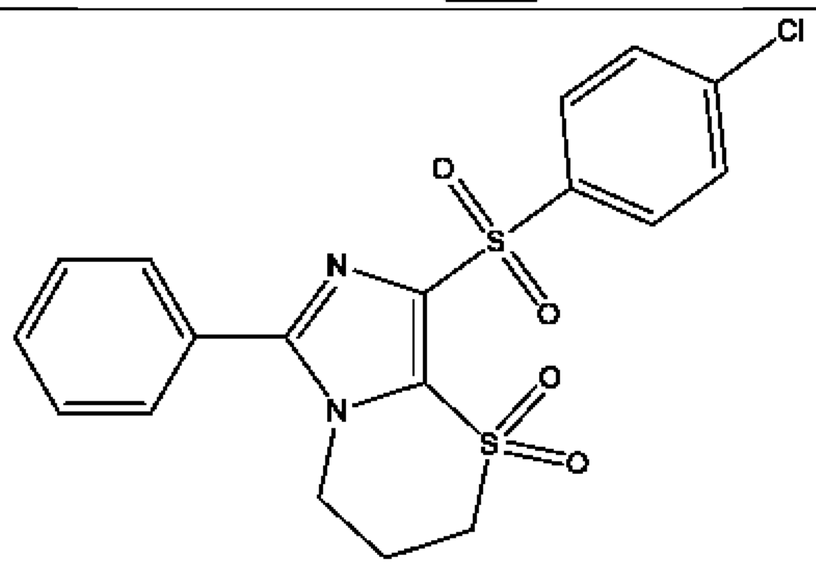
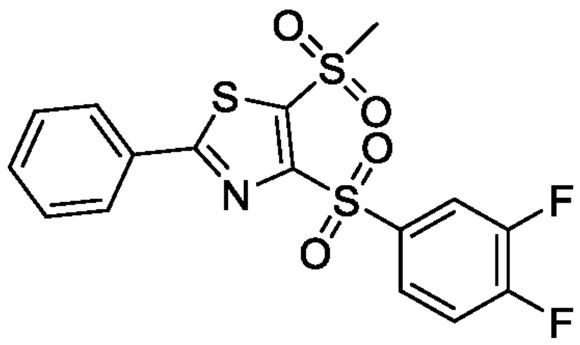
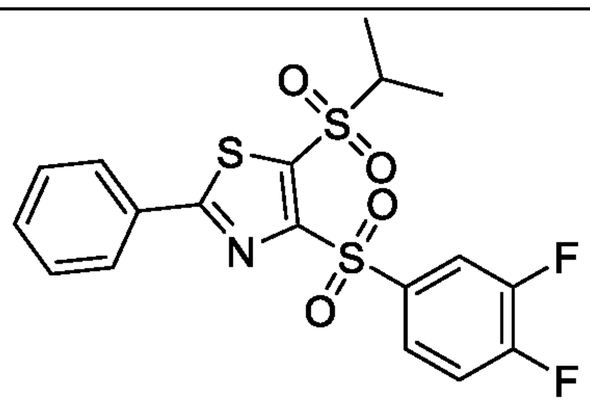
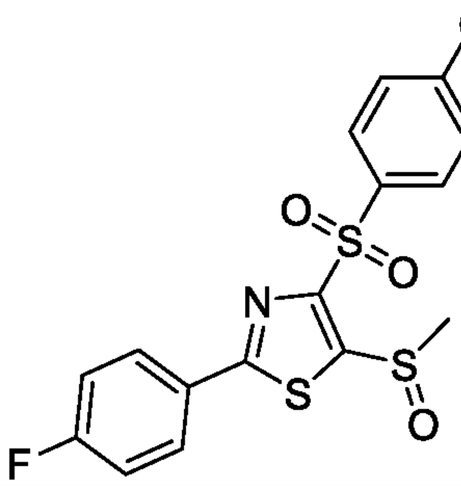
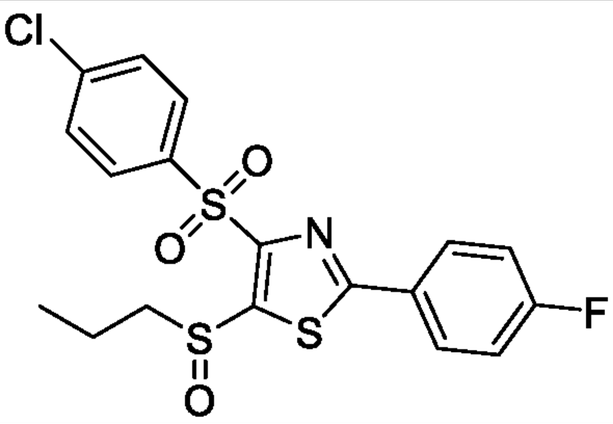
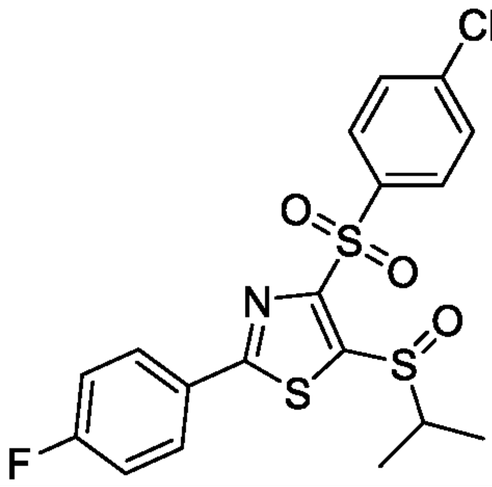
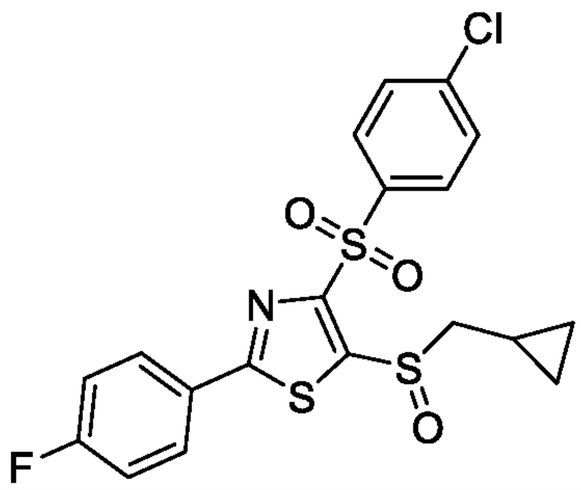
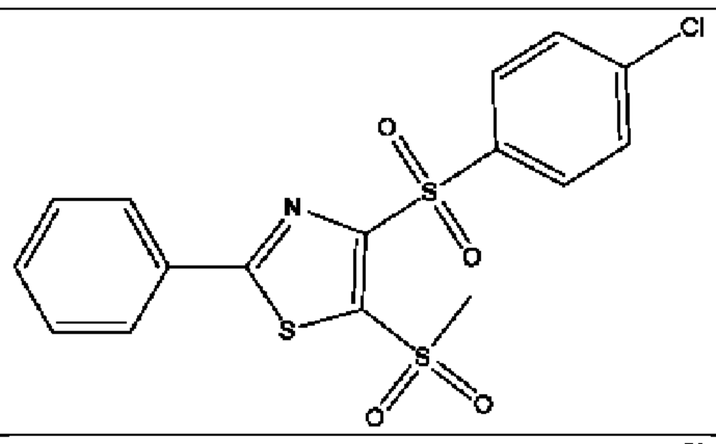
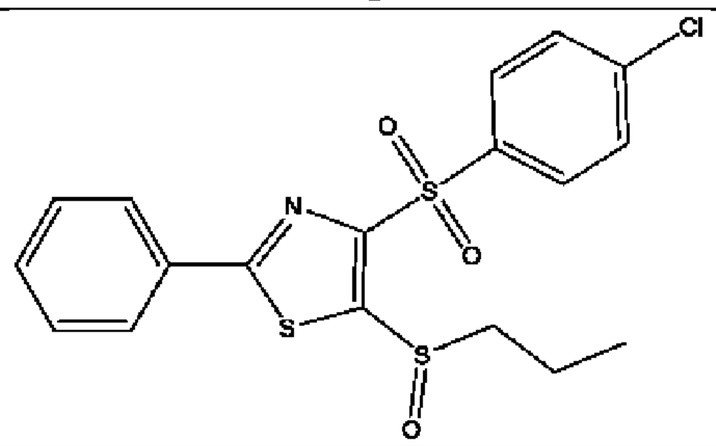
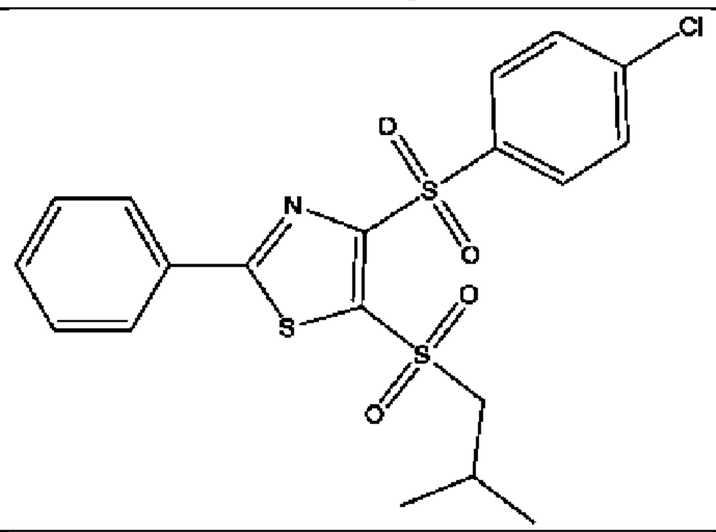
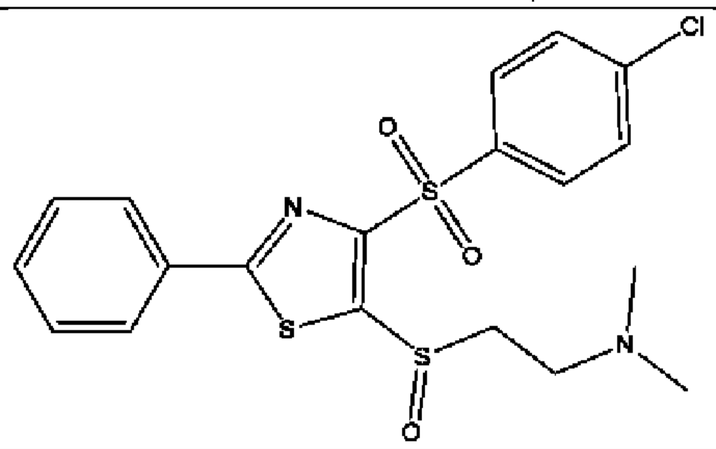
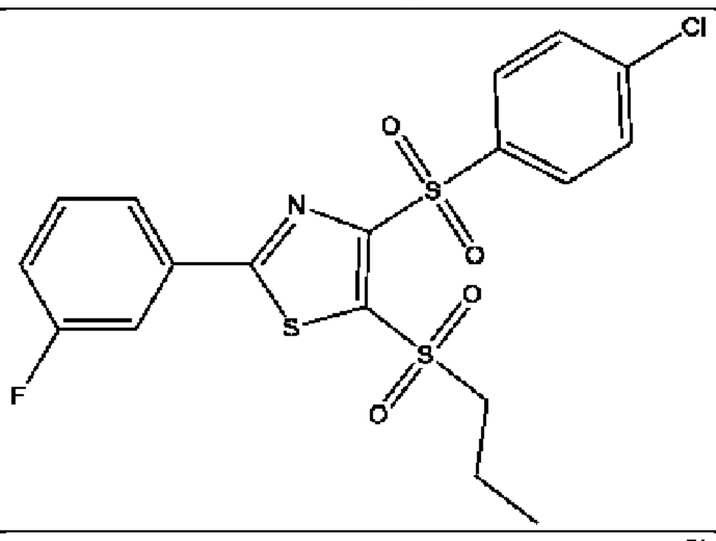
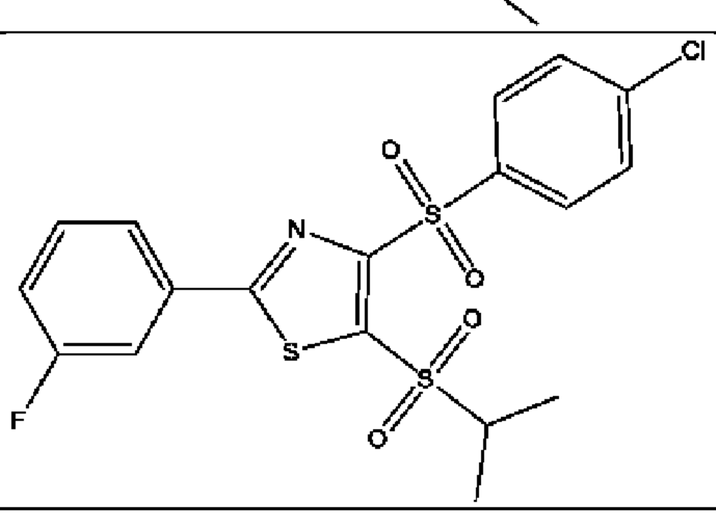
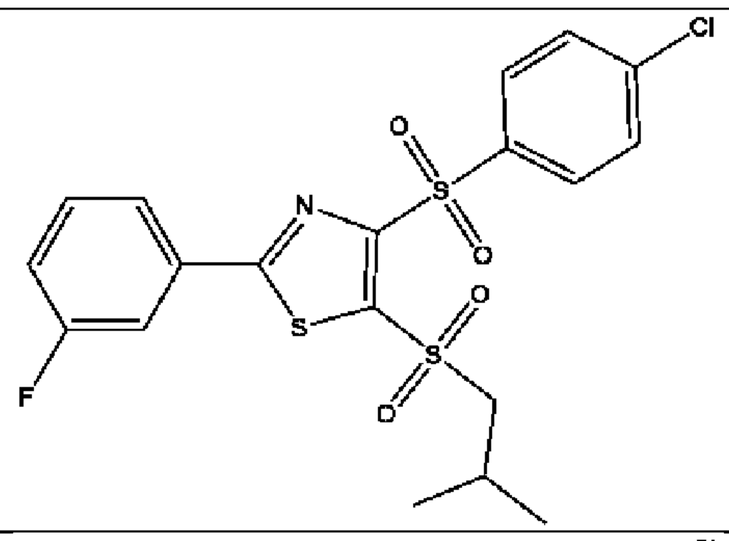
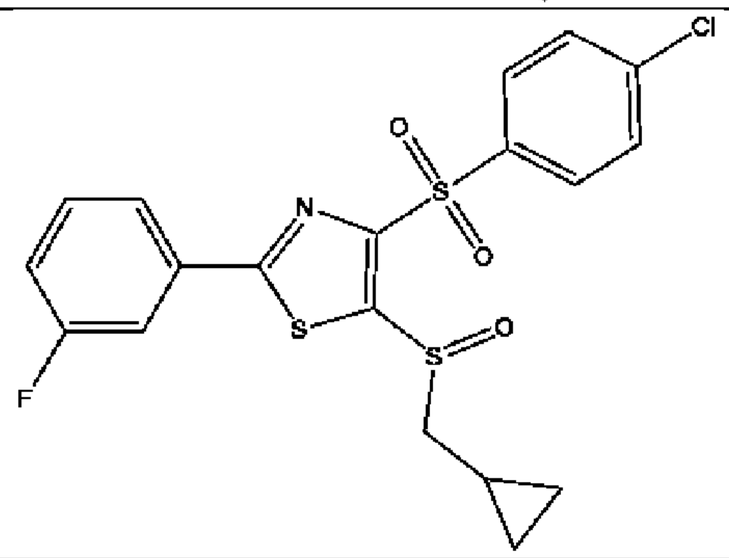
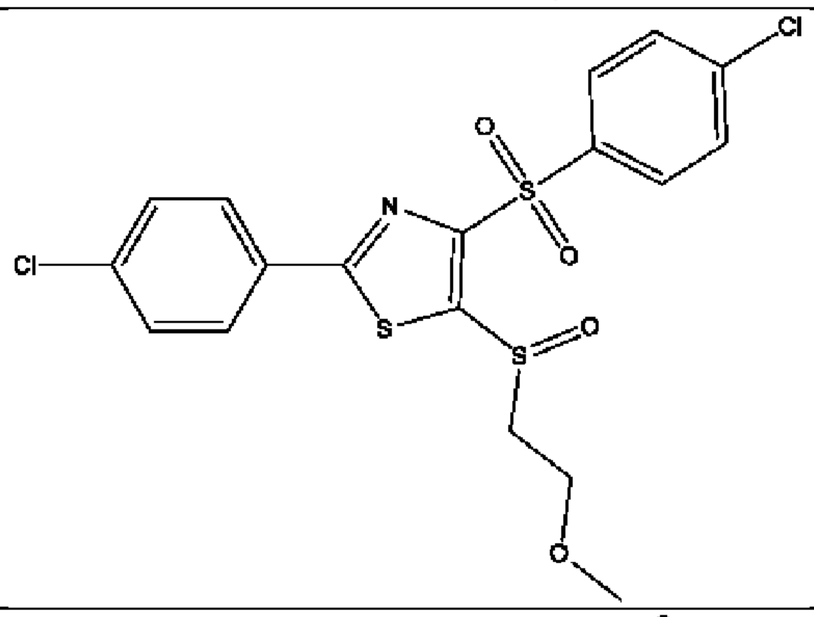
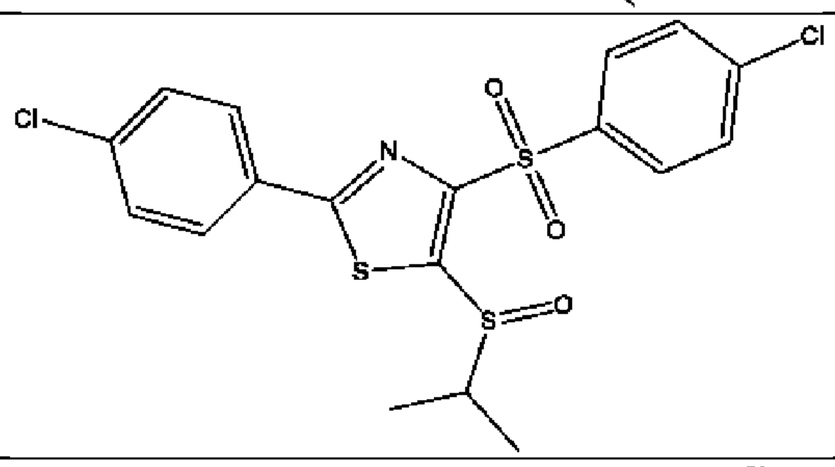
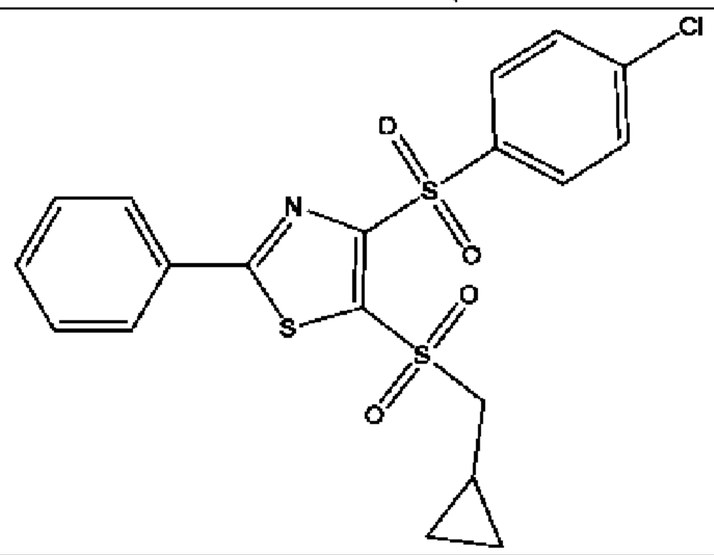
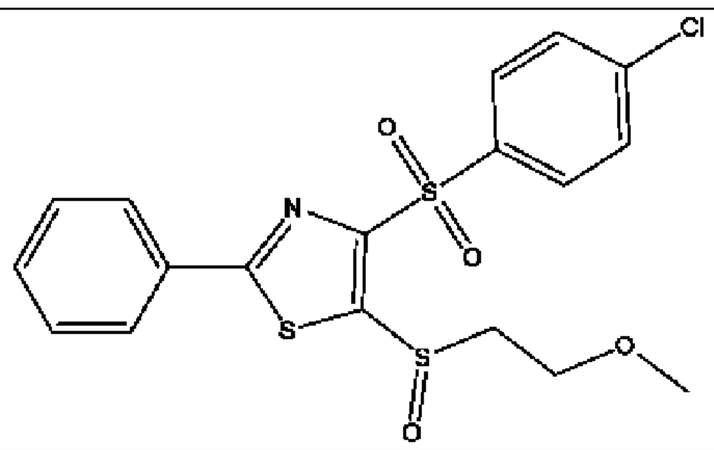
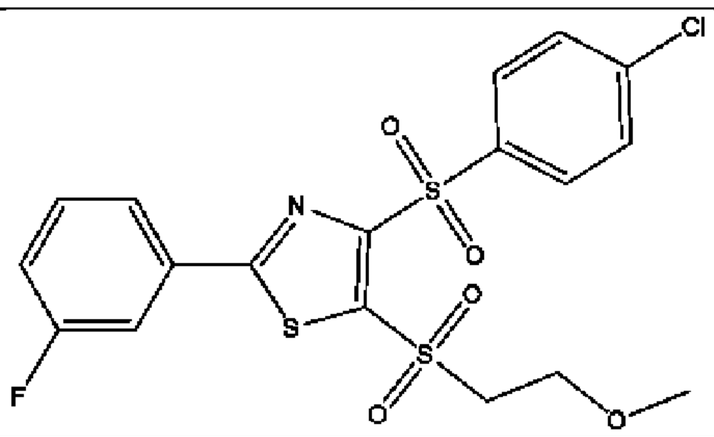
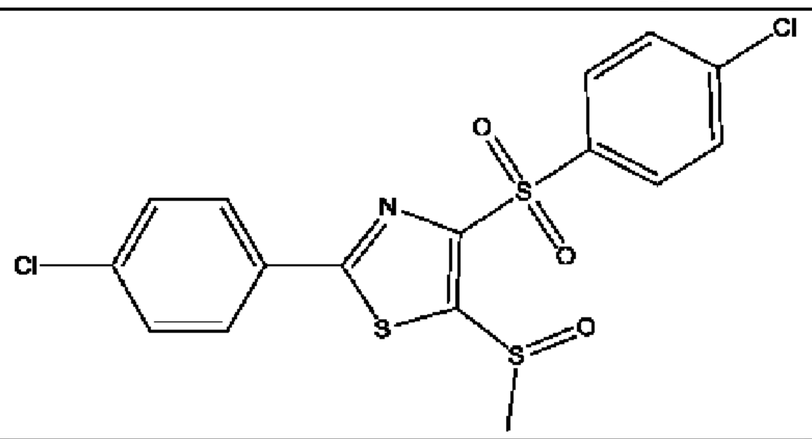
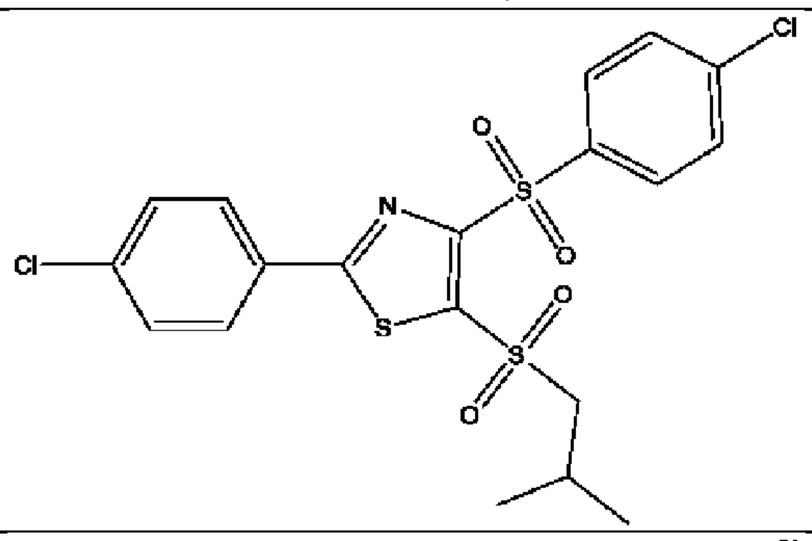
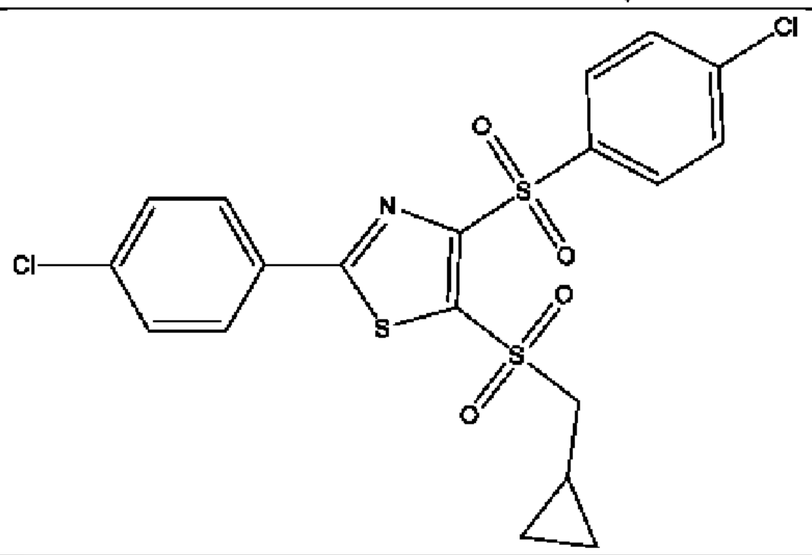
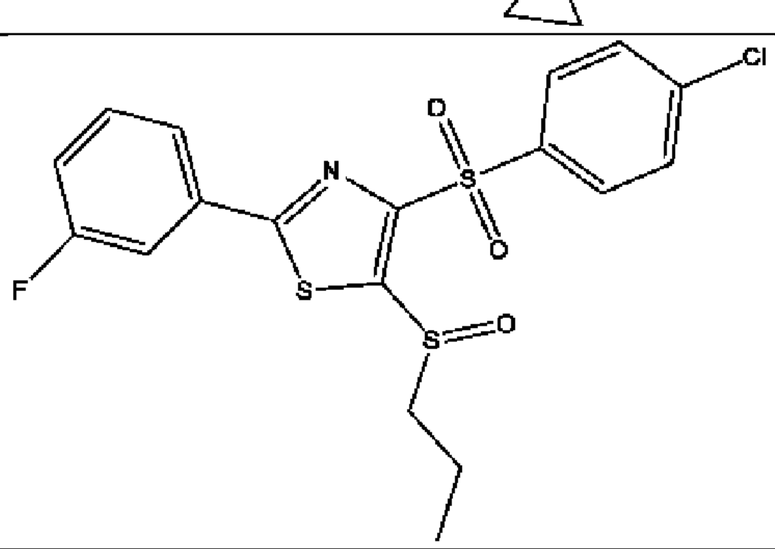
BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19542		+	+
BC19647		+	++

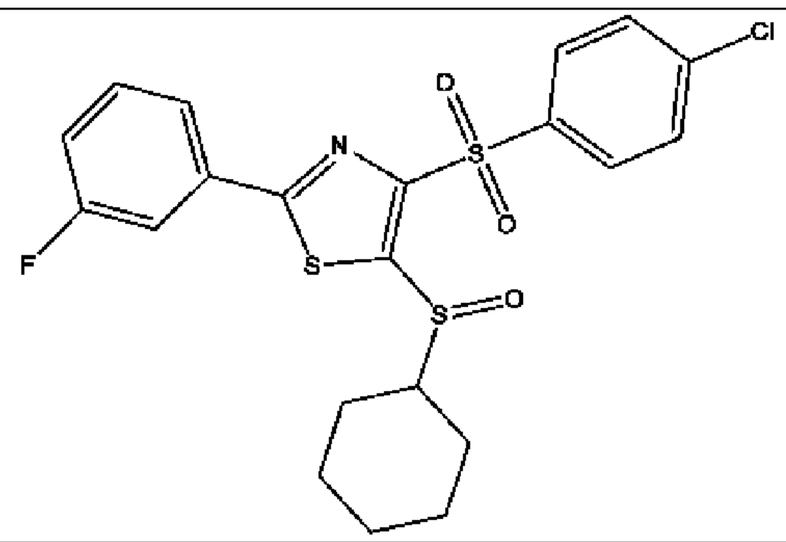
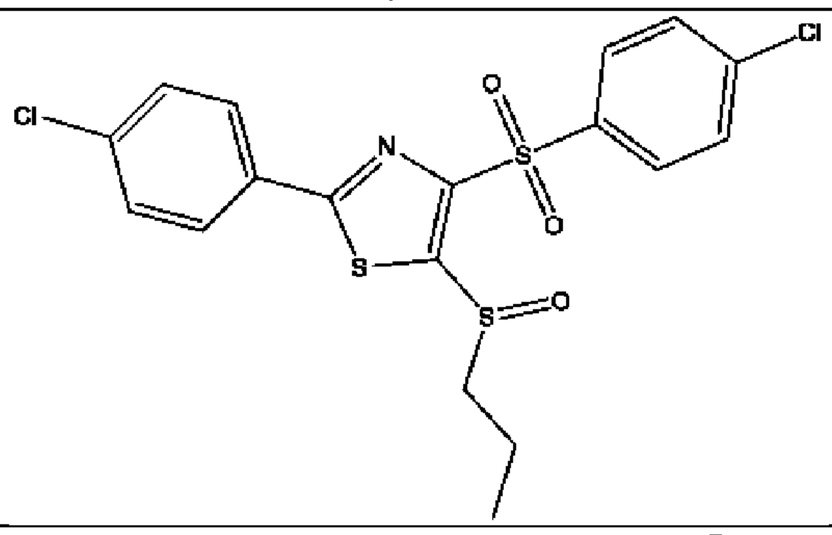
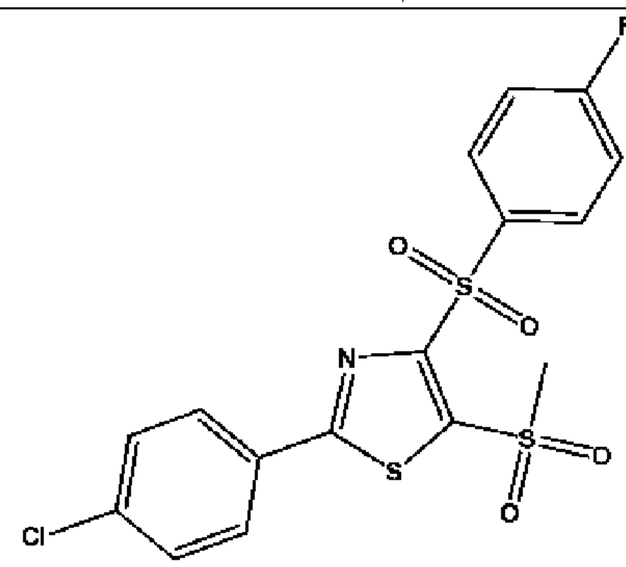
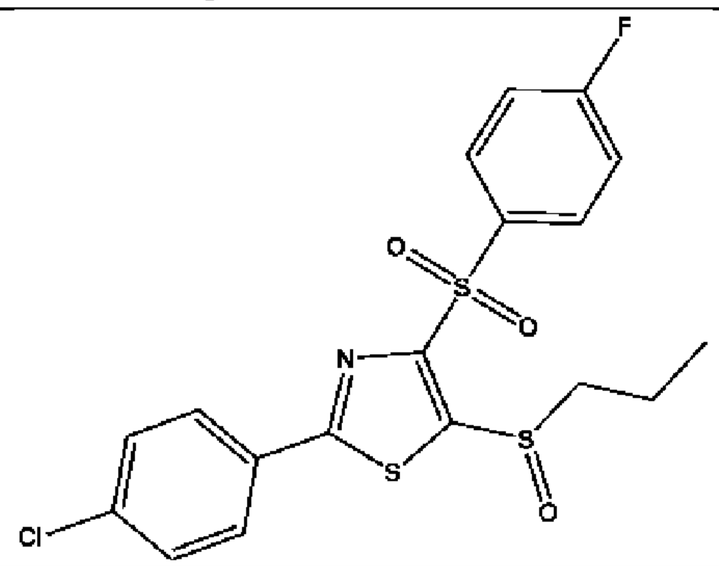
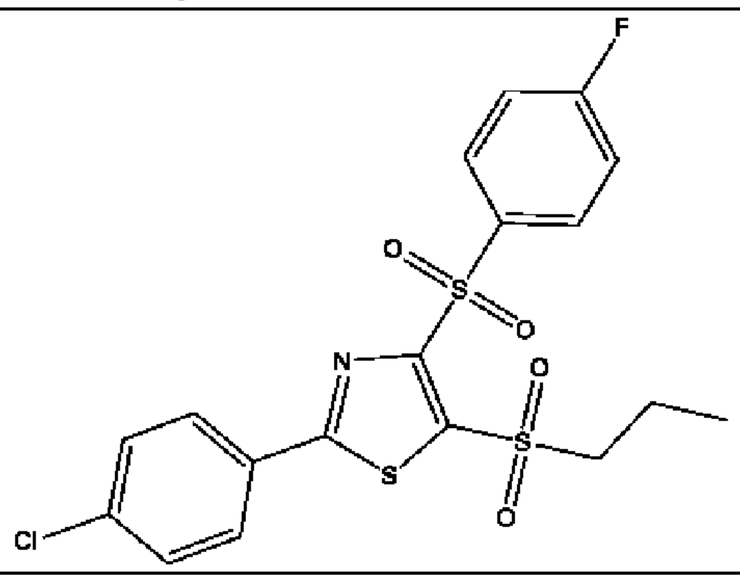
Table 10

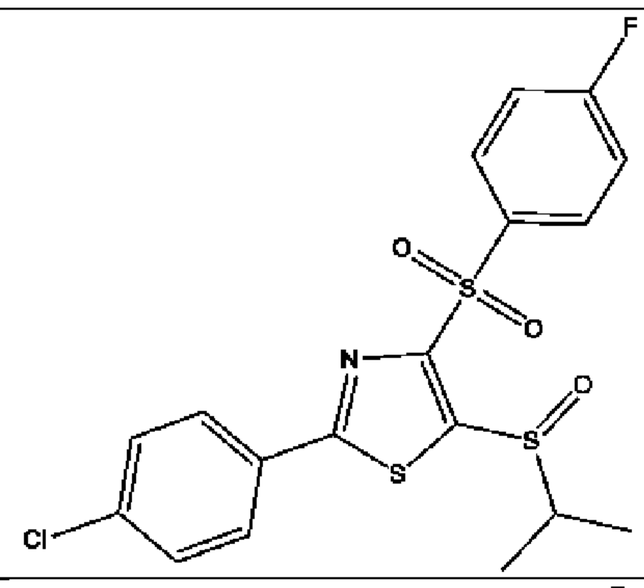
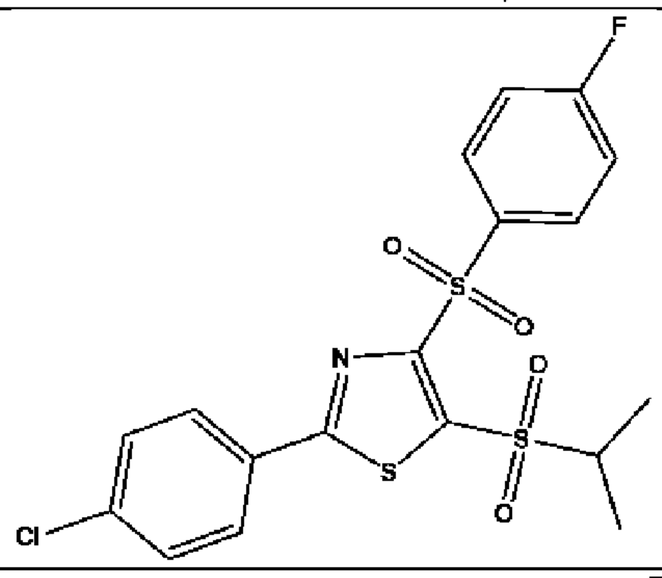
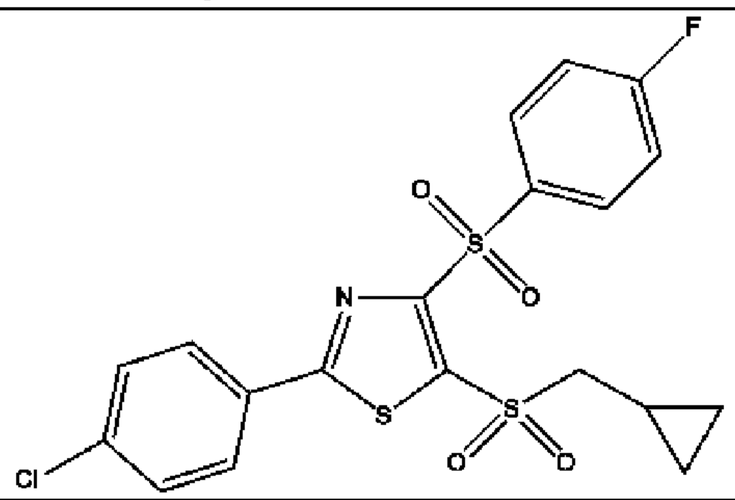
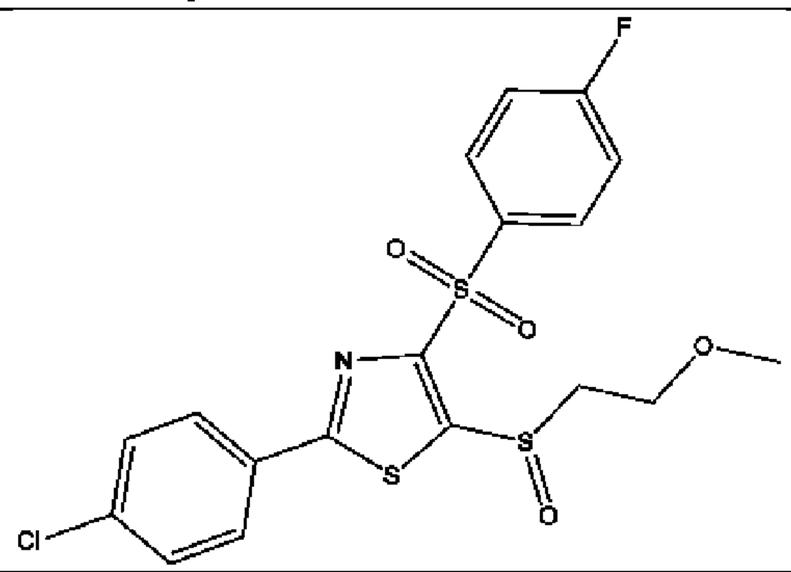
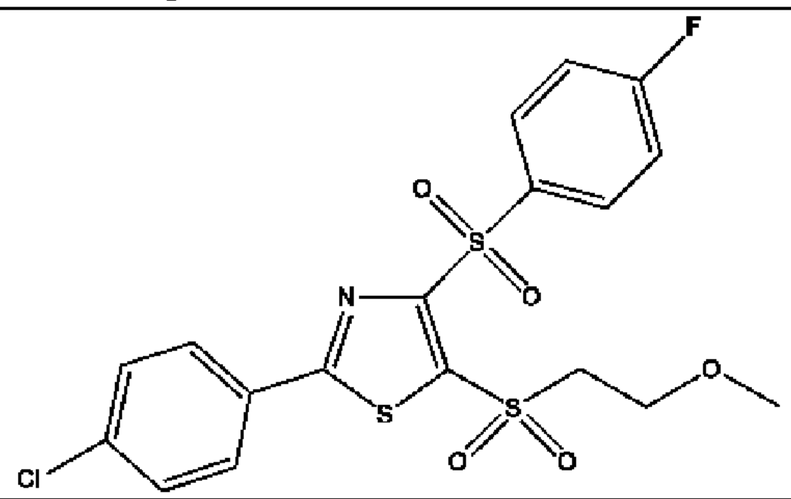
BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19279		+++	+++
BC19334		+	++
BC19413		+	++
BC19414		+	+
BC19415		+	++
BC19416		+	+

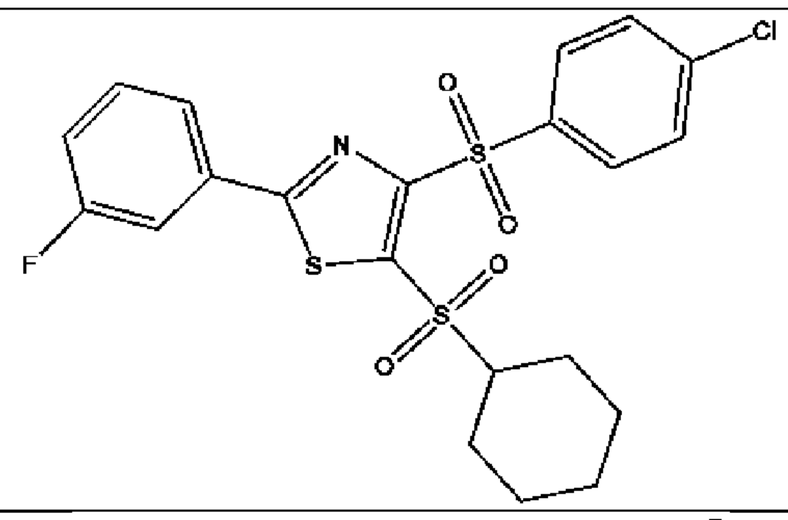
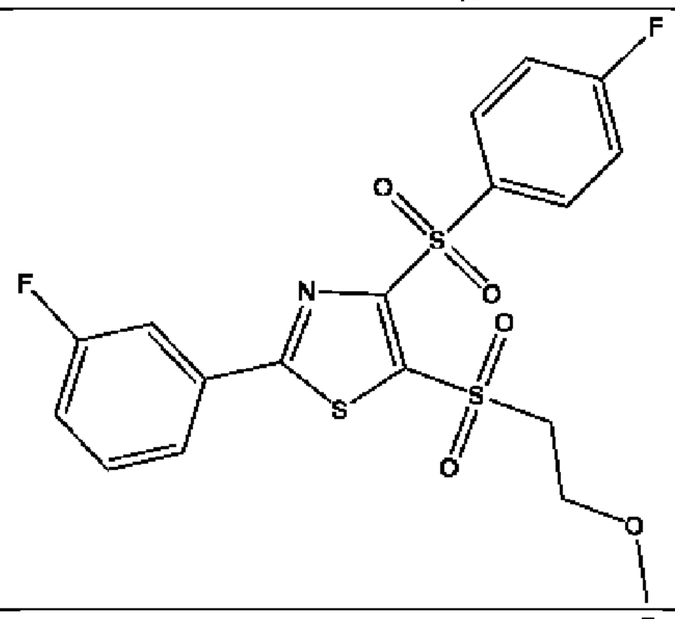
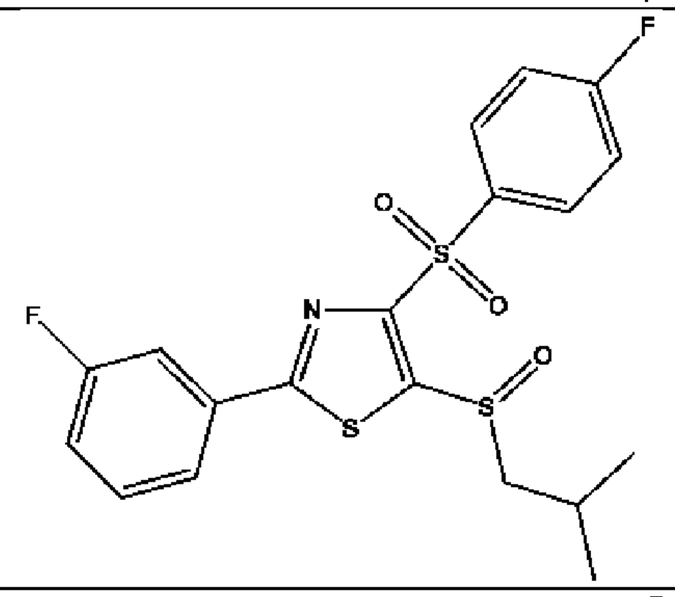
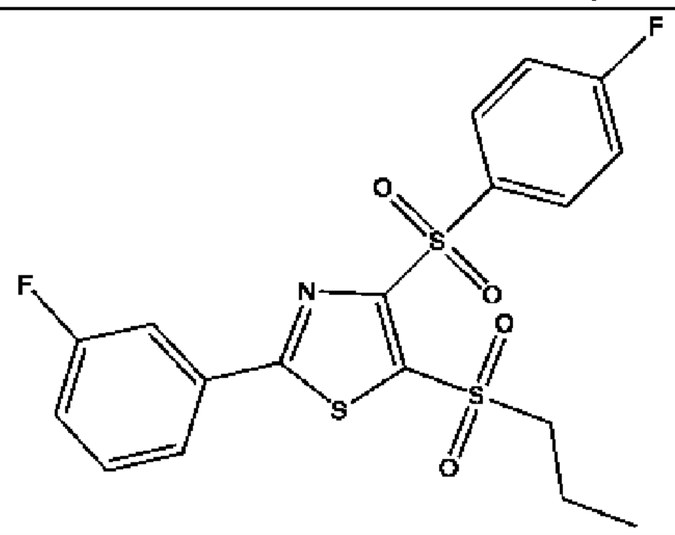
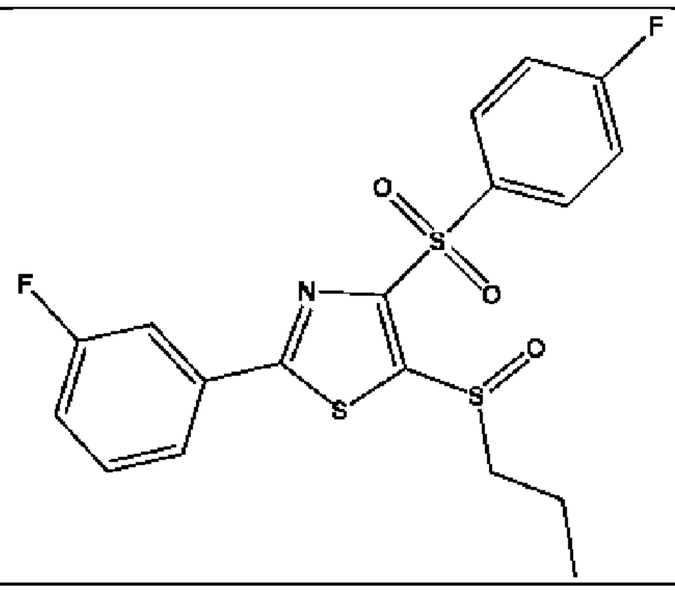
BC19471		++	++
BC19472		+	+
BC19473		+	+
BC19474		++	+
BC19475		++	++
BC19476		+	+

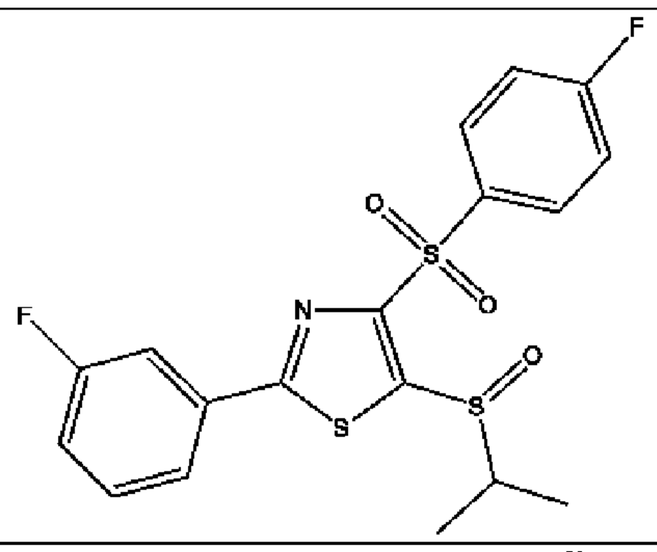
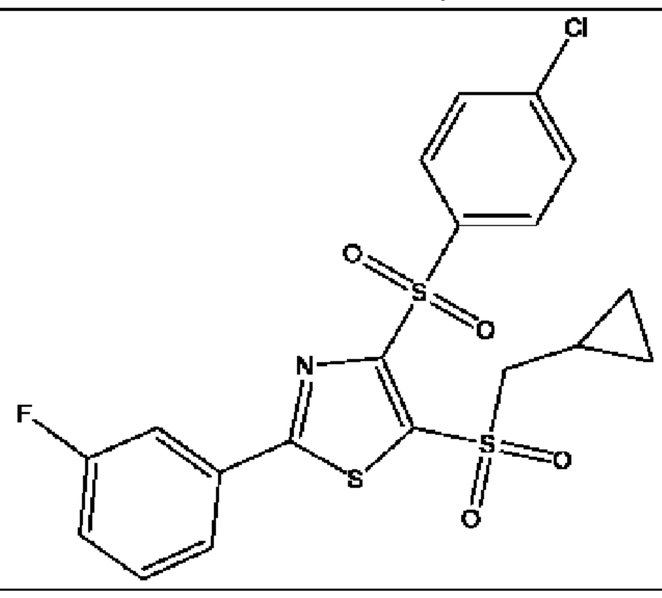
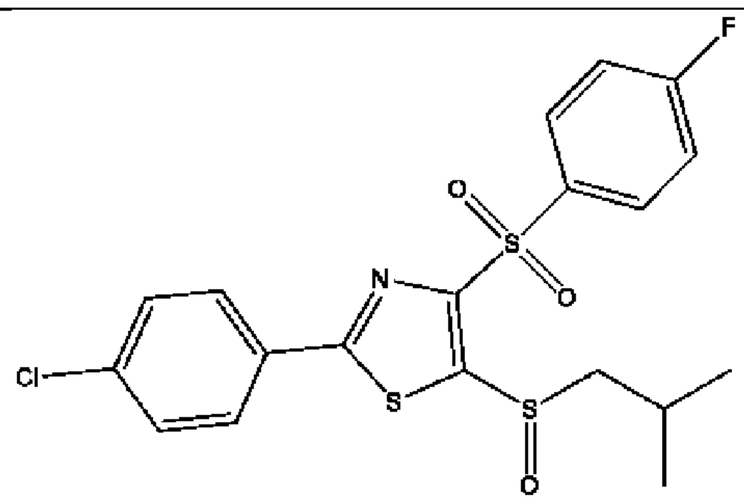
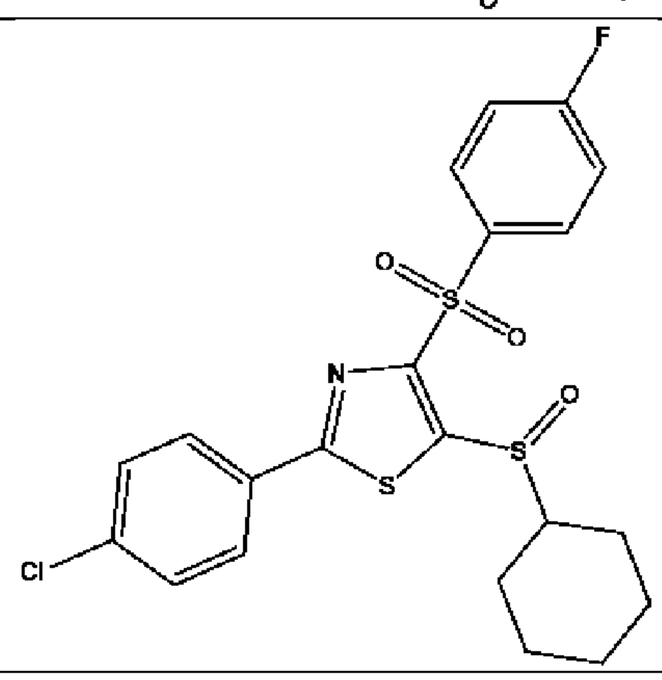
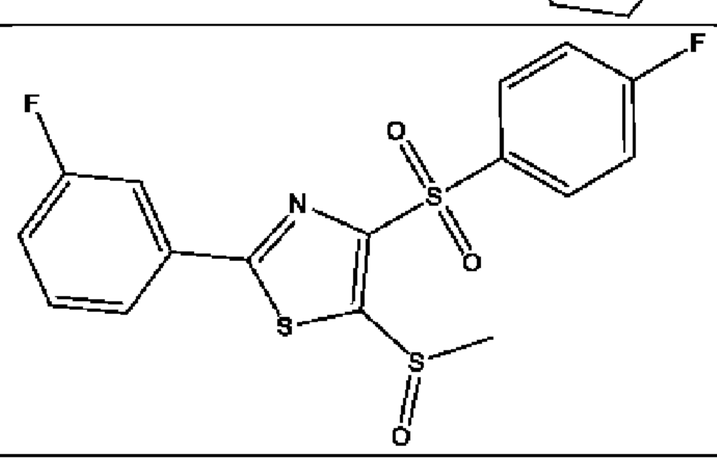
BC19477		+	+
BC19478		+	++
BC19479		+	+
BC19480		+	+
BC19525		++	++

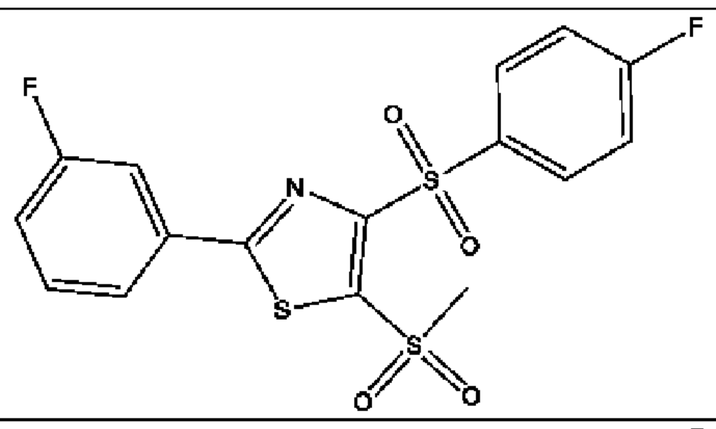
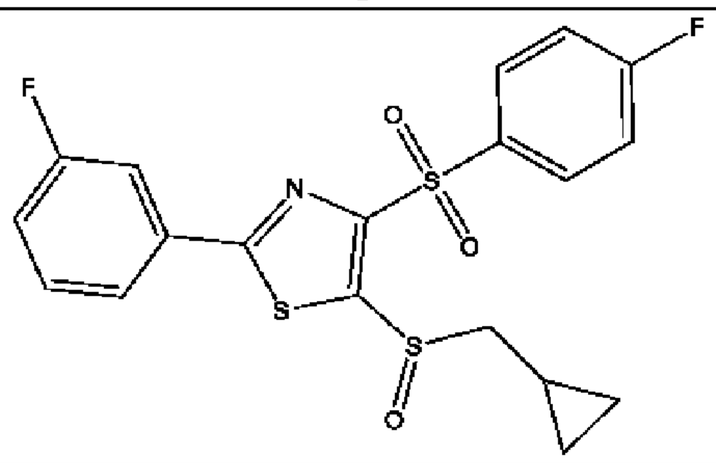
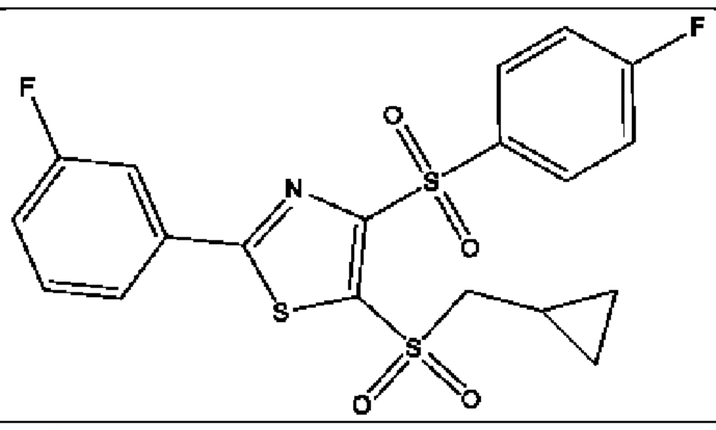
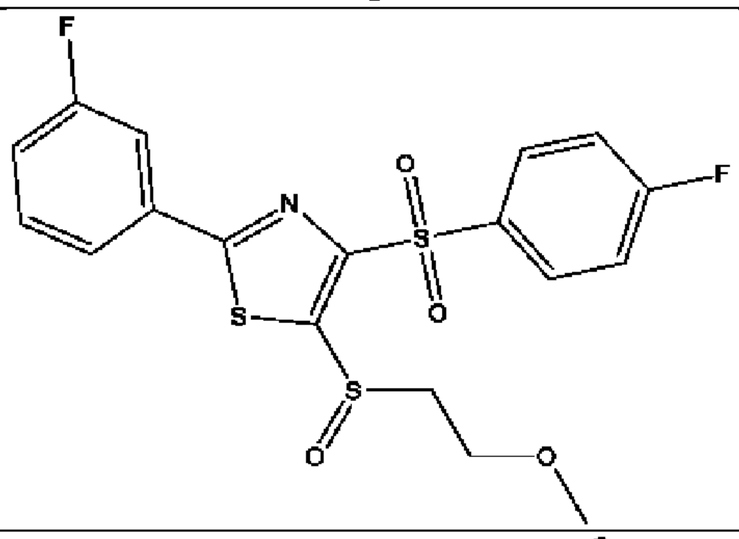
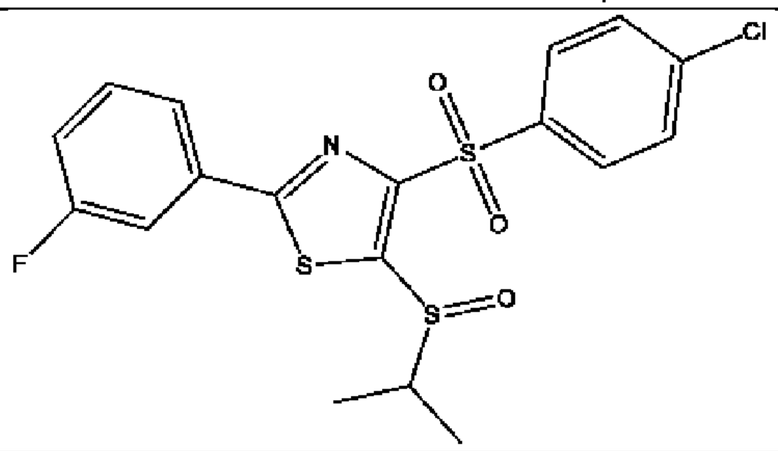
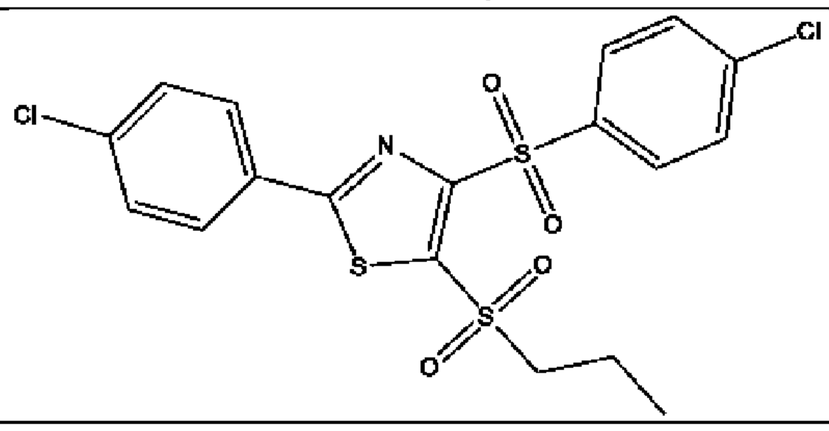
BC19526		++	++
BC19527		++	++
BC19528		++	+++
BC19529		+	++
BC19530		++	++
BC19531		++	+++

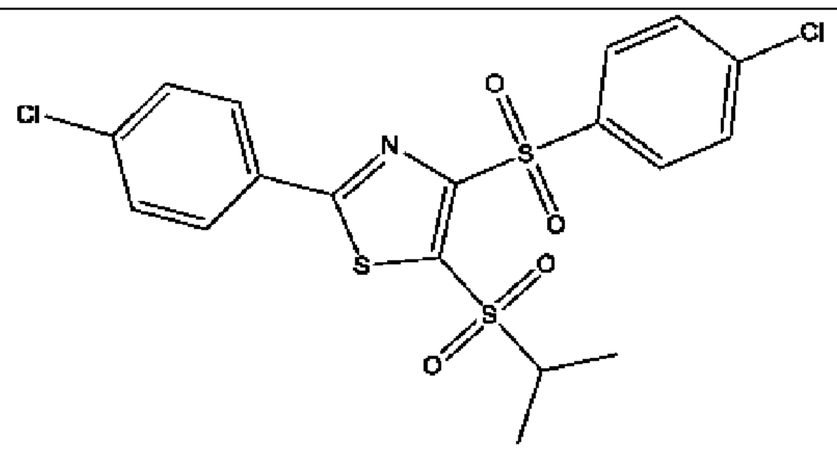
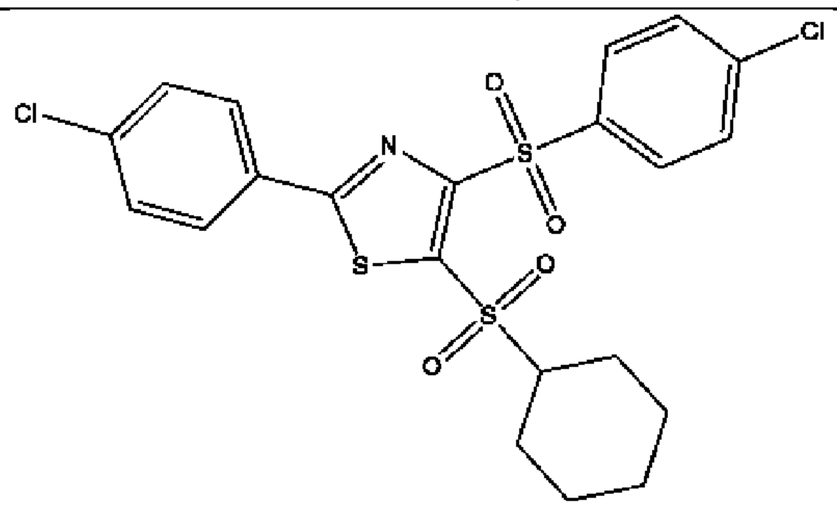
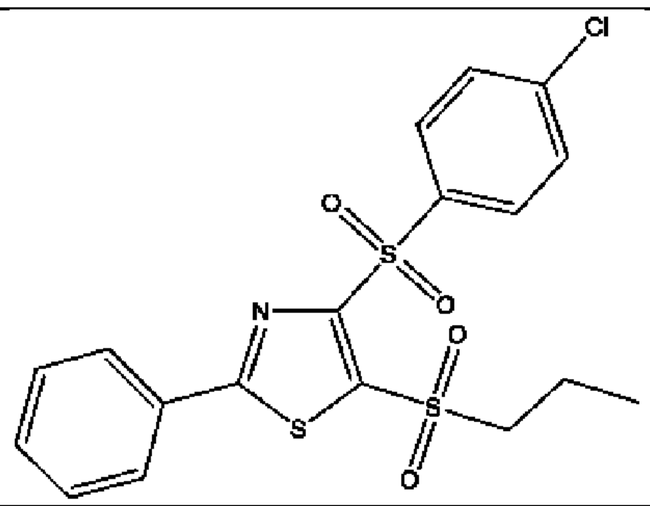
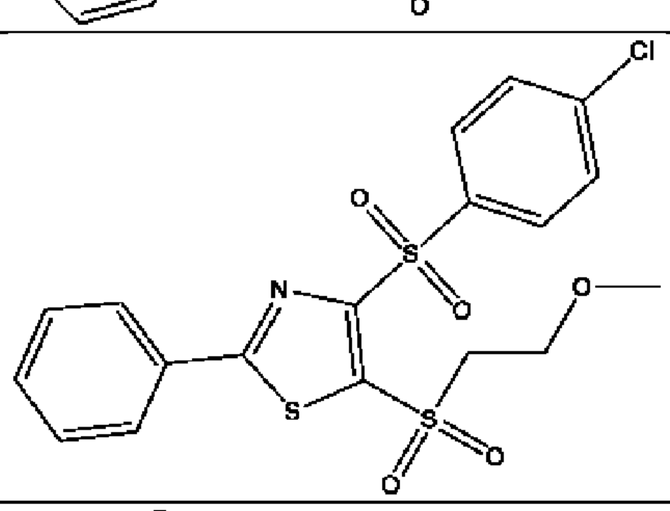
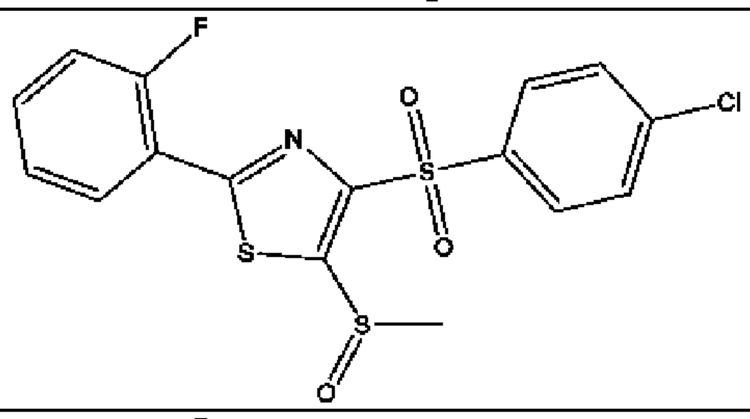
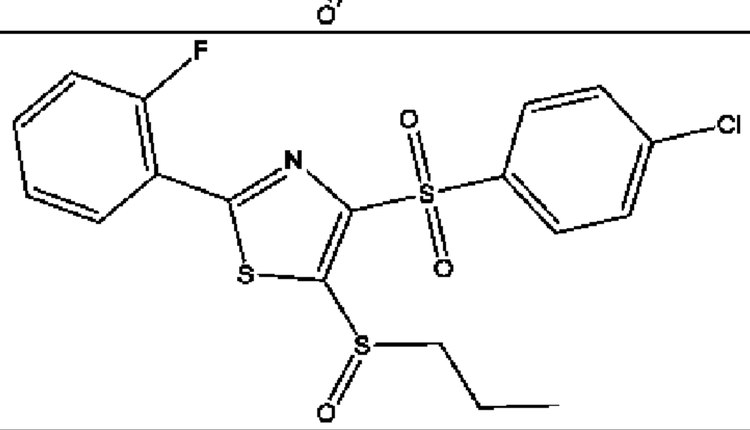
BC19532		+	+
BC19533		++	++
BC19534		++	++
BC19535		++	++
BC19536		++	+++

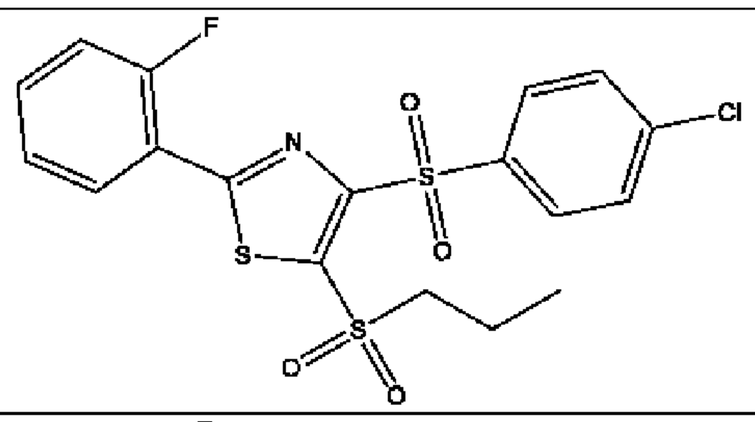
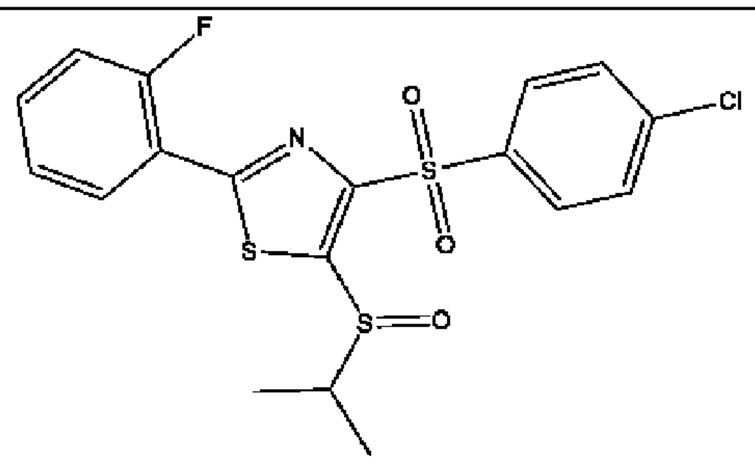
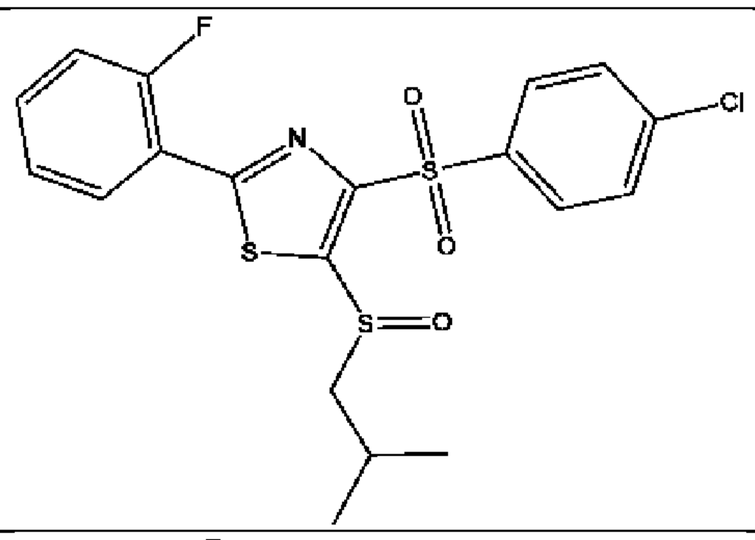
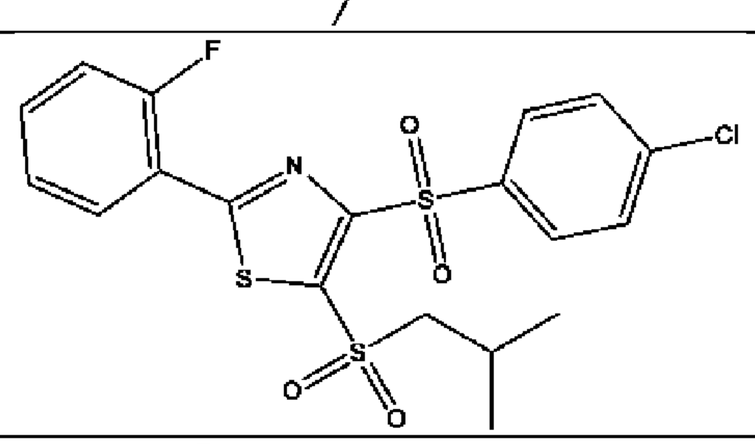
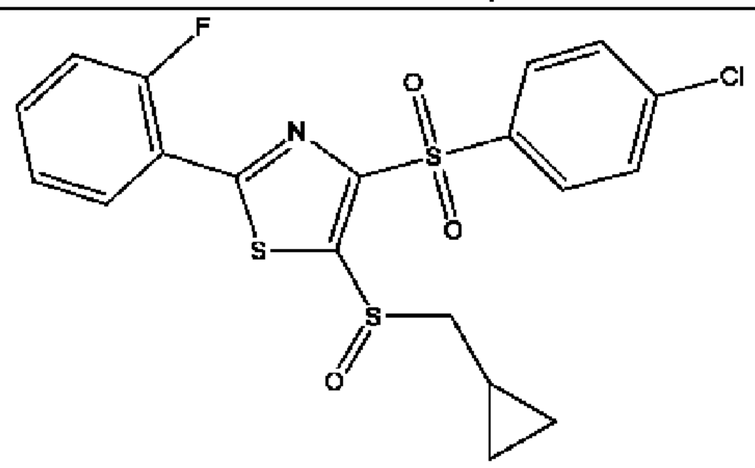
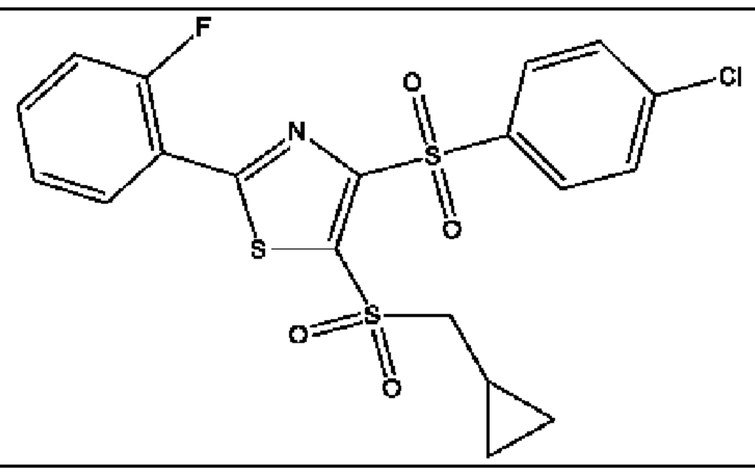
BC19537		+	+
BC19538		++	++
BC19539		++	++
BC19540		++	++
BC19541		++	++

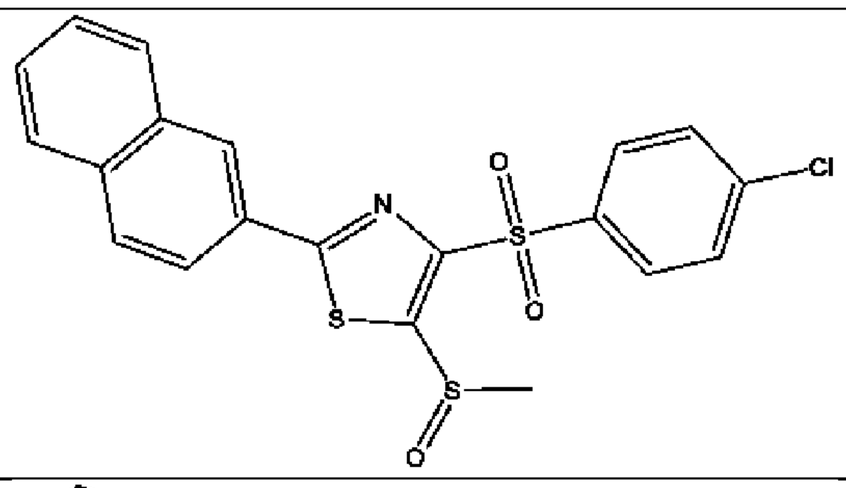
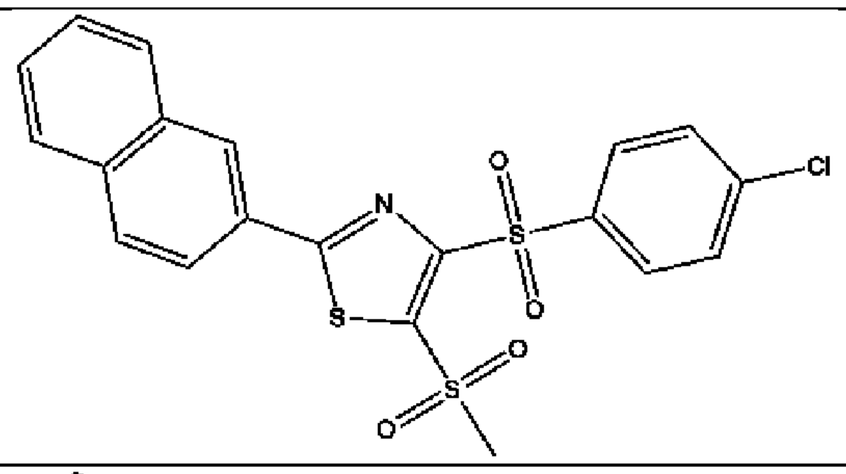
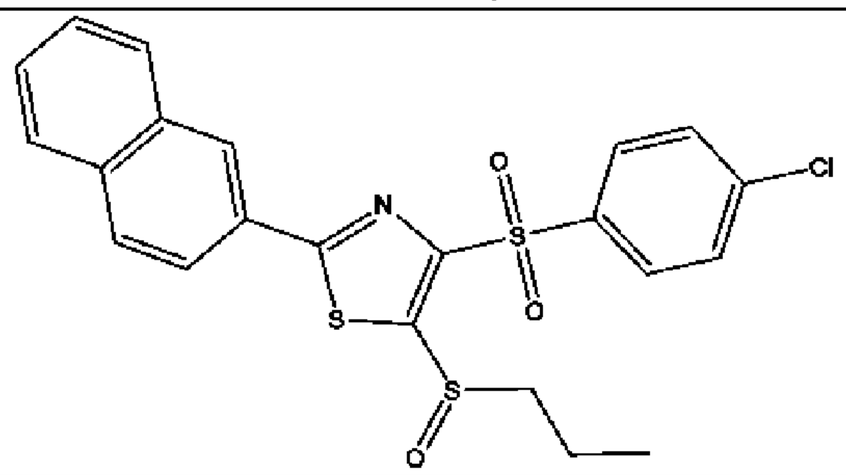
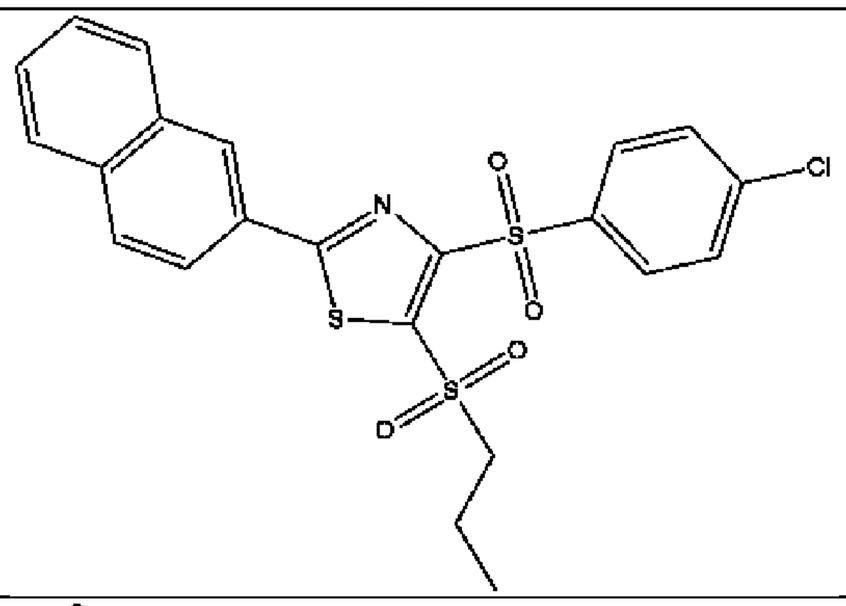
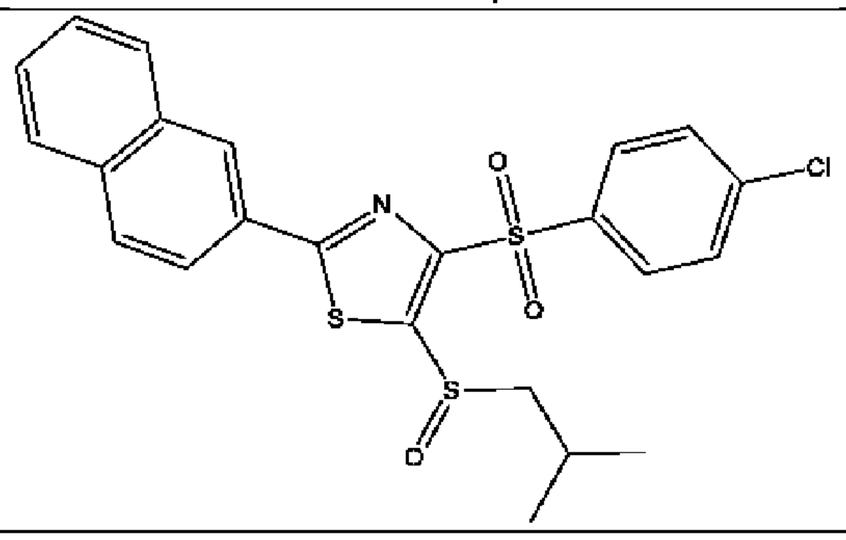
BC19583		+	+
BC19587		++	++
BC19588		++	+
BC19589		++	++
BC19590		++	++

BC19591		++	++
BC19592		++	++
BC19593		+++	++
BC19594		+	+
BC19595		+++	+++

BC19596		+++	++
BC19597		++	+
BC19598		++	++
BC19599		++	++
BC19620		+	+
BC19621		++	++

BC19622		++	++
BC19623		+	+
BC19624		++	++
BC19625		++	++
BC19626		++	++
BC19627		++	+

BC19628		+	+
BC19629		+	+
BC19630		+	++
BC19631		++	+
BC19632		+	+
BC19633		++	++

BC19671		++	++++
BC19672		++	+++
BC19673		++	+
BC19674		++	+
BC19675		++	++

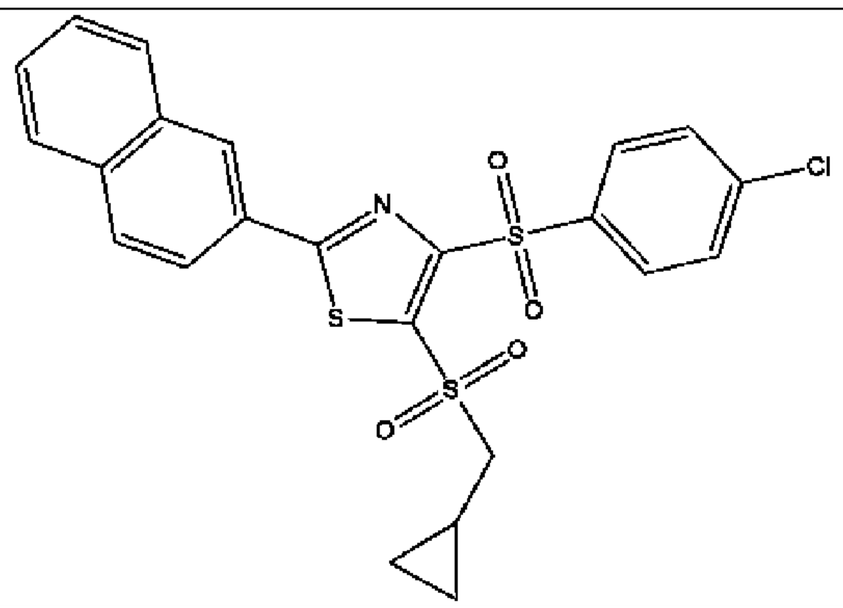
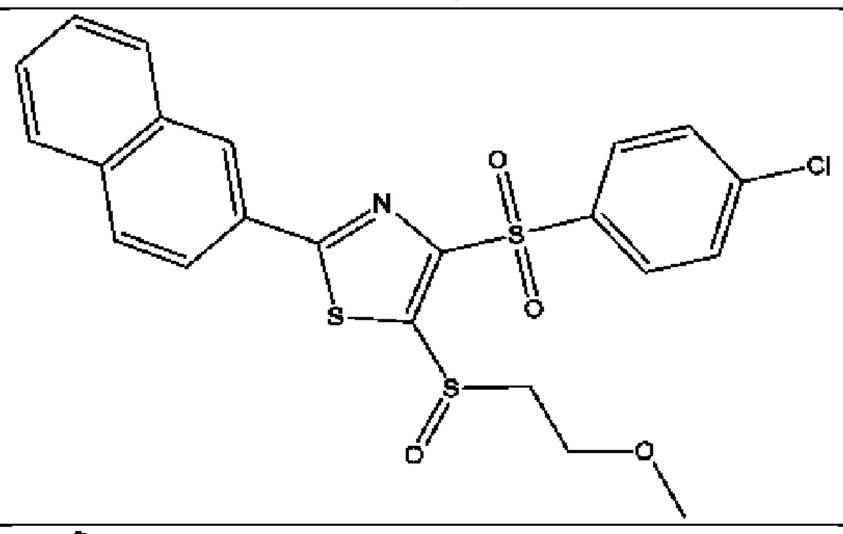
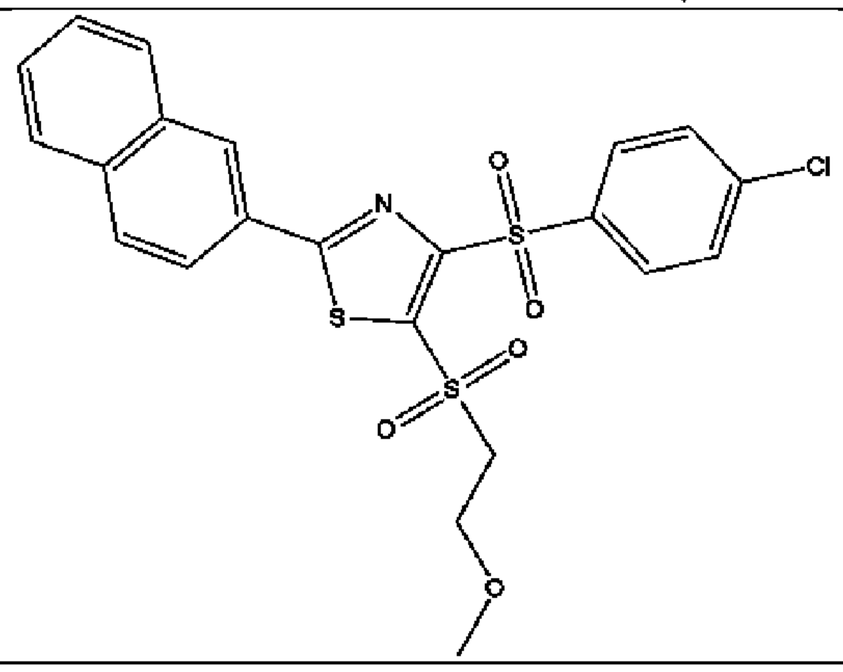
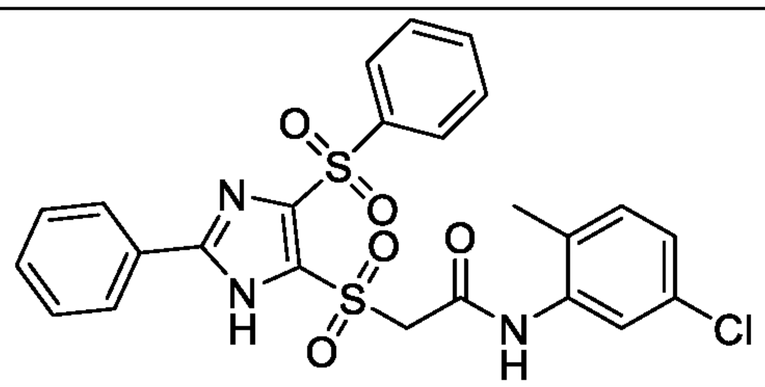
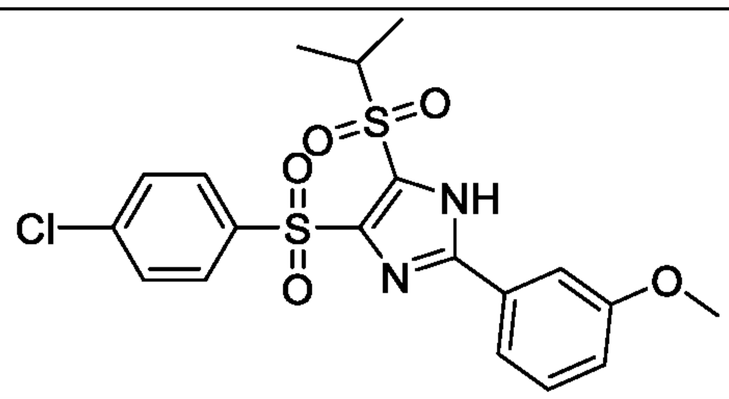
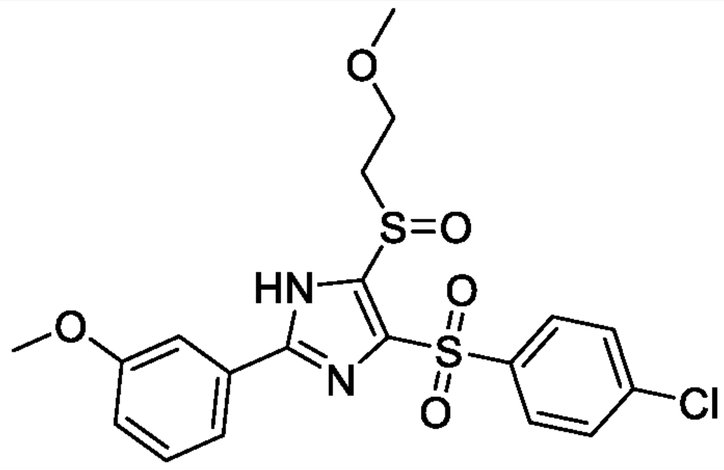
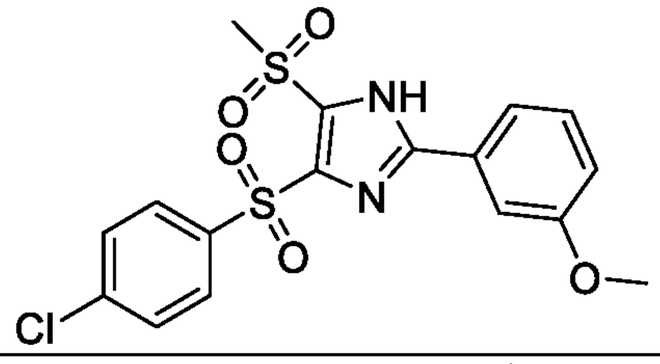
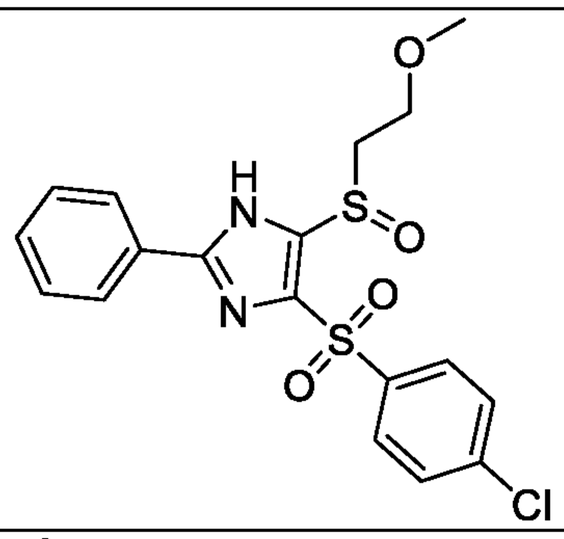
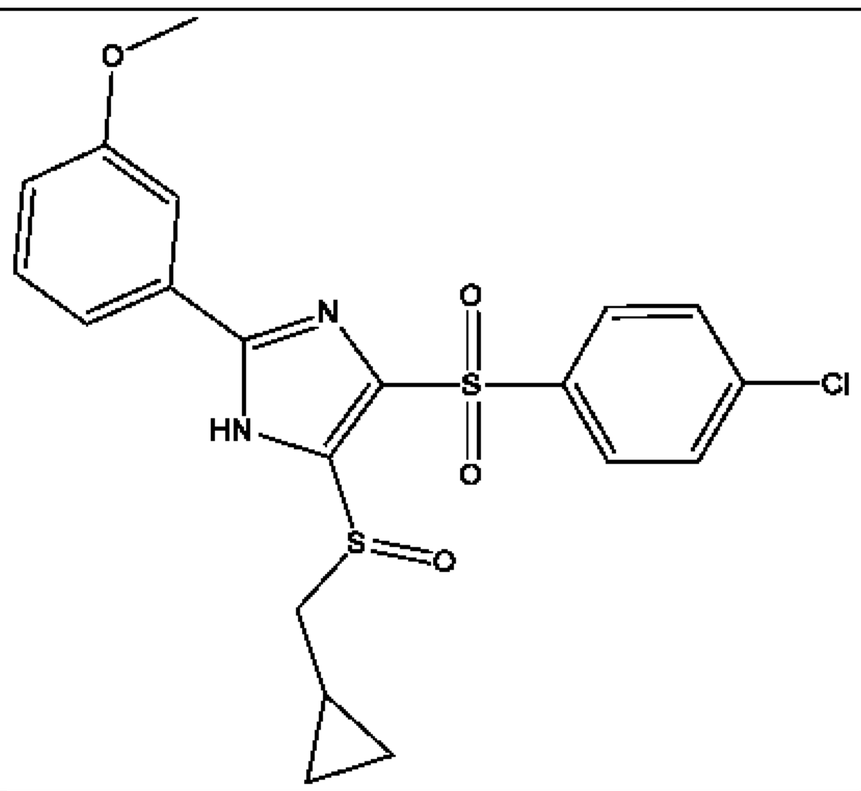
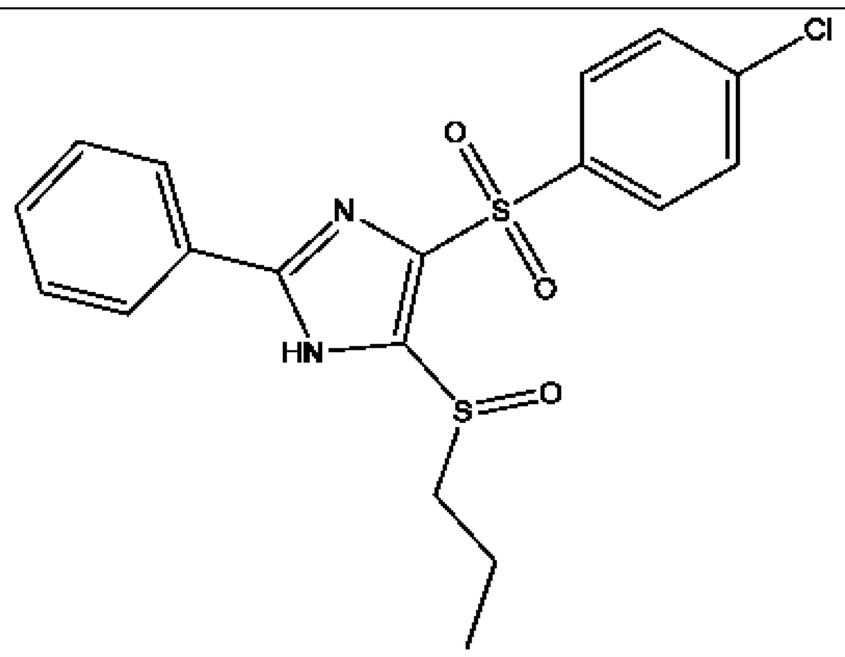
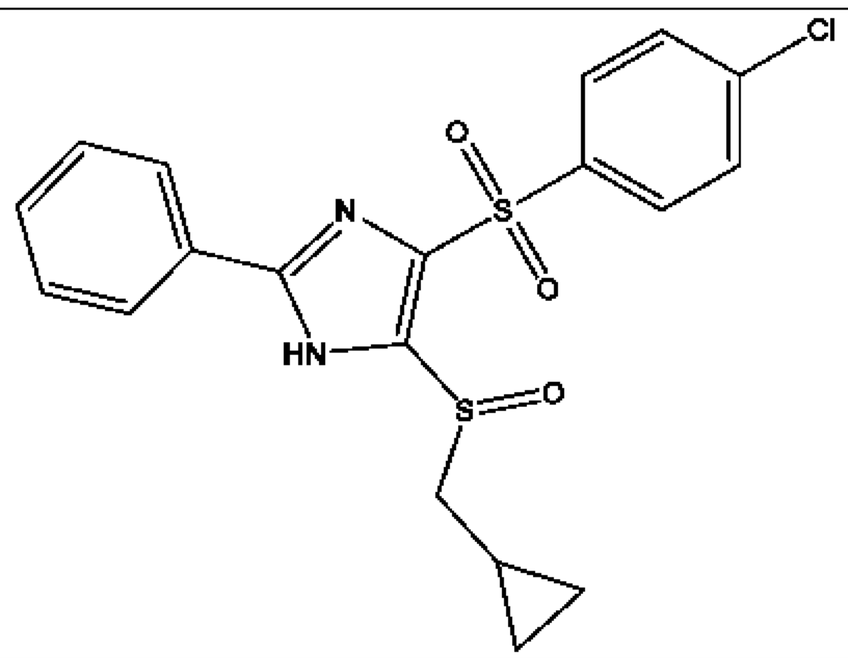
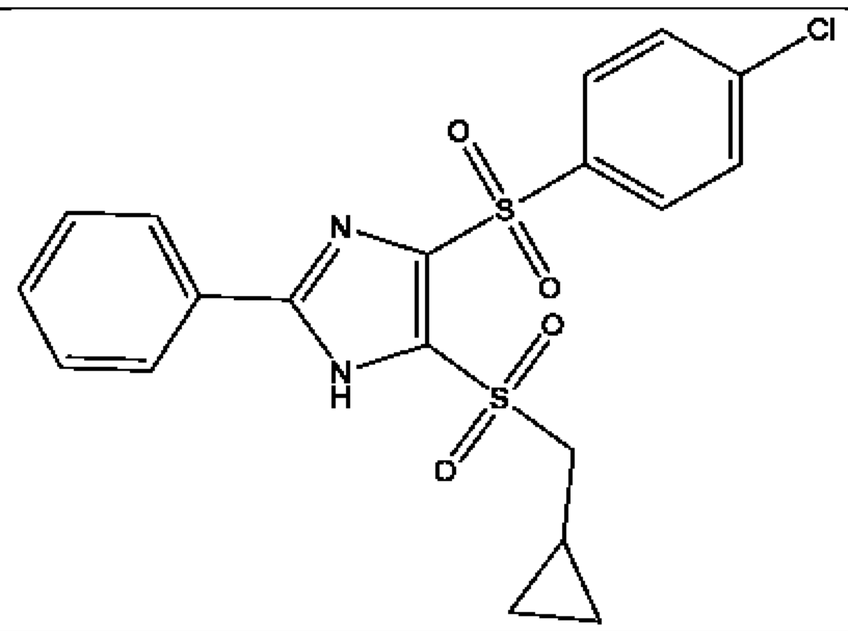
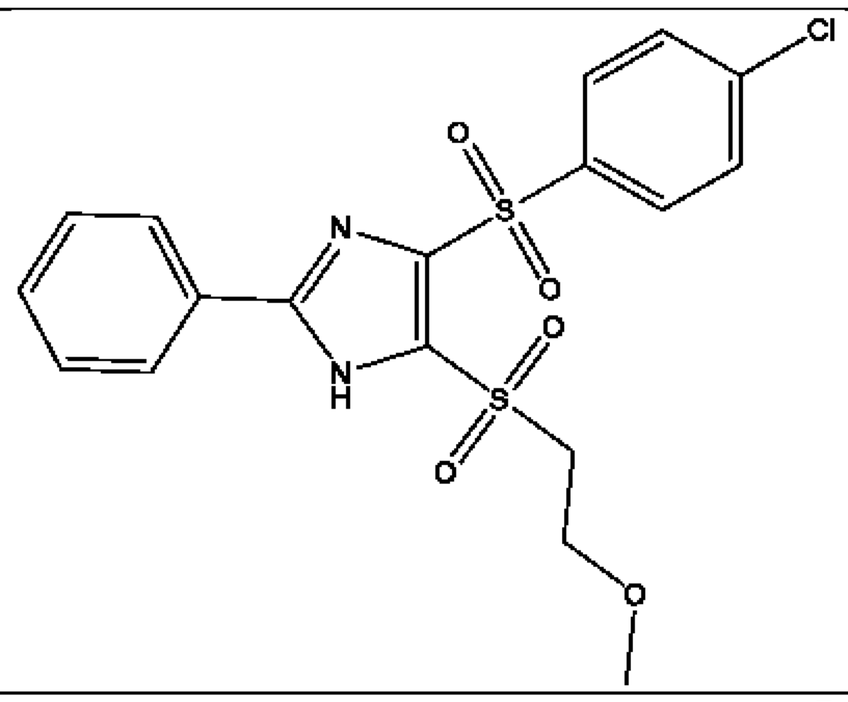
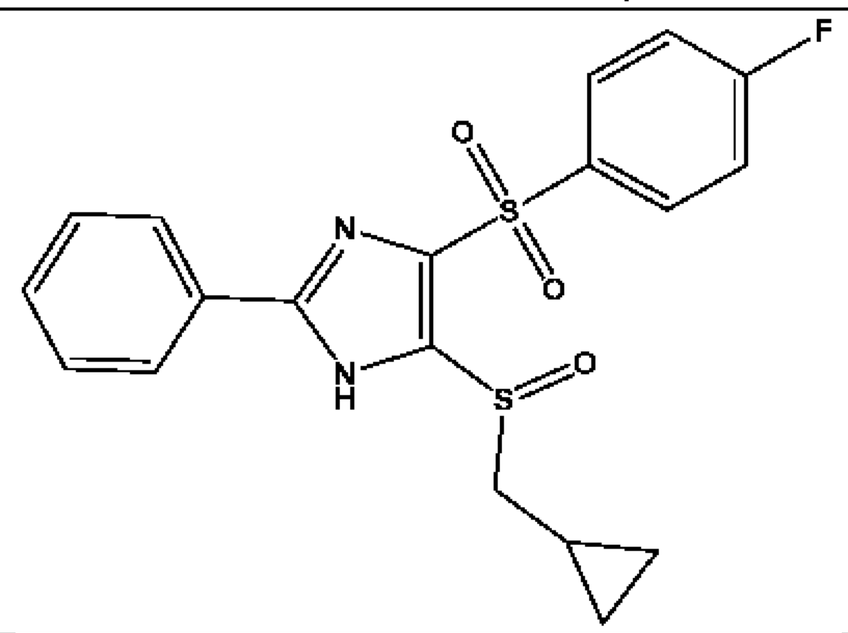
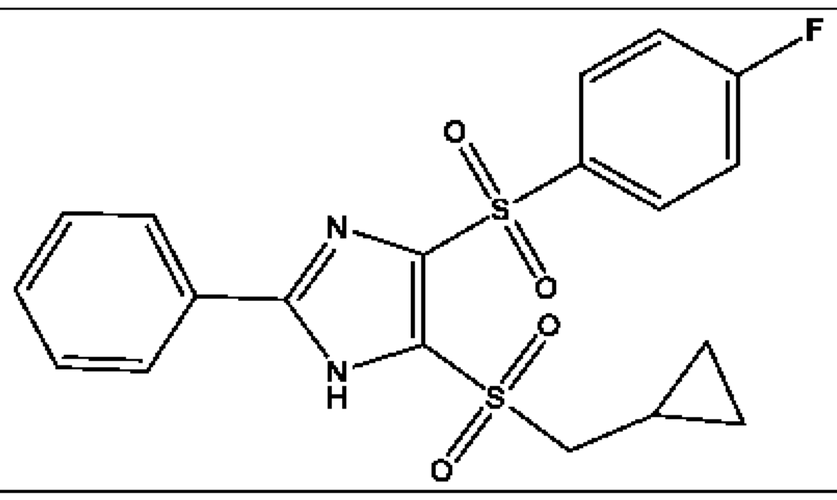
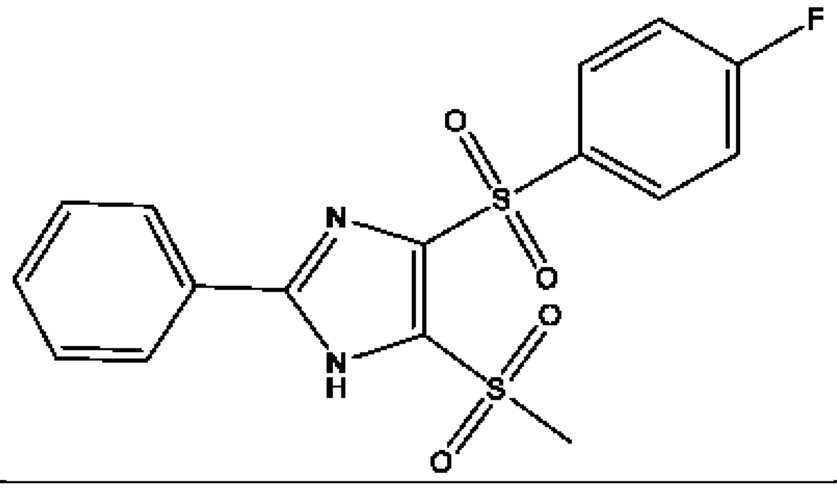
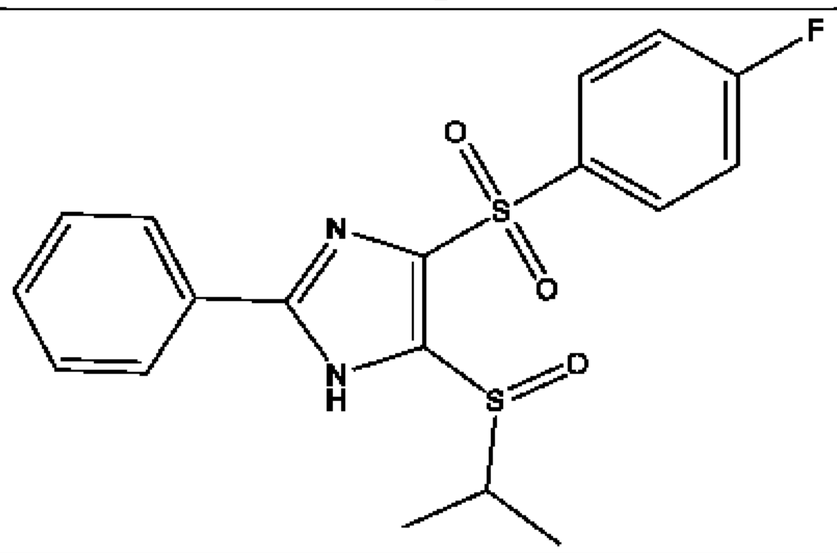
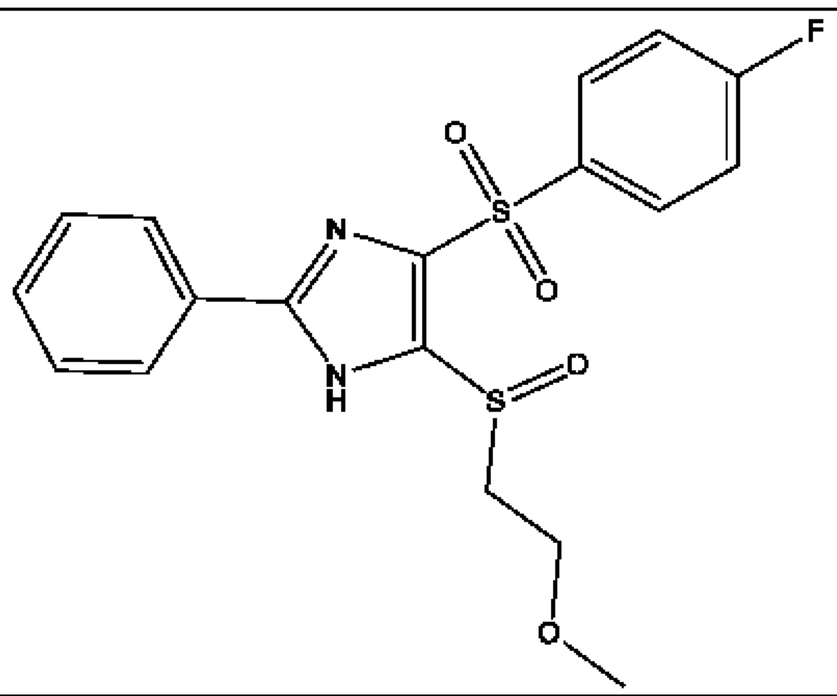
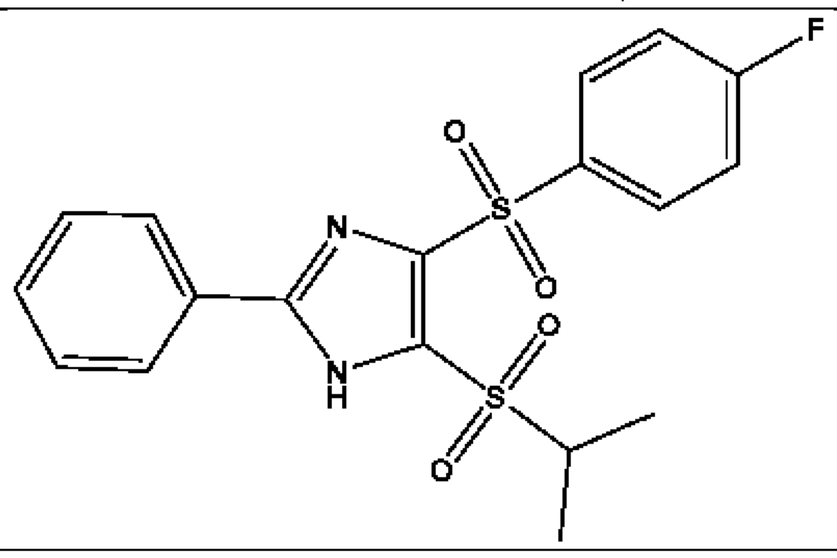
BC19676		++	+
BC19677		++	++
BC19678		++	++

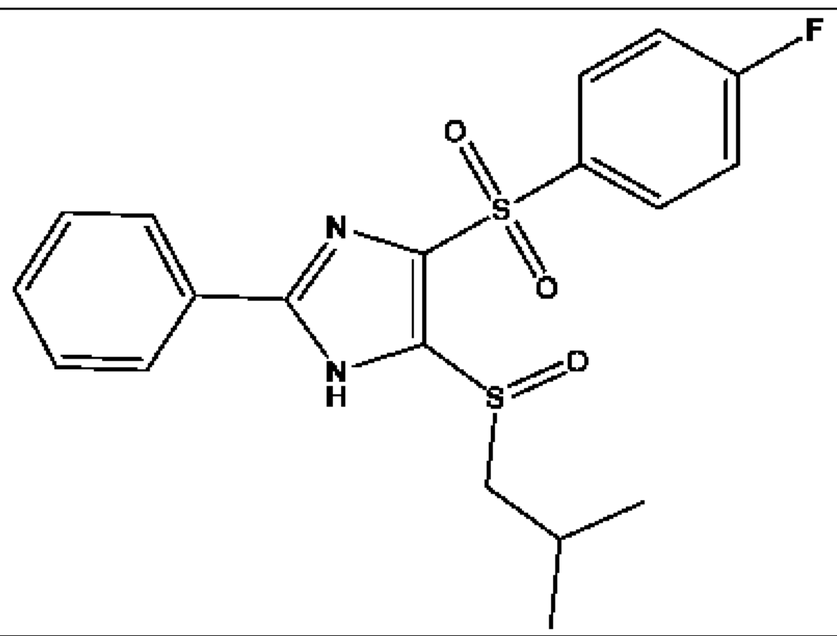
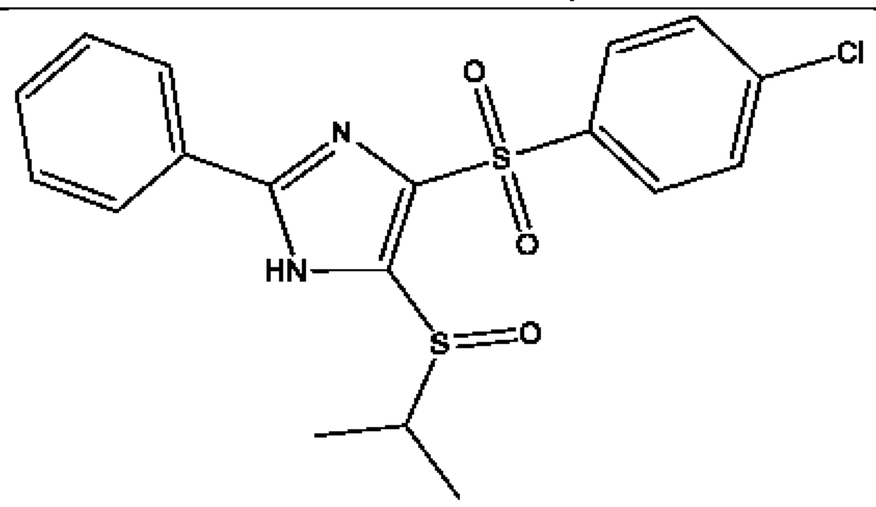
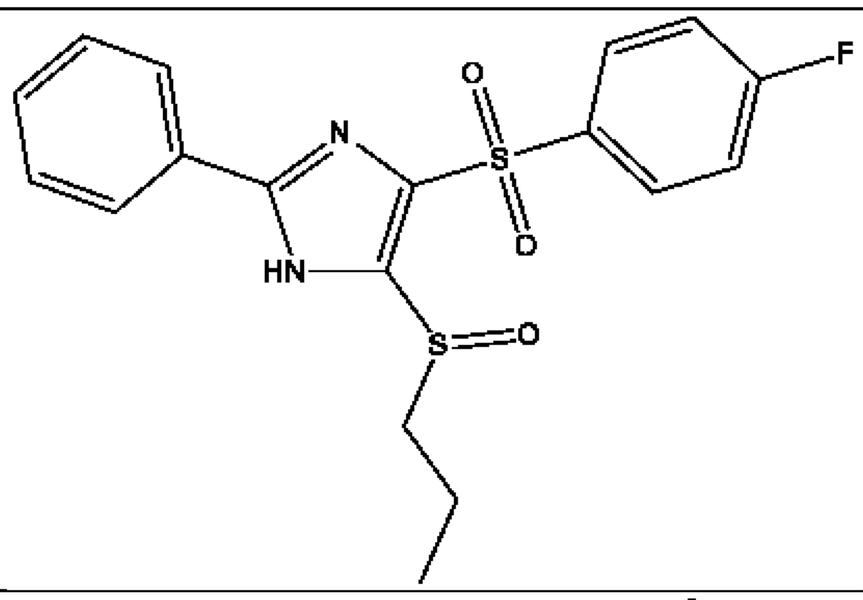
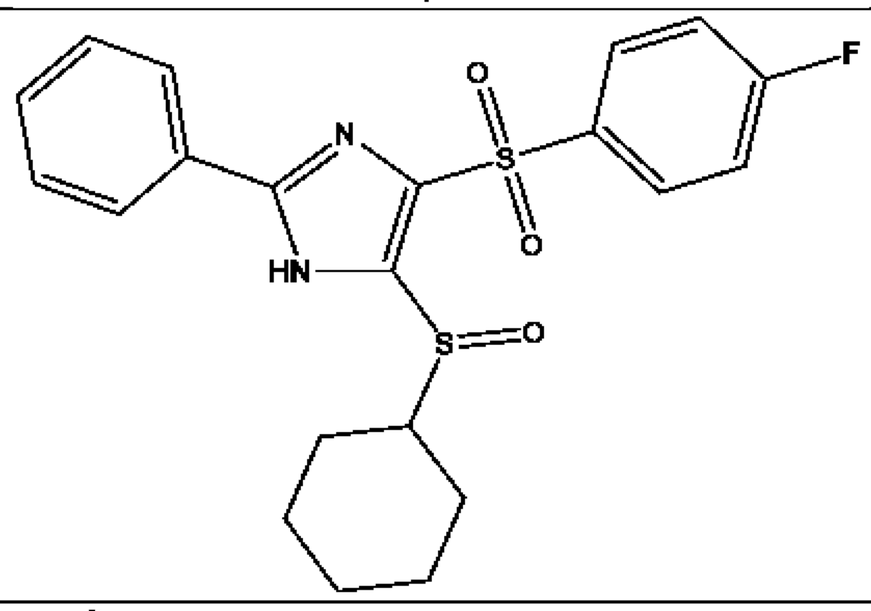
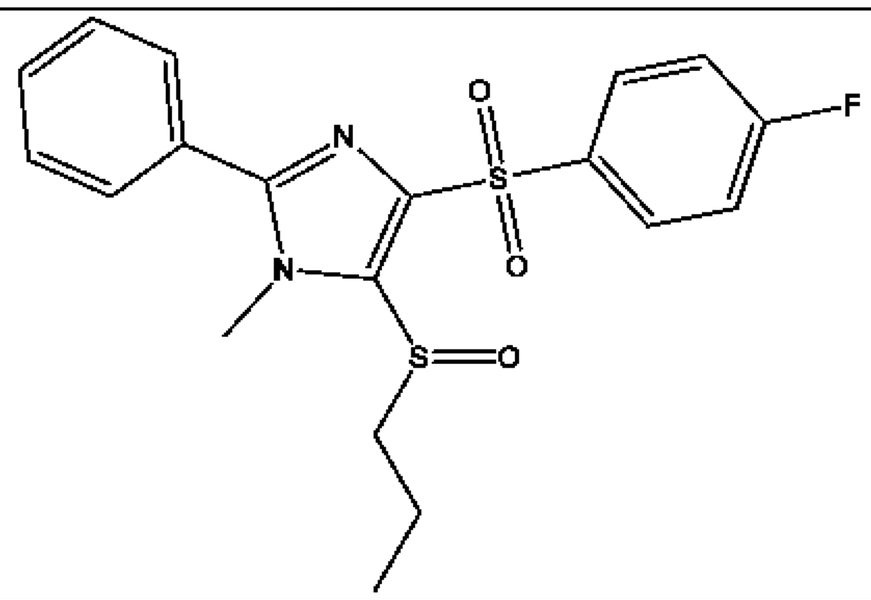
Table 11

BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19335		+	+
BC19336		+	+

BC19337		+	+
BC19410		+++	+
BC19420		+	+
BC19462		++	+
BC19465		++	+

BC19466		++	+
BC19467		++	++
BC19468		++	+
BC19469		++	+

BC19470		+	+
BC19522		++	+
BC19523		++	+
BC19524		+	+
BC19581		+	+

BC19582		++	+
BC19584		++	+
BC19585		++	+
BC19586		++	+
BC19600		+	+

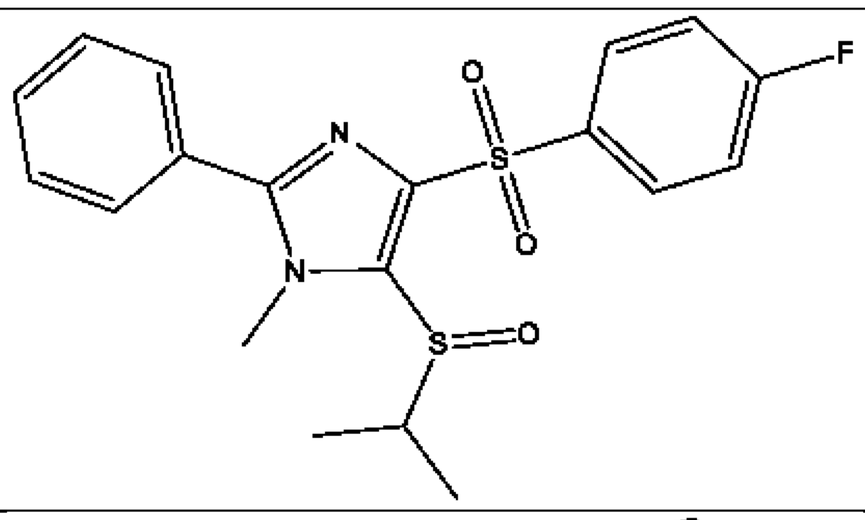
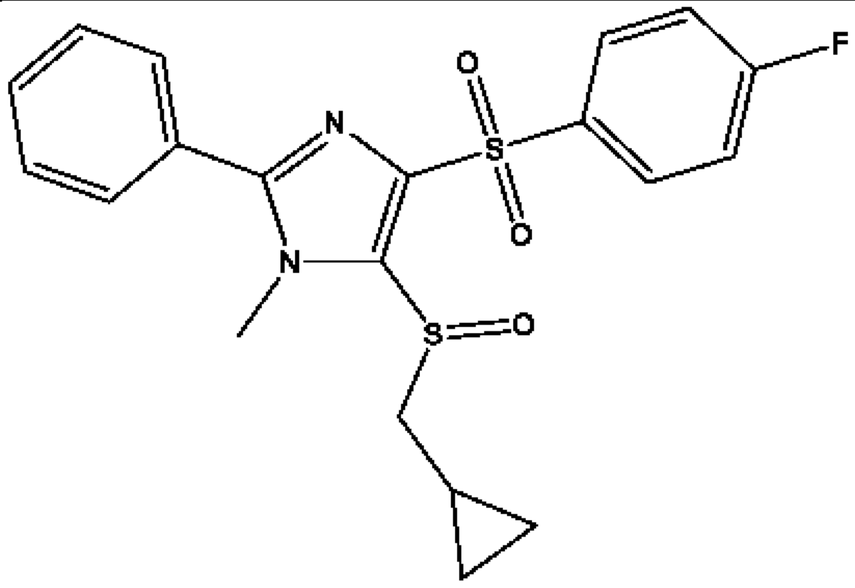
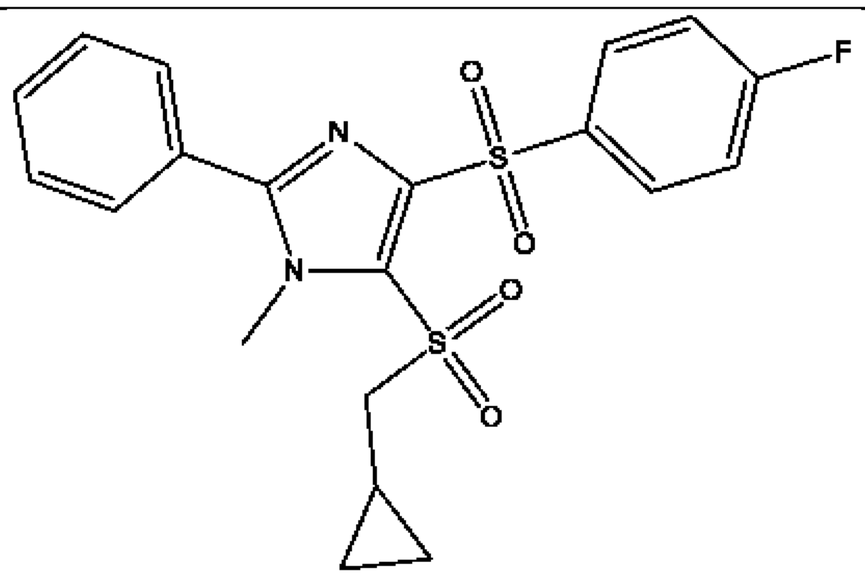
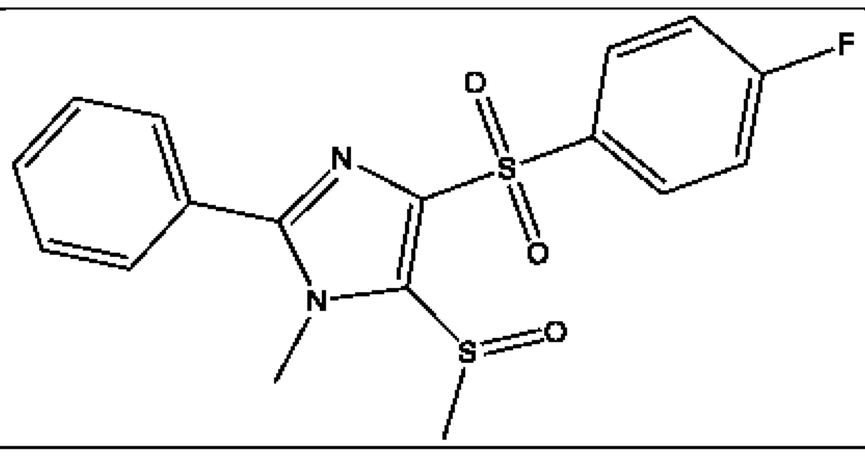
BC19601		+	+
BC19602		+	+
BC19634		+	+
BC19644		+	+

Table 12

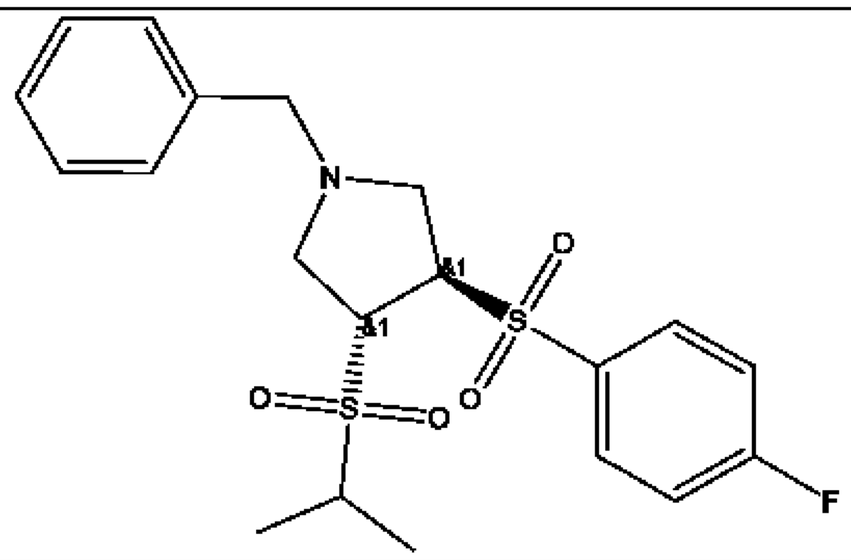
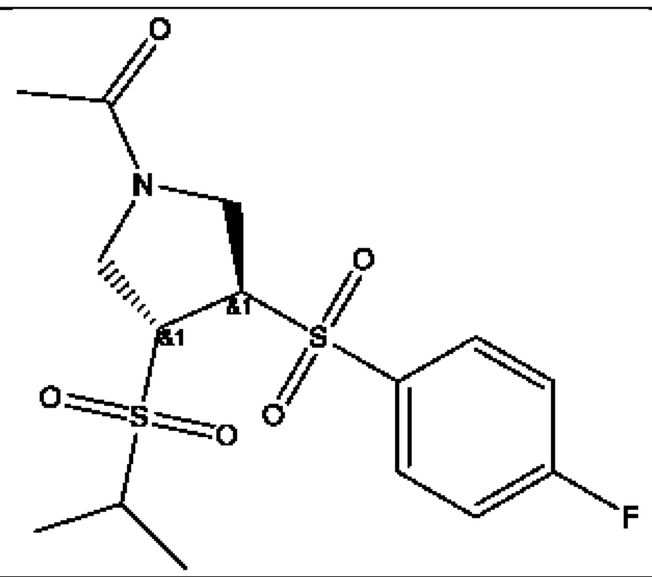
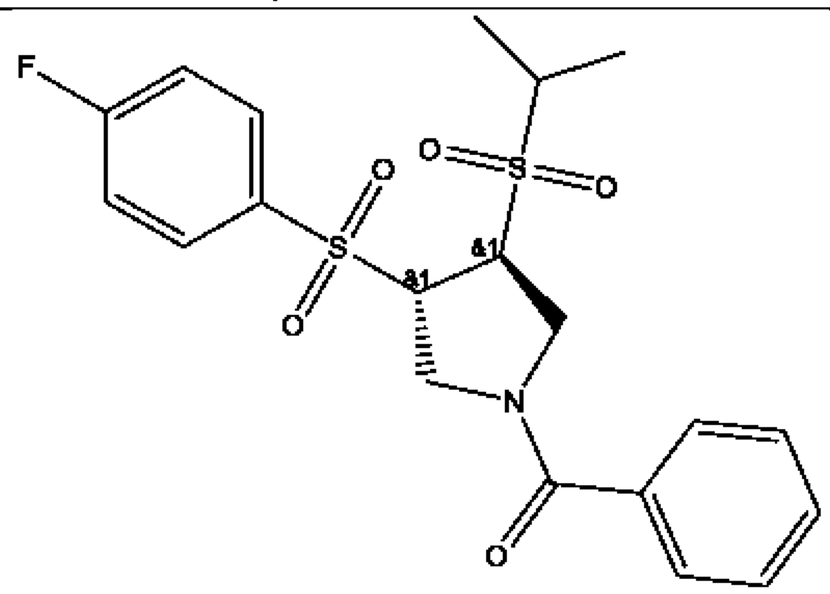
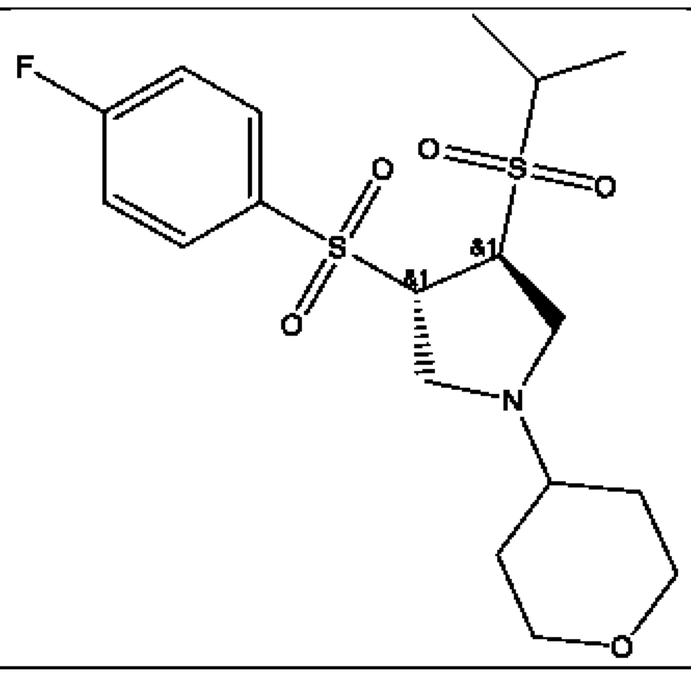
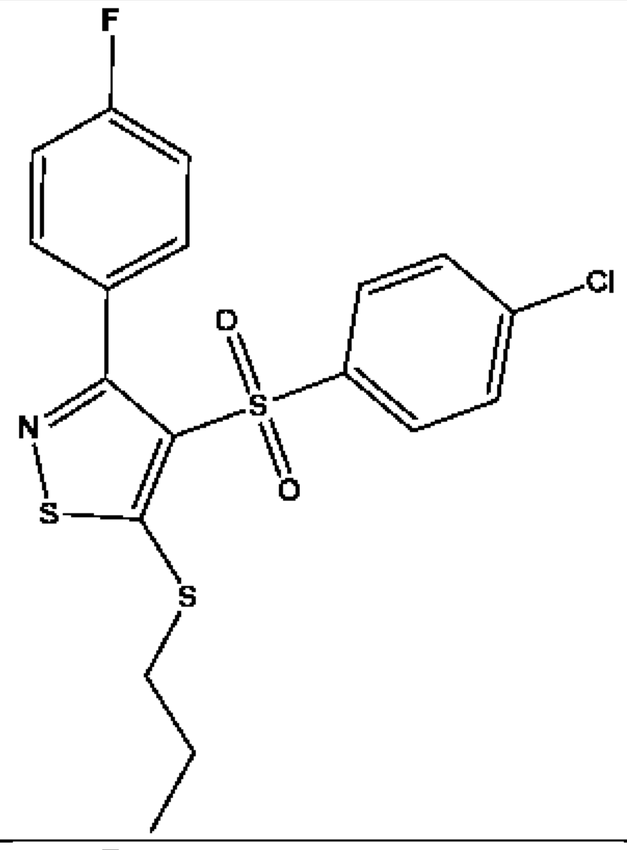
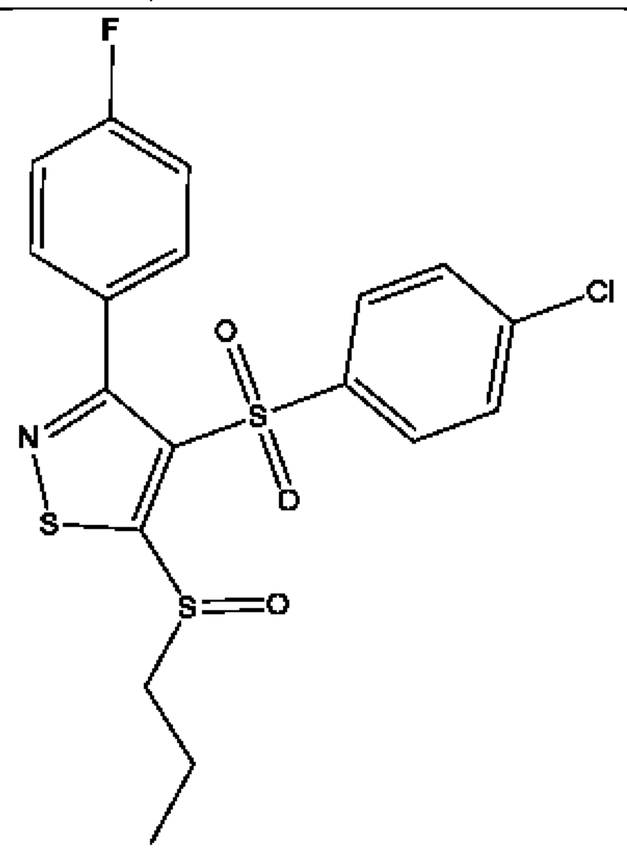
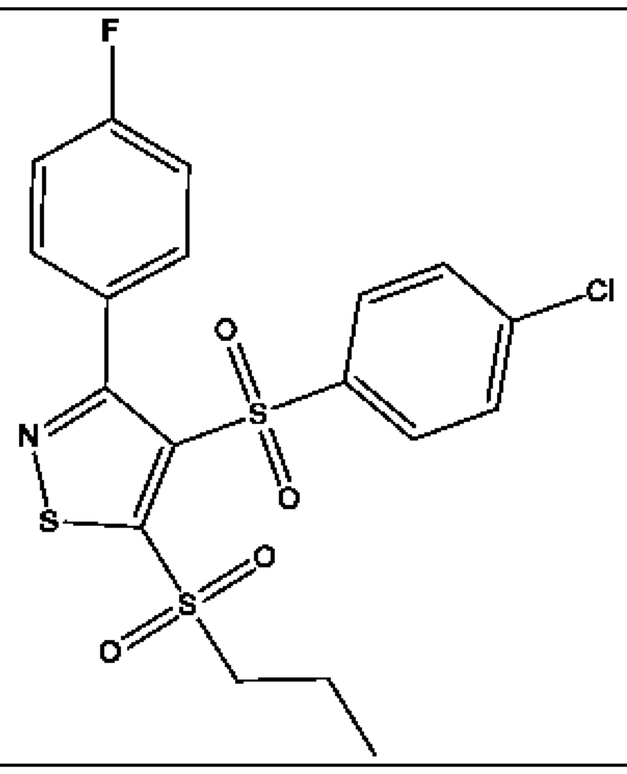
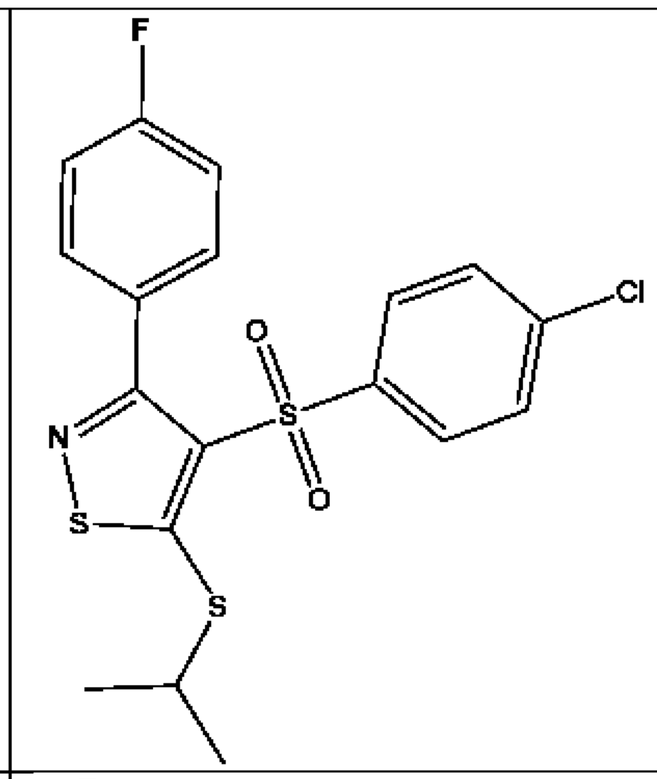
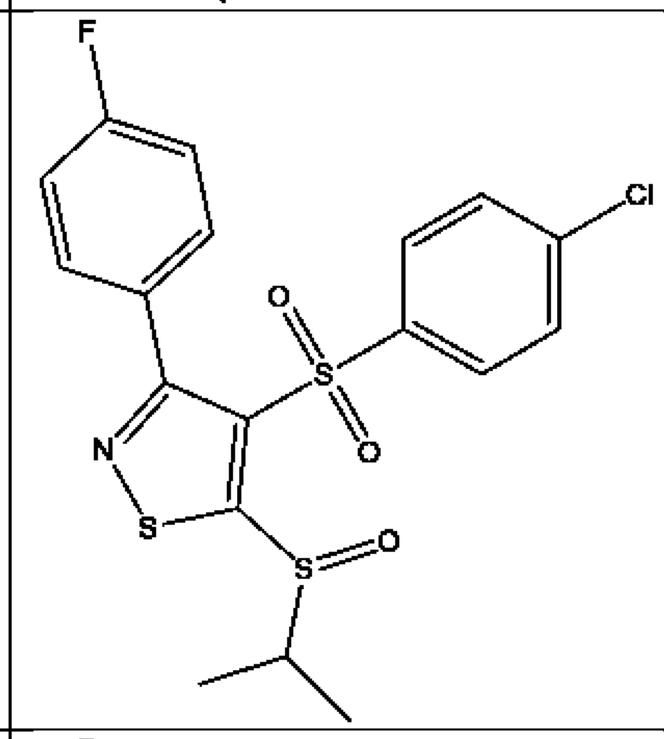
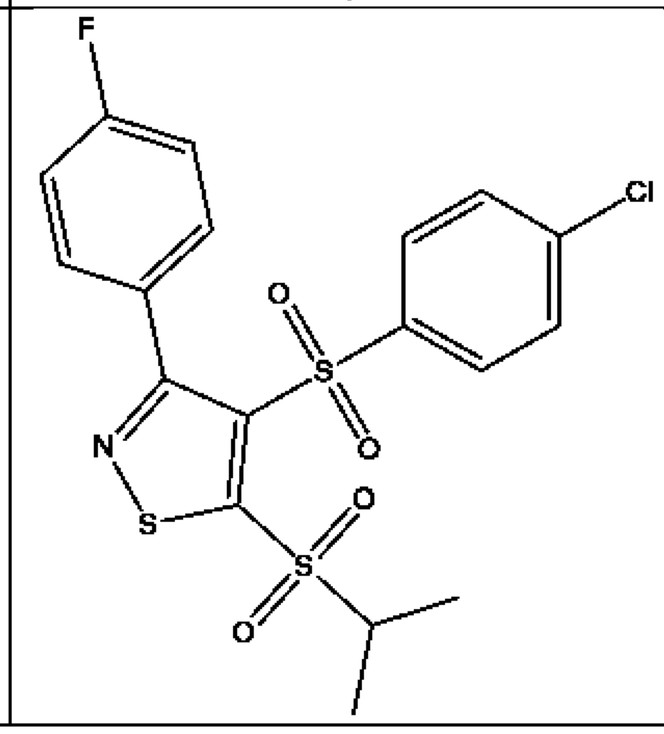
BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19643		+	+
BC19670		++	++
BC19683		+	++
BC19684		+	+

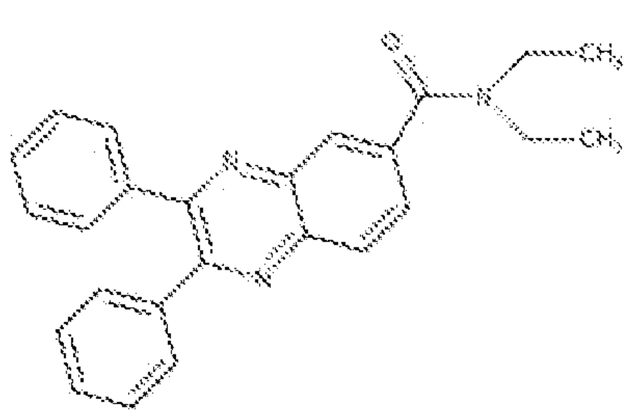
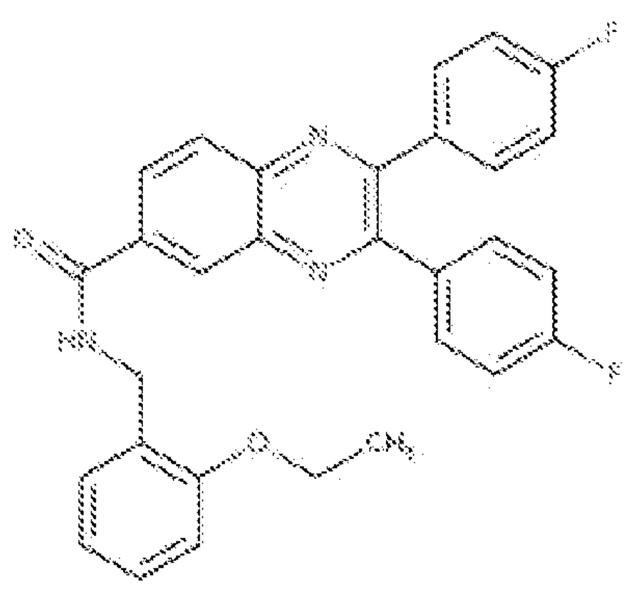
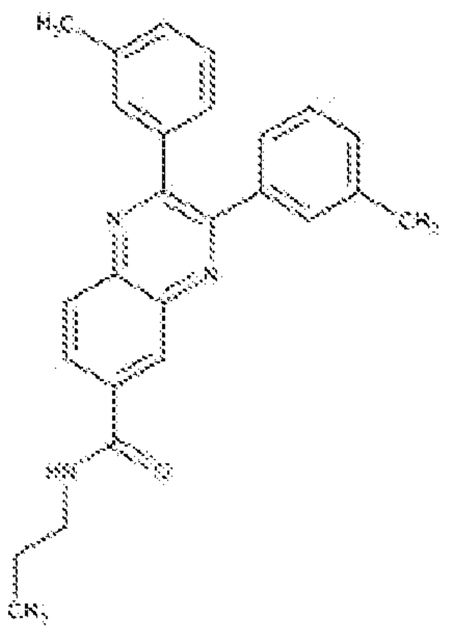
Table 15

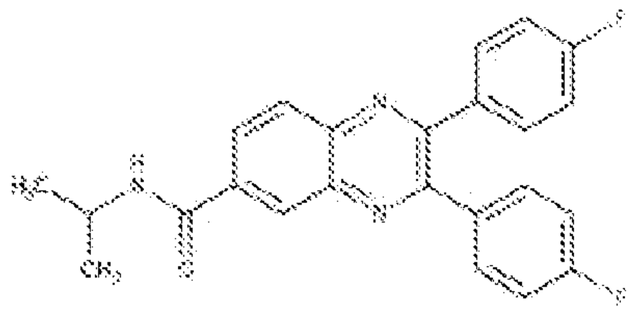
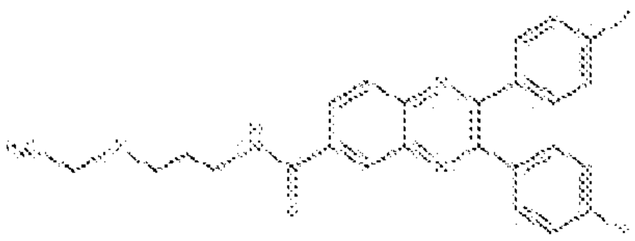
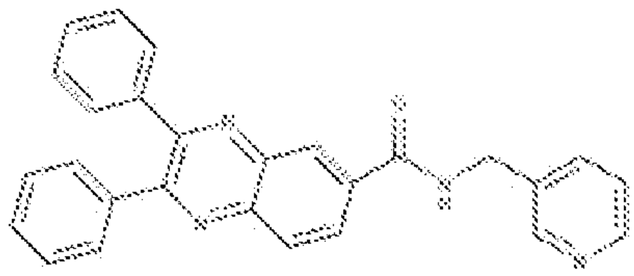
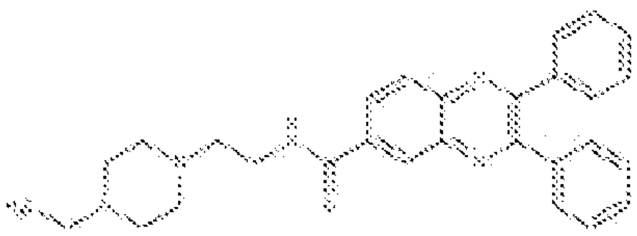
BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19680		+	+
BC19681		+++	++++
BC19682		+++	++++

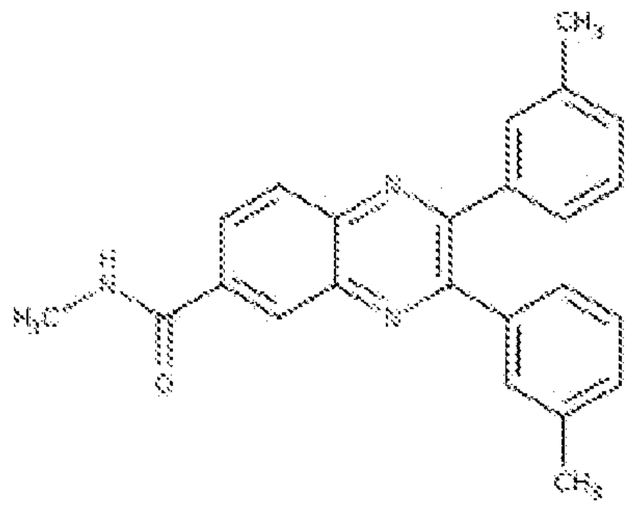
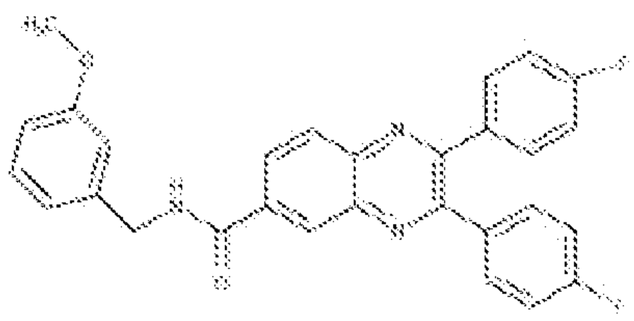
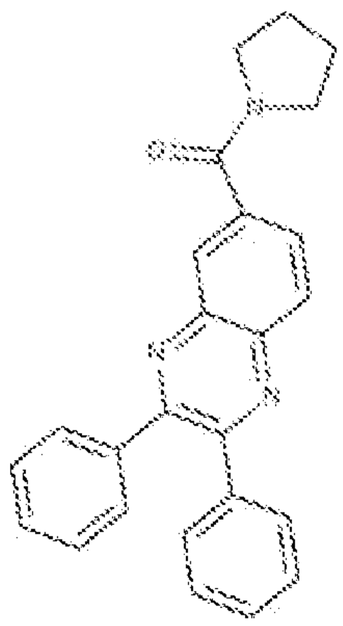
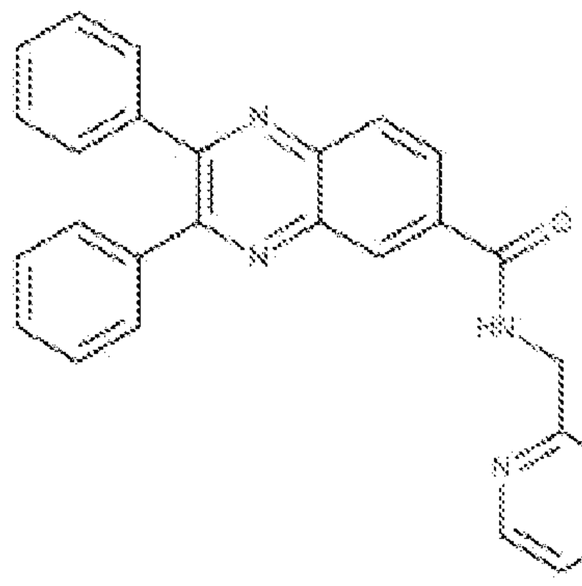
BC19726		+	+
BC19727		++	++
BC19728		+	++

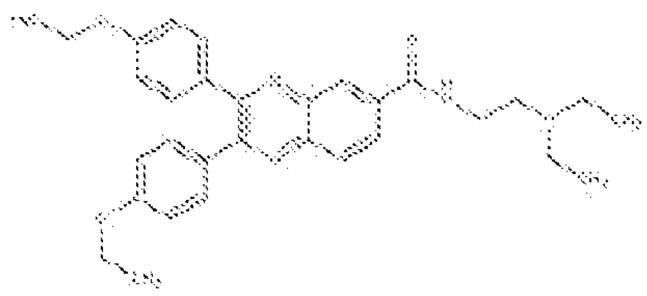
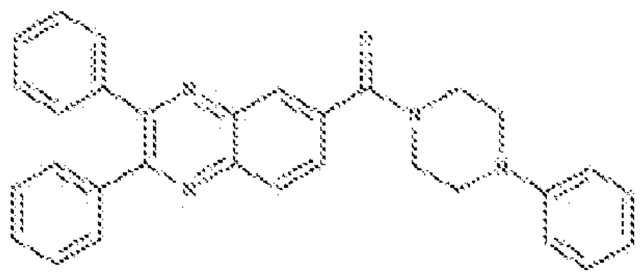
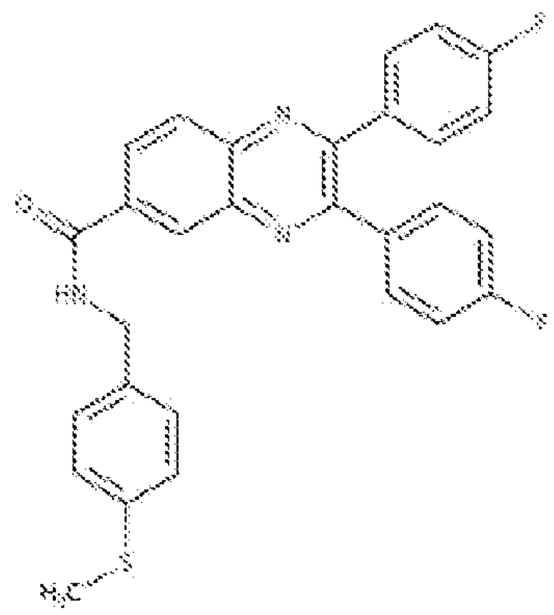
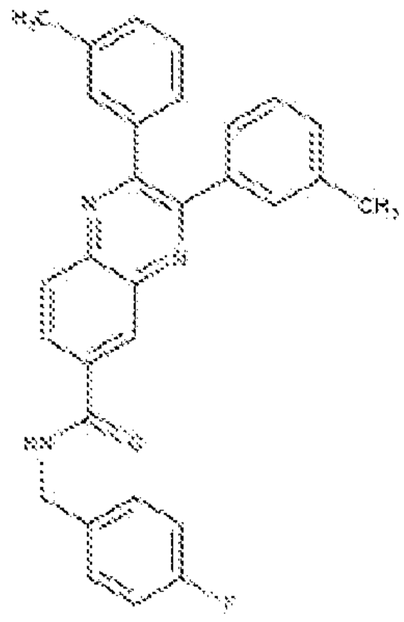
Example 4 – Bioassay data for tested compounds

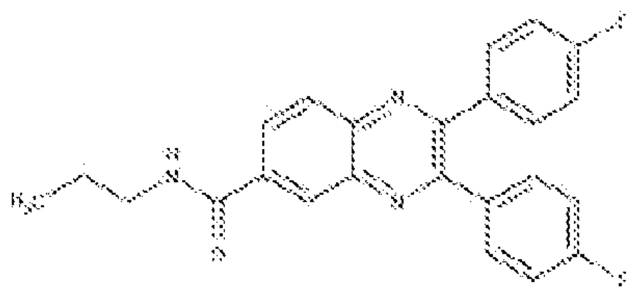
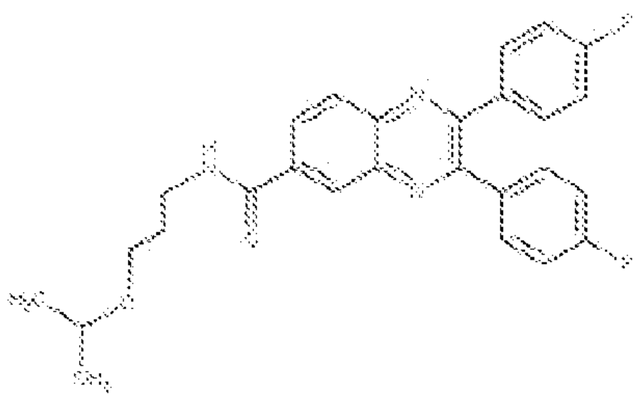
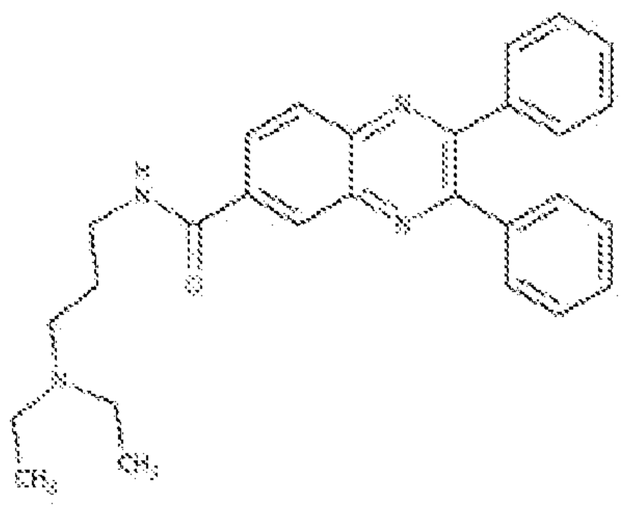
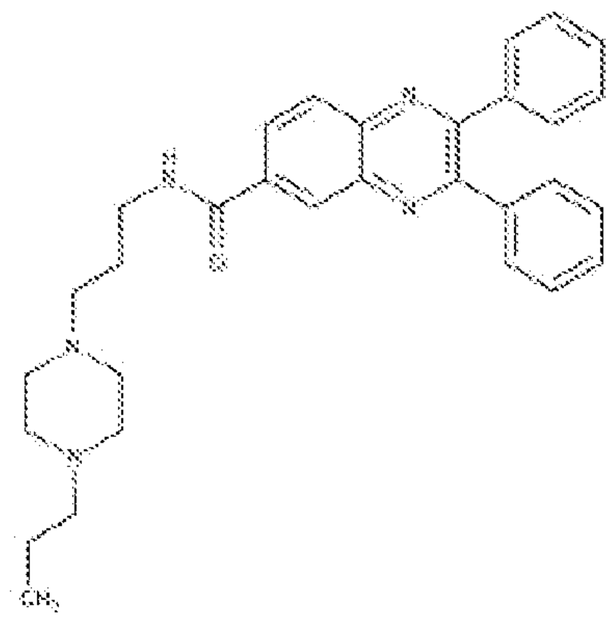
Table 4a

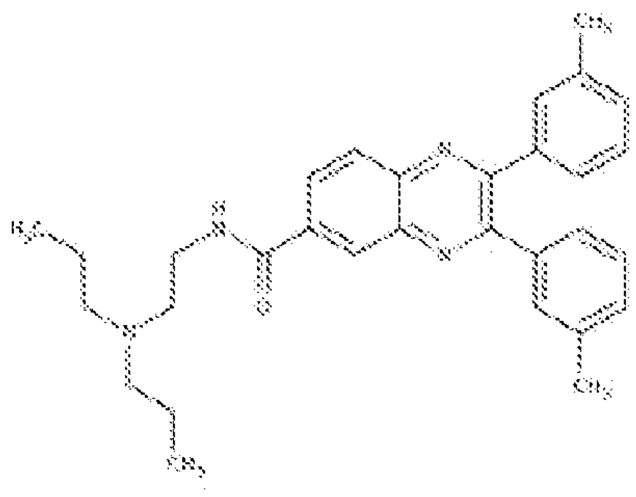
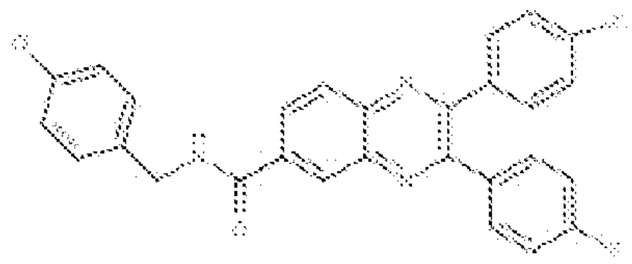
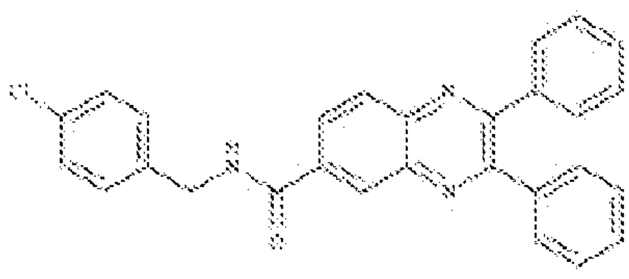
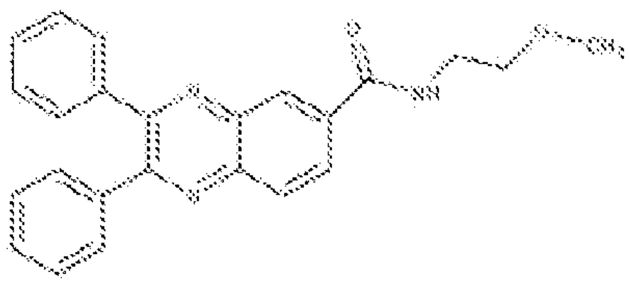
BC No.	Compound	IC_{50} (NF-κB assay)
BC18400		++++
BC18401		+++
BC18402		++

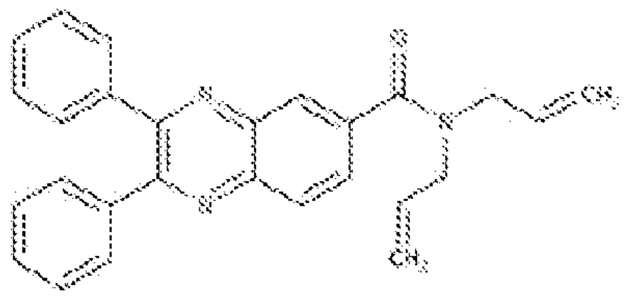
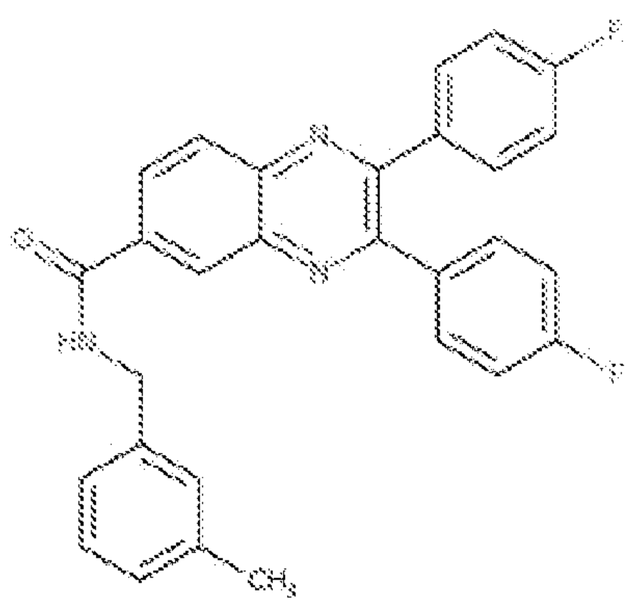
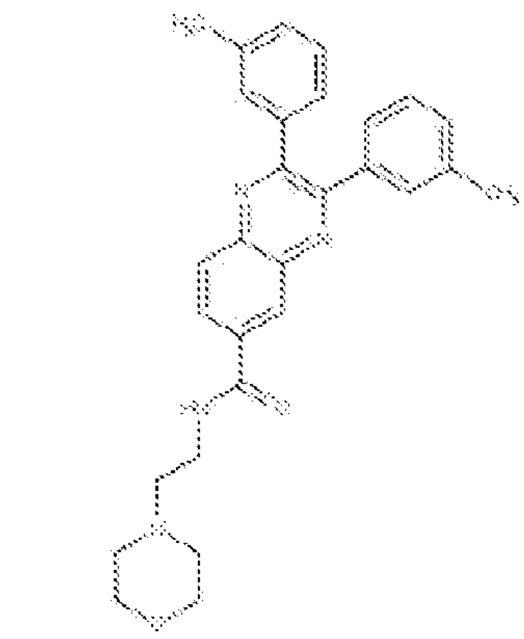
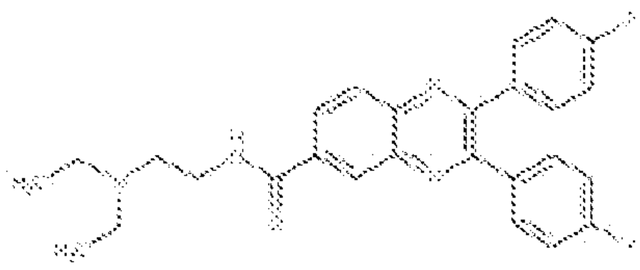
BC18403		++++
BC18404		++++
BC18405		++++
BC18406		++++

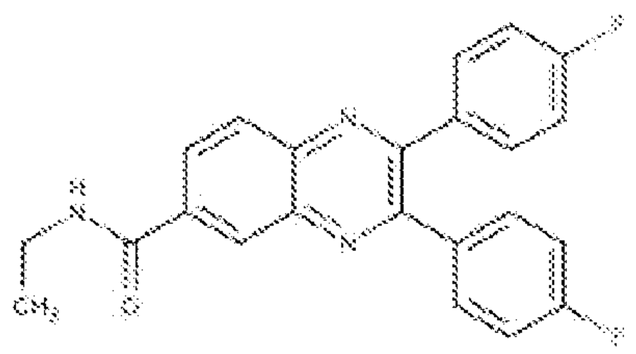
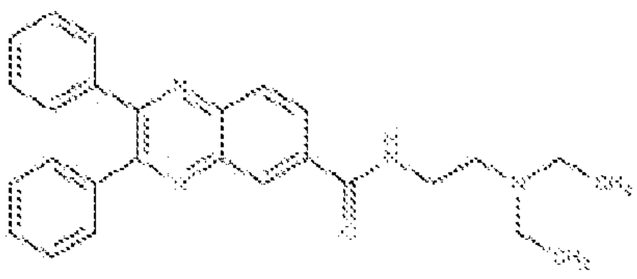
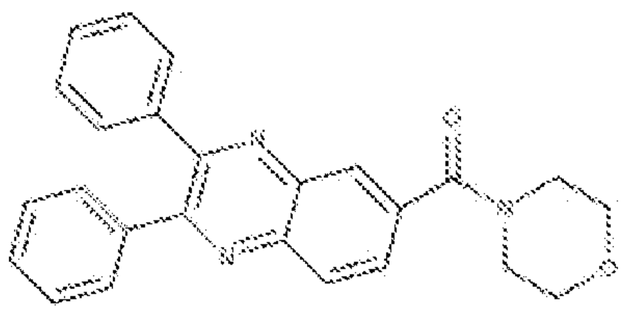
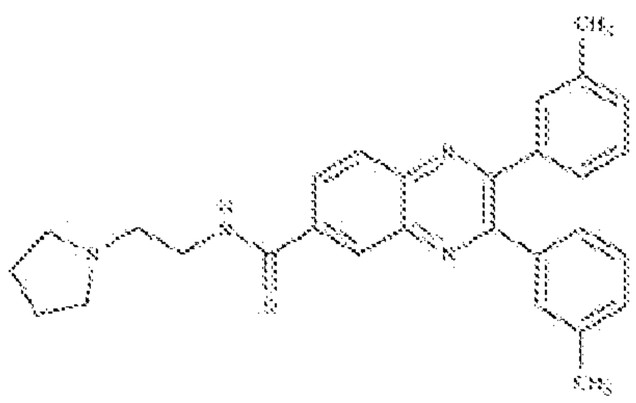
BC18407		++
BC18408		+++
BC18409		++++
BC18410		++++

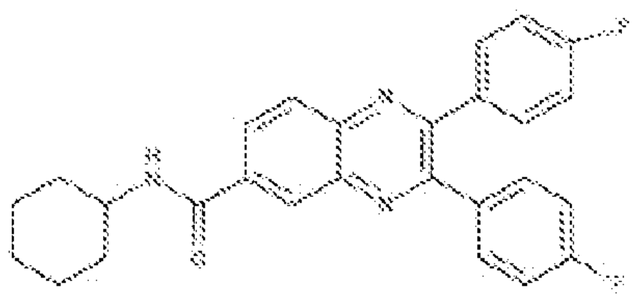
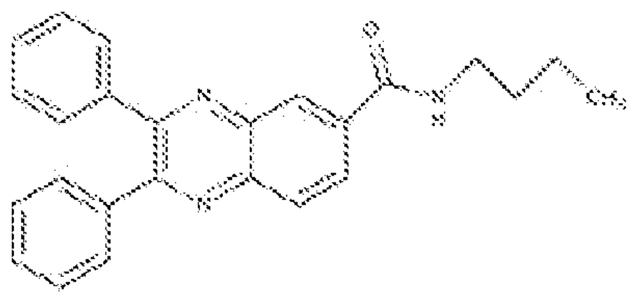
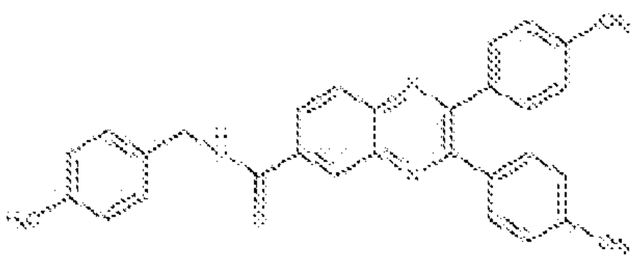
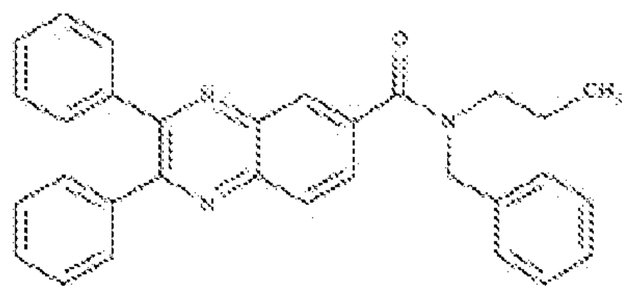
BC18411		++
BC18412		++
BC18413		+++
BC18414		+

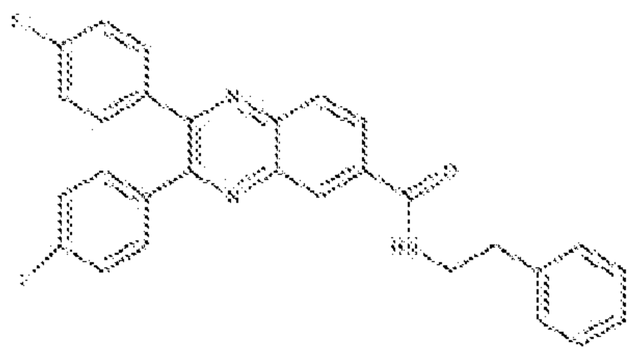
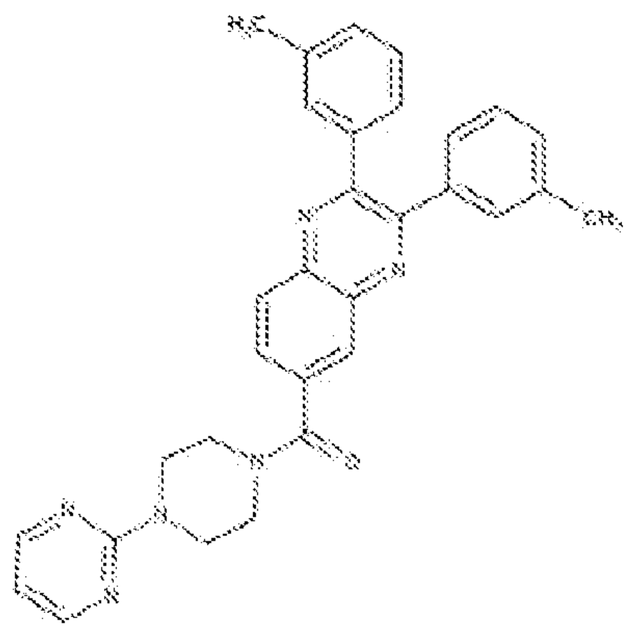
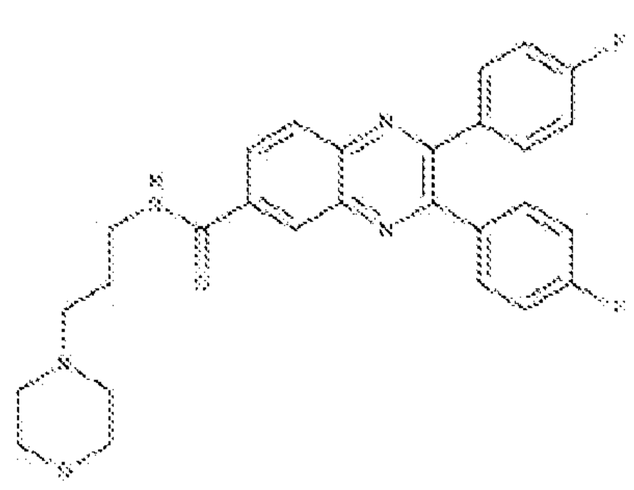
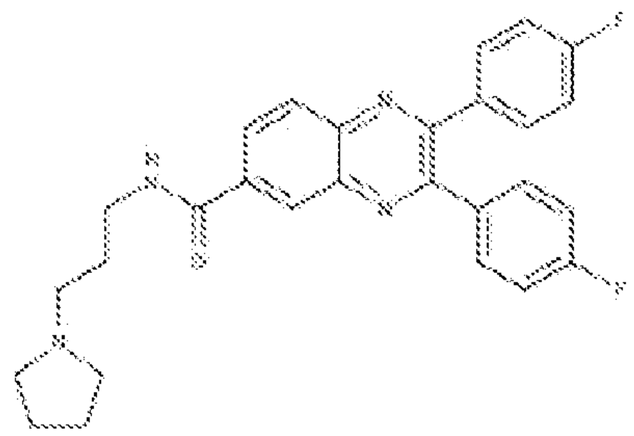
BC18415		++++
BC18416		++++
BC18417		++++
BC18418		+++

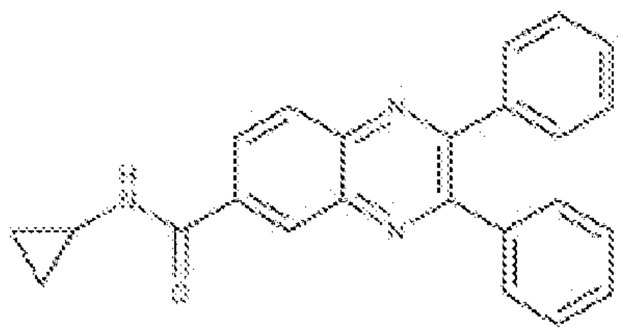
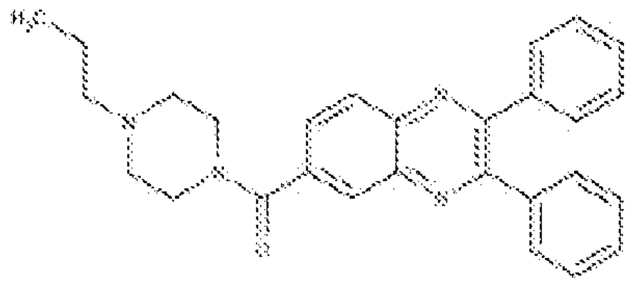
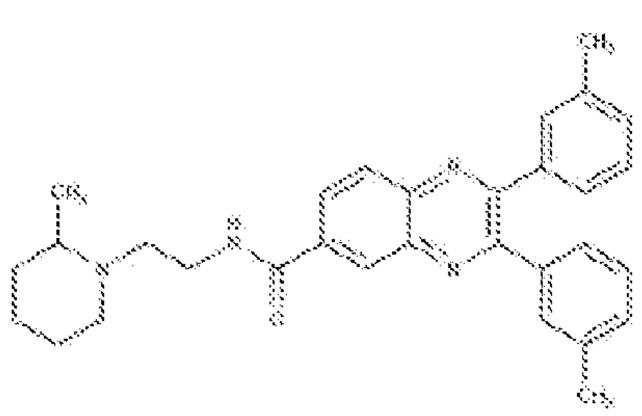
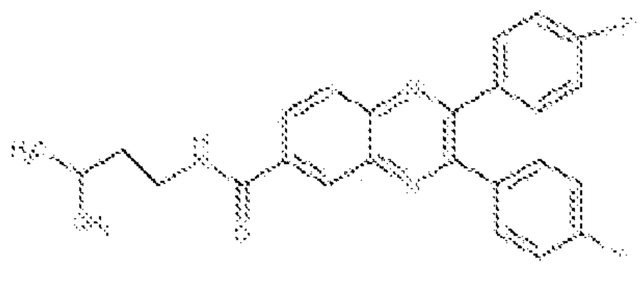
BC18419		++
BC18420		+++
BC18421		+
BC18422		++++

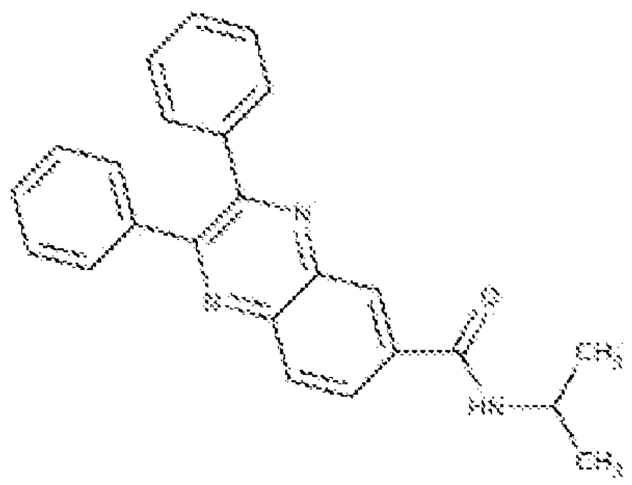
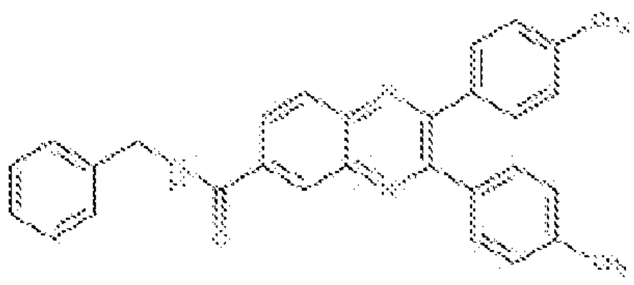
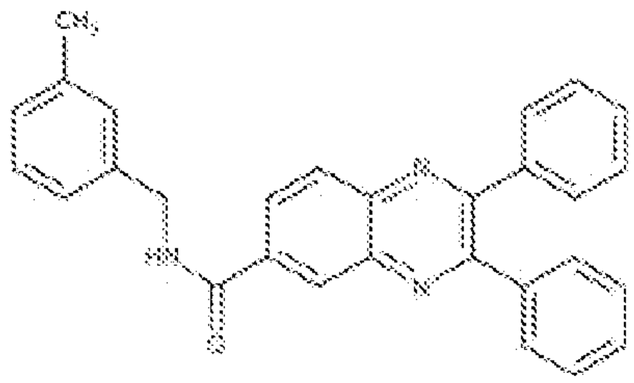
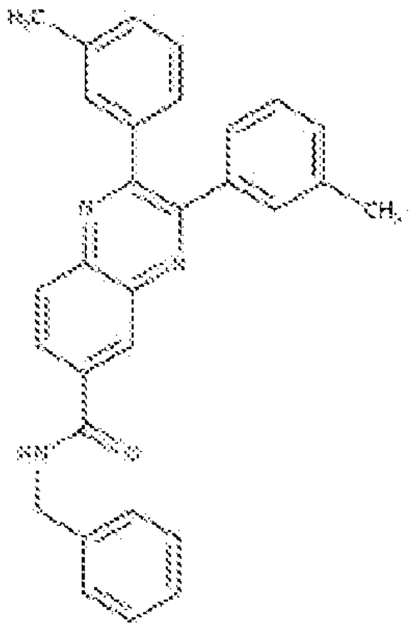
BC18423		++++
BC18424		+++
BC18425		++
BC18426		++++

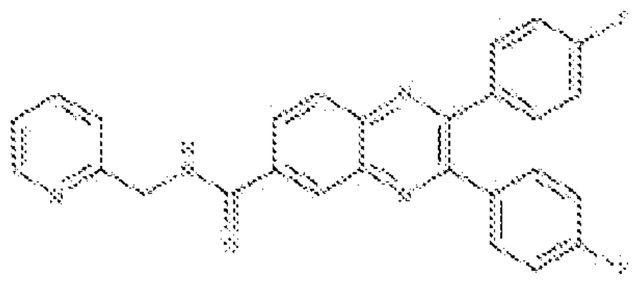
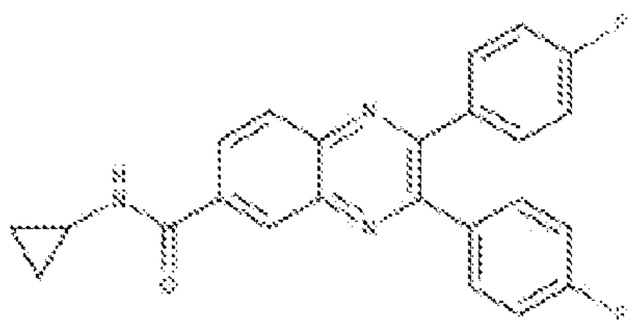
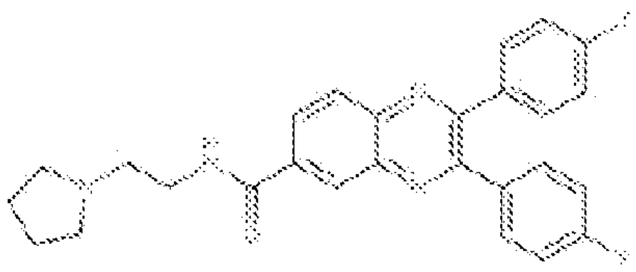
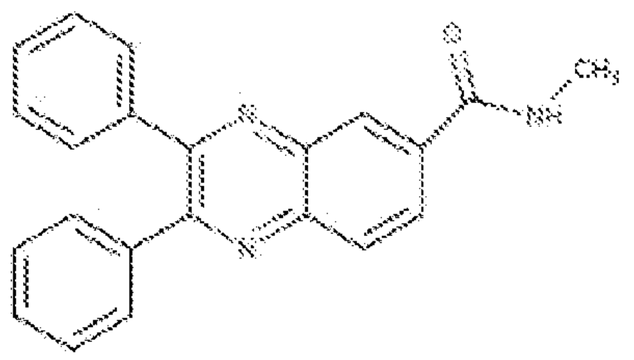
BC18427		++++
BC18428		++++
BC18429		++++
BC18430		++

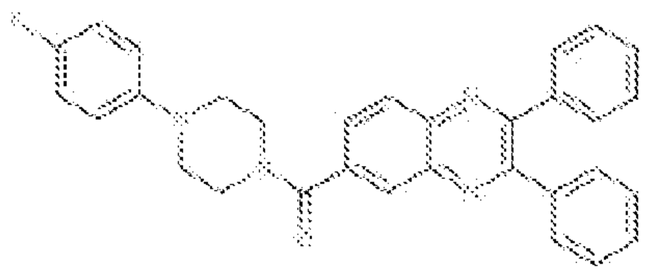
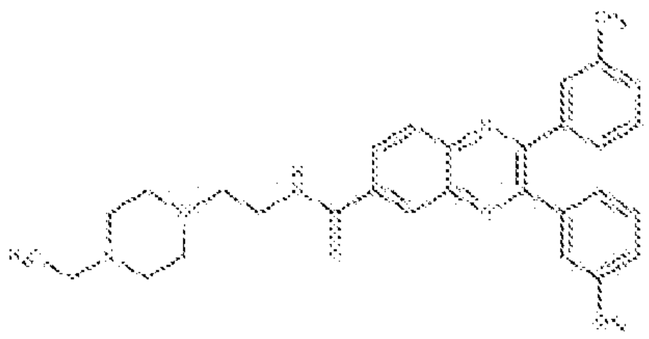
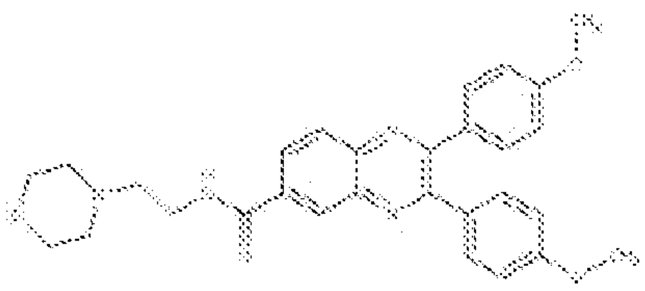
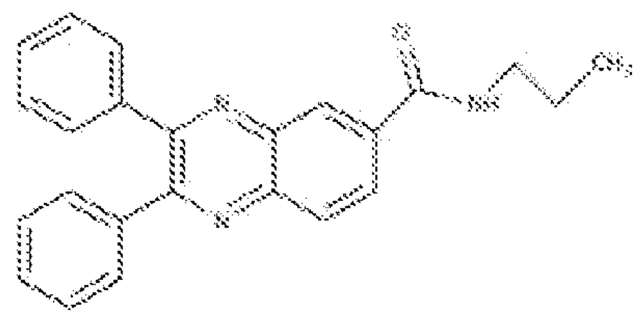
BC18431		+++
BC18432		+++
BC18433		+
BC18434		+++

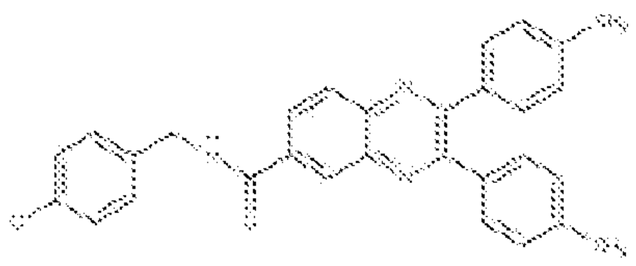
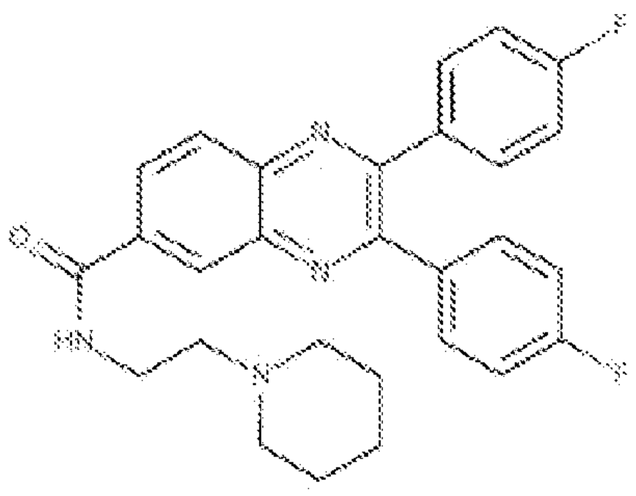
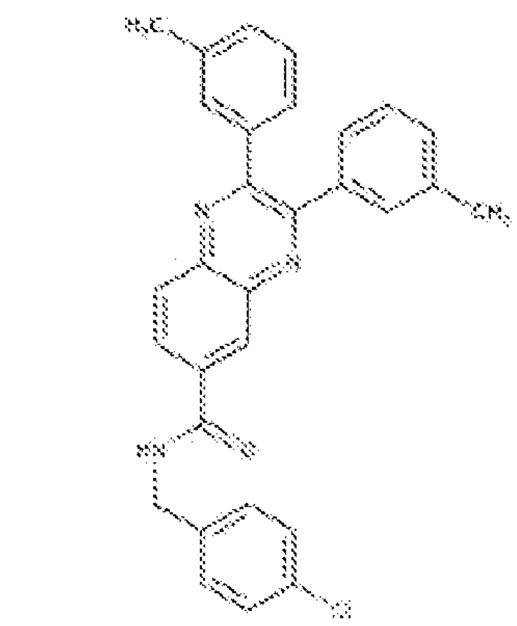
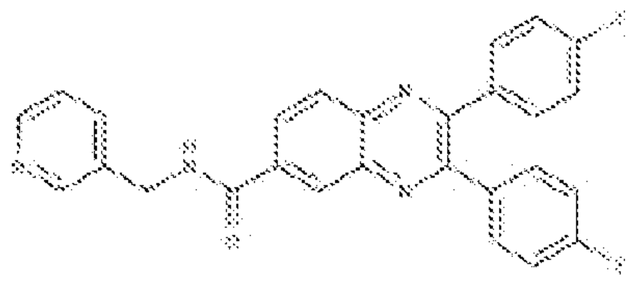
BC18435		+++
BC18436		++
BC18437		++++
BC18438		++++

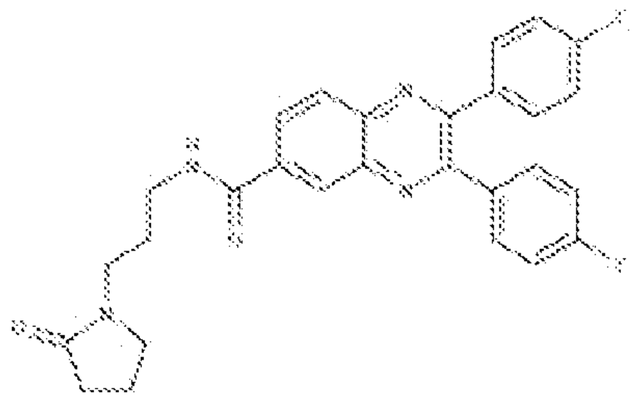
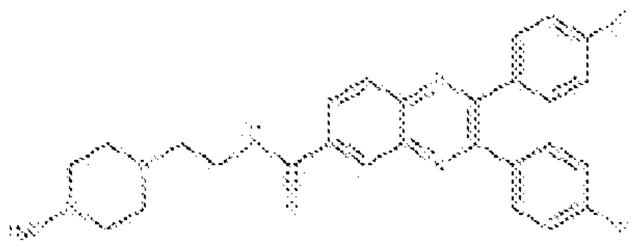
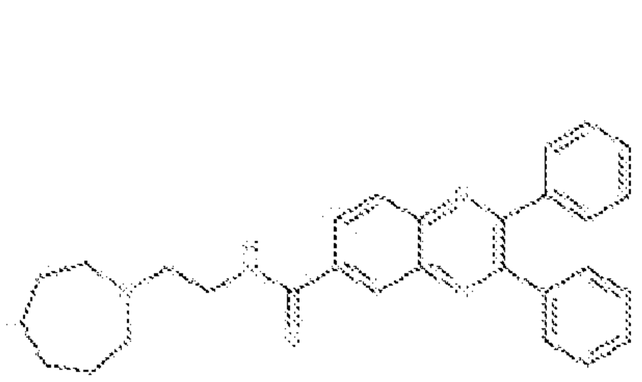
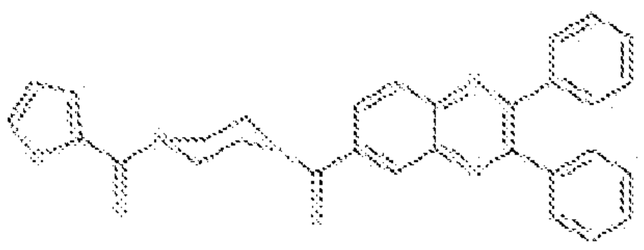
BC18439		++++
BC18440		++++
BC18441		++
BC18442		++++

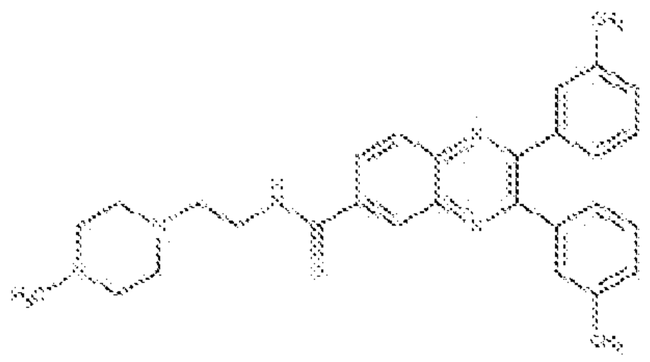
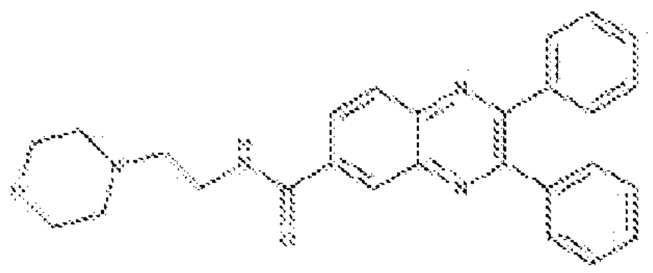
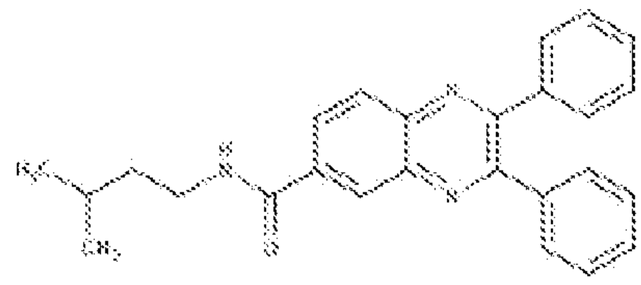
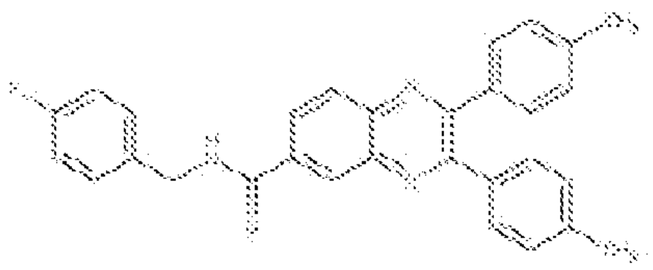
BC18443		++++
BC18444		+
BC18445		+++
BC18446		+

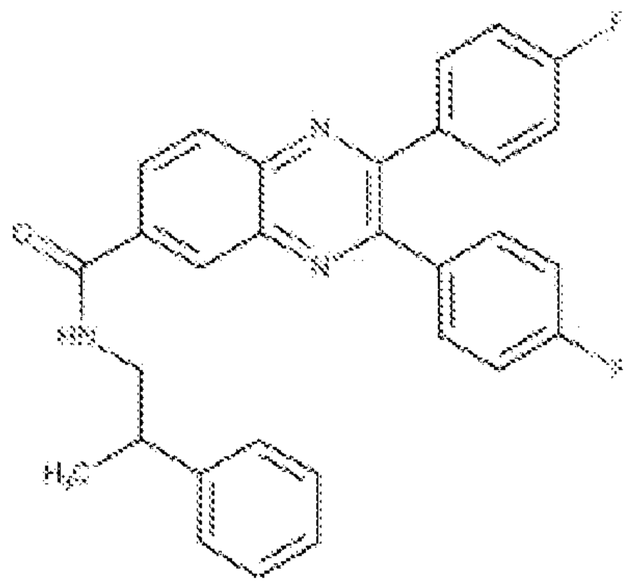
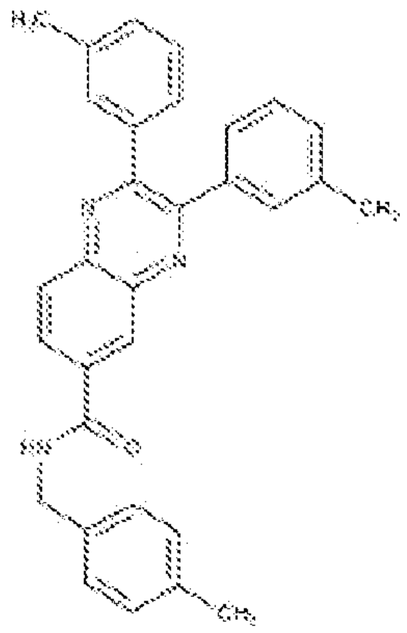
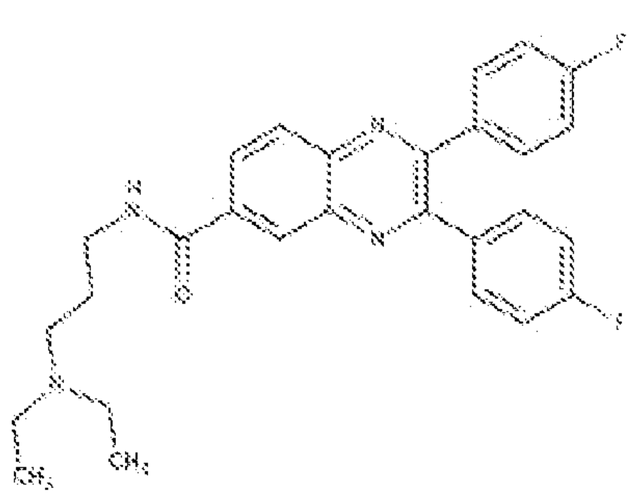
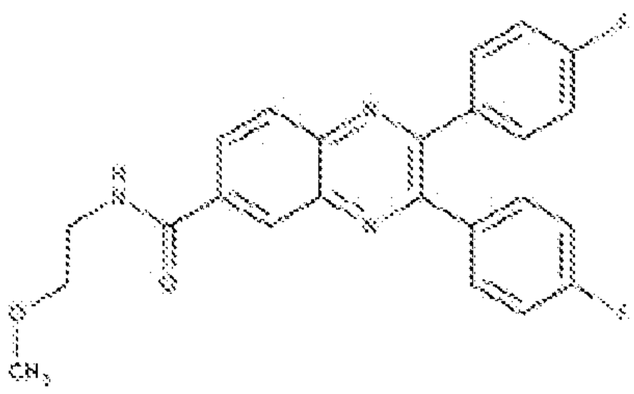
BC18447		++++
BC18448		++++
BC18449		++++
BC18450		++++

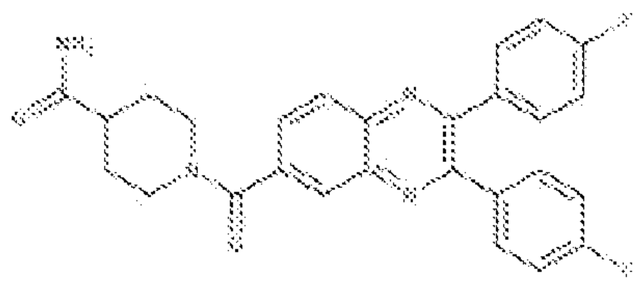
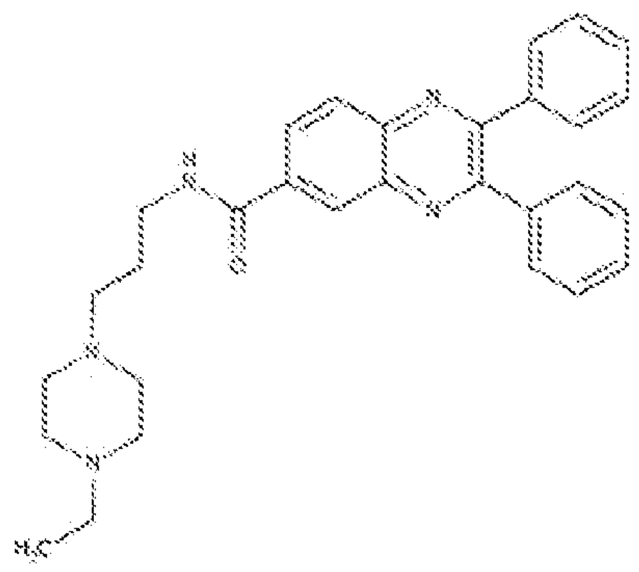
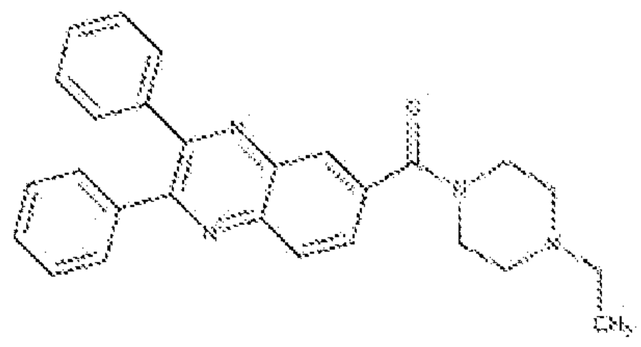
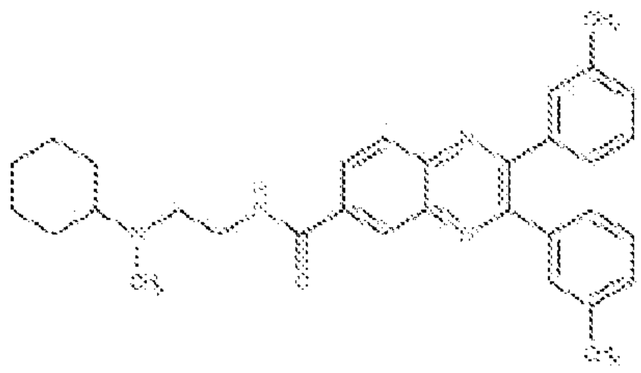
BC18451		+++
BC18452		++
BC18453		++
BC18454		+++

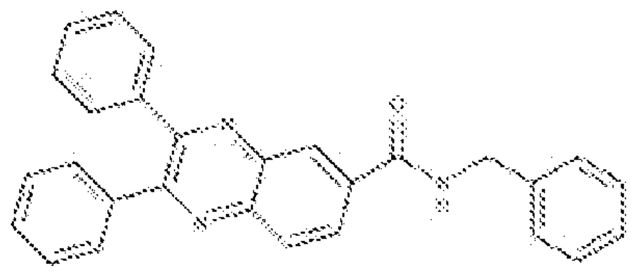
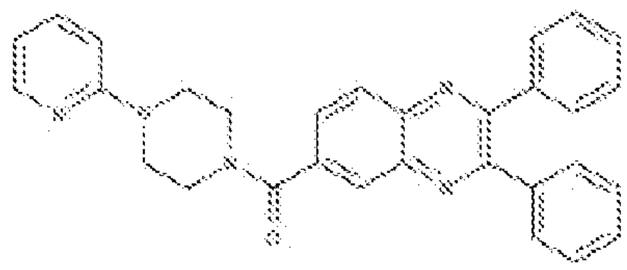
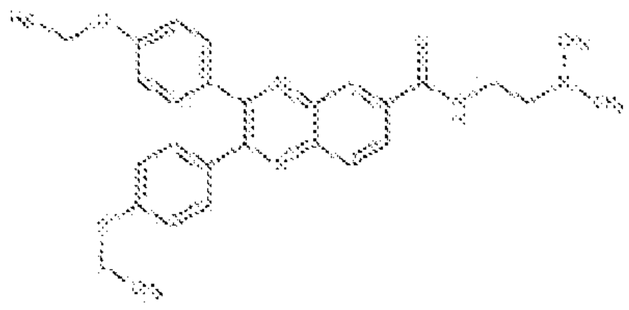
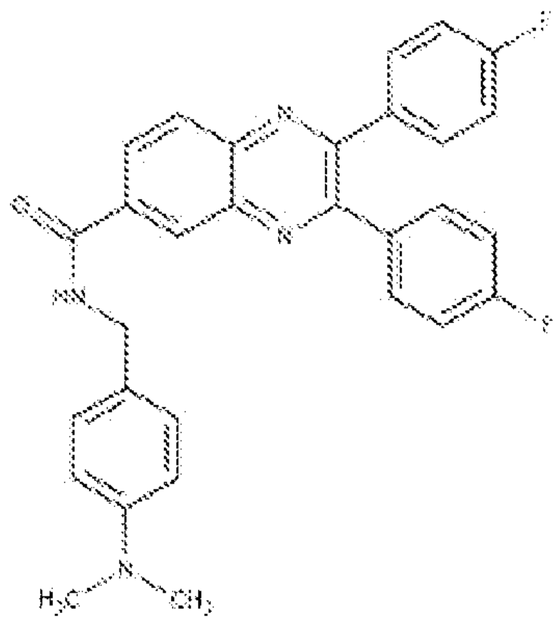
BC18455		+
BC18456		++++
BC18457		+
BC18458		++++

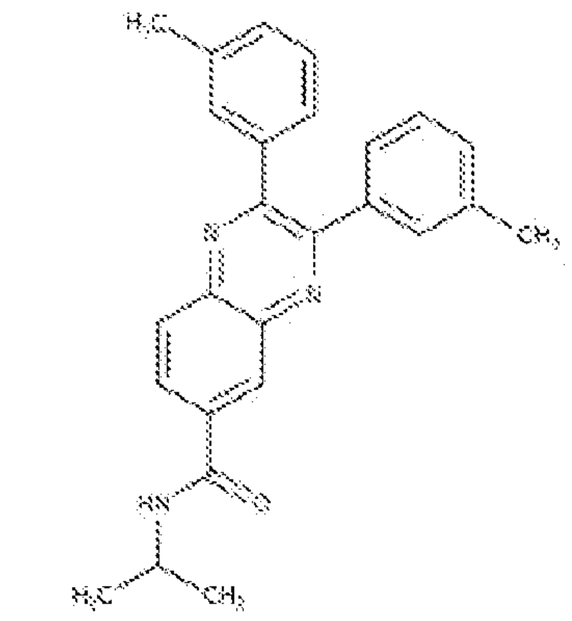
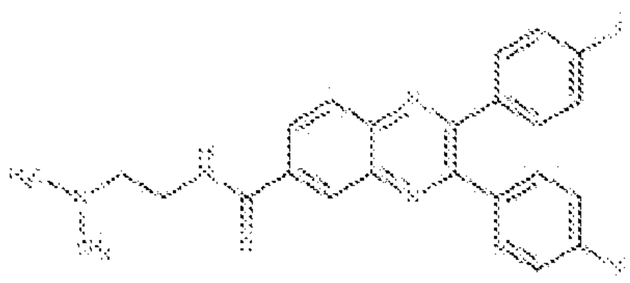
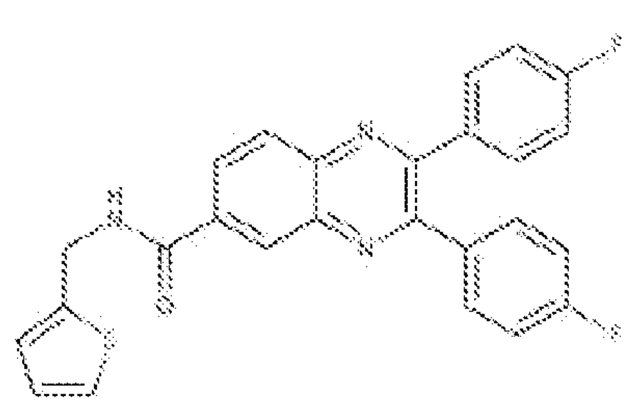
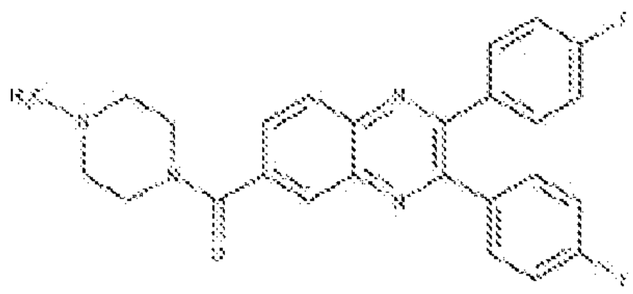
BC18459		++++
BC18460		++++
BC18461		++++
BC18462		++++

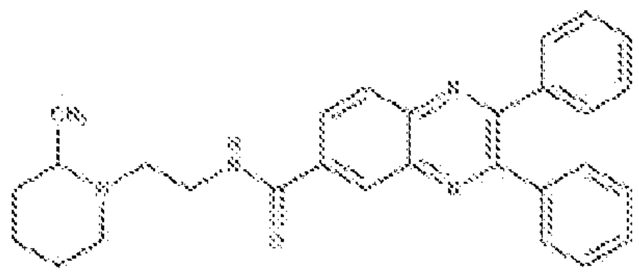
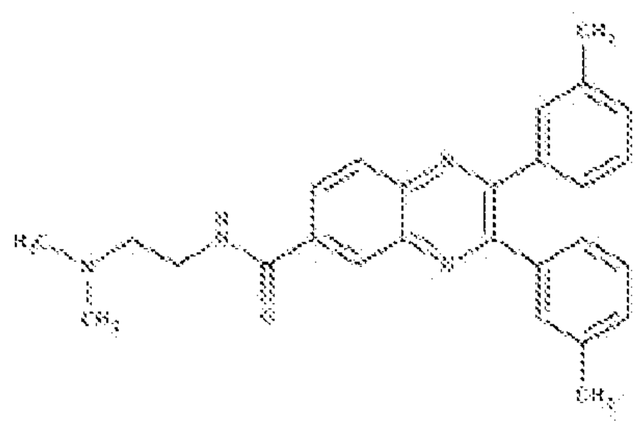
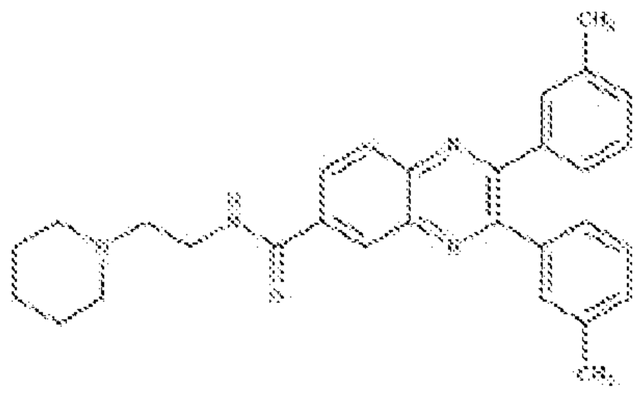
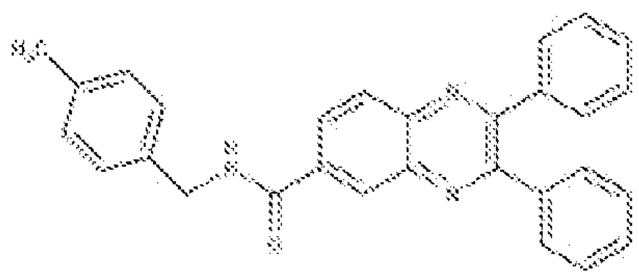
BC18463		++
BC18464		++++
BC18465		+++
BC18466		+

BC18467		+++
BC18468		+
BC18469		++++
BC18470		++++

BC18471		++++
BC18472		+++
BC18473		++++
BC18474		++

BC18475		+
BC18476		+++
BC18477		++
BC18478		+++

BC18479		++
BC18480		++++
BC18481		++++
BC18482		++++

BC18483		++++
BC18484		++
BC18485		++
BC18486		+

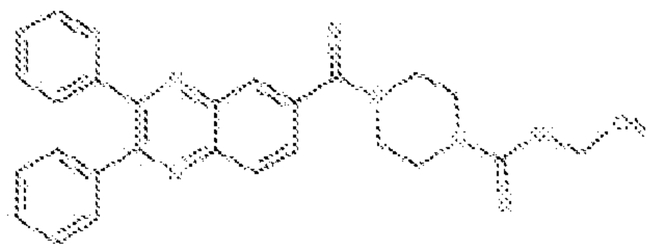
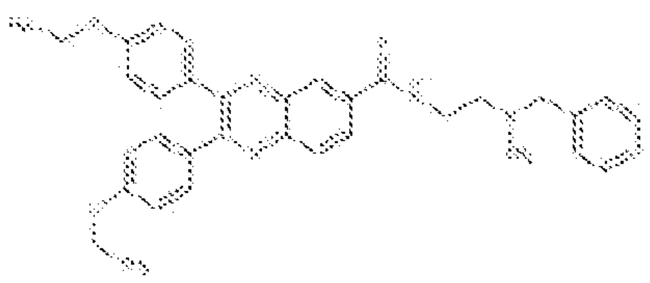
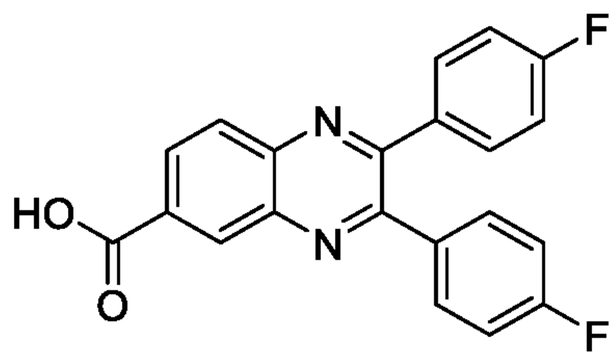
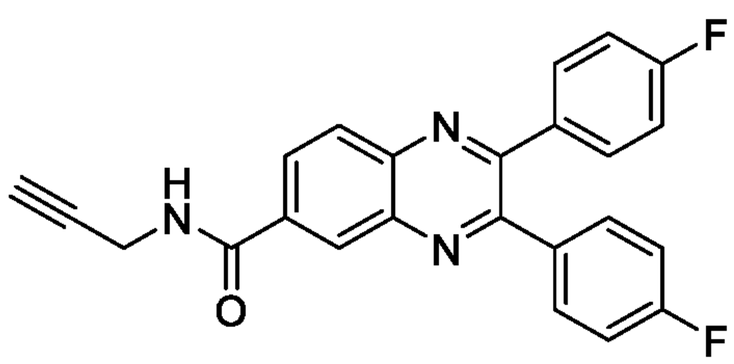
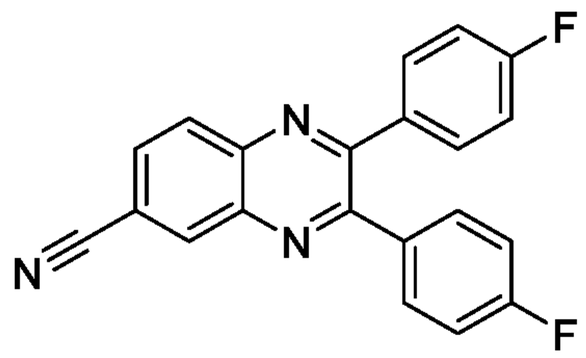
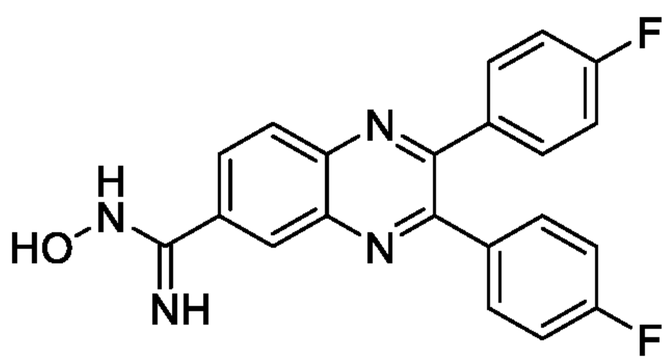
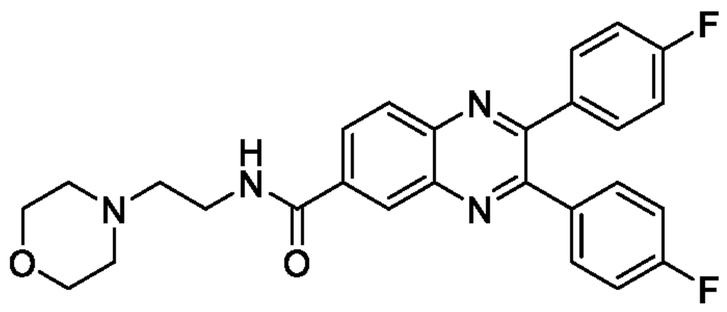
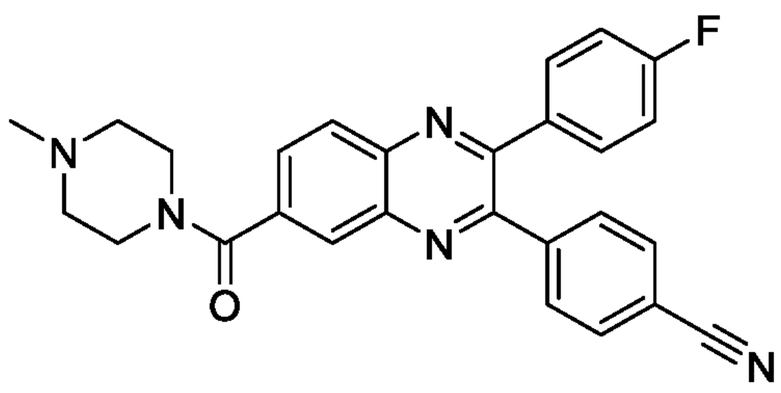
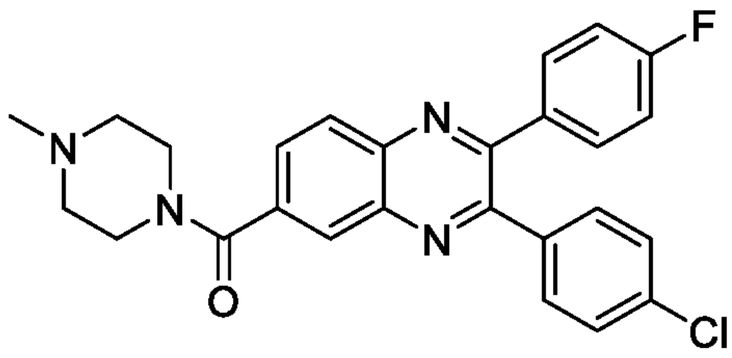
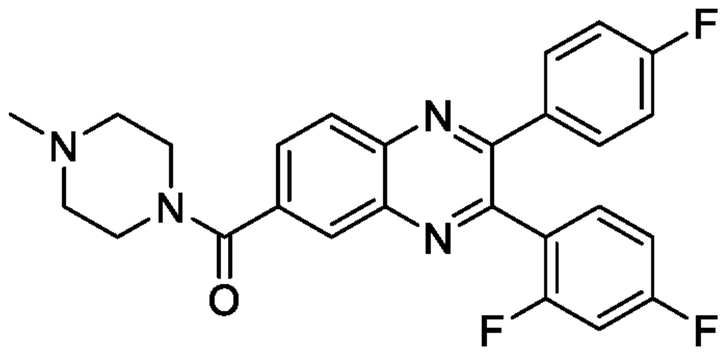
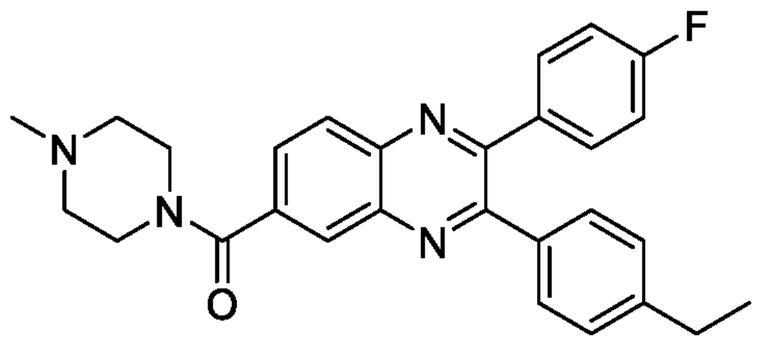
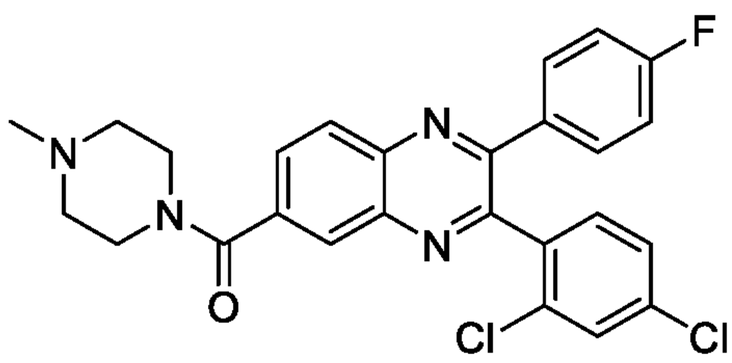
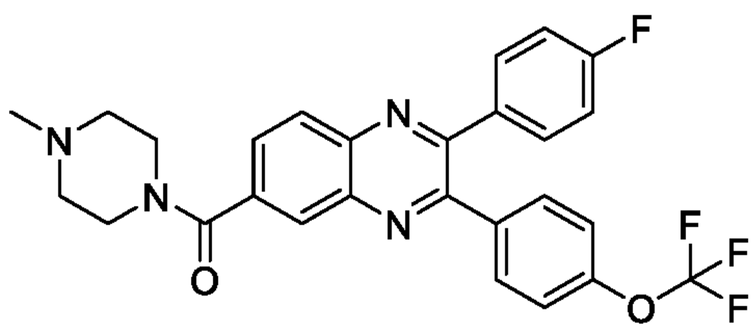
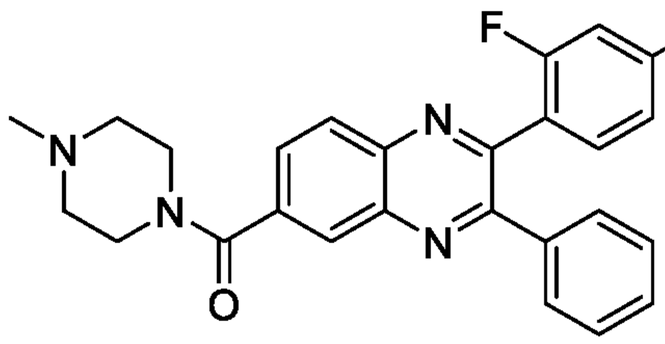
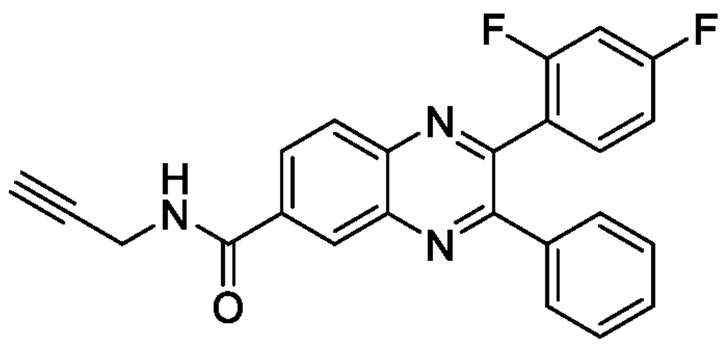
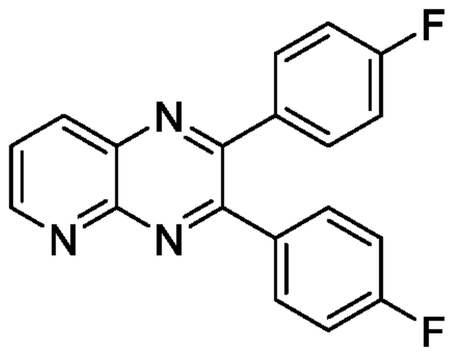
BC18487		++++
BC18488		++

Table 4b

BC No.	ZE No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19118	ZE18-0085		++	+
BC19154	ZE18-0097		++++	+

BC19192	ZE18-0147		+++	+
BC19194	ZE18-0149		++++	+
BC19237	ZE18-0150		++++	+
BC19316	ZE18-0198		+++	+
BC19317	ZE18-0199		++++	+
BC19318	ZE18-0200		++++	+

BC19319	ZE18-0204		++	+
BC19398	ZE18-0203		+++	+
BC19399	ZE18-0205		+	+
BC19405	ZE18-0216		+++	+
BC19406	ZE18-0217		+++	+
BC19403	ZE18-0214		+++	+

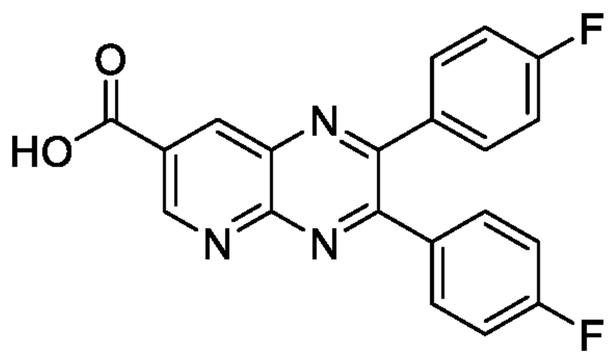
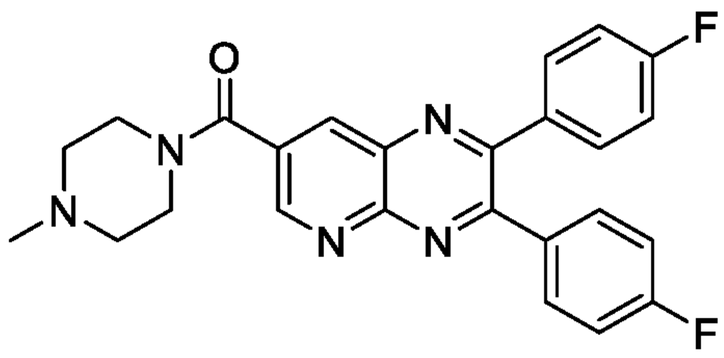
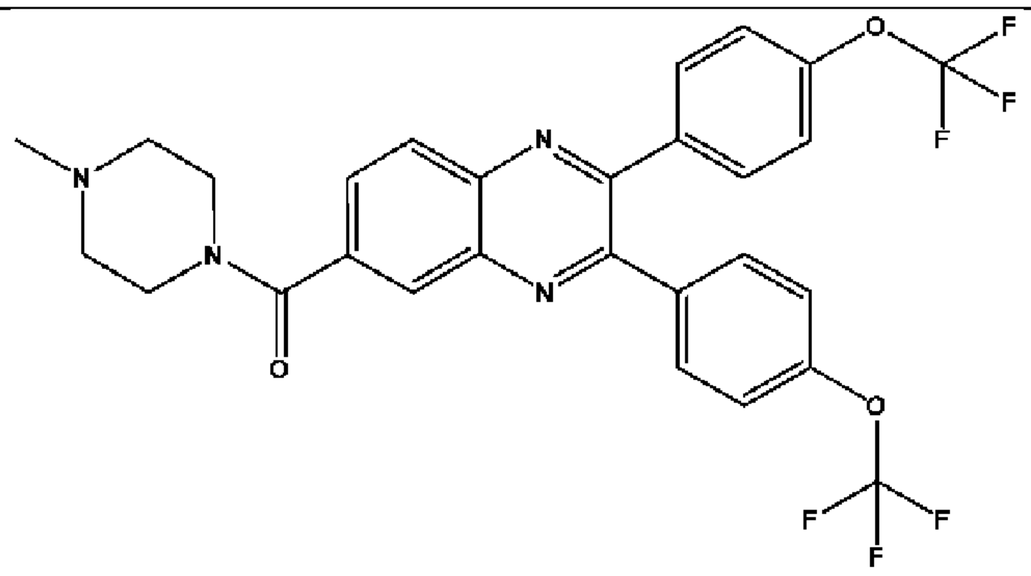
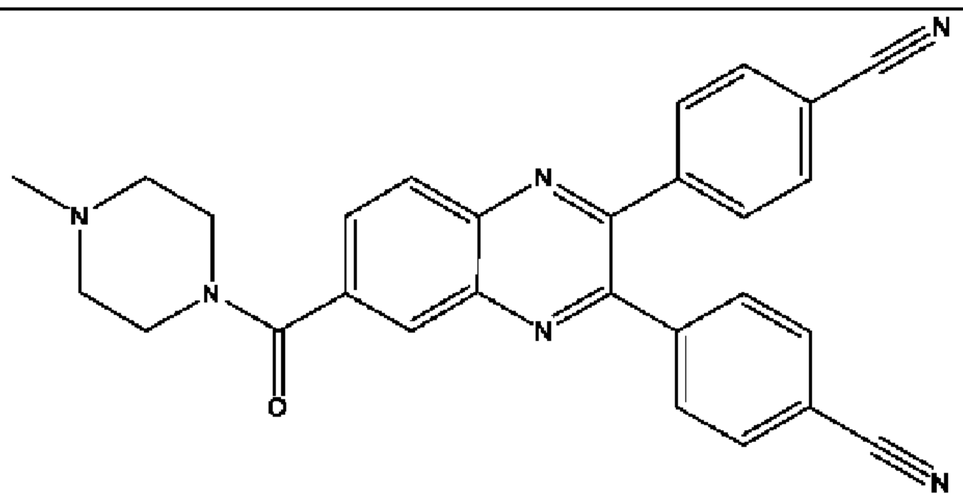
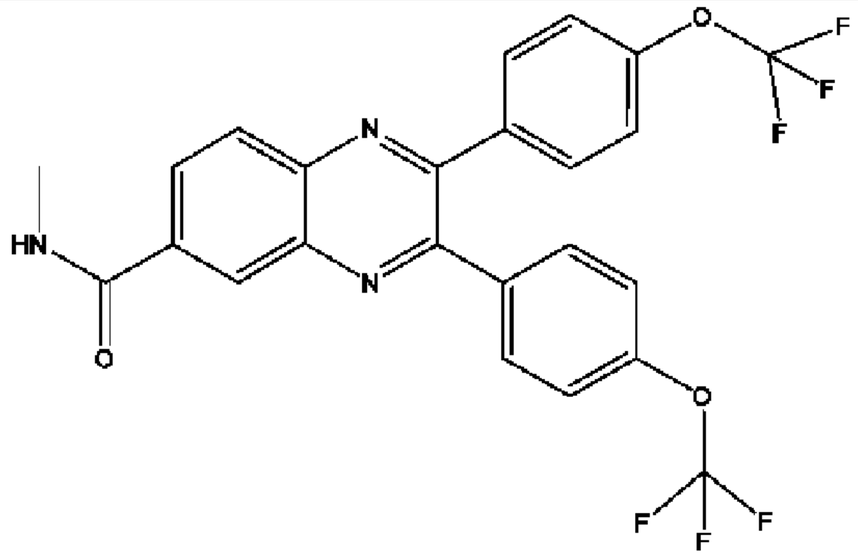
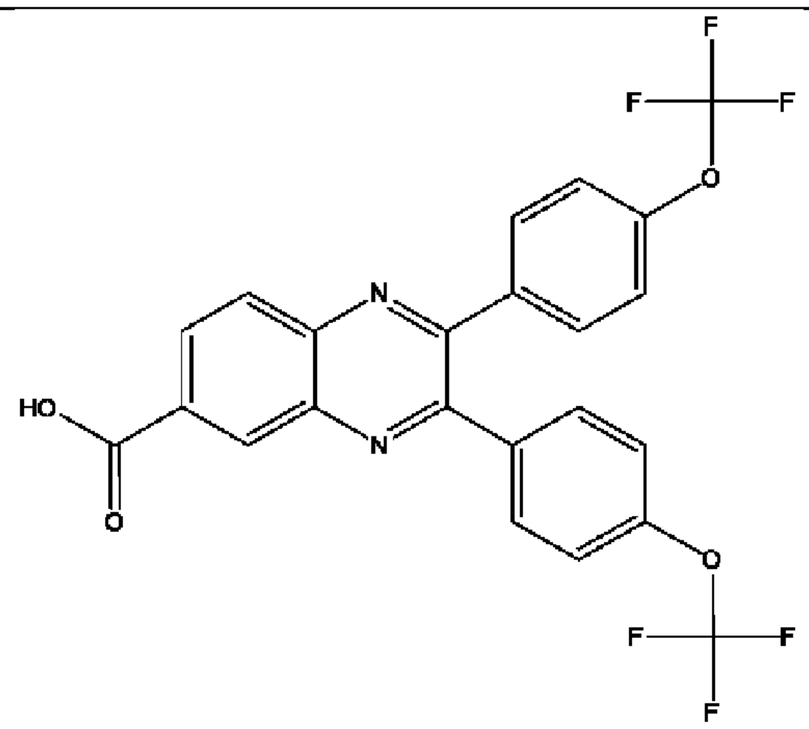
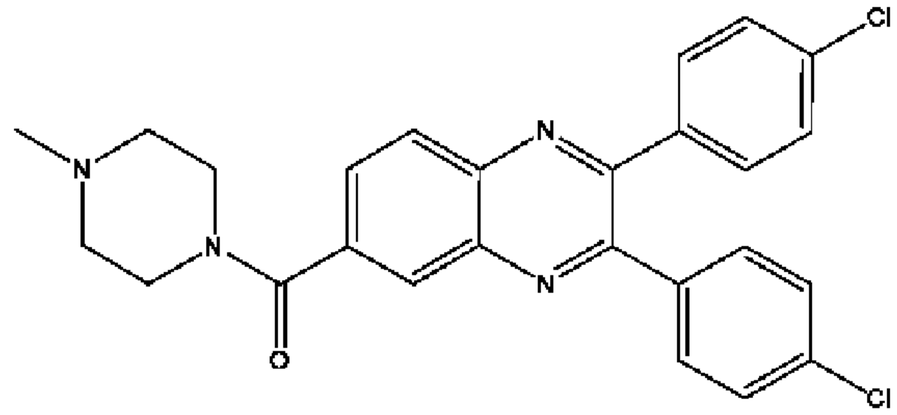
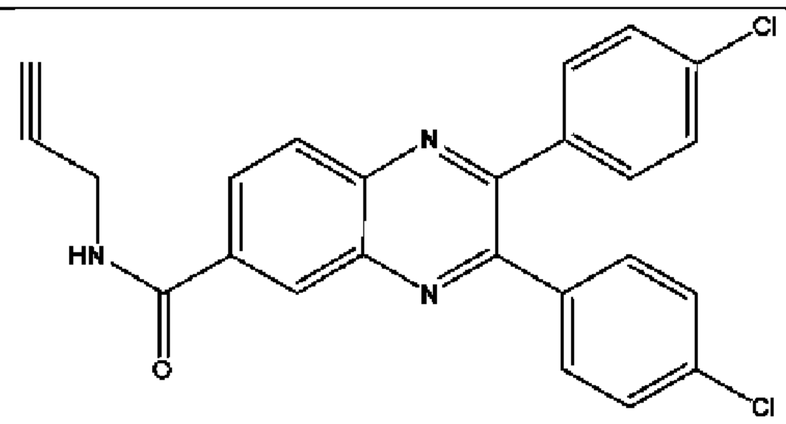
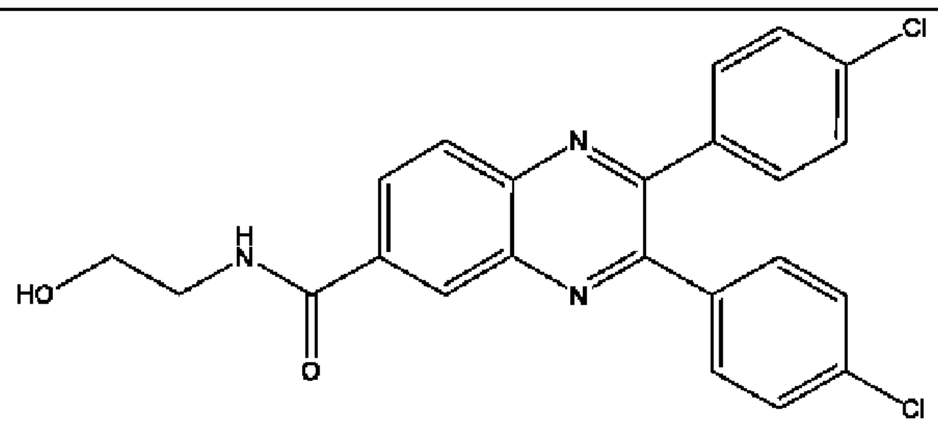
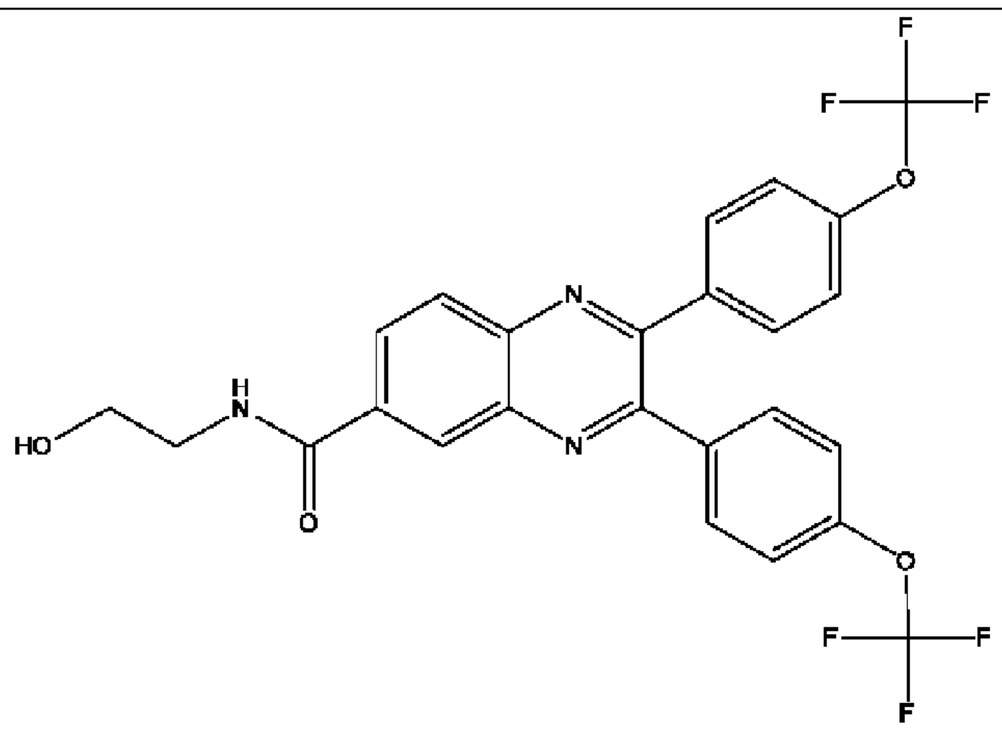
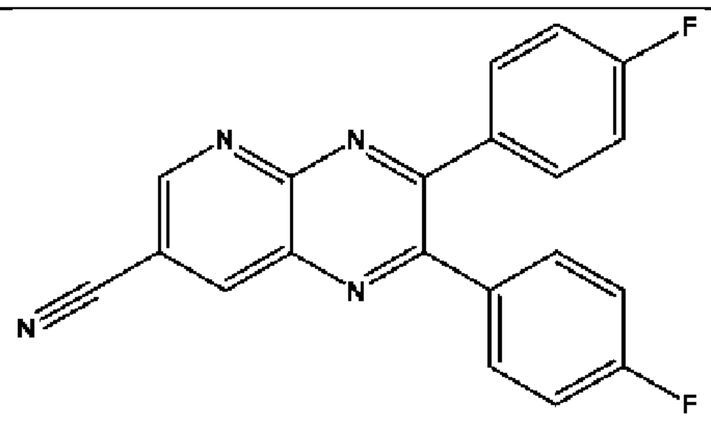
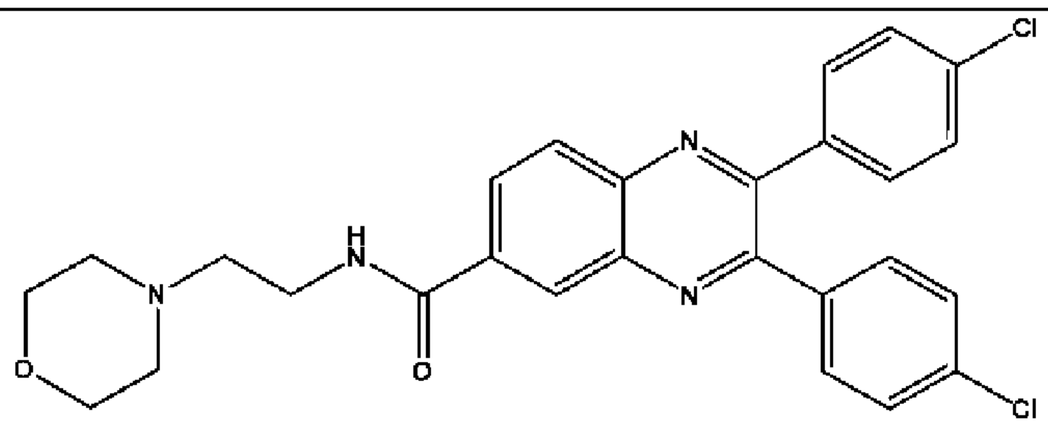
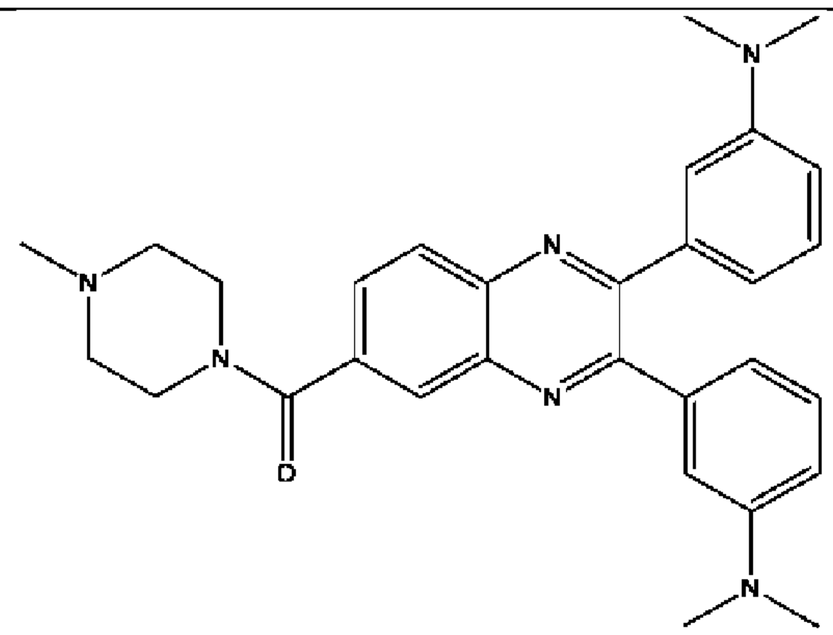
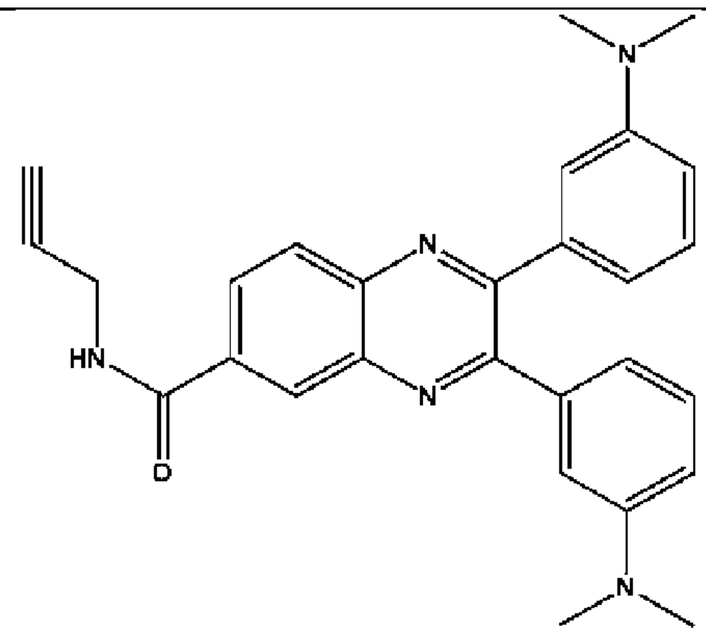
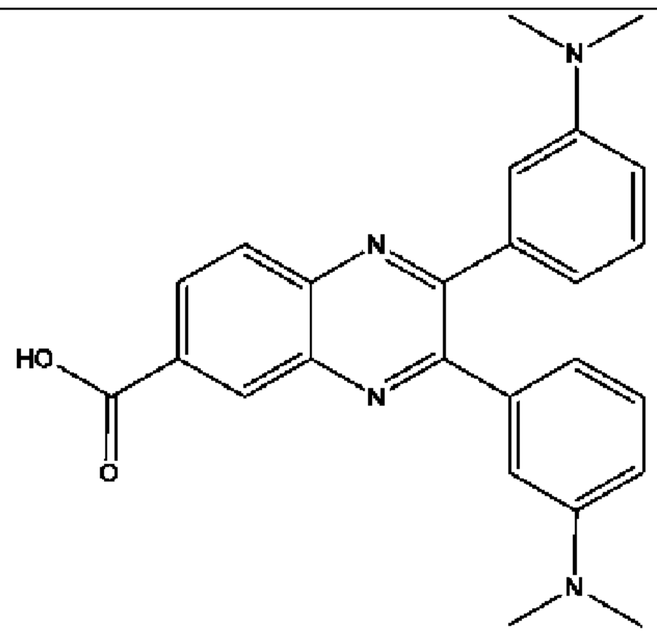
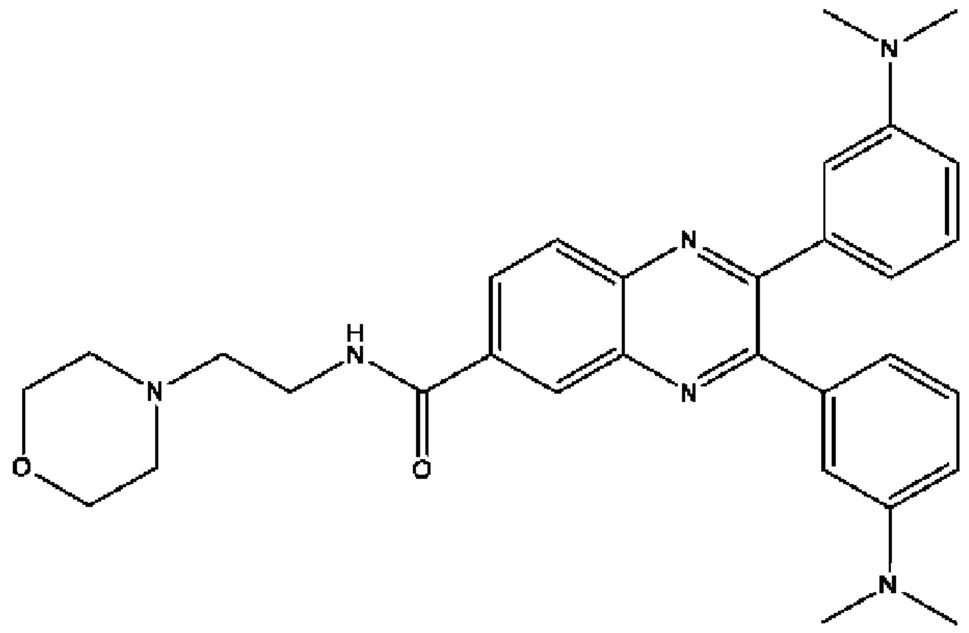
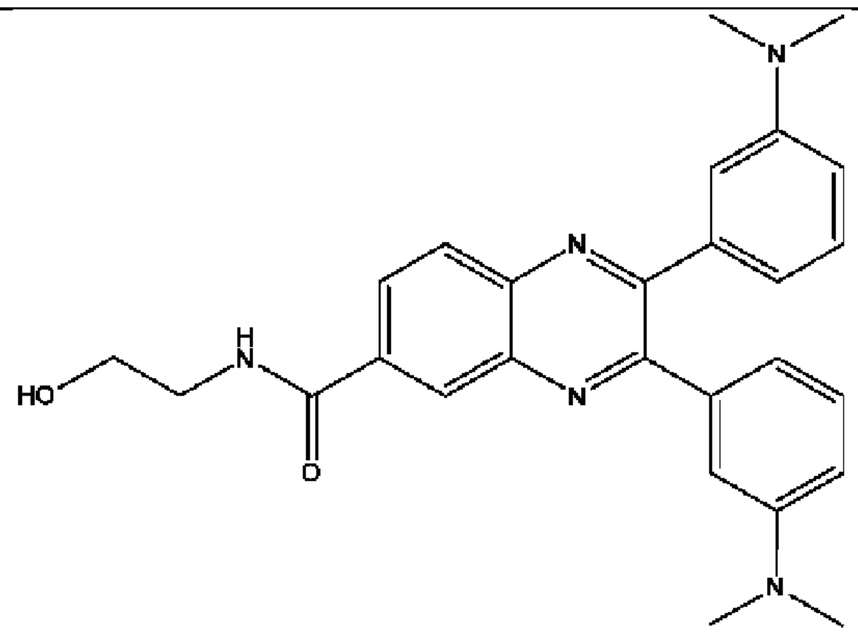
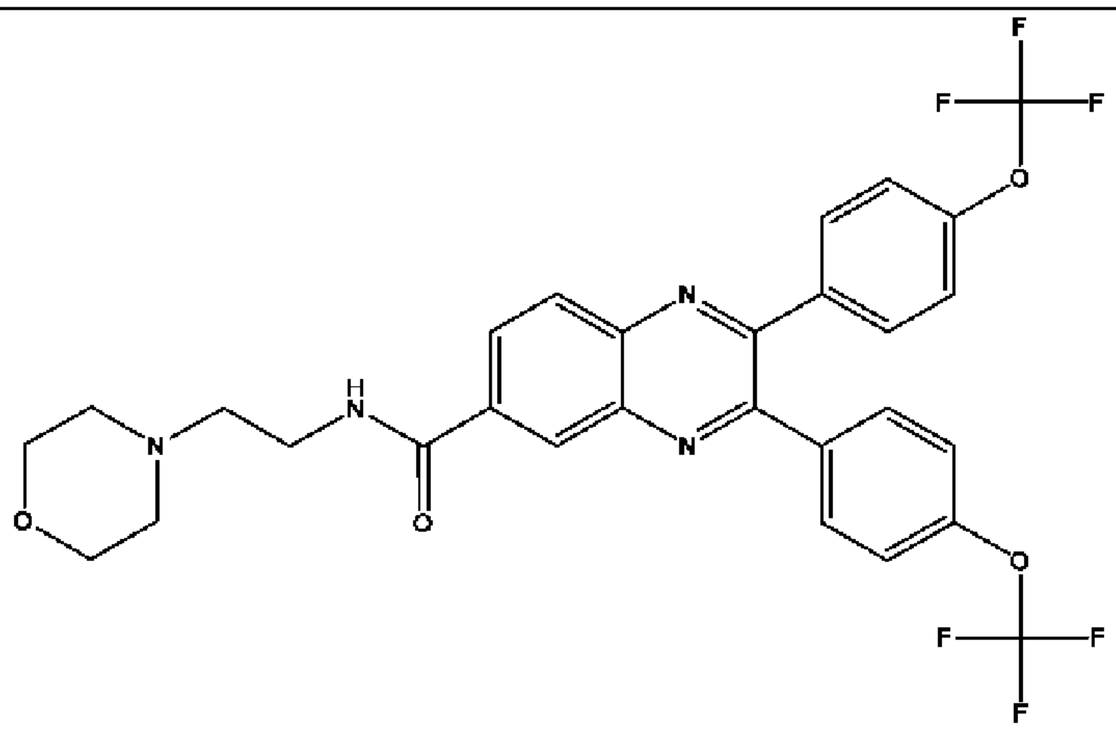
BC19407	ZE18-0224		+++	+
BC19408	ZE18-0225		+++	+

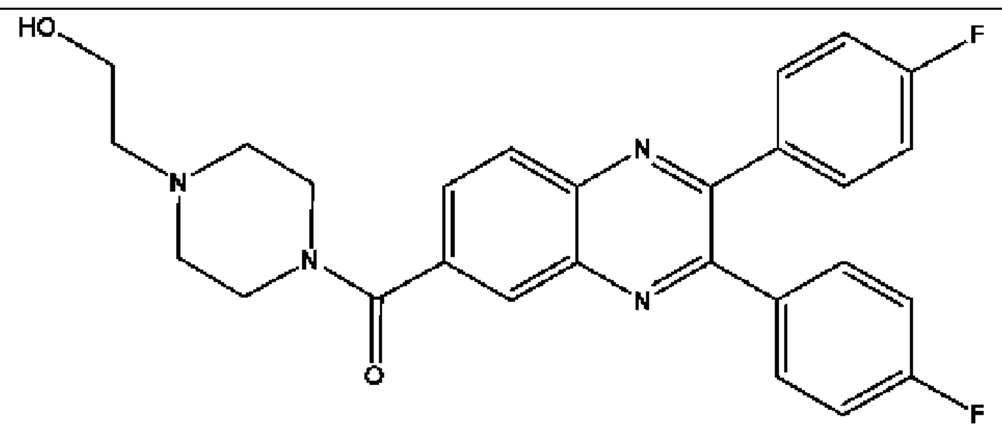
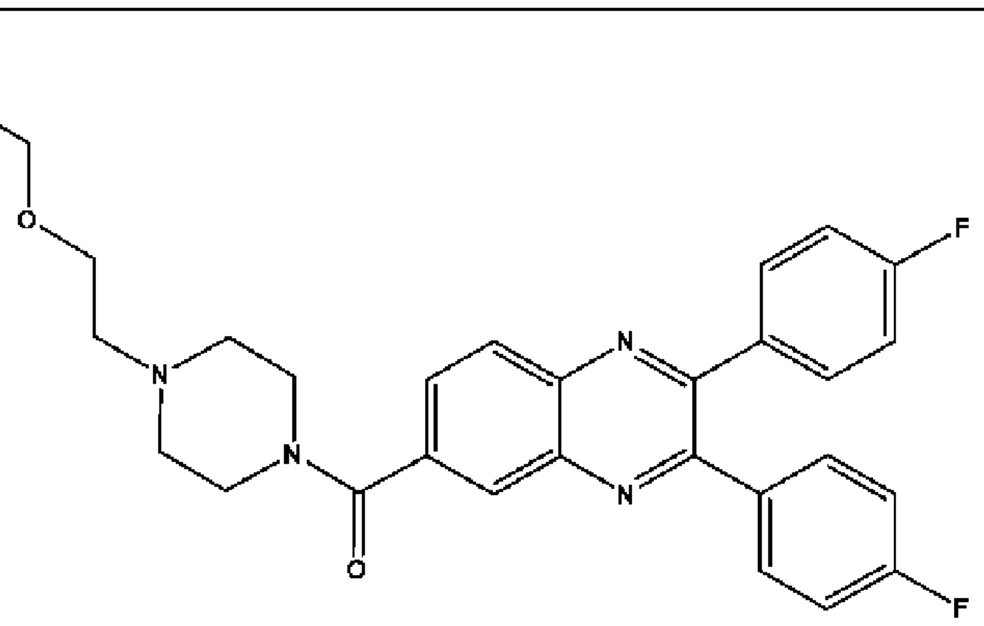
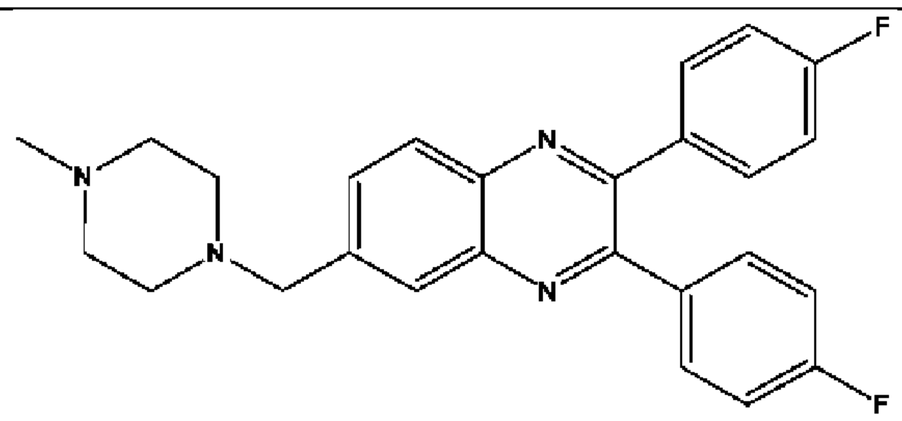
Table 4b-2

BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19445		+	+
BC19446		+	+

BC19447		+	+
BC19449		+	+
BC19450		++	+
BC19451		+++	+
BC19452		+++	+

BC19453		+	+
BC19495		+++	+
BC19497		++++	+
BC19498		+	+
BC19499		++	+

BC19500		+	+
BC19501		+	+
BC19502		+	+
BC19503		++	++

BC19513		++++	+
BC19514		+++	++
BC19577		+++	+
BC19578		+	+
BC19512		+++	+

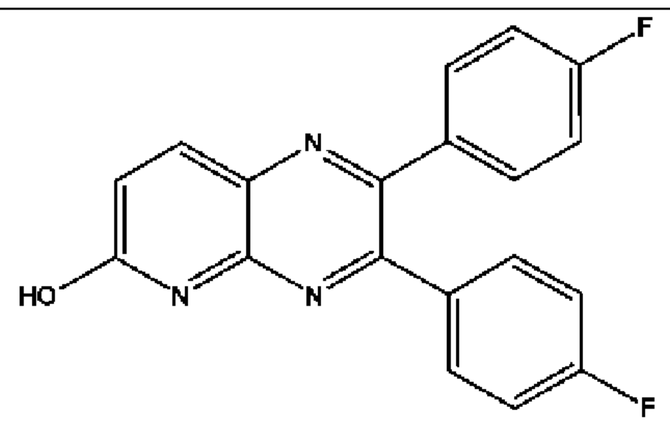
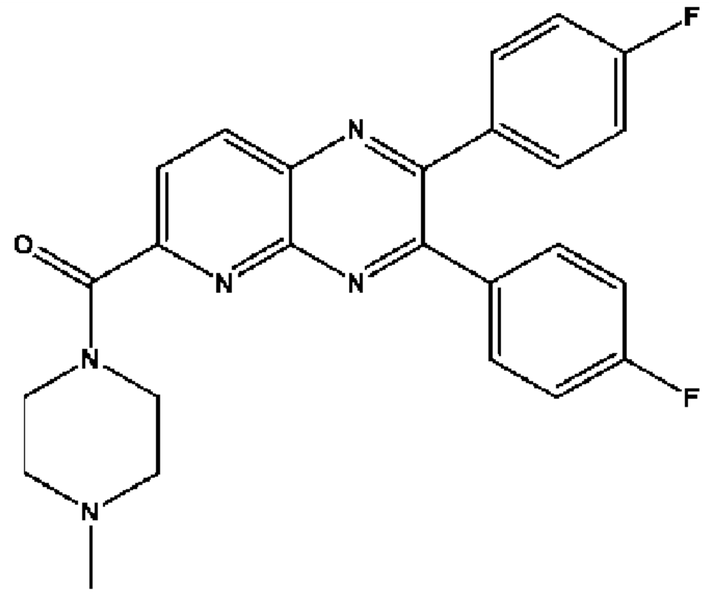
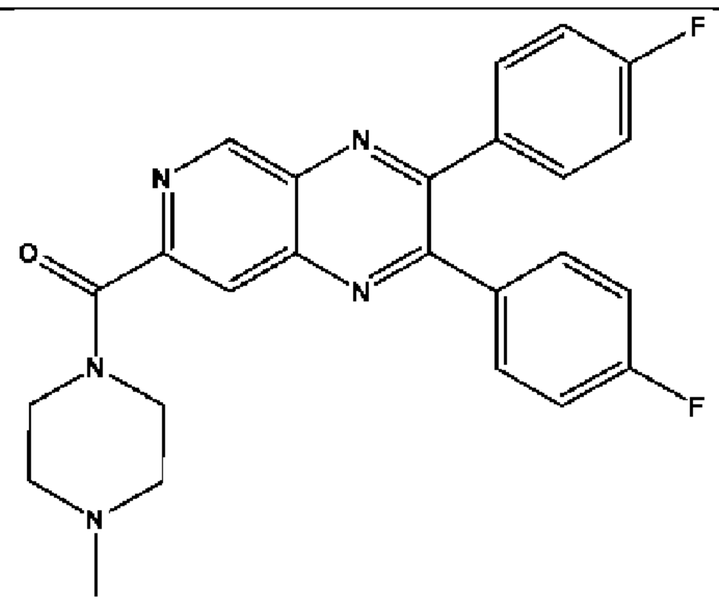
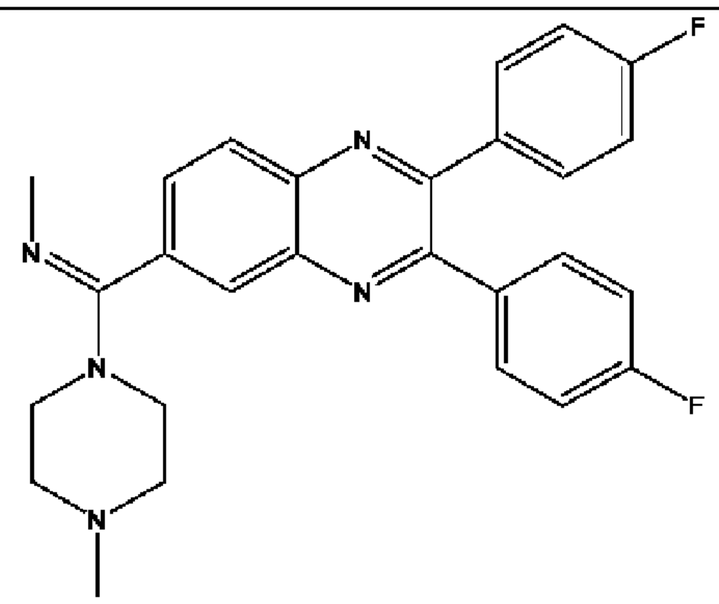
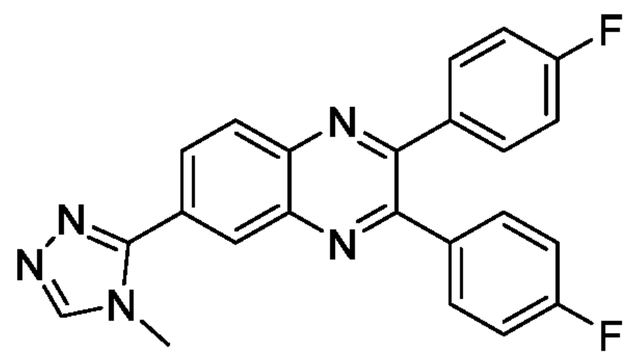
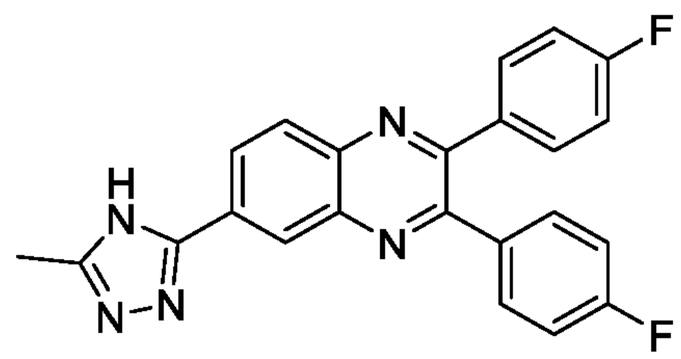
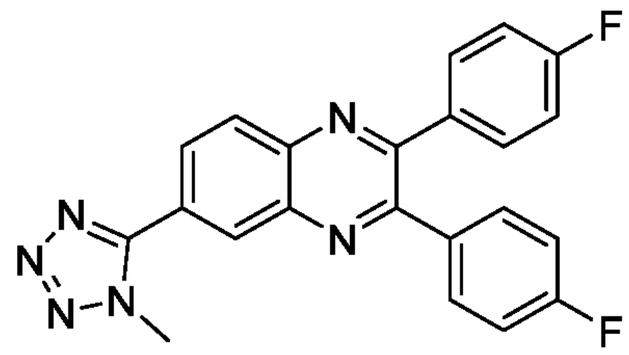
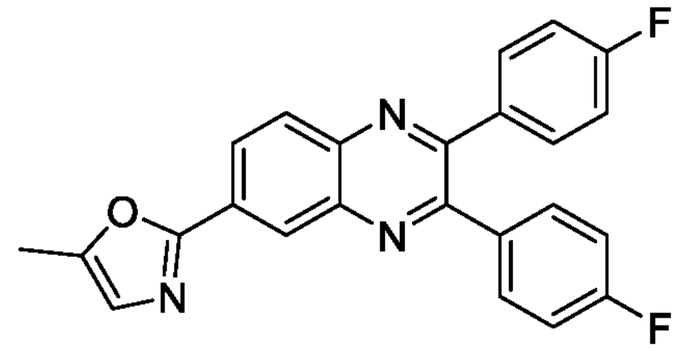
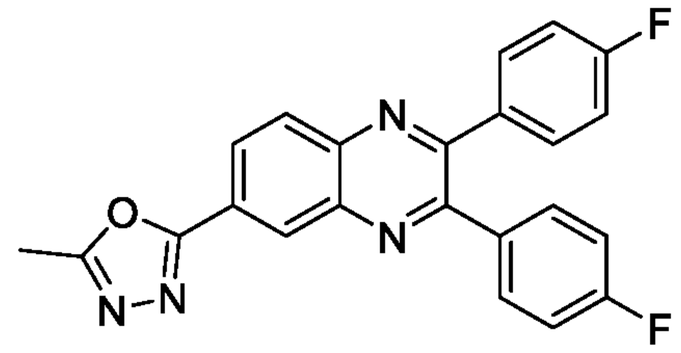
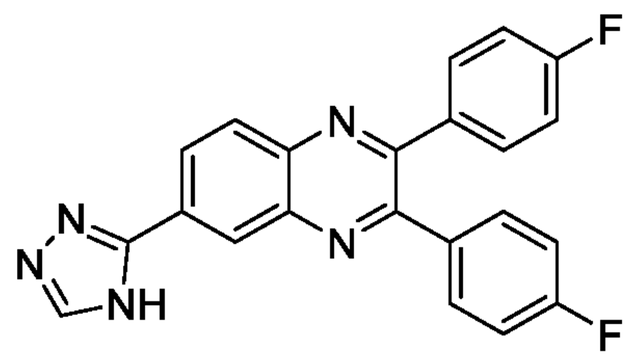
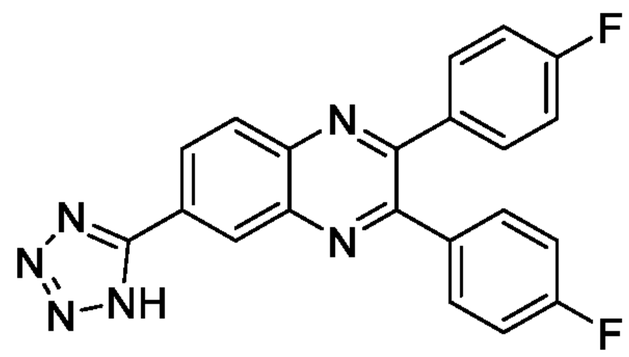
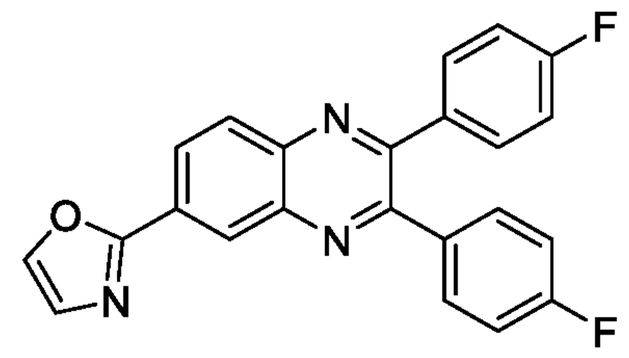
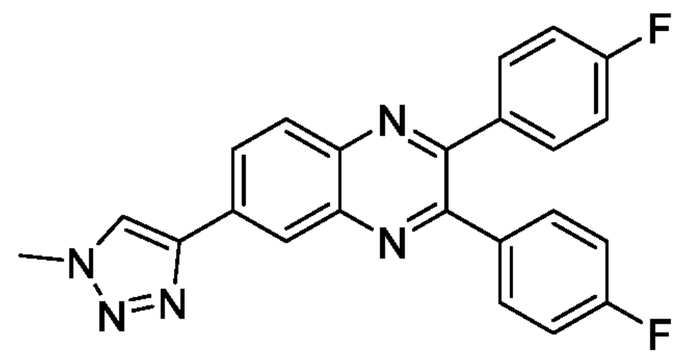
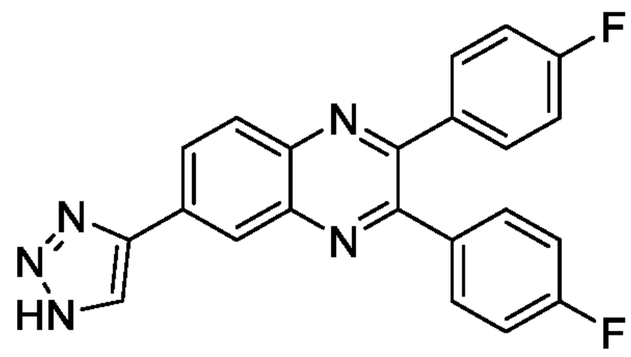
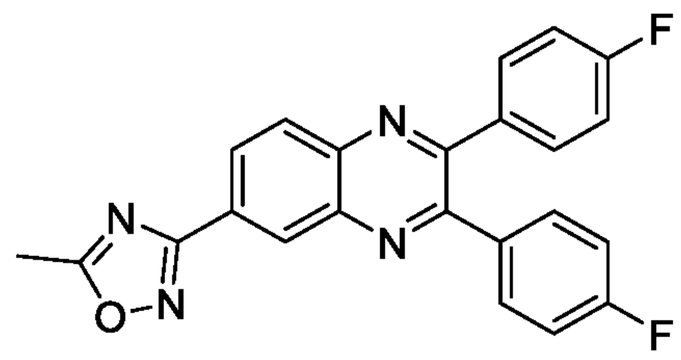
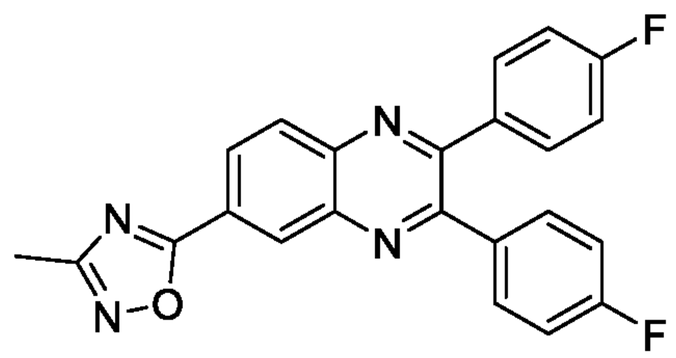
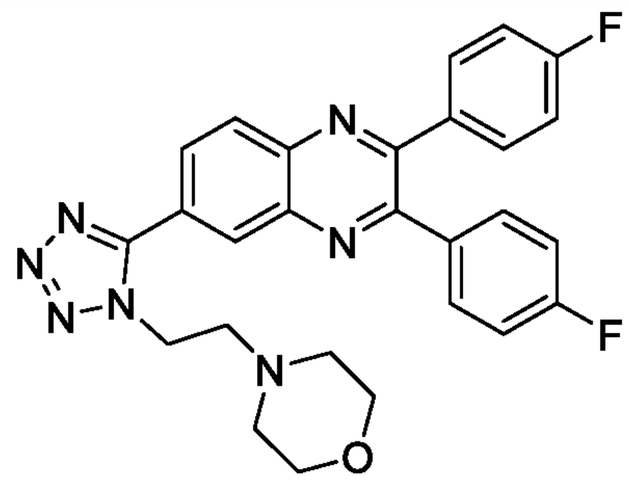
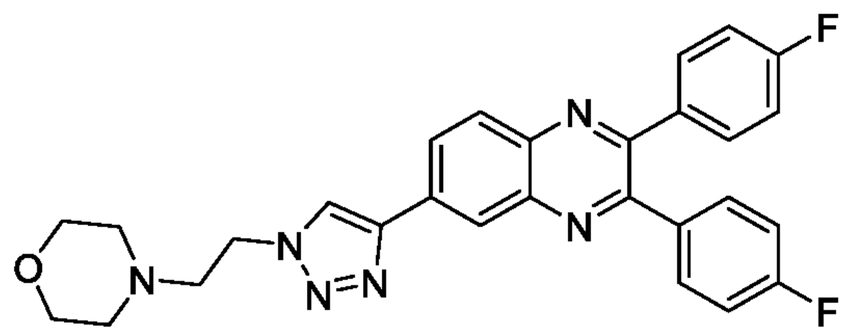
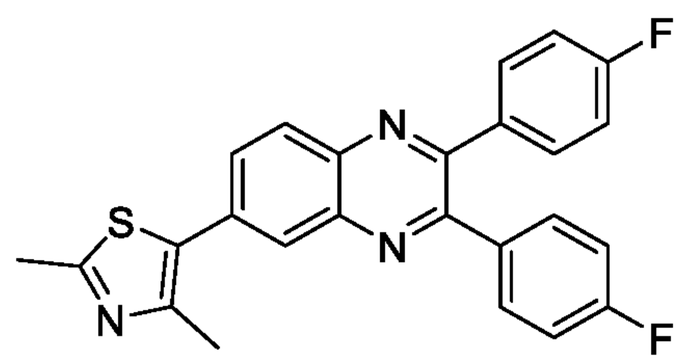
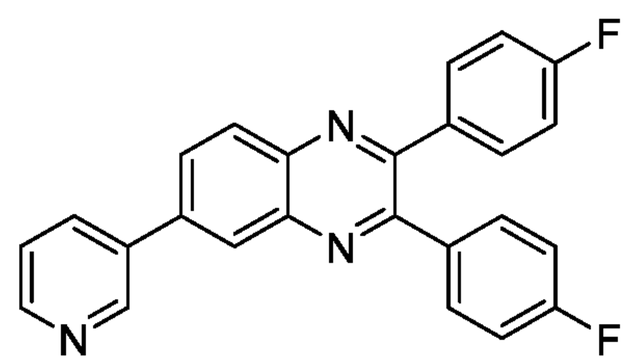
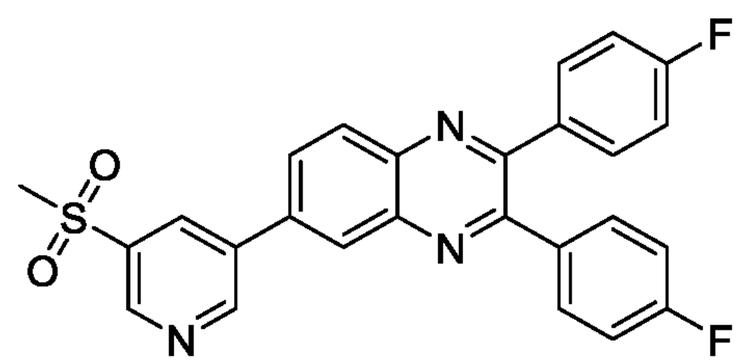
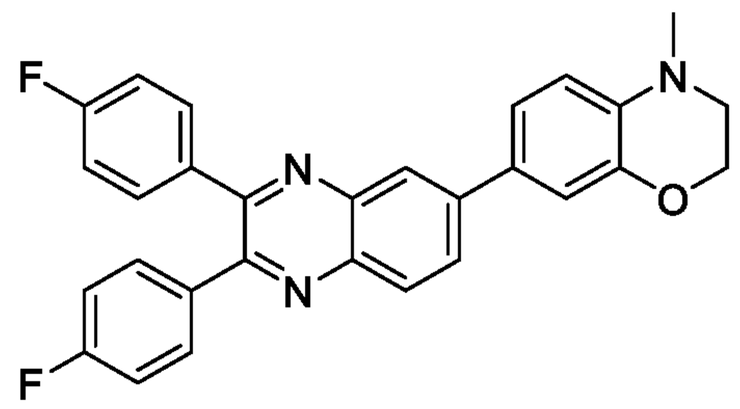
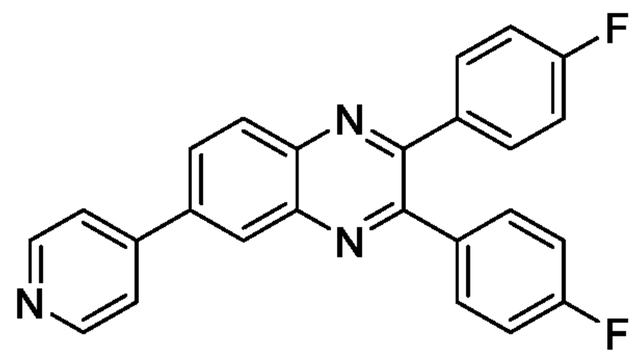
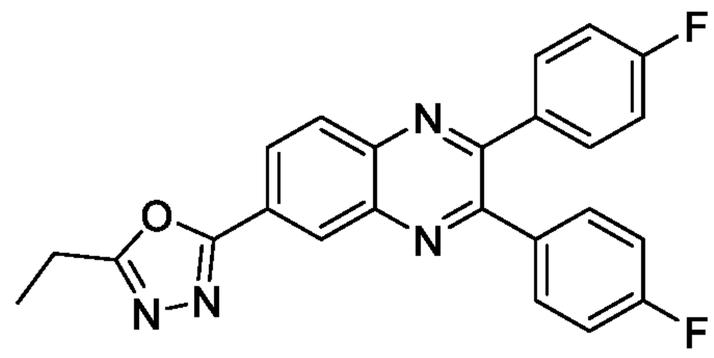
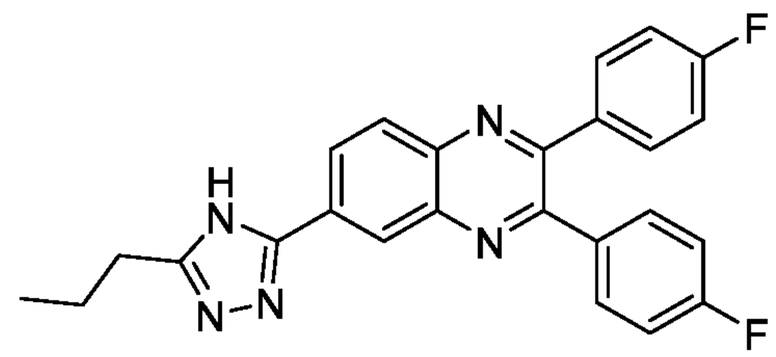
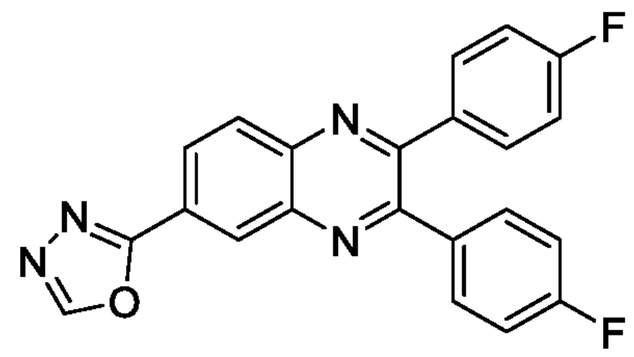
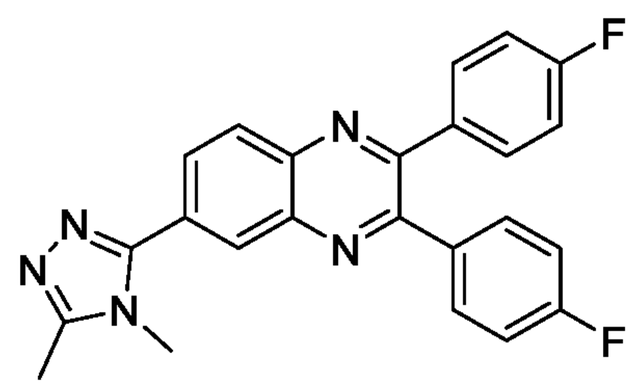
BC19448		+++	+
BC19618		+++	+
BC19666		+++	+
BC19668		+++	+

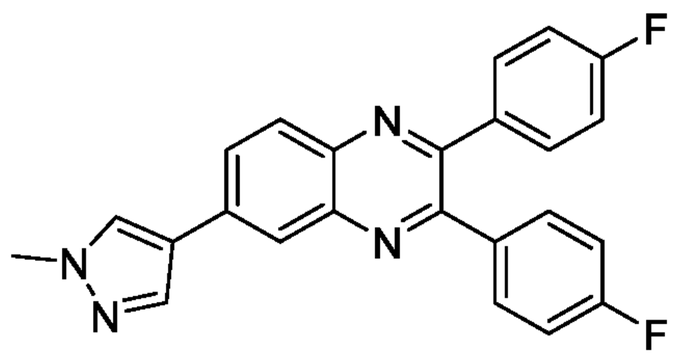
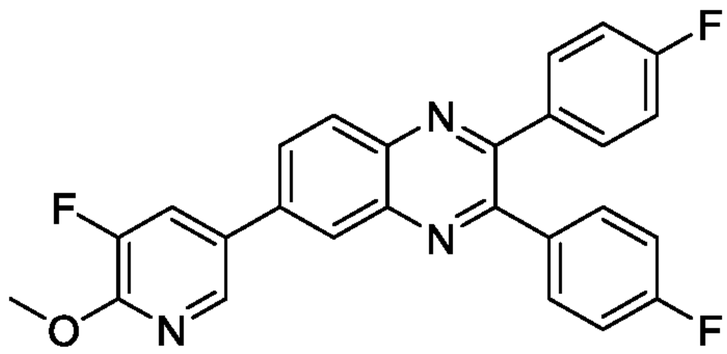
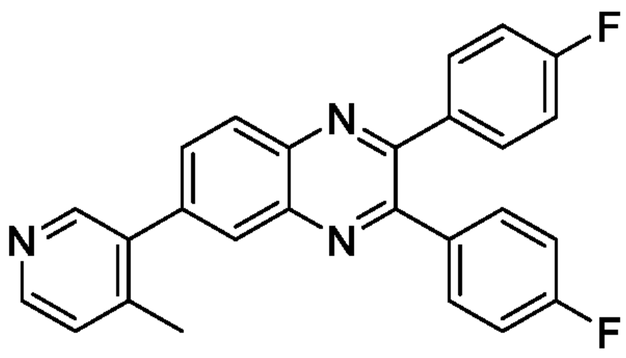
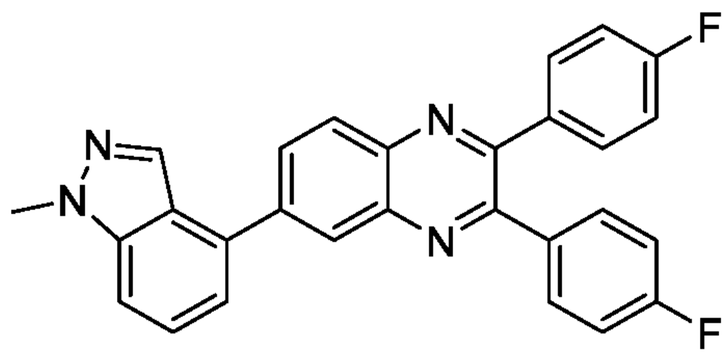
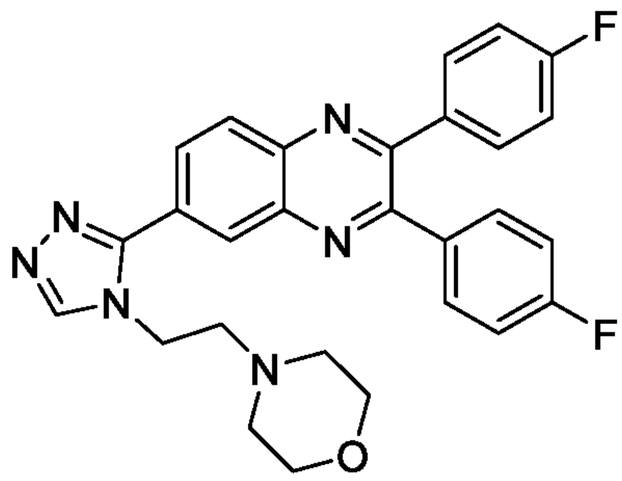
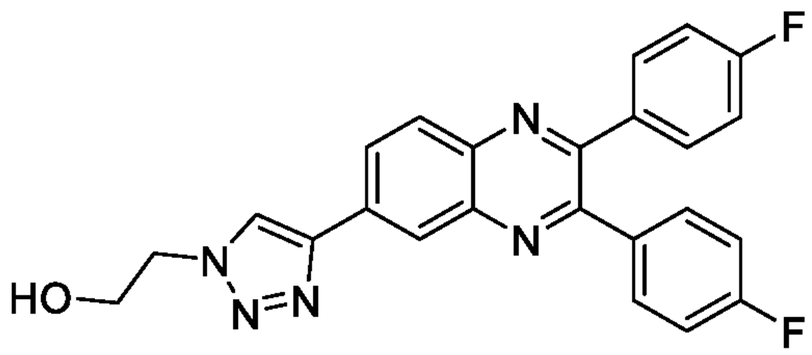
Table 4c

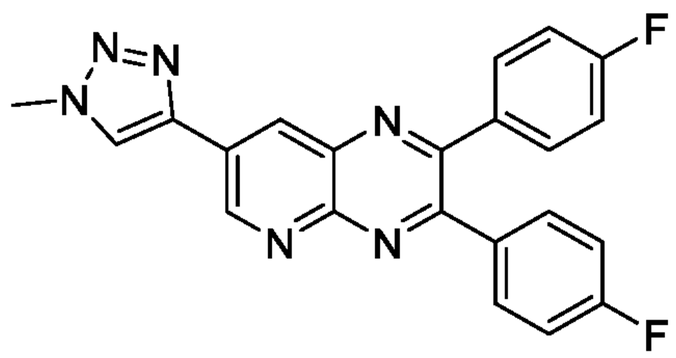
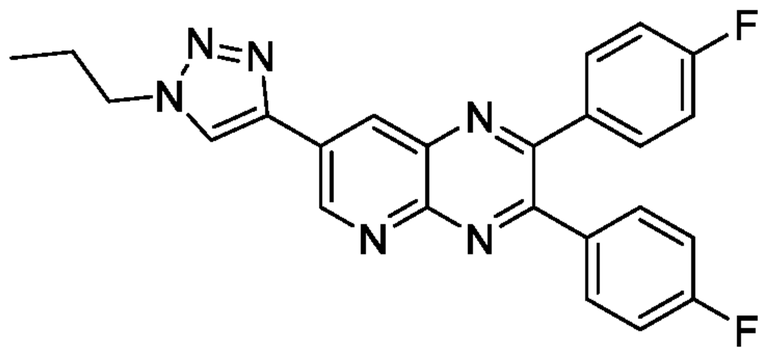
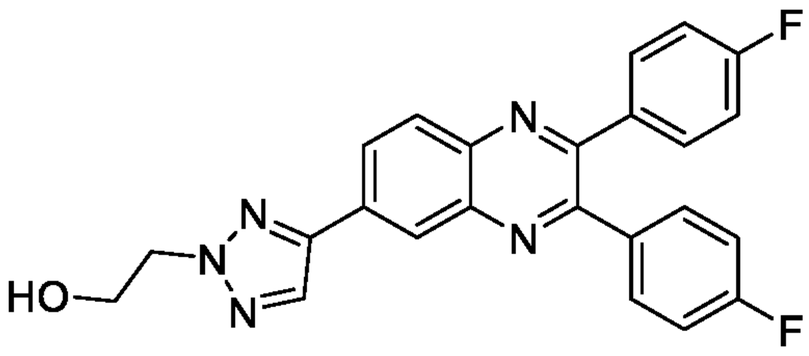
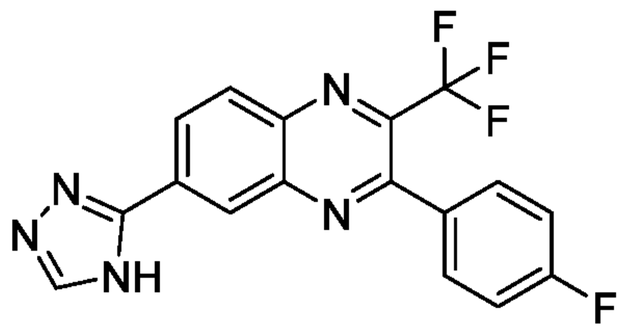
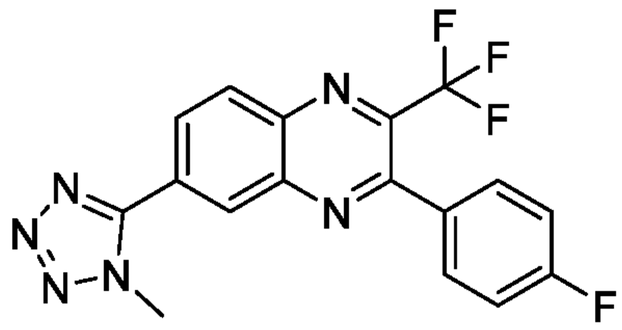
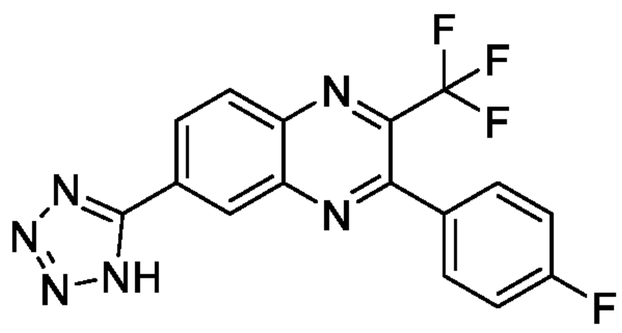
BC No.	ZE No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19101	ZE18-0001		++++	+
BC19102	ZE18-0006		+++	+
BC19139	ZE18-0003		++++	+
BC19140	ZE18-0004		++	+
BC19141	ZE18-0005		+++	+

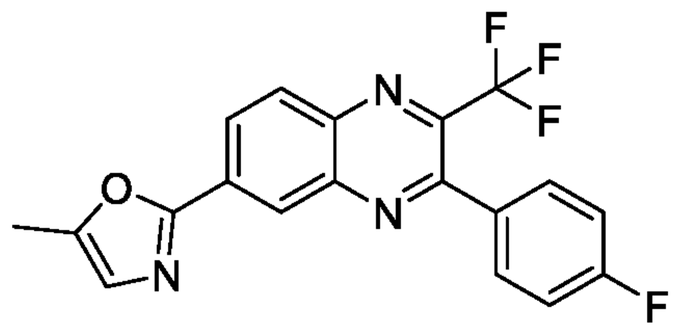
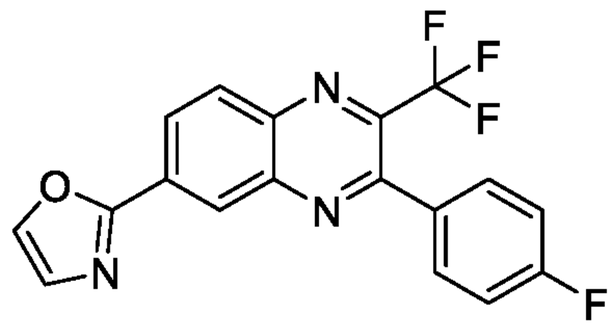
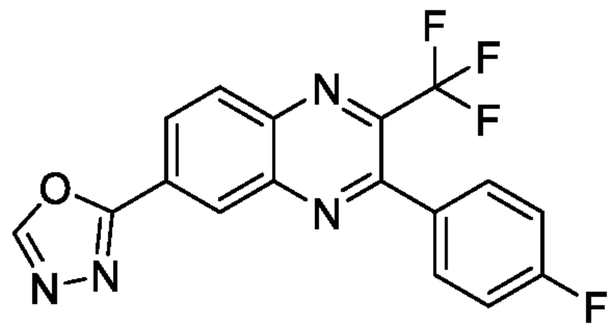
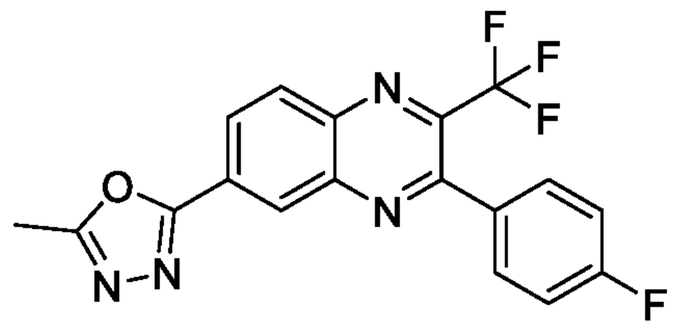
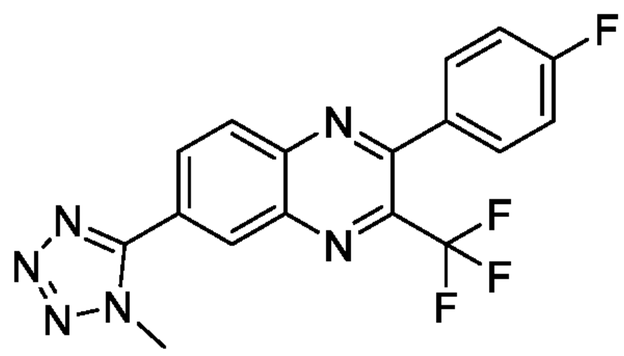
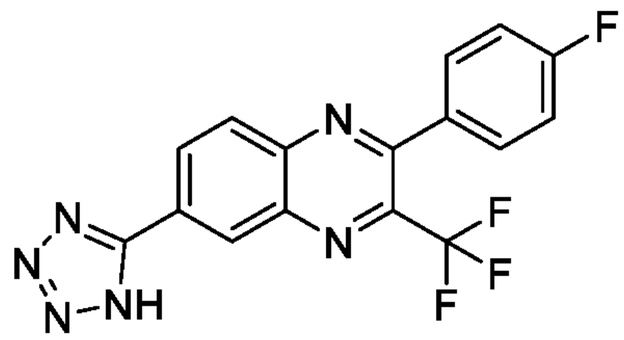
BC19143	ZE18-0031		+++	+
BC19144	ZE18-0033		++	+
BC19145	ZE18-0046		++	+
BC19148	ZE18-0002		++++	+
BC19150	ZE18-0032		+++	++
BC19190	ZE18-0119		+++	+

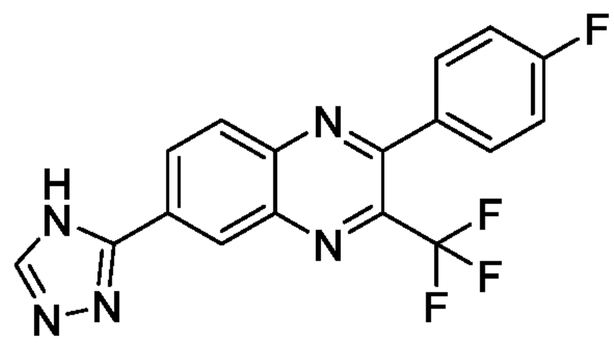
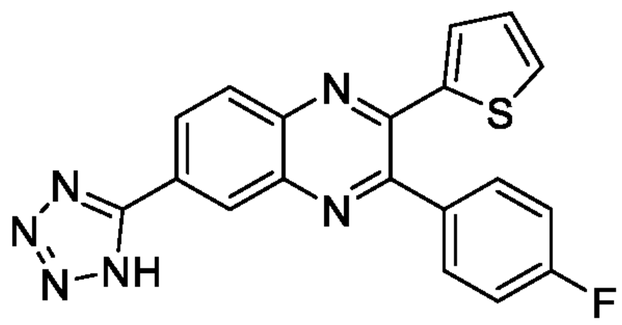
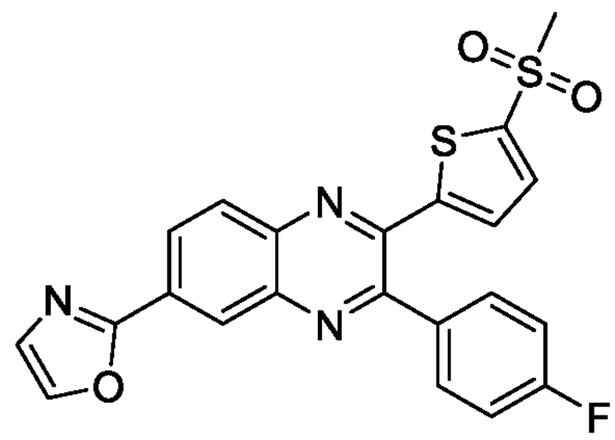
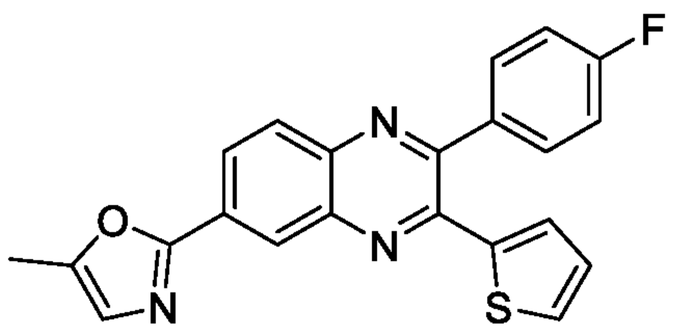
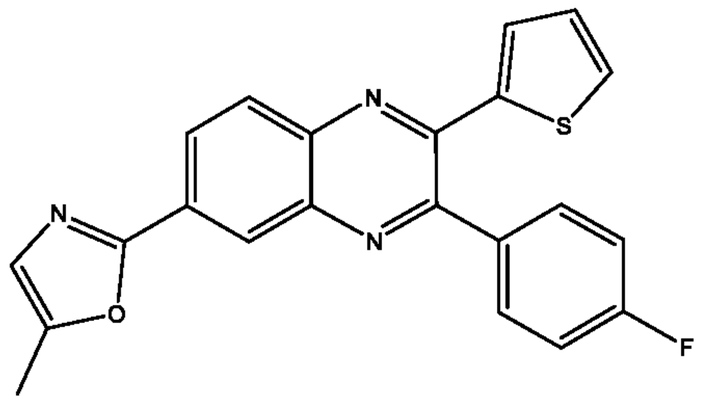
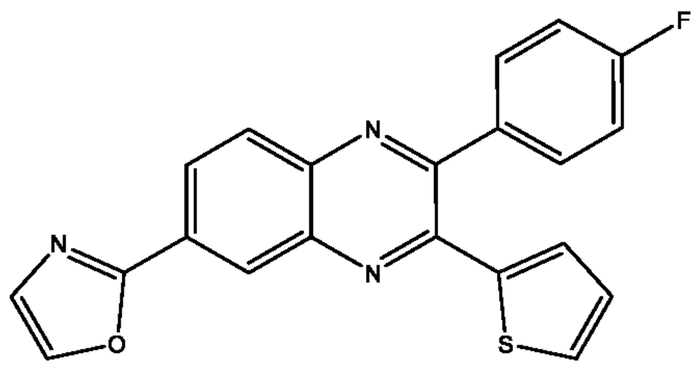
BC19193	ZE18-0148		+++	+
BC19238	ZE18-0151		++++	+
BC19240	ZE18-0156		++++	+
BC19241	ZE18-0157		++	+
BC19242	ZE18-0163		+++	+
BC19243	ZE18-0165		+++	+

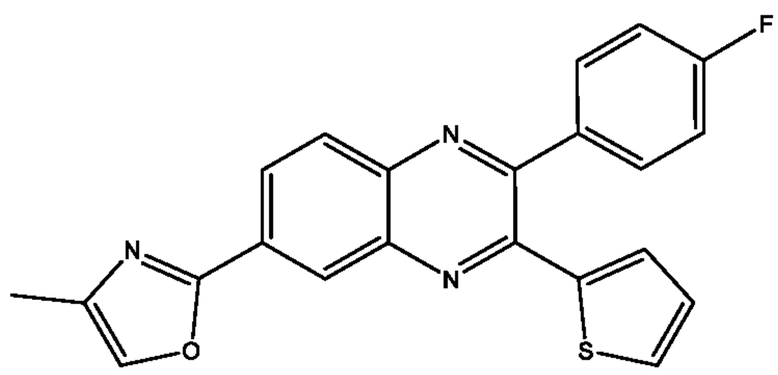
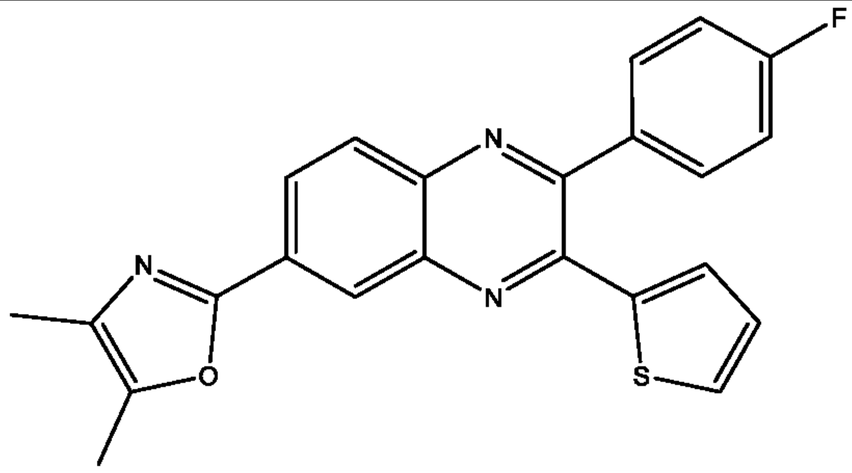
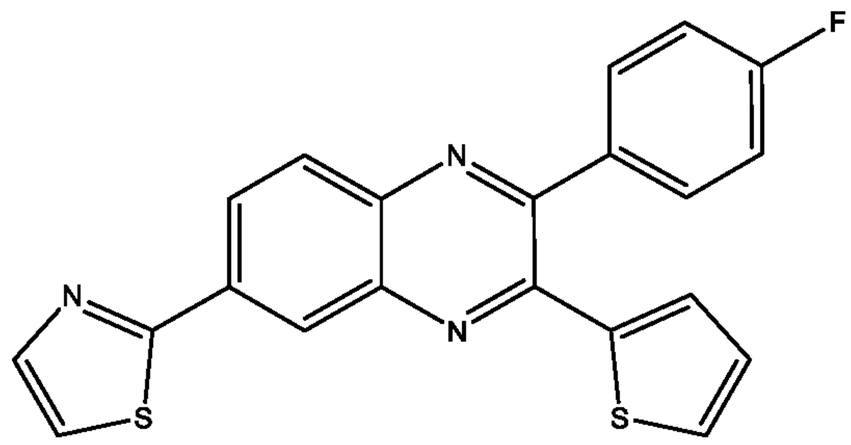
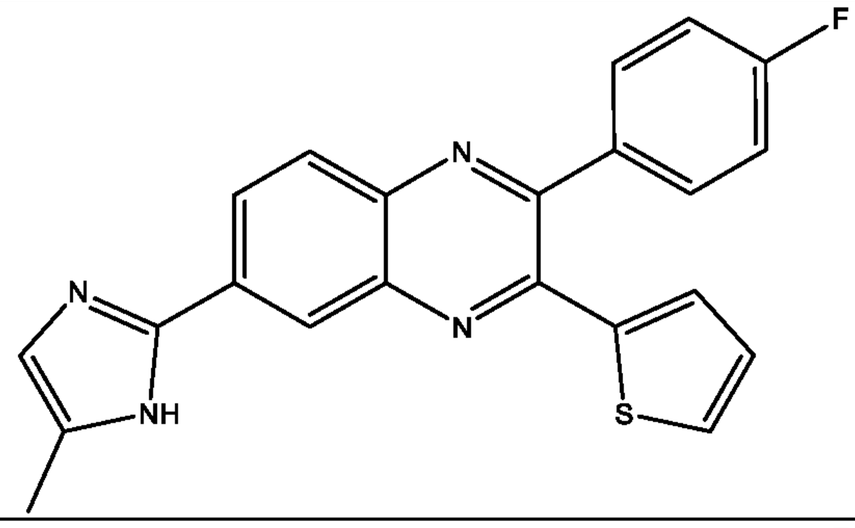
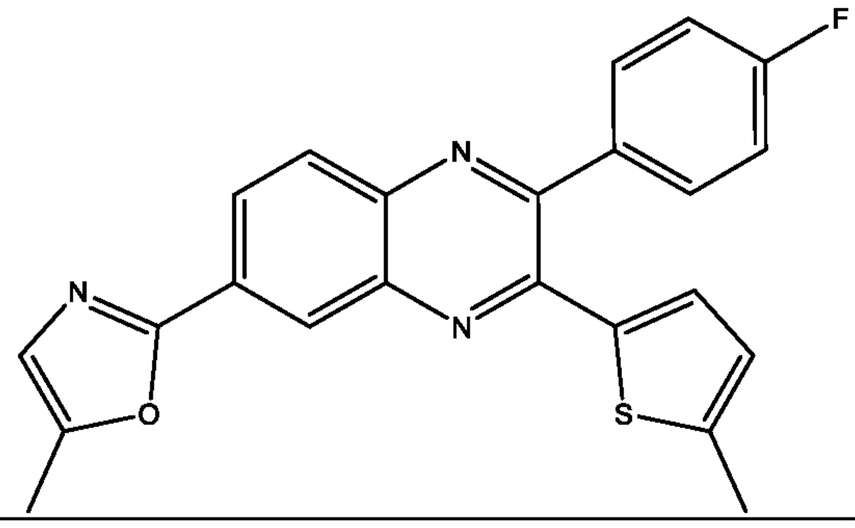
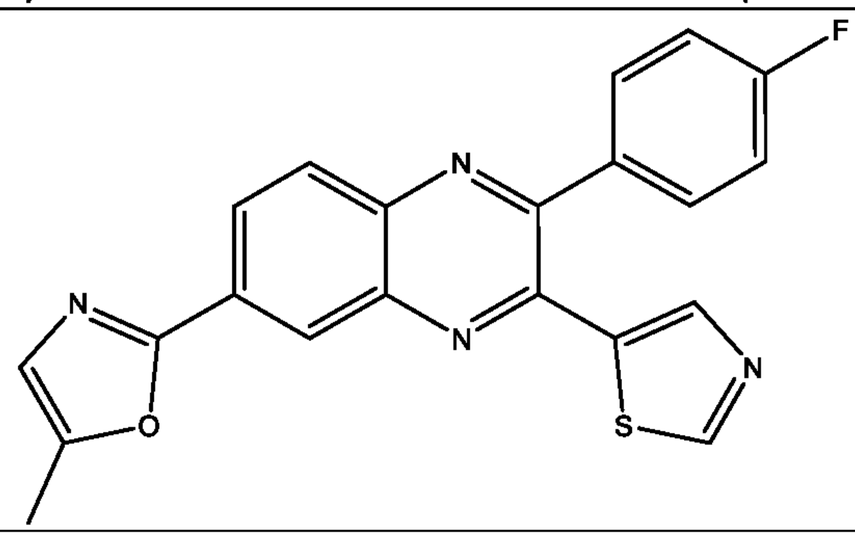
BC19244	ZE18-0169		+	+
BC19245	ZE18-0171		++	+
BC19246	ZE18-0177		++	+
BC19247	ZE18-0178		++	+
BC19250	ZE18-0182		++++	+
BC19301	ZE18-0155		++++	+

BC19302	ZE18-0162		++	+
BC19303	ZE18-0164		+	+
BC19304	ZE18-0167		++	+
BC19305	ZE18-0170		+	+
BC19306	ZE18-0180		+++	+
BC19396	ZE18-0188		++++	+

BC19401	ZE18-0212		++++	+
BC19402	ZE18-0213		++++	+
BC19404	ZE18-0215		++	+
BC19111	ZE18-0061		+	+
BC19112	ZE18-0062		+	+
BC19113	ZE18-0063		+	+

BC19114	ZE18-0064		+	+
BC19115	ZE18-0065		+	+
BC19116	ZE18-0067		+	+
BC19151	ZE18-0066		+	+
BC19152	ZE18-0079		+	+
BC19153	ZE18-0080		+	+

BC19159	ZE18-0144		+	+
BC19186	ZE18-0071		++	+
BC19248	ZE18-0179		+	+
BC19249	ZE18-0181		++	+
	ZE18-0075			
	ZE18-0591			

	ZE18-0592			
	ZE18-0593			
	ZE18-0594			
	ZE18-0595			
	ZE18-0596			
	ZE18-0597			

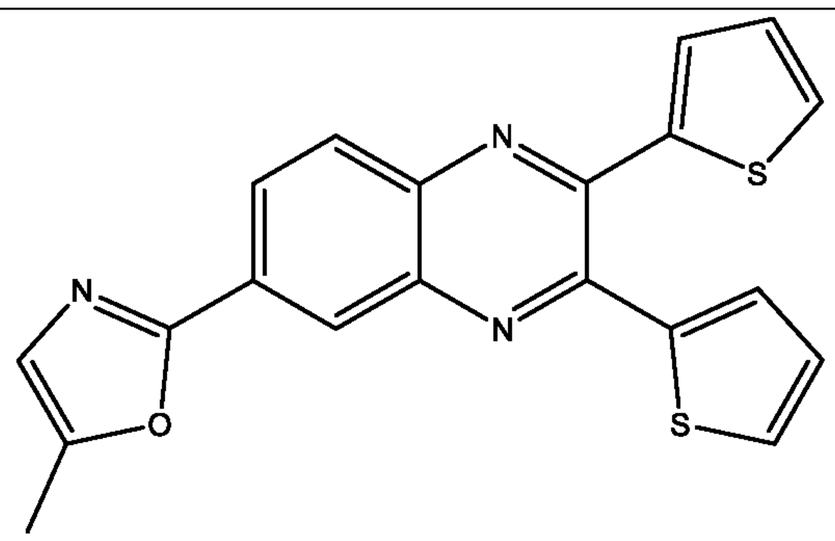
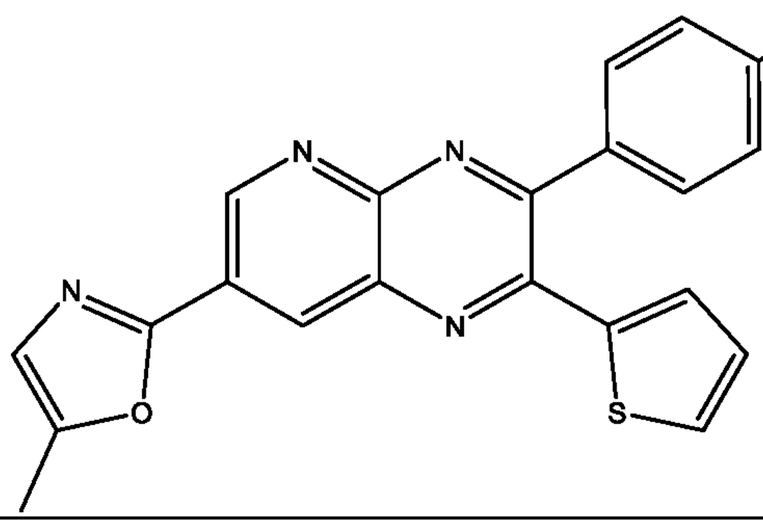
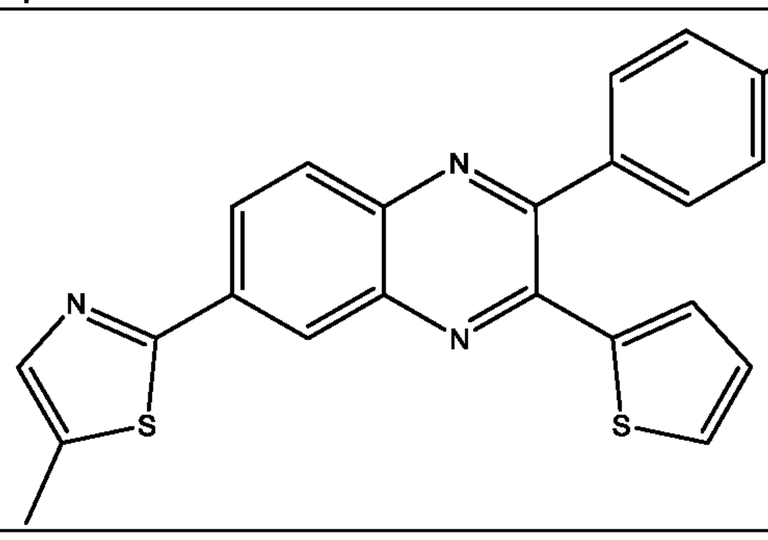
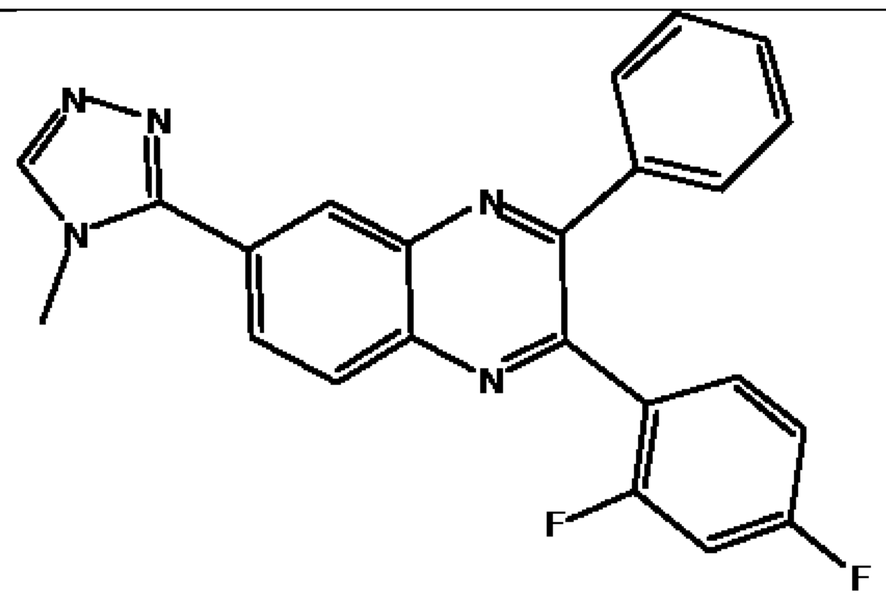
	ZE18-0598			
	ZE18-0600			
	ZE18-0601			

Table 4c-2

BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19444		+++	+

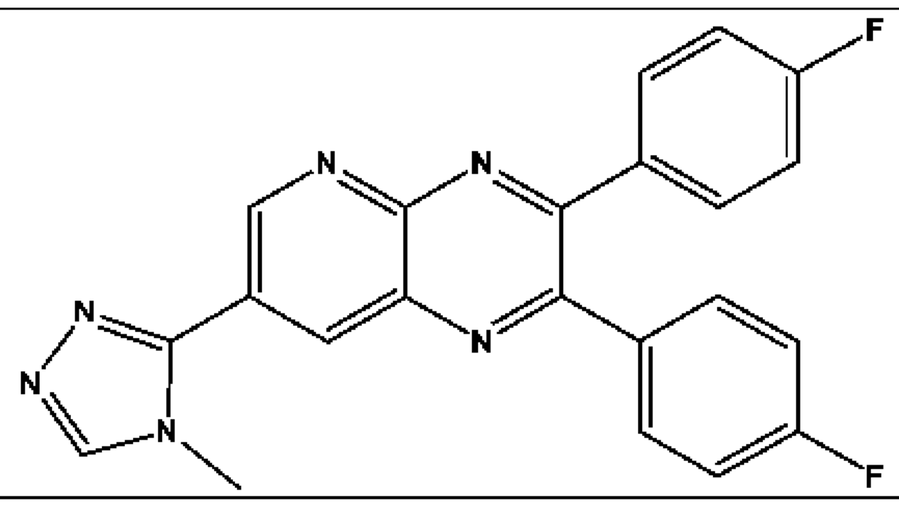
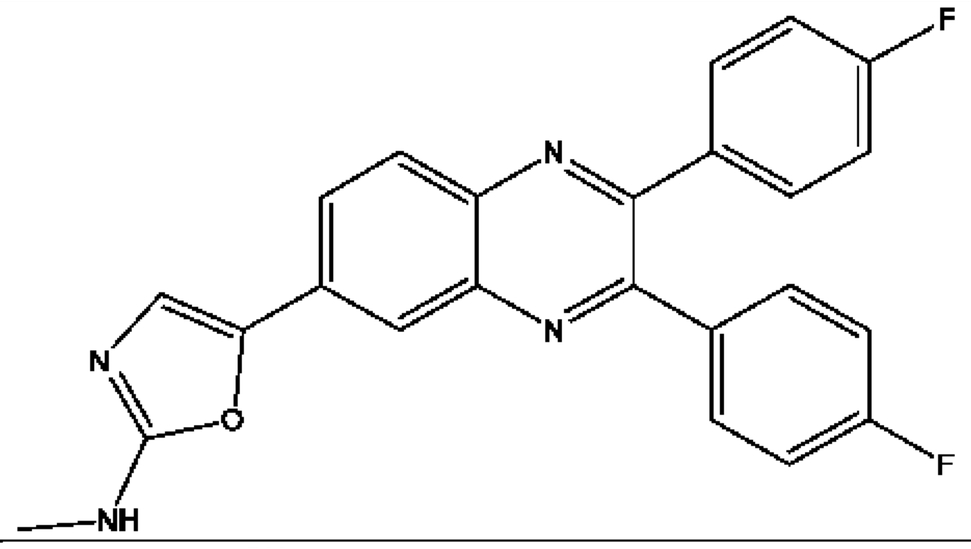
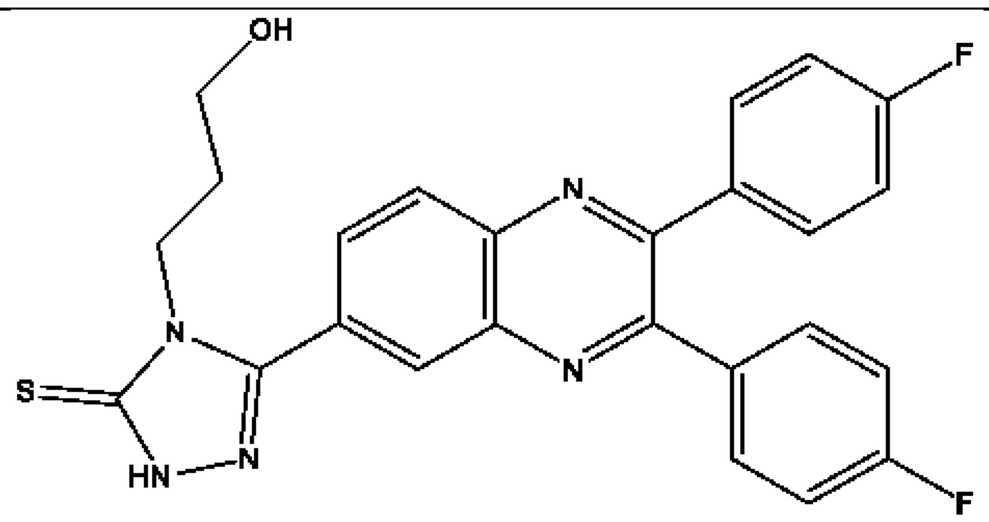
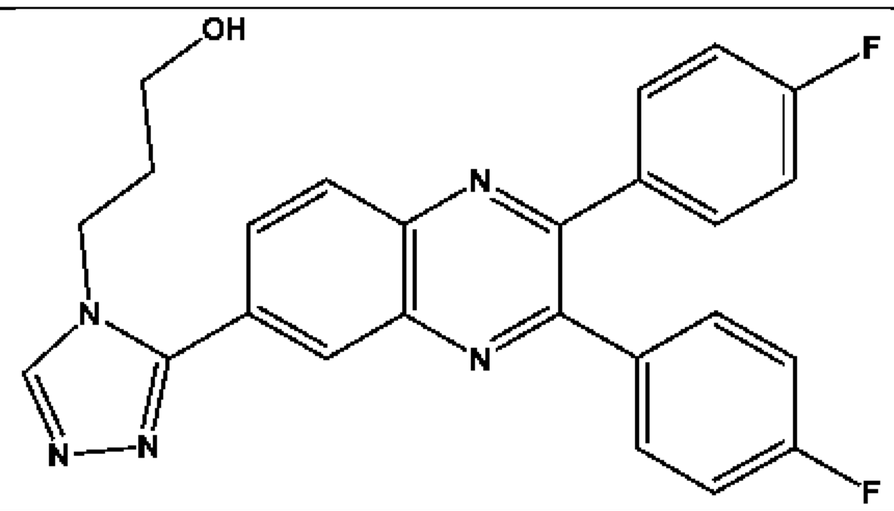
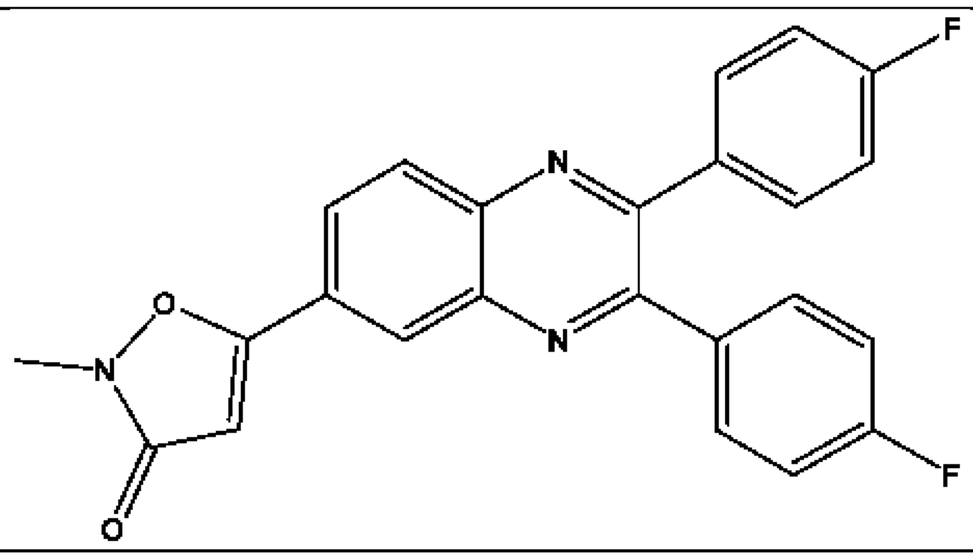
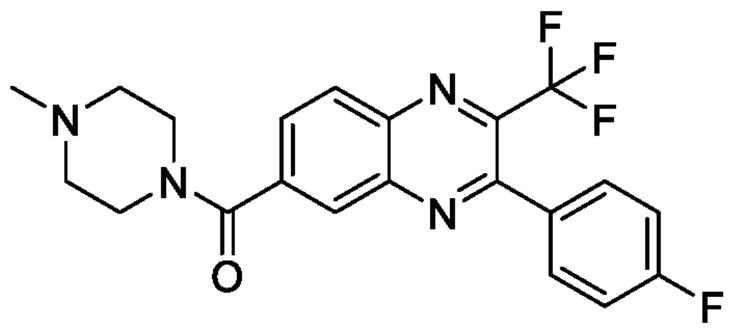
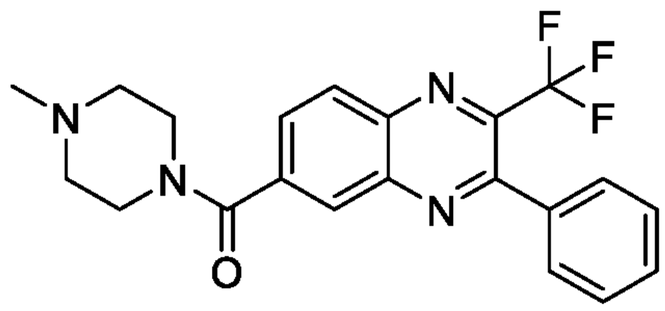
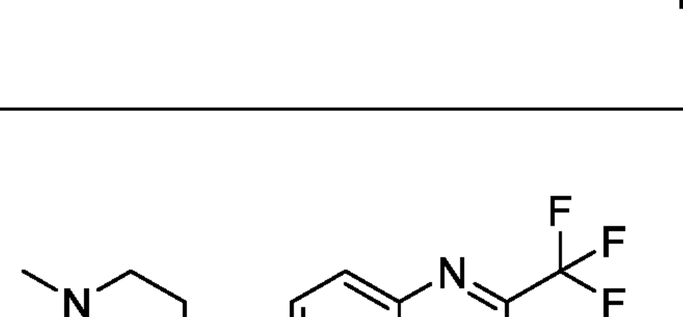
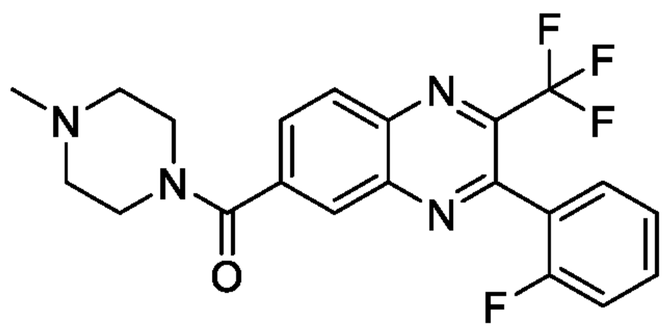
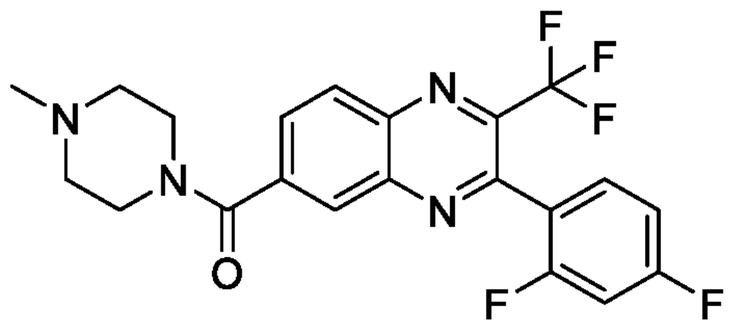
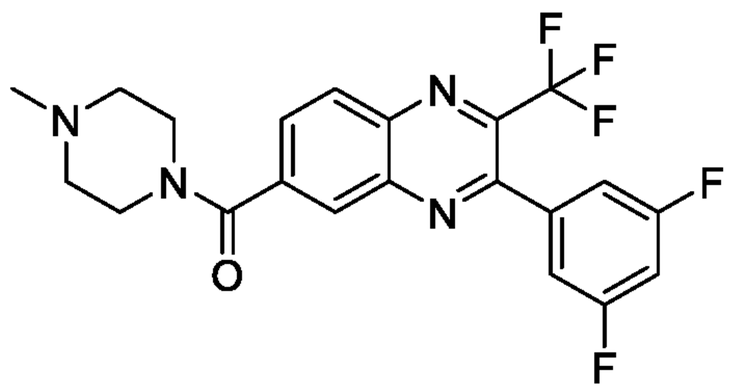
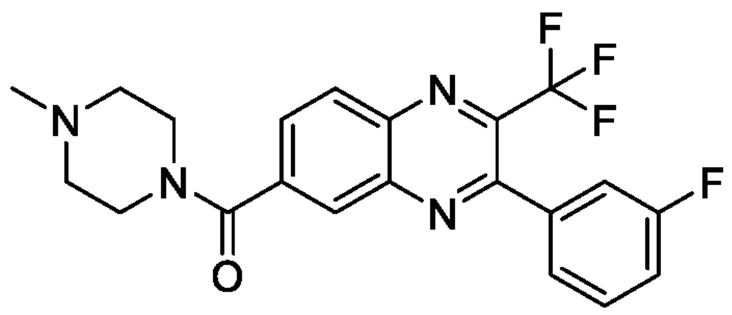
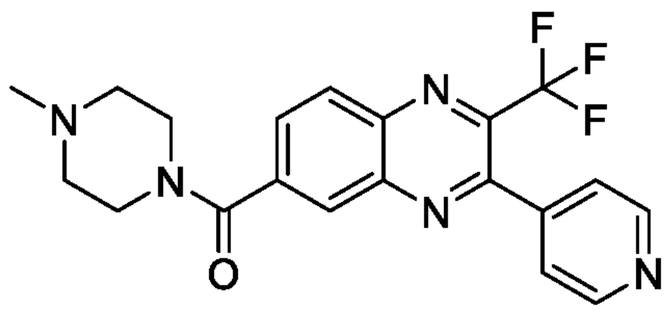
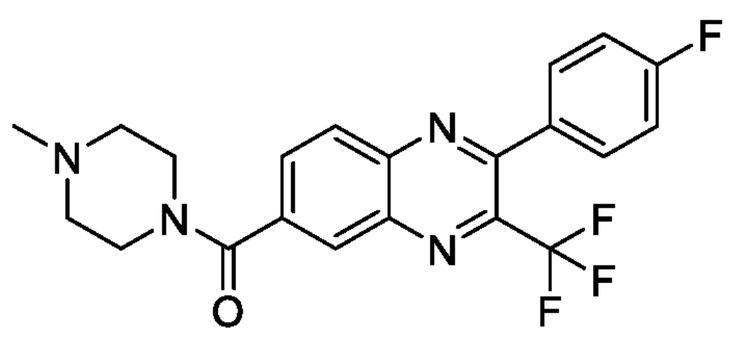
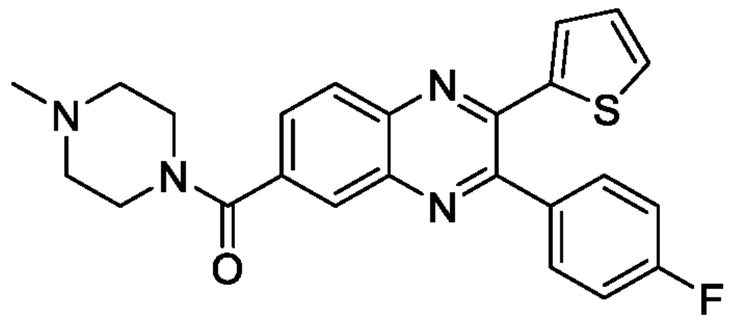
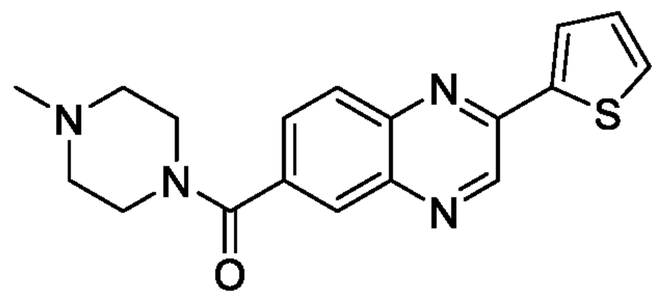
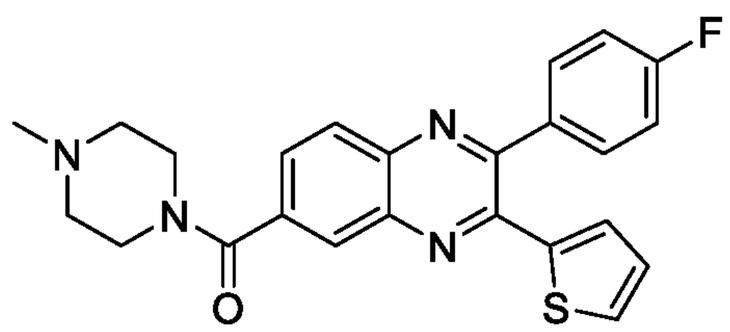
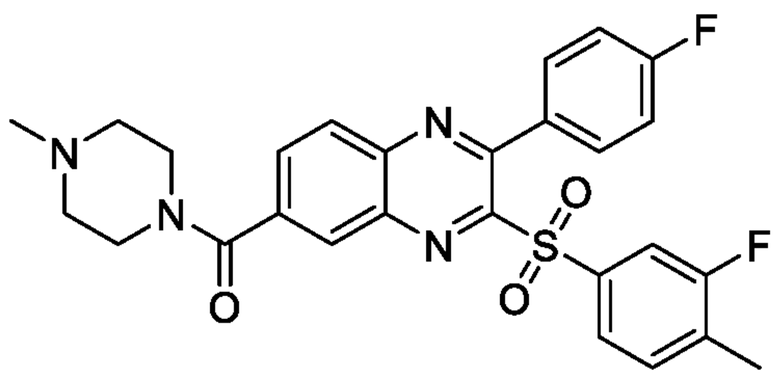
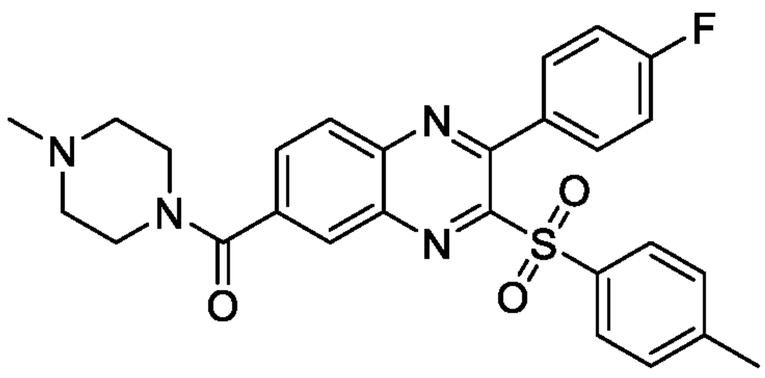
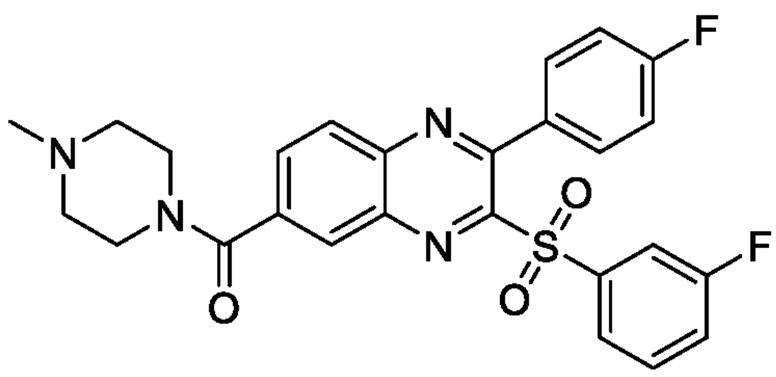
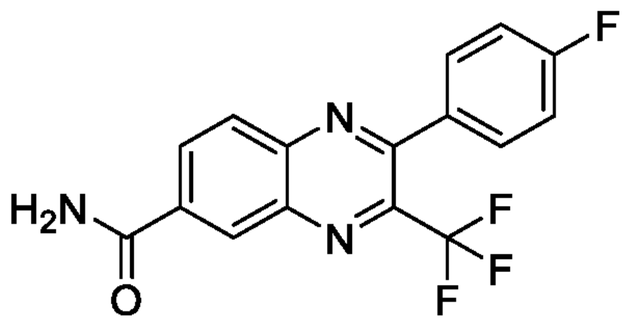
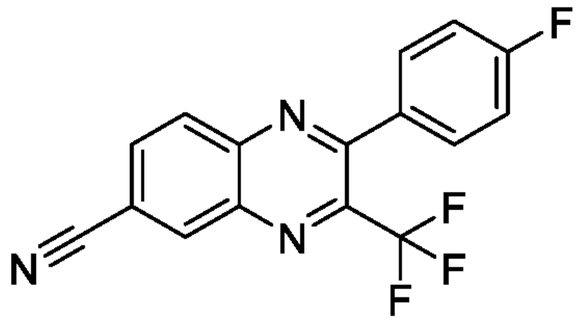
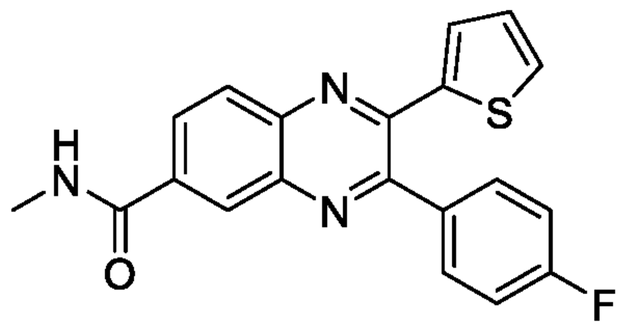
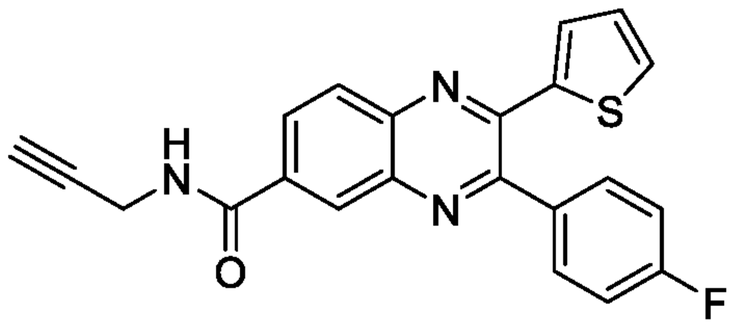
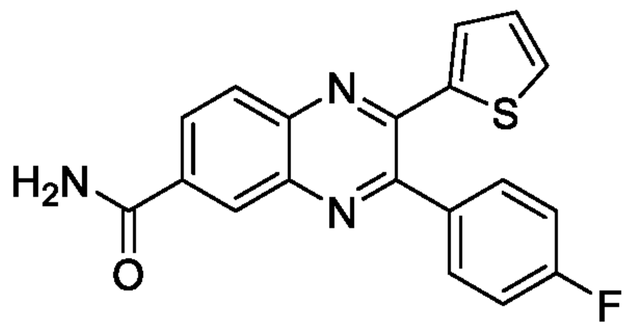
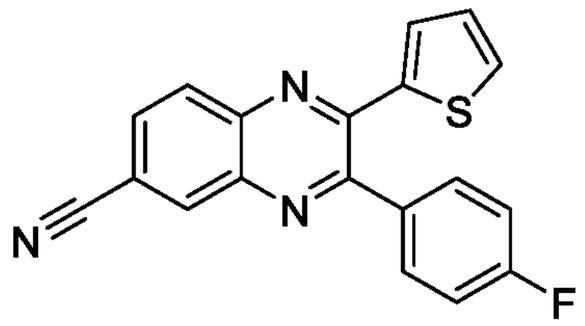
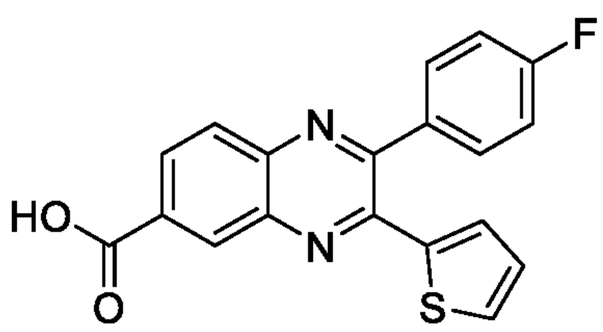
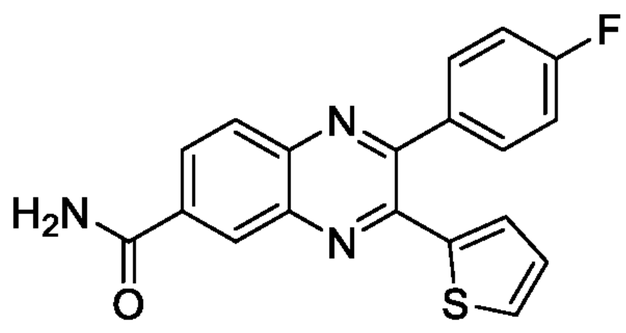
BC19496		++++	+
BC19619		++	+
BC19664		+++	+++
BC19665		++++	++
BC19667		+	+

Table 4d

BC No.	ZE No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19103	ZE18-0007		+	+
BC19104	ZE18-0008		+	+
BC19105	ZE18-0010		+	+
BC19106	ZE18-0012		+	+
BC19107	ZE18-0013		+	+

BC19108	ZE18-0014		+	+
BC19142	ZE18-0011		+	+
BC19149	ZE18-0009		+	+
BC19110	ZE18-0034		+	+
BC19109	ZE18-0017		+++	+
BC19191	ZE18-0125		+	+

BC19185	ZE18-0026		++++	+
BC19307	ZE18-0185		+++	++++
BC19308	ZE18-0155		+++	++++
BC19395	ZE18-0184		+++	++++
BC19117	ZE18-0083		+	+
BC19158	ZE18-0124		+	+

BC19119	ZE18-0103		++++	++++
BC19120	ZE18-0105		++++	++++
BC19155	ZE18-0099		+++	++
BC19157	ZE18-0104		+	+
BC19156	ZE18-0101		++	+
BC19187	ZE18-0114		+++	+

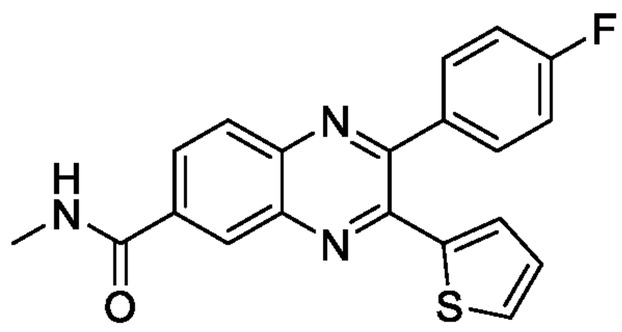
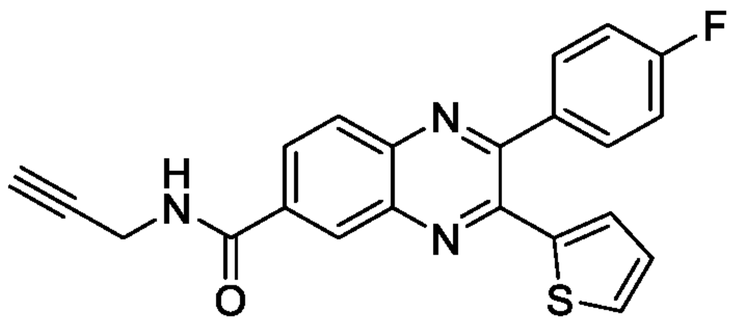
BC19188	ZE18-0115		+++	+
BC19189	ZE18-0116		+++	+

Table 4e

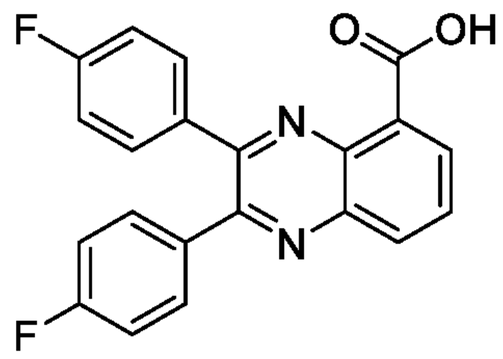
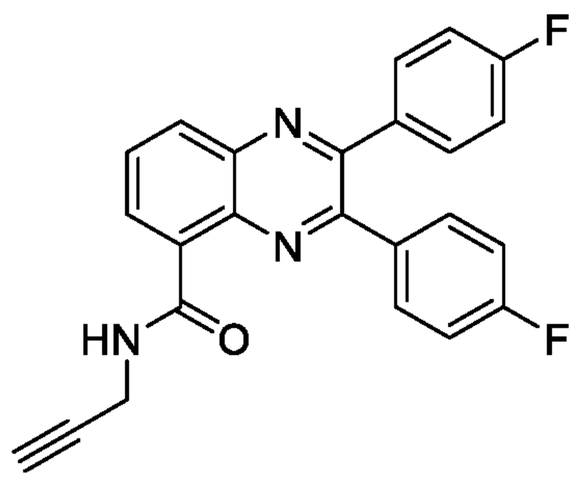
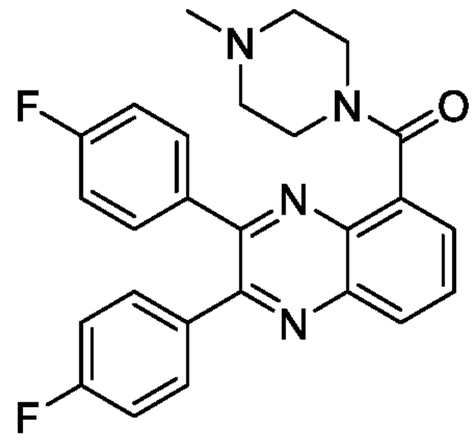
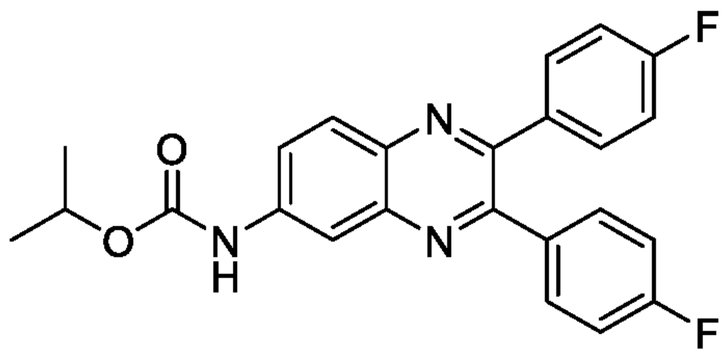
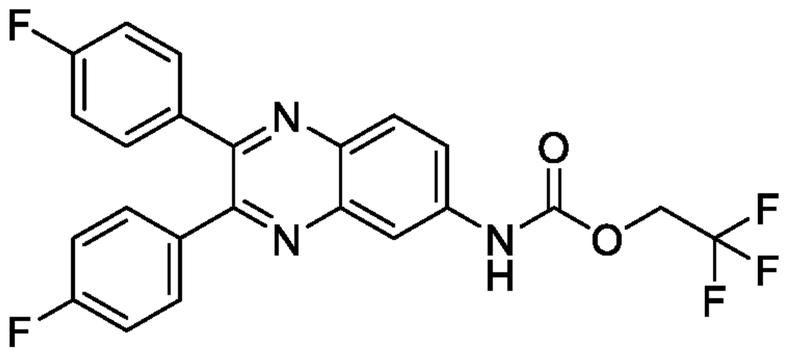
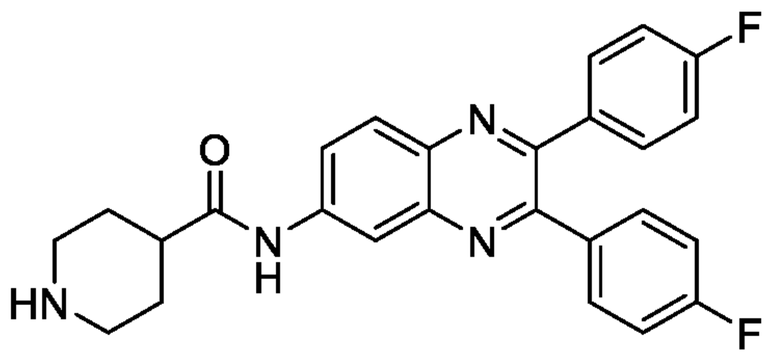
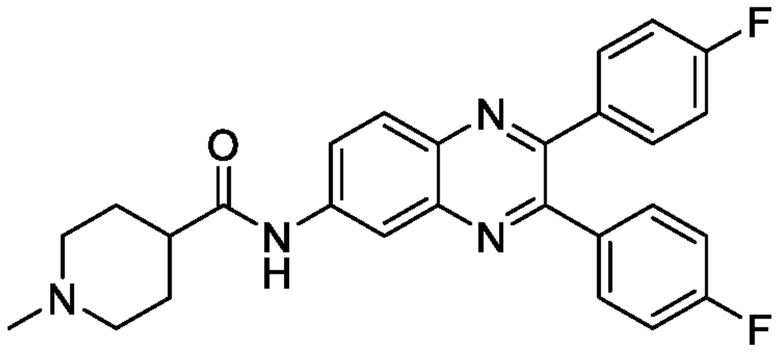
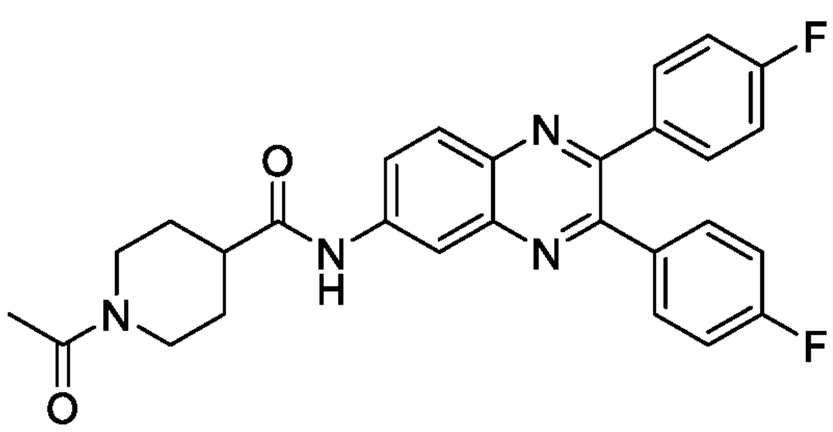
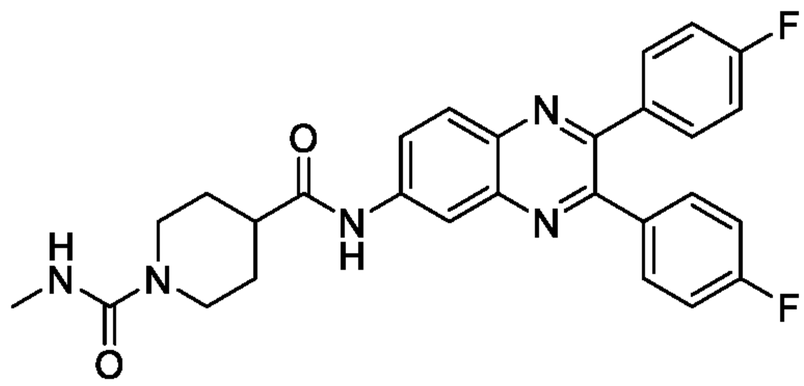
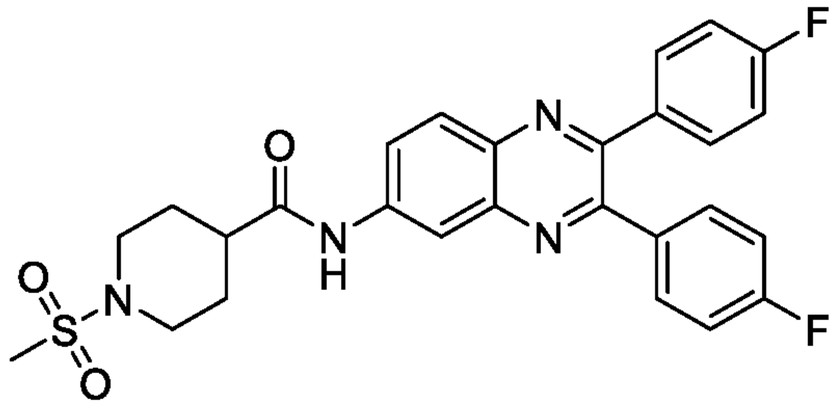
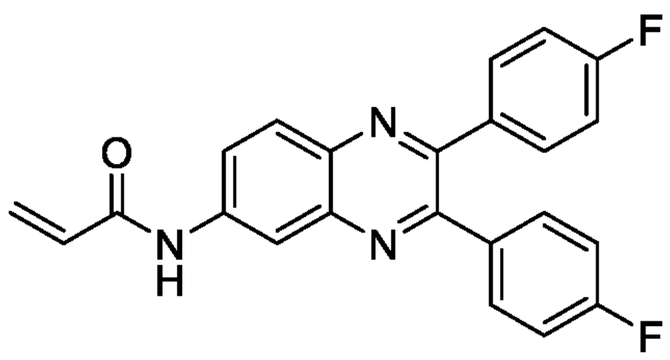
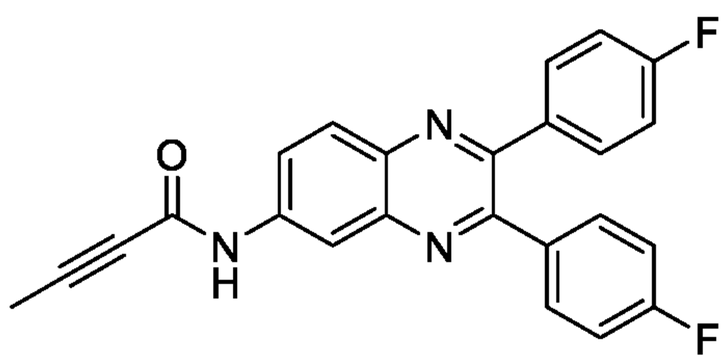
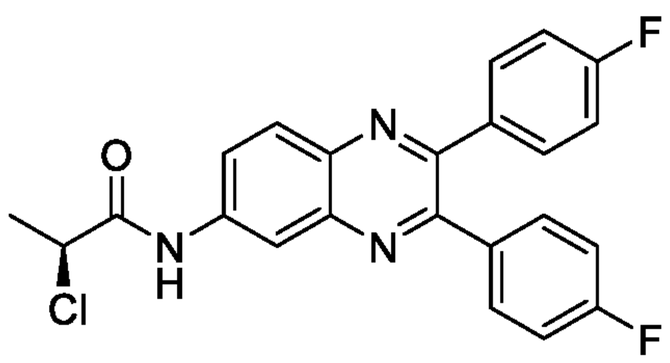
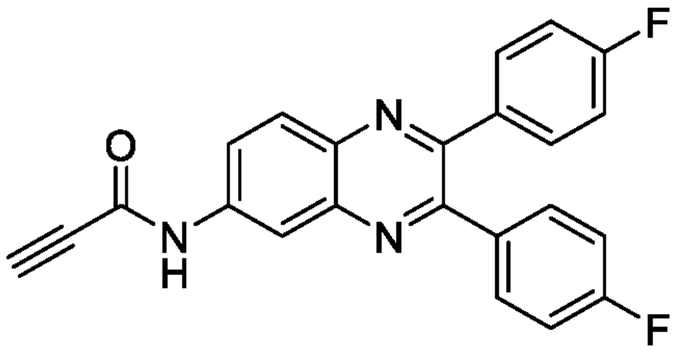
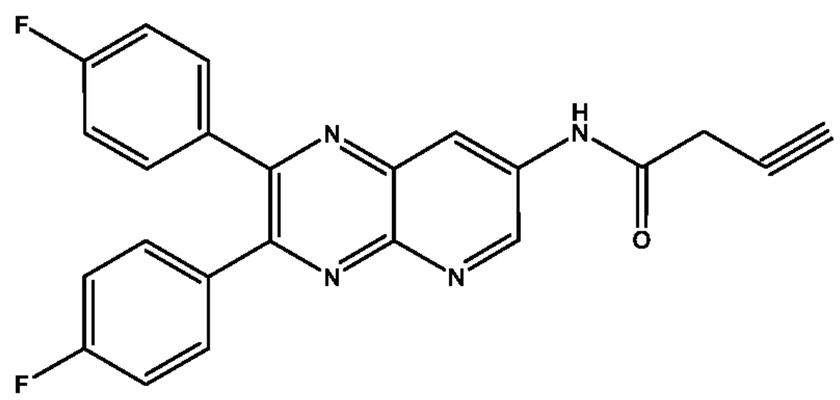
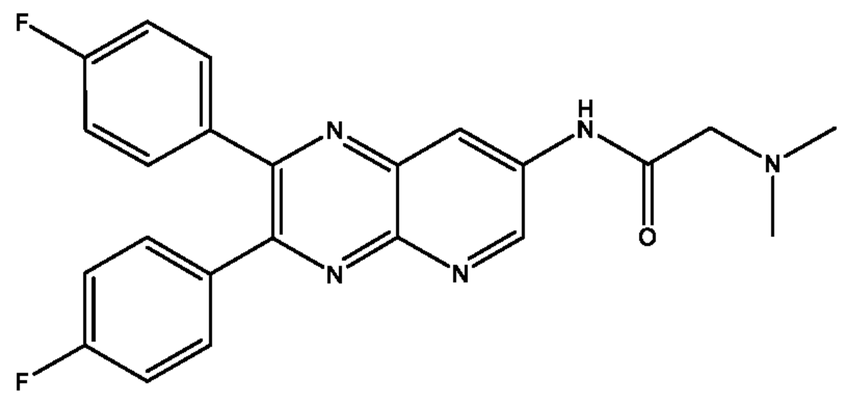
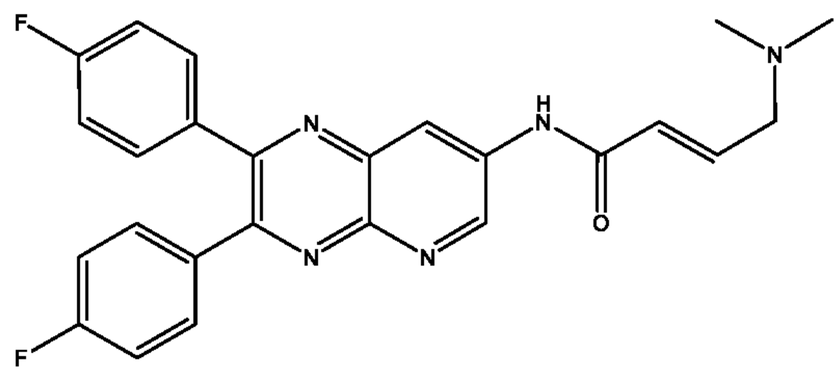
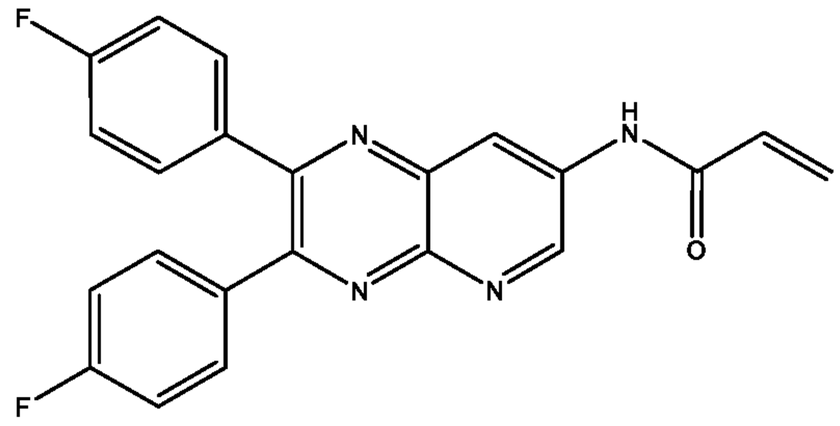
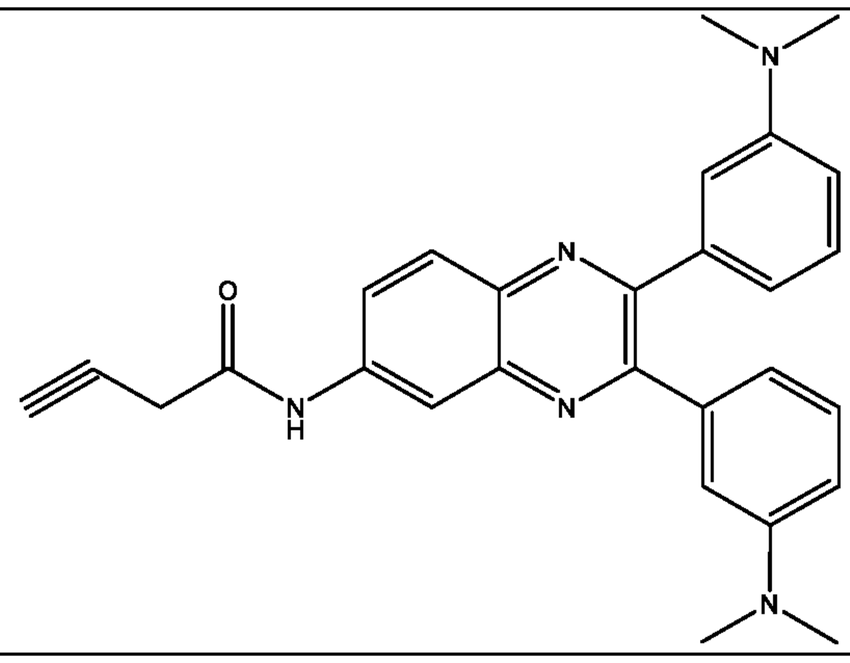
BC No.	ZE No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19320	ZE18-0209		+	+
BC19321	ZE18-0211		++	+
BC19400	ZE18-0210		+	+

Table 4f

BC No.	ZE No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19195	ZE18 -0152		++	+
BC19239	ZE18 -0154		+++	+
BC19251	ZE18 -0187		++++	++
BC19309	ZE18 -0189		+++	++
BC19310	ZE18 -0190		++++	+

BC19311	ZE18-0192		++++	+
BC19312	ZE18-0193		++++	++
BC19313	ZE18-0194		+++	++
BC19314	ZE18-0196		++++	++
BC19315	ZE18-0197		+++	+
BC19397	ZE18-0195		++++	+++

	ZE18-0568			
	ZE18-0569			
	ZE18-0570			
	ZE18-0571			
	ZE18-0581			

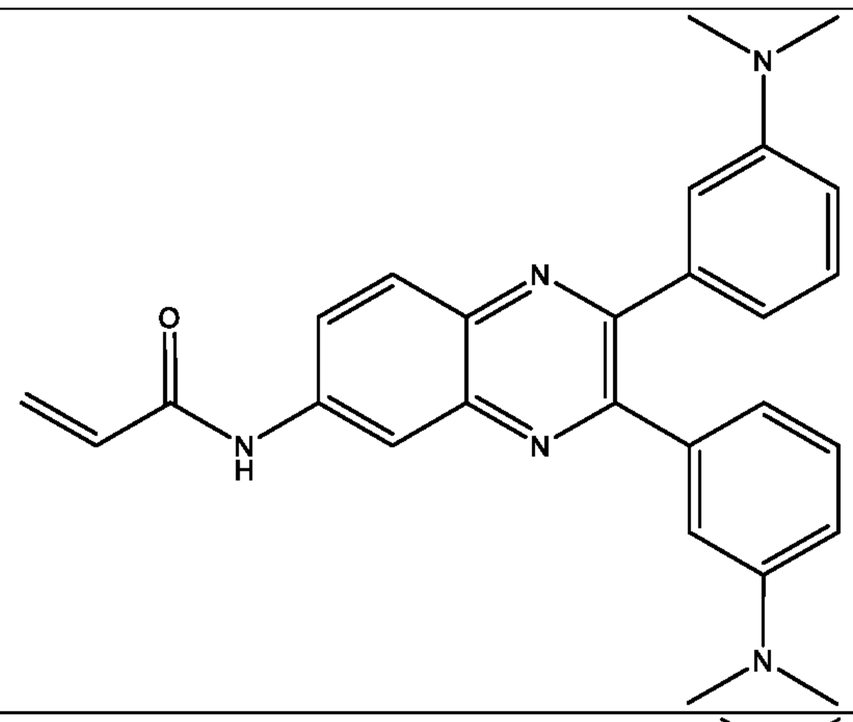
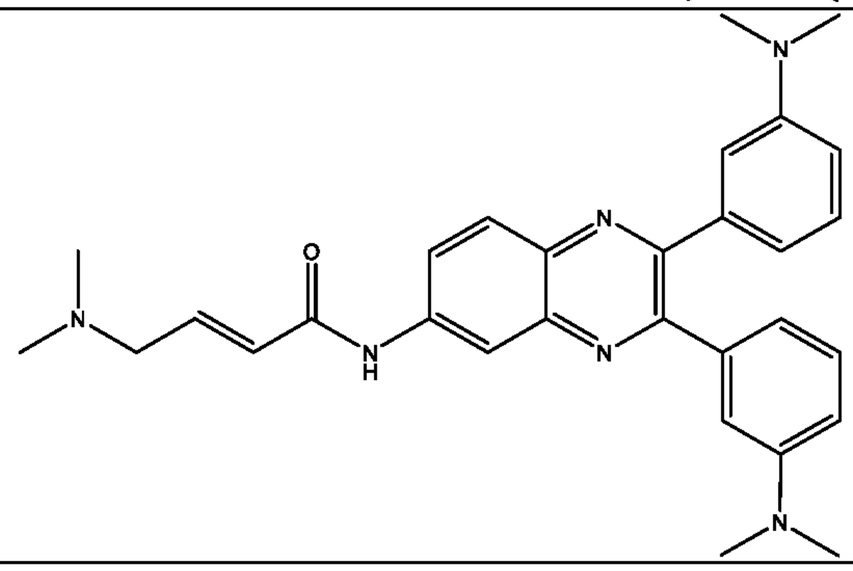
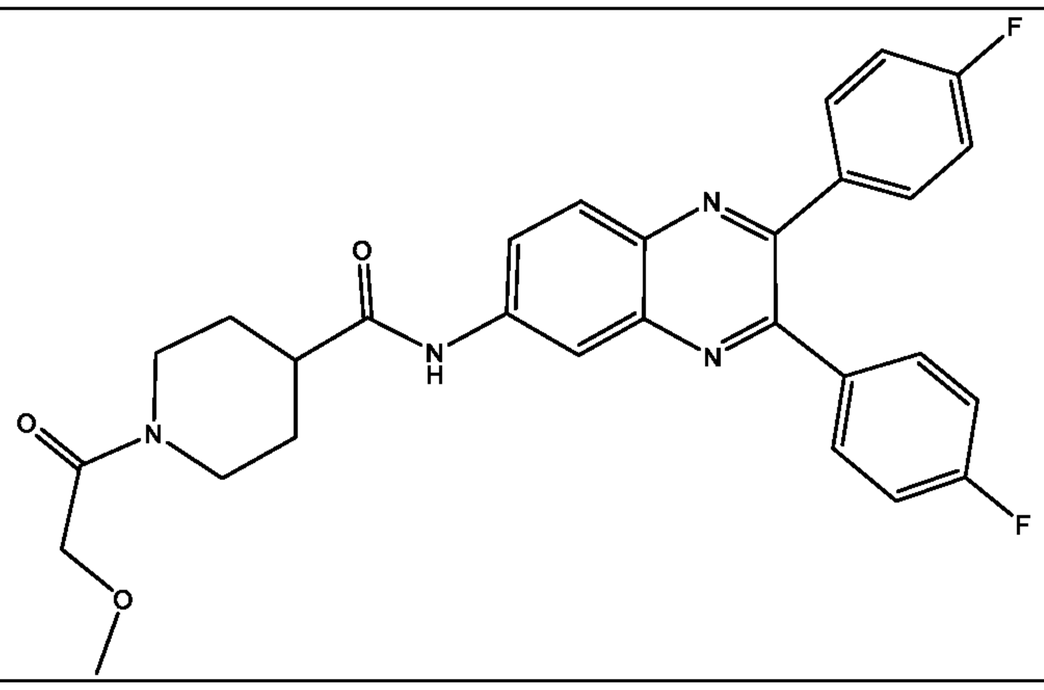
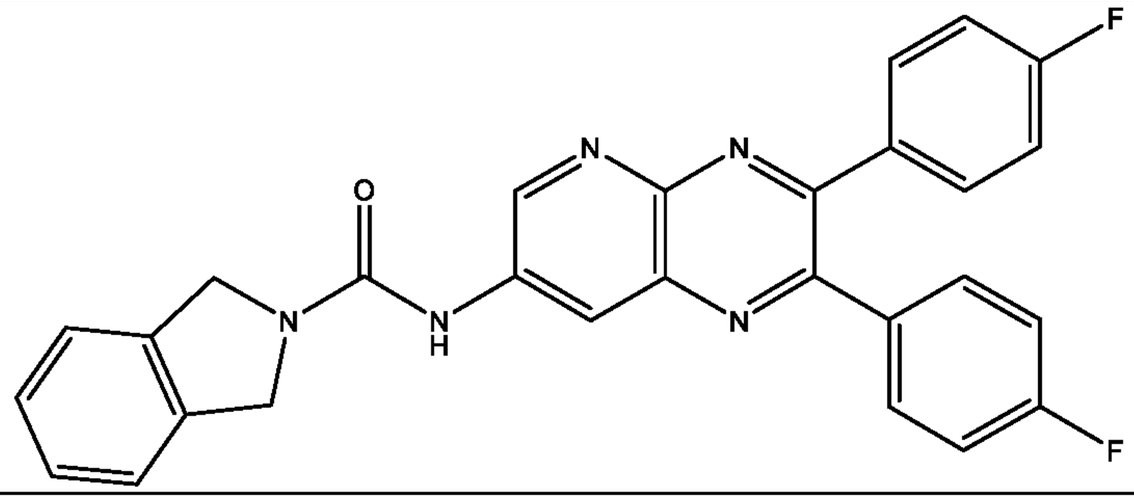
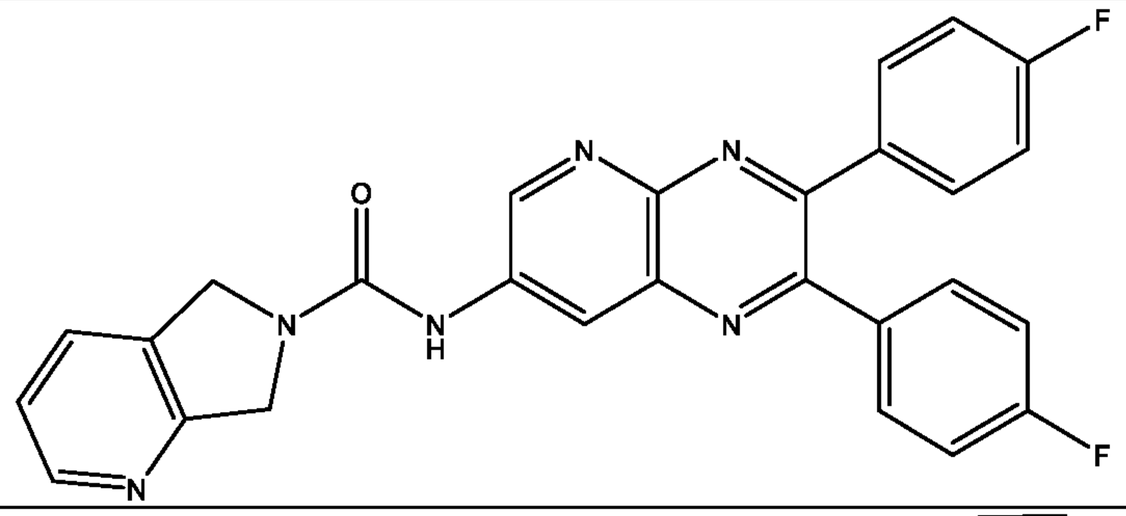
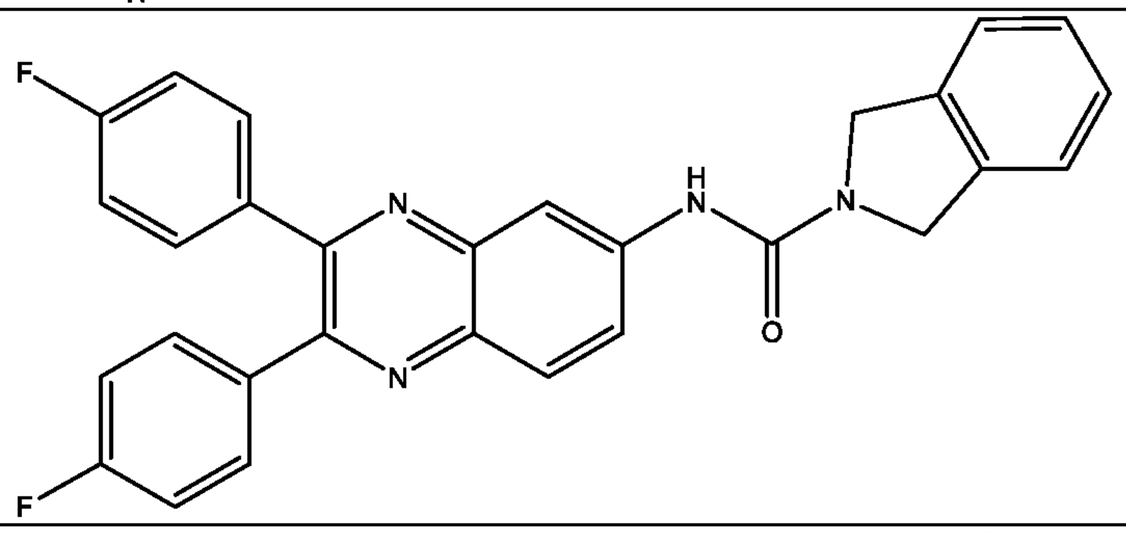
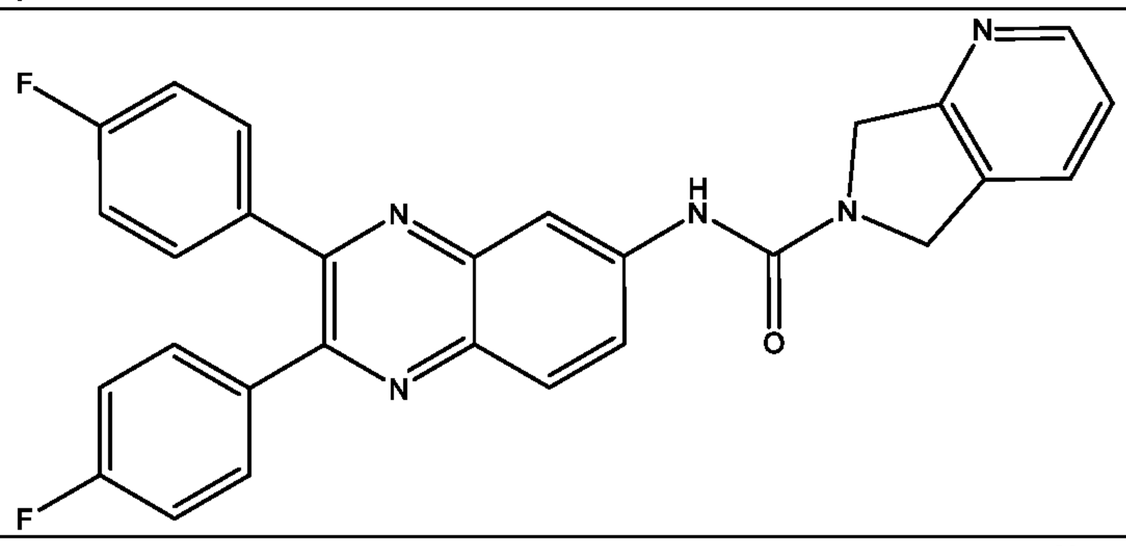
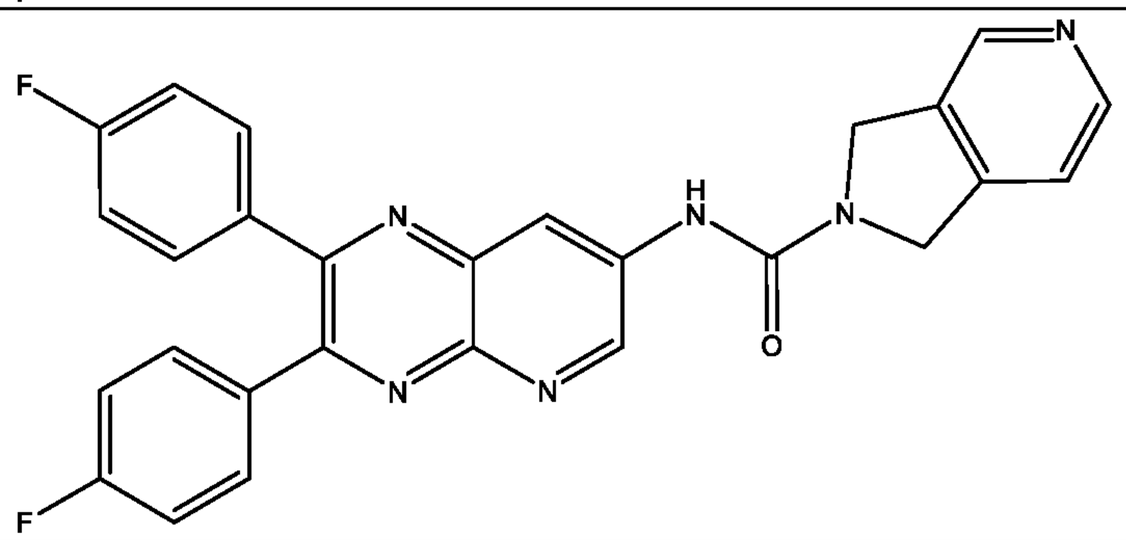
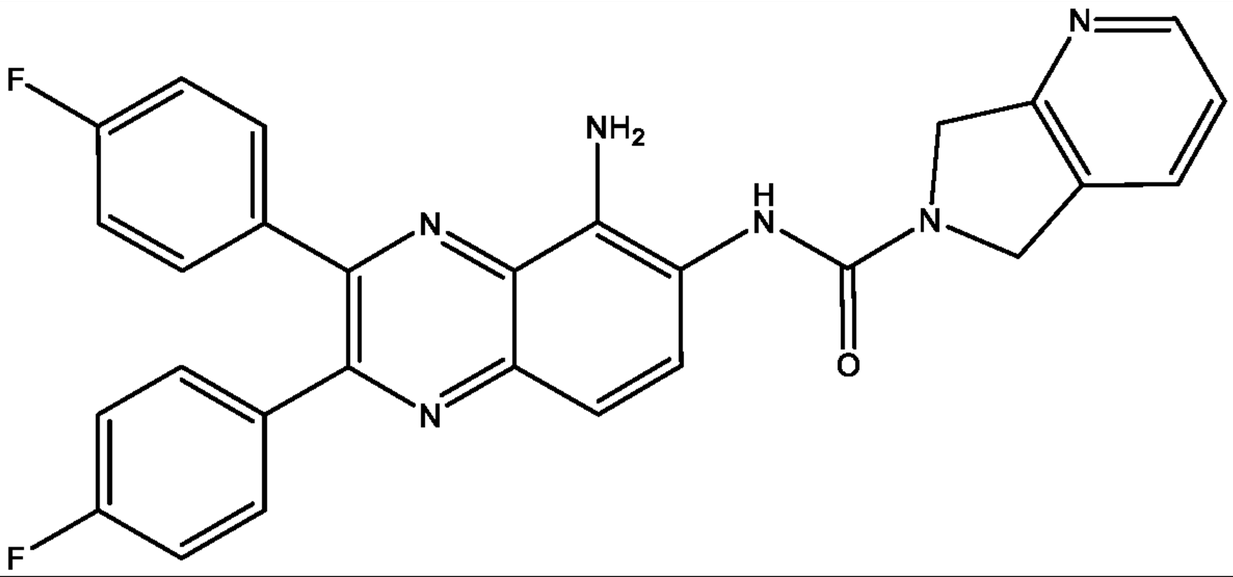
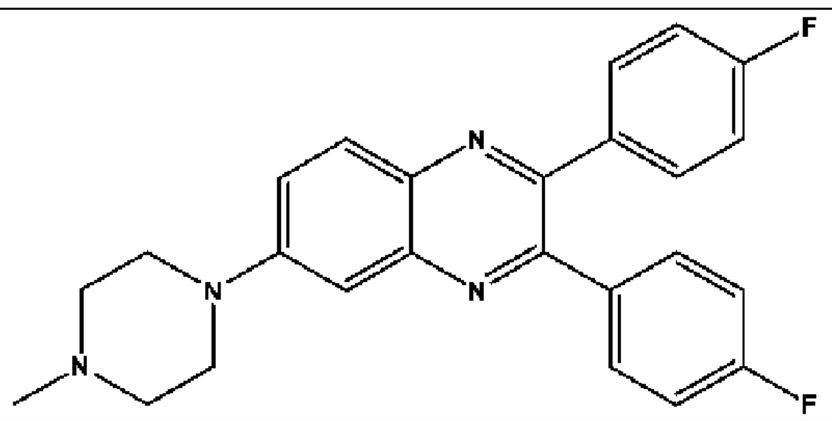
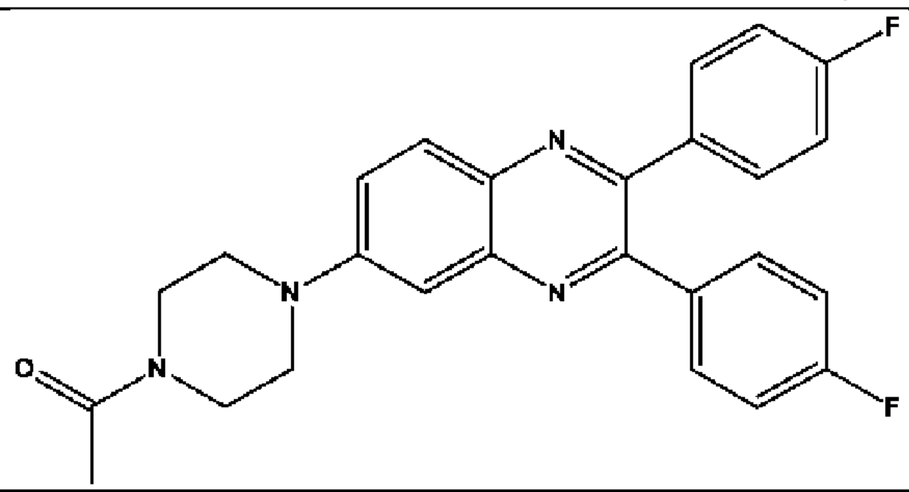
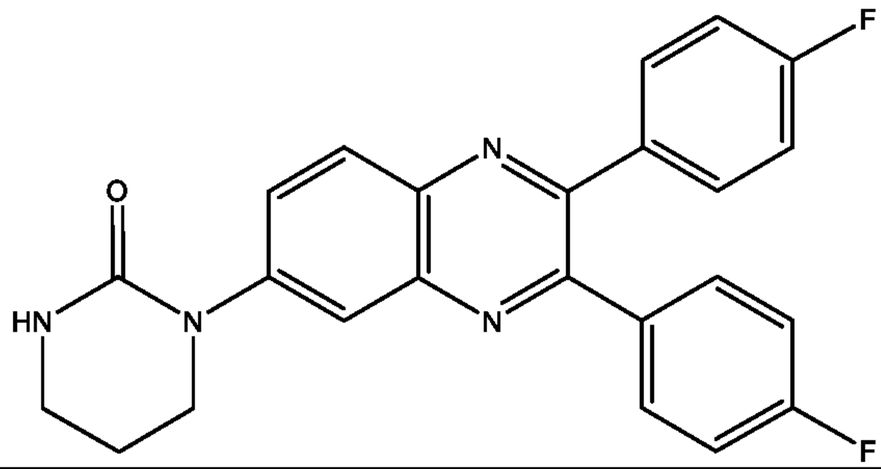
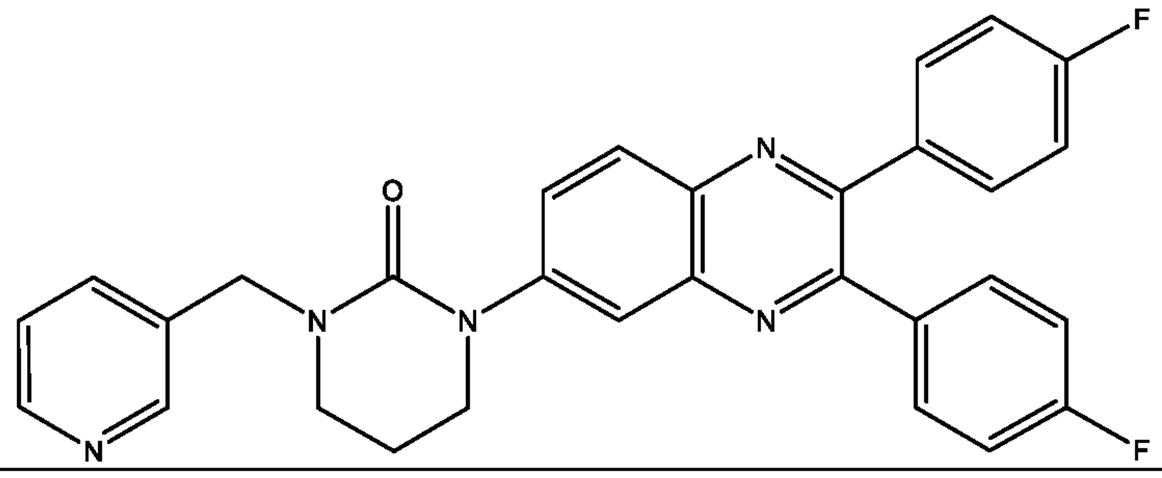
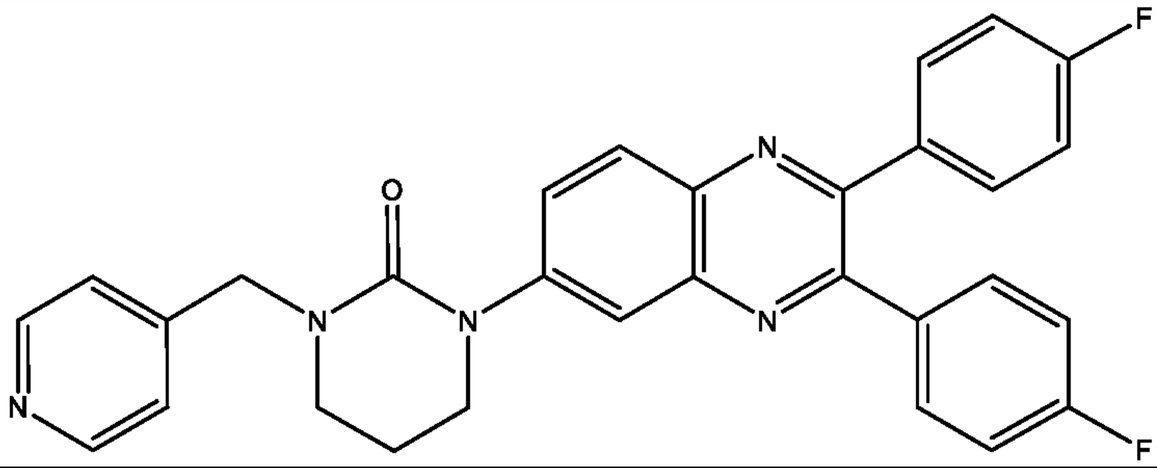
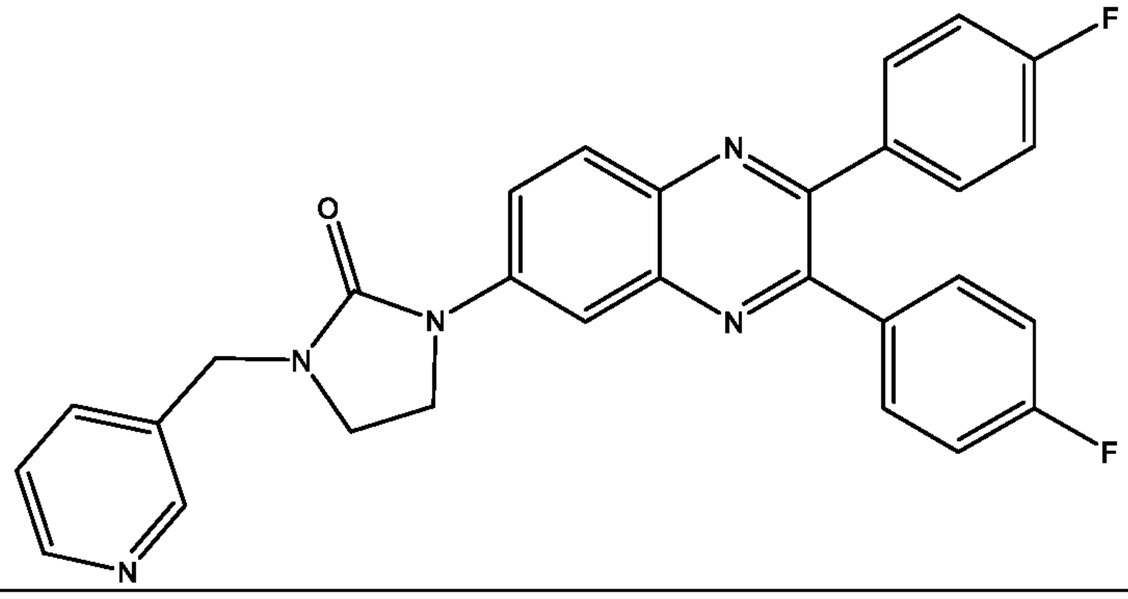
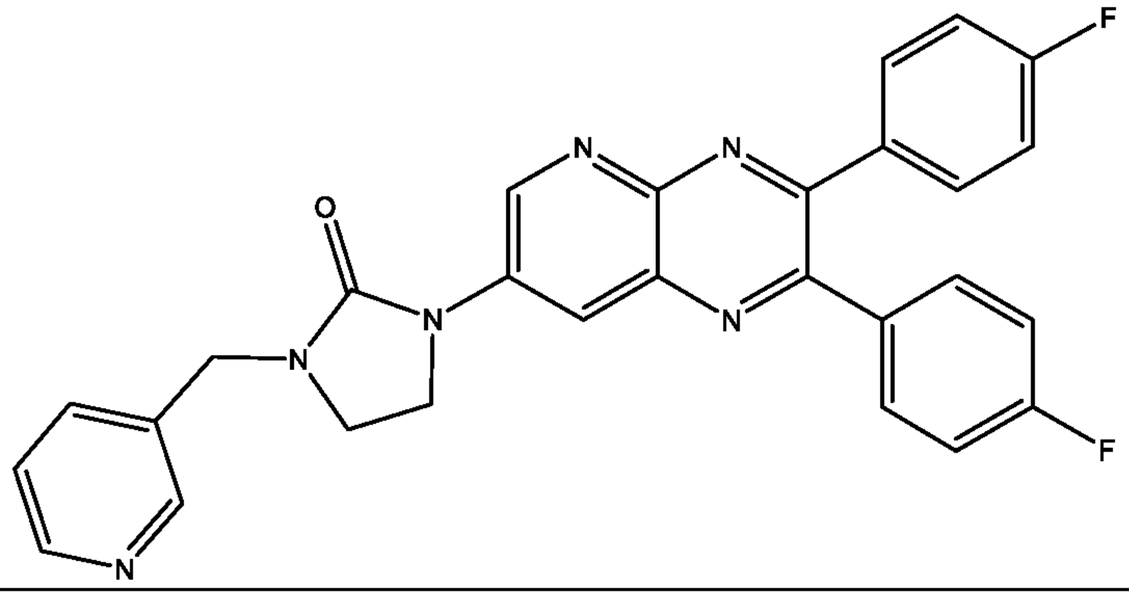
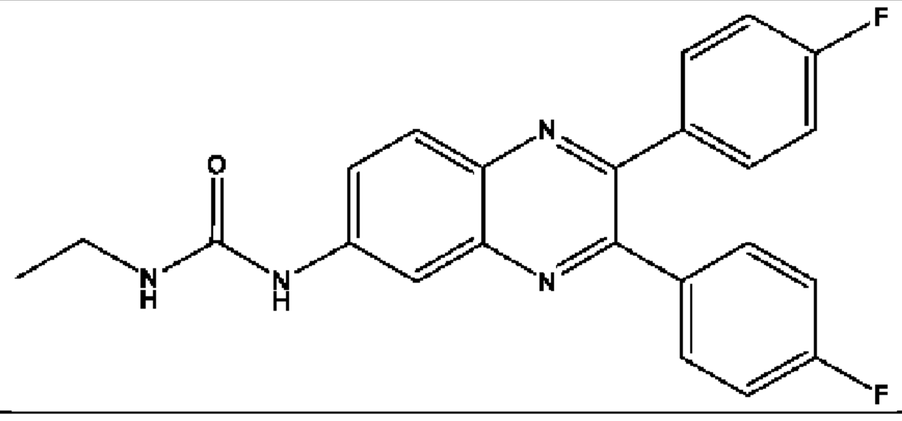
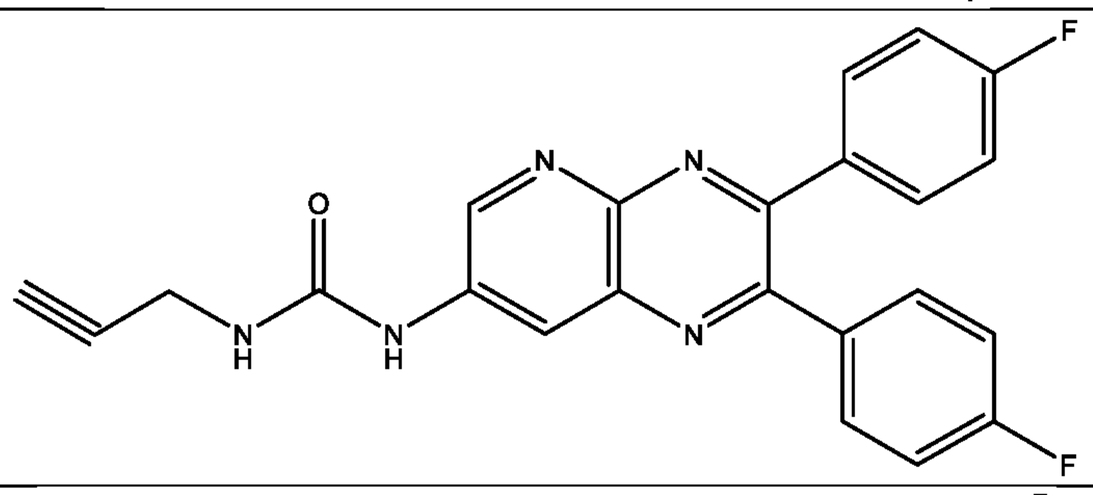
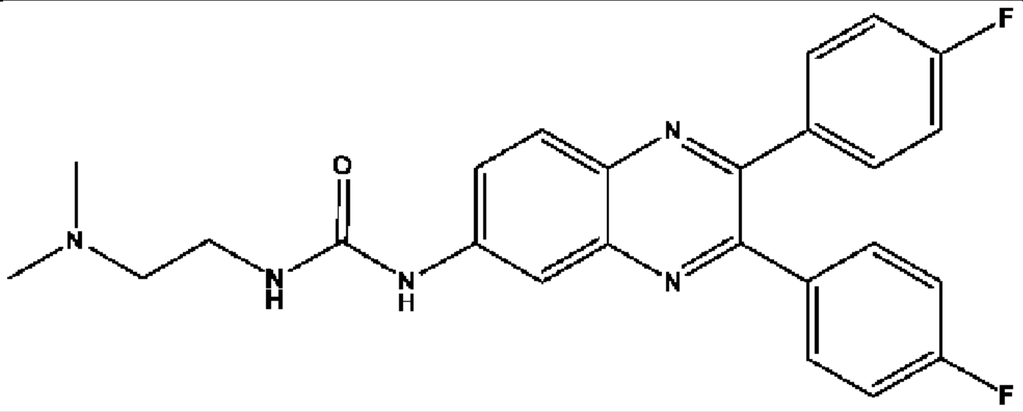
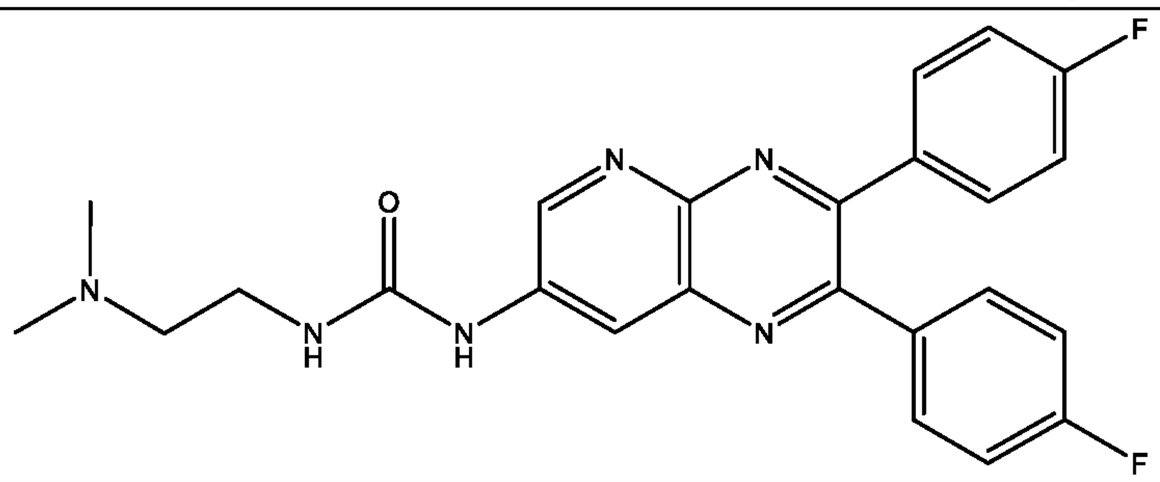
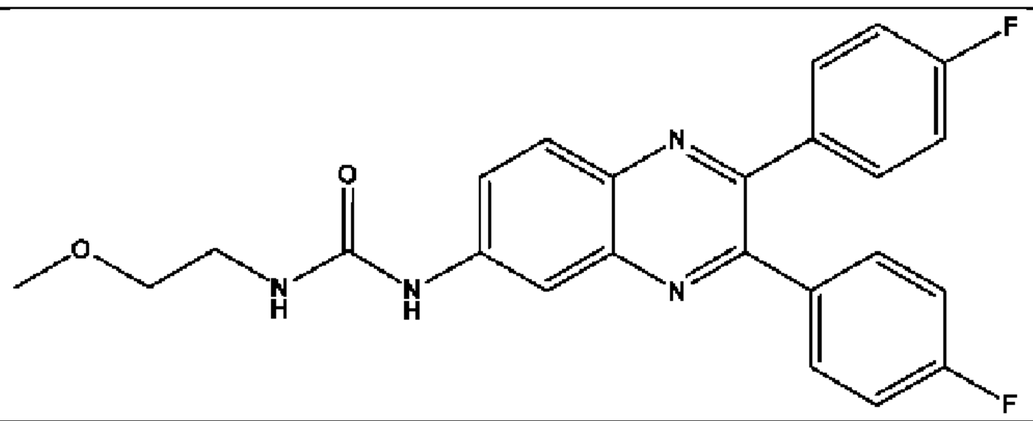
	ZE18-0586			
	ZE18-0588			

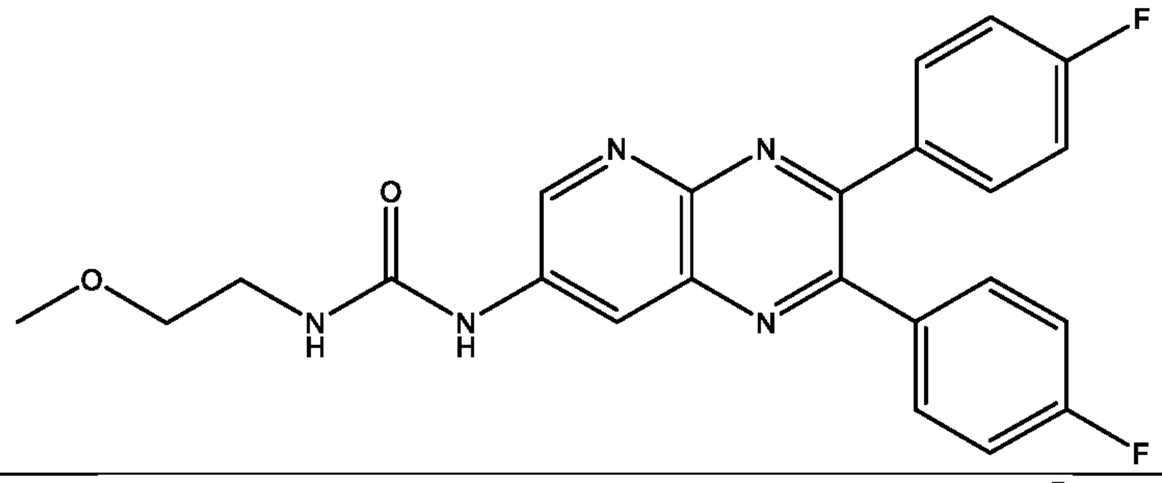
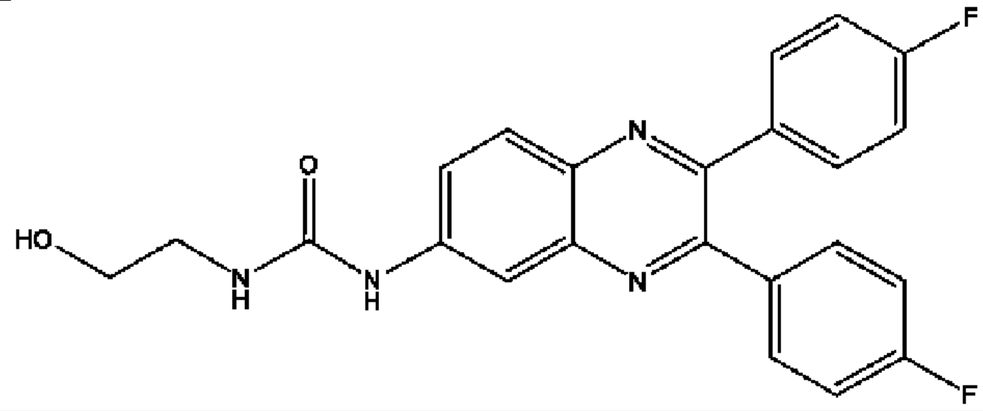
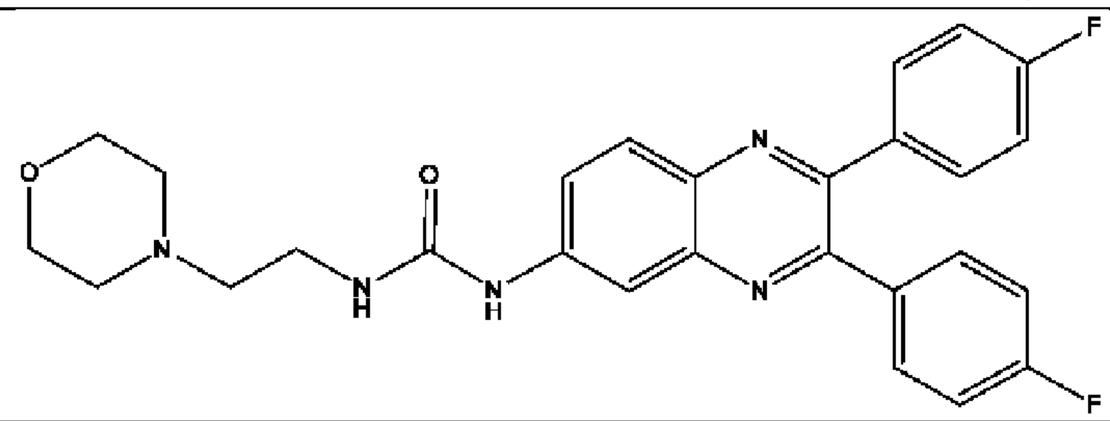
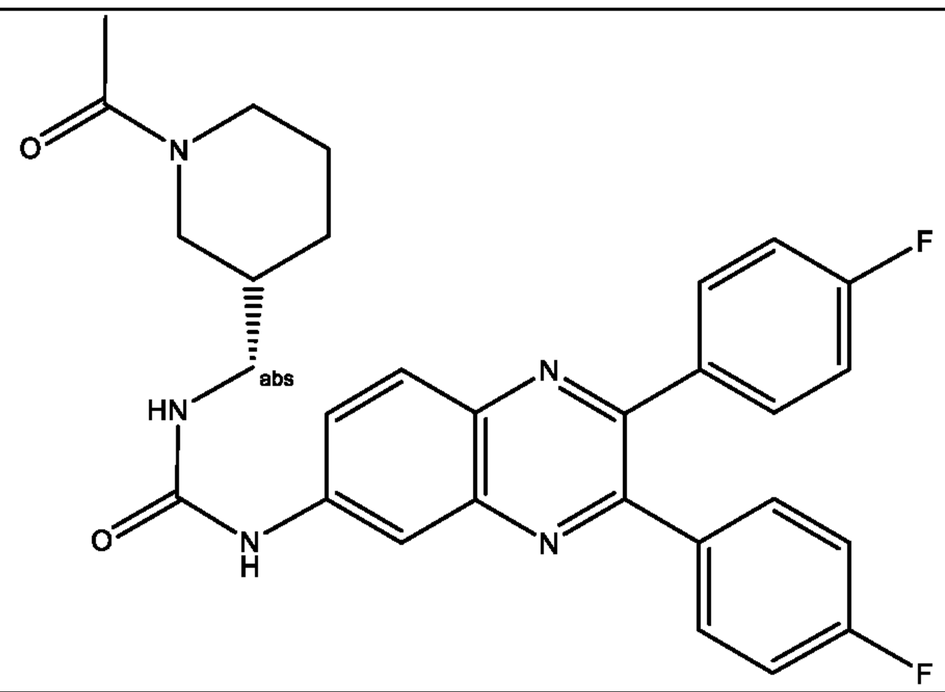
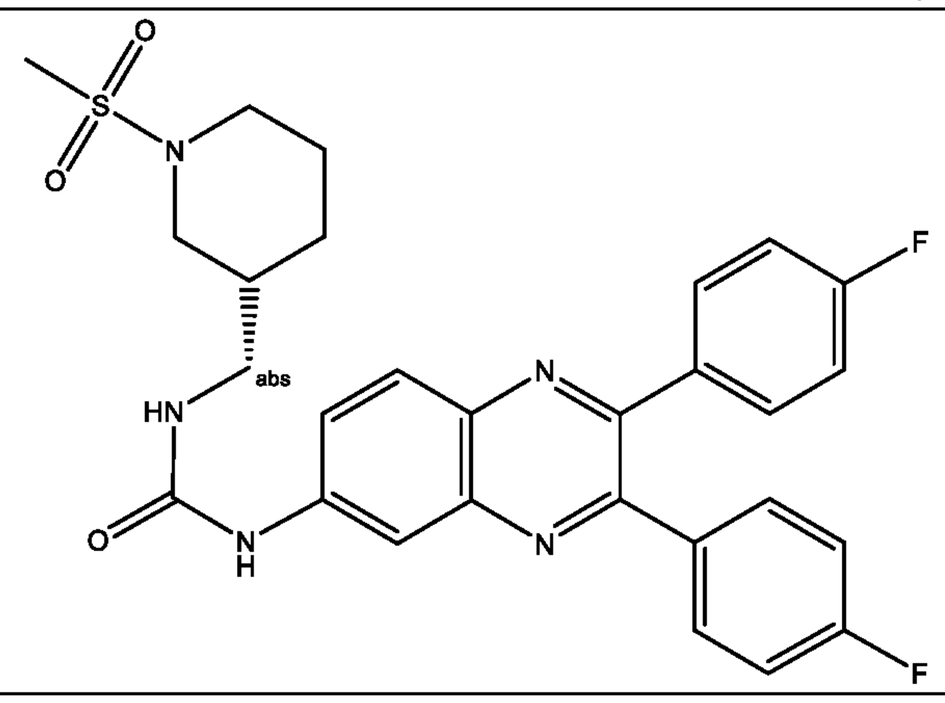
Table 4f-2

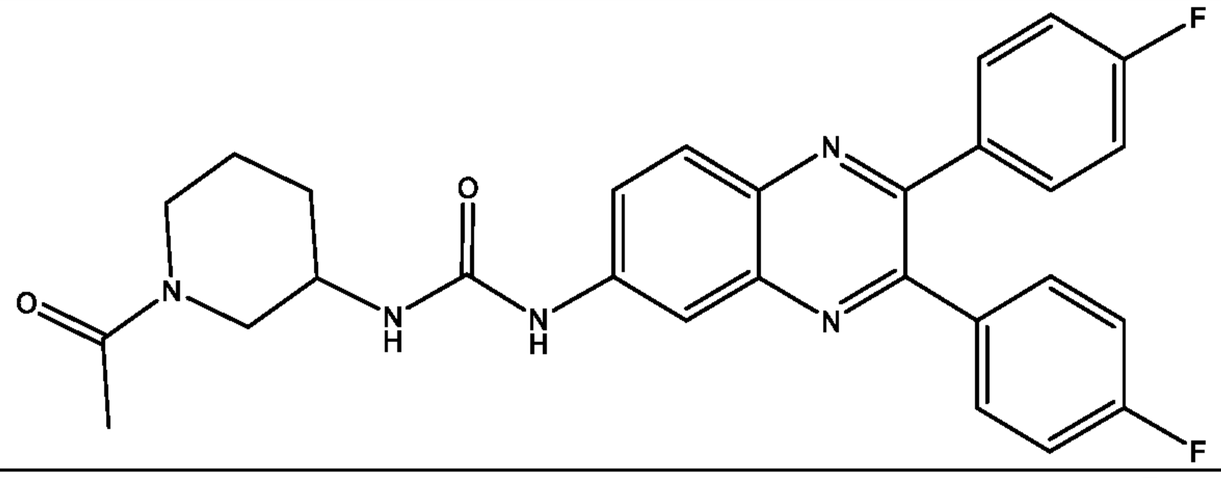
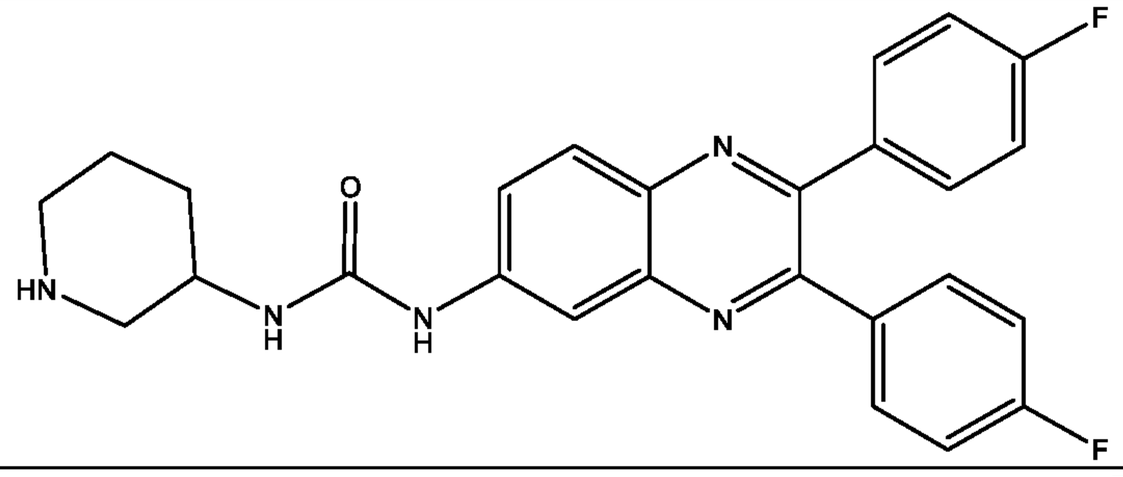
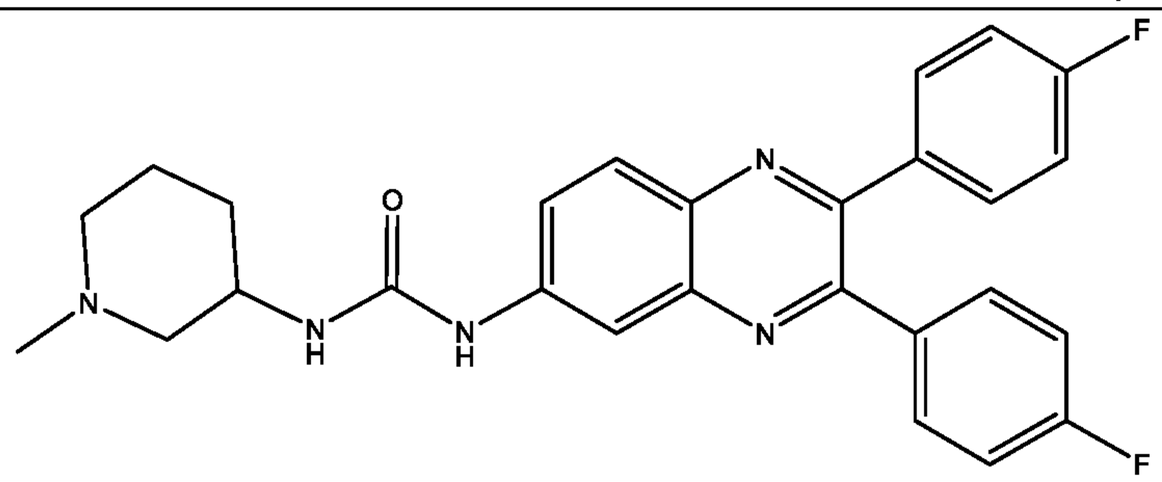
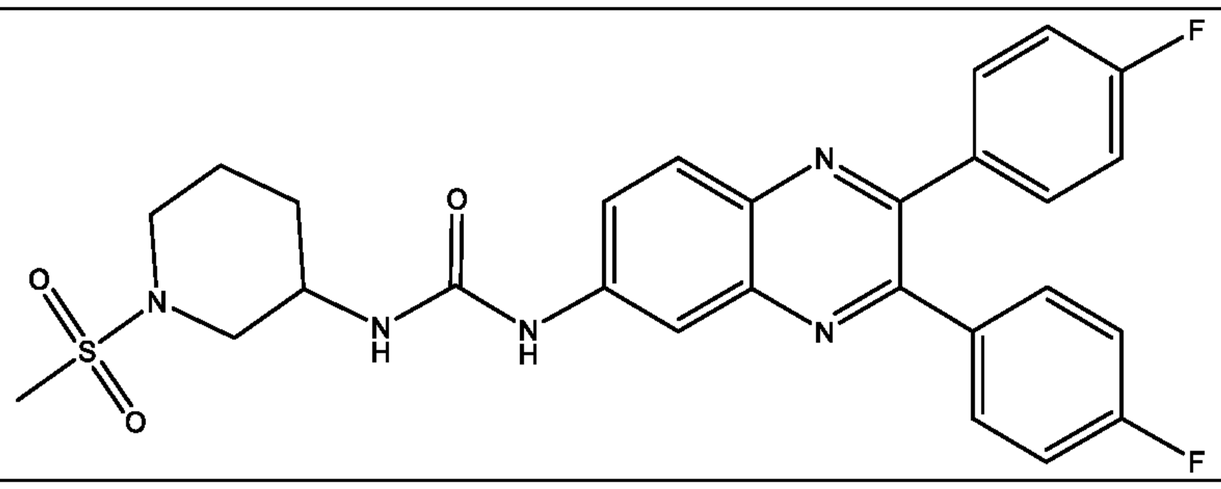
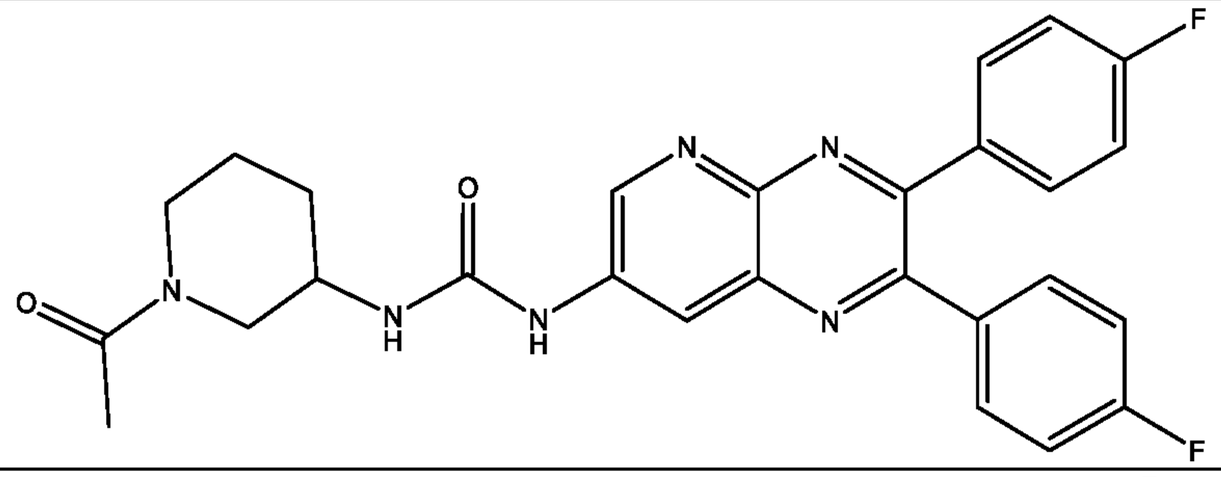
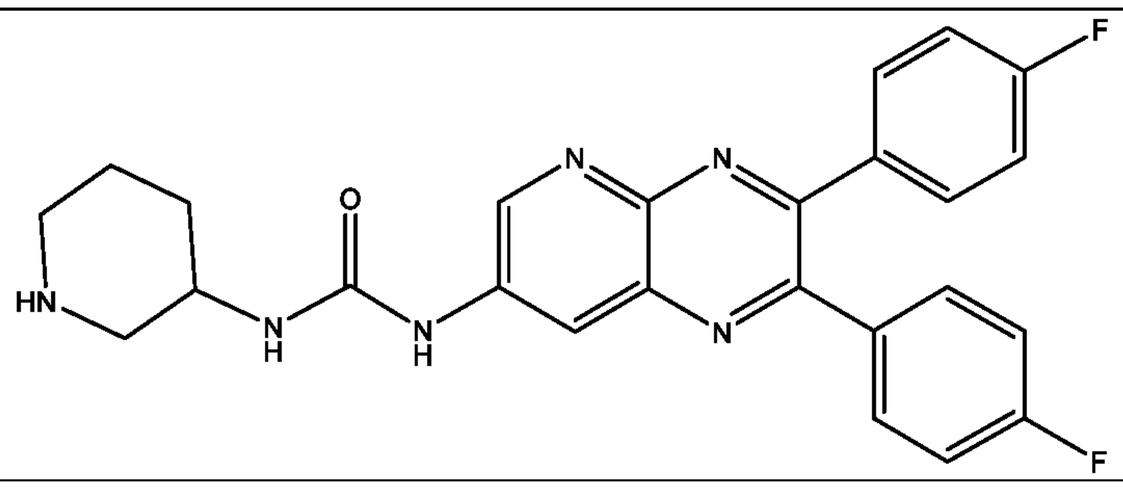
BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19494		+++	+
BC20317			

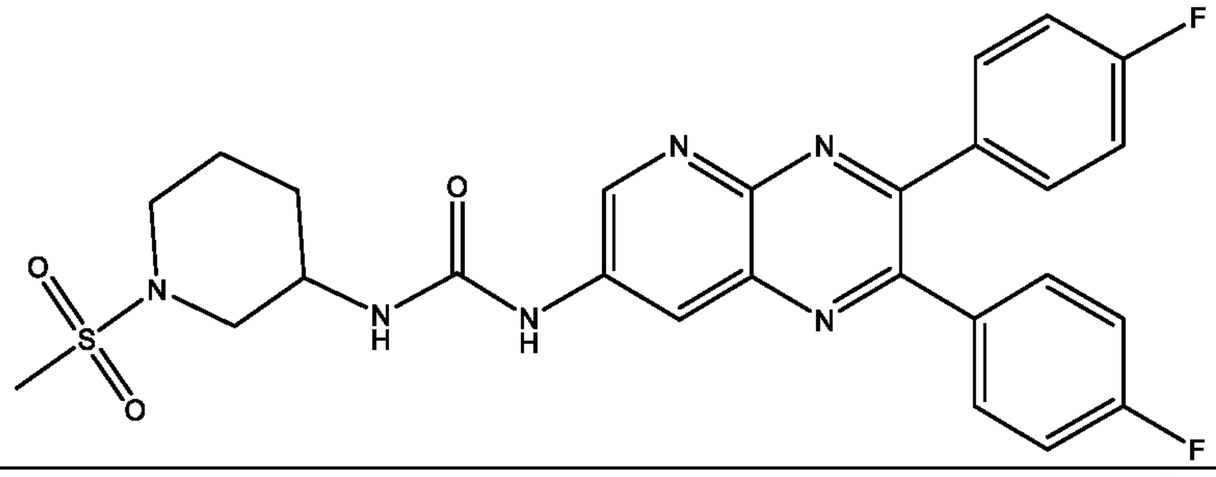
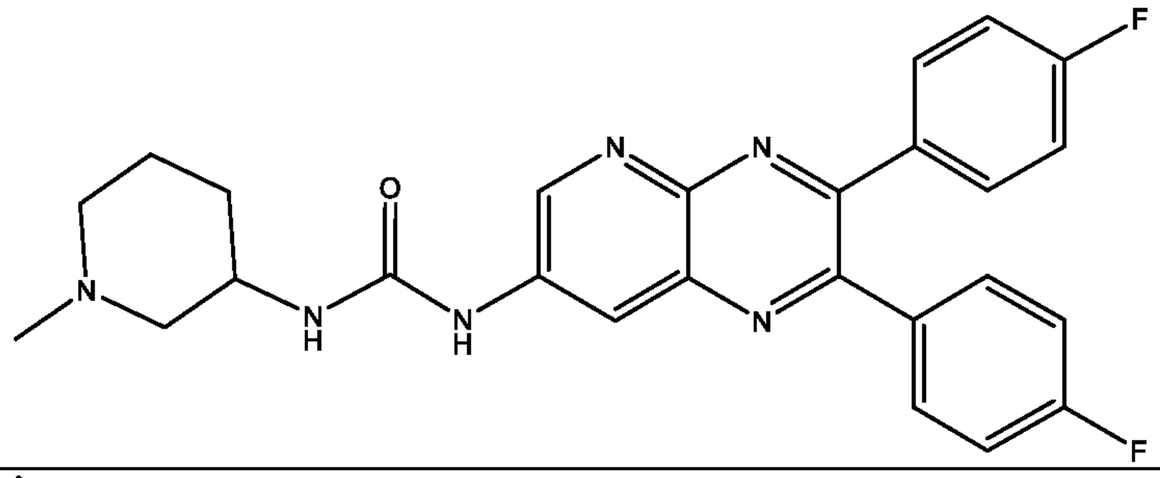
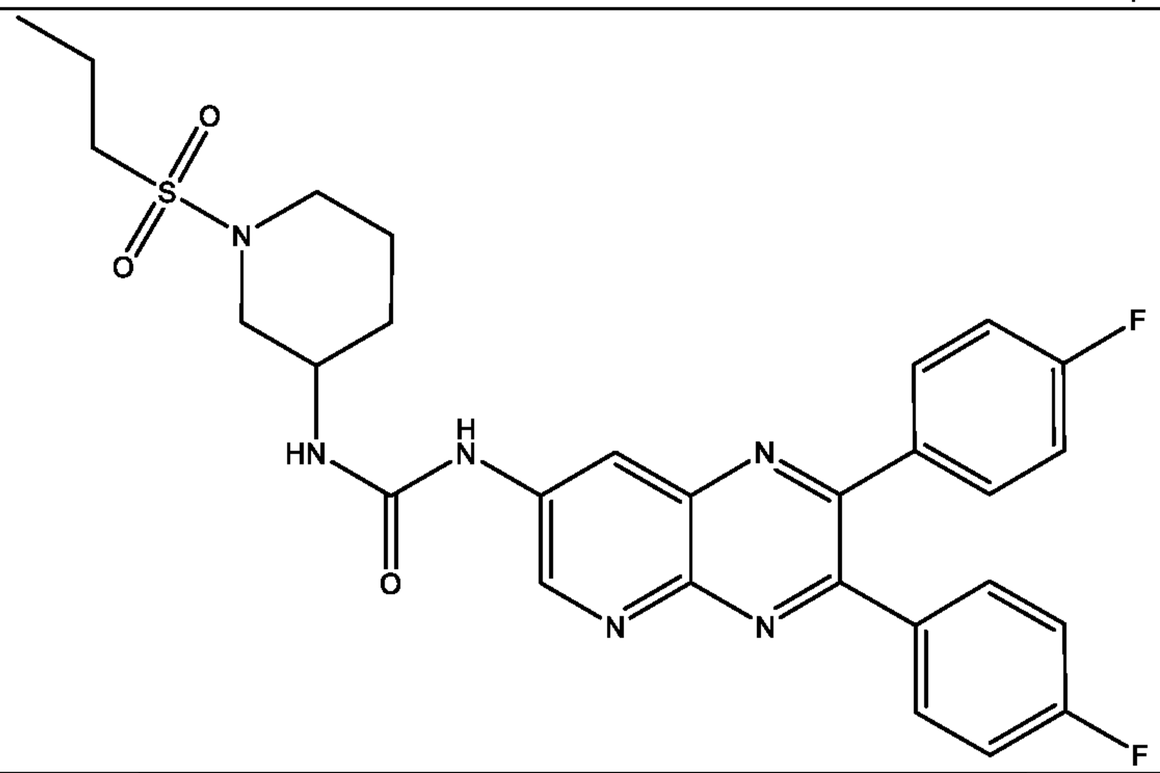
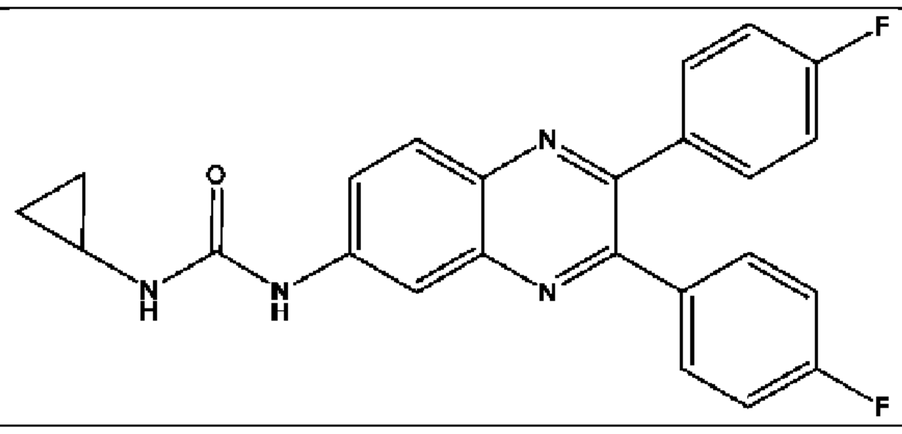
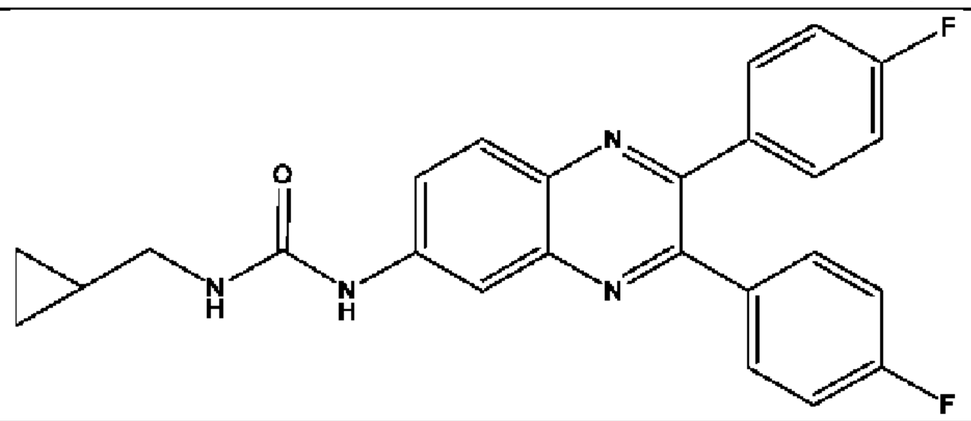
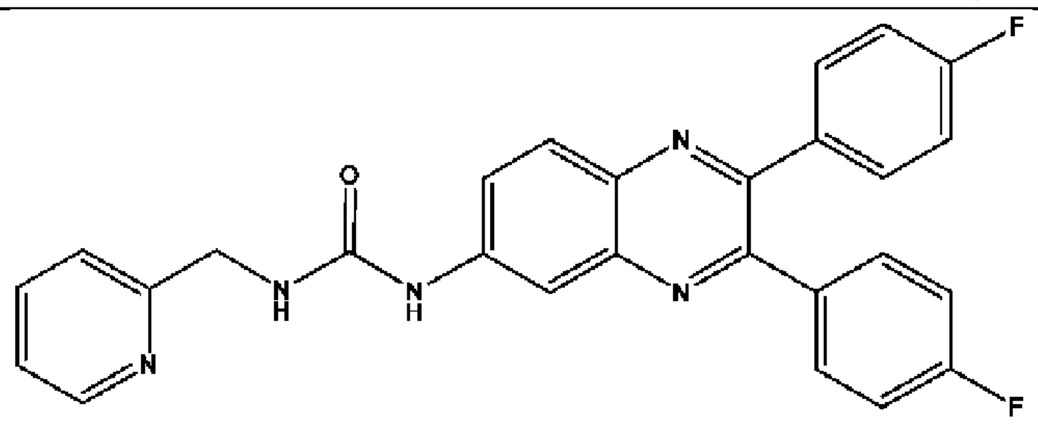
BC20321			
BC20330			
BC20333			
BC20334			
ZE18-0567			

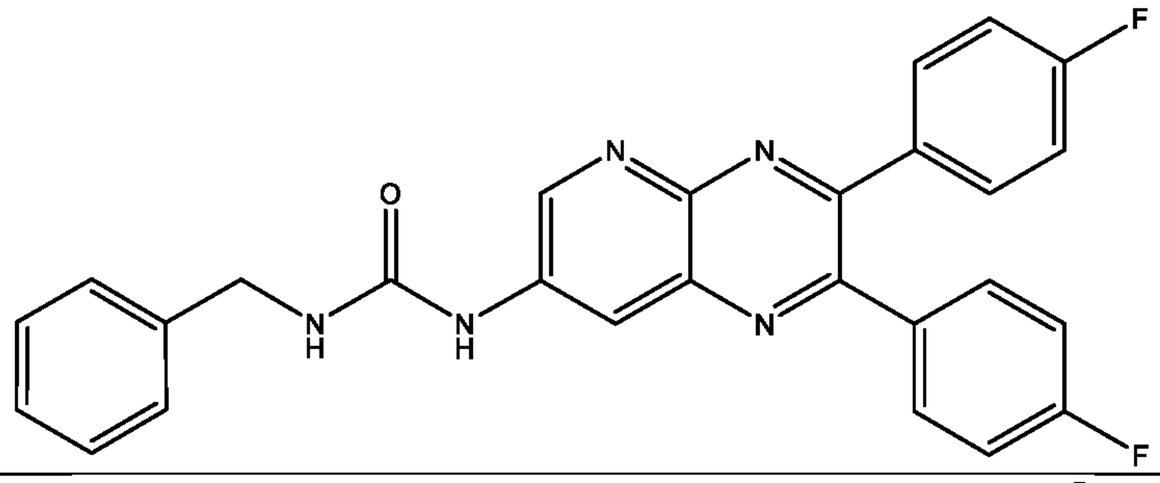
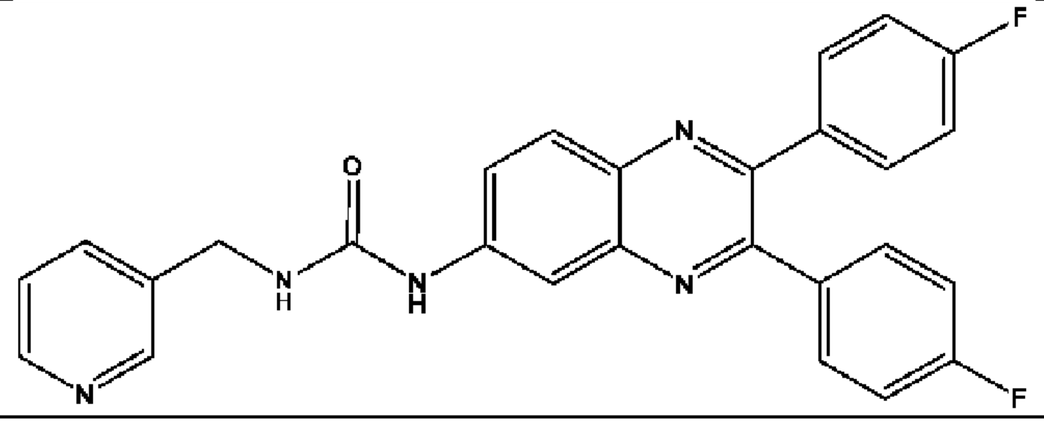
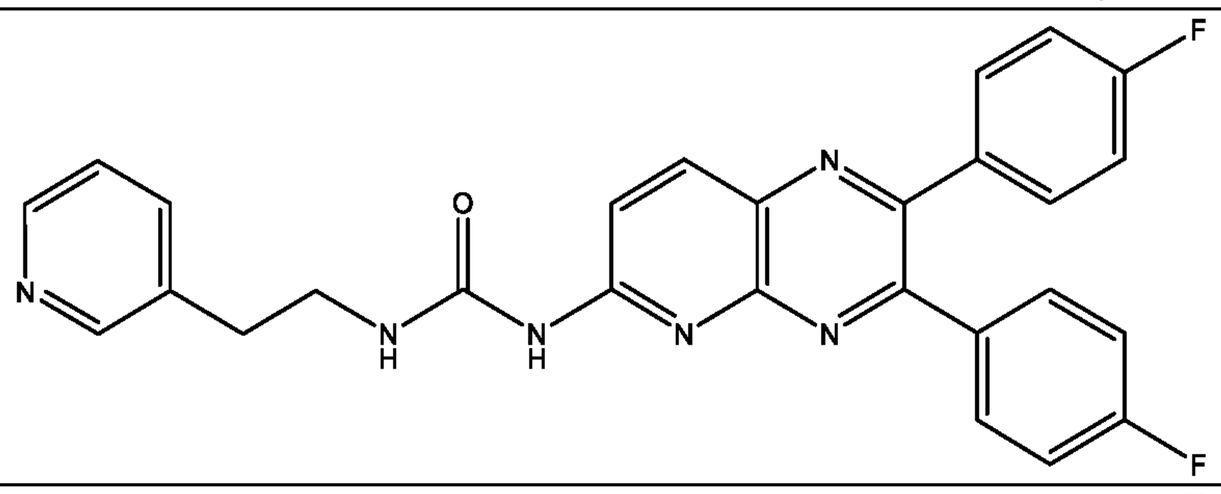
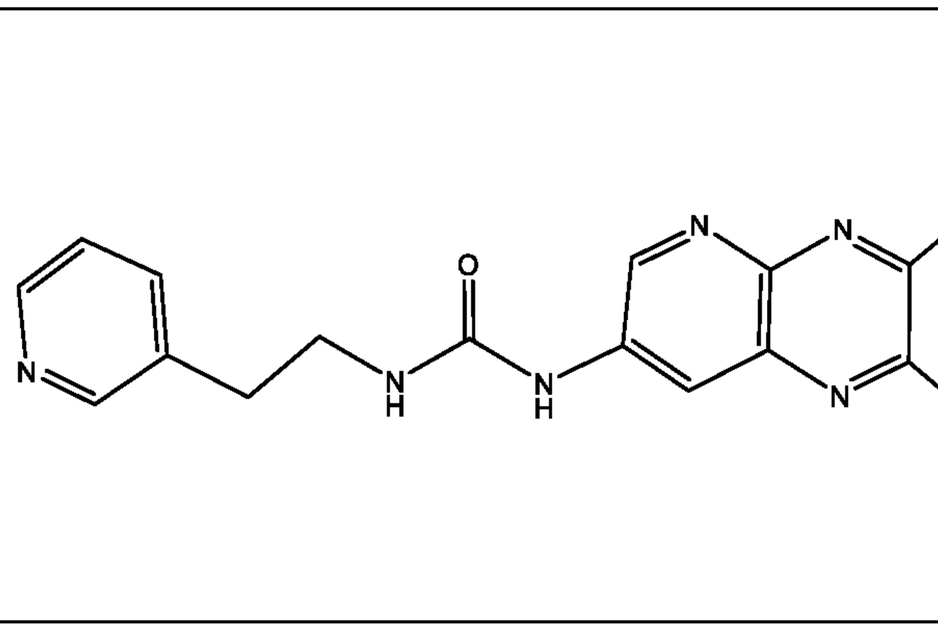
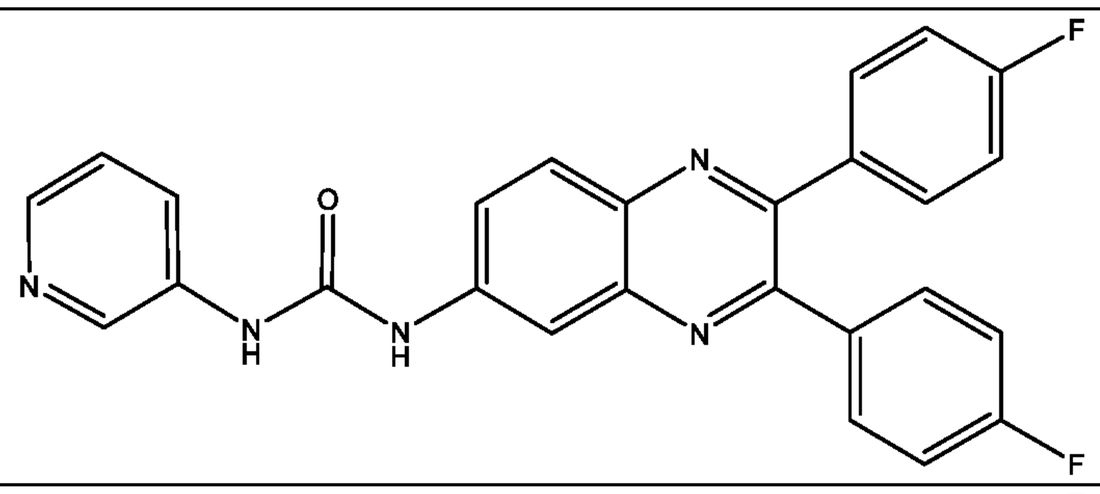
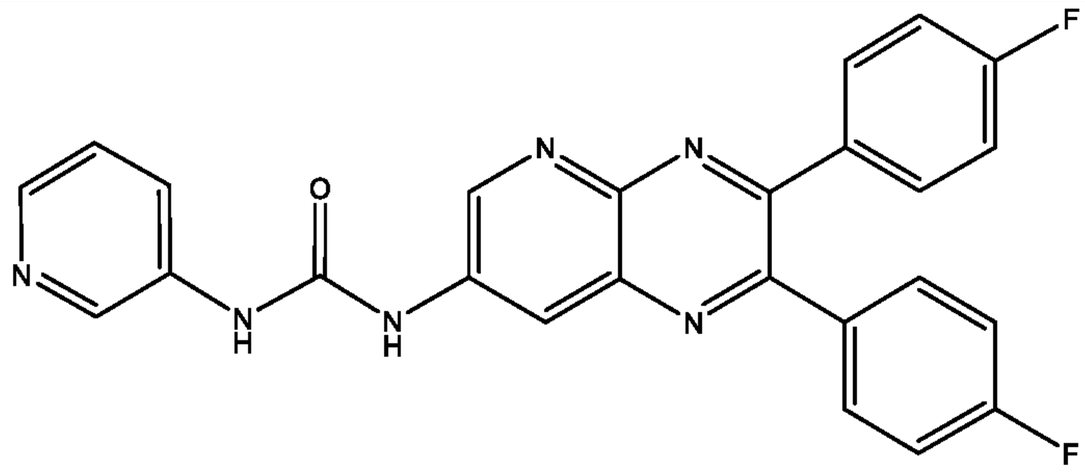
BC19510		+++	+
BC19511		++++	+
BC20218			
BC20219			
BC20226			
BC20277			

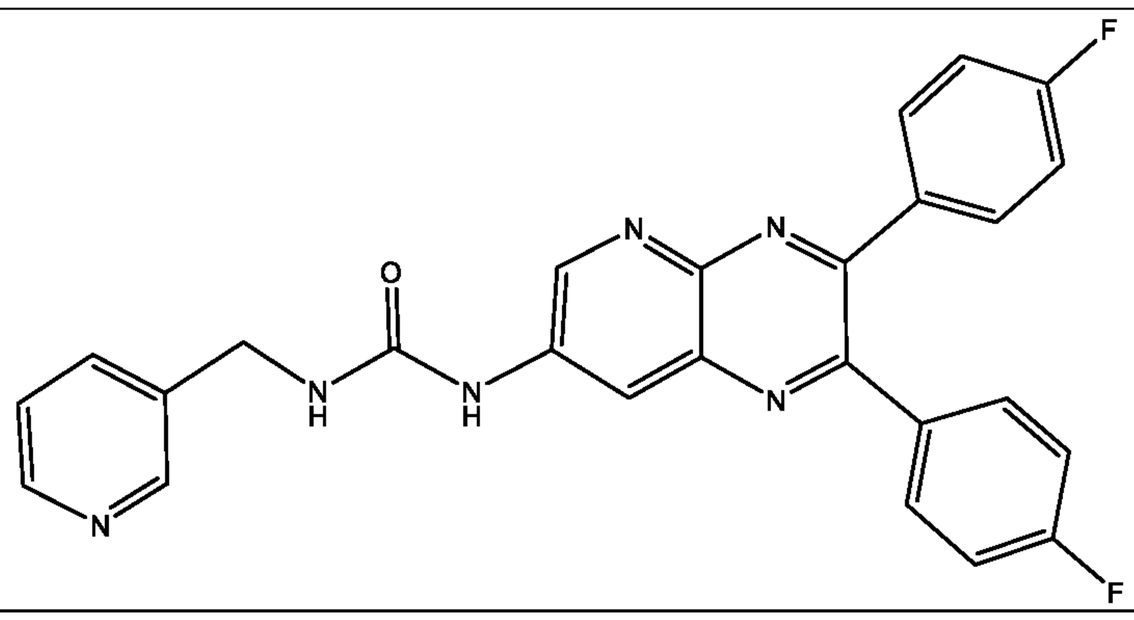
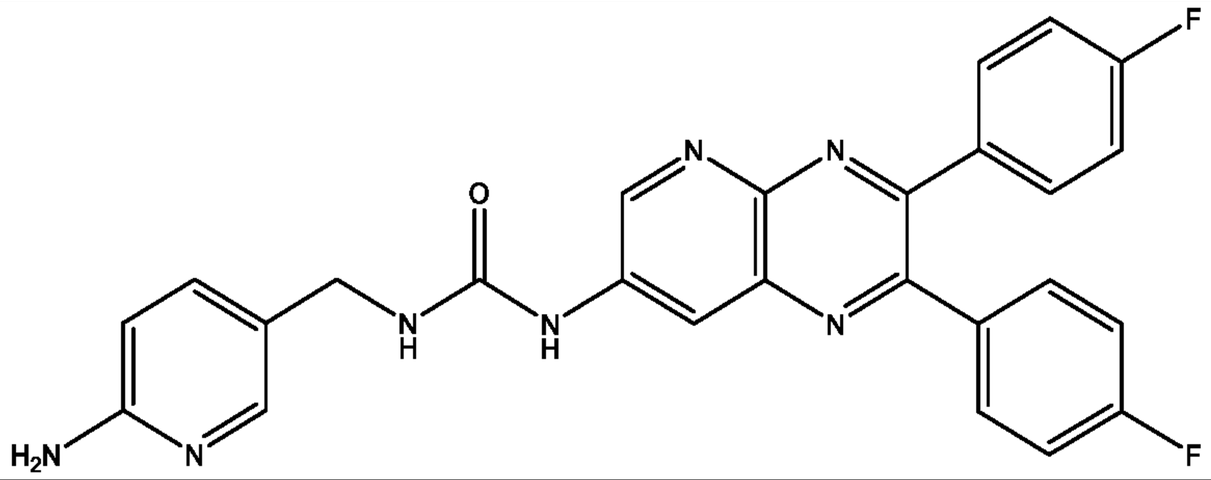
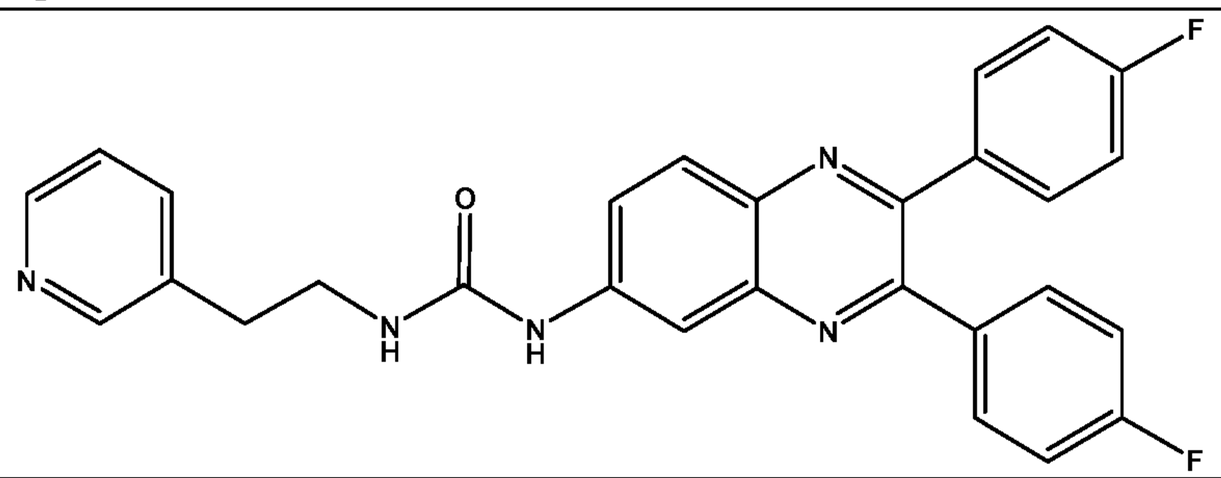
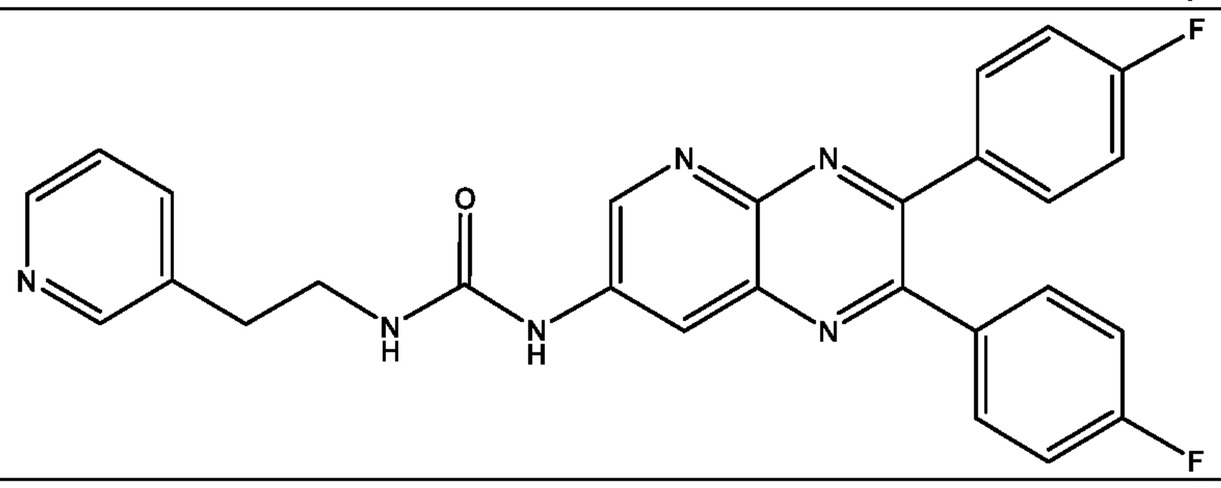
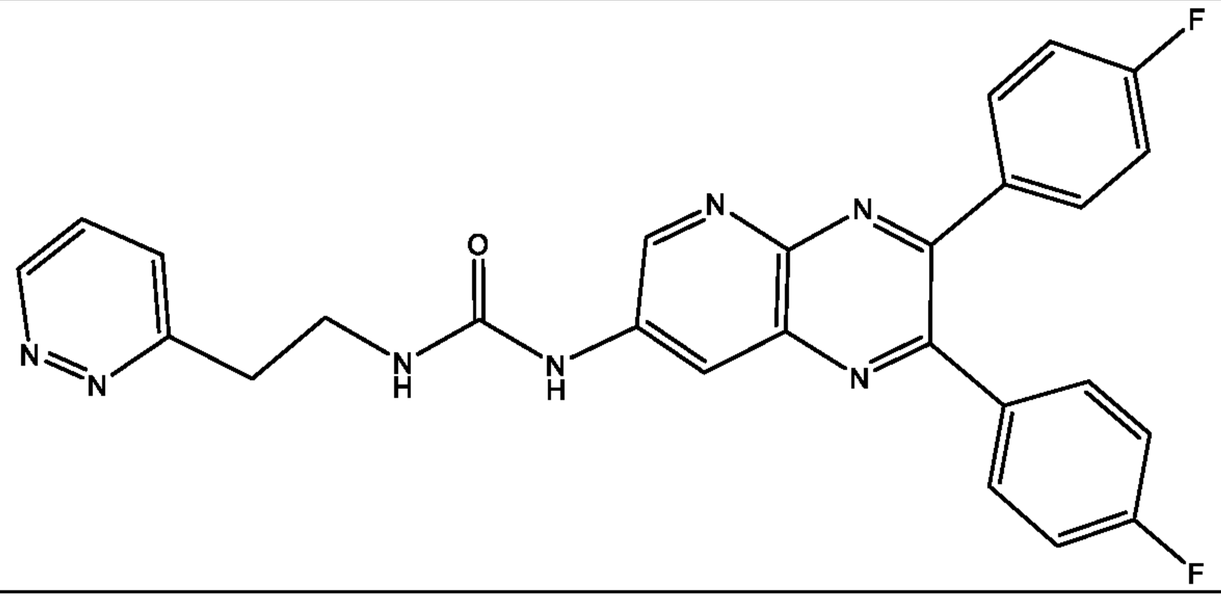
BC20291			
BC19563		++++	+
BC20297			
BC19564		++++	++
BC20312			
BC19565		++++	+

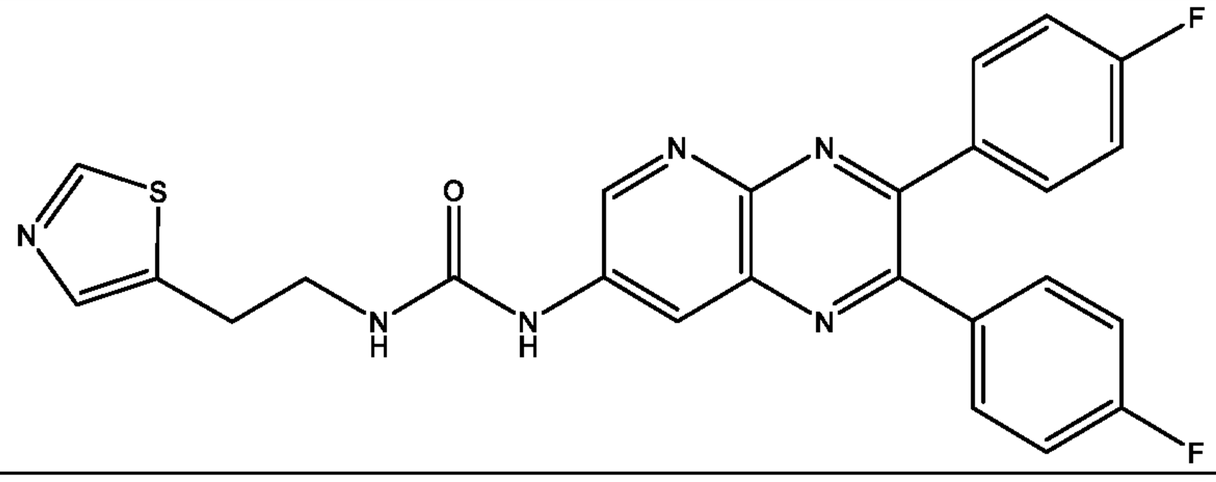
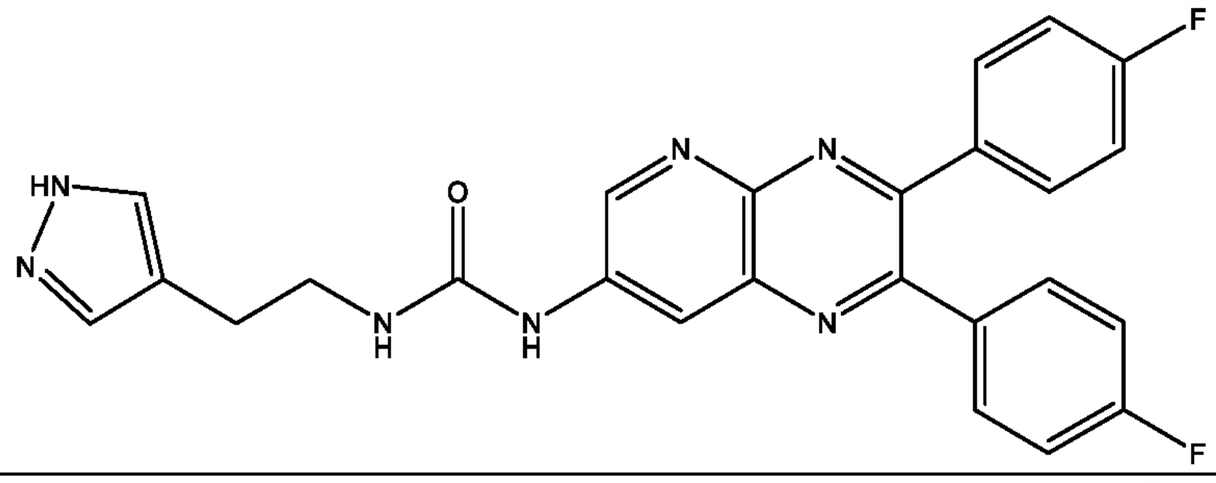
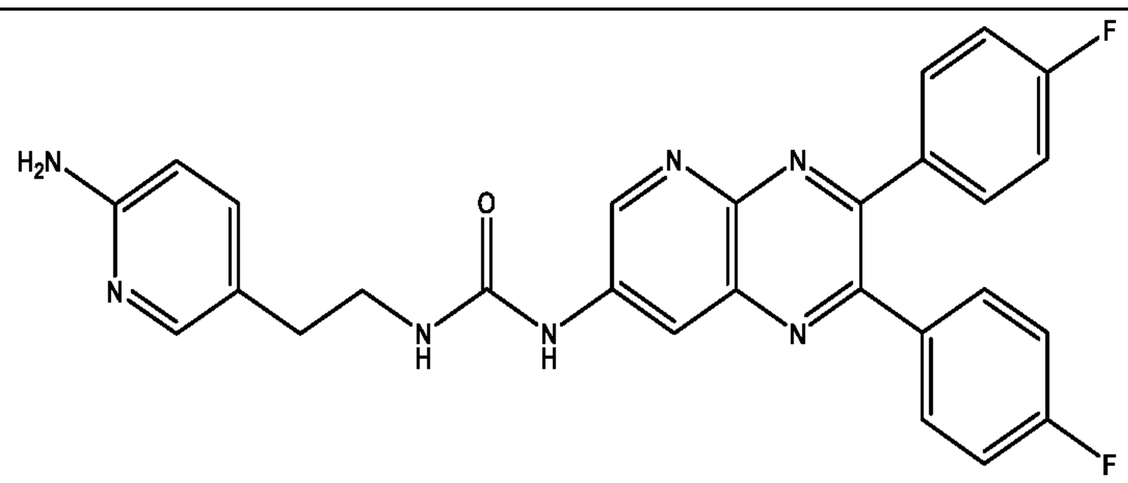
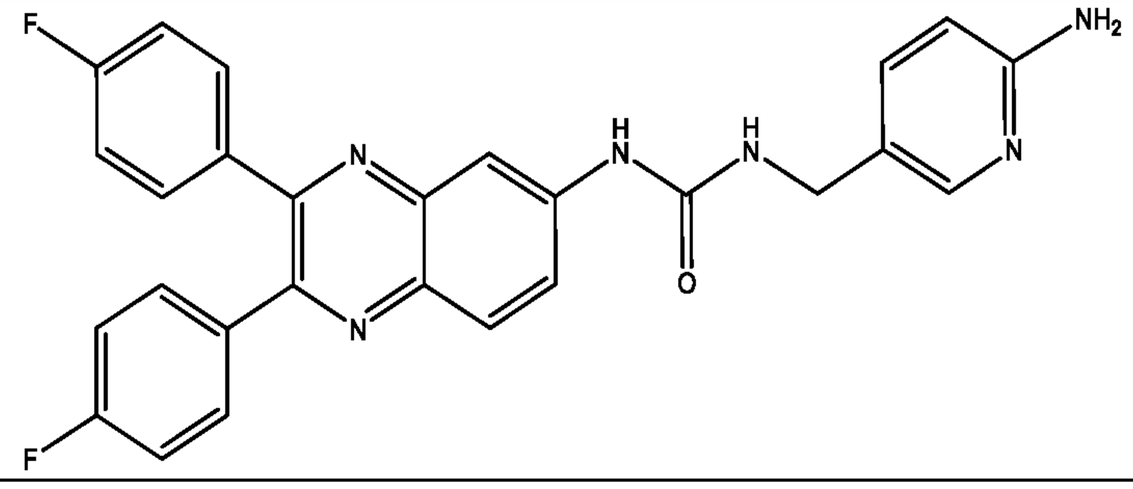
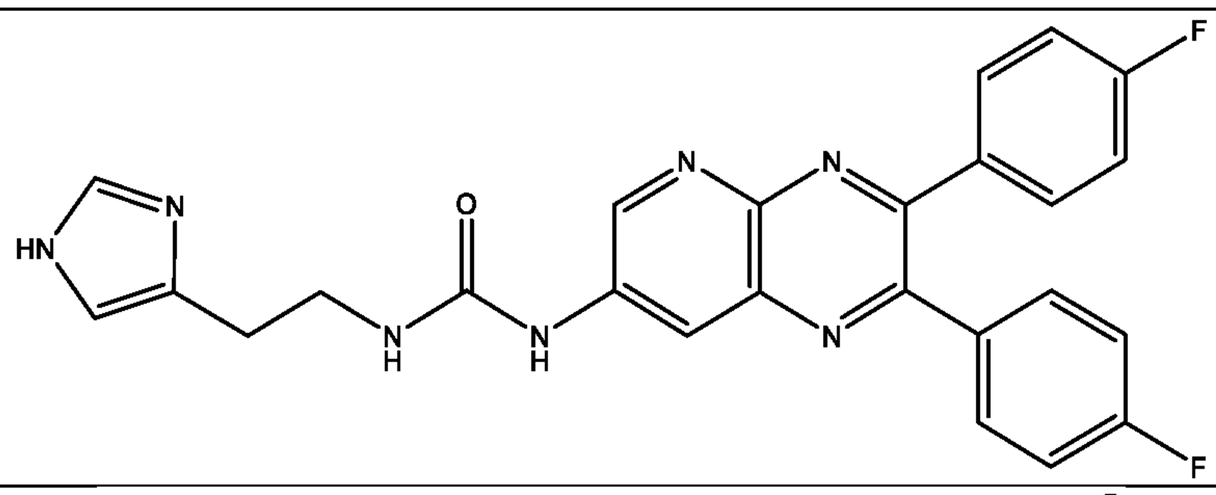
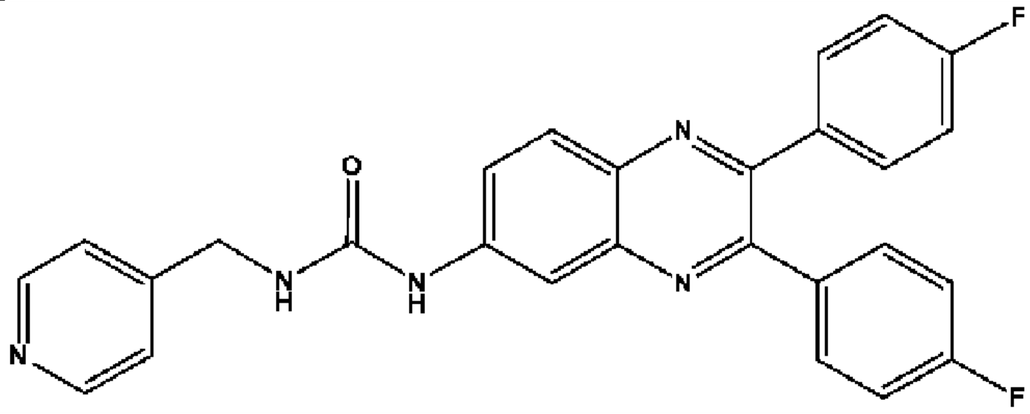
BC20298			
BC19566		++++	+
BC19567		+++	++
BC20299			
BC20300			

BC20217			
BC20225			
BC20237			
BC20238			
BC20239			
BC20255			

BC20256			
BC20269			
BC20293			
BC19568		+++	+
BC19569		+++	+
BC19570		+++	+

BC20207			
BC19571		+++	++
BC20310			
BC20311			
BC20224			
BC20254			

BC20213			
BC20316			
BC20216			
BC20268			
BC20314			

BC20315			
BC20318			
BC20320			
BC20331			
BC20319			
BC19572		+++	+

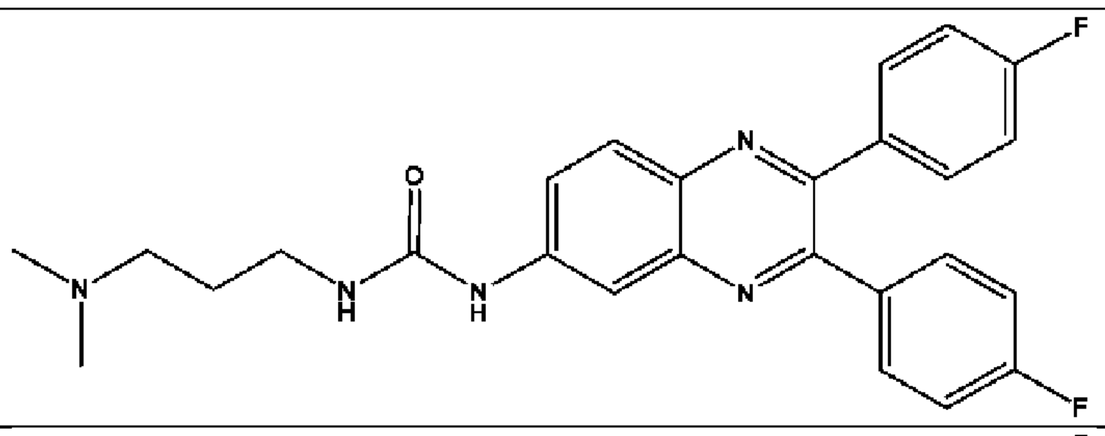
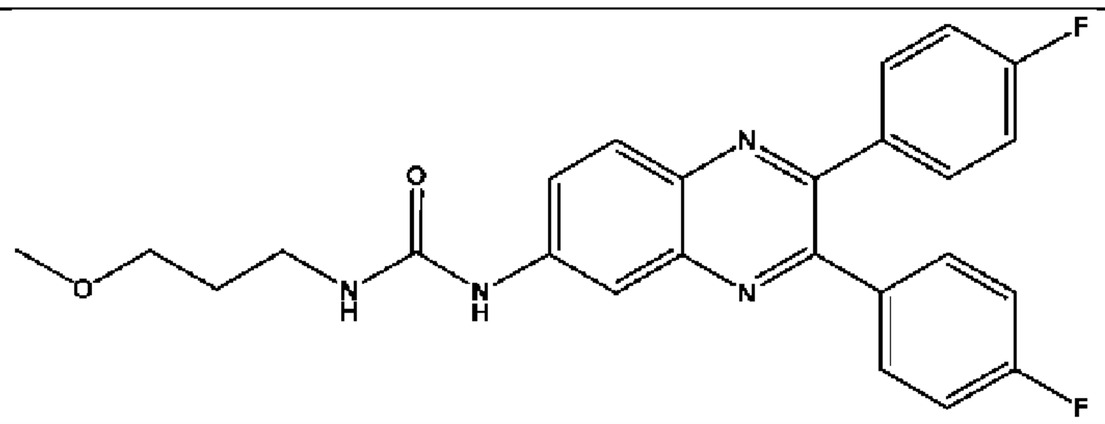
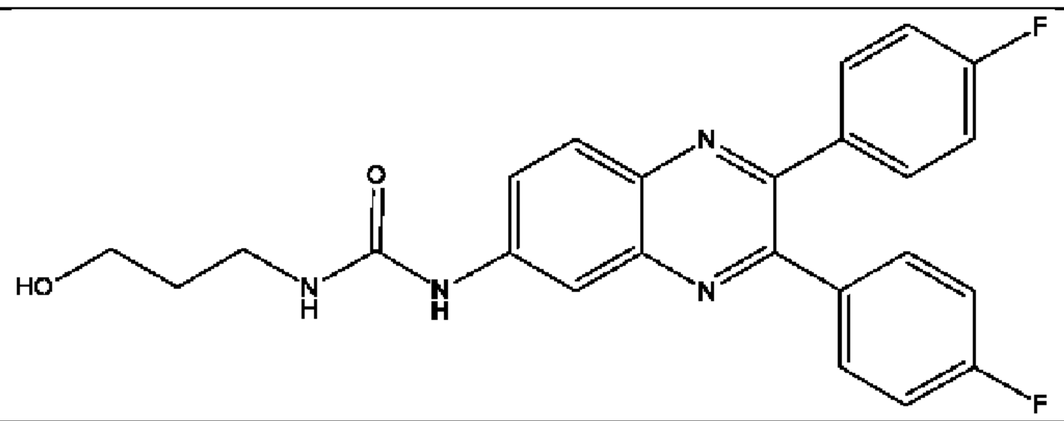
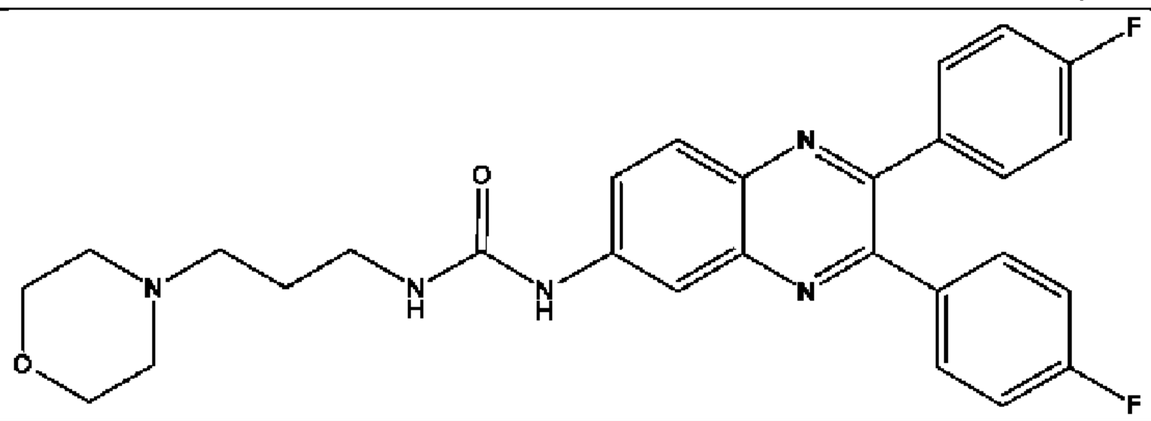
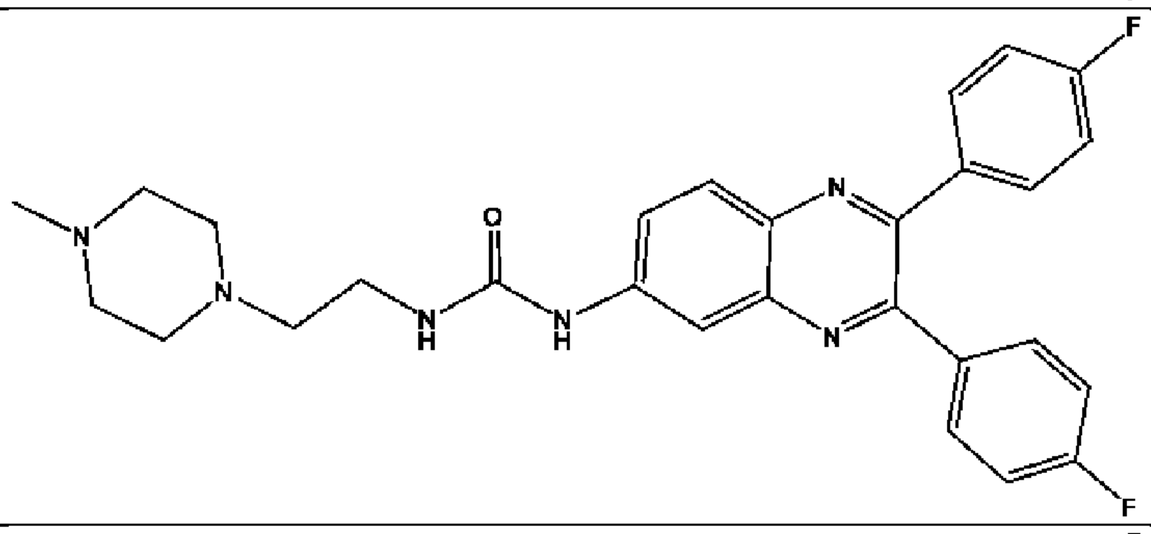
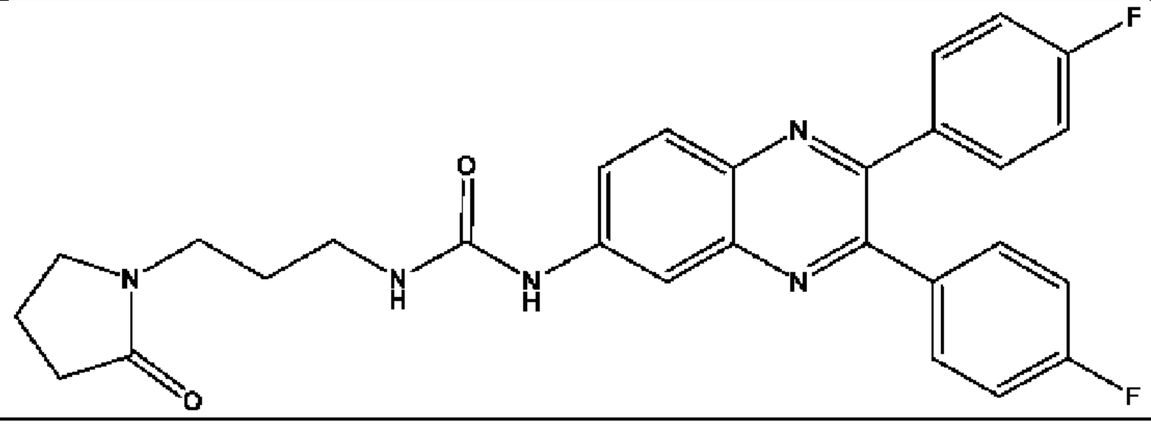
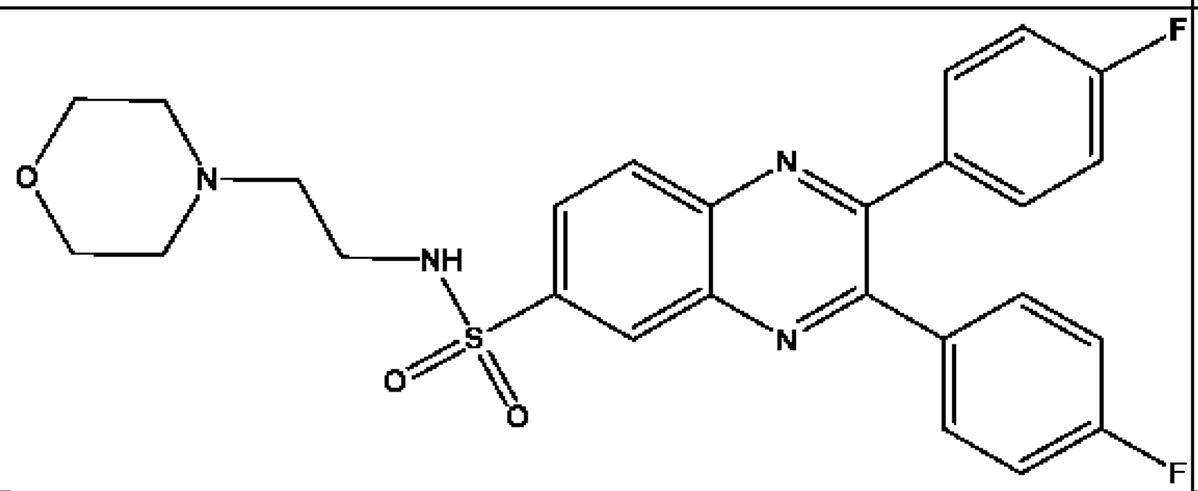
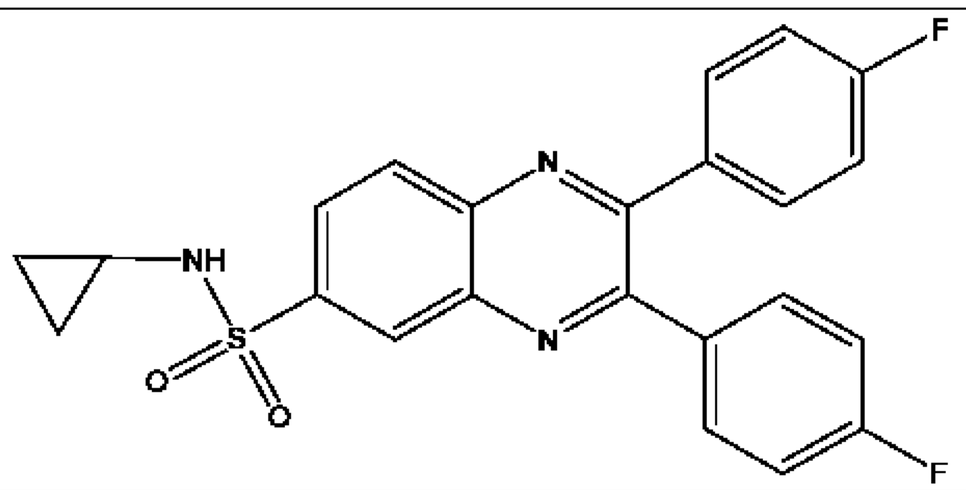
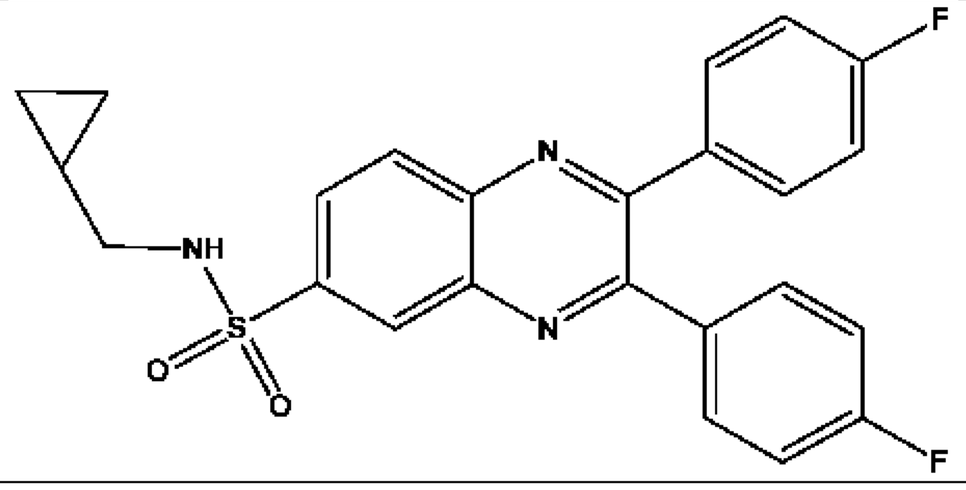
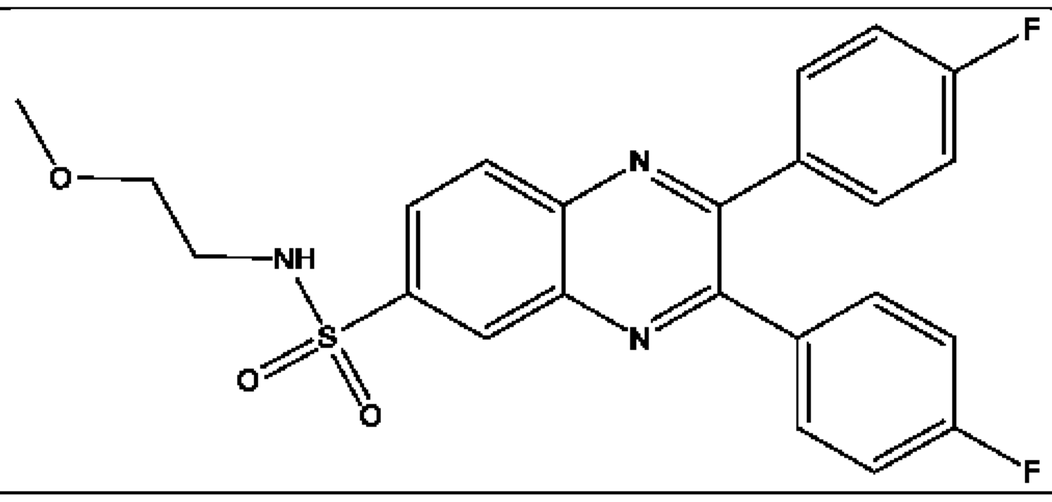
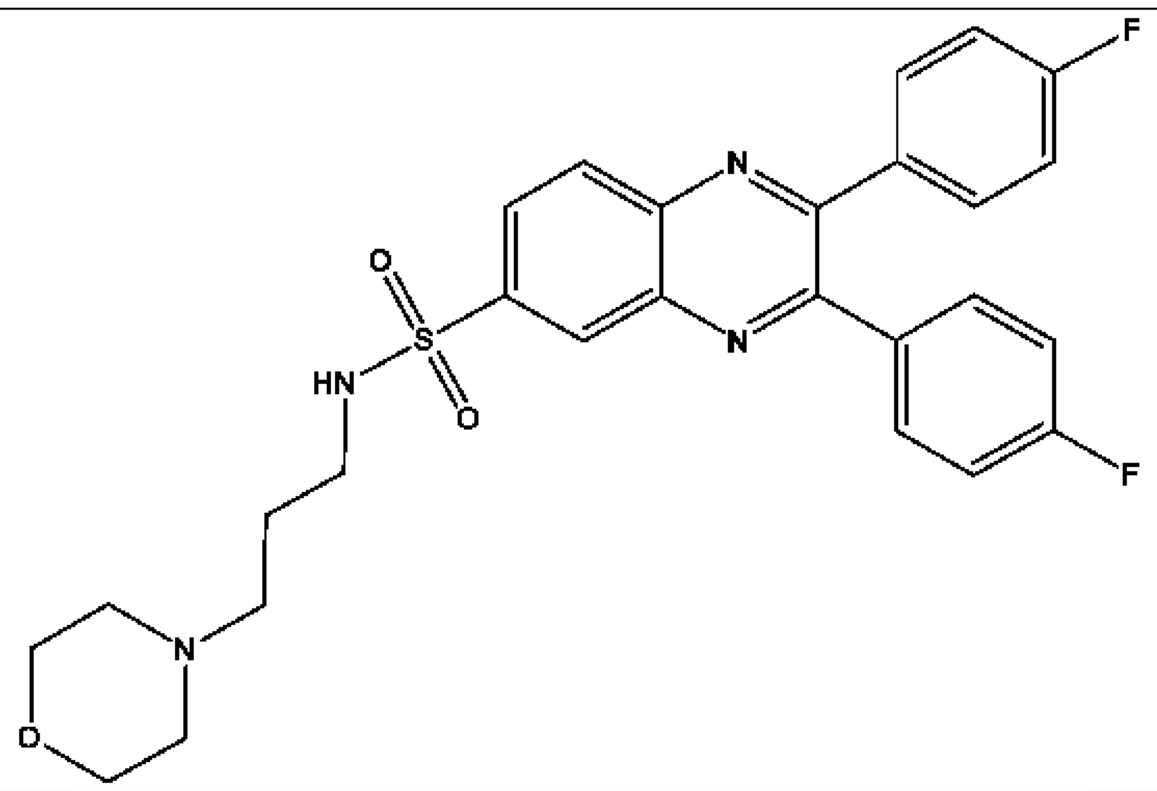
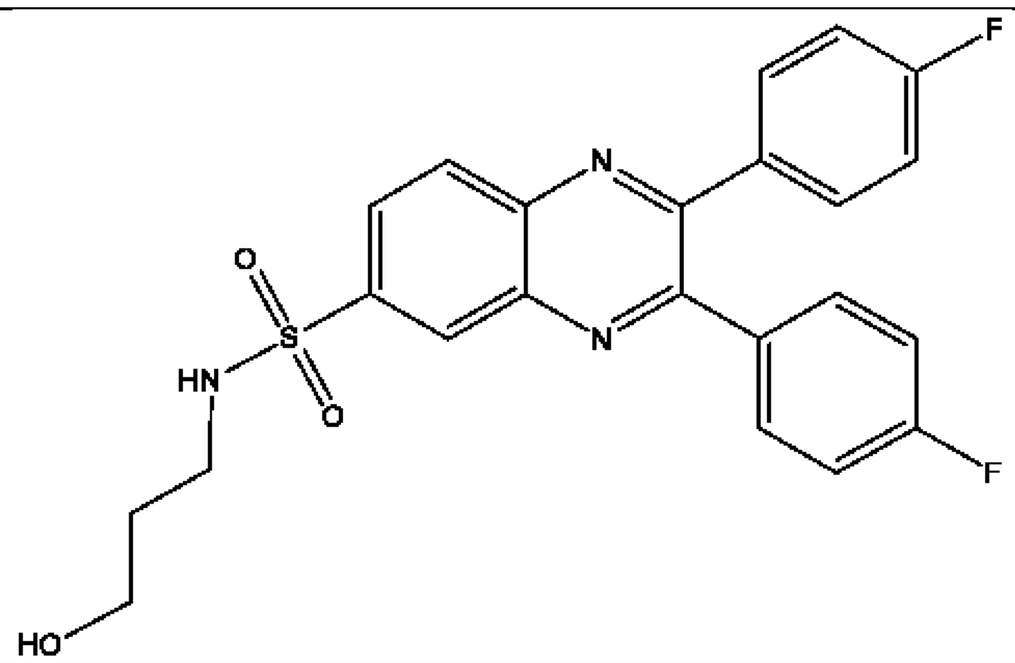
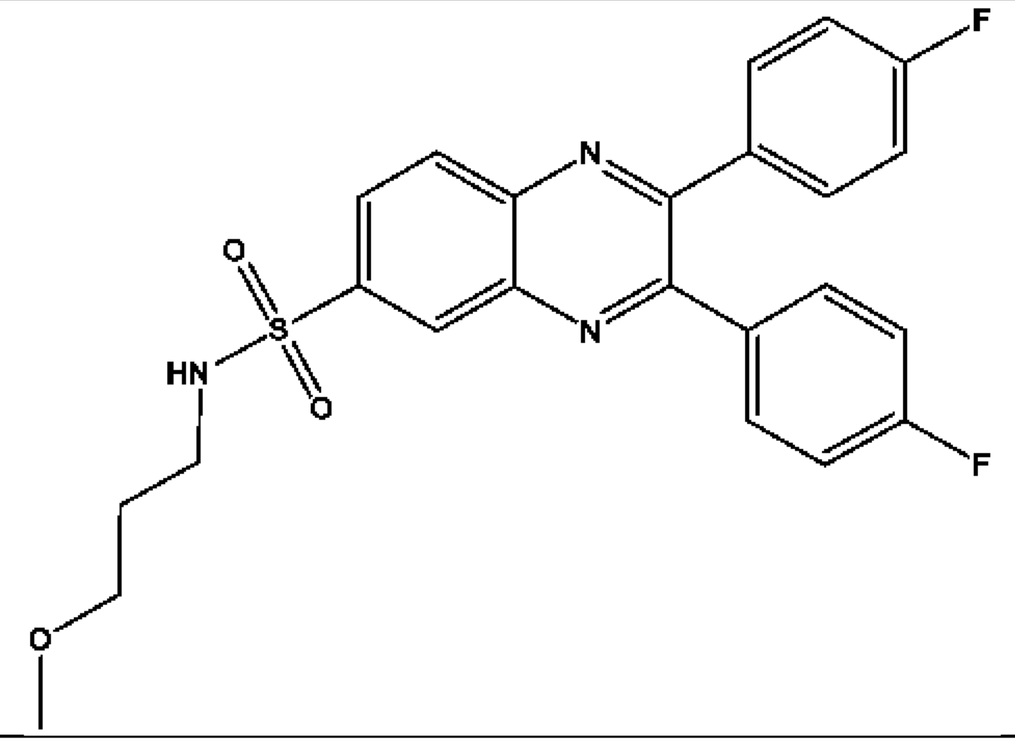
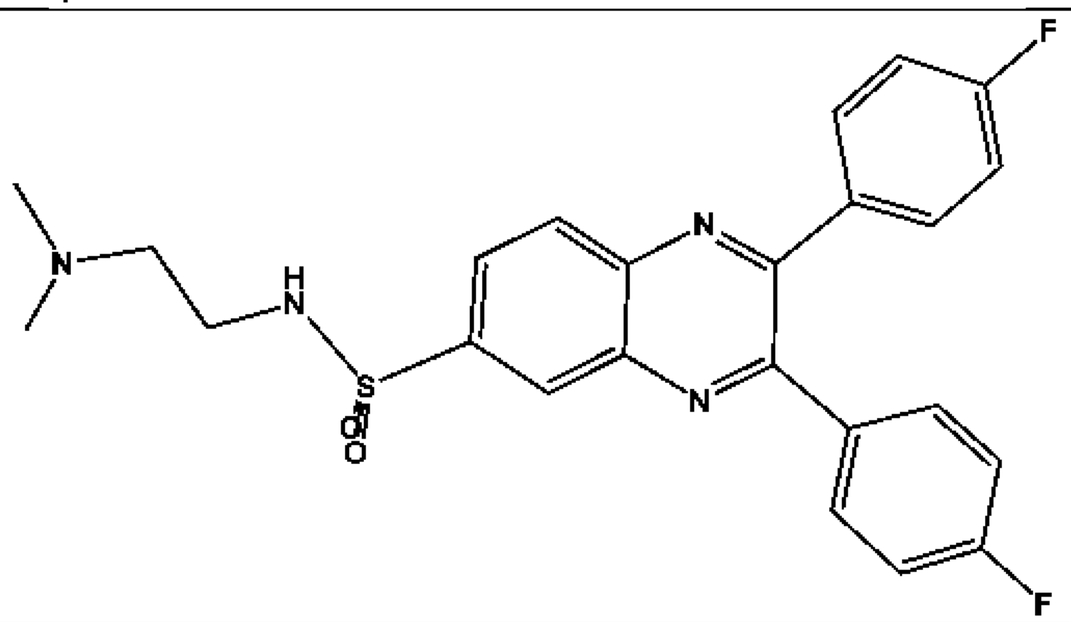
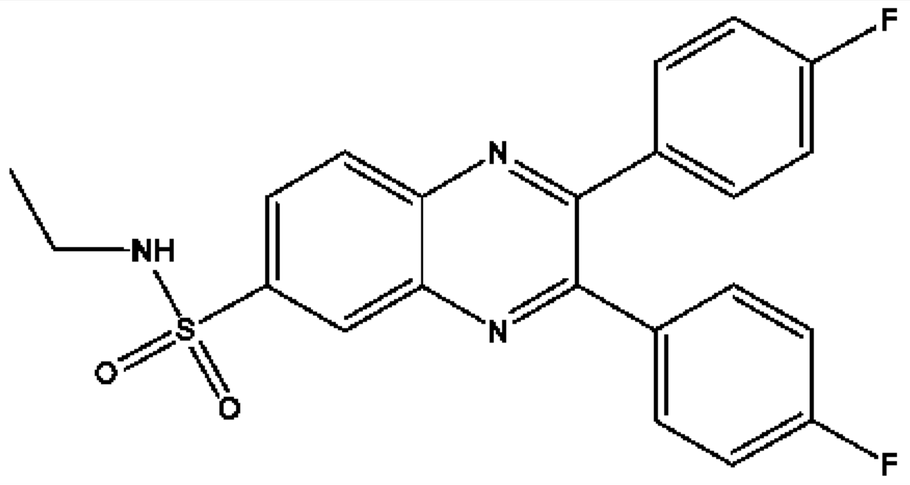
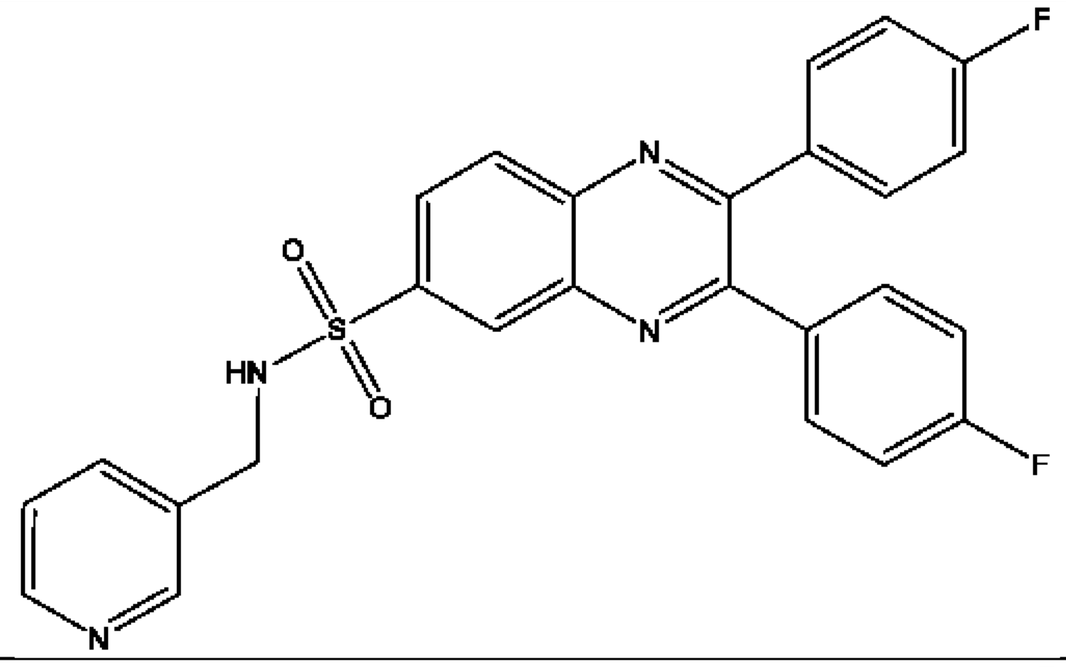
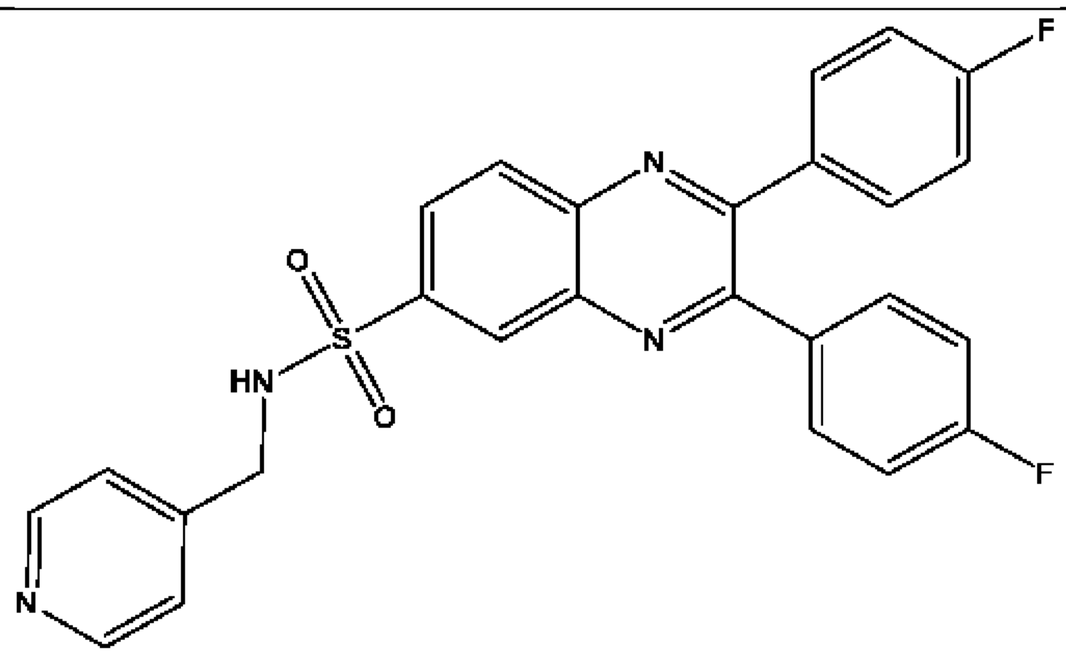
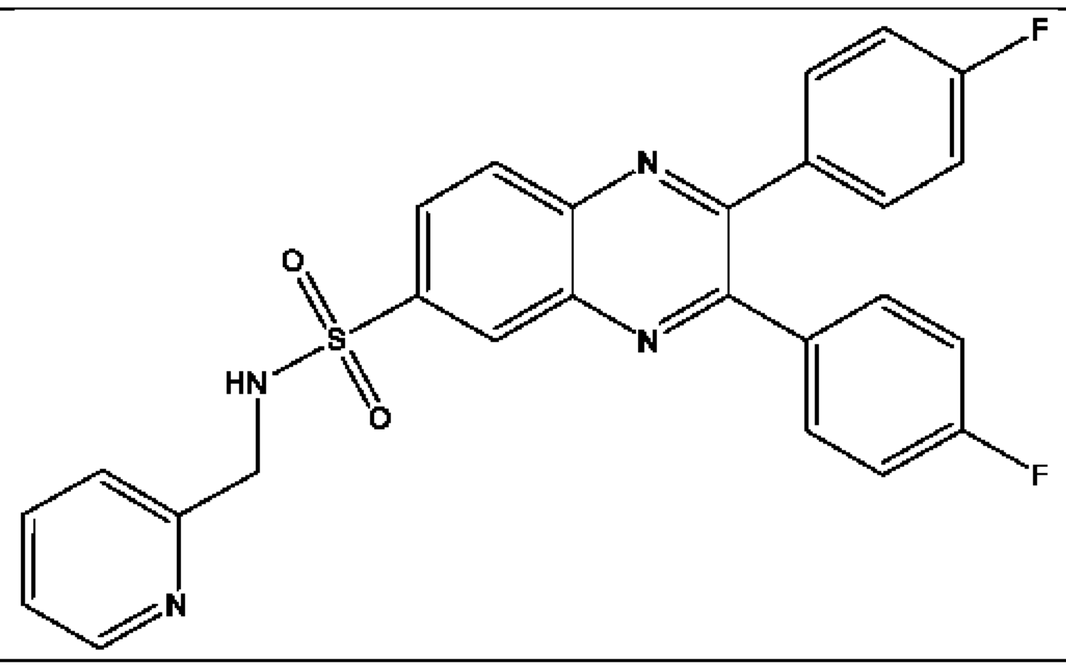
BC19573		+++	+++
BC19574		+++	+
BC19575		+++	+
BC19576		+++	+
BC19616		+++	++
BC19617		+++	+

Table 4g

BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19504		+++	+
BC19505		+++	+
BC19506		+++	+
BC19507		++++	+

BC19508		+++	++
BC19509		++++	+
BC19554		++++	+
BC19555		++++	++

BC19556		+++	+
BC19557		++++	+
BC19558		+++	+
BC19559		++++	+

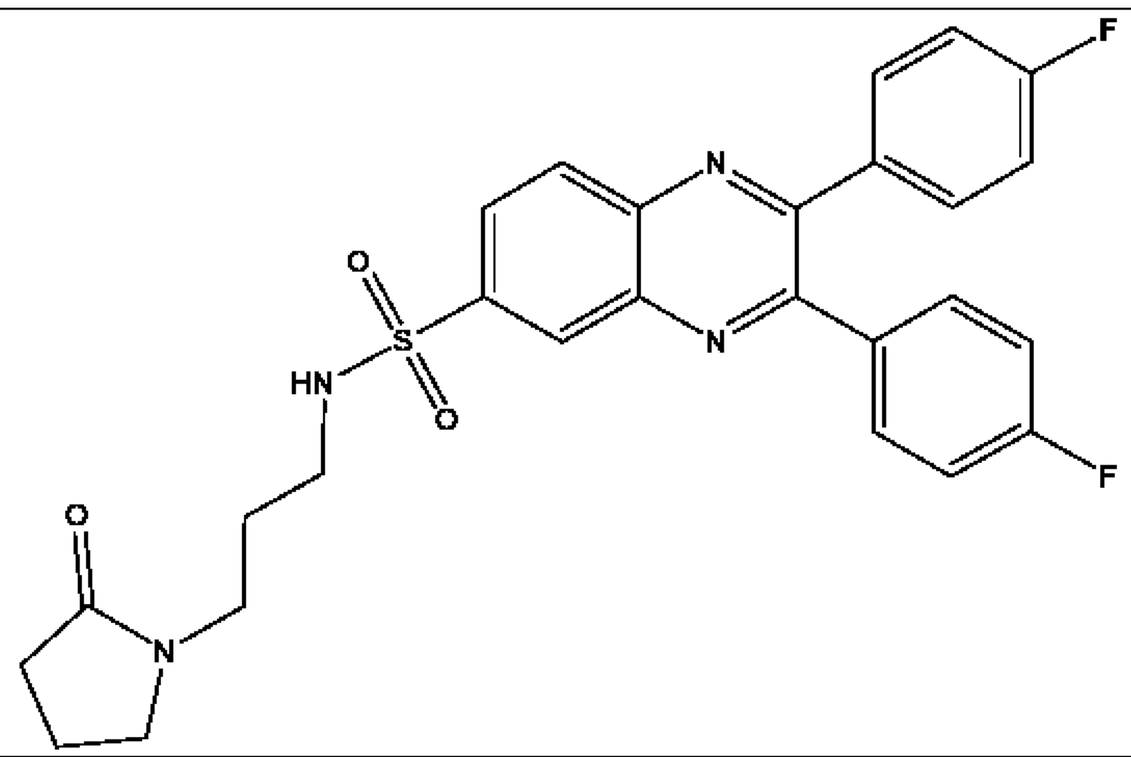
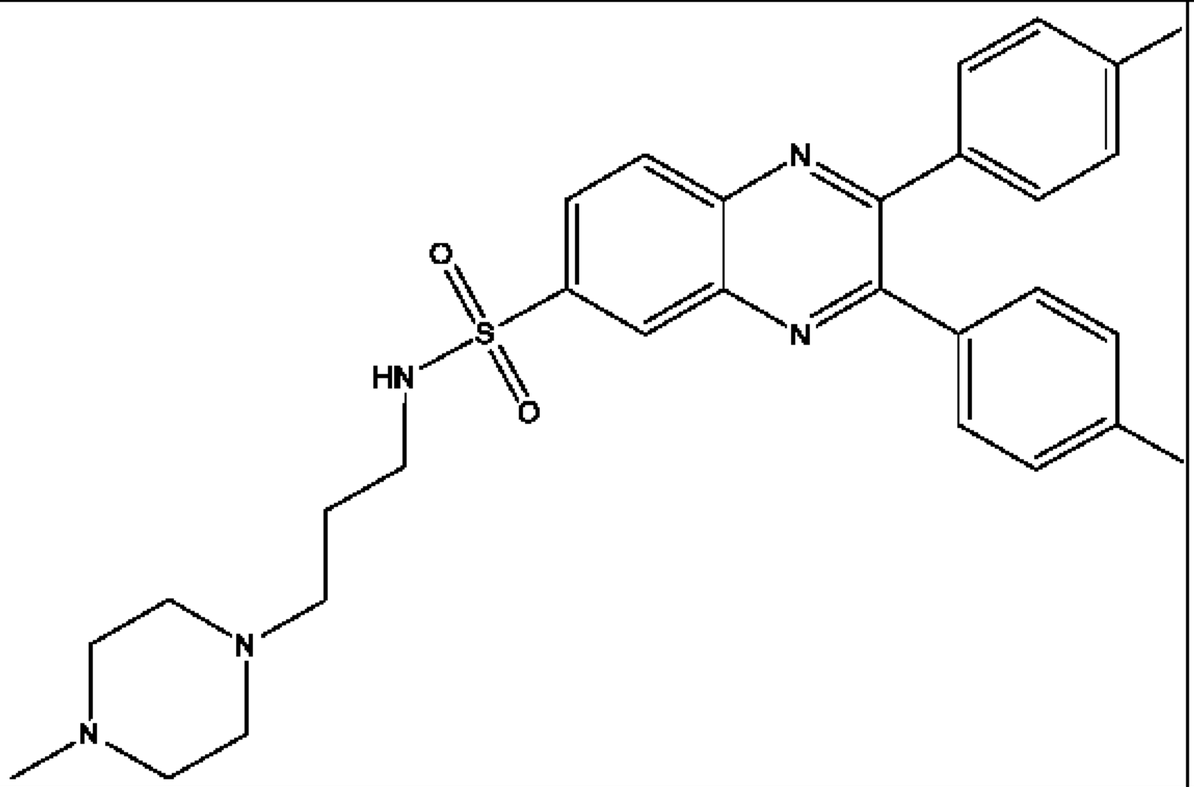
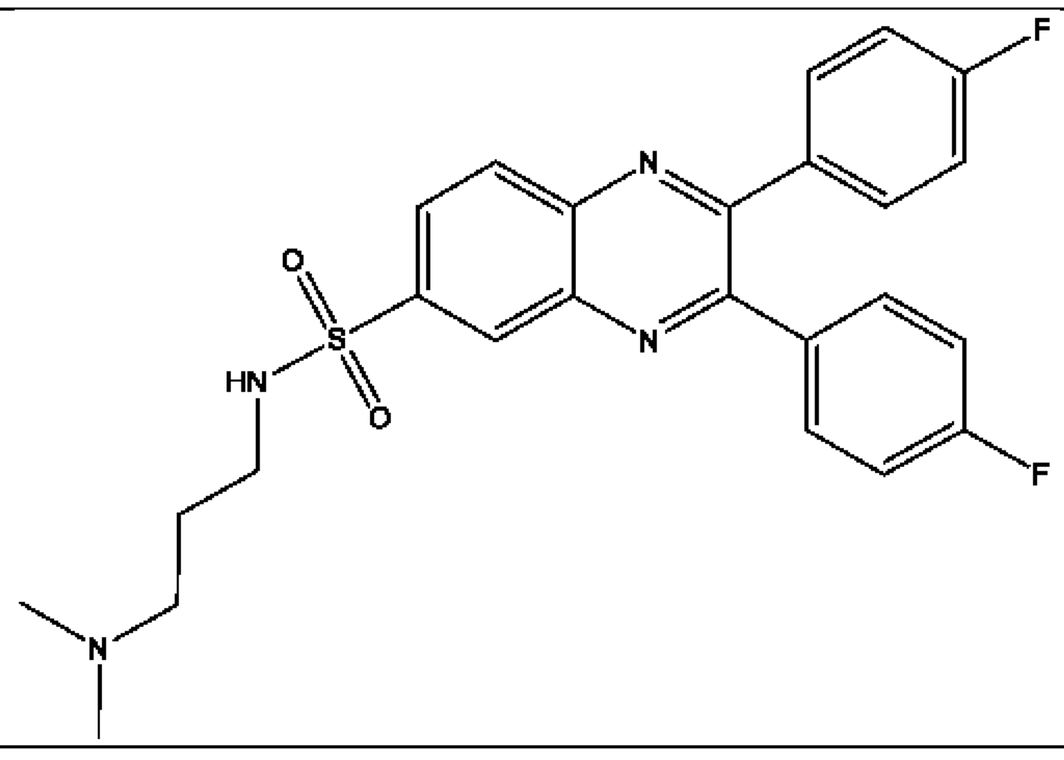
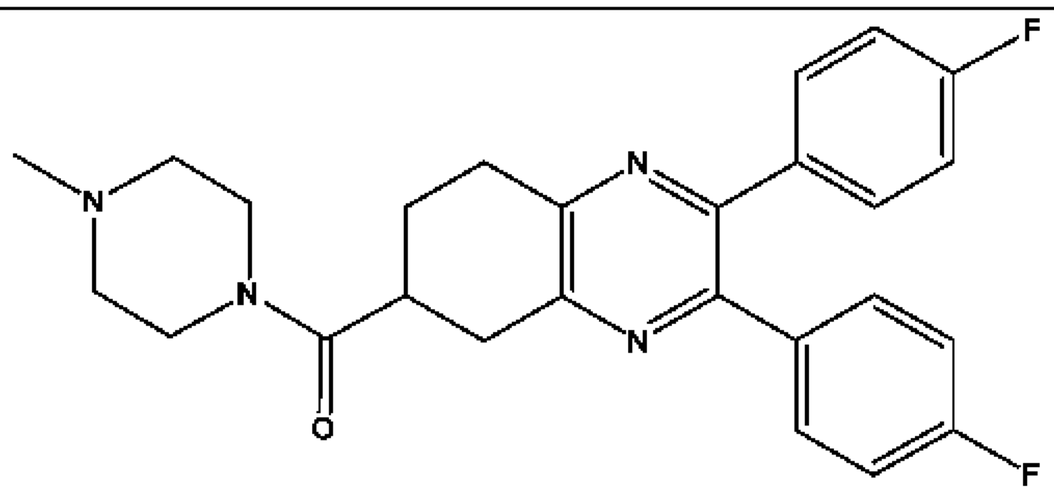
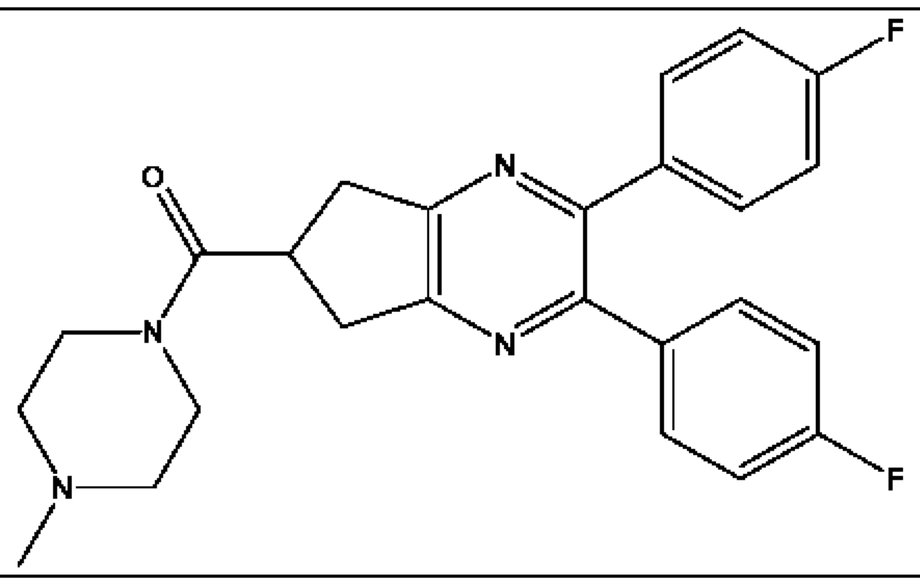
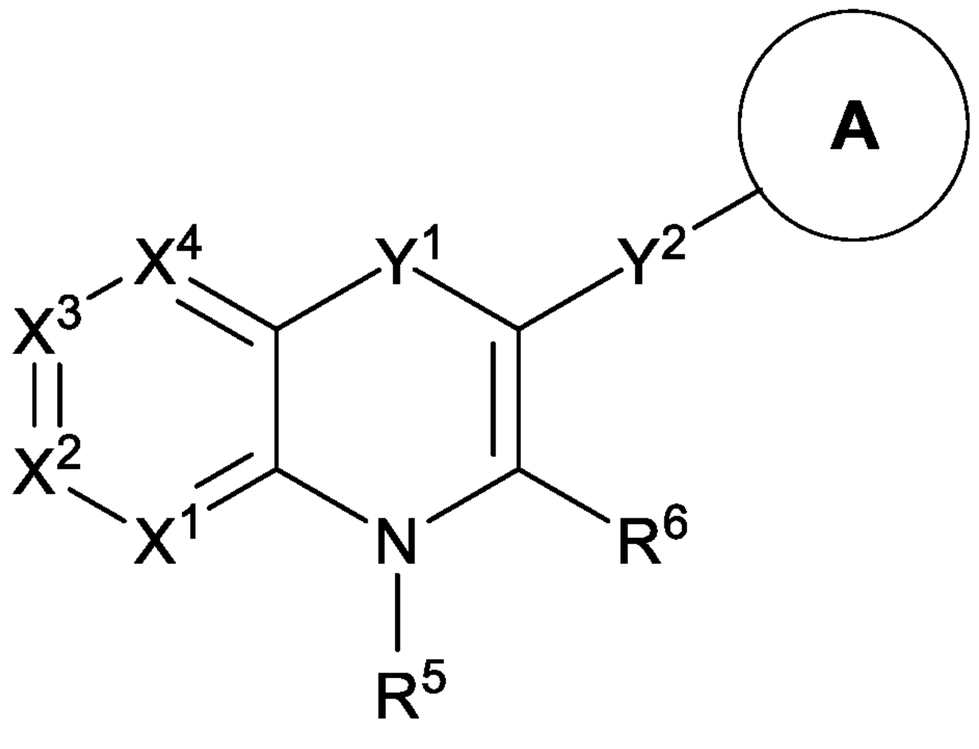
BC19560		++++	+
BC19561		+++	+
BC19562		+++	++

Table 17

BC No.	Structure	IC_{50} (NF-κB assay)	IC_{50} (TNF assay)
BC19663		+++	+
BC19723		+++	+

NUMBERED PARAGRAPHS

1. A method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is selected from C(O) and $S(O)_2$;

Y^2 is selected from C(O) and $S(O)_2$;

X^1 is selected from N and CR^1;

X^2 is selected from N and CR^2;

X^3 is selected from N and CR^3;

X^4 is selected from N and CR^4;

provided that no more than two of X^1, X^2, X^3, and X^4 are N;

each of R^1, R^2, R^3, R^4, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^5 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from Cy^1, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

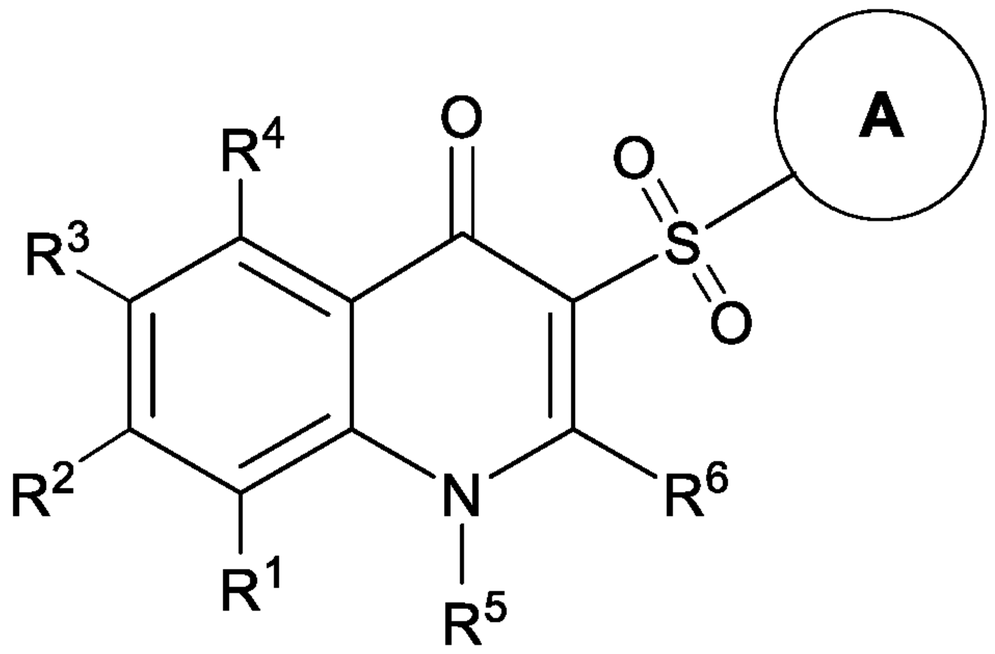
2. The method of paragraph 1, wherein Y^1 is C(O).

3. The method of paragraph 1, wherein Y^1 is $S(O)_2$.

4. The method of any one of paragraphs 1-3, wherein Y^2 is C(O).

5. The method of any one of paragraphs 1-3, wherein Y^2 is $S(O)_2$.

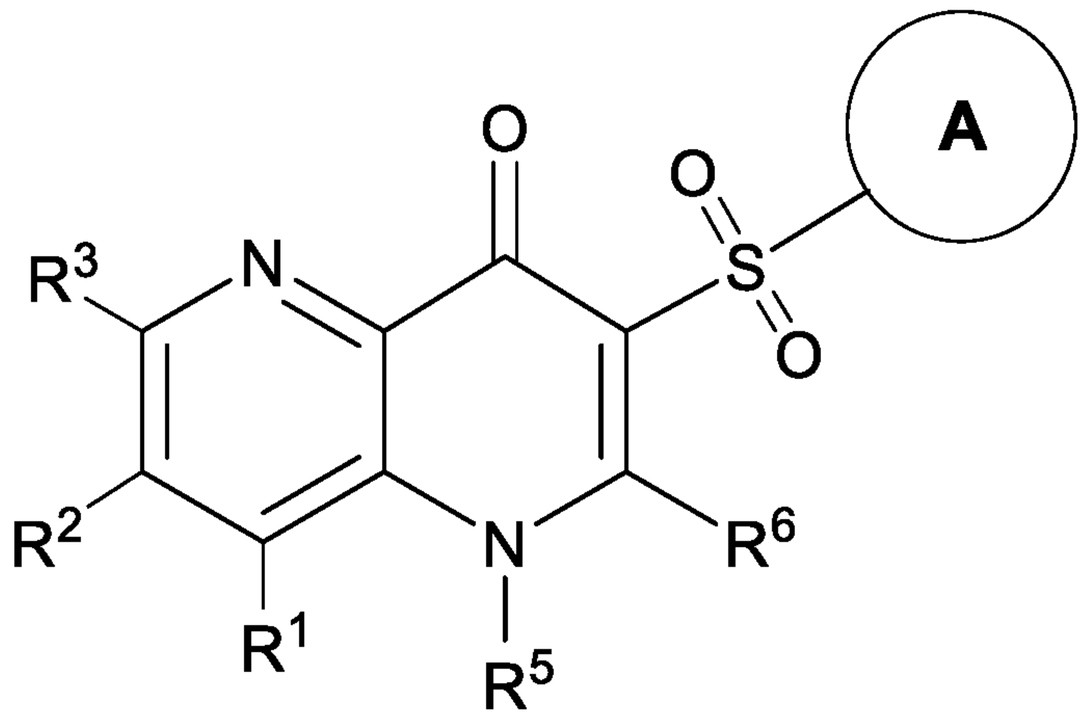
6. The method of paragraph 1, wherein the compound of Formula (Ia) has formula:



,

or a pharmaceutically acceptable salt thereof.

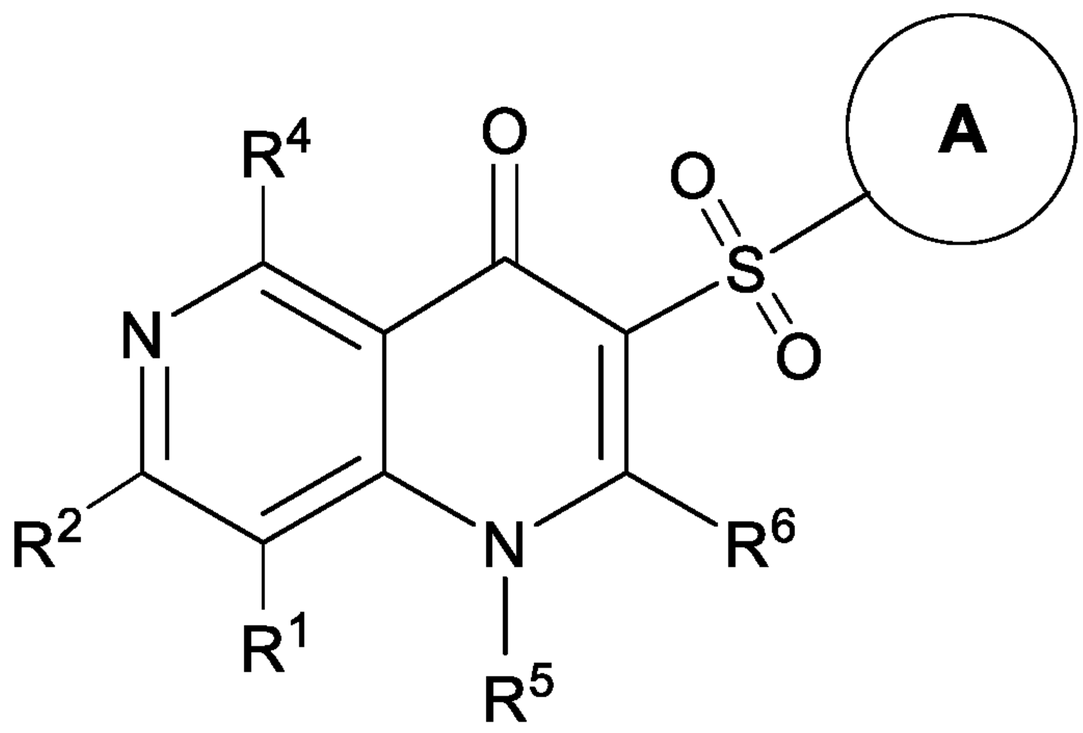
7. The method of paragraph 1, wherein the compound of Formula (Ia) has formula:



,

or a pharmaceutically acceptable salt thereof.

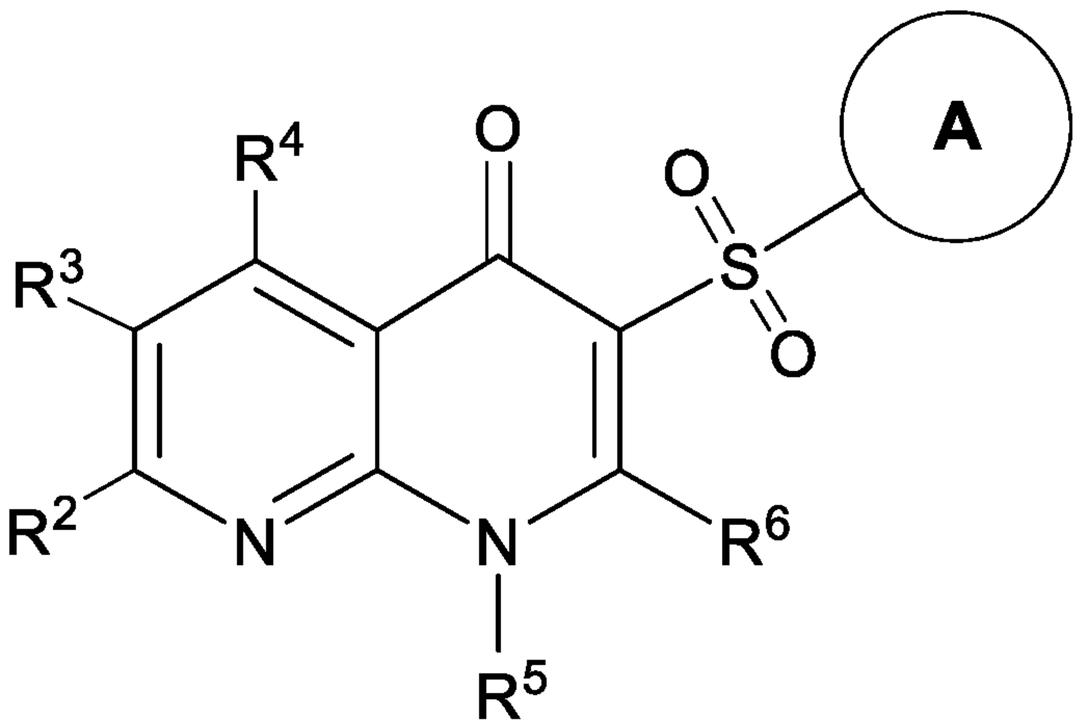
8. The method of paragraph 1, wherein the compound of Formula (Ia) has formula:



,

or a pharmaceutically acceptable salt thereof.

9. The method of paragraph 1, wherein the compound of Formula (Ia) has formula:



,

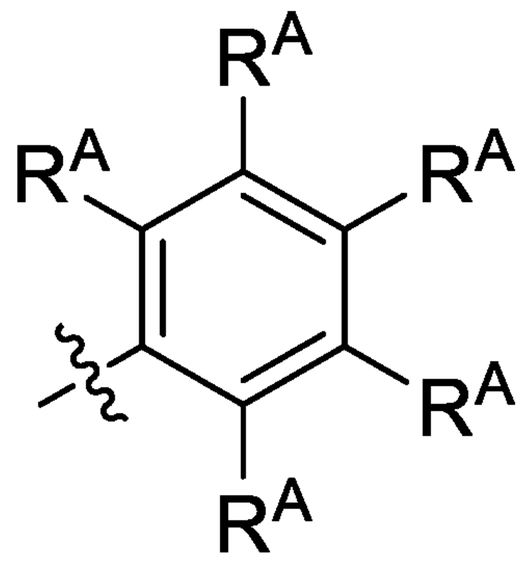
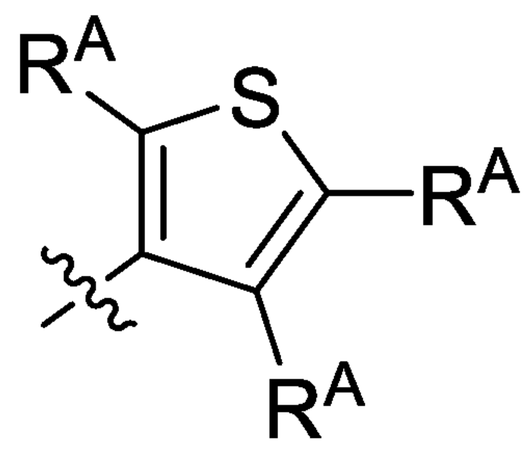
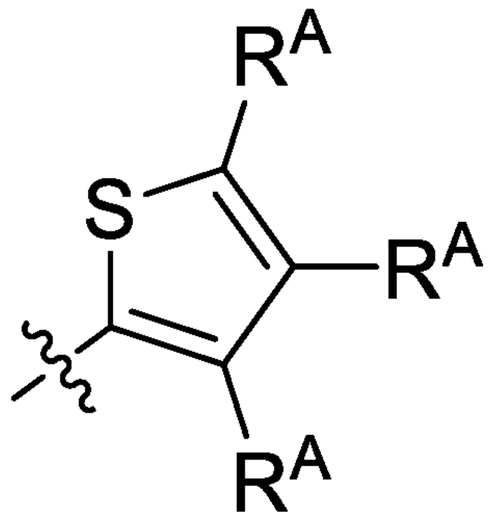
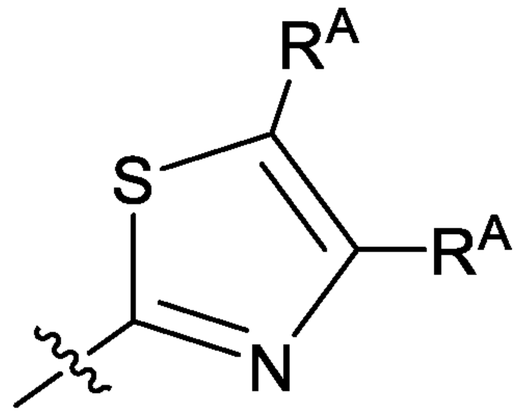
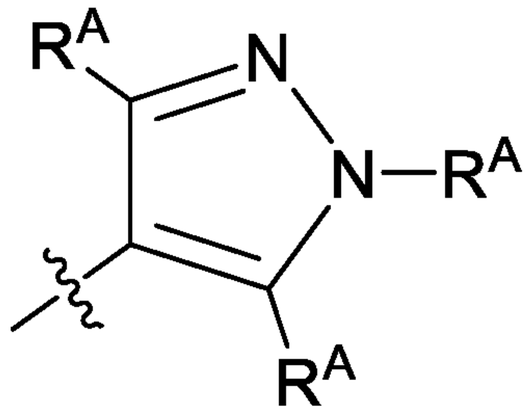
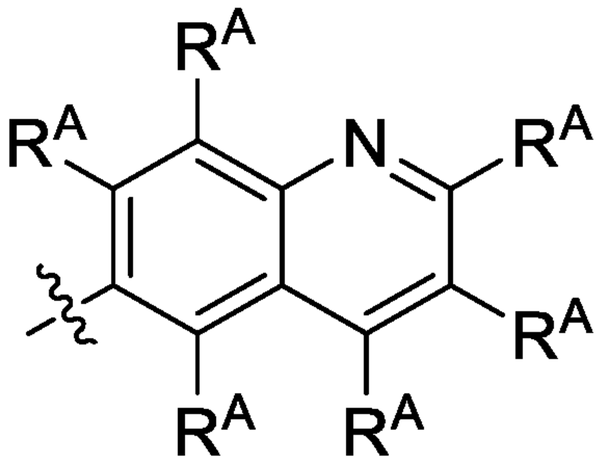
or a pharmaceutically acceptable salt thereof.

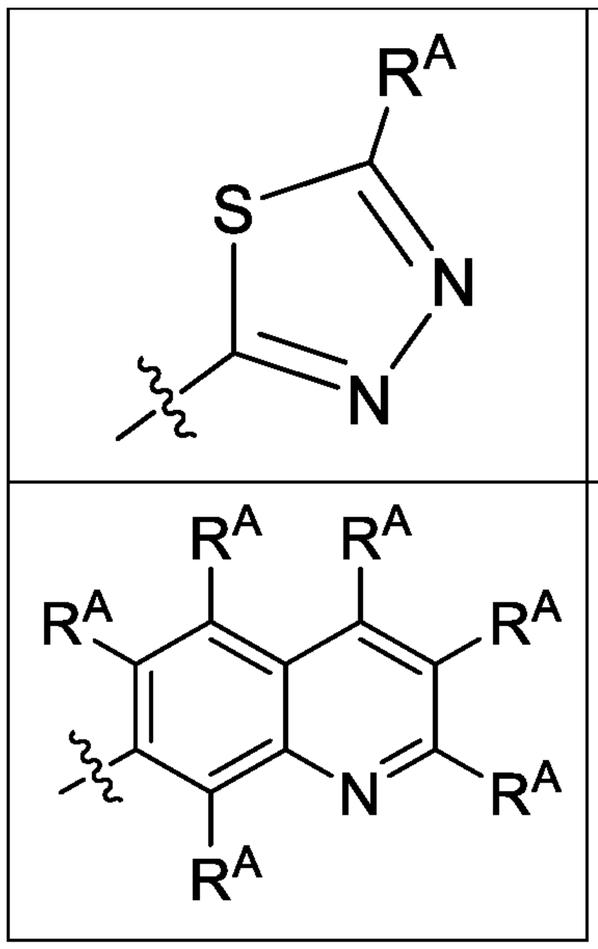
10. The method of any one of paragraphs 1-9, wherein ring A is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1-6 substituents independently selected from R^A.

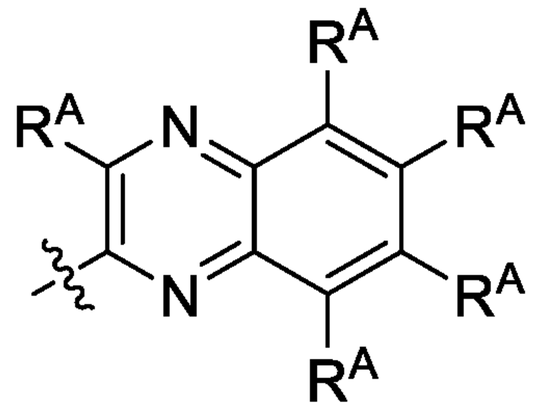
11. The method of any one of paragraphs 1-9, wherein ring A is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A.

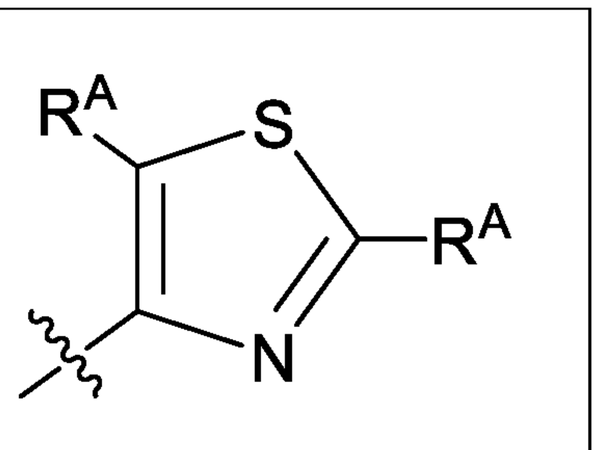
12. The method of any one of paragraphs 1-9, wherein ring A is 5-10 membered heteroaryl, optionally substituted with 1-6 substituents independently selected from R^A.

13. The method of any one of paragraphs 1-9, wherein ring A is selected from any one of the following moieties:

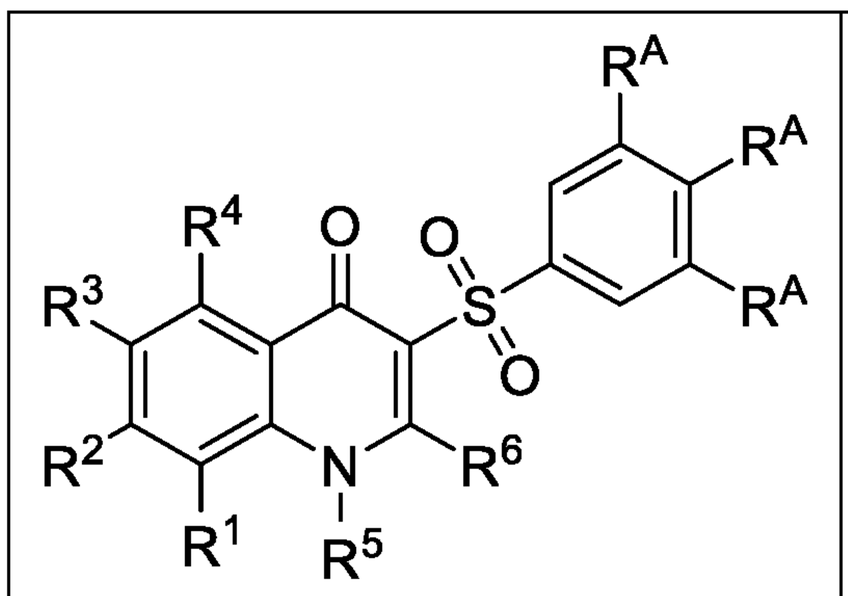
		
		

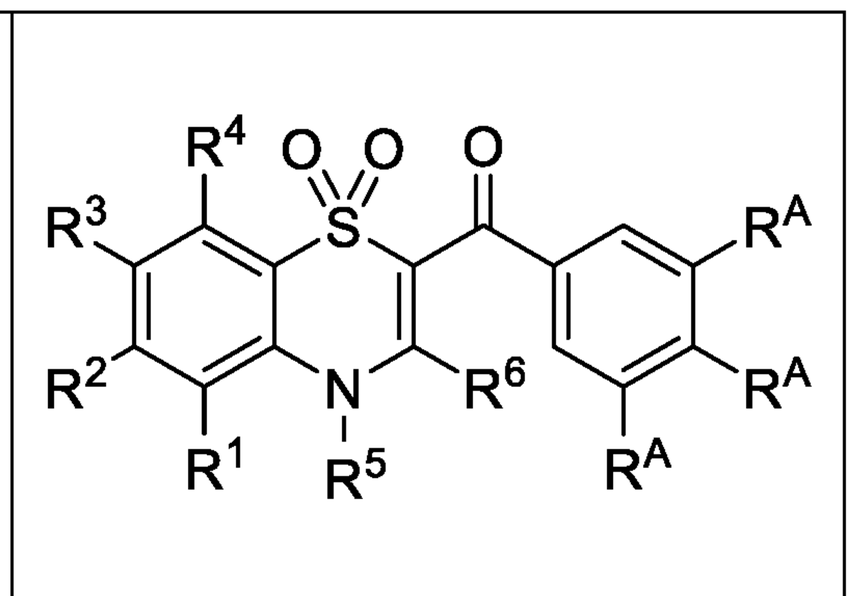


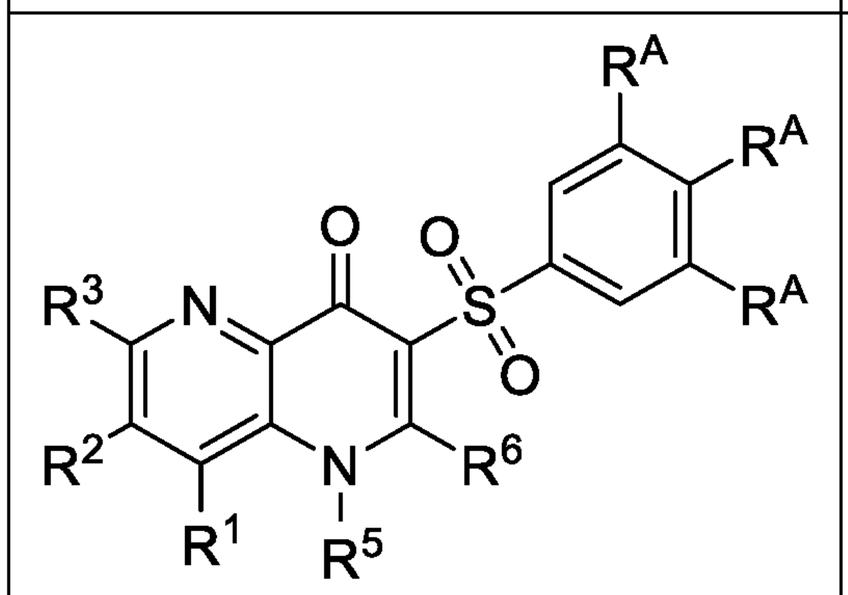


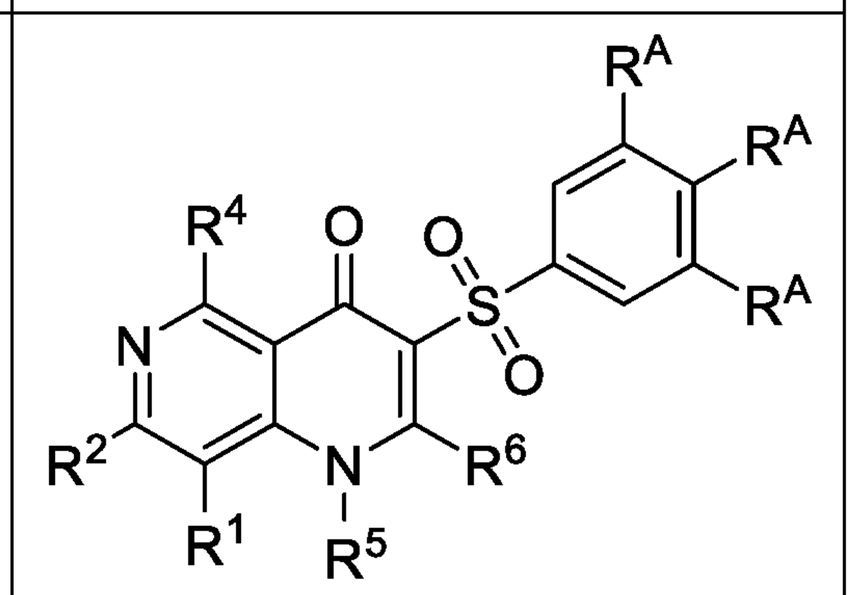


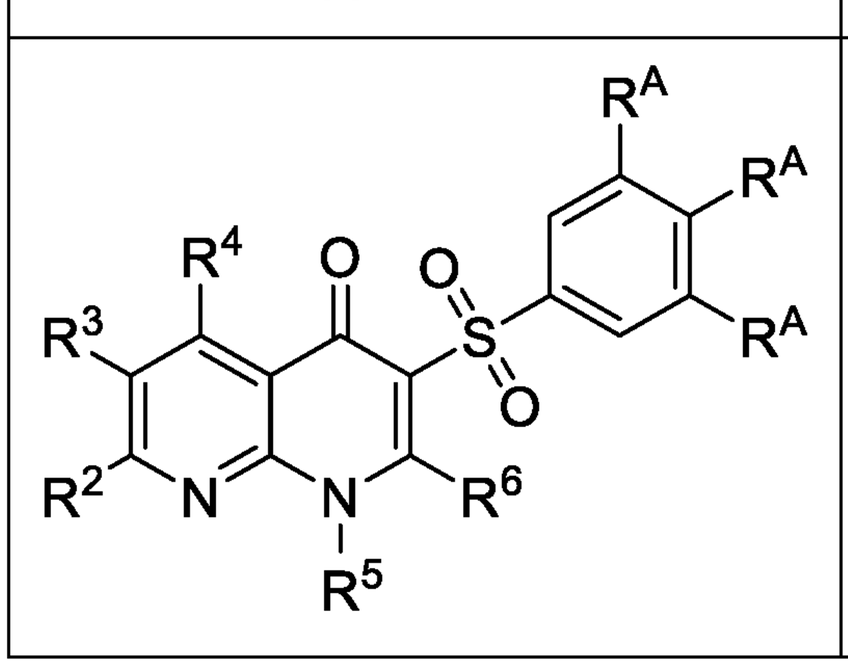
14. The method of paragraph 1, wherein the compound of Formula (Ia) is selected from any one of the following compounds:

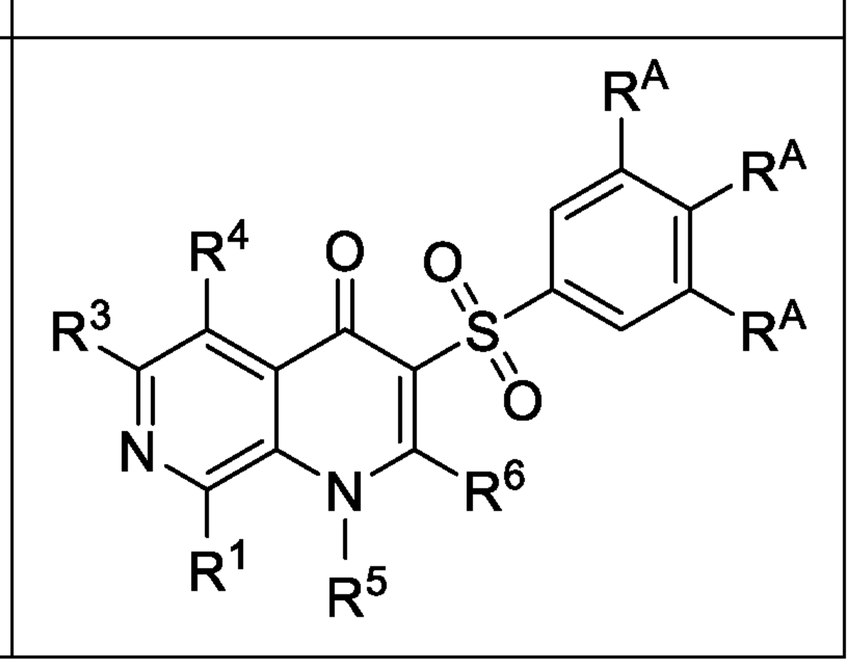












or a pharmaceutically acceptable salt thereof.

15. The method of any one of paragraphs 1-14, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

16. The method of any one of paragraphs 1-15, wherein each R^9 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$.

17. The method of any one of paragraphs 1-15, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy.

18. The method of any one of paragraphs 1-17, wherein each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^7.

19. The method of any one of paragraphs 1-17, wherein each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, C_{1-6} alkyl, and OR^{a1}.

20. The method of any one of paragraphs 1-17, wherein:

R^1, if present in the compound of Formula (Ia), is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^2, if present in the compound of Formula (Ia), is selected from H, CN, halo, C_{1-6} alkoxy, and C_{1-6} alkyl;

R^3, if present in the compound of Formula (Ia), is selected from H, CN, halo, C_{1-6} alkoxy, and C_{1-6} alkyl;

R^4, if present in the compound of Formula (Ia), is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R^6, if present in the compound of Formula (Ia), is selected from H and OH.

21. The method of any one of paragraphs 1-18, wherein R^7 is selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$.

22. The method of any one of paragraphs 1-21, wherein R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8.

23. The method of any one of paragraphs 1-22, wherein R^8 is selected from Cy^1, CN, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

24. The method of paragraph 23, wherein R^8 is selected from Cy^1 and $C(O)NR^{c1}R^{d1}$.

25. The method of any one of paragraphs 1-21, wherein R^5 is Cy^1.

26. The method of any one of paragraphs 1-21, wherein R^5 is C_{1-6} alkyl, optionally substituted with Cy^1.

27. The method of any one of paragraphs 1-26, wherein Cy^1 is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1}.

28. The method of any one of paragraphs 1-26, wherein Cy^1 is C_{6-10} aryl, optionally substituted with R^{Cy1}.

29. The method of any one of paragraphs 1-28, wherein R^{Cy1} is selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl.

30. The method of any one of paragraphs 1-28, wherein Cy^1 is C_{6-10} aryl, optionally substituted with halo.

31. The method of any one of paragraphs 1-21, wherein R^5 is H.

32. The method of any one of paragraphs 1-21, wherein R^5 is C_{1-6} alkyl, optionally substituted with $C(O)NR^{c1}R^{d1}$.

33. The method of any one of paragraphs 1-32, wherein each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

34. The method of any one of paragraphs 1-32, wherein each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

35. The method of any one of paragraphs 1-34, wherein each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

36. The method of any one of paragraphs 1-34, wherein each R^g is independently selected from halo and C_{1-6} alkyl.

37. The method of any one of paragraphs 1-14, wherein:

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$;

each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

R^7 is selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$;

R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from Cy^1, CN, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

38. The method of any one of paragraphs 1-14, wherein:

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy;

each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, C_{1-6} alkyl, and OR^{a1};

R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from Cy^1 and $C(O)NR^{c1}R^{d1}$;

Cy^1 is C_{6-10} aryl, optionally substituted with R^{Cy1};

R^{Cy1} is selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} haloalkyl;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

wherein each R^g is independently selected from halo and C_{1-6} alkyl.

39. The method of any one of paragraphs 1-14, wherein:

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^1, if present in the compound of Formula (Ia), is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^2, if present in the compound of Formula (Ia), is selected from H, CN, halo, C_{1-6} alkoxy, and C_{1-6} alkyl;

R^3, if present in the compound of Formula (Ia), is selected from H, CN, halo, C_{1-6} alkoxy, and C_{1-6} alkyl;

R^4, if present in the compound of Formula (Ia), is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R^6, if present in the compound of Formula (Ia), is selected from H and OH.

R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from Cy^1 and $C(O)NR^{c1}R^{d1}$;

Cy^1 is C_{6-10} aryl, optionally substituted with halo;

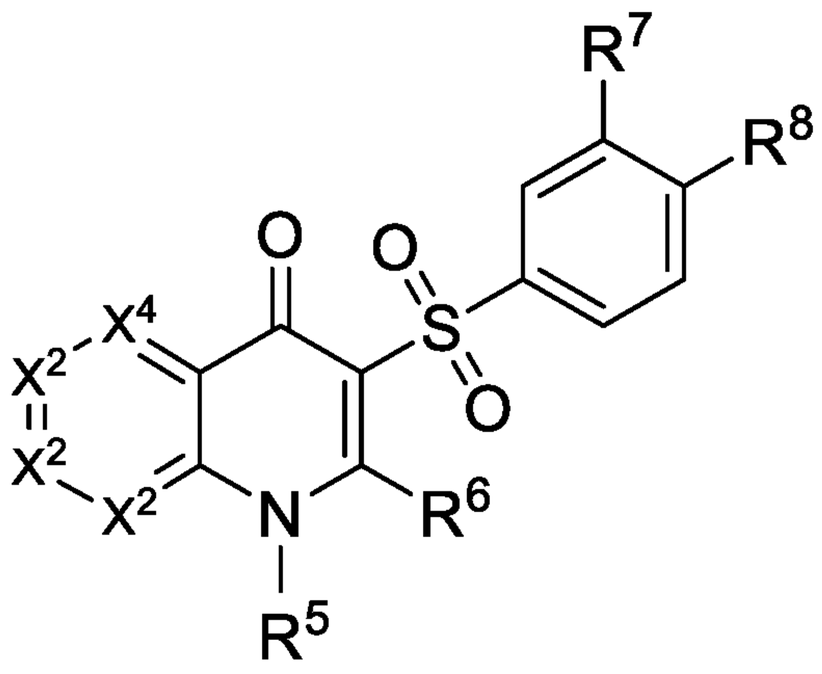
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and

C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

wherein each R^g is independently selected from halo and C_{1-6} alkyl.

40. The method of any one of paragraphs 1-39, wherein the compound of Formula (Ia) is selected from any one of the compounds of Table 1a, Table 1d, or Table 1e, or a pharmaceutically acceptable salt thereof.

41. A compound of Formula (Ib):



(Ib),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^1;

X^2 is selected from N and CR^2;

X^3 is selected from N and CR^3;

X^4 is selected from N and CR^4;

provided that at least one of X^1, X^2, X^3, and X^4 is N;

each of R^1, R^2, R^3, R^4, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^5 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from Cy^1, CN, NO_2, OR^{a1}, $C(O)R^{b1}$,

$C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^7 and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{12};

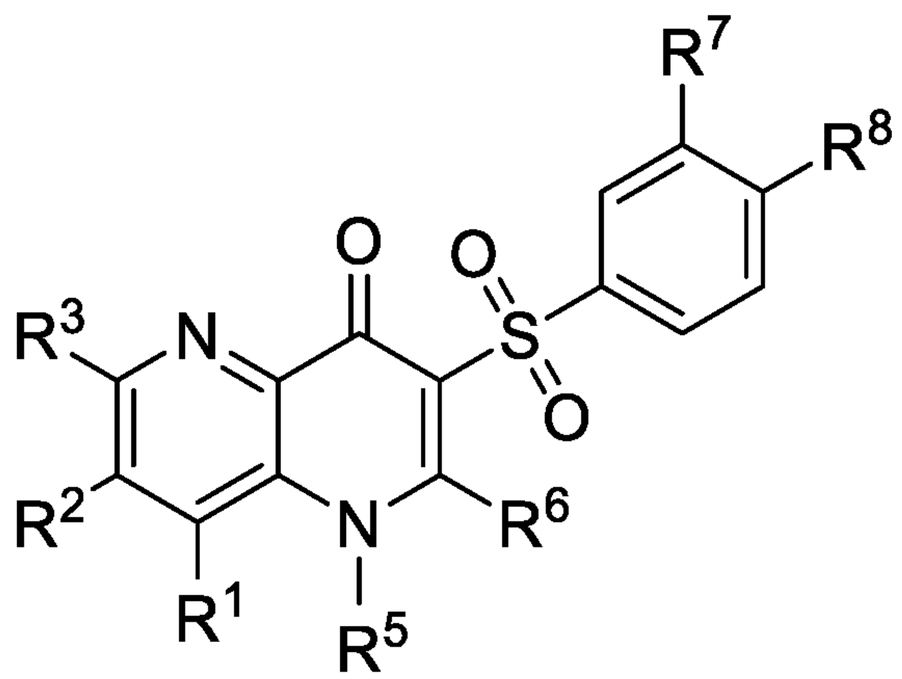
each R^{12} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

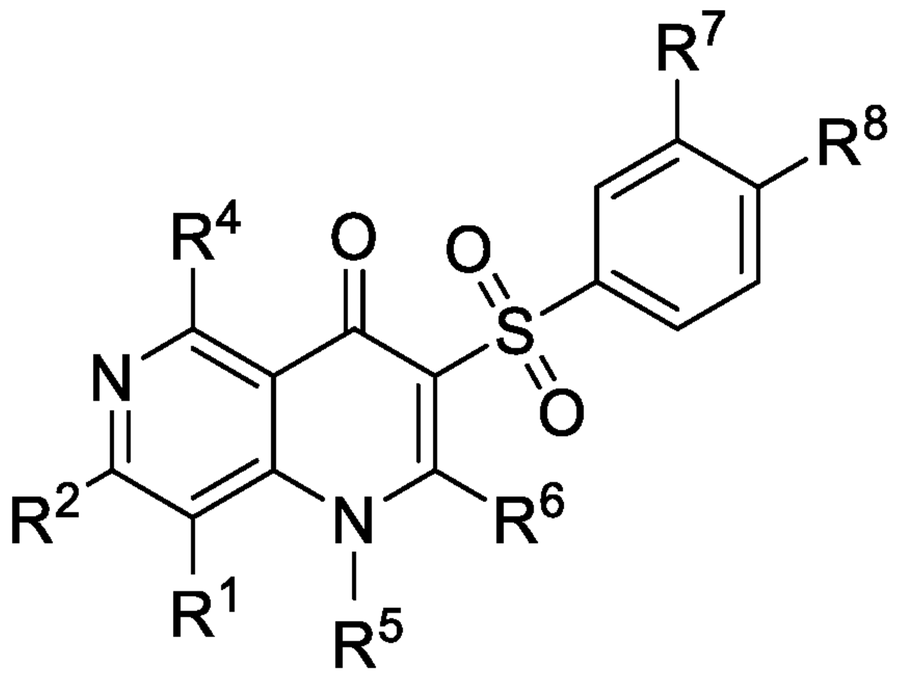
42. The compound of paragraph 41, wherein the compound of Formula (Ib) has formula:



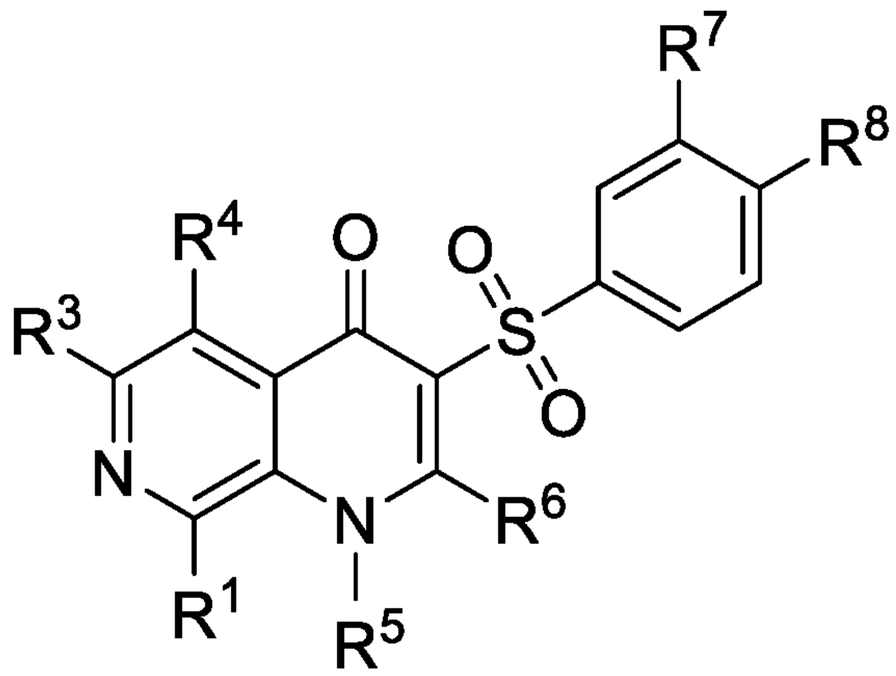
,

or a pharmaceutically acceptable salt thereof.

43. The compound of paragraph 41, wherein the compound of Formula (Ib) is selected from:



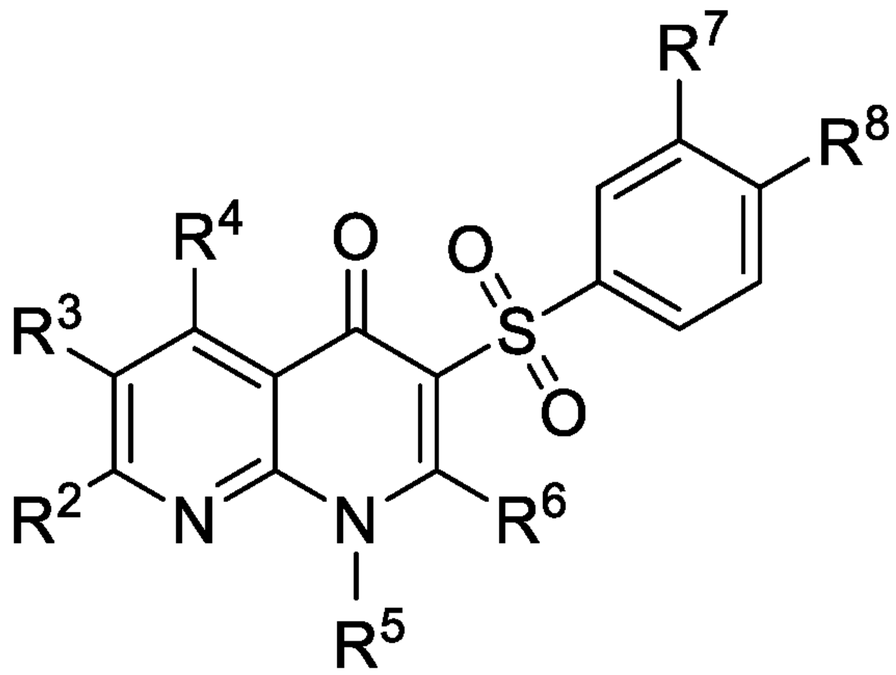
, and



;

or a pharmaceutically acceptable salt thereof.

44. The compound of paragraph 41, wherein the compound of Formula (Ib) has formula:



,

or a pharmaceutically acceptable salt thereof.

45. The compound of any one of paragraphs 41-44, wherein R^7 and R^8 are each independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$,

and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

46. The compound of any one of paragraphs 41-44, wherein R^7 and R^8 are each independently selected from H, halo, and C_{1-6} alkyl.

47. The compound of any one of paragraphs 41-46, wherein each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ib), is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

48. The compound of any one of paragraphs 41-46, wherein each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ib), is independently selected from H, halo, and OR^{a1}.

49. The compound of any one of paragraphs 41-46, wherein:
each of R^1, R^2, R^3, and R^4, if present in the compound of Formula (Ib), is independently selected from H, halo, and C_{1-6} alkoxy; and
R^6 is selected from H and OH.

50. The compound of any one of paragraphs 41-49, wherein R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

51. The compound of any one of paragraphs 41-49, wherein R^5 is selected from H and C_{1-6} alkyl.

52. The compound of any one of paragraphs 41-49, wherein R^5 is H.

53. The compound of any one of paragraphs 41-52, wherein each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

54. The compound of any one of paragraphs 41-52, wherein each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H and C_{1-6} alkyl.

55. The compound of paragraph 41, wherein:

R^7 and R^8 are each independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ib), is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 is selected from H, C_{1-6} alkyl, and Cy^1, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, wherein said C_{1-6} alkyl and C_{6-10} aryl are optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

56. The compound of paragraph 41, wherein:

R^7 and R^8 are each independently selected from H, halo, and C_{1-6} alkyl;

each of R^1, R^2, R^3, and R^4, if present in the compound of Formula (Ib), is independently selected from H, halo, and C_{1-6} alkoxy;

R^6 is selected from H and OH;

R^5 is selected from H and C_{1-6} alkyl; and

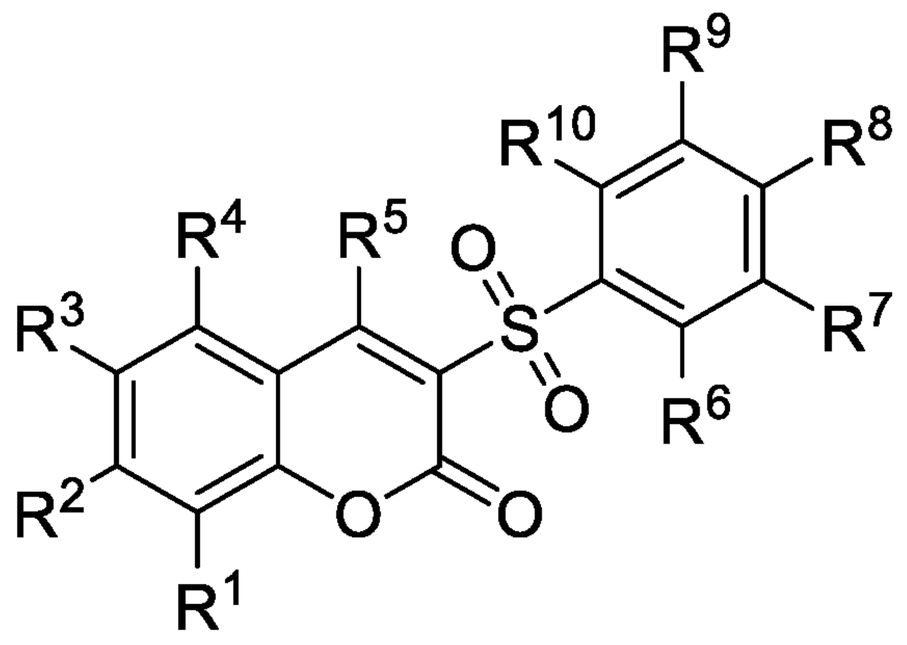
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H and C_{1-6} alkyl.

57. The compound of paragraph 41, wherein the compound of Formula (Ib) is selected from any one of the compounds of Table 1d, or a pharmaceutically acceptable salt thereof.

58. A compound selected from any one of the compounds of Table 1e, or a pharmaceutically acceptable salt thereof.

59. A pharmaceutical composition comprising a compound of any one of paragraphs 41-58, or a pharmaceutically acceptable salt thereof, and a pharmaceutically available carrier.

60. A method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (Ic):



(Ic),

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^B;

each R^B is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^C;

each R^C is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10

membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

61. The method of paragraph 60, wherein each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^B.

62. The method of paragraph 60 or 61, wherein each R^B is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

63. The method of paragraph 60, wherein each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, and C_{1-6} alkoxy.

64. The method of any one of paragraphs 60-63, wherein each of R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^C.

65. The method of paragraph 64, wherein each R^C is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

66. The method of any one of paragraphs 60-63, wherein each of R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, and C_{1-6} alkyl.

67. The method of any one of paragraphs 60-66, wherein each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g.

68. The method of any one of paragraphs 60-66, wherein each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H and C_{1-6} alkyl.

69. The method of any one of paragraphs 60-67, wherein each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

70. The method of paragraph 60, wherein:

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^B;

each R^B is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^C;

each R^C is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

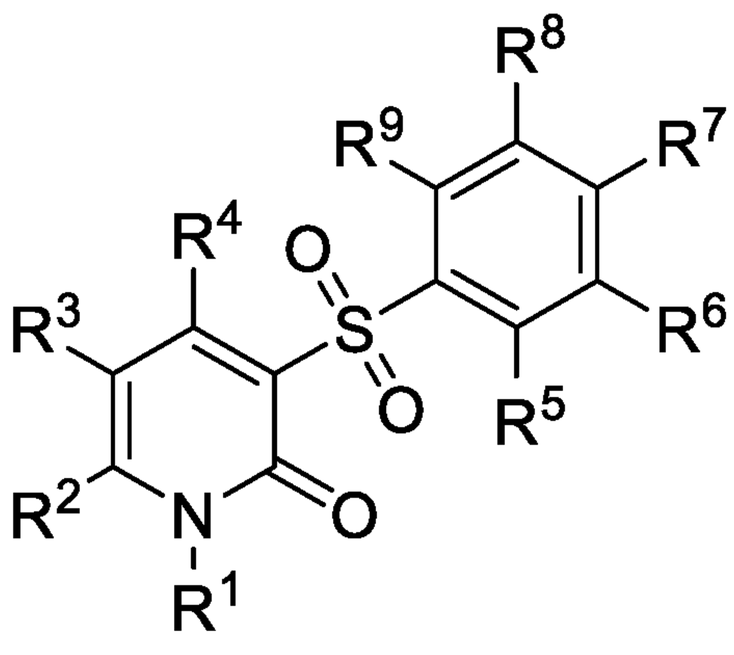
71. The method of paragraph 60, wherein:

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, and C_{1-6} alkoxy; and

each of R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, and C_{1-6} alkyl.

72. The method of paragraph 60, wherein the compound of Formula (Ic) is selected from any one of the compound of Table 1b, or a pharmaceutically acceptable salt thereof.

73. A method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (Id):



(Id),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^2, R^3, and R^4 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^B;

each R^B independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^C;

each R^C is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

74. The method of paragraph 73, wherein R^1 is H.

75. The method of paragraph 73 or 74, wherein each of R^2, R^3, and R^4 is independently selected from H and C_{1-6} alkyl.

76. The method of any one of paragraphs 73-75, wherein each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H and halo.

77. The method of paragraph 73, wherein:

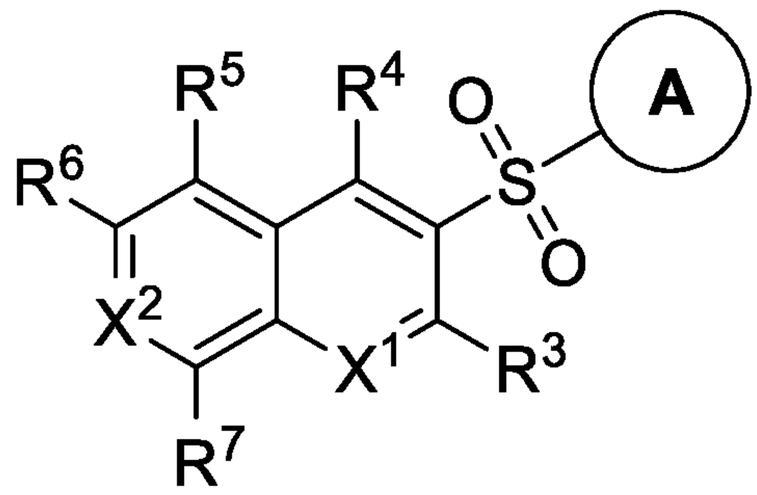
R^1 is H;

each of R^2, R^3, and R^4 is independently selected from H and C_{1-6} alkyl; and

each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H and halo.

78. The method of paragraph 73, wherein the compound of Formula (Id) is selected from any one of the compounds of Table 1c, or a pharmaceutically acceptable salt thereof.

79. A compound of Formula (Ie):



(Ie),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^1;

X^2 is selected from N and CR^2;

each R^1, R^2, R^3, R^4, R^5, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^7 is selected from OR^{a2} and $NR^{c2}R^{d2}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each

optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

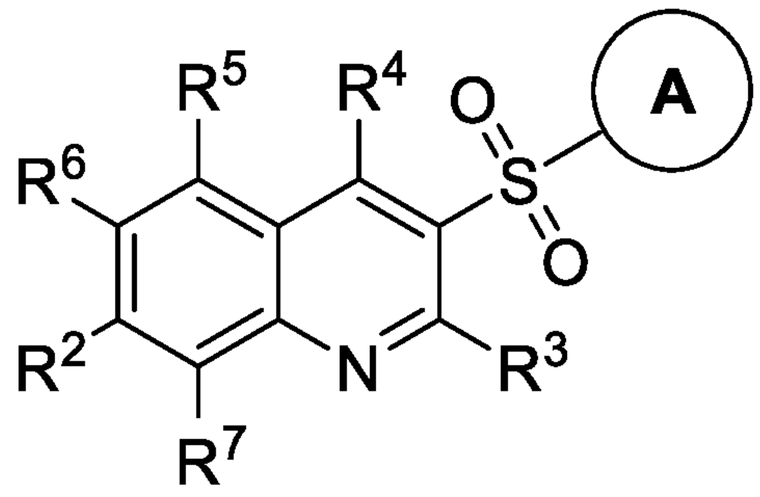
each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

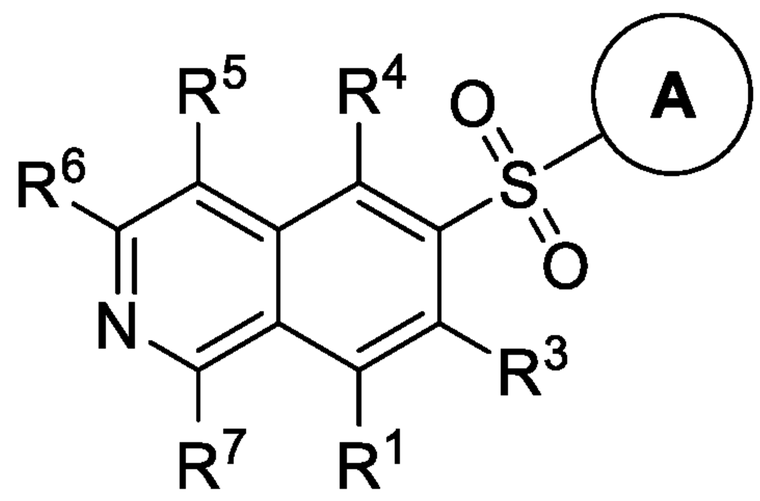
80. The compound of paragraph 79, wherein the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

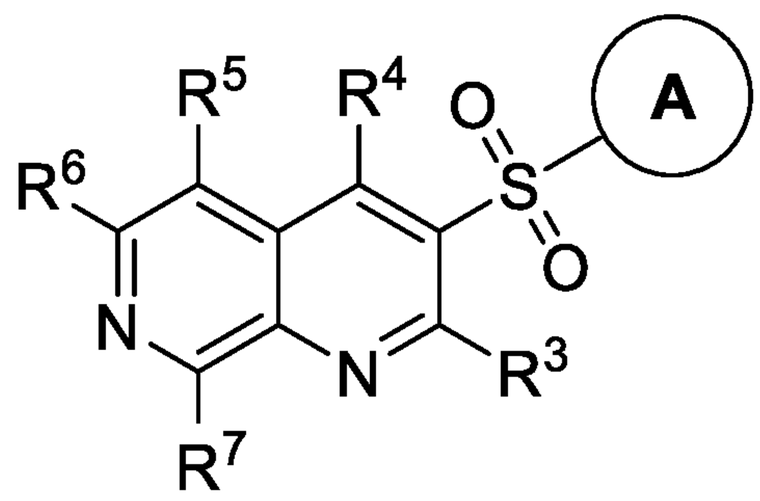
81. The compound of paragraph 79, wherein the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

82. The compound of paragraph 79, wherein the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

83. The compound of any one of paragraphs 79-82, wherein each of R^1, R^2, R^3, R^4, and R^6 is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8.

84. The compound of any one of paragraphs 79-83, wherein each R^8 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$.

85. The compound of any one of paragraphs 79-82, wherein each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, OH, C_{1-6} alkyl, and C_{1-6} alkoxy.

86. The compound of any one of paragraphs 79-85, wherein R^7 is OR^{a2}.

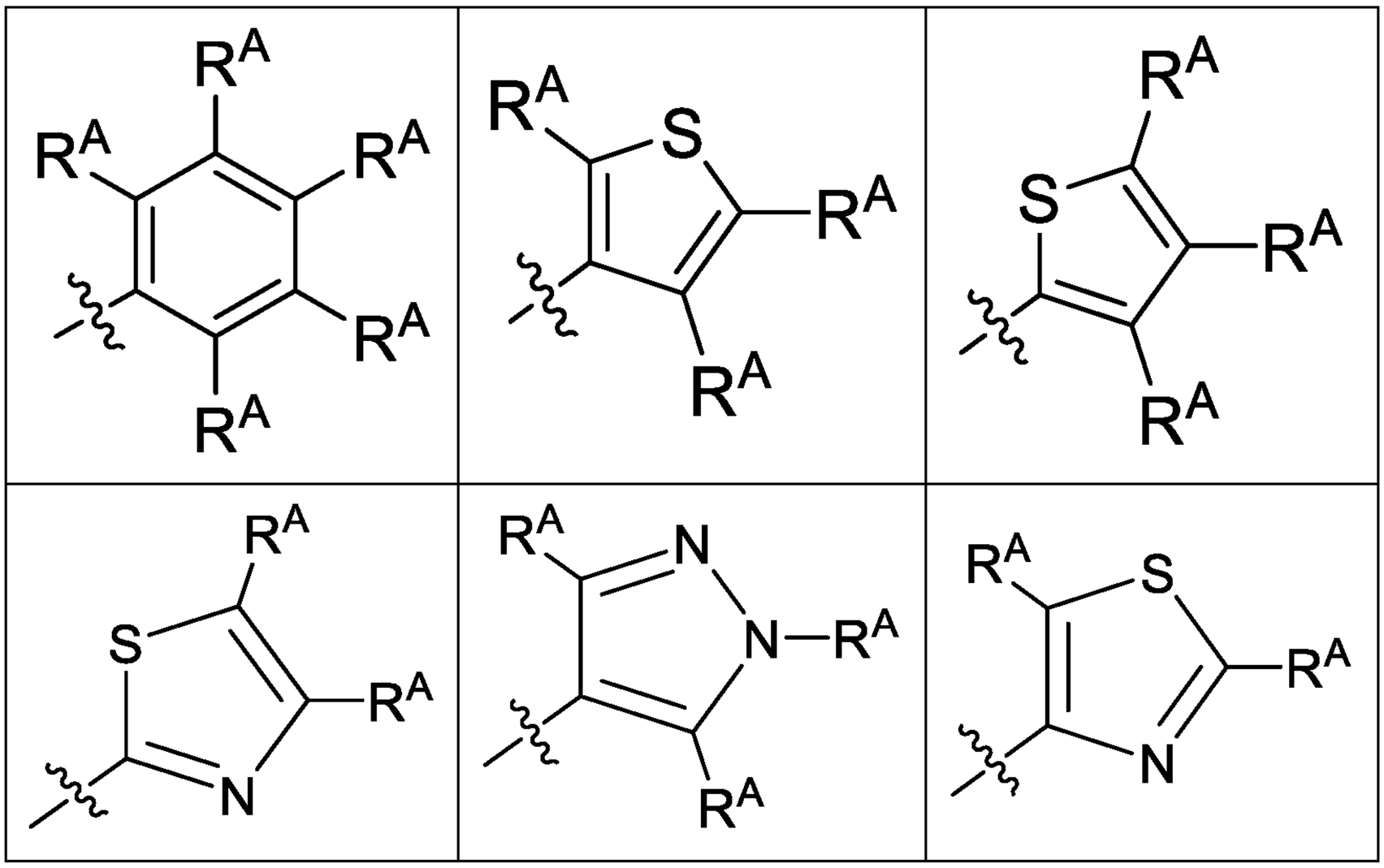
87. The compound of any one of paragraphs 79-85, wherein R^7 is $NR^{c2}R^{d2}$.

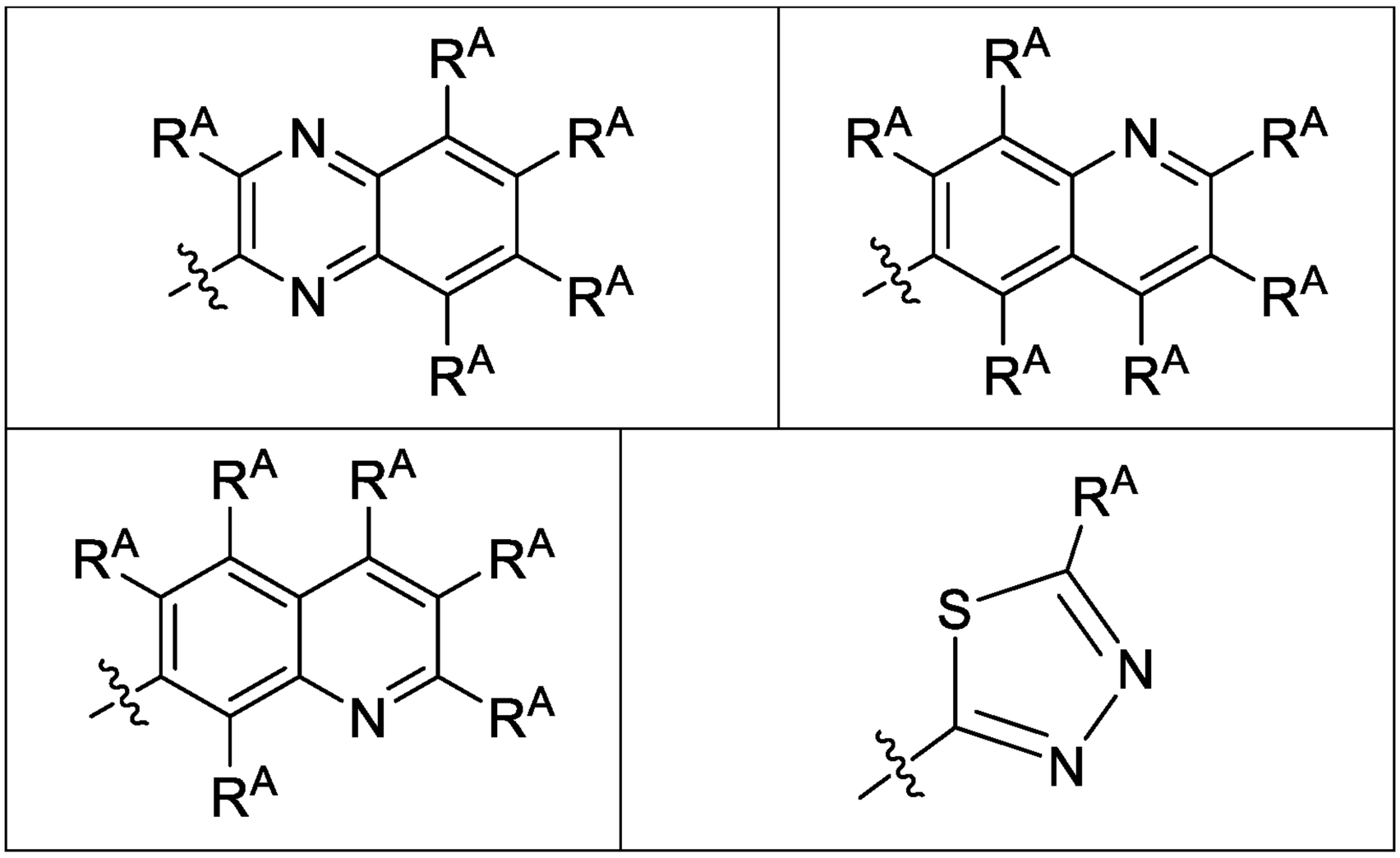
88. The compound of any one of paragraphs 79-87, wherein ring A is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1-6 substituents independently selected from R^A.

89. The compound of any one of paragraphs 79-87, wherein ring A is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A.

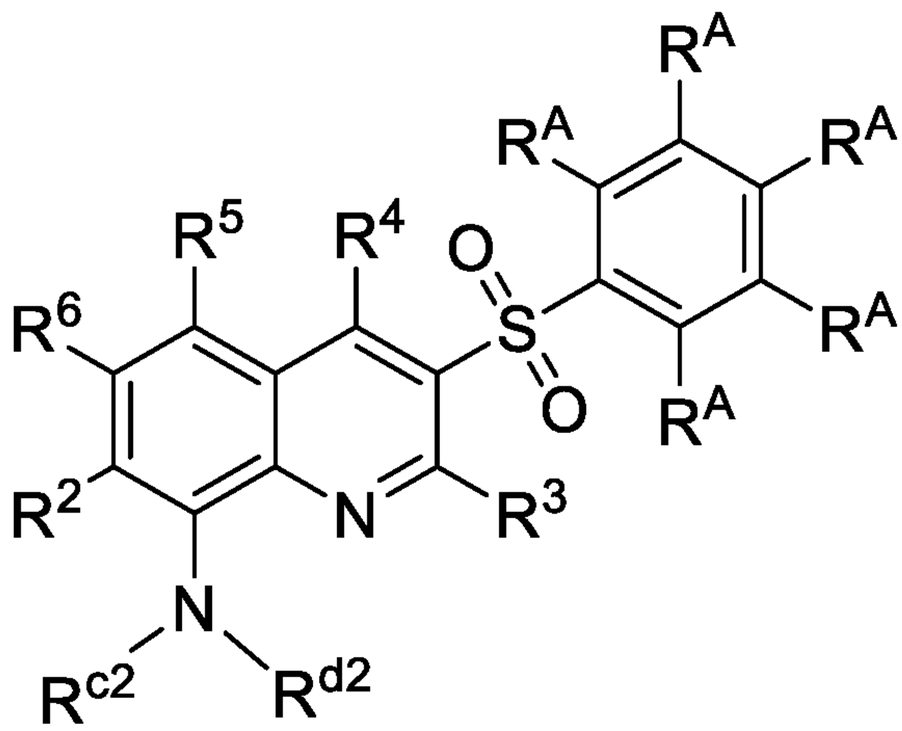
90. The compound of any one of paragraphs 79-87, wherein ring A is 5-10 membered heteroaryl, optionally substituted with 1-6 substituents independently selected from R^A.

91. The compound of any one of paragraphs 79-87, wherein ring A is selected from any one of the following moieties:





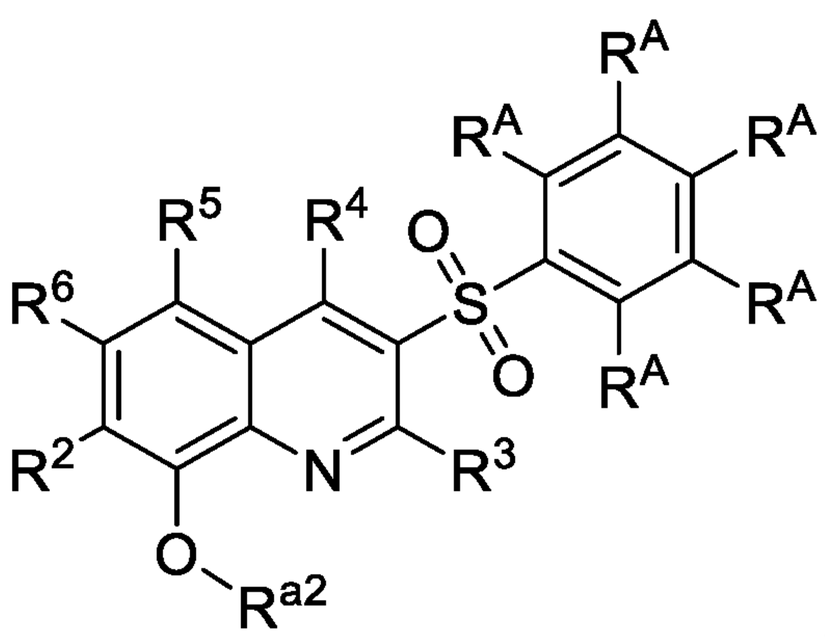
92. The compound of paragraph 79, wherein the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

93. The compound of paragraph 79, wherein the compound of Formula (Ie) has formula:



,

or a pharmaceutically acceptable salt thereof.

94. The compound of any one of paragraphs 79-93, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

95. The compound of any one of paragraphs 79-94, wherein each R^9 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$.

96. The compound of any one of paragraphs 79-93, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy.

97. The compound of any one of paragraphs 79-96, wherein each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

98. The compound of any one of paragraphs 79-97, wherein each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

99. The compound of any one of paragraphs 79-96, wherein each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H and C_{1-6} alkyl.

100. The compound of paragraph 79, wherein

R^1, R^2, R^3, R^4, and R^6 is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$;

ring A is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1-6 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is

optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, NH_2, and $S(O)_2NH_2$;

each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

101. The compound of paragraph 79, wherein:

each of R^1, R^2, R^3, R^4, and R^6, if present in the compound of Formula (Ia), is independently selected from H, halo, CN, OH, C_{1-6} alkyl, and C_{1-6} alkoxy;

ring A is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1-6 substituents independently selected from R^A;

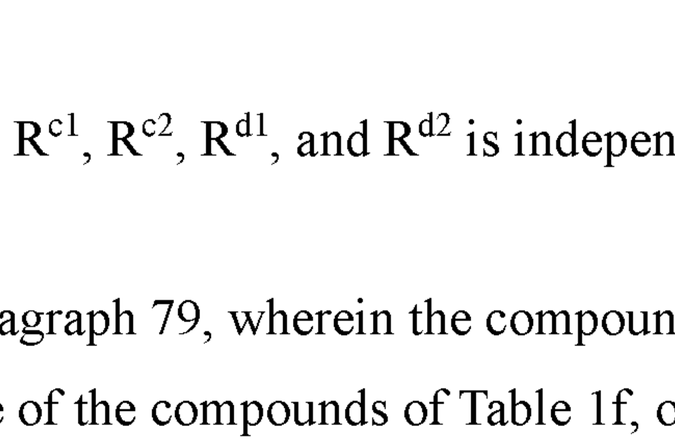
each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, and C_{1-6} alkoxy; and

each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H and C_{1-6} alkyl.

102. The compound of paragraph 79, wherein the compound of Formula (Ie) is selected from any one of the compounds of Table 1f, or a pharmaceutically acceptable salt thereof.

103. A pharmaceutical composition comprising a compound of any one of paragraphs 79-102, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

104. A compound of Formula (If):



(If),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

R^1, R^3, R^4, R^5, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered

heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

105. The compound of paragraph 104, wherein X^1 is S.

106. The compound of paragraph 104, wherein X^1 is S(O).

107. The compound of paragraph 104, wherein X^1 is $S(O)_2$.

108. The compound of any one of paragraphs 104-107, wherein R^1, R^3, R^4, R^5, and R^6 is independently selected from H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

109. The compound of any one of paragraphs 104-107, wherein R^1, R^3, R^4, R^5, and R^6 are each H.

110. The compound of any one of paragraphs 104-109, wherein R^2 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl.

111. The compound of any one of paragraphs 104-110, wherein ring A is C_{6-10} aryl, optionally substituted with 1 or 2 substituents independently selected from halo and C_{1-6} alkyl.

112. The compound of paragraph 104, wherein:

R^1, R^3, R^4, R^5, and R^6 is independently selected from H, halo, OH, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino;

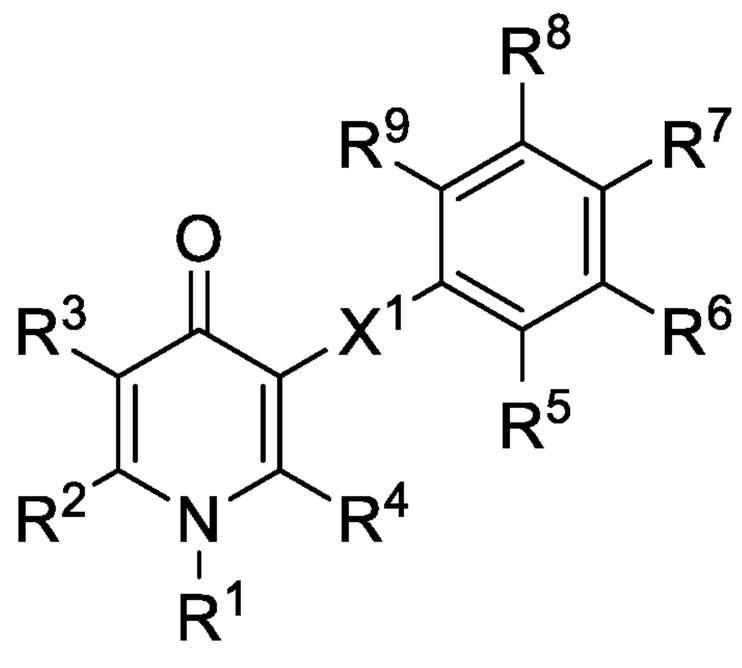
R^2 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

ring A is C_{6-10} aryl, optionally substituted with 1 or 2 substituents independently selected from halo and C_{1-6} alkyl.

113. The compound of paragraph 104, wherein the compound is selected from any one of the compound of Table 1g, or a pharmaceutically acceptable salt thereof.

114. A pharmaceutical composition of comprising a compound of any one of paragraphs 104-113, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

115. A compound of Formula (Ig):



(Ig),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

R^1 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^2, R^3, and R^4 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^B;

each R^B independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^C;

each R^C is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

116. The compound of paragraph 115, wherein X^1 is selected from S(O) and $S(O)_2$.

117. The compound of paragraph 115, wherein R^1 is H.

118. The compound of any one of paragraphs 115-117, wherein each of R^2, R^3, and R^4 is independently selected from H and C_{1-6} alkyl.

119. The compound of any one of paragraphs 115-118, wherein each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H, halo, and C_{1-6} alkyl.

120. The compound of paragraph 115, wherein:

X^1 is S(O) or $S(O)_2$;

R^1 is H;

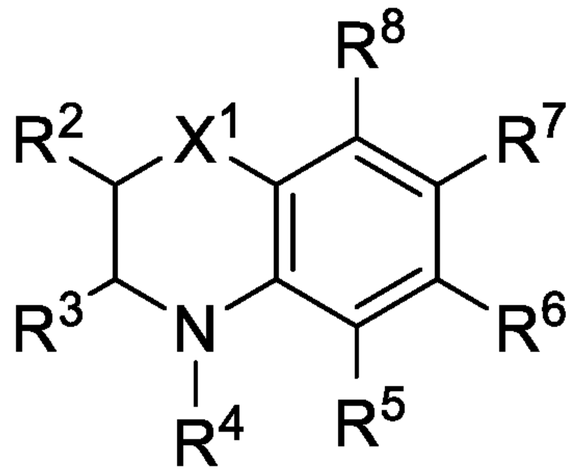
each of R^2, R^3, and R^4 is independently selected from H and C_{1-6} alkyl; and

each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H, C_{1-6} alkyl and halo.

121. The compound of paragraph 115, wherein the compound of Formula (Ig) is selected from any one of the compounds of Table 1h, or a pharmaceutically acceptable salt thereof.

122. A pharmaceutical composition comprising a compound of any one of paragraphs 115-121, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

123. A method of inhibiting activation of an NF-κB pathway within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (IIa):



(IIa),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from O and NR^1;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^3 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and oxo, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

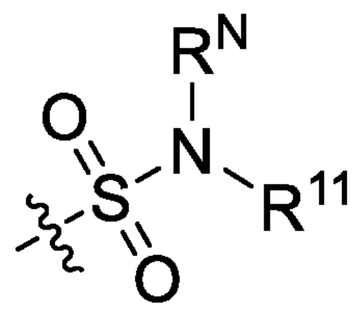
R^1 and R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each

optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^1 and R^2, together with N atom to which R^1 is attached and C atom to which R^2 is attached, form a 4-10 membered heterocycloalkyl ring, which is substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$; and a group of formula (i):



(i),

wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

provided that at least one of R^7 and R^8 is a group of formula (i);

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, for a -10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

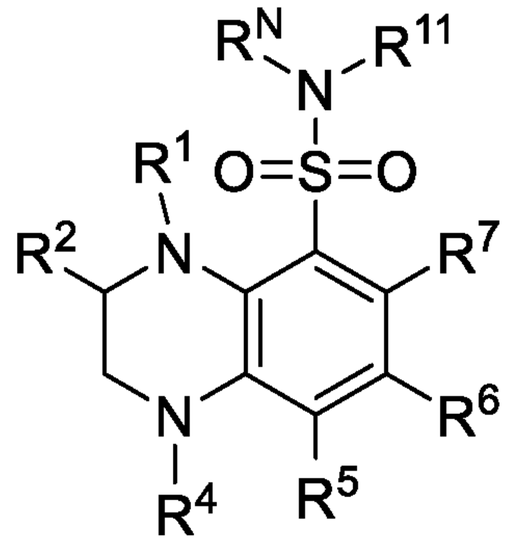
each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

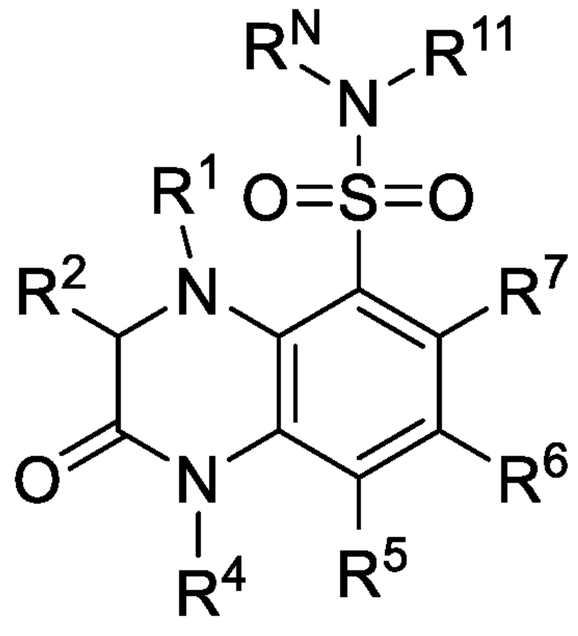
124. The method of paragraph 123, wherein the compound of Formula (IIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

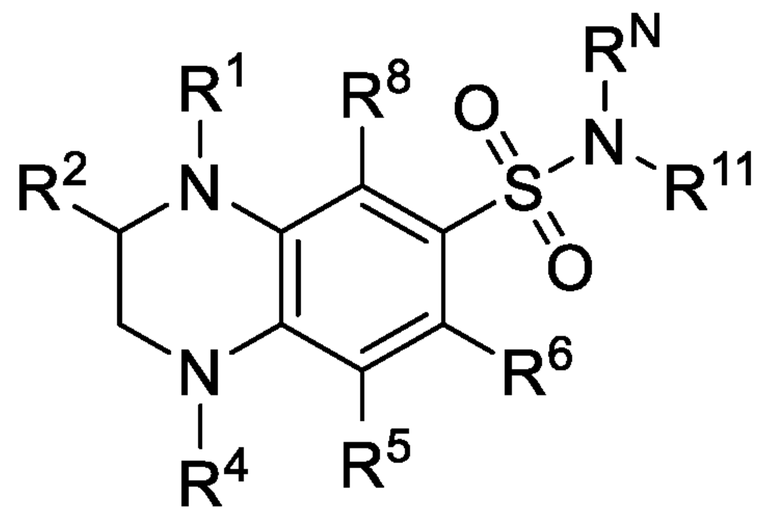
125. The method of paragraph 123, wherein the compound of Formula (IIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

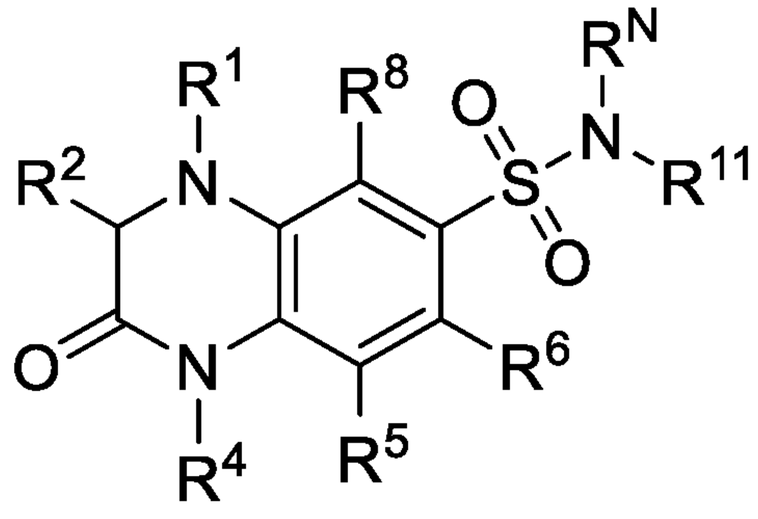
126. The method of paragraph 123, wherein the compound of Formula (IIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

127. The method of paragraph 123, wherein the compound of Formula (IIa) has formula:



,

or a pharmaceutically acceptable salt thereof.

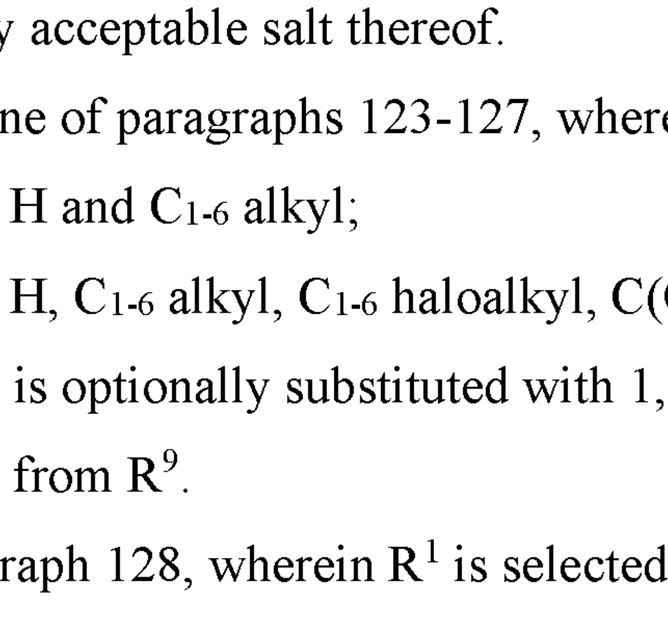
128. The method of any one of paragraphs 123-127, wherein:

R^2 is selected from H and C_{1-6} alkyl;

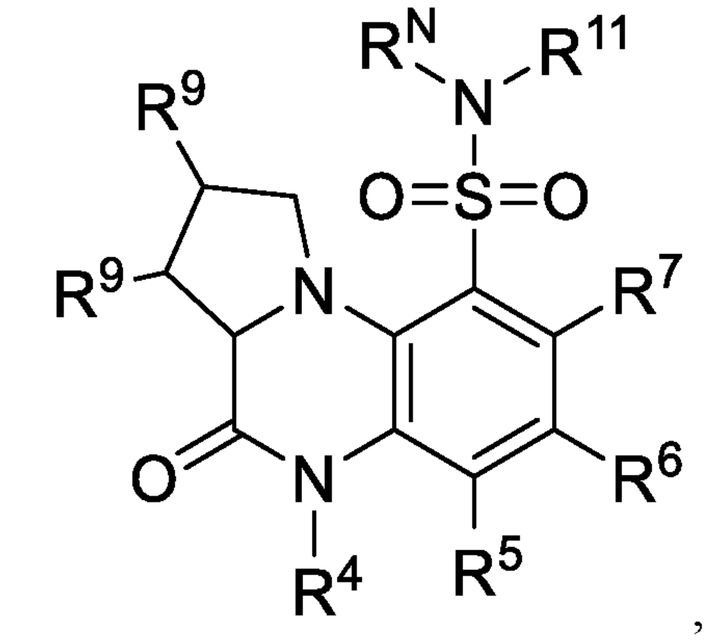
R^1 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

129. The method of paragraph 128, wherein R^1 is selected from C_{1-6} alkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$.

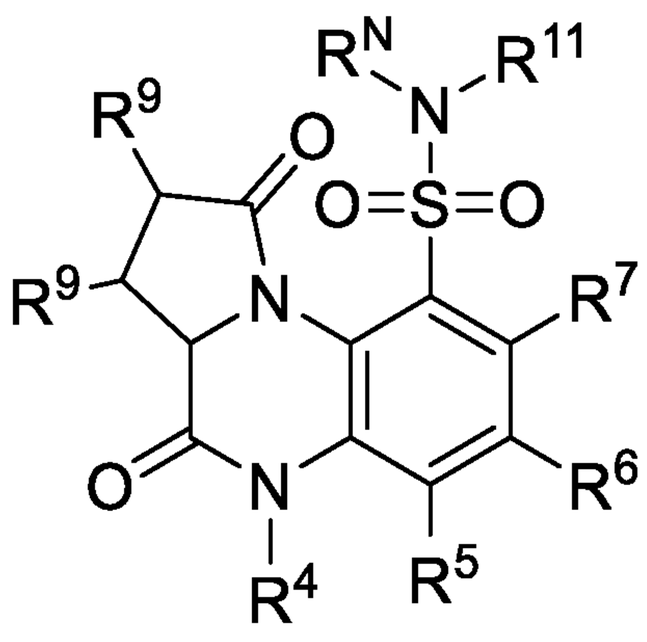
130. The method of paragraph 123, wherein the compound of Formula (IIa) is selected from:



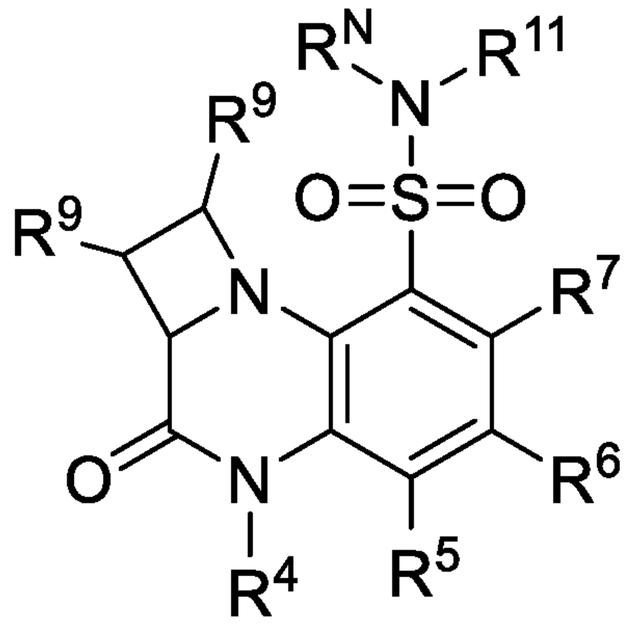
,



,



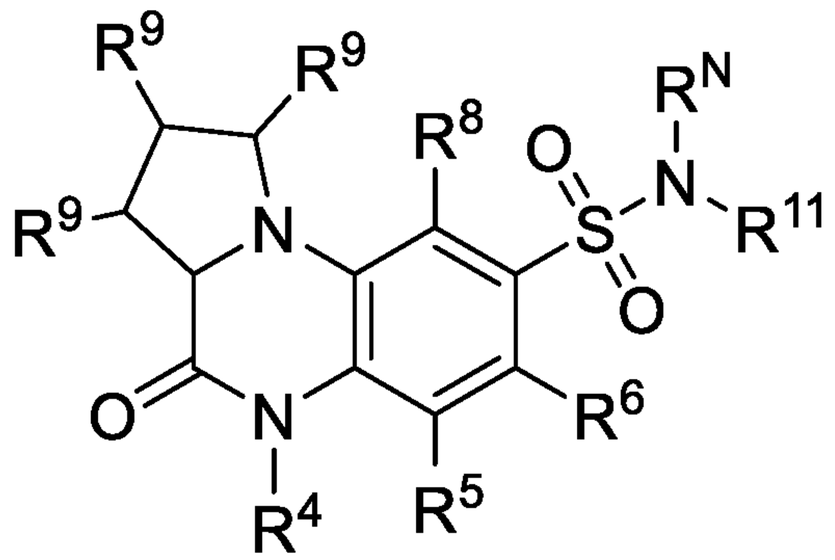
, and



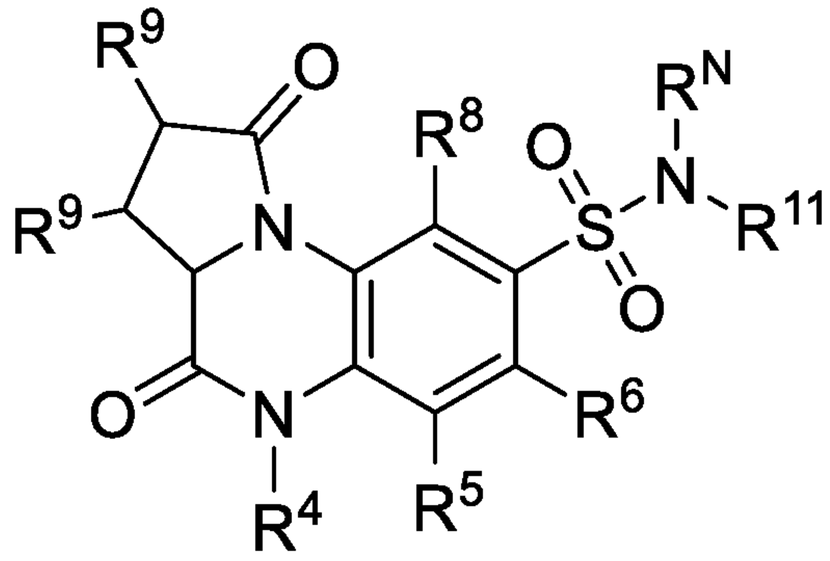
,

or a pharmaceutically acceptable salt thereof.

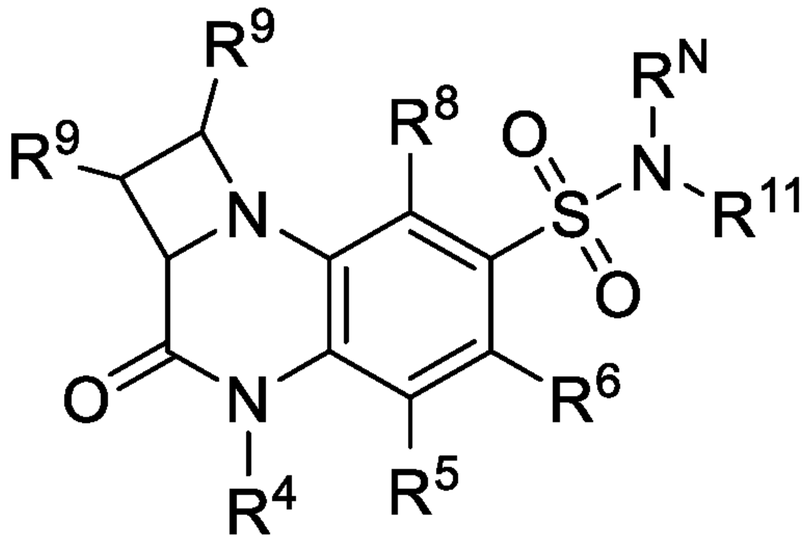
131. The method of paragraph 123, wherein the compound of Formula (IIa) is selected from:



,



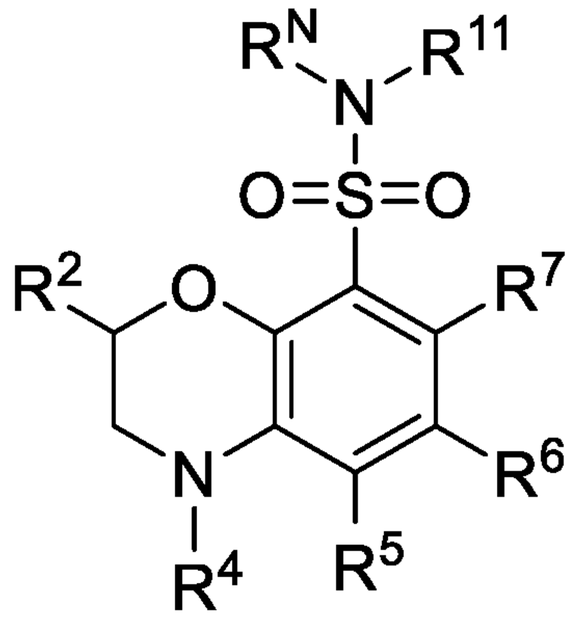
, and



,

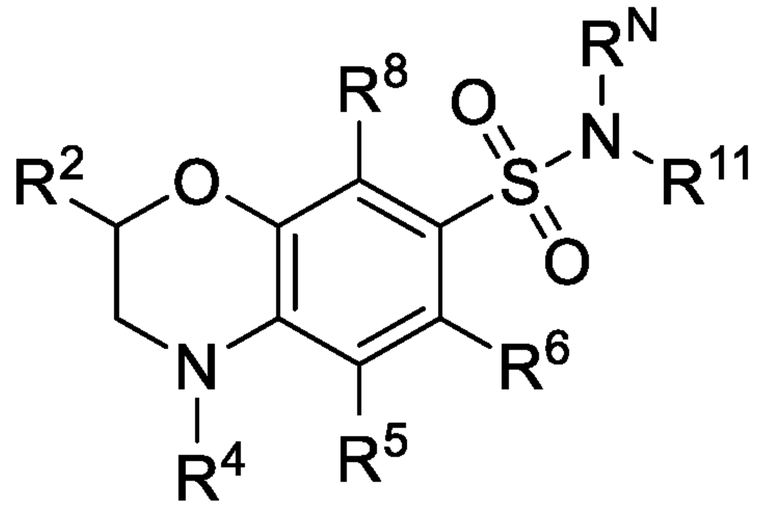
or a pharmaceutically acceptable salt thereof.

132. The method of paragraph 123, wherein the compound of Formula (IIa) has formula:



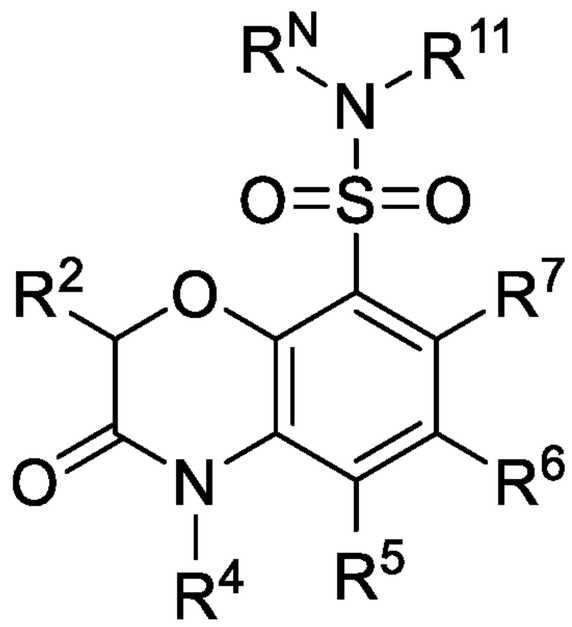
or a pharmaceutically acceptable salt thereof.

133. The method of paragraph 123, wherein the compound of Formula (IIa) has formula:



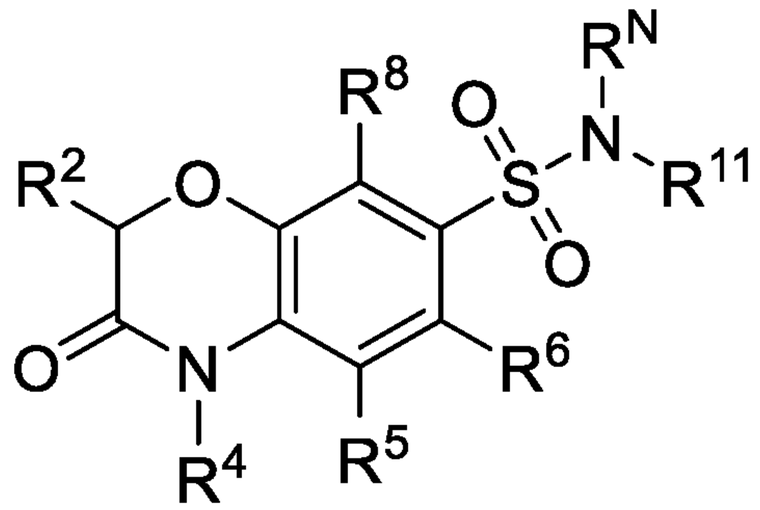
or a pharmaceutically acceptable salt thereof.

134. The method of paragraph 123, wherein the compound of Formula (IIa) has formula:



or a pharmaceutically acceptable salt thereof.

135. The method of paragraph 123, wherein the compound of Formula (IIa) has formula:



or a pharmaceutically acceptable salt thereof.

136. The method of any one of paragraphs 132-135, wherein R^2 is selected from H and C_{1-6} alkyl.

137. The method of any one of paragraphs 123-136, wherein R^4 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

138. The method of any one of paragraphs 123-136, wherein R^4 is H.

139. The method of any one of paragraphs 123-138, wherein R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

140. The method of any one of paragraphs 123-138, wherein R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with R^9.

141. The method of paragraph 140, wherein R^5 is H and R^6 is C_{1-6} alkyl, optionally substituted with $NR^{c1}R^{d1}$.

142. The method of paragraph 140, wherein R^5 is H and R^6 is halo.

143. The method of paragraph 140, wherein R^5 is H and R^6 is $S(O)_2R^{b1}$.

144. The method of any one of paragraphs 123-143, wherein R^7 is selected from H and C_{1-6} alkyl.

145. The method of any one of paragraphs 123-144, wherein R^8 is selected from H and C_{1-6} alkyl.

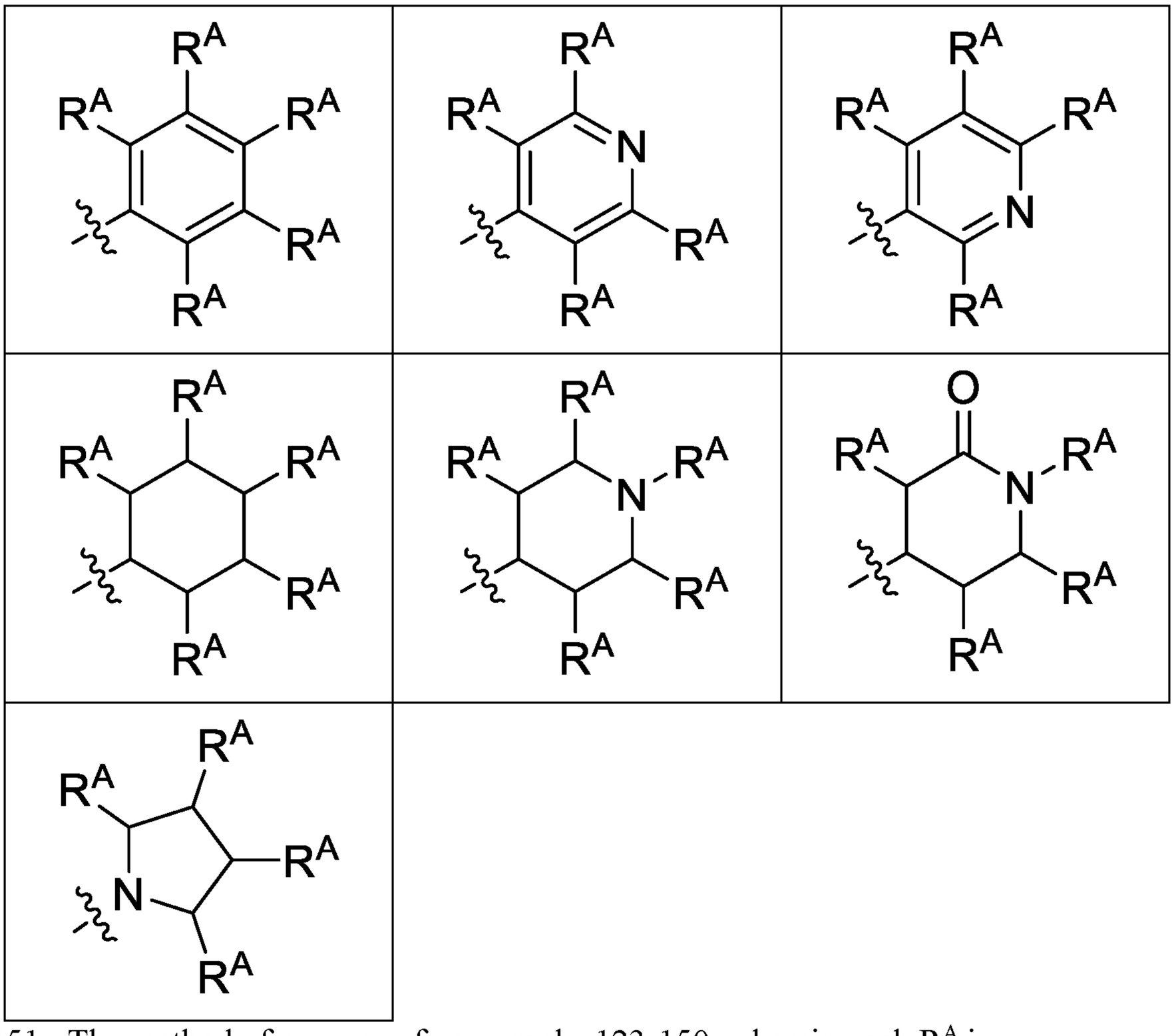
146. The method of any one of paragraphs 123-145, wherein R^N is selected from H and C_{1-6} alkyl.

147. The method of any one of paragraphs 123-146, wherein R^{11} is ring A.

148. The method of any one of paragraphs 123-146, wherein R^{11} is C_{1-6} alkyl, optionally substituted with ring A.

149. The method of any one of paragraphs 123-145, wherein R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from morpholinyl, piperidinyl, and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

150. The method of any one of paragraphs 123-148, wherein ring A is selected from any one of the following moieties:



151. The method of any one of paragraphs 123-150, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

152. The method of any one of paragraphs 123-150, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1},

$C(O)R^{b1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, and $NR^{c1}C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

153. The method of any one of paragraphs 123-152, wherein each R^{10} is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

154. The method of any one of paragraphs 123-150, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, and $NR^{c1}C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with $C(O)OR^{a1}$.

155. The method of any one of paragraphs 123-154, wherein each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

156. The method of any one of paragraph 123-155, wherein each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

157. The method of paragraph 123, wherein:

R^2 is selected from H and C_{1-6} alkyl;

R^1 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^1 and R^2, together with N atom to which R^1 is attached and C atom to which R^2 is attached, form a 4-10 membered heterocycloalkyl ring, which is substituted with 1, 2, or 3 substituents independently selected from R^9;

R^3 is selected from H and oxo;

R^4 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are independently selected from H, C_{1-6} alkyl, and a moiety of formula (i);

R^N is selected from H and C_{1-6} alkyl; or

R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from morpholinyl, piperidinyl, and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^{10} is independently selected from OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

158. The method of paragraph 123, wherein:

R^2 is selected from H and C_{1-6} alkyl;

R^1 is selected from C_{1-6} alkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$.

R^1 and R^2, together with N atom to which R^1 is attached and C atom to which R^2 is attached, form a 4-10 membered heterocycloalkyl ring, which is substituted with 1, 2, or 3 substituents independently selected from R^9;

R^3 is selected from H and oxo;

R^4 is H;

R^5 and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with R^9;

R^7 and R^8 are independently selected from H, C_{1-6} alkyl, and a moiety of formula (i);

R^N is selected from H and C_{1-6} alkyl; or

R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from morpholinyl, piperidinyl, and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, and $NR^{c1}C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with $C(O)OR^{a1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H and C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

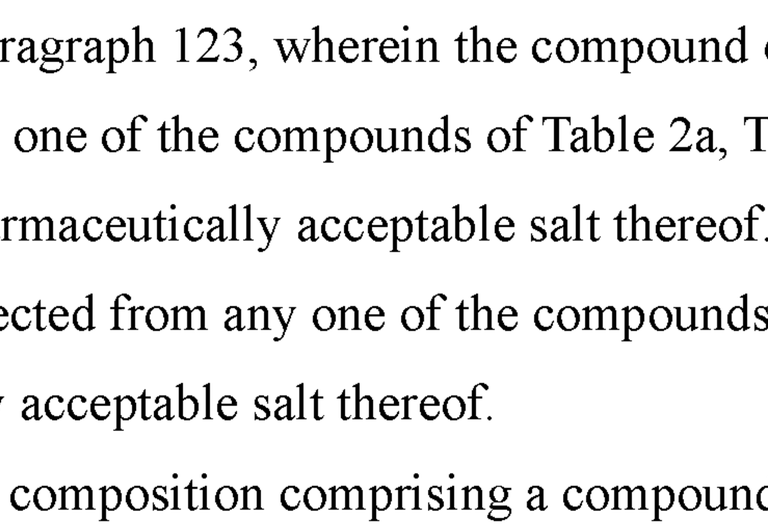
159. The method of paragraph 123, wherein the compound of Formula (IIa) is selected from any one of the compounds of Table 2a, Table 2c, Table 2c-2, Table 2d, Table 2d-2, Table 2e, or Table 16, or a pharmaceutically acceptable salt thereof.

160. The method of paragraph 123, wherein the compound of Formula (IIa) is selected from any one of the compounds of Table 2a, Table 2c, Table 2d, or Table 2e, or a pharmaceutically acceptable salt thereof.

161. A compound selected from any one of the compounds of Table 16, or a pharmaceutically acceptable salt thereof.

162. A pharmaceutical composition comprising a compound of any one of paragraphs 123-161, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

163. A compound of Formula (IIb):



(IIb),

or a pharmaceutically acceptable salt thereof, wherein:

Hal is a halogen;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, for a -10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are

each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

164. The compound of paragraph 163, wherein R^2 is selected from H and C_{1-6} alkyl.

165. The compound of paragraph 163 or 164, wherein R^4, R^5, and R^8 are each H.

166. The compound of any one of paragraphs 163-165, wherein R^N is H.

167. The compound of any one of paragraphs 163-165, wherein R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from pyrrolidinyl, morpholinyl, and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

168. The compound of any one of paragraphs 163-166, wherein ring A is selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1-10 substituents independently selected from R^A.

169. The compound of any one of paragraphs 163-168, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, and $C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

170. The compound of any one of paragraphs 163-168, wherein each R^A is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, and $C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

171. The compound of paragraphs 163, wherein:

R^2 is selected from H and C_{1-6} alkyl;

R^4, R^5, and R^8 are each H;

R^N is H; or

R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from pyrrolidinyl, morpholinyl, and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

ring A is selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1-10 substituents independently selected from R^A; and

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, and $C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

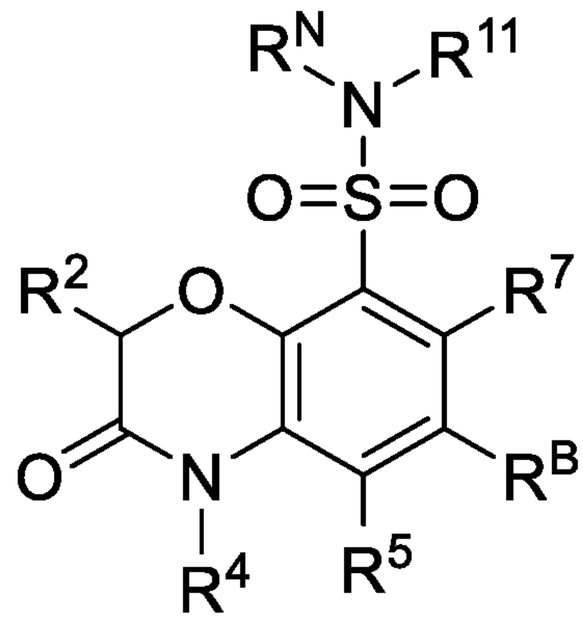
172. The compound of paragraph 171, wherein R^A is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, and $C(O)R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

173. The compound of any one of paragraphs 163-172, wherein the compound of Formula (IIb) is selected from any one of the compounds of Table 2c or Table 2c-2, or a pharmaceutically acceptable salt thereof.

174. The compound of paragraph 163, wherein the compound of Formula (IIb) is selected from any one of the compounds of Table 2c, or a pharmaceutically acceptable salt thereof.

175. A pharmaceutical composition comprising a compound of any one of paragraphs 163-174, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

176. A compound of Formula (IIc):



(IIc),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

177. The compound of paragraph 176, wherein R^B is a halogen.

178. The compound of paragraph 176, wherein R^B is $S(O)_2R^{b1}$.

179. The compound of any one of paragraphs 176-178, wherein R^2 is selected H and C_{1-6} alkyl.

180. The compound of any one of paragraphs 176-179, wherein R^4 is H.

181. The compound of any one of paragraphs 176-180, wherein R^5 is H.

182. The compound of any one of paragraphs 176-181, wherein R^7 is selected H and C_{1-6} alkyl.

183. The compound of any one of paragraphs 176-182, wherein R^N is H.

184. The compound of any one of paragraphs 176-182, wherein R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from morpholinyl and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

185. The compound of any one of paragraphs 176-183, wherein ring A is selected from C_{6-10} aryl and C_{3-10} cycloalkyl, optionally substituted with 1-10 substituents independently selected from R^A.

186. The compound of any one of paragraphs 176-185, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

187. The compound of any one of paragraphs 176-179, wherein:

R^2 is selected H and C_{1-6} alkyl;

R^4 is H;

R^5 is H;

R^7 is selected H and C_{1-6} alkyl;

R^N is H; or

R^N and R^{11}, together with the N atom to which they are attached, form a ring selected from morpholinyl and piperazinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

ring A is selected from C_{6-10} aryl and C_{3-10} cycloalkyl, optionally substituted with 1-10 substituents independently selected from R^A; and

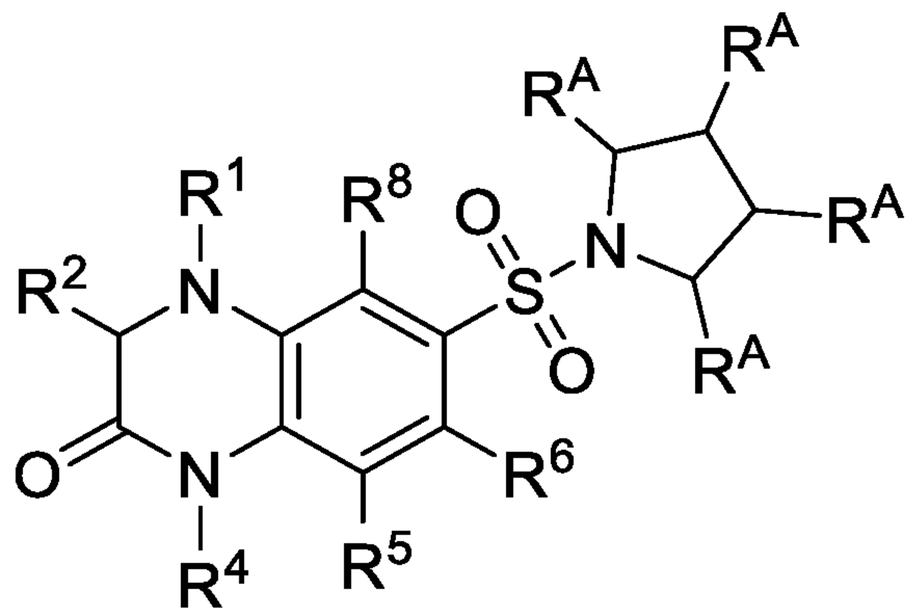
each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

188. The compound of paragraph 176, wherein the compound of Formula (IIc) is selected from any one of the compounds of Table 2d or Table 2d-2, or a pharmaceutically acceptable salt thereof.

189. The compound of paragraph 176, wherein the compound of Formula (IIc) is selected from any one of the compounds of Table 2d, or a pharmaceutically acceptable salt thereof.

190. A pharmaceutical composition comprising a compound of any one of paragraphs 176-189, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

191. A compound of Formula (IId):



(IId),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5, R^6, and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and

$S(O)_2NR^{c1}R^{d1}$;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

192. The compound of paragraph 191, wherein R^2 is selected from H and C_{1-6} alkyl.

193. The compound of paragraph 191 or paragraph 192, wherein R^4 is H.

194. The compound of any one of paragraphs 191-193, wherein R^5, R^6, and R^8 are each H.

195. The compound of any one of paragraphs 191-194, wherein R^1 is selected from H, C_{1-6} alkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

196. The compound of any one of paragraphs 191-195, wherein each R^A is H.

197. The compound of paragraph 191, wherein:

R^2 is selected from H and C_{1-6} alkyl;

R^4 is H;

R^5, R^6, and R^8 are each H;

R^1 is selected from H, C_{1-6} alkyl, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

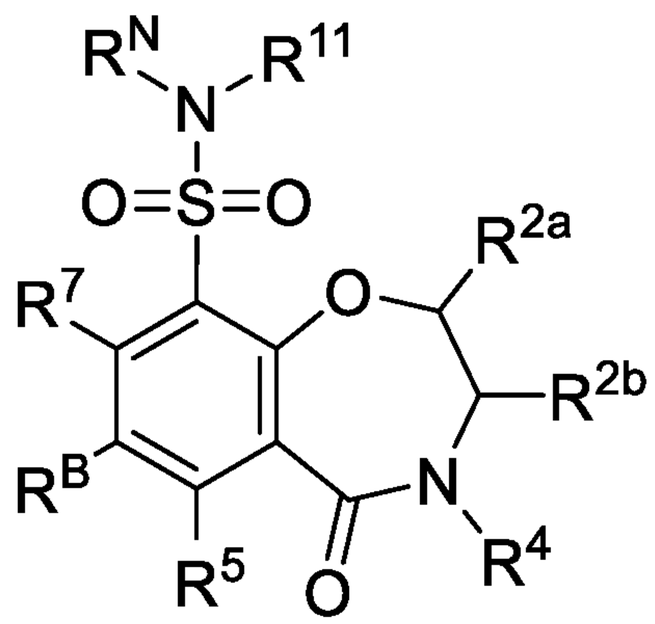
each R^9 is independently selected from OH, C_{1-6} alkoxy, carboxy, $C(O)NH_2$, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino; and

each R^A is H.

198. The compound of paragraph 191, wherein the compound of Formula (IId) is selected from any one of the compounds of Table 2e, or a pharmaceutically acceptable salt thereof.

199. A pharmaceutical composition comprising a compound of any one of paragraphs 191-198, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

200. A compound of Formula (IIe)



(IIe),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered

heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

201. The compound of paragraph 200, wherein R^B is a halogen.

202. The compound of paragraph 200, wherein R^B is $S(O)_2R^{b1}$.

203. The compound of any one of paragraphs 200-202, wherein R^{2a} and R^{2b} are each independently selected from H and C_{1-6} alkyl.

204. The compound of any one of paragraphs 200-203 wherein R^4 is H.

205. The compound of any one of paragraphs 200-204, wherein R^5 is H.

206. The compound of any one of paragraphs 200-205, wherein R^7 is selected H and C_{1-6} alkyl.

207. The compound of any one of paragraphs 200-206, wherein R^N is H.

208. The compound of any one of paragraphs 200-207, wherein ring A is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A.

209. The compound of any one of paragraphs 200-208, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

210. The compound of paragraph 200, wherein:

R^{2a} and R^{2b} are each independently selected H and C_{1-6} alkyl;

R^4 is H;

R^5 is H;

R^7 is selected H and C_{1-6} alkyl;

R^N is H;

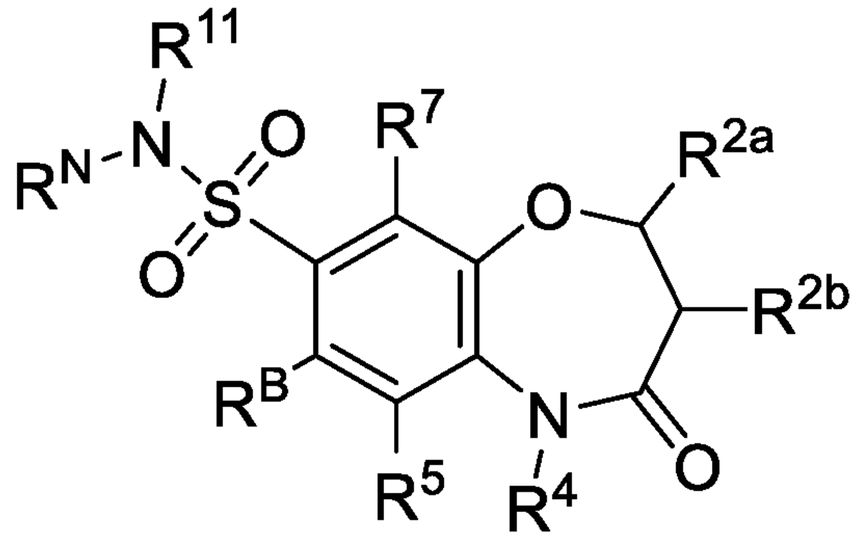
R^{11} is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A; and

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

211. The compound of paragraph 200, wherein the compound of Formula (IIe) is selected from any one of the compounds of Table 2f, or a pharmaceutically acceptable salt thereof.

212. A pharmaceutical composition comprising a compound of any one of paragraphs 200-211, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

213. A compound of Formula (IIf):



(IIf),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl,

C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a

4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

214. The compound of paragraph 213, wherein R^B is a halogen.

215. The compound of paragraph 213, wherein R^B is $S(O)_2R^{b1}$.

216. The compound of any one of paragraphs 213-215, wherein R^{2a} and R^{2b} are each independently selected from H and C_{1-6} alkyl.

217. The compound of any one of paragraphs 213-216, wherein R^4 is H.

218. The compound of any one of paragraphs 213-217, wherein R^5 is H.

219. The compound of any one of paragraphs 213-218, wherein R^7 is selected H and C_{1-6} alkyl.

220. The compound of any one of paragraphs 213-219, wherein R^N is H.

221. The compound of any one of paragraphs 213-220, wherein ring A is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A.

222. The compound of any one of paragraphs 213-221, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

223. The compound of paragraph 213, wherein:

R^{2a} and R^{2b} are each independently selected H and C_{1-6} alkyl;

R^4 is H;

R^5 is H;

R^7 is selected H and C_{1-6} alkyl;

R^N is H;

R^{11} is C_{6-10} aryl, optionally substituted with 1-5 substituents independently

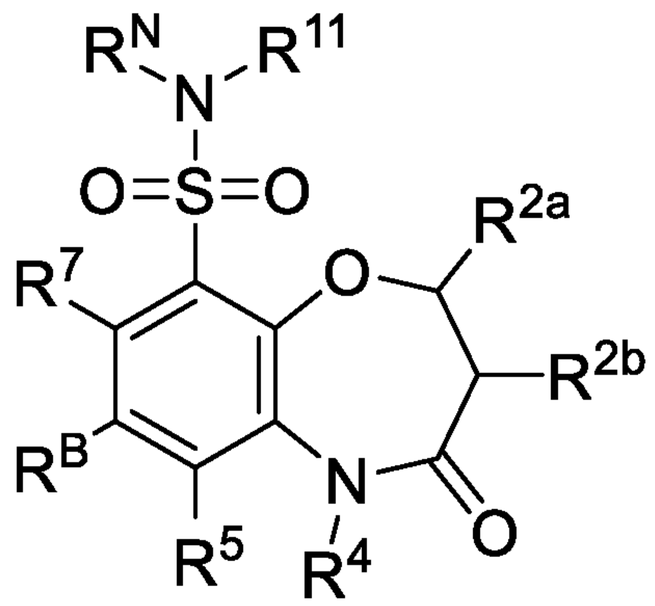
selected from R^A; and

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

224. The compound of paragraph 213, wherein the compound of Formula (IIf) is selected from any one of the compounds of Table 2g, or a pharmaceutically acceptable salt thereof.

225. A pharmaceutical composition comprising a compound of any one of paragraphs 213-224, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

226. A compound of Formula (IIg):



(IIg),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl,

di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

227. The compound of paragraph 226, wherein R^B is a halogen.

228. The compound of paragraph 226, wherein R^B is $S(O)_2R^{b1}$.

229. The compound of any one of paragraphs 226-228, wherein R^{2a} and R^{2b} are each independently selected from H and C_{1-6} alkyl.

230. The compound of any one of paragraphs 226-229, wherein R^4 is H.

231. The compound of any one of paragraphs 226-230, wherein R^5 is H.

232. The compound of any one of paragraphs 226-231, wherein R^7 is selected H and C_{1-6} alkyl.

233. The compound of any one of paragraphs 226-232, wherein R^N is H.

234. The compound of any one of paragraphs 226-233, wherein ring A is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A.

235. The compound of any one of paragraphs 226-234, wherein each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and OR^{a1}; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

236. The compound of paragraph 226, wherein:

R^{2a} and R^{2b} are each independently selected H and C_{1-6} alkyl;

R^4 is H;

R^5 is H;

R^7 is selected H and C_{1-6} alkyl;

R^N is H;

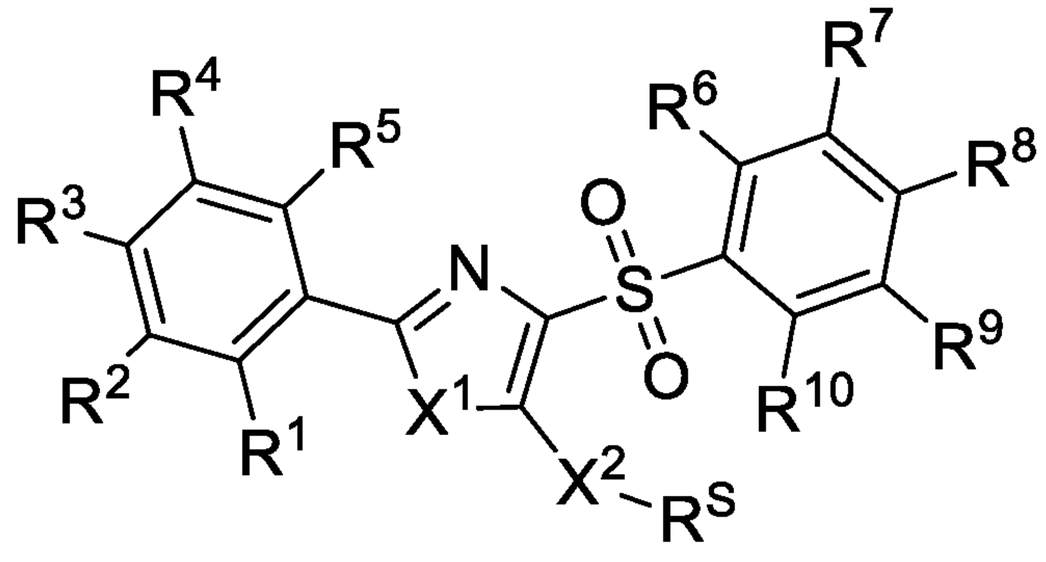
R^{11} is C_{6-10} aryl, optionally substituted with 1-5 substituents independently selected from R^A; and

each R^A is independently selected from H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

237. The compound of paragraph 226, wherein the compound of Formula (IIg) is selected from any one of the compounds of Table 2h, or a pharmaceutically acceptable salt thereof.

238. A pharmaceutical composition comprising a compound of any one of paragraphs 226-237, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

239. A method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (IIIa):



(IIIa),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from O, S, and NR^N;

R^N is selected from H and C_{1-6} alkyl;

X^2 is selected from S, S(O), and $S(O)_2$;

R^S is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

or any two adjacent R^1, R^2, R^3, R^4, and R^5 groups, together with the carbon atoms to which they are attached, form a C_{6-10} aryl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6}

alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{12};

each R^{12} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10

membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

240. The method of paragraph 239, wherein:

X^1 is selected from O, S, and NR^N;

R^N is selected from H and C_{1-6} alkyl;

X^2 is selected from S, S(O), and $S(O)_2$;

R^S is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$,

$NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{12};

each R^{12} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

241. The method of paragraph 239 or 240, wherein X^1 is O.

242. The method of paragraph 239 or 240, wherein X^1 is S.

243. The method of paragraph 239 or 240, wherein X^1 is NR^N.

244. The method of any one of paragraphs 239-243, wherein X^2 is S.

245. The method of any one of paragraphs 239-243, wherein X^2 is S(O).

246. The method of any one of paragraphs 239-243, wherein X^2 is $S(O)_2$.

247. The method of any one of paragraphs 239-246, wherein R^S is selected from C_{1-6} alkyl, C_{6-10} aryl, and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}.

248. The method of paragraph 247, wherein R^S is C_{1-6} alkyl, optionally substituted with Cy^1, OR^{a1}, $C(O)R^{b1}$, $NR^{c1}R^{d1}$, and $C(O)NR^{c1}R^{d1}$.

249. The method of paragraph 247, wherein R^S is C_{1-6} alkyl, optionally substituted with Cy^1, OR^{a1}, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$.

250. The method of paragraph 247, wherein R^S is selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from halo and C_{1-6} alkyl.

251. The method of any one of paragraphs 239-250, wherein each R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$.

252. The method of ony one of paragraphs 239-251, wherein each Cy^1 is independently selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1}.

253. The method of any one of paragraphs 239-252, wherein each R^{Cy1} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{12}.

254. The method of any one of paragraphs 239-252, wherein each R^{Cy1} is independently selected from halo, CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and $S(O)_2NH_2$.

255. The method of any one of paragraphs 239-254, wherein each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

256. The method of any one of paragraphs 239-254, wherein each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, each of which is

optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

257. The method of any one of paragraphs 239-256, wherein each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

258. The method of paragraph 239, wherein:

R^S is selected from C_{1-6} alkyl, C_{6-10} aryl, and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, $NR^{c1}R^{d1}$, and $C(O)NR^{c1}R^{d1}$;

Cy^1 is independently selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{12};

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

259. The method of paragraph 258, wherein R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$.

260. The method of paragraph 239, wherein:

R^S is selected from C_{1-6} alkyl, C_{6-10} aryl, and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, $NR^{c1}R^{d1}$, and $C(O)NR^{c1}R^{d1}$;

Cy^1 is independently selected from C_{6-10} aryl and C_{3-10} cycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, OH, C_{1-6} alkoxy, $C(O)NH_2$, C(O)OH, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and $S(O)_2NH_2$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

261. The method of paragraph 260, wherein R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, and $C(O)NR^{c1}R^{d1}$;

262. The method of paragraph 239, wherein the compound of Formula (IIIa) is selected from any one of the compounds of Table 3a, Table 3b, Table 3b-2, Table 10, or Table 11.

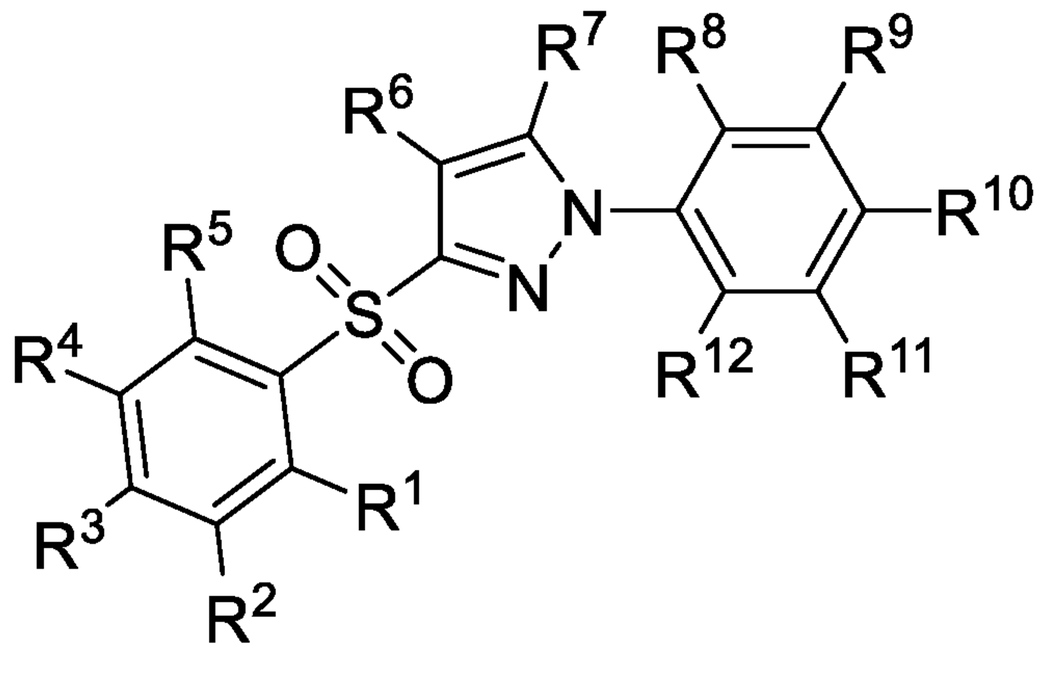
263. The method of paragraph 239, wherein the compound of Formula (IIIa) is selected from any one of the compounds of Table 3a or Table 3b, or a pharmaceutically acceptable salt thereof.

264. A compound selected from any one of the compounds of Table 3b or Table 3b-2, or a pharmaceutically acceptable salt thereof.

265. A compound selected from any one of the compounds of Table 3b, or a pharmaceutically acceptable salt thereof.

266. A pharmaceutical composition comprising a compound of paragraph 264 or 265, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

267. A compound of Formula (IIIc):



(IIIc),

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{13};

each R^{13} independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

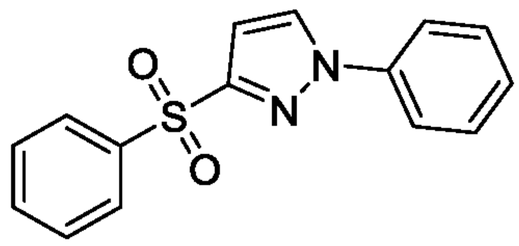
each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6}

alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

268. The compound of paragraph 267, wherein each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy.

269. The compound of paragraph 267, wherein each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, OH, C_{1-6} alkyl, and C_{1-6} alkoxy.

270. The compound of paragraph 267, wherein the compound of Formula (IIIc) is:

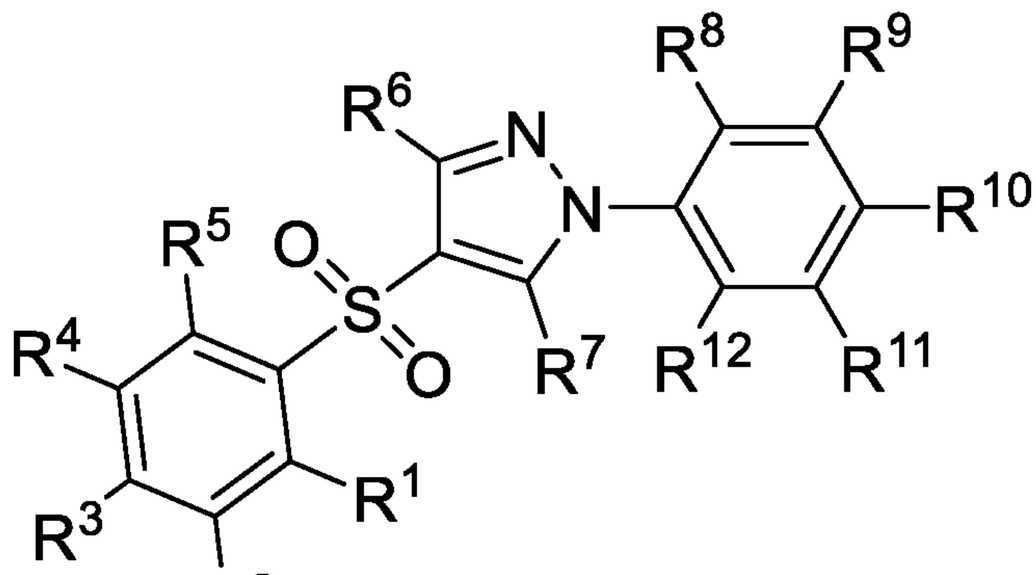


,

or a pharmaceutically acceptable salt thereof.

271. A pharmaceutical composition comprising a compound of any one of paragraphs 267-270, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

272. A compound of Formula (IIId):



(IIId),

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently

selected from R^{13};

each R^{13} independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

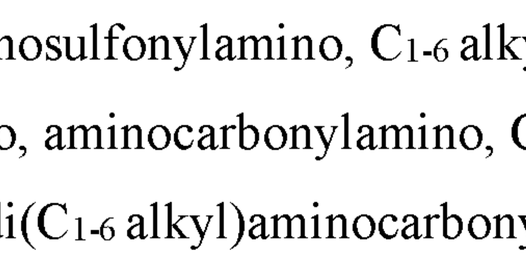
or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

273. The compound of paragraph 272, wherein each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

274. The compound of paragraph 272, wherein each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, OH, C_{1-6} alkyl, and C_{1-6} alkoxy.

275. The compound of paragraph 272, wherein the compound of Formula (IIId) is:

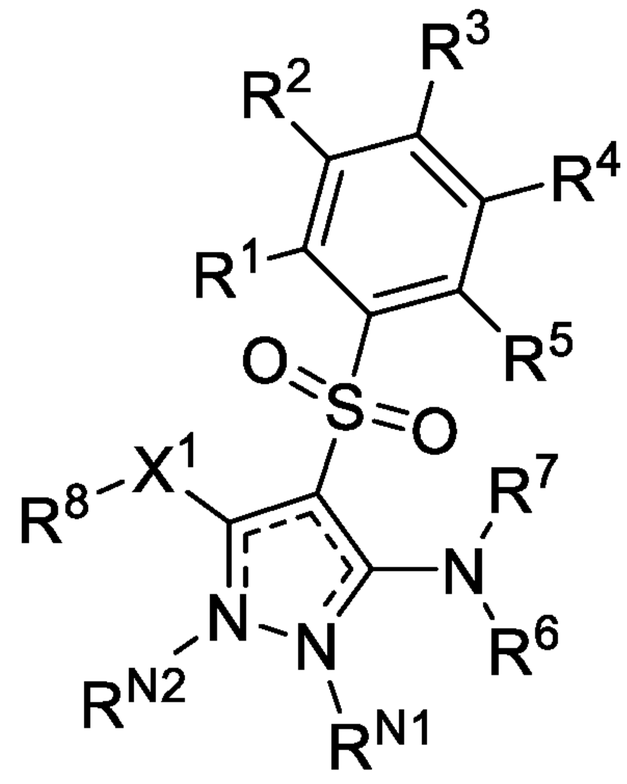


,

or a pharmaceutically acceptable salt thereof.

276. A pharmaceutical composition comprising a compound of any one of paragraphs 272-275, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

277. A compound of Formula (IIIe):



(IIIe),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

each ⫶ represents a single bond or a double bond, provided that not more than two of ⫶ are double bonds;

R^{N2} is absent if ⫶ between the N atom to which R^{N2} is attached and the C atom to which X^1 is attached is a double bond; or

R^{N2} is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{N1} is absent if ⫶ between the N atom to which R^{N1} is attached and the C atom to which NR^6R^7 is attached is a double bond; or

R^{N1} is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$,

$S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^9;

R^6 and R^7 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

or R^6 and R^{N1} together with the N atoms to which they are attached from a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^9 independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{10} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

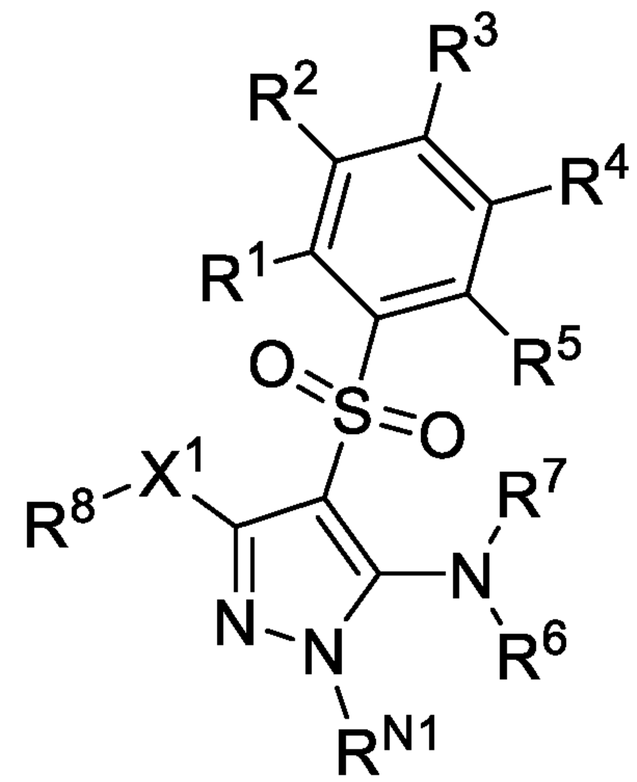
each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

278. The compound of paragraph 277, wherein X^1 is selected from S(O) and $S(O)_2$.

279. The compound of paragraph 277, wherein $X^1$is S(O).

280. The compound of paragraph 277, wherein X^1 is $S(O)_2$.

281. The compound of any one of paragraphs 277-280, wherein the compound of Formula (IIIe) has formula:



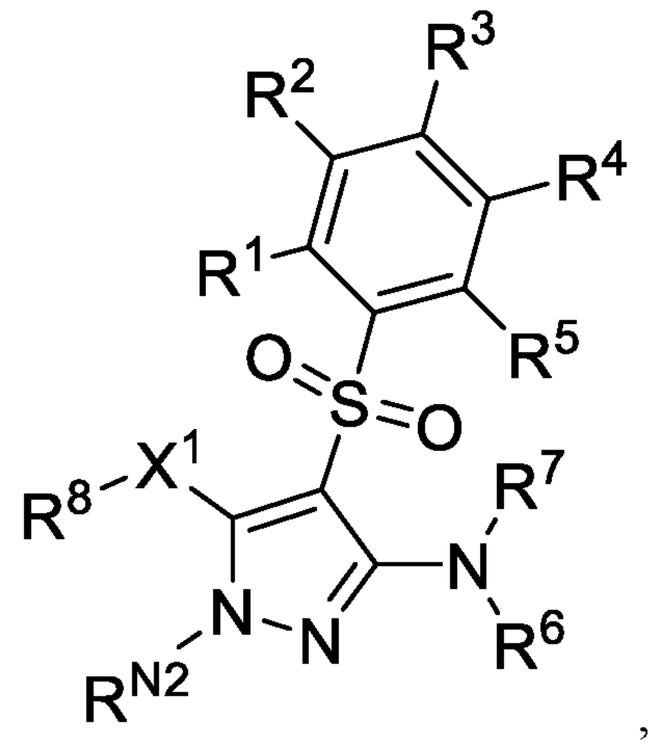
,

or a pharmaceutically acceptable salt thereof.

282. The compound of paragraph 281, wherein R^{N1} is selected from H and C_{1-6} alkyl.

283. The compound of paragraph 282, wherein R^{N1} is H.

284. The compound of any one of paragraphs 281-283, wherein the compound of Formula (IIIe) has formula:



,

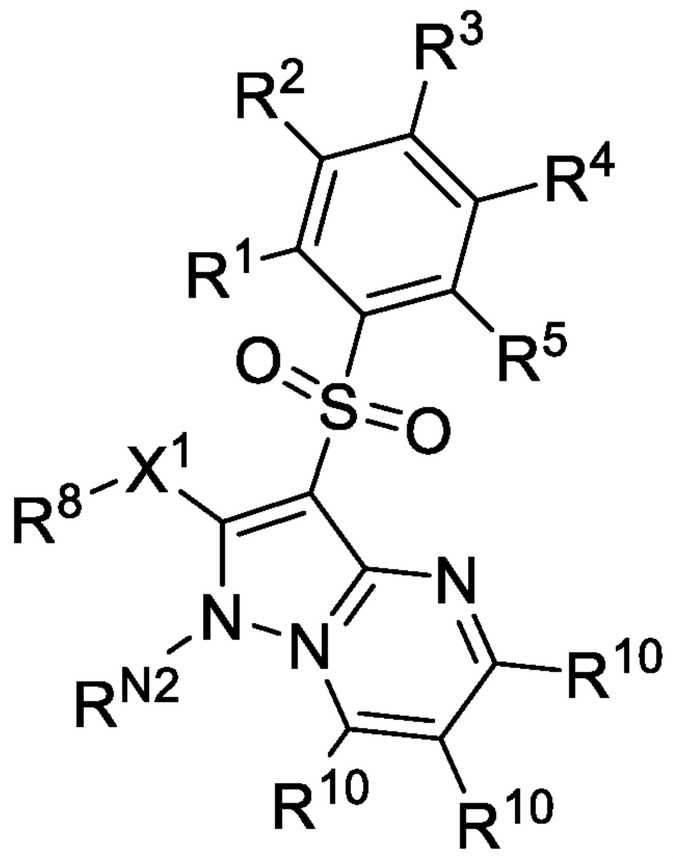
or a pharmaceutically acceptable salt thereof.

285. The compound of any one of paragraphs 277-284, wherein R^6 and R^7 are each independently selected from H and C_{1-6} alkyl.

286. The compound of paragraph 285, wherein R^6 and R^7 are both H.

287. The compound of any one of paragraphs 277-281, wherein R^6 and R^{N1} together with the N atoms to which they are attached from a 5-10 membered heteroaryl, substituted with 1, 2, or 3 substituents independently selected from R^{10}.

288. The compound of paragraph 287, wherein the compound of Formula (IIIe) has formula:



,

or a pharmaceutically acceptable salt thereof.

289. The compound of any one of paragraphs 277-288, wherein each R^{10} is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

290. The compound of any one of paragraphs 277-288, wherein each R^{10} is independently selected from H, halo, OH, C_{1-6} alkyl, and C_{1-6} alkoxy.

291. The compound of any one of paragraphs 277-288, wherein each R^{10} is independently selected from H, OH, and C_{1-6} alkyl.

292. The compound of any one of paragraphs 284-291, wherein R^{N2} is selected from H and C_{1-6} alkyl.

293. The compound of paragraph 292, wherein R^{N2} is H.

294. The compound of any one of paragraphs 277-293, wherein each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

295. The compound of paragraph 294, wherein each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

296. The compound of any one of paragraphs 277-295, wherein R^8 is C_{1-6} alkyl.

297. The compound of paragraph 288, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each R^{10} is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy;

R^{N2} is selected from H and C_{1-6} alkyl;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

R^8 is C_{1-6} alkyl.

298. The compound of paragraph 288, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each R^{10} is independently selected from H, OH, and C_{1-6} alkyl;

R^{N2} is H;

R^1, R^2, R^3, R^4, and R^5 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R^8 is C_{1-6} alkyl.

299. The compound of paragraph 281, wherein:

X^1 is selected from S(O) and $S(O)_2$;

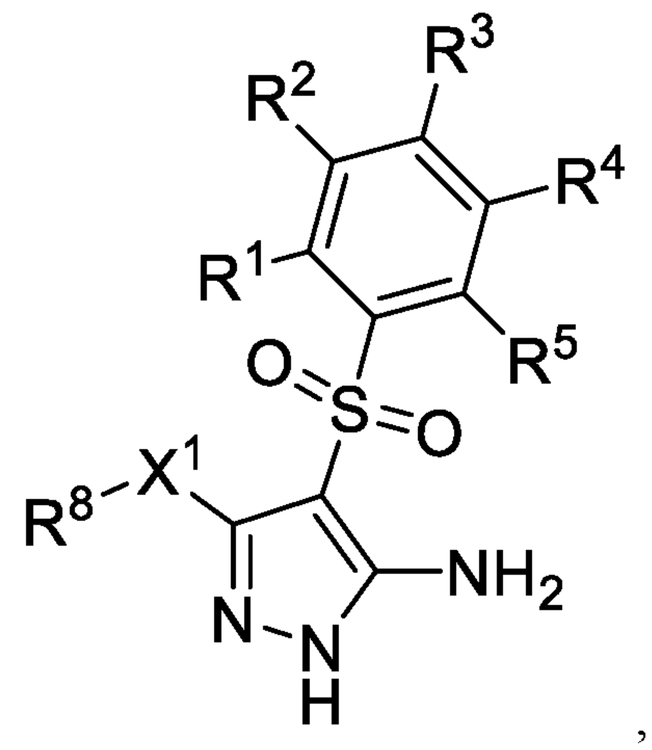
each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl;

R^{N1} is selected from H and C_{1-6} alkyl; and

R^6 and R^7 are each independently selected from H and C_{1-6} alkyl.

300. The compound of paragraph 299, wherein the compound of Formula (IIIe) has formula:



,

or a pharmaceutically acceptable salt thereof.

301. The compound of paragraph 284, wherein:

X^1 is selected from S(O) and $S(O)_2$;

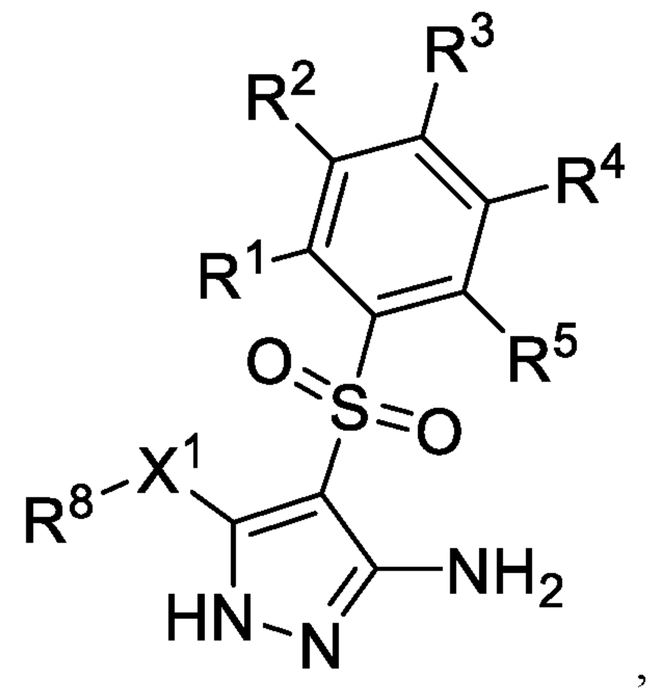
each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl;

R^{N2} is selected from H and C_{1-6} alkyl; and

R^6 and R^7 are each independently selected from H and C_{1-6} alkyl.

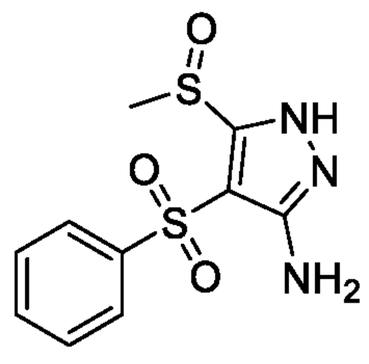
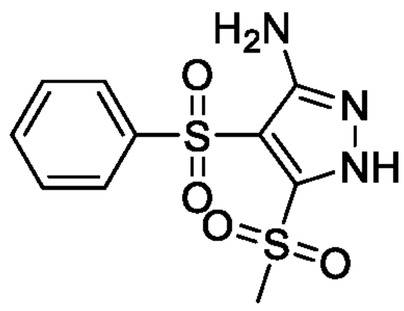
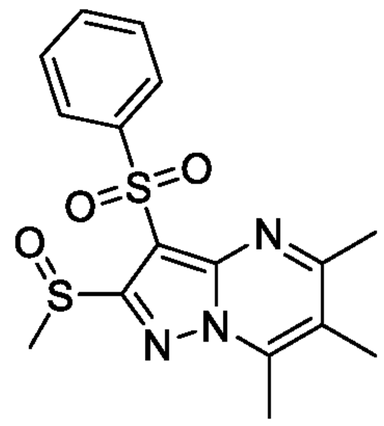
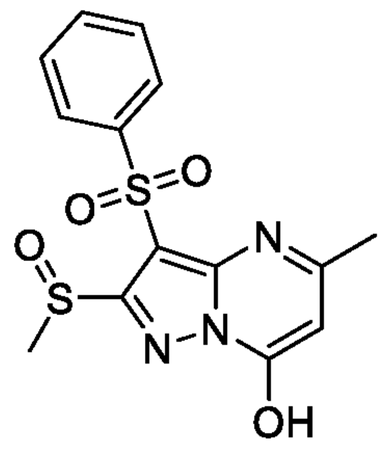
302. The compound of paragraph 301, wherein the compound of Formula (IIIe) has formula:



,

or a pharmaceutically acceptable salt thereof.

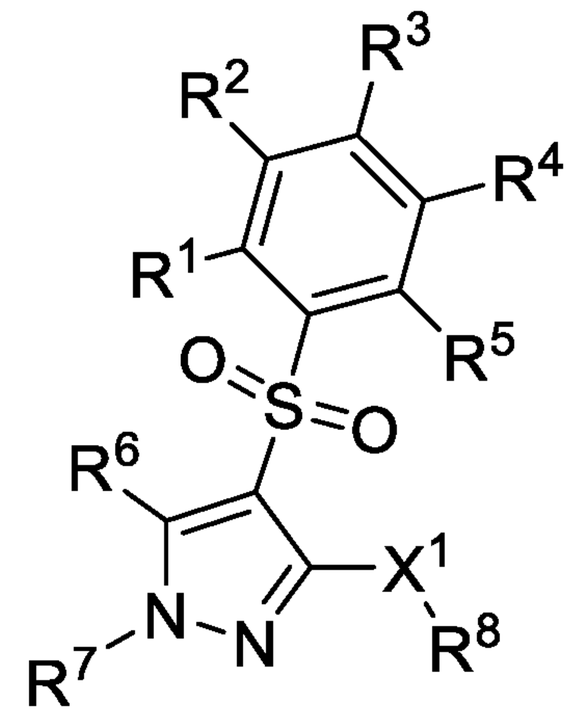
303. The compound of paragraph 277, wherein the compound of Formula (IIIe) is selected from any one of the following compounds:

BC19338	ZE23-0091	
BC19339	ZE23-0092	
BC19340	ZE23-0096	
BC19341	ZE23-0098	

or a pharmaceutically acceptable salt thereof.

304. A pharmaceutical composition comprising a compound of any one of paragraphs 277-303, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

305. A compound of Formula (IIIf):



(IIIf),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^9;

R^6 and R^7 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

provided that at least one of R^6 and R^7 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

or R^6 and R^7, together with the C atom to which R^6 is attached and N atom to which R^7 is attached, from a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^9 independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{10} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

306. The compound of paragraph 305, wherein X^1 is selected from S(O) and $S(O)_2$.

307. The compound of paragraph 305, wherein $X^1$is S(O).

308. The compound of paragraph 305, wherein X^1 is $S(O)_2$.

309. The compound of any one of paragraphs 305-308, wherein each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

310. The compound of any one of paragraphs 305-308, wherein each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

311. The compound of any one of paragraphs 305-310, wherein R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$.

312. The compound of any one of paragraphs 305-308, wherein R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

313. The compound of any one of paragraphs 305-312, wherein:

R^6 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

R^7 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

314. The compound of any one of paragraphs 305-312, wherein:

R^6 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^7 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

315. The compound of any one of paragraphs 305-312, wherein:

R^7 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

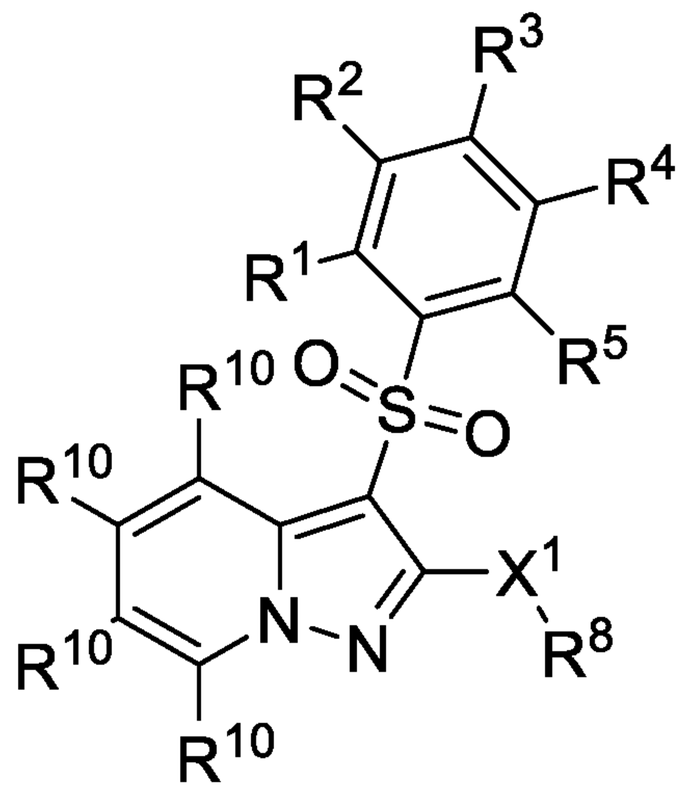
R^6 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

316. The compound of any one of paragraphs 305-312, wherein:

R^7 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^6 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

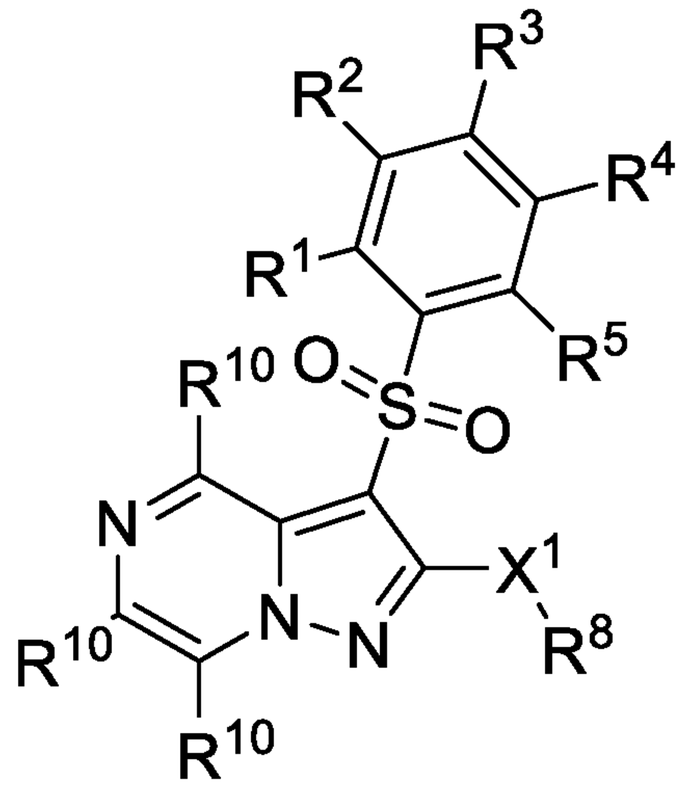
317. The compound of any one of paragraphs 305-312, wherein the compound of Formula (IIIf) has formula:



,

or a pharmaceutically acceptable salt thereof.

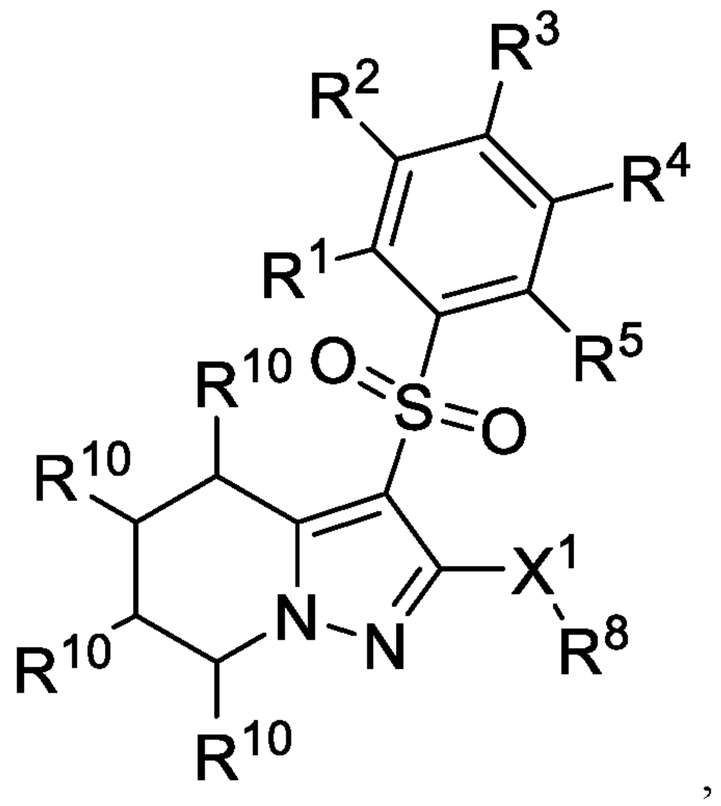
318. The compound of any one of paragraphs 305-312, wherein the compound of Formula (IIIf) has formula:



,

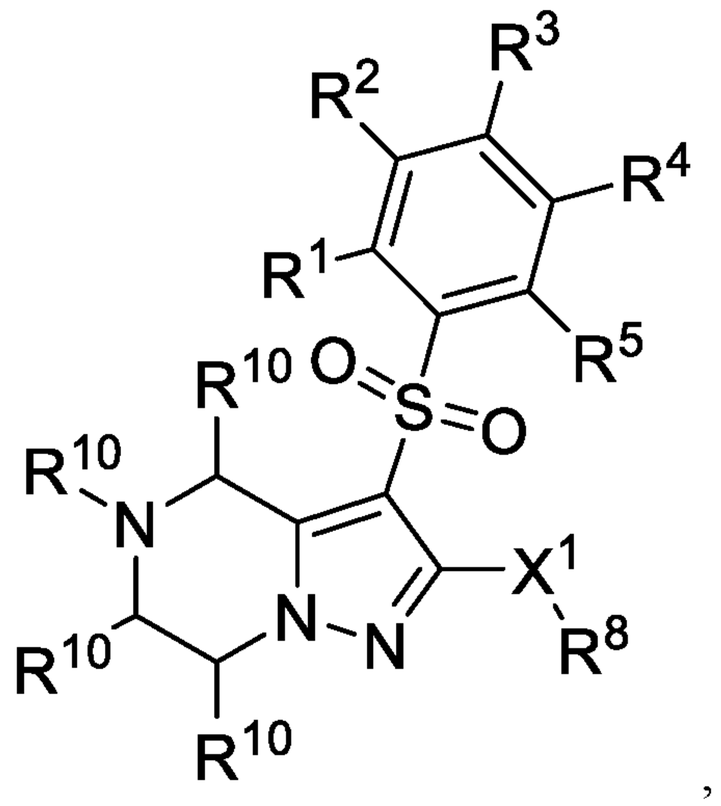
or a pharmaceutically acceptable salt thereof.

319. The compound of any one of paragraphs 305-312, wherein the compound of Formula (IIIf) has formula:



or a pharmaceutically acceptable salt thereof.

320. The compound of any one of paragraphs 305-312, wherein the compound of Formula (IIIf) has formula:



or a pharmaceutically acceptable salt thereof.

321. The compound of any one of paragraphs 305-320, wherein each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

322. The compound of any one of paragraphs 305-321, wherein each R^{10} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

323. The compound of paragraph 305, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN,

NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^6 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

324. The compound of paragraph 305, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^6 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^7 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

325. The compound of paragraph 305, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently

selected from R^9;

R^7 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^6 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

326. The compound of paragraph 305, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl; and

R^6 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

327. The compound of any one of paragraphs 305 and 319-321, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

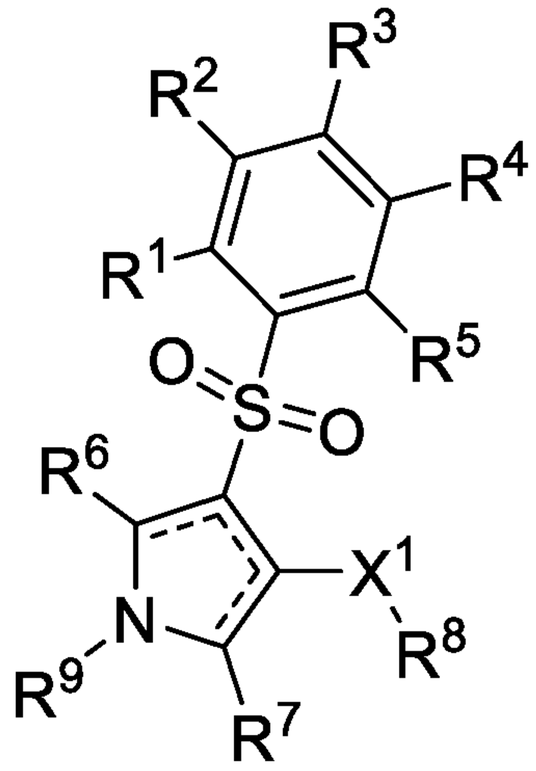
R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

each R^{10} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

328. A pharmaceutical composition comprising a compound of any one of paragraphs 305-327, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

329. A compound of Formula (IIIg-2):



(IIIg-2),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

each ┆ represents a single bond or a double bond, provided that not more than two of ┆ are double bonds;

each of R^1, R^2, R^3, R^4, R^5, R^6, and R^7 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^9 is selected from $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein each of said

C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}; or

R^7 and R^9, together with the N atom to which R^9 is attached and C atom to which R^7 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}; or

R^6 and R^9, together with the N atom to which R^9 is attached and C atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each R^{10} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

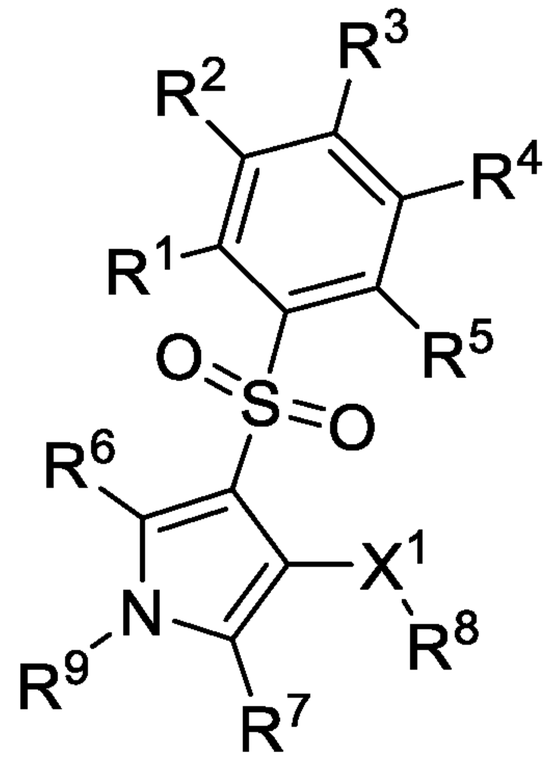
each R^{11} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

330. The compound of paragraph 329, wherein the compound has formula:



(IIIg),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

each of R^1, R^2, R^3, R^4, R^5, R^6, and R^7 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently

selected from R^{10};

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^9 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}; or

R^7 and R^9, together with the N atom to which R^9 is attached and C atom to which R^7 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}; or

R^6 and R^9, together with the N atom to which R^9 is attached and C atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each R^{10} independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{11} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

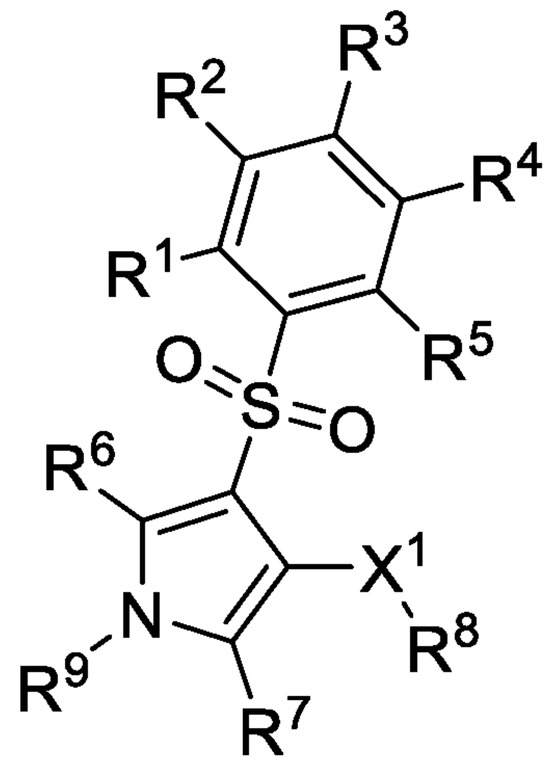
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5

substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

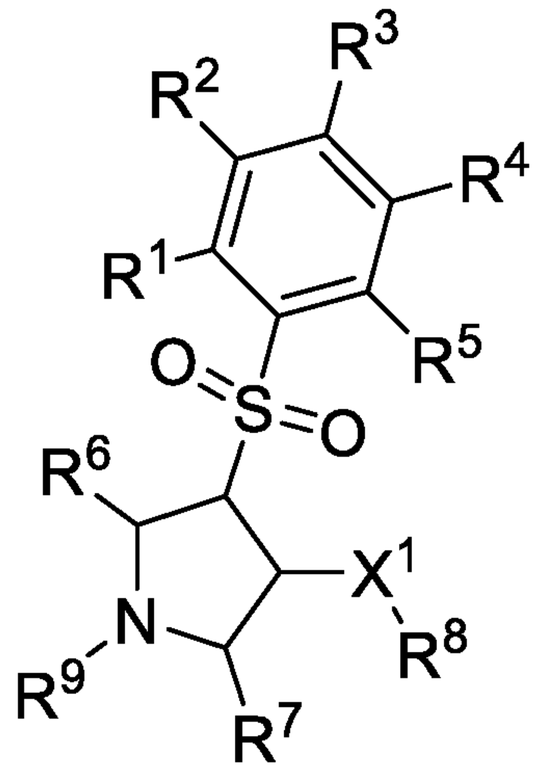
331. The compound of paragraph 329, having formula:



(IIIg),

or a pharmaceutically acceptable salt thereof.

332. The compound of paragraph 329, having formula:



,

or a pharmaceutically acceptable salt thereof.

333. The compound of any one of paragraphs 329-332, wherein X^1 is selected from S(O) and $S(O)_2$.

334. The compound of any one of paragraphs 329-332, wherein X^1 is S(O).

335. The compound of any one of paragraphs 329-332, wherein X^1 is $S(O)_2$.

336. The compound of any one of paragraphs 329-335, wherein each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

337. The compound of any one of paragraphs 329-335, wherein each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

338. The compound of any one of paragraphs 329-337, wherein R^6 and R^7 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

339. The compound of any one of paragraphs 329-337, wherein:

R^6 is H or C_{1-6} alkyl; and

R^7 is H or C_{1-6} alkyl.

340. The compound of any one of paragraphs 329-337, wherein:

R^6 is H or C_{1-6} alkyl; and

R^7 is selected from halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

341. The compound of any one of paragraphs 329-337, wherein:

R^7 is H or C_{1-6} alkyl; and

R^6 is selected from halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6}

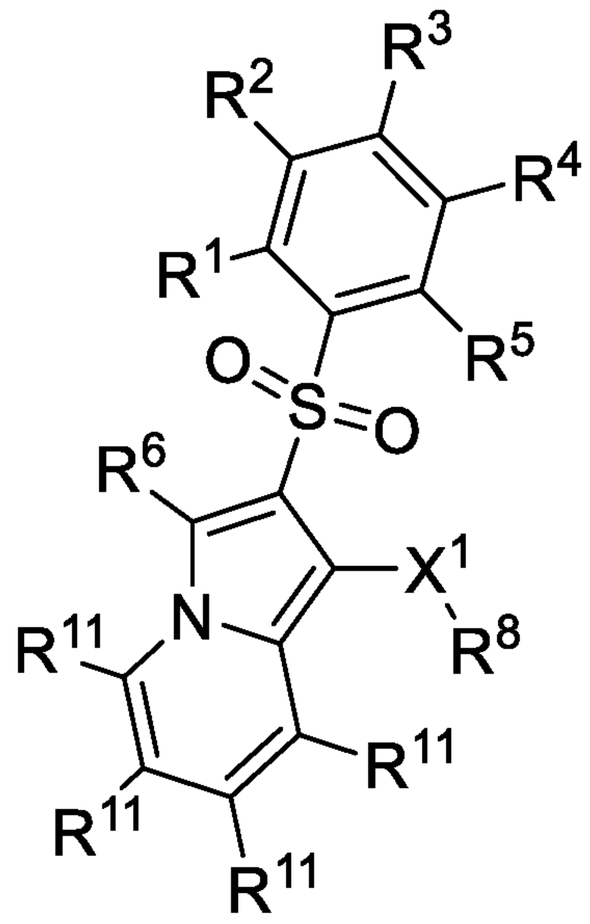
alkoxy, and C_{1-6} haloalkoxy.

342. The compound of any one of paragraphs 329-337, wherein:

R^6 is H or C_{1-6} alkyl; and

R^7 and R^9, together with the N atom to which R^9 is attached and C atom to which R^7 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}.

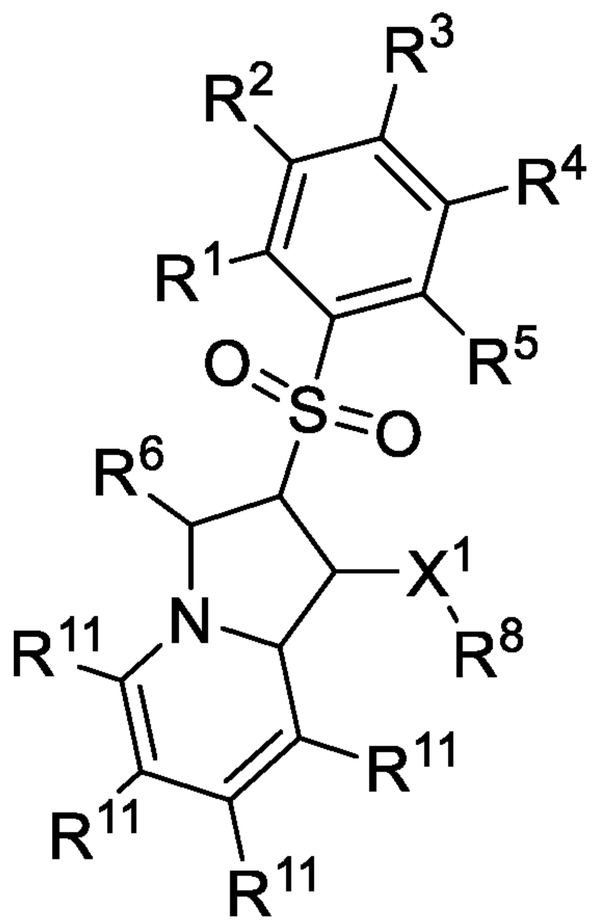
343. The compound of paragraph 342, wherein the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

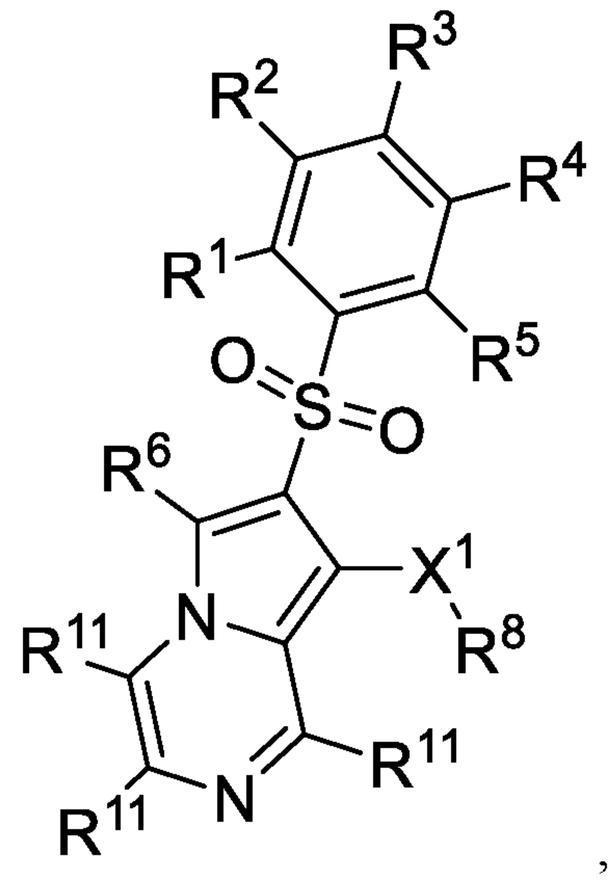
344. The compound of paragraph 342, wherein the compound has formula:



,

or a pharmaceutically acceptable salt thereof.

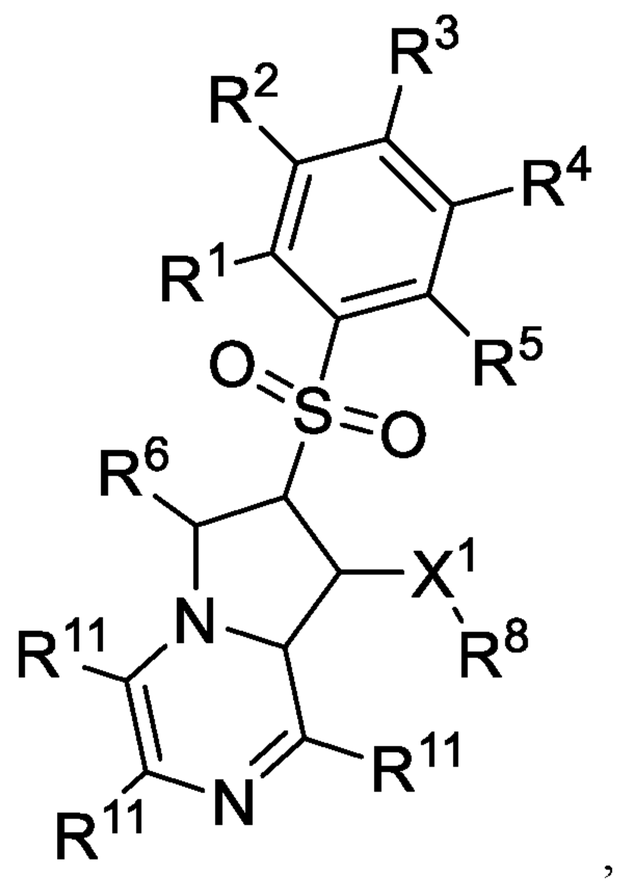
345. The compound of paragraph 342, wherein the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

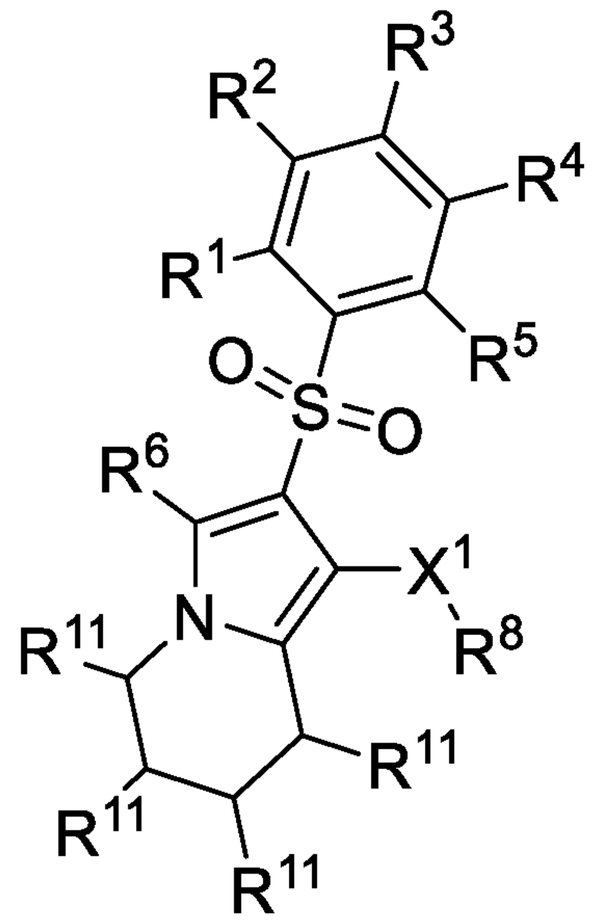
346. The compound of paragraph 342, having formula:



,

or a pharmaceutically acceptable salt thereof.

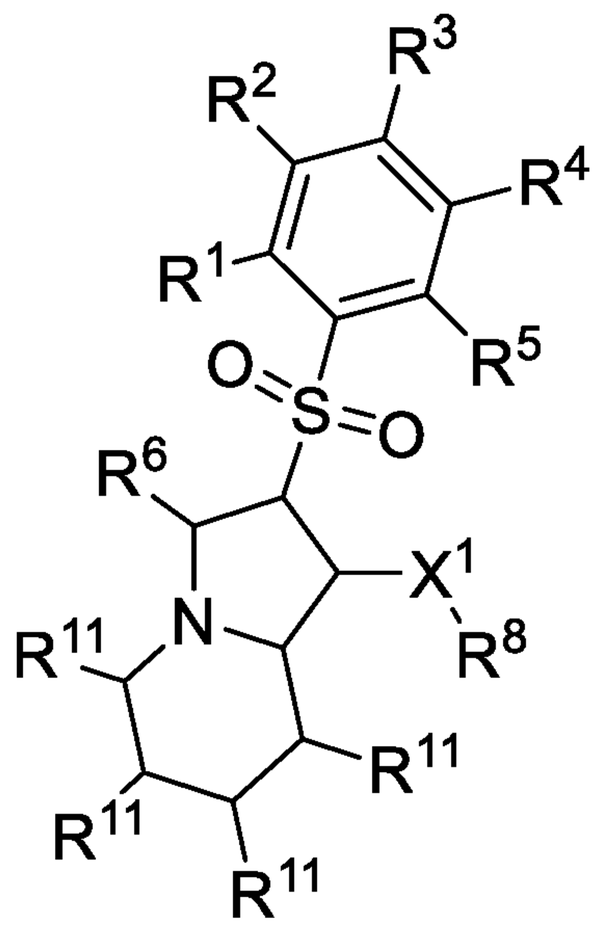
347. The compound of paragraph 342, wherein the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

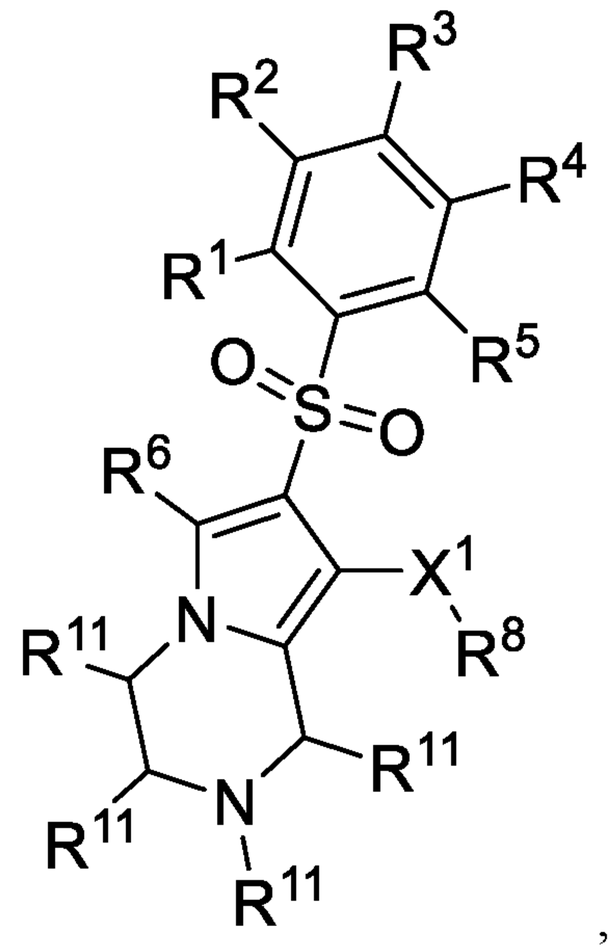
348. The compound of paragraph 342, wherein the compound has formula:



,

or a pharmaceutically acceptable salt thereof.

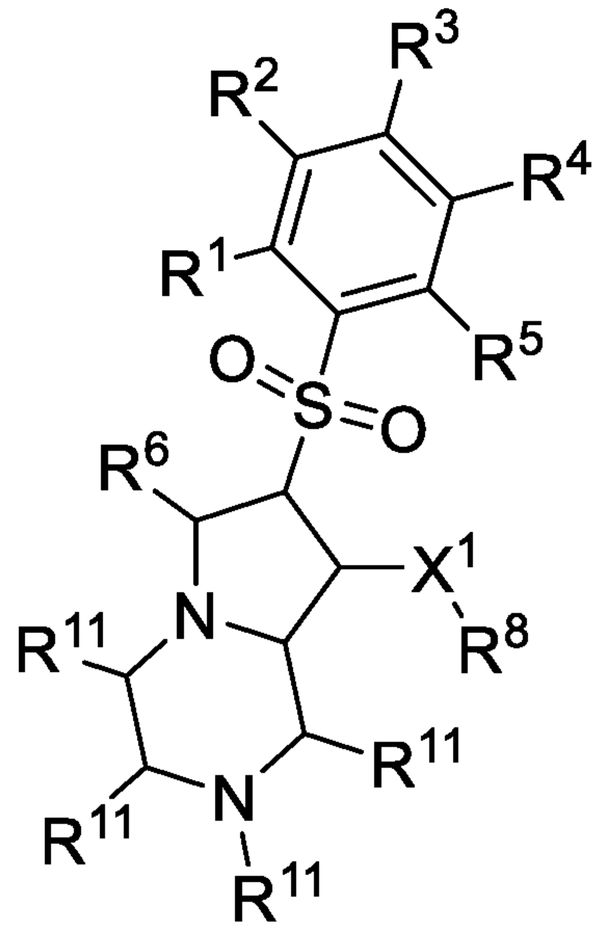
349. The compound of paragraph 342, wherein the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

350. The compound of paragraph 342, having the formula:



,

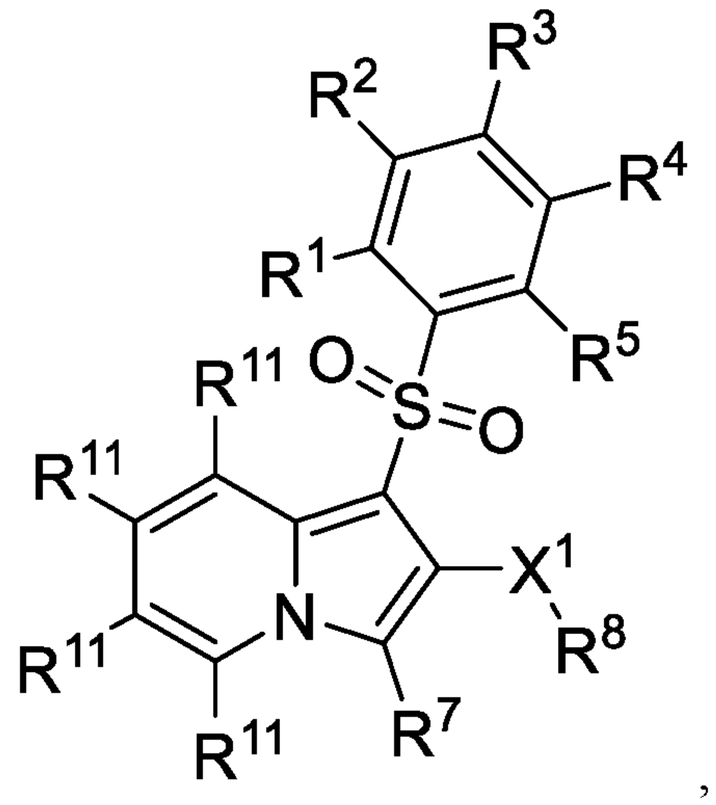
or a pharmaceutically acceptable salt thereof.

351. The compound of any one of paragraphs 329-337, wherein:

R^7 is H or C_{1-6} alkyl; and

R^6 and R^9, together with the N atom to which R^9 is attached and C atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}.

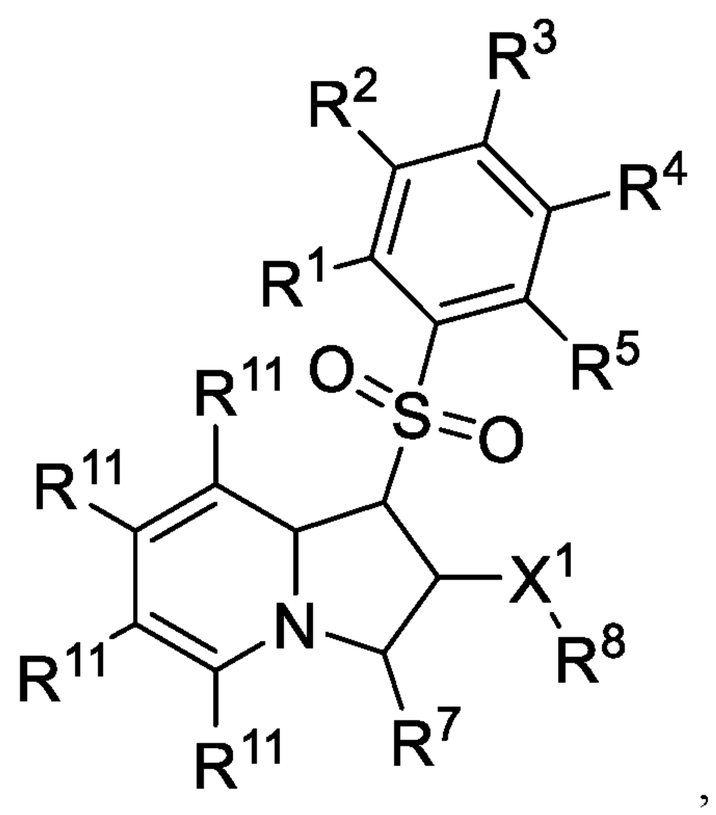
352. The compound of paragraph 351, wherein the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

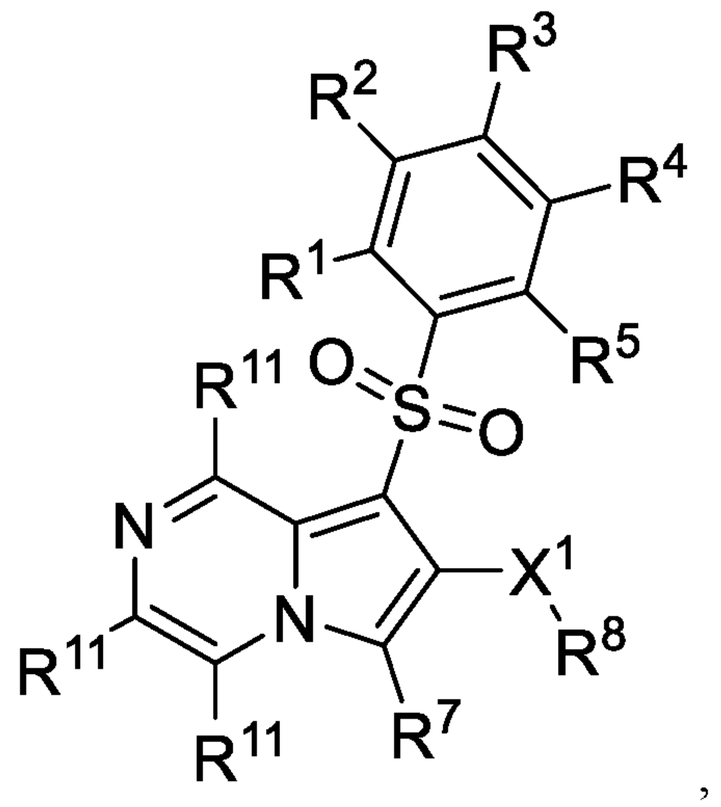
353. The compound of calim 351, having the formula:



,

or a pharmaceutically acceptable salt thereof.

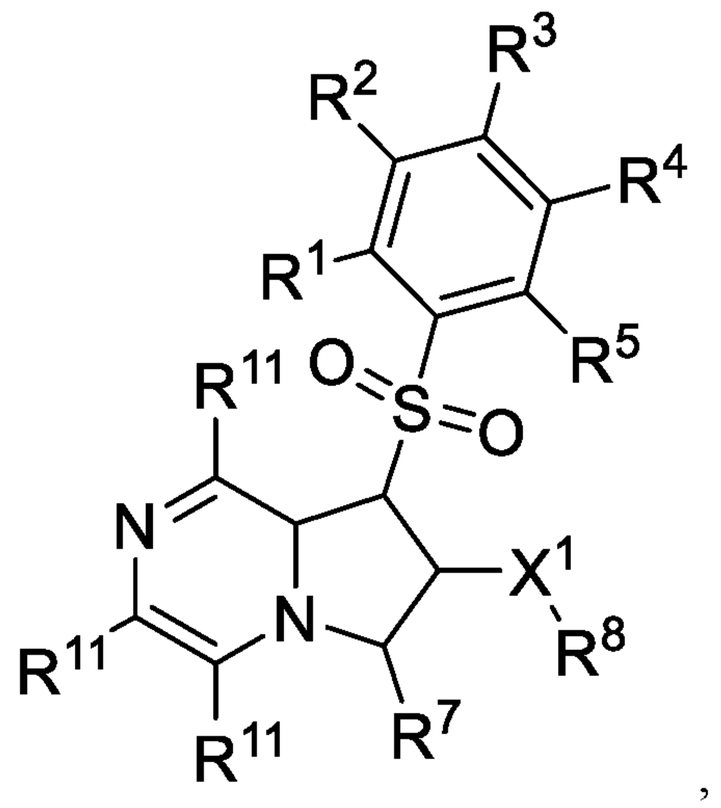
354. The compound of paragraph 351, wherein the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

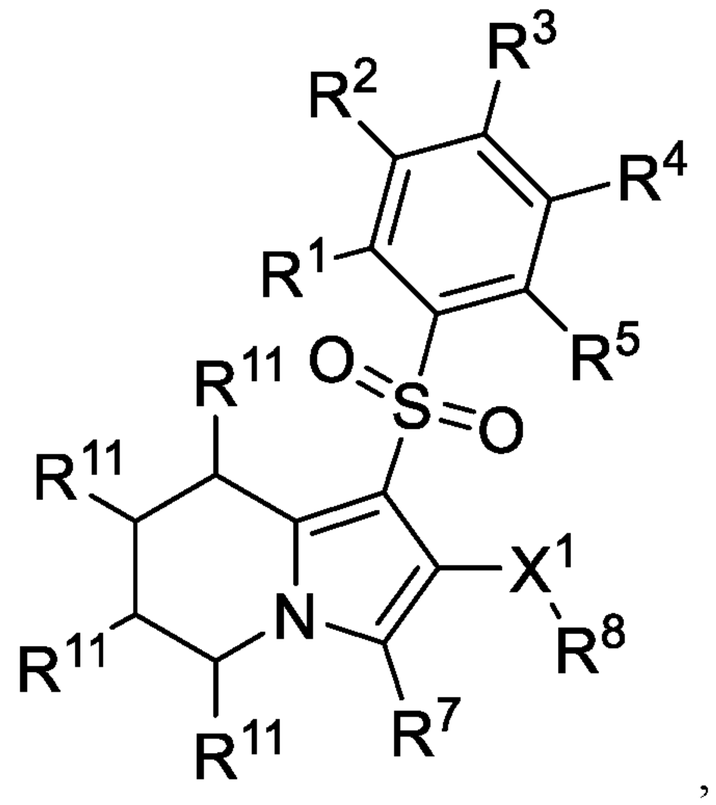
355. The compound of paragraph 351, having the formula:



,

or a pharmaceutically acceptable salt thereof.

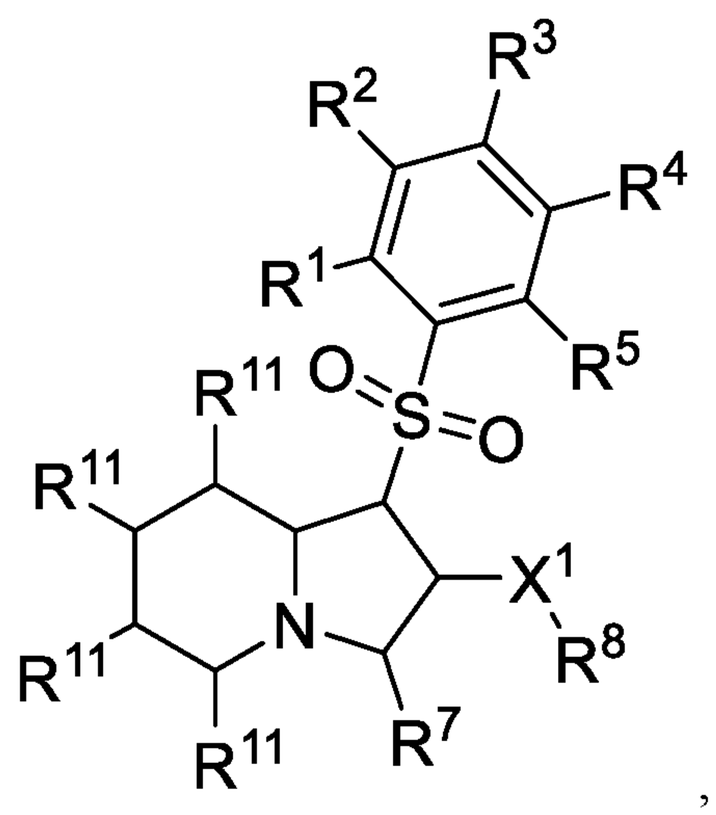
356. The compound of paragraph 351, wherein the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

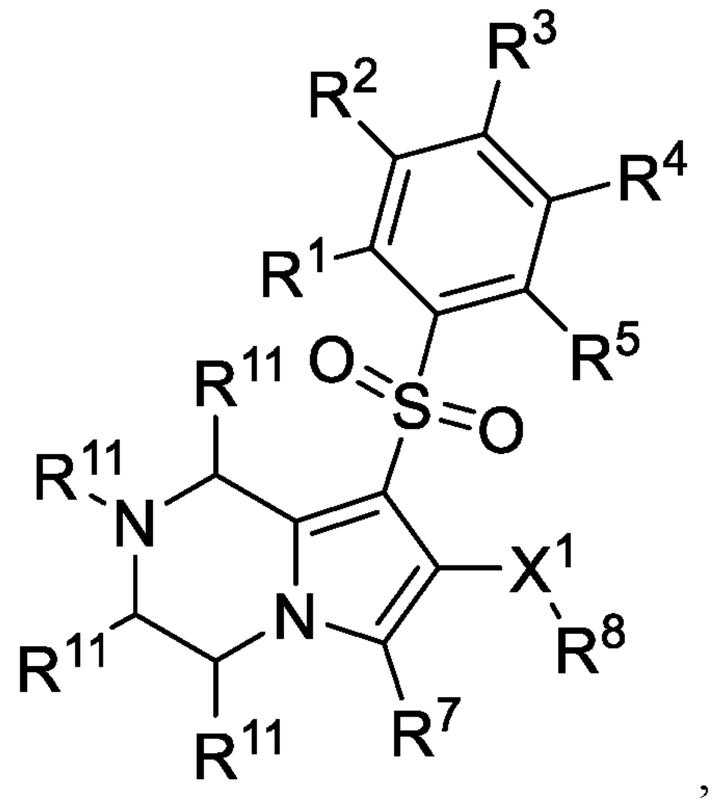
357. The compound of paragraph 351, having the formula:



,

or a pharmaceutically acceptable salt thereof.

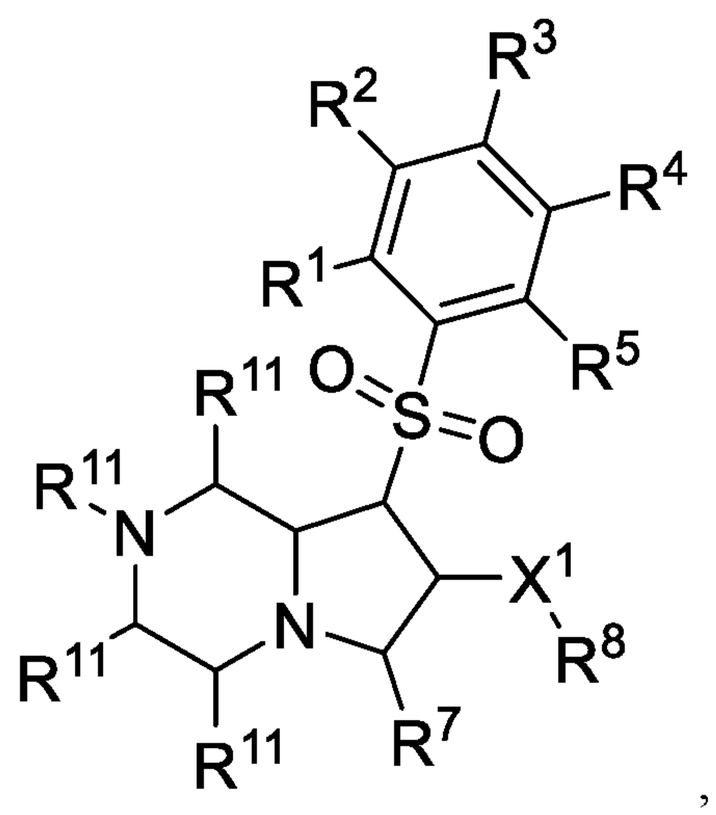
358. The compound of paragraph 351, wherein the compound of Formula (IIIg) has formula:



,

or a pharmaceutically acceptable salt thereof.

359. The compound of paragraph 351, wherein the compound has the formula:



,

or a pharmaceutically acceptable salt thereof.

360. The compound of any one of paragraphs 329-341, wherein R^9 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

361. The compound of any one of paragraphs 329-341, wherein R^9 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

362. The compound of any one of paragraphs 329-341, wherein R^9 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently

selected from R^{10}.

363. The compound of any one of paragraphs 329-341, wherein R^9 is $C(O)R^{b1}$.

364. The compound of any one of paragraphs 329-341, wherein R^9 is 4-10 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

365. The compound of any one of paragraphs 329-364, wherein R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$.

366. The compound of any one of paragraphs 329-365, wherein R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

367. The compound of any one of paragraphs 329-366, wherein R^{10} is independently selected from C_{6-12} aryl, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

368. The compound of any one of paragraphs 329-366, wherein R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

369. The compound of any one of paragraphs 329-368, wherein R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

370. The compound of paragraph 329, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^6 and R^7 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^9 is selected from $C(O)R^{b1}$, C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein said C_{1-6} alkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3

substituents independently selected from R^{10}; and

each R^{10} is independently selected from C_{6-12} aryl, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

371. The compound of paragraph 329, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^6 and R^7 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

372. The compound of paragraph 329, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^6 is H or C_{1-6} alkyl;

R^7 is selected from halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

373. The compound of paragraph 329, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^7 is H or C_{1-6} alkyl;

R^6 is selected from halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6}

alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

374. The compound of paragraph 329, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^6 is H or C_{1-6} alkyl;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

375. The compound of paragraph 329, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^7 is H or C_{1-6} alkyl;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

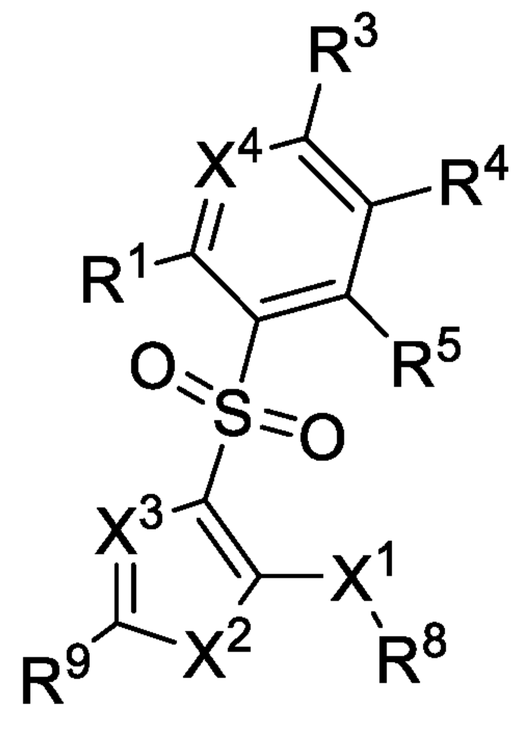
each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

376. The compound of paragraph 329, wherein the compound is selected from any one of the compounds of Table 12, or a pharmaceutically acceptable salt thereof.

377. A pharmaceutical composition comprising a compound of any one of paragraphs 329-376, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

378. A compound of Formula (IIIh):



(IIIh),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

X^4 is selected from N and CR^2;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

X^2 is selected from O, S, and NR^6;

R^6 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

X^3 is selected from N and CR^7;

R^7 is selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-}

$_6$ alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^9 is selected from $S(O)_2R^{b1}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}; or

R^9 and R^6, together with the carbon atom to which R^9 is attached and the N atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}; or

R^6 and R^8, together with N atom to which R^6 is attached and S atom to which R^8 is attached, form 4-10 membered heterocycloalkyl substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each R^{10} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

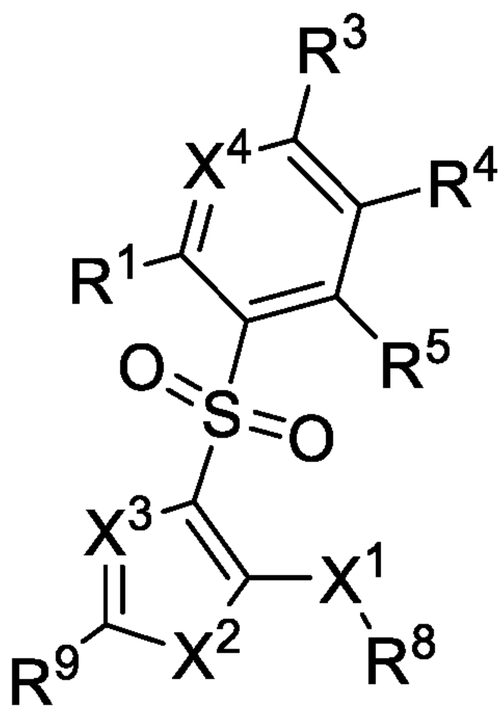
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino;

provided that if X^3 is N and X^2 is O, then R^9 is selected from $S(O)_2R^{b1}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}.

379. A compound of Formula (IIIh):



(IIIh),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5

substituents independently selected from R^{10};

X^4 is selected from N and CR^2;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

X^2 is selected from O, S, and NR^6;

R^6 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

X^3 is selected from N and CR^7;

R^7 is selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^9 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}; or

R^9 and R^6, together with the carbon atom to which R^9 is attached and the N atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}; or

R^6 and R^8, together with N atom to which R^6 is attached and S atom to which R^8 is attached, form 4-10 membered heterocycloalkyl substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each R^{10} independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{11} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

380. The compound of paragraph 378 or 379, wherein X^1 is selected from S(O) and $S(O)_2$.

381. The compound of paragraph 378 or 379, wherein X^1 is S(O).

382. The compound of paragraph 378 or 379, wherein X^1 is $S(O)_2$.

383. The compound of any one of paragraphs 378-382, wherein X^4 is CR^2.

384. The compound of any one of paragraphs 378-383, wherein each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

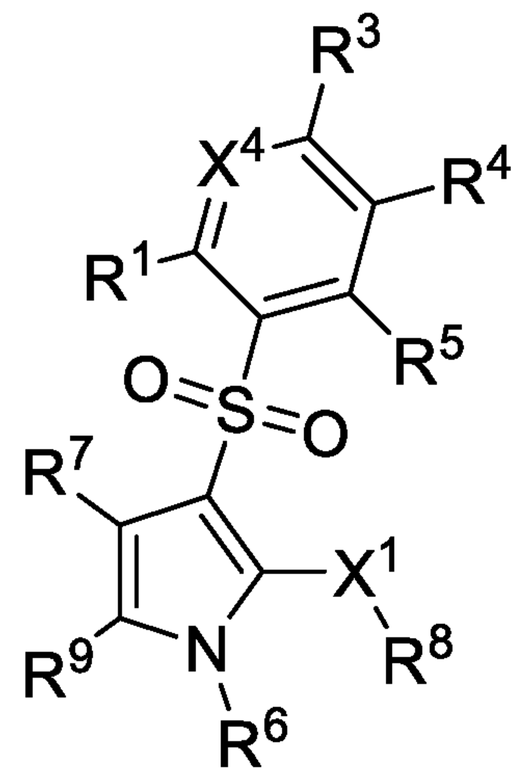
385. The compound of any one of paragraphs 378-383, wherein each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

386. The compound of any one of paragraphs 378-385, wherein X^4 is N.

387. The compound of any one of paragraphs 378-386, wherein R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$.

388. The compound of any one of paragraphs 378-387, wherein R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

389. The compound of any one of paragraphs 378-388, wherein the compound of Formula (IIIh) has formula:



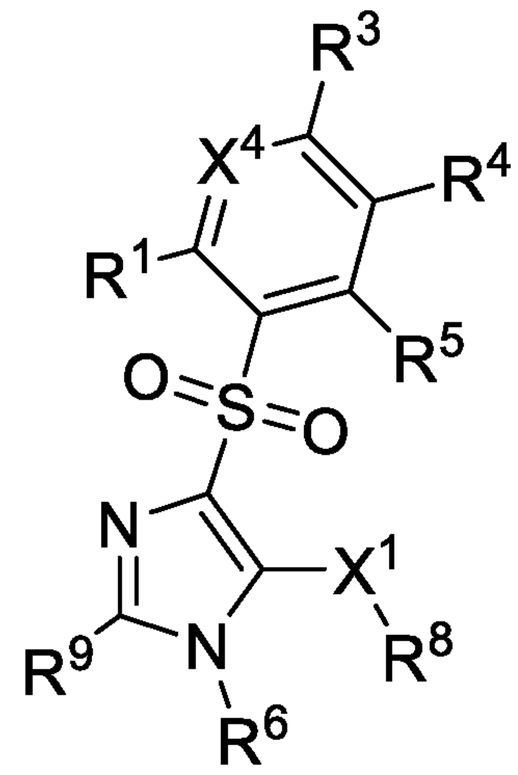
,

or a pharmaceutically acceptable salt thereof.

390. The compound of any one of paragraphs 378-389, wherein R^7 is selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

391. The compound of any one of paragraphs 378-389, wherein R^7 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

392. The compound of any one of paragraphs 378-388, wherein the compound of Formula (IIIh) has formula:



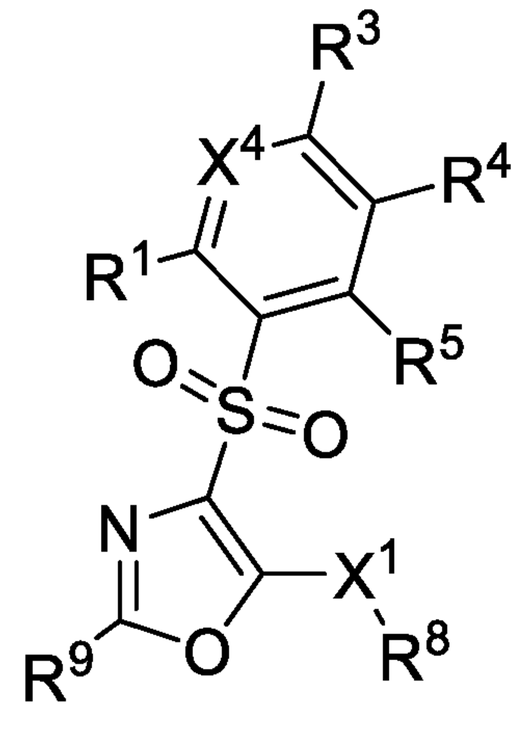
,

or a pharmaceutically acceptable salt thereof.

393. The compound of any one of paragraphs 378-392, wherein R^6 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

394. The compound of any one of paragraphs 378-393, wherein R^6 is selected from H and C_{1-6} alkyl.

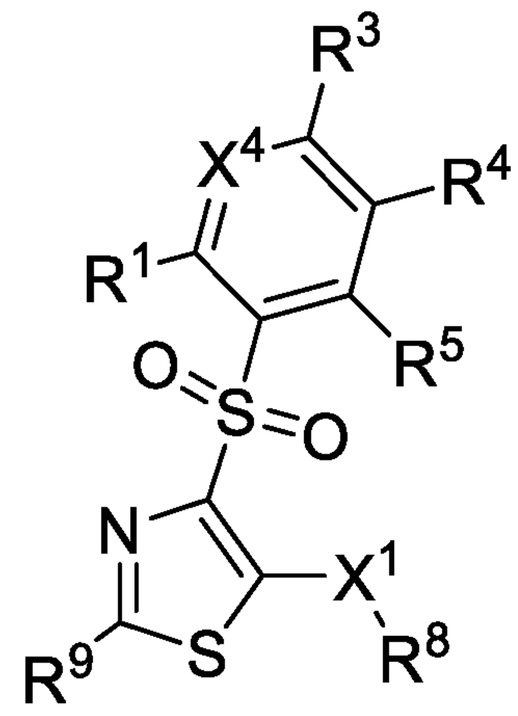
395. The compound of any one of paragraphs 378-388, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

396. The compound of any one of paragraphs 378-388, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

397. The compound of any one of paragraphs 378-396, wherein R^9 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

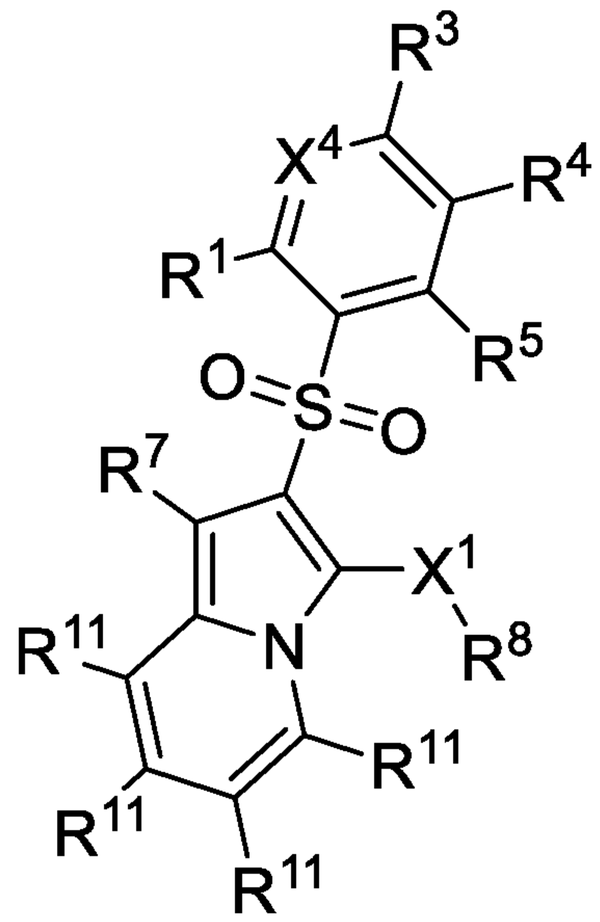
398. The compound of any one of paragraphs 378-396, wherein R^9 is $S(O)_2R^{b1}$.

399. The compound of any one of paragraphs 378-396, wherein R^9 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

400. The compound of any one of paragraphs 378-396, wherein R^9 is selected from C_{3-10} cycloalkyl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

401. The compound of paragraph 399, wherein R^9 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

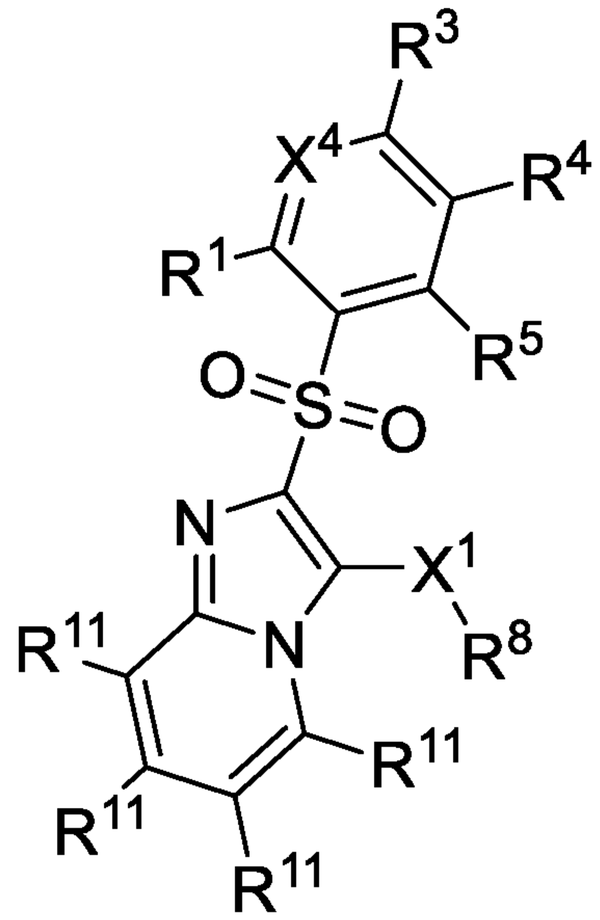
402. The compound of any one of paragraphs 378-392, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

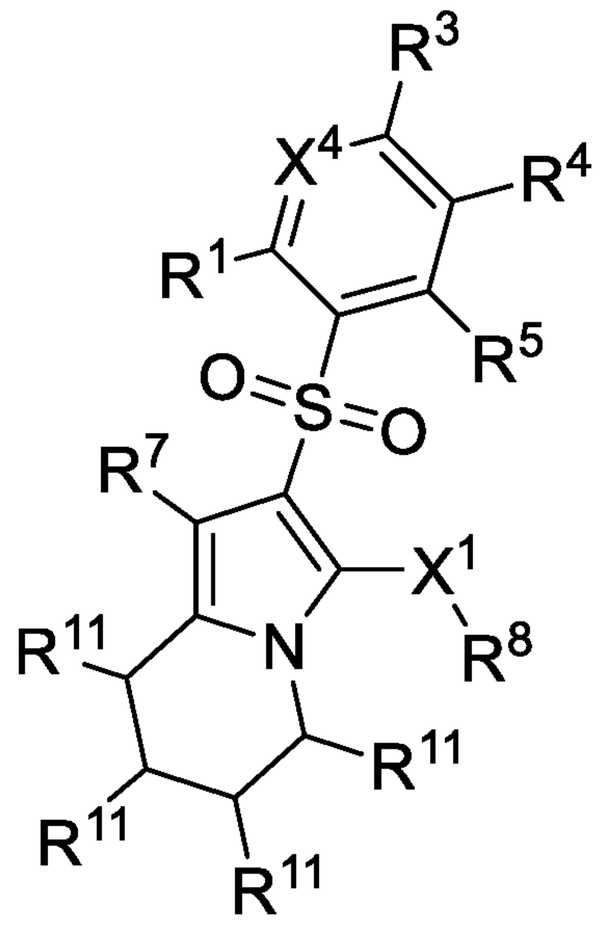
403. The compound of any one of paragraphs 378-388, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

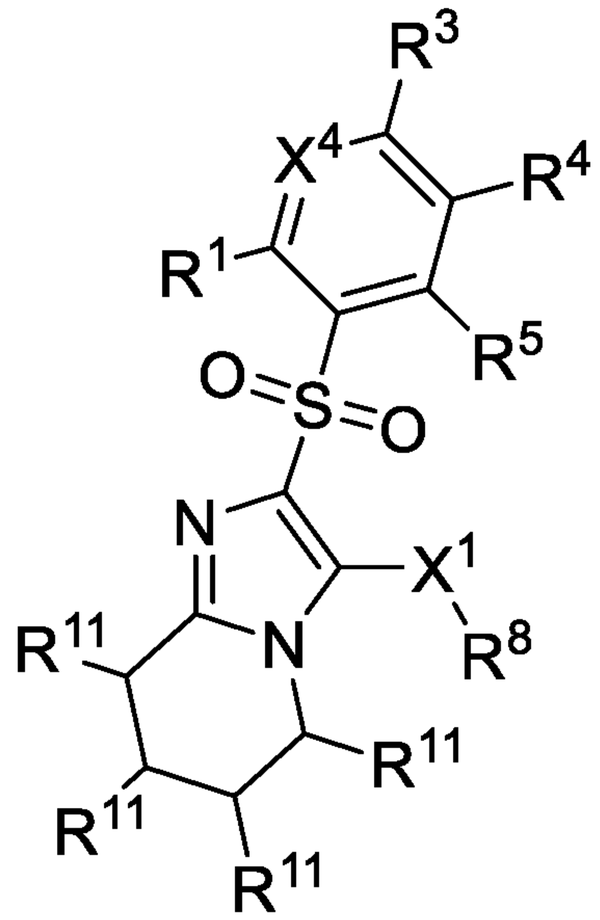
404. The compound of any one of paragraphs 378-392, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

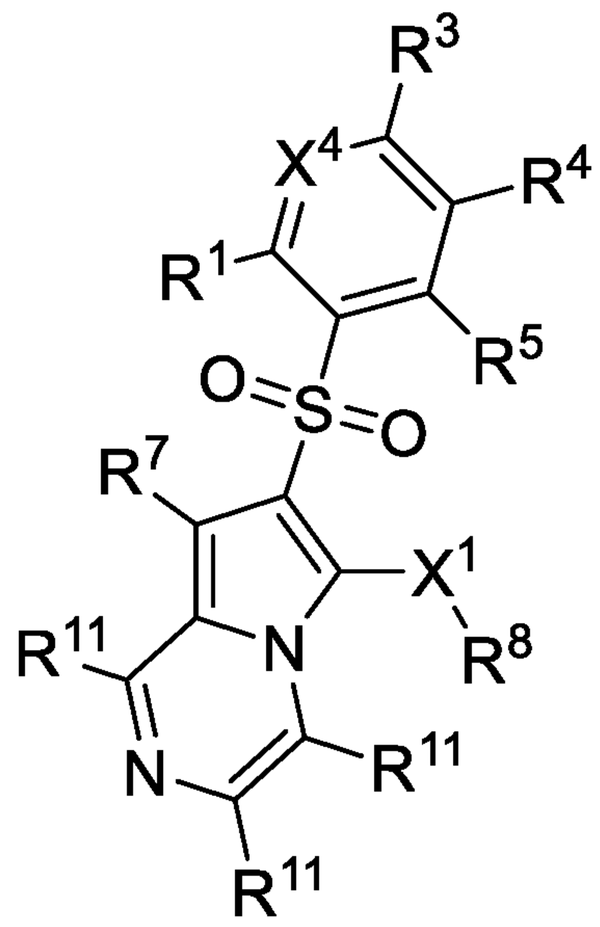
405. The compound of any one of paragraphs 378-388, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

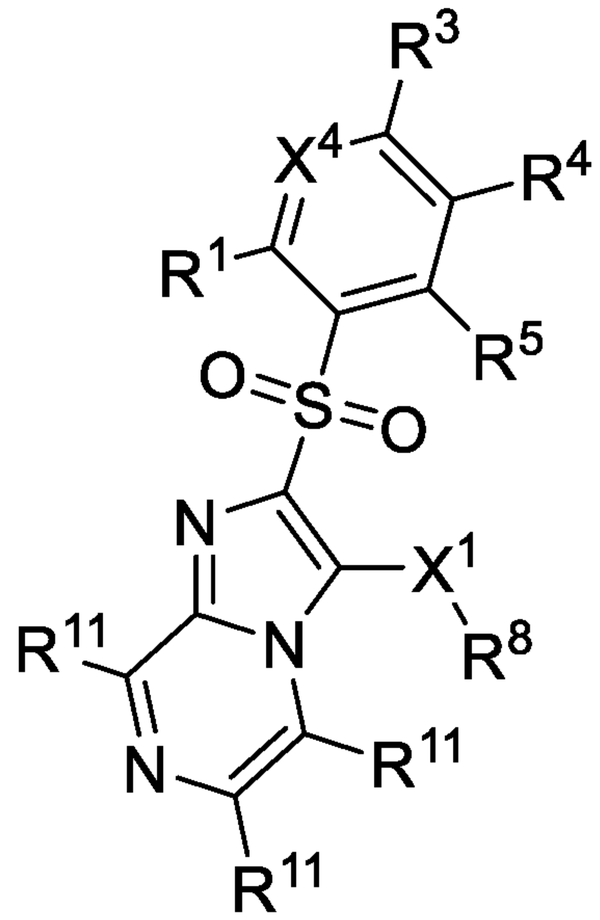
406. The compound of any one of paragraphs 378-392, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

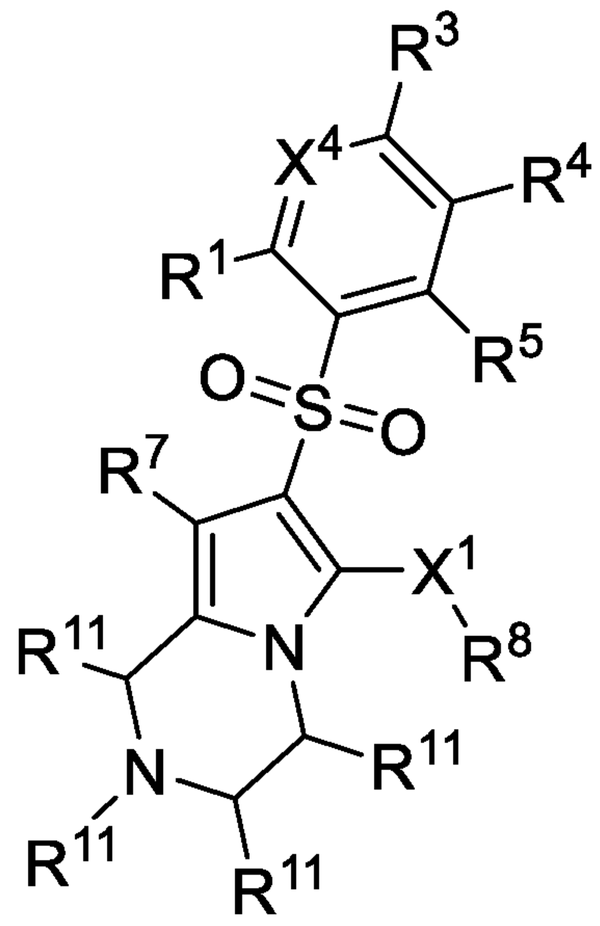
407. The compound of any one of paragraphs 378-388, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

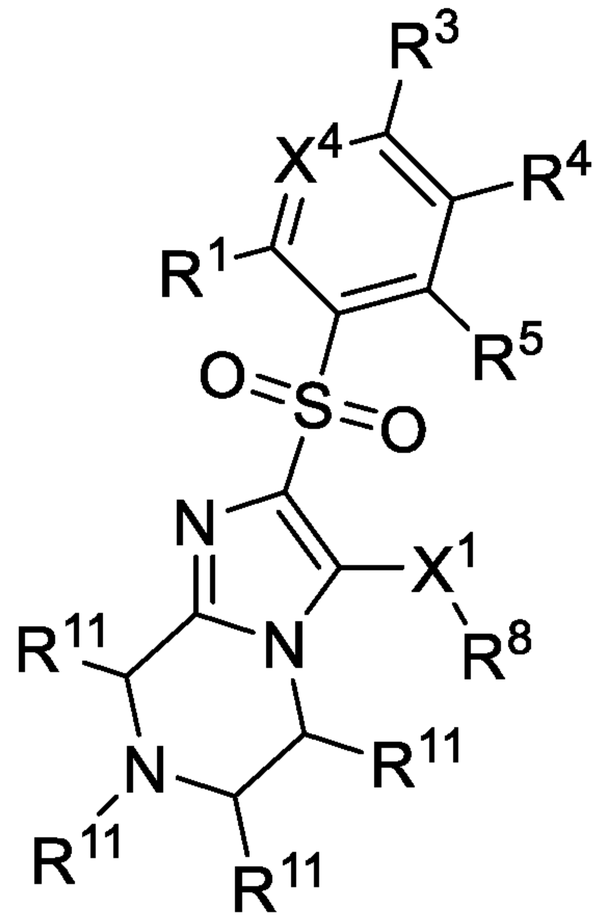
408. The compound of any one of paragraphs 378-392, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

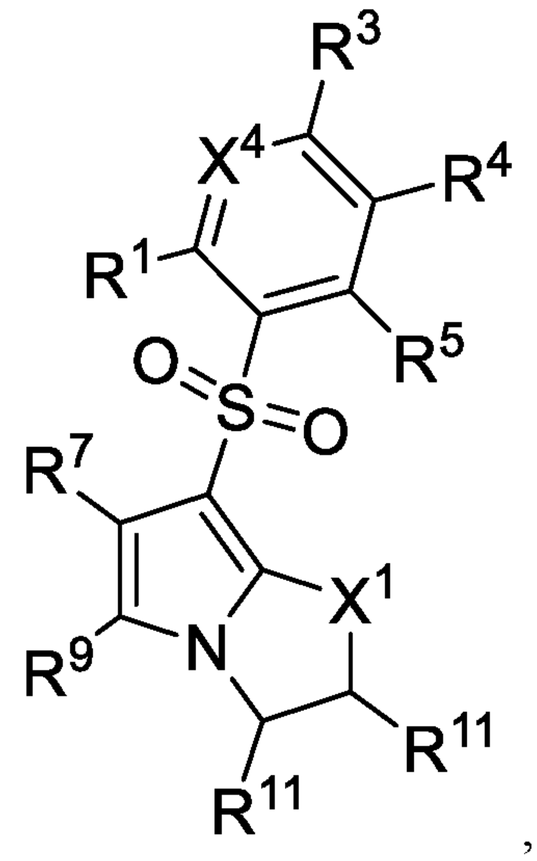
409. The compound of any one of paragraphs 378-388, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

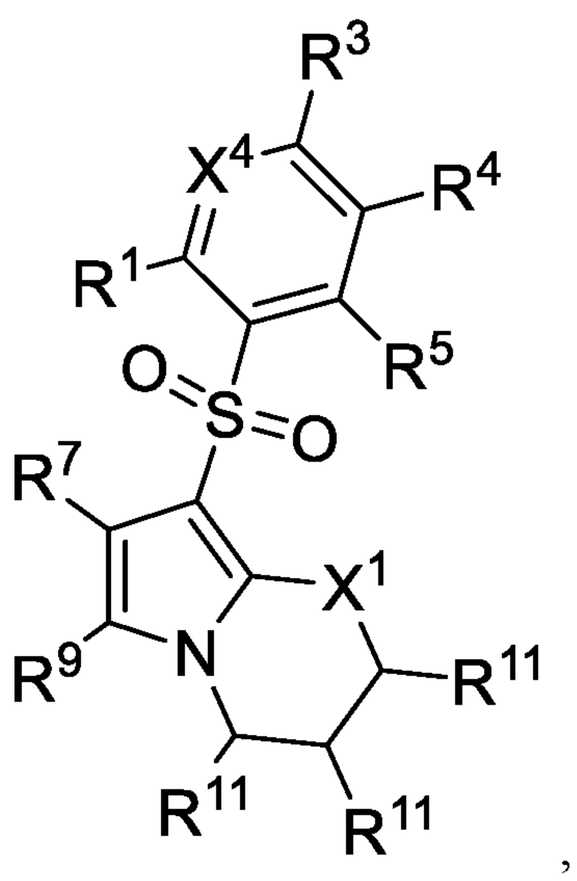
410. The compound of any one of paragraphs 378-401, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

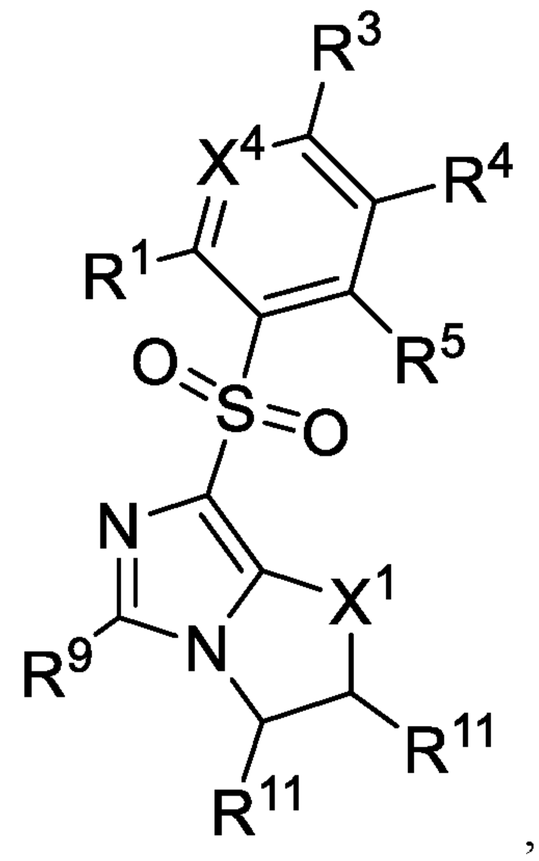
411. The compound of any one of paragraphs 378-401, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

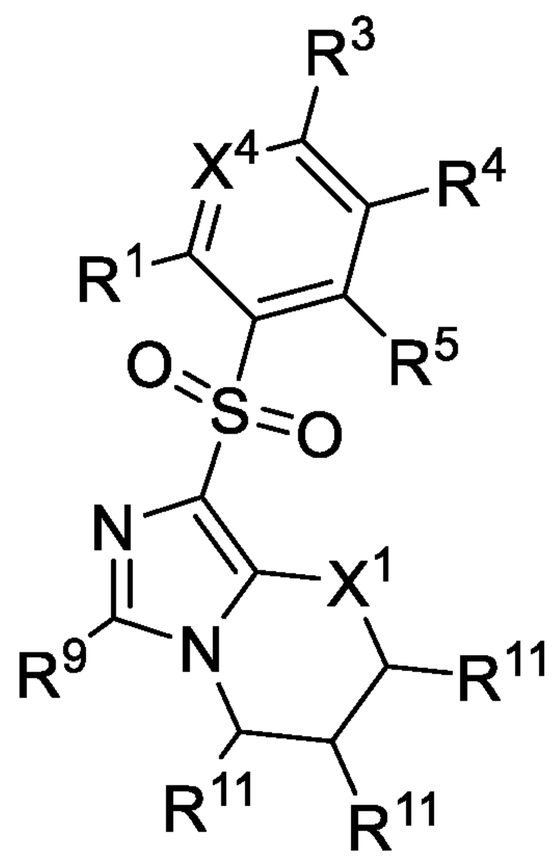
412. The compound of any one of paragraphs 378-401, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

413. The compound of any one of paragraphs 378-401, wherein the compound of Formula (IIIh) has formula:



,

or a pharmaceutically acceptable salt thereof.

414. The compound of any one of paragraphs 378-409, wherein each R^{10} is independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, and $NR^{c1}R^{d1}$.

415. The compound of any one of paragraphs 378-409, wherein Cy^1 is C_{3-10} cycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{11}.

416. The compound of any one of paragraphs 378-409, wherein each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

417. The compound of any one of paragraphs 378-409, wherein each R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

418. The compound of paragraph 378, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^7 is selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^6 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^9 is selected from $S(O)_2R^{b1}$ and C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; or

R^9 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, and $NR^{c1}R^{d1}$; and

each R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

419. The compound of paragraph 378, wherein:

X^1 is selected from S(O) and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^7 is selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^6 is selected from H, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^9 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; or

R^9 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

each R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

420. The compound of paragraph 378, wherein:

X^1 is selected from S(O) and $S(O)_2$;

R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^8 is C_{1-6} alkyl, optionally substituted with OR^{a1} or $NR^{c1}R^{d1}$; or

R^8 is selected from C_{3-10} cycloalkyl and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^7 is selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^6 is selected from H and C_{1-6} alkyl;

R^9 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; or

R^9 is selected from phenyl, naphthyl, pyridinyl, cyclohexyl, tetrahydropyranyl, and piperidinyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

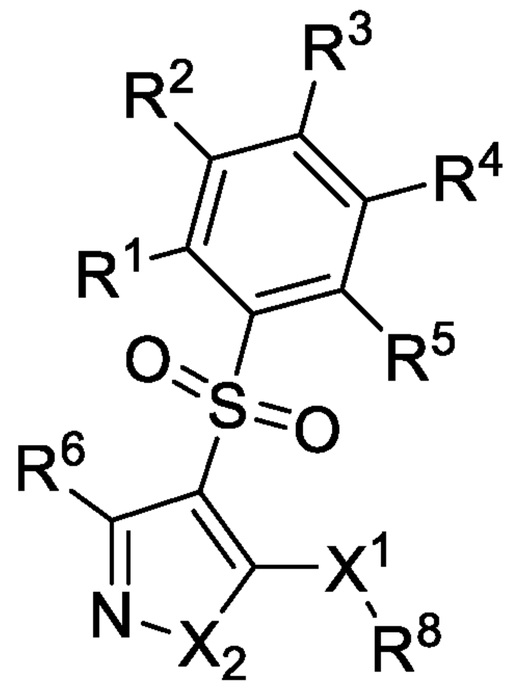
each R^{10} is independently selected from halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy; and

each R^{11} is independently selected from H, halo, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

421. The compound of paragraph 378, wherein the compound of Formula (IIIh) is selected from any one of the compounds of Table 8, Table 9, Table 10, and Table 11, or a pharmaceutically acceptable salt thereof.

422. A pharmaceutical composition comprising a compound of any one of paragraphs 378-421, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

423. A compound of Formula (IIIi):



(IIIi),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

X^2 is selected from S and NR^7;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^9;

R^6 and R^7 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1,

2, or 3 substituents independently selected from R^9;

provided that at least one of R^6 and R^7 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

or R^6 and R^7, together with the C atom to which R^6 is attached and N atom to which R^7 is attached, from a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^9 independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{10} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

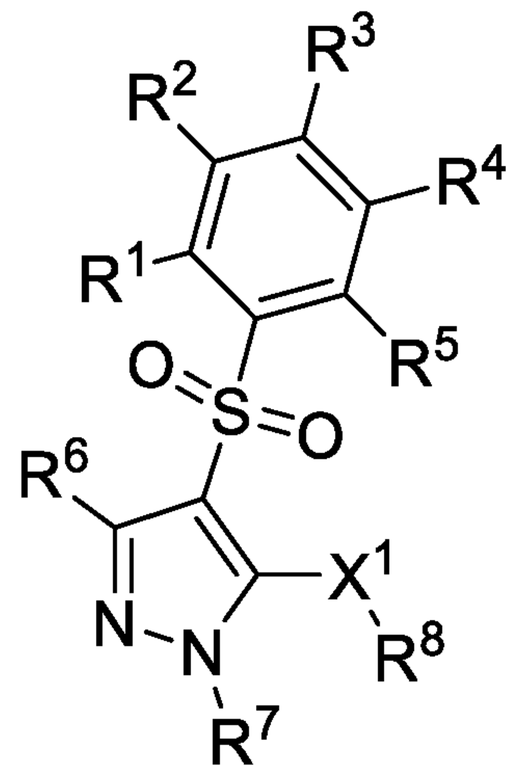
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene,

C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

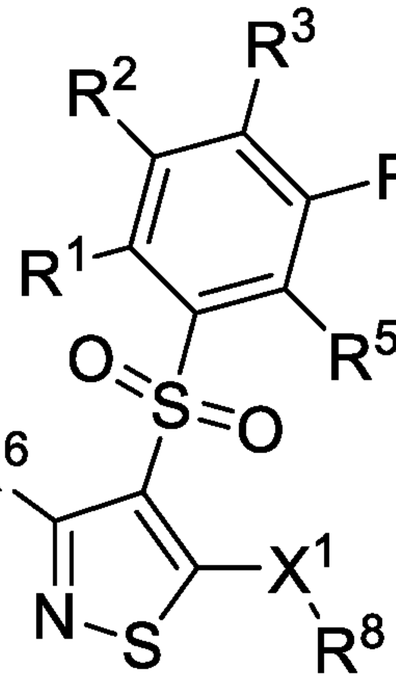
424. The compound of paragraph 423, having the formula:



,

or a pharmaceutically acceptable salt thereof.

425. The compound of paragraph 423, having the formula:



,

or a pharmaceutically acceptable salt thereof.

426. The compound of any one of paragraphs 423-425, wherein each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H and halo.

427. The compound of any one of paragraphs 423-426, wherein R^6 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

428. The compound of any one of paragraphs 423-427, wherein R^8 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

429. The compound of paragraph 423, wherein:

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H and halo;

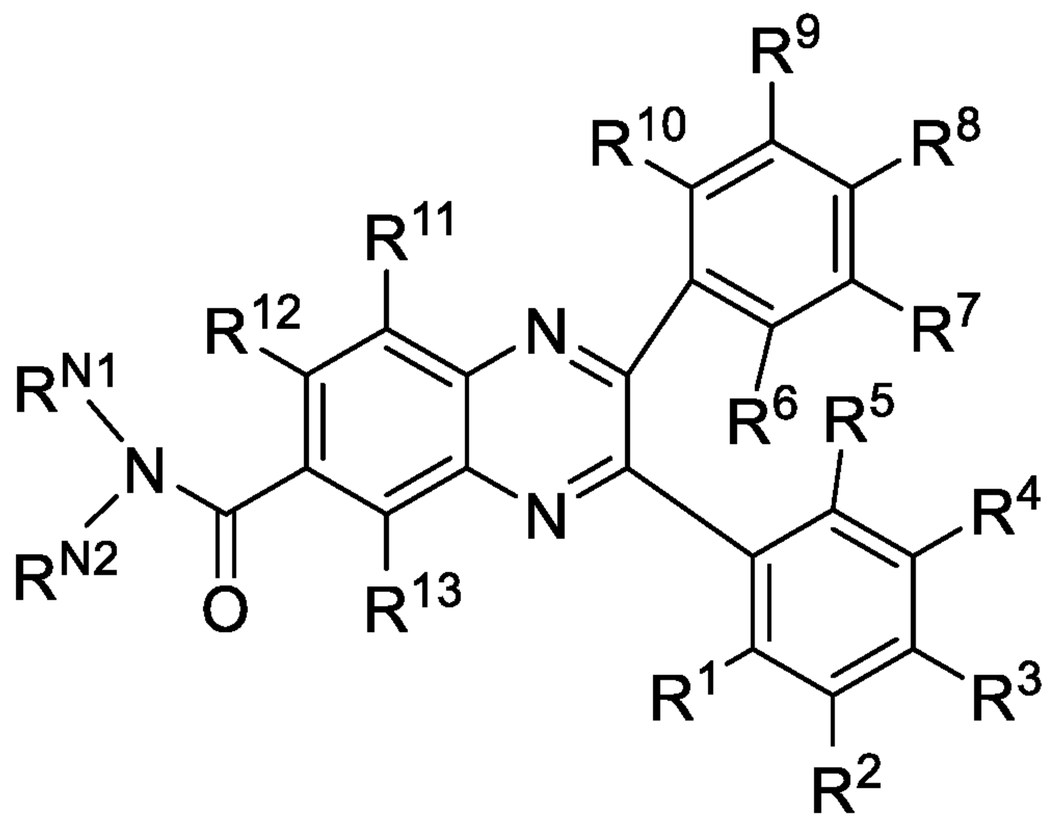
R^6 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9; and

R^8 is C_{1-6} alkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

430. The compound of paragraph 423, wherein the compound is selected from any one of the compounds of Table 15, or a pharmaceutically acceptable salt thereof.

431. A pharmaceutical composition comprising a compound of any one of paragraphs 423-430, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

432. A method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (IVa):



(IVa),

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$,

$NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

or R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{14};

each R^{14} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered

heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

433. The method of paragraph 432, wherein each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

434. The method of paragraph 432, wherein each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

435. The method of any one of paragraphs 432-434, wherein R^{N1} is selected from H, C_{1-6} alkyl, and C_{2-6} alkenyl.

436. The method of any one of paragraphs 432-435, wherein R^{N2} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

437. The method of any one of paragraphs 432-436, wherein R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3

substituents independently selected from R^{14}.

438. The method of paragraph 437, wherein the 4-10 membered heterocycloalkyl is selected from pyrrolidine, piperazine, morpholine, and piperidine.

439. The method of any one of paragraphs 432-438, wherein each R^{14} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$.

440. The method of any one of paragraphs 432-438, wherein each R^{14} independently selected from Cy^1, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$.

441. The method of any one of paragraphs 432-440, wherein each Cy^1 is independently selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3, substituents independently selected from R^{Cy1}.

442. The method of any one of paragraphs 432-440, wherein each Cy^1 is independently selected from phenyl, piperidine, thiophene, pyridine, piperazine, morpholine, azepane, pyrrolidone, pyrrolidine, and pyrimidine, each of which is optionally substituted with 1, 2, or 3, substituents independently selected from R^{Cy1}.

443. The method of any one of paragraphs 432-442, wherein each R^{Cy1} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$.

444. The method of any one of paragraphs 432-442, wherein each R^{Cy1} is independently selected from halo, C_{1-6} alkyl, OR^{a1}, SR^{a1}, and $NR^{c1}R^{d1}$.

445. The method of any one of paragraphs 432-444, wherein each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

446. The method of any one of paragraphs 432-444, wherein each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

447. The method of any one of paragraphs 432-446, wherein each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

448. The method of paragraph 432, wherein

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

R^{N1} is selected from H, C_{1-6} alkyl, and C_{2-6} alkenyl;

R^{N2} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

R^{14} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$;

Cy^1 is independently selected from C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3, substituents independently selected from R^{Cy1};

R^{Cy1} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, SR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

449. The method of paragraph 432, wherein:

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^{N1} is selected from H, C_{1-6} alkyl, and C_{2-6} alkenyl;

R^{N2} is selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2} together with the N atom to which they are attached from pyrrolidine, piperazine, morpholine, or piperidine, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

each R^{14} independently selected from Cy^1, C_{1-6} alkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$;

each Cy^1 is independently selected from phenyl, piperidine, thiophene, pyridine, piperazine, morpholine, azepane, pyrrolidone, pyrrolidine, and pyrimidine, each of which is optionally substituted with 1, 2, or 3, substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, C_{1-6} alkyl, OR^{a1}, SR^{a1}, and $NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and C_{6-10} aryl-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, and carboxy.

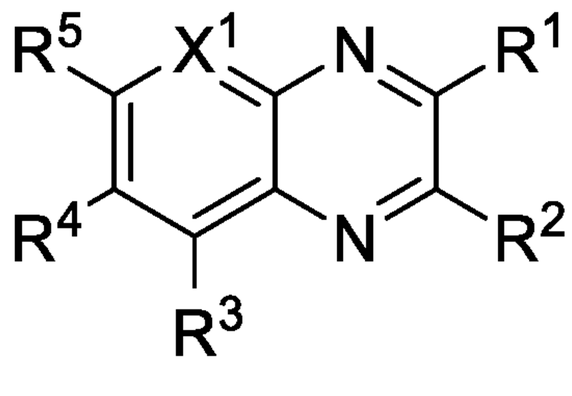
450. The method of paragraph 432, wherein the compound of Formula (IVa) is selected from any one of the compounds of Table 4a, or a pharmaceutically acceptable salt thereof.

451. A compound selected from any one of the compounds of Table 4b or Table 4b-2, or a pharmaceutically acceptable salt thereof.

452. A compound selected from any one of the compounds of Table 4b, or a pharmaceutically acceptable salt thereof.

453. A pharmaceutical composition comprising a compound of paragraph 451 or 452, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

454. A compound of Formula (IVb):



(IVb),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^8;

each R^8 is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl ,4-10 membered heterocycloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and

$S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

R^1 and R^2 are each independently selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene,

C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

455. The compound of paragraph 454, wherein X^1 is CR^6.

456. The compound of any one of paragraphs 454-455, wherein R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

457. The compound of any one of paragraphs 454-455, wherein R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

458. The compound of paragraphs 454, wherein X^1 is N.

459. The compound of any one of paragraphs 454-458, wherein R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8.

460. The compound of any one of paragraphs 454-459, wherein each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9.

461. The compound of any one of paragraphs 454-460, wherein each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$.

462. The compound of any one of paragraphs 454-461, wherein:

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

463. The compound of any one of paragraphs 454-461, wherein:

R^1 is C_{1-6} haloalkyl; and

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

464. The compound of any one of paragraphs 454-461, wherein:

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^2 is C_{1-6} haloalkyl.

465. The compound of any one of paragraphs 454-461, wherein:

R^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

466. The compound of any one of paragraphs 454-461, wherein

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^2 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

467. The compound of any one of paragraphs 465-466, wherein the 5-10 membered heteroaryl is thiophene.

468. The compound of any one of paragraphs 462-466, wherein the C_{6-10} aryl is phenyl.

469. The compound of any one of paragraphs 454-468, wherein each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

470. The compound of paragraph 454, wherein:

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents

independently selected from R^{10};

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

471. The compound of paragraph 454, wherein:

R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^2 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

472. The compound of paragraph 454, wherein:

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is C_{1-6} haloalkyl;

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

473. The compound of paragraph 454, wherein:

R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is trifluoromethyl;

R^2 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

474. The compound of paragraph 454, wherein:

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^2 is C_{1-6} haloalkyl;

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

475. The compound of paragraph 454, wherein:

R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-

oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^2 is trifluoromethyl;

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

476. The compound of paragraph 454, wherein:

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

477. The compound of paragraph 454, wherein:

R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is thiophenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^2 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

478. The compound of paragraph 454, wherein:

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^2 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

479. The compound of paragraph 454, wherein:

R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

R^4 is selected from 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiophenyl, indolyl, pyrimidinyl, pyrrolopyridinyl, benzoxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-oxadiazolyl, thiazolyl, pyridinyl, benzoxazinyl, pyrazolyl, and indazolyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from halo, C_{1-6} alkyl, OR^{a1}, and $S(O)_2R^{b1}$, wherein said C_{1-6} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from OR^{a1} and $NR^{c1}R^{d1}$;

R^1 is phenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^2 is thiophenyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

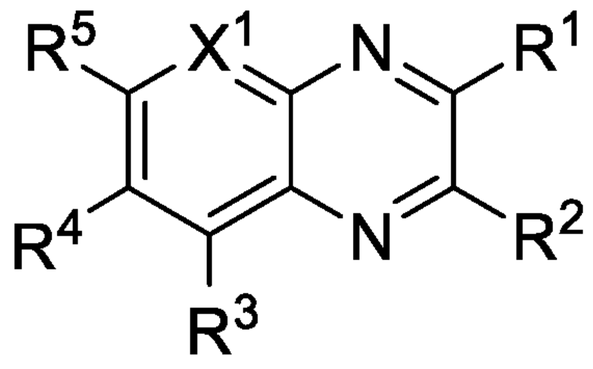
each R^{10} is independently selected from halo and $S(O)_2R^{b1}$.

480. The compound of paragraph 454, wherein the compound of Formula (IVb) is selected from any one of the compounds of Table 4c or Table 4c-2, or a pharmaceutically acceptable salt thereof.

481. The compound of paragraph 454, wherein the compound of Formula (IVb) is selected from any one of the compounds of Table 4c, or a pharmaceutically acceptable salt thereof.

482. A pharmaceutical composition comprising a compound of any one of paragraphs 454-481, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

483. A compound of Formula (IVc):



(IVc),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^4 is selected from $C(O)NR^{N1}R^{N2}$, $C(O)OR^{a1}$, and CN;

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6}

haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14};

each R^{14} independently selected from H, Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from R^8 and $S(O)_2R^8$;

R^8 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

provided that R^1 and R^2 are not both C_{6-10} aryl;

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and

$S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

484. The compound of paragraph 483, wherein X^1 is CR^6.

485. The compound of any one of paragraphs 483-484, wherein R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

486. The compound of any one of paragraphs 483-484, wherein R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

487. The compound of any one of paragraphs 483-486, wherein R^4 is $C(O)NR^{N1}R^{N2}$.

488. The compound of any one of paragraphs 483-486, wherein R^4 is $C(O)OR^{a1}$.

489. The compound of any one of paragraphs 483-486, wherein R^4 is CN.

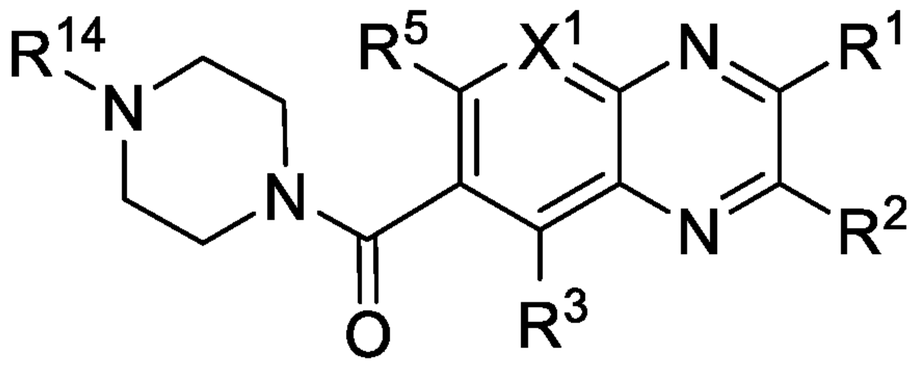
490. The compound of any one of paragraphs 483-489, wherein each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

491. The compound of any one of paragraphs 483-489, wherein R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14}.

492. The compound of any one of paragraphs 483-491, wherein each R^{14} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

493. The compound of any one of paragraphs 483-491, wherein each R^{14} is independently selected from C_{1-6} alkyl and $NR^{c1}R^{d1}$.

494. The compound of paragraph 483, wherein the compound of Formula (IVc) has formula:



,

or a pharmaceutically acceptable salt thereof.

495. The compound of any one of paragraphs 483-494, wherein:

R^1 is C_{1-6} haloalkyl; and

R^2 is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 independently selected R^{10}.

496. The compound of any one of paragraphs 483-494, wherein:

R^1 is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 independently selected R^{10}; and

R^2 is C_{1-6} haloalkyl.

497. The compound of any one of paragraphs 483-494, wherein:

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

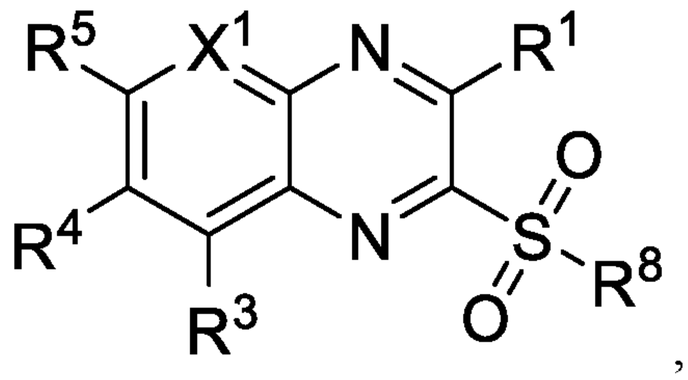
R^2 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

498. The compound of any one of paragraphs 483-494, wherein:

R^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

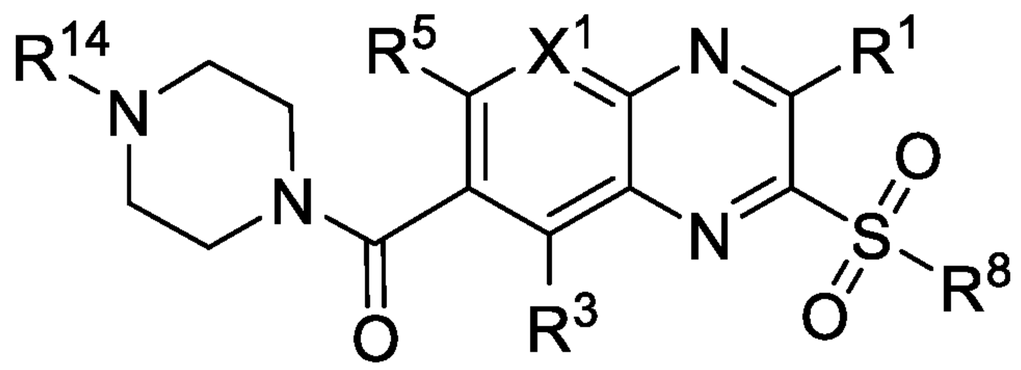
499. The compound of paragraph 483, wherein the compound of Formula (IVc) has formula:



,

or a pharmaceutically acceptable salt thereof.

500. The compound of paragraph 499, wherein the compound of Formula (IVc) has formula:



,

or a pharmaceutically acceptable salt thereof.

501. The compound of any one of paragraphs 499-500, wherein:

R^1 is C_{1-6} haloalkyl; and

R^8 is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 independently selected R^{10}.

502. The compound of any one of paragraphs 499-500, wherein:

R^1 is selected from C_{6-10} aryl and 5-10 membered heteroaryl, each of which is optionally substituted with 1, 2, or 3 independently selected R^{10}; and

R^8 is C_{1-6} haloalkyl.

503. The compound of any one of paragraphs 499-500, wherein:

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

R^8 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

504. The compound of any one of paragraphs 499-500, wherein:

R^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

R^8 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

505. The compound of any one of paragraphs 499-500, wherein:

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

R^8 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

506. The compound of any one of paragraphs 499-500, wherein:

R^1 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

R^8 is 5-10 membered heteroaryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

507. The compound of any one of paragraphs 499-500, wherein:

the 5-10 membered heteroaryl is selected from thiophenyl and pyridinyl; and

the C_{6-10} aryl is phenyl.

508. The compound of any one of paragraphs 499-500, wherein:

R^1 is C_{1-6} haloalkyl; and

R^8 is C_{1-6} haloalkyl.

509. The compound of any one of paragraphs 483-508, wherein each R^{10} is independently selected from halo and C_{1-6} alkyl.

510. The compound of paragraph 483, wherein:

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14};

each R^{14} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; and

each R^{10} is independently selected from halo and C_{1-6} alkyl.

511. The compound of paragraph 510, wherein:

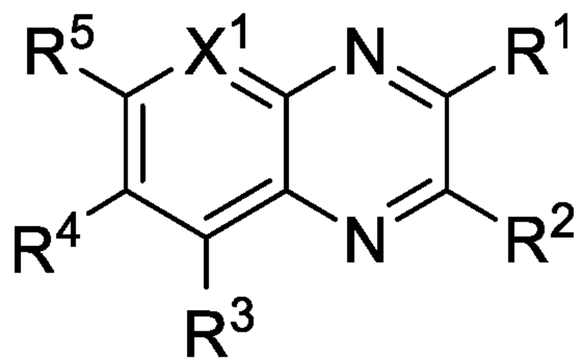
R^3, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy; and

R^{14} is independently selected from C_{1-6} alkyl and $NR^{c1}R^{d1}$.

512. The compound of paragraph 483, wherein the compound of Formula (IVc) is selected from any one of the compounds of Table 4d, or a pharmaceutically acceptable salt thereof.

513. A pharmaceutical composition comprising a compound of any one of paragraphs 483-512, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

514. A compound of Formula (IVd):



(IVd),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are

each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^3 is selected from $C(O)NR^{N1}R^{N2}$ and $C(O)OR^{a1}$;

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14};

each R^{14} independently selected from H, Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from R^8 and $S(O)_2R^8$;

R^8 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino,

aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

515. The compound of paragraph 514, wherein X^1 is CR^6.

516. The compound of any one of paragraphs 514-515, wherein R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

517. The compound of any one of paragraphs 514-515, wherein R^4, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

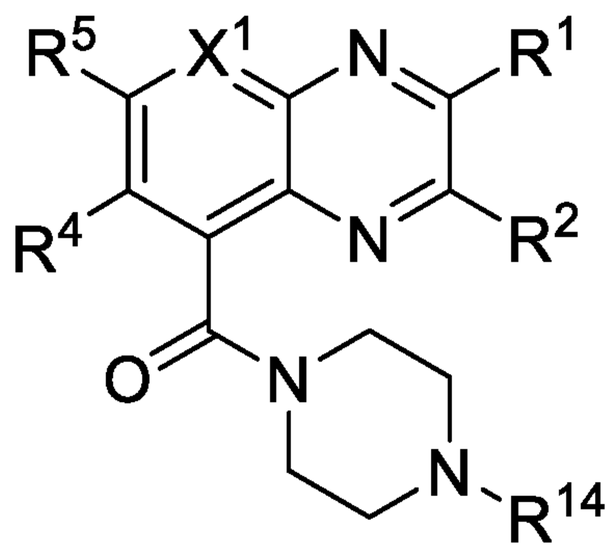
518. The compound of any one of paragraphs 514-517, wherein R^3 is $C(O)NR^{N1}R^{N2}$.

519. The compound of any one of paragraphs 514-517, wherein R^3 is $C(O)OR^{a1}$.

520. The compound of any one of paragraphs 514-519, wherein each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}.

521. The compound of any one of paragraphs 514-519, wherein R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14}.

522. The compound of any one of paragraph 521, wherein the compound of Formula (IVd) has formula:



;

or a pharmaceutically acceptable salt thereof.

523. The compound of any one of paragraphs 514-522, wherein each R^{14} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$.

524. The compound of any one of paragraphs 514-522, wherein each R^{14} is independently selected from C_{1-6} alkyl and $NR^{c1}R^{d1}$.

525. The compound of any one of paragraphs 514-524, wherein:

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

526. The compound of any one of paragraphs 514-525, wherein each R^{10} is independently selected from halo and C_{1-6} alkyl.

527. The compound of paragraph 514, wherein:

R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-6 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14};

wherein each R^{14} is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; and

each R^{10} is independently selected from halo and C_{1-6} alkyl.

528. The compound of paragraph 527, wherein:

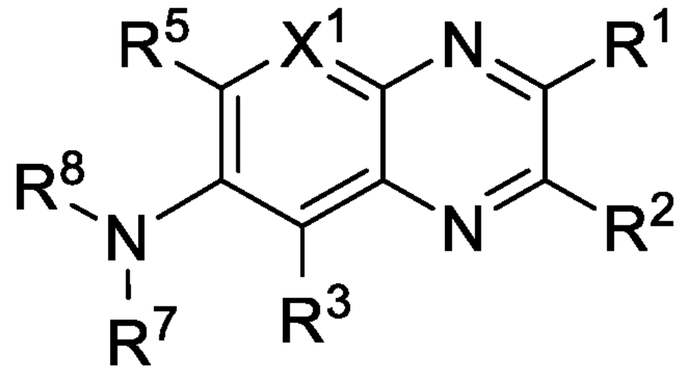
R^4, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each R^{14} is independently selected from C_{1-6} alkyl and $NR^{c1}R^{d1}$.

529. The compound of paragraph 514, wherein the compound of Formula (IVd) is selected from any one of the compound of Table 4e, or a pharmaceutically acceptable salt thereof.

530. A pharmaceutical composition comprising a compound of any one of paragraphs 514-529, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

531. A compound of Formula (IVe):



(IVe),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

or R^7 and R^8 together with the N atom to which they are attached form a 4-10 membered heterocycloalkyl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from R^{8a} and $S(O)_2R^{8a}$;

R^{8a} is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino, and any C_{1-6} alkyl, C_{1-6} alkoxy, C_{6-10} aryl,

C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

532. The compound of paragraph 531, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from R^{8a} and $S(O)_2R^{8a}$;

R^{8a} is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

533. The compound of paragraph 531 or 532, wherein X^1 is CR^6.

534. The compound of any one of paragraphs 531-533, wherein R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

535. The compound of any one of paragraphs 531-534, wherein R^4, R^5, and R^6 are each independently selected from H, halo, C_{1-6} alkyl, and C_{1-6} alkoxy.

536. The compound of any one of paragraphs 531-535, wherein:

R^7 is selected from H and C_{1-6} alkyl; and

R^8 is selected from $C(O)R^{b1}$ and $C(O)OR^{a1}$.

537. The compound of any one of paragraphs 531-535, wherein:

R^7 is selected from H and C_{1-6} alkyl;

R^8 is $C(O)NR^{c1}R^{d1}$.

538. The compound of any one of paragraphs 531-537, wherein:

each R^{c1} and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl and C_{3-10} cycloalkyl are each optionally substituted with 1 or 2 independently selected R^g.

539. The compound of any one of paragraphs 531-538, wherein each R^{a1} and R^{b1} is independently selected from C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g.

540. The compound of any one of paragraphs 531-539, wherein each R^g is independently selected from OH, halo, C_{1-6} alkyl, C_{1-6} alkoxy, 4-10 membered heterocycloalkyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkylsulfonyl, C_{1-6} alkylcarbamyl, and C_{1-6} alkylcarbonyl, and any C_{1-6} alkyl, C_{1-6} alkoxy, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1 or 2 substituents independently selected from C_{1-6} alkyl and C_{1-6} alkoxy.

541. The compound of any one of paragraphs 531-539, wherein each R^g is independently selected from halo, C_{1-6} alkyl, 4-10 membered heterocycloalkyl, amino, C_{1-6} alkylsulfonyl, C_{1-6} alkylcarbamyl, and C_{1-6} alkylcarbonyl.

542. The compound of any one of paragraphs 531-541, wherein:

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}.

543. The compound of any one of paragraphs 531-542, wherein each R^{10} is independently selected from halo and C_{1-6} alkyl.

544. The compound of paragraph 531, wherein:

R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^7 is selected from H and C_{1-6} alkyl;

R^8 is selected from $C(O)R^{b1}$ and $C(O)OR^{a1}$;

each R^{a1} and R^{b1} is independently selected from C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

each R^g is independently selected from halo, C_{1-6} alkyl, 4-10 membered heterocycloalkyl, amino, C_{1-6} alkylsulfonyl, C_{1-6} alkylcarbamyl, and C_{1-6} alkylcarbonyl;

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10};

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

each R^{10} is independently selected from halo and C_{1-6} alkyl.

545. The compound of paragraph 531, wherein:

R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, OH, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy;

R^7 is selected from H and C_{1-6} alkyl;

R^8 is $C(O)NR^{c1}R^{d1}$;

each R^{c1} and R^{d1} is independently selected from H, C_{1-6} alkyl, and C_{3-10} cycloalkyl, wherein said C_{1-6} alkyl and C_{3-10} cycloalkyl are each optionally substituted with 1 or 2 independently selected R^g;

each R^g is independently selected from OH, halo, C_{1-6} alkyl, C_{1-6} alkoxy, 4-10 membered heterocycloalkyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-6} alkylsulfonyl, C_{1-6} alkylcarbamyl, and C_{1-6} alkylcarbonyl, and any C_{1-6} alkyl, C_{1-6} alkoxy, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1 or 2 substituents independently selected from C_{1-6} alkyl and C_{1-6} alkoxy;

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10};

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 independently selected R^{10}; and

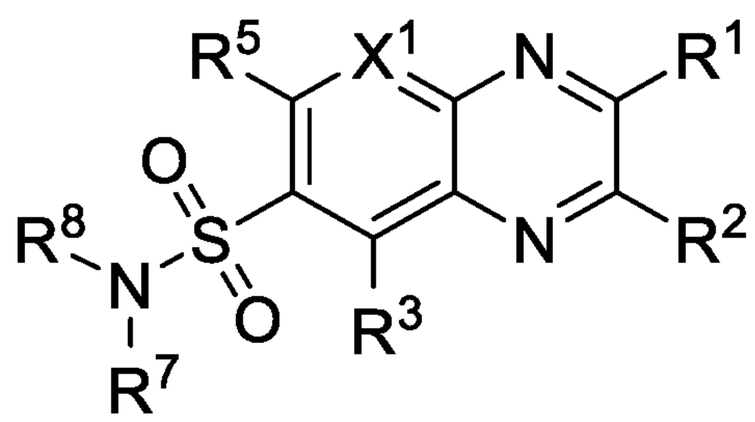
each R^{10} is independently selected from halo and C_{1-6} alkyl.

546. The compound of paragraph 531, wherein the compound of Formula (IVe) is selected from any one of the compounds of Table 4f or Table 4f-2, or a pharmaceutically acceptable salt thereof.

547. The compound of paragraph 531, wherein the compound of Formula (IVe) is selected from any one of the compounds of Table 4f, or a pharmaceutically acceptable salt thereof.

548. A pharmaceutical composition comprising a compound of any one of paragraphs 531-547, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

549. A compound of Formula (IVf):



(IVf),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and

$S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

or R^7 and R^8 together with the N atom to which they are attached form a 4-10 membered heterocycloalkyl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino, and any C_{1-6} alkyl, C_{1-6} alkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

550. The compound of paragraph 549, wherein X is N.

551. The compound of paragraph 549, wherein X is CR^6.

552. The compound of any one of paragraphs 549-551, wherein R^3, R^5, and R^6 are each independently selected from H, halo, OH, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

553. The compound of paragraph 552, wherein R^3, R^5, and R^6 are each H.

554. The compound of any one of paragraphs 549-553, wherein:

R^7 is H; and

R^8 is selected from C_{1-6} alkyl and C_{3-10} cycloalkyl, each of which is independently selected from 1 or 2 substituents independently selected from R^9.

555. The compound of any one of paragraphs 549-554, wherein R^9 is independently selected from C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$; wherein said C_{3-10} cycloalkyl, 5-10 membered

heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{10}.

556. The compound of any one of paragraphs 549-555, wherein

R^1 is C_{6-10} aryl, optionally substituted with 1 or 2 independently selected R^{10}; and

R^2 is C_{6-10} aryl, optionally substituted with 1 or 2 independently selected R^{10}.

557. The compound of any one of paragraphs 549-556, wherein each R^{10} is independently selected from halo, OH, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

558. The compound of paragraph 549, wherein:

R^1 is C_{6-10} aryl, optionally substituted with 1 or 2 independently selected R^{10};

R^2 is C_{6-10} aryl, optionally substituted with 1 or 2 independently selected R^{10};

X is CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, OH, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino;

R^7 is H;

R^8 is selected from C_{1-6} alkyl and C_{3-10} cycloalkyl, each of which is independently selected from 1 or 2 substituents independently selected from R^9;

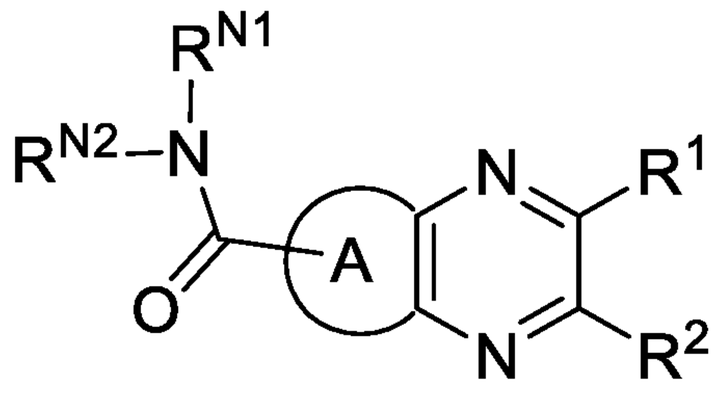
each R^9 is independently selected from C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, CN, OR^{a1}, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $NR^{c1}R^{d1}$; wherein said C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1 or 2 substituents independently selected from R^{10}; and

each R^{10} is independently selected from halo, OH, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, amino, C_{1-6} alkylamino, and di(C_{1-6} alkyl)amino.

559. The compound of paragraph 549, wherein the compound is selected from any one of the compounds of Table 4g, or a pharmaceutically acceptable salt thereof.

560. A pharmaceutical composition comprising a compound of any one of paragraphs 549-559, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

561. A compound of Formula (IVg)



(IVg),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{3-8} cycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

or R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{14};

each R^{14} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

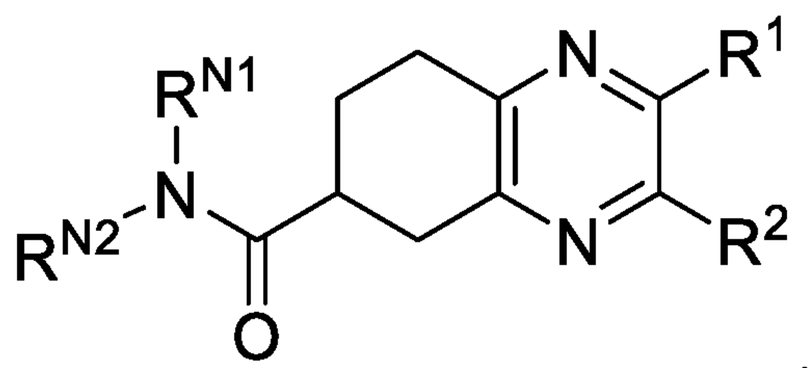
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl,

C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino, and any C_{1-6} alkyl, C_{1-6} alkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

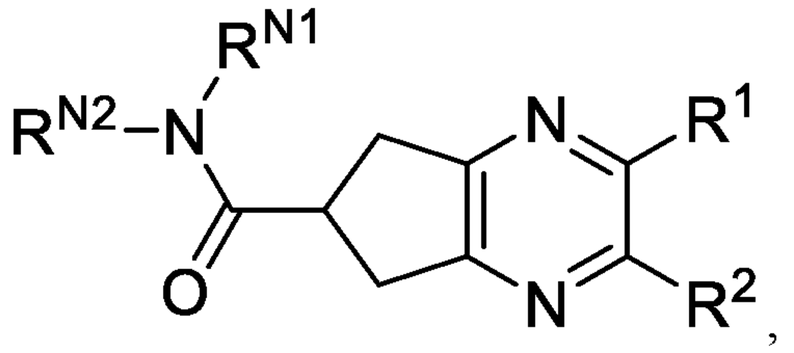
562. The compound of paragraph 561, having a formula:



,

or a pharmaceutically acceptable salt thereof.

563. The compound of paragraph 561, having a formula:



,

or a pharmaceutically acceptable salt thereof.

564. The compound of paragraph 561, wherein:

R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

R^1 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}; and

R^2 is C_{6-10} aryl, optionally substituted with 1, 2, or 3 substituents independently selected from R^{10}.

565. The compound of paragraph 561, wherein the compound is selected from any one of the compounds of Table 17, or a pharmaceutically acceptable salt thereof.

566. A pharmaceutical composition comprising a compound of any one of paragraphs 561-565, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

567. A method of treating a mammal having a disease, disorder, or condition responsive to inhibiting NF-κB activity within a cell, wherein said method comprises administering, to said mammal,

a compound selected from (i) a compound of any one of paragraphs 41-58, 79-102, 104-113, 115-121, 161, 163-174, 176-189, 191-198, 200-211, 213-224, 226-237, 264, 265, 267-270, 272-275, 277-303, 305-327, 329-376, 378-421, 423-430, 451, 452, 454-481, 483-512, 514-529, 531-547, 549-559, and 561-565, or a pharmaceutically acceptable salt thereof; and (ii) a compound as recited in any one of paragraphs 1-40, 60-72, 73-78, 123-160, 239-263, and 432-450, or a pharmaceutically acceptable salt thereof; or

a pharmaceutical composition of any one of paragraphs 59, 103, 114, 122, 162, 175, 190, 199, 212, 225, 238, 266, 271, 276, 304, 328, 377, 422, 431, 453, 482, 513, 530, 548, 560, and 566.

568. The method of paragraph 567, wherein the mammal is human.

569. The method of any one of paragraphs 567-568, wherein said method comprises treating a mammal having a cancer.

570. The method of any one of paragraphs 567-569, wherein said method comprises treating a mammal having an inflammation.

571. The method of paragraph 570, wherein the inflammation is an autoimmune disease.

572. A method for inhibiting NF-κB activity within cells of a mammal, wherein said method comprises administering, to said mammal,

a compound selected from (i) a compound of any one of paragraphs 41-58, 79-102, 104-113, 115-121, 161, 163-174, 176-189, 191-198, 200-211, 213-224, 226-237, 264, 265, 267-270, 272-275, 277-303, 305-327, 329-376, 378-421, 423-430, 451, 452, 454-481, 483-512, 514-529, 531-547, 549-559, and 561-565, or a pharmaceutically acceptable salt thereof; and (ii) a compound as recited in any one of paragraphs 1-40, 60-72, 73-78, 123-160, 239-263, and 432-450, or a pharmaceutically acceptable salt thereof; or

a pharmaceutical composition of any one of paragraphs 59, 103, 114, 122, 162, 175, 190, 199, 212, 225, 238, 266, 271, 276, 304, 328, 377, 422, 431, 453,

482, 513, 530, 548, 560, and 566.

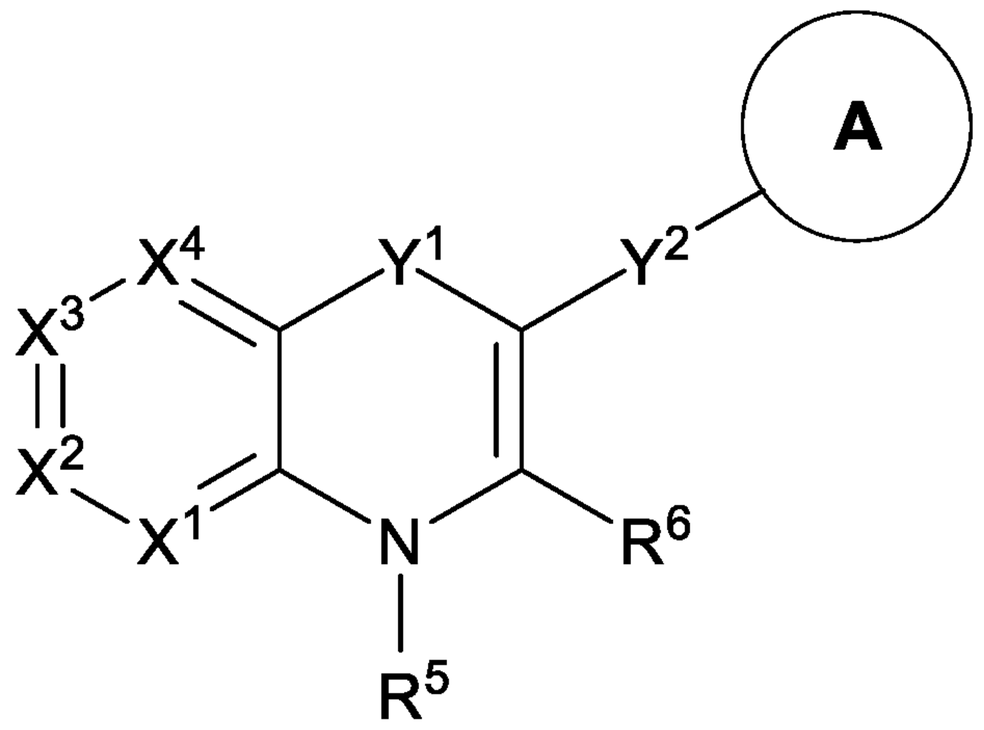
573. The method of paragraph 572, wherein the mammal is human.

OTHER EMBODIMENTS

It is to be understood that while the present application has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the present application, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is selected from C(O) and $S(O)_2$;

Y^2 is selected from C(O) and $S(O)_2$;

X^1 is selected from N and CR^1;

X^2 is selected from N and CR^2;

X^3 is selected from N and CR^3;

X^4 is selected from N and CR^4;

provided that no more than two of X^1, X^2, X^3, and X^4 are N;

each of R^1, R^2, R^3, R^4, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^5 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 is independently selected from Cy^1, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-

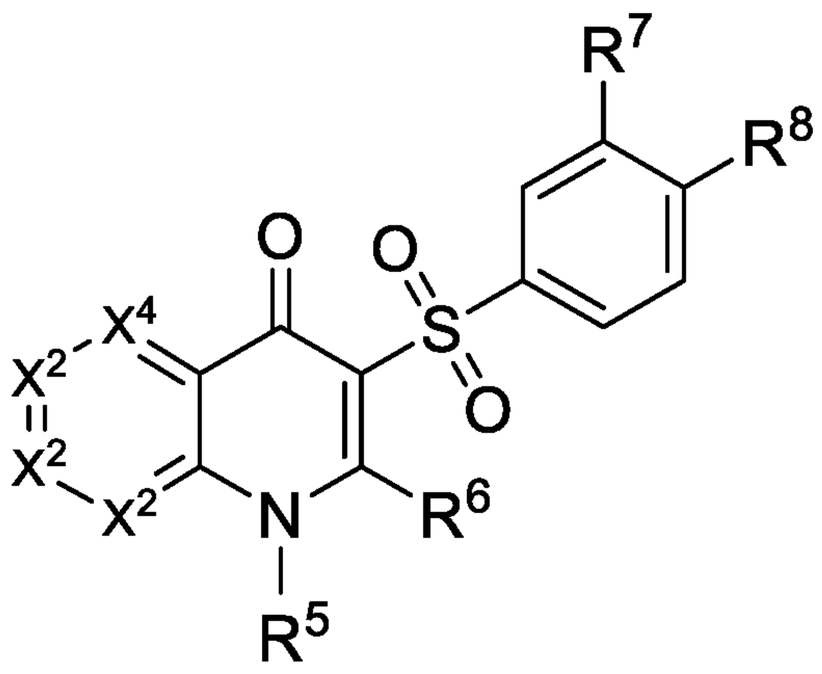
4 alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

2. The method of claim 1, wherein the compound of Formula (Ia) is selected from any one of the compounds of Table 1a, Table 1d, or Table 1e, or a pharmaceutically acceptable salt thereof.

3. A compound of Formula (Ib):



(Ib),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^1;

X^2 is selected from N and CR^2;

X^3 is selected from N and CR^3;

X^4 is selected from N and CR^4;

provided that at least one of X^1, X^2, X^3, and X^4 is N;

each of R^1, R^2, R^3, R^4, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^5 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and Cy^1, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from Cy^1, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^7 and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each

optionally substituted with 1, 2, or 3 substituents independently selected from R^{12};

each R^{12} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

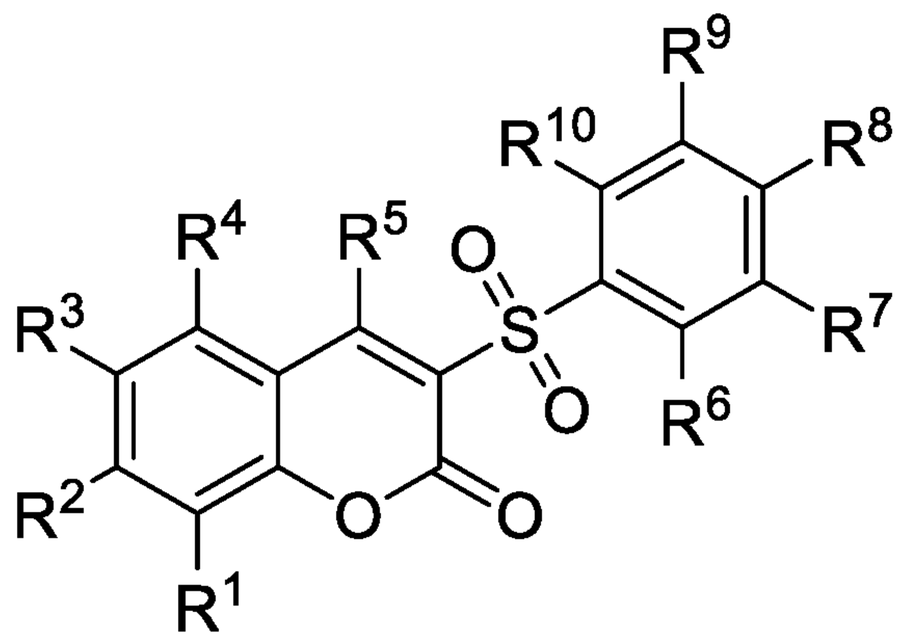
or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

4. The compound of claim 3, wherein the compound of Formula (Ib) is selected from any one of the compounds of Table 1d, or a pharmaceutically acceptable salt thereof.

5. A compound selected from any one of the compounds of Table 1e, or a pharmaceutically acceptable salt thereof.

6. A method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (Ic):



(Ic),

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^B;

each R^B is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^C;

each R^C is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

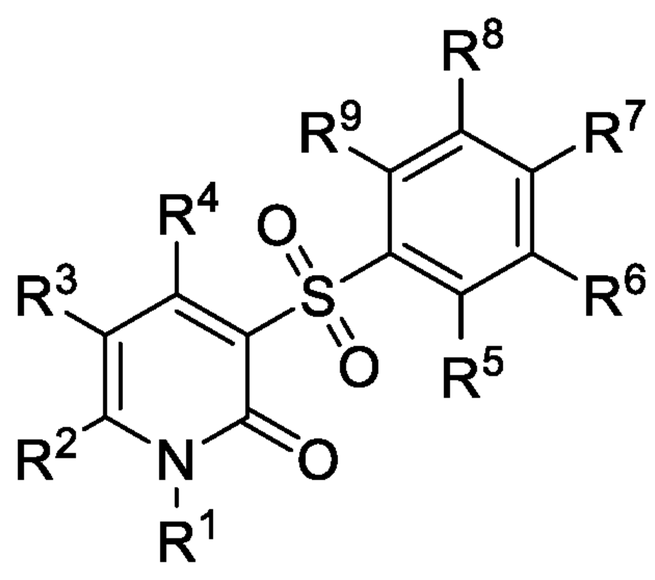
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

7. The method of claim 6, wherein the compound of Formula (Ic) is selected from any one of the compound of Table 1b, or a pharmaceutically acceptable salt thereof.

8. A method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (Id):



(Id),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^2, R^3, and R^4 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^B;

each R^B independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^C;

each R^C is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

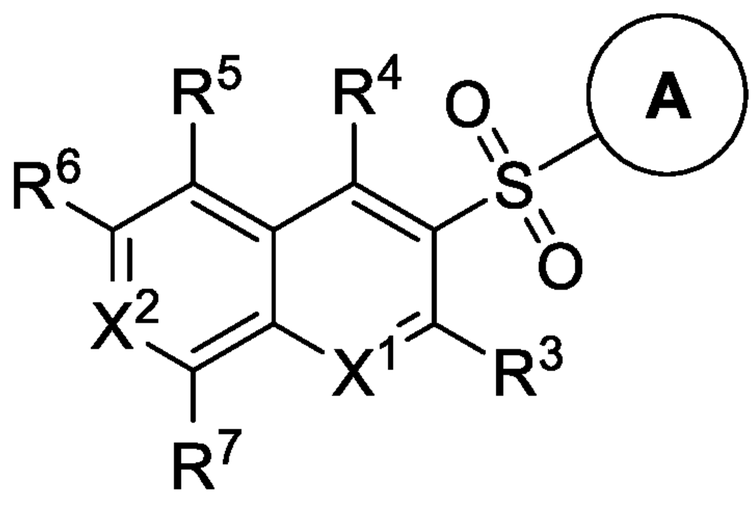
or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3}

alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

9. The method of claim 8, wherein the compound of Formula (Id) is selected from any one of the compounds of Table 1c, or a pharmaceutically acceptable salt thereof.

10. A compound of Formula (Ie):



(Ie),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^1;

X^2 is selected from N and CR^2;

each R^1, R^2, R^3, R^4, R^5, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^8;

each R^8 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^7 is selected from OR^{a2} and $NR^{c2}R^{d2}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl,

and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{a2}, R^{b1}, R^{c1}, R^{c2}, R^{d1}, and R^{d2} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

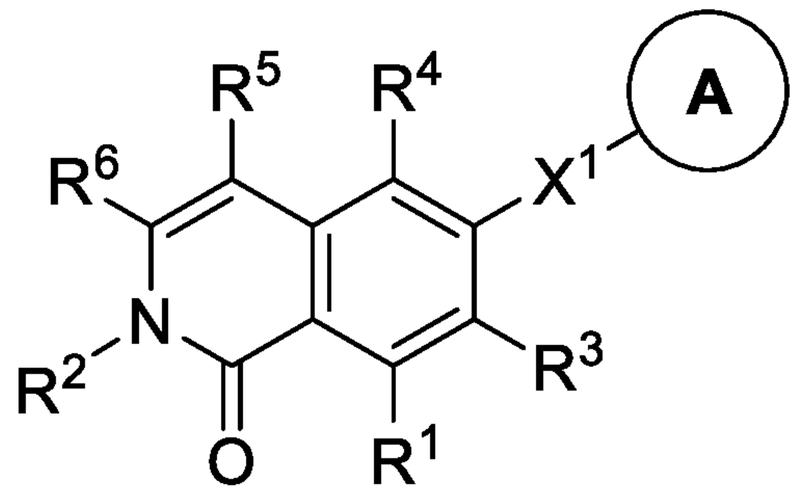
or any R^{c2} and R^{d2} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6}

alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

11. The compound of claim 10, wherein the compound of Formula (Ie) is selected from any one of the compounds of Table 1f, or a pharmaceutically acceptable salt thereof.

12. A compound of Formula (If):



(If),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

R^1, R^3, R^4, R^5, and R^6 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

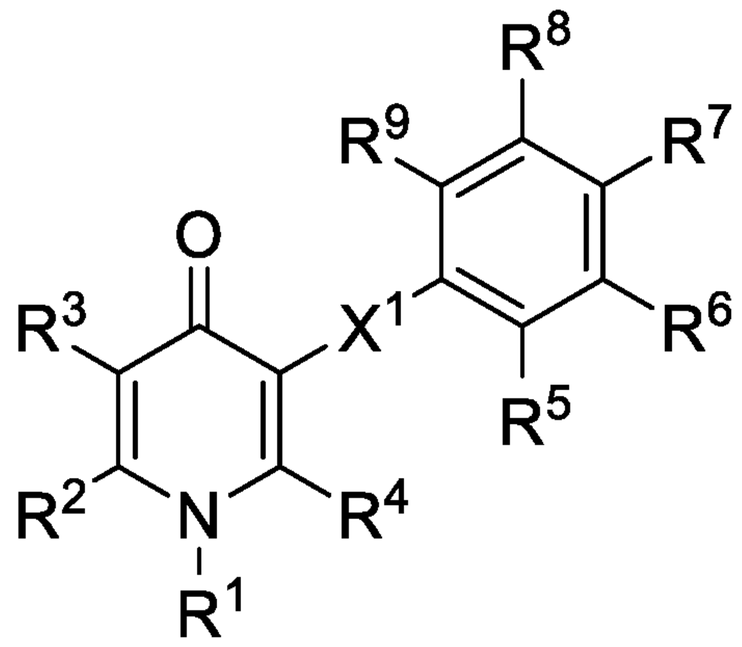
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

13. The compound of claim 12, wherein the compound is selected from any one of the compound of Table 1g, or a pharmaceutically acceptable salt thereof.

14. A compound of Formula (Ig):



(Ig),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

R^1 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^2, R^3, and R^4 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^B;

each R^B independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each of R^5, R^6, R^7, R^8, and R^9 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^C;

each R^C is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

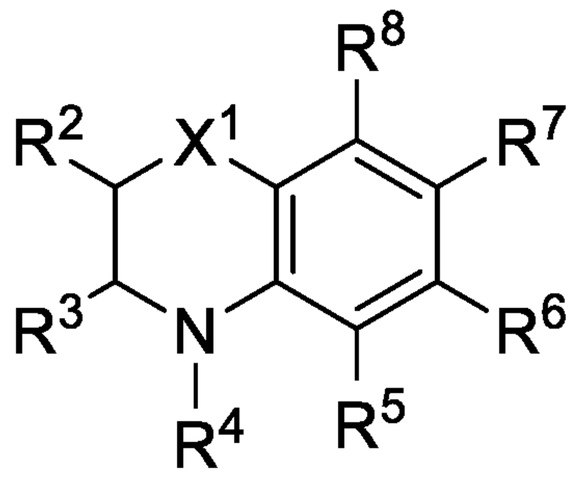
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

15. The compound of claim 14, wherein the compound of Formula (Ig) is selected from any one of the compounds of Table 1h, or a pharmaceutically acceptable salt thereof.

16. A method of inhibiting activation of an NF-κB pathway within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (IIa):



(IIa),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from O and NR^1;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

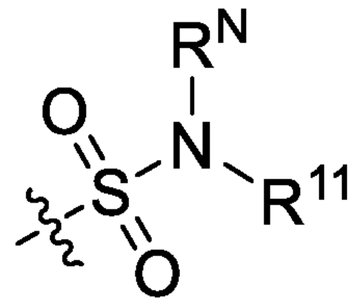
R^3 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and oxo, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^1 and R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^1 and R^2, together with N atom to which R^1 is attached and C atom to which R^2 is attached, form a 4-10 membered heterocycloalkyl ring, which is substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$; and a group of formula (i):



(i),

wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

provided that at least one of R^7 and R^8 is a group of formula (i);

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, for a -10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10-} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10

membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

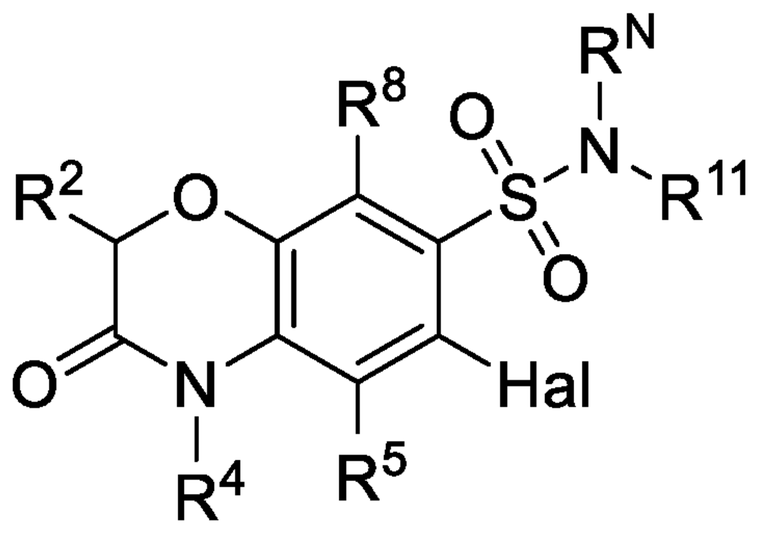
or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

17. The method of claim 16, wherein the compound of Formula (IIa) is selected from any one of the compounds of Table 2a, Table 2c, Table 2c-2, Table 2d, Table 2d-2, Table 2e, or Table 16, or a pharmaceutically acceptable salt thereof.

18. A compound selected from any one of the compounds of Table 16, or a pharmaceutically acceptable salt thereof.

19. A compound of Formula (IIb):



(IIb),

or a pharmaceutically acceptable salt thereof, wherein:

Hal is a halogen;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, for a -10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

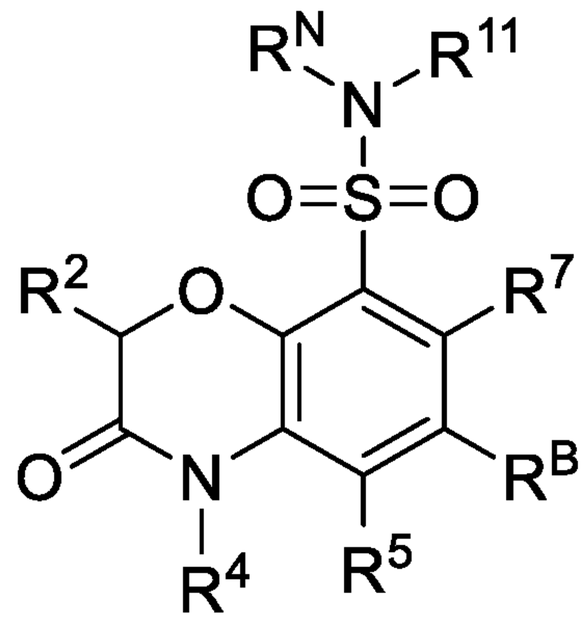
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

20. The compound of claim 19, wherein the compound of Formula (IIb) is selected from any one of the compounds of Table 2c or Table 2c-2, or a pharmaceutically acceptable salt thereof.

21. A compound of Formula (IIc):



(IIc),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$,

$NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

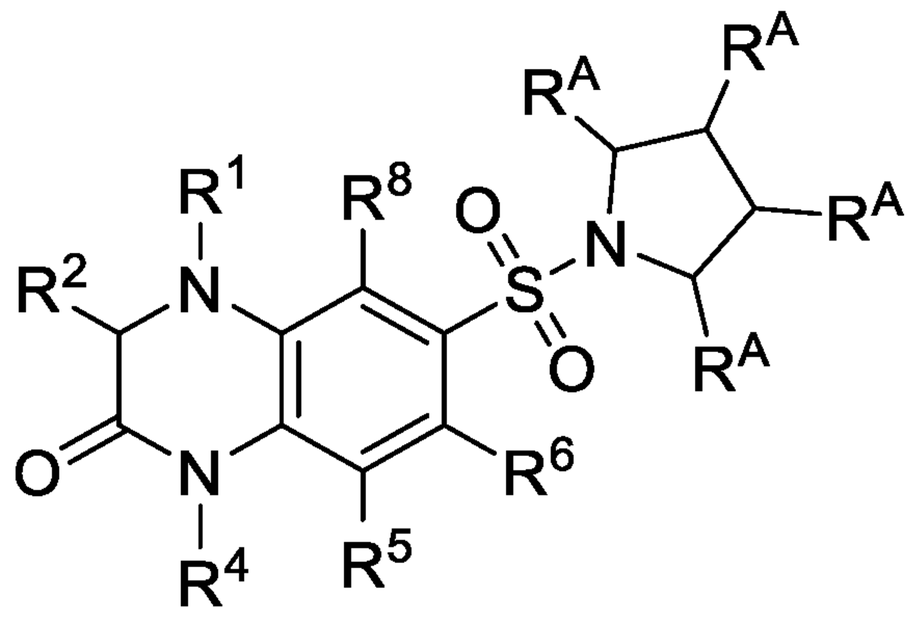
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

22. The compound of claim 21, wherein the compound of Formula (IIc) is selected from any one of the compounds of Table 2d or Table 2d-2, or a pharmaceutically acceptable salt thereof.

23. A compound of Formula (IId):



(IId),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^2 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5, R^6, and R^8 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

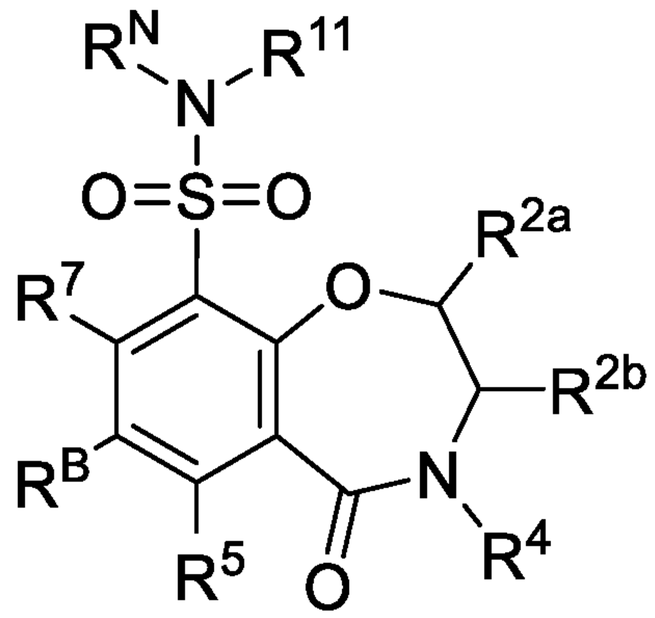
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

24. The compound of claim 23, wherein the compound of Formula (IId) is selected from any one of the compounds of Table 2e, or a pharmaceutically acceptable salt thereof.

25. A compound of Formula (IIe)



(IIe),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$,

$NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

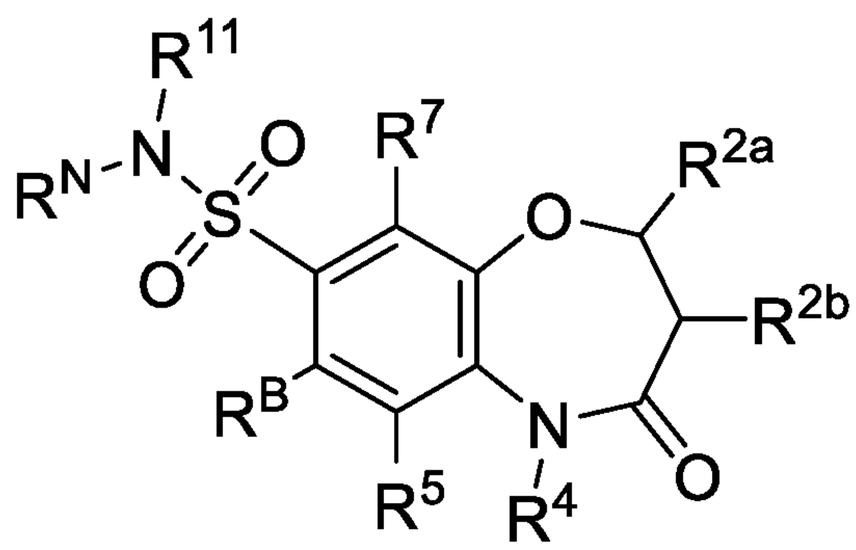
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

26. The compound of claim 25, wherein the compound of Formula (IIe) is selected from any one of the compounds of Table 2f, or a pharmaceutically acceptable salt thereof.

27. A compound of Formula (IIf):



(IIf),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

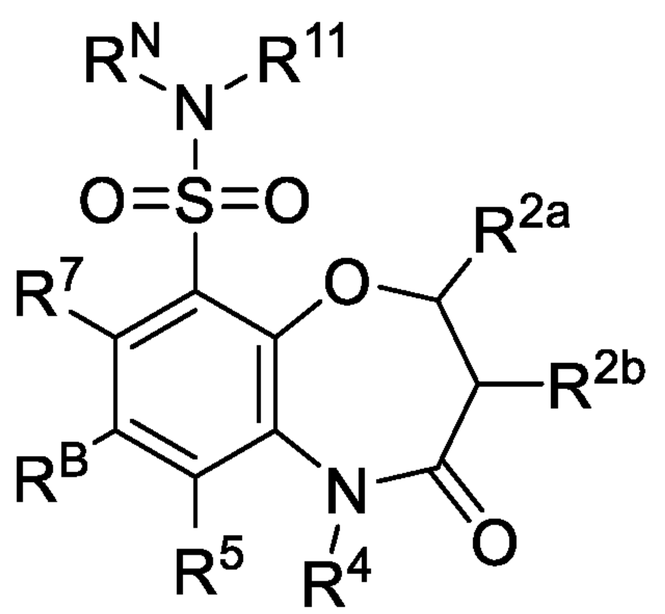
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

28. The compound of claim 27, wherein the compound of Formula (IIf) is selected from any one of the compounds of Table 2g, or a pharmaceutically acceptable salt thereof.

29. A compound of Formula (IIg):



(IIg),

or a pharmaceutically acceptable salt thereof, wherein:

R^B is selected from halogen and $S(O)_2R^{b1}$;

R^{2a} and R^{2b} are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^4 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^5 and R^7 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{11} is selected from C_{1-6} alkyl and ring A, wherein said C_{1-6} alkyl is optionally substituted with ring A;

R^N is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9; or

R^{11} and R^N, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

ring A is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is substituted with 1-10 substituents independently selected from R^A;

each R^A is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

each R^{10} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

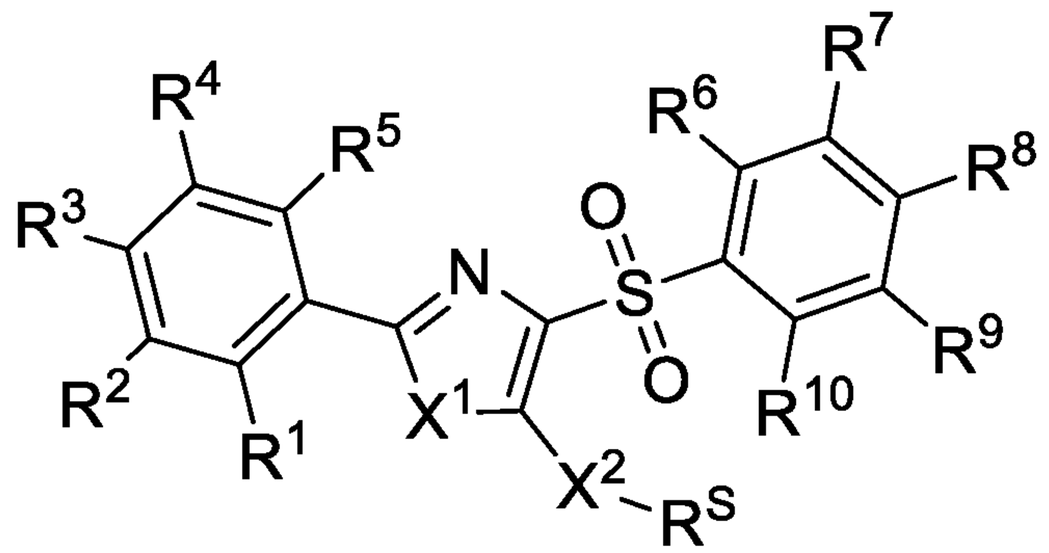
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

30. The compound of claim 29, wherein the compound of Formula (IIg) is selected from any one of the compounds of Table 2h, or a pharmaceutically acceptable salt thereof.

31. A method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (IIIa):



(IIIa),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from O, S, and NR^N;

R^N is selected from H and C_{1-6} alkyl;

X^2 is selected from S, S(O), and $S(O)_2$;

R^S is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

or any two adjacent R^1, R^2, R^3, R^4, and R^5 groups, together with the carbon atoms to which they are attached, form a C_{6-10} aryl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6}

alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{12};

each R^{12} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

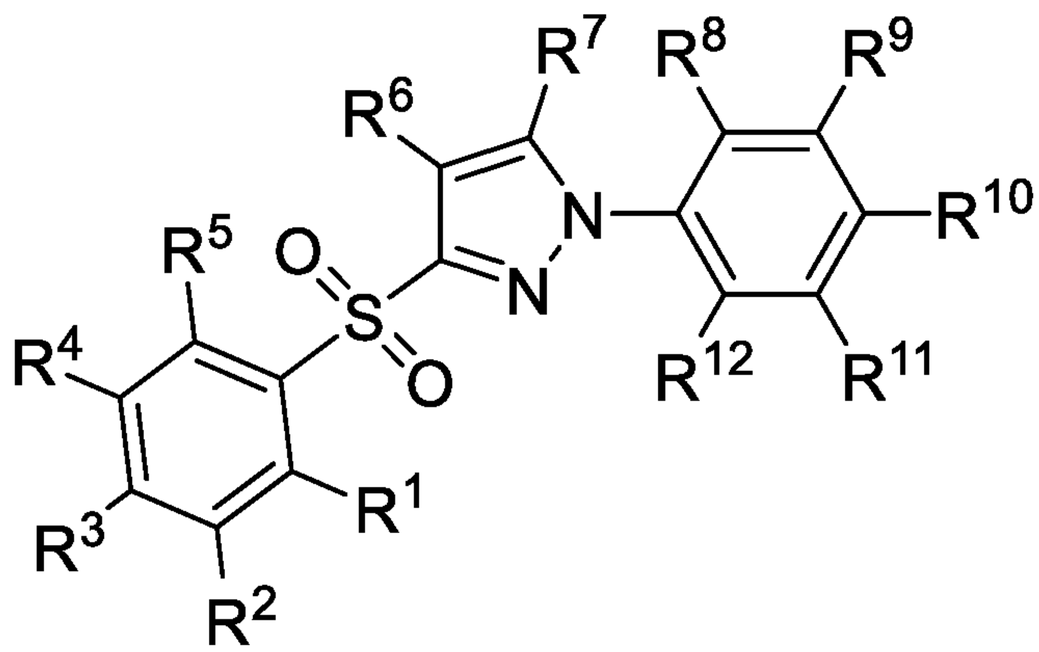
each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10

membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

32. The method of claim 31, wherein the compound of Formula (IIIa) is selected from any one of the compounds of Table 3a, Table 3b, Table 3b-2, Table 10, or Table 11.

33. A compound selected from any one of the compounds of Table 3b or Table 3b-2, or a pharmaceutically acceptable salt thereof.

34. A compound of Formula (IIIc):



(IIIc),

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{13};

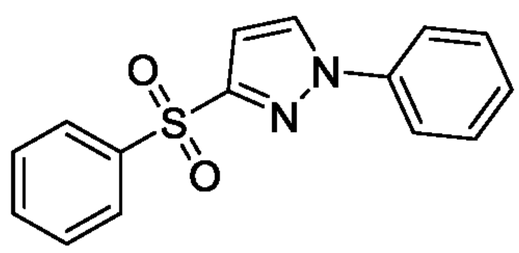
each R^{13} independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

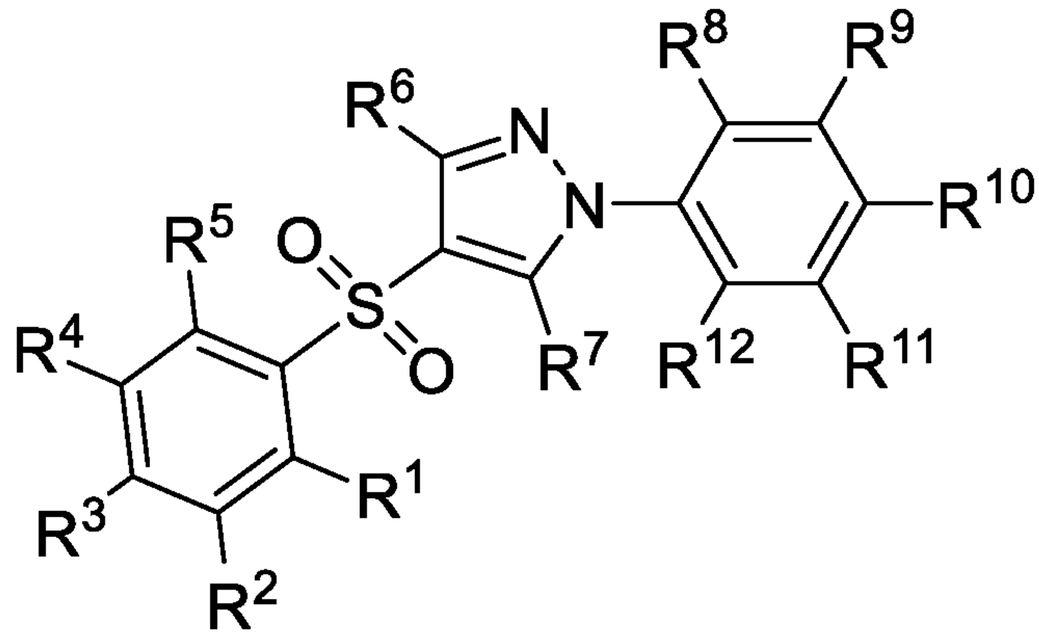
35. The compound of claim 34, wherein the compound of Formula (IIIc) is:



,

or a pharmaceutically acceptable salt thereof.

36. A compound of Formula (IIId):



(IIId),

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{13};

each R^{13} independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

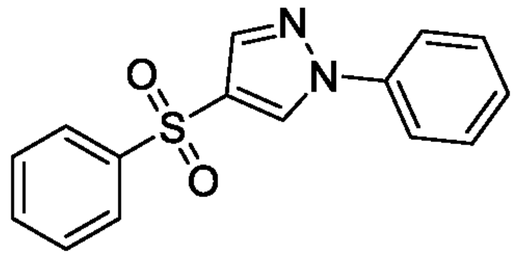
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl,

di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

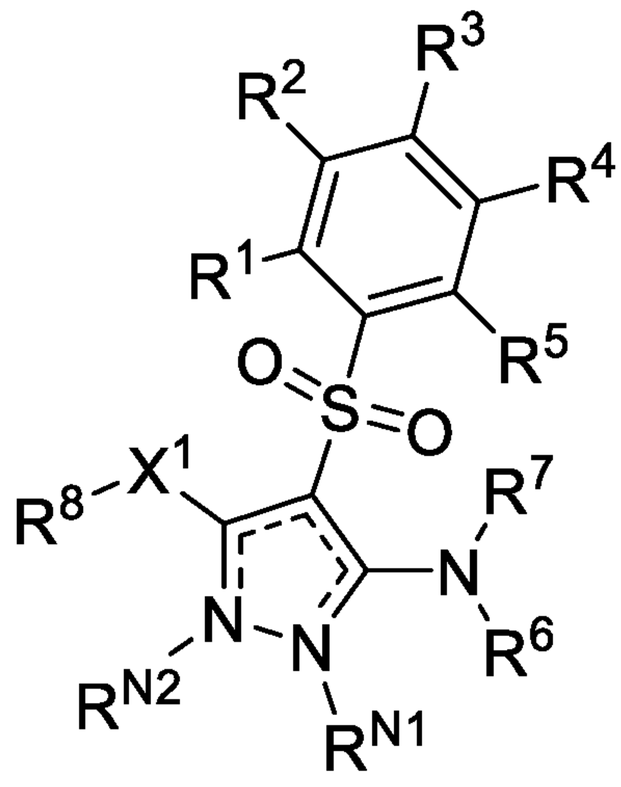
37. The compound of claim 36, wherein the compound of Formula (IIId) is:



;

or a pharmaceutically acceptable salt thereof.

38. A compound of Formula (IIIe):



(IIIe),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

each ⁞ represents a single bond or a double bond, provided that not more than two of ⁞ are double bonds;

R^{N2} is absent if ⁞ between the N atom to which R^{N2} is attached and the C atom to which X^1 is attached is a double bond; or

R^{N2} is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^{N1} is absent if ⁞ between the N atom to which R^{N1} is attached and the C atom to which NR^6R^7 is attached is a double bond; or

R^{N1} is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^9;

R^6 and R^7 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

or R^6 and R^{N1} together with the N atoms to which they are attached from a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^9 independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{10} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

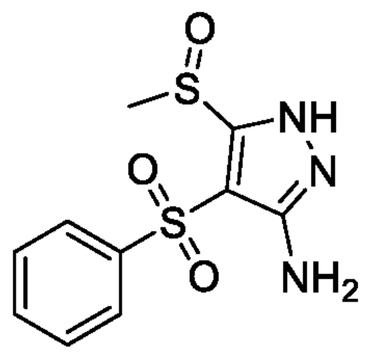
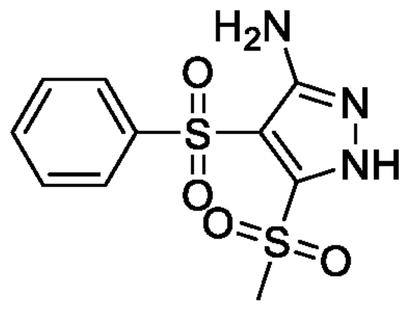
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10

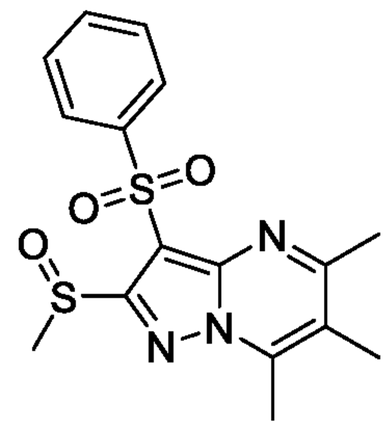
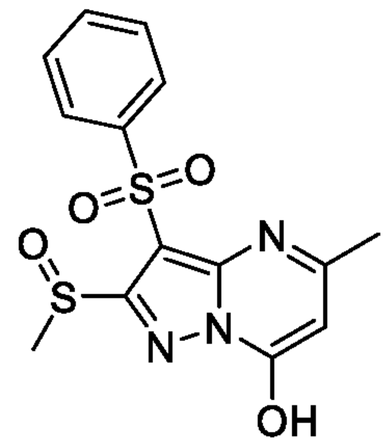
membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6}

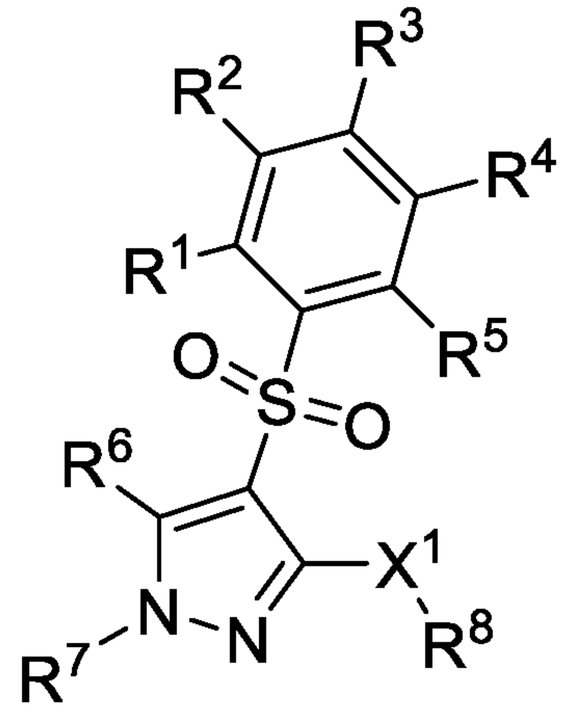
39. The compound of claim 38, wherein the compound of Formula (IIIe) is selected from any one of the following compounds:

BC19338	ZE23-0091	
BC19339	ZE23-0092	

BC19340	ZE23-0096	
BC19341	ZE23-0098	

or a pharmaceutically acceptable salt thereof.

40. A compound of Formula (IIIf):



(IIIf),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5

substituents independently selected from R^9;

R^6 and R^7 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

provided that at least one of R^6 and R^7 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

or R^6 and R^7, together with the C atom to which R^6 is attached and N atom to which R^7 is attached, from a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^9 independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

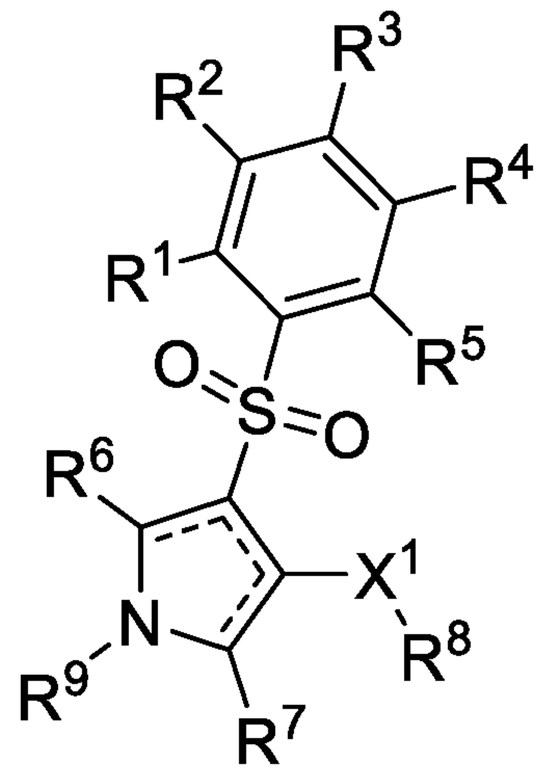
each R^{10} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

41. A compound of Formula (IIIg-2):



(IIIg-2),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

each ⫴ represents a single bond or a double bond, provided that not more than two of ⫴ are double bonds;

each of R^1, R^2, R^3, R^4, R^5, R^6, and R^7 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6}

alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^9 is selected from $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein each of said C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}; or

R^7 and R^9, together with the N atom to which R^9 is attached and C atom to which R^7 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}; or

R^6 and R^9, together with the N atom to which R^9 is attached and C atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each R^{10} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10}

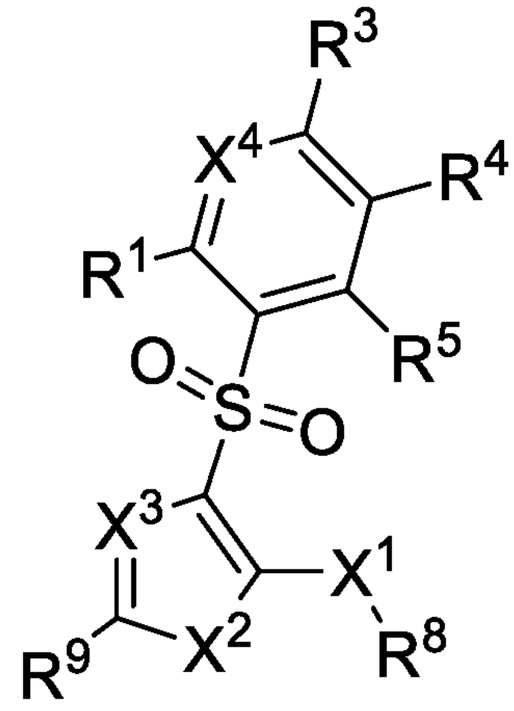
cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

42. The compound of claim 41, wherein the compound is selected from any one of the compounds of Table 12, or a pharmaceutically acceptable salt thereof.

43. A compound of Formula (IIIh):



(IIIh),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

X^4 is selected from N and CR^2;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

X^2 is selected from O, S, and NR^6;

R^6 is selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

X^3 is selected from N and CR^7;

R^7 is selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

R^9 is selected from $S(O)_2R^{b1}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}; or

R^9 and R^6, together with the carbon atom to which R^9 is attached and the N atom to which R^6 is attached, form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11}; or

R^6 and R^8, together with N atom to which R^6 is attached and S atom to which R^8 is attached, form 4-10 membered heterocycloalkyl substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{11};

each R^{10} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

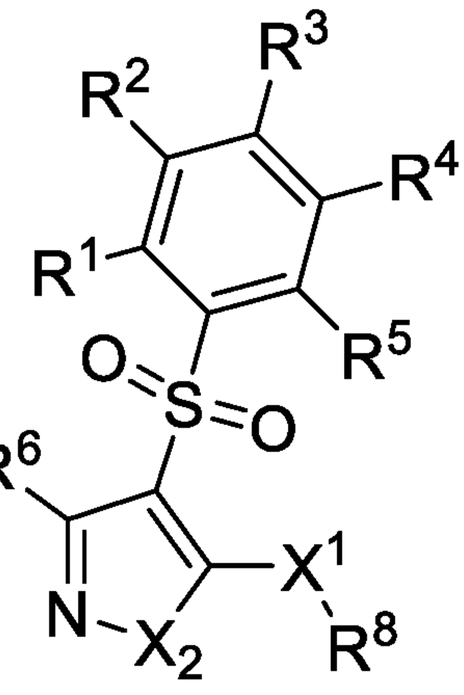
each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino;

provided that if X^3 is N and X^2 is O, then R^9 is selected from $S(O)_2R^{b1}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10}.

haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

44. The compound of claim 43, wherein the compound of Formula (IIIh) is selected from any one of the compounds of Table 8, Table 9, Table 10, and Table 11, or a pharmaceutically acceptable salt thereof.

45. A compound of Formula (IIIi):



(IIIi),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from S, S(O), and $S(O)_2$;

X^2 is selected from S and NR^7;

each of R^1, R^2, R^3, R^4, and R^5 is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^8 is selected from C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^9;

R^6 and R^7 are independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

provided that at least one of R^6 and R^7 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl; each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

or R^6 and R^7, together with the C atom to which R^6 is attached and N atom to which R^7 is attached, from a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, each of which is substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^9 independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{10} independently selected from H, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10

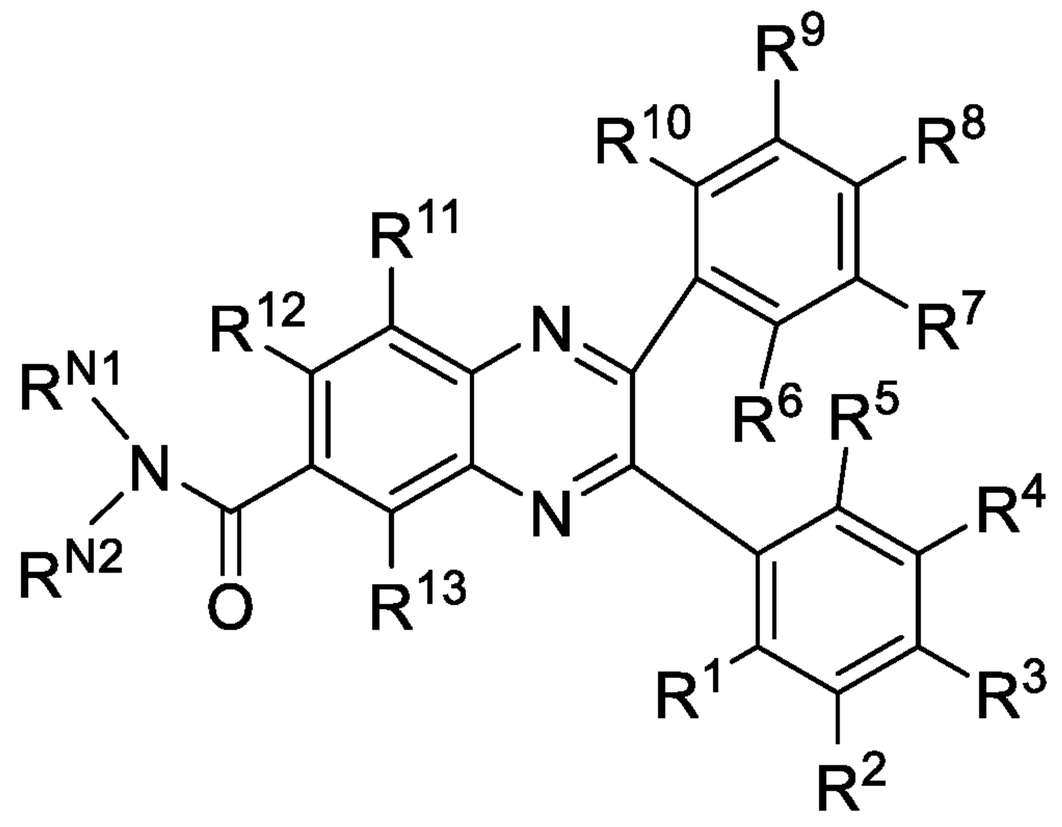
membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

46. The compound of claim 45, wherein the compound is selected from any one of the compounds of Table 15, or a pharmaceutically acceptable salt thereof.

47. A method for inhibiting NF-κB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound of Formula (IVa):



(IVa),

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} is independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

or R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{14};

each R^{14} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is

optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

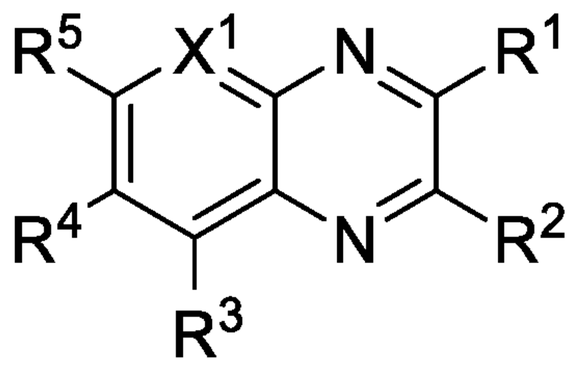
each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino,

aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

48. The method of claim 47, wherein the compound of Formula (IVa) is selected from any one of the compounds of Table 4a, or a pharmaceutically acceptable salt thereof.

49. A compound selected from any one of the compounds of Table 4b or Table 4b-2, or a pharmaceutically acceptable salt thereof.

50. A compound of Formula (IVb):



(IVb),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^4 is 5-10 membered heteroaryl, optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^8;

each R^8 is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl ,4-10 membered heterocycloalkyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered

heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, halo, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

R^1 and R^2 are each independently selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

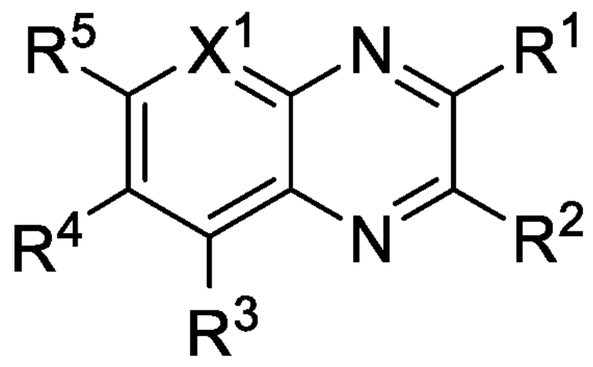
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

51. The compound of claim 50, wherein the compound of Formula (IVb) is selected from any one of the compounds of Table 4c or Table 4c-2, or a pharmaceutically acceptable salt thereof.

52. A compound of Formula (IVc):



(IVc),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^4 is selected from $C(O)NR^{N1}R^{N2}$, $C(O)OR^{a1}$, and CN;

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14};

each R^{14} independently selected from H, Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from R^8 and $S(O)_2R^8$;

R^8 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

provided that R^1 and R^2 are not both C_{6-10} aryl;

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

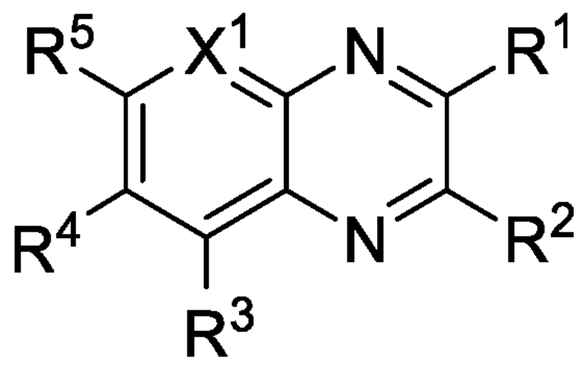
or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6}

alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

53. The compound of claim 52, wherein the compound of Formula (IVc) is selected from any one of the compounds of Table 4d, or a pharmaceutically acceptable salt thereof.

54. A compound of Formula (IVd):



(IVd),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^4, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^7;

each R^7 is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^3 is selected from $C(O)NR^{N1}R^{N2}$ and $C(O)OR^{a1}$;

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14}; or

R^{N1} and R^{N2}, together with the N atom to which they are attached, form a 4-10 membered heterocycloalkyl, which is substituted with 1, 2, or 3 substituents independently selected from R^{14};

each R^{14} independently selected from H, Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from R^8 and $S(O)_2R^8$;

R^8 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

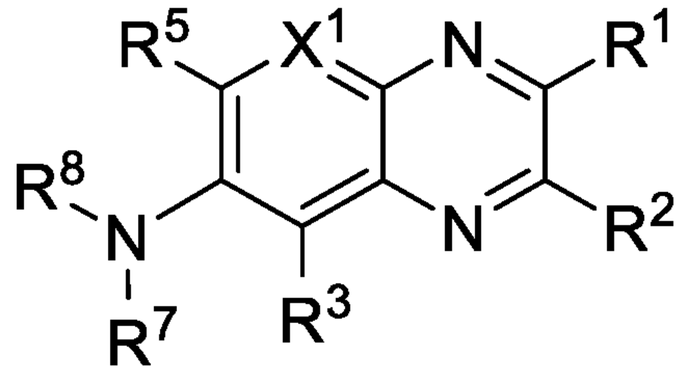
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino.

55. The compound of claim 54, wherein the compound of Formula (IVd) is selected from any one of the compound of Table 4e, or a pharmaceutically acceptable salt thereof.

56. A compound of Formula (IVe):



(IVe),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

or R^7 and R^8 together with the N atom to which they are attached form a 4-10 membered heterocycloalkyl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from R^{8a} and $S(O)_2R^{8a}$;

R^{8a} is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

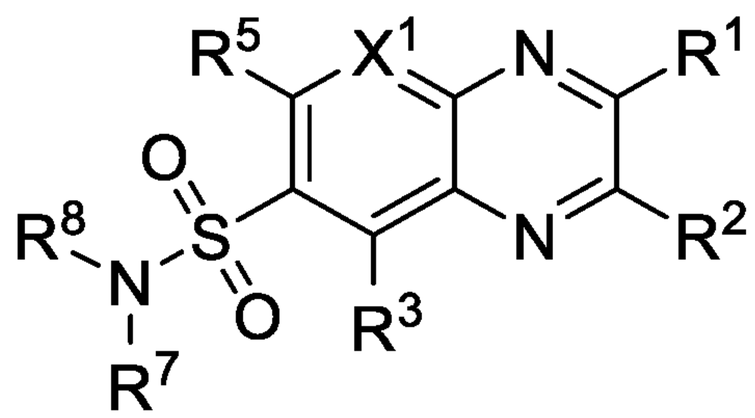
or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino, and any C_{1-6} alkyl, C_{1-6} alkoxy, C_{6-10} aryl,

C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

57. The compound of claim 56, wherein the compound of Formula (IVe) is selected from any one of the compounds of Table 4f or Table 4f-2, or a pharmaceutically acceptable salt thereof.

58. A compound of Formula (IVf):



(IVf),

or a pharmaceutically acceptable salt thereof, wherein:

X^1 is selected from N and CR^6;

R^3, R^5, and R^6 are each independently selected from H, halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

R^7 and R^8 are each independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^9;

each R^9 is independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{10};

or R^7 and R^8 together with the N atom to which they are attached form a 4-10 membered heterocycloalkyl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

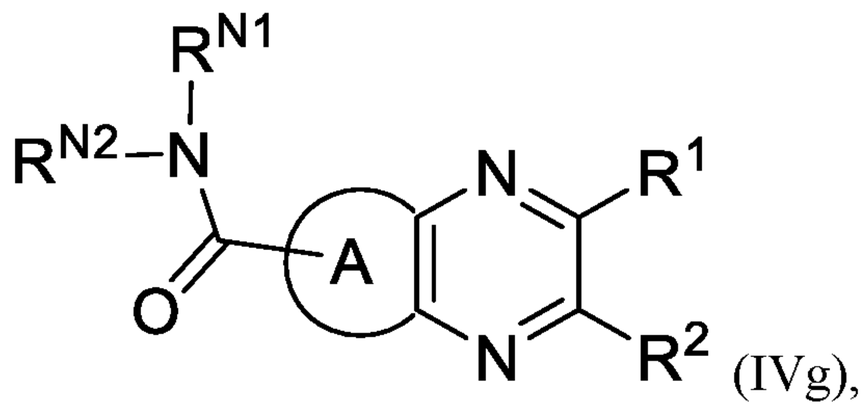
each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino, and any C_{1-6} alkyl, C_{1-6} alkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

59. The compound of claim 58, wherein the compound is selected from any one of the compounds of Table 4g, or a pharmaceutically acceptable salt thereof.

60. A compound of Formula (IVg):



(IVg),

or a pharmaceutically acceptable salt thereof, wherein:

ring A is C_{3-8} cycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

each of R^{N1} and R^{N2} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from R^{14};

or R^{N1} and R^{N2} together with the N atom to which they are attached from a 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{14};

each R^{14} independently selected from Cy^1, halo, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, SR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{15};

each R^{15} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

R^1 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

R^2 is selected from C_{1-6} haloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^{10};

each R^{10} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$; wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted with 1, 2, or 3 substituents independently selected from R^{11};

each R^{11} is independently selected from CN, NO_2, OR^{a1}, $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}S(O)_2R^{b1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$;

each R^{a1}, R^{b1}, R^{c1}, and R^{d1} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, and (4-10 membered heterocycloalkyl)-C_{1-4} alkylene are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^g;

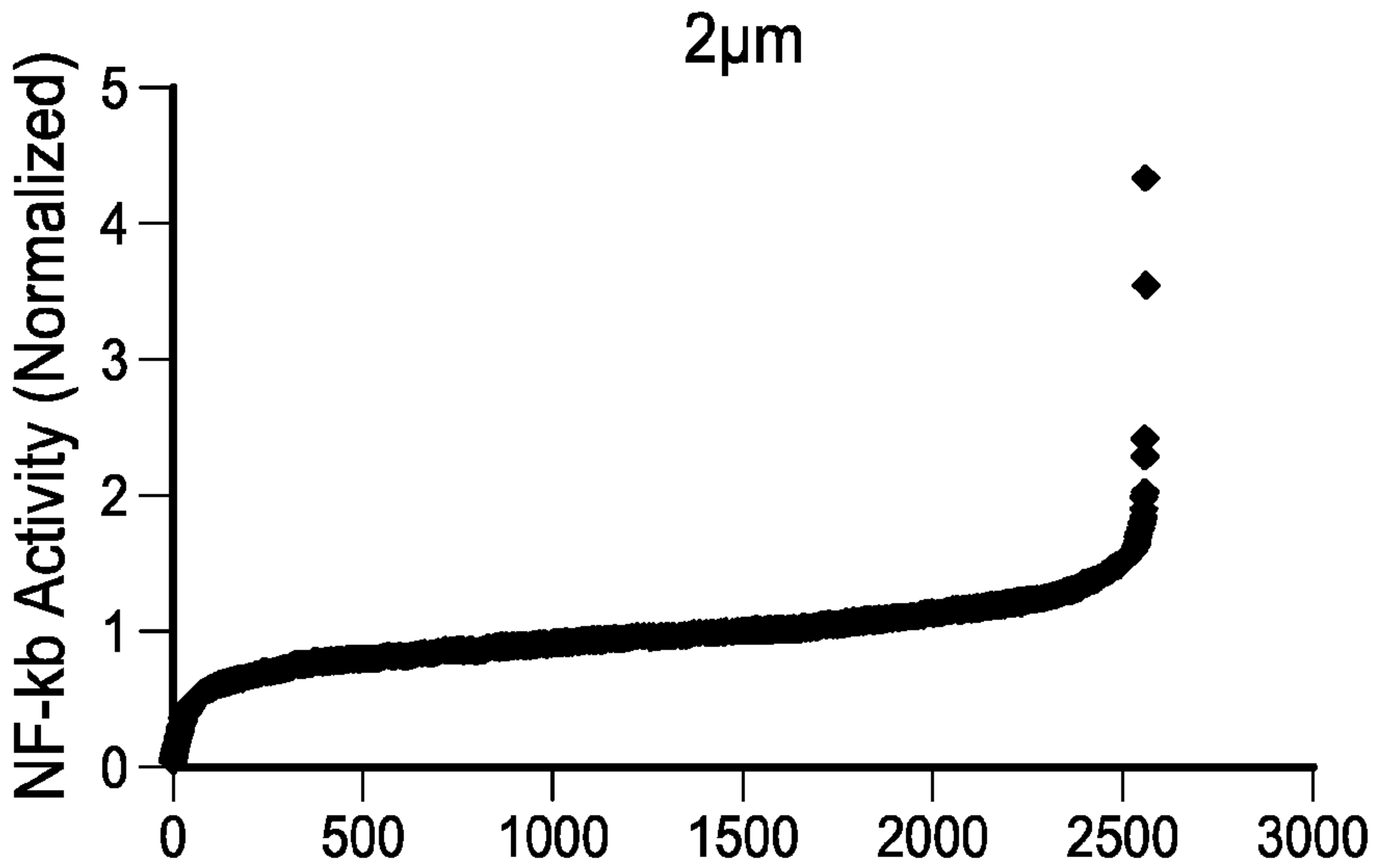
or any R^{c1} and R^{d1} together with the N atom to which they are attached form a 4-7 membered heterocycloalkyl, which is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano-C_{1-3} alkylene, HO-C_{1-3} alkylene, C_{6-10} aryl, C_{6-10} aryloxy, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, C_{6-10} aryl-C_{1-4} alkylene, C_{3-10} cycloalkyl-C_{1-4} alkylene, (5-10 membered heteroaryl)-C_{1-4} alkylene, (4-10 membered heterocycloalkyl)-C_{1-4} alkylene, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thio, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carbamyl, C_{1-6} alkylcarbamyl, di(C_{1-6} alkyl)carbamyl, carboxy, C_{1-6} alkylcarbonyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkylsulfonylamino, aminosulfonyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-6} alkylaminosulfonylamino, di(C_{1-6} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-6} alkylaminocarbonylamino, and di(C_{1-6} alkyl)aminocarbonylamino, and any C_{1-6} alkyl, C_{1-6} alkoxy, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl of R^g is optionally substituted with 1, 2, or 3 substituents independently selected from OH, NO_2, CN, halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, and C_{1-6} haloalkoxy.

61. The compound of claim 60, wherein the compound is selected from any one of the compounds of Table 17, or a pharmaceutically acceptable salt thereof.

62. A method of treating a mammal having a disease, disorder, or condition responsive to inhibiting NF-κB activity within a cell, wherein said method comprises administering, to said mammal, a compound selected from (i) a compound of any one of claims 3-5, 10-15, 18-30, 33-46, and 49-61, or a pharmaceutically acceptable salt thereof; and (ii) a compound as recited in any one of claims 1, 2, 6-9, 16, 17, 31, 32, 47, and 48, or a pharmaceutically acceptable salt thereof.

63. The method of claim 62, wherein said method comprises treating a mammal having a a disease or condition selected from cancer, inflammation, an autoimmune disease.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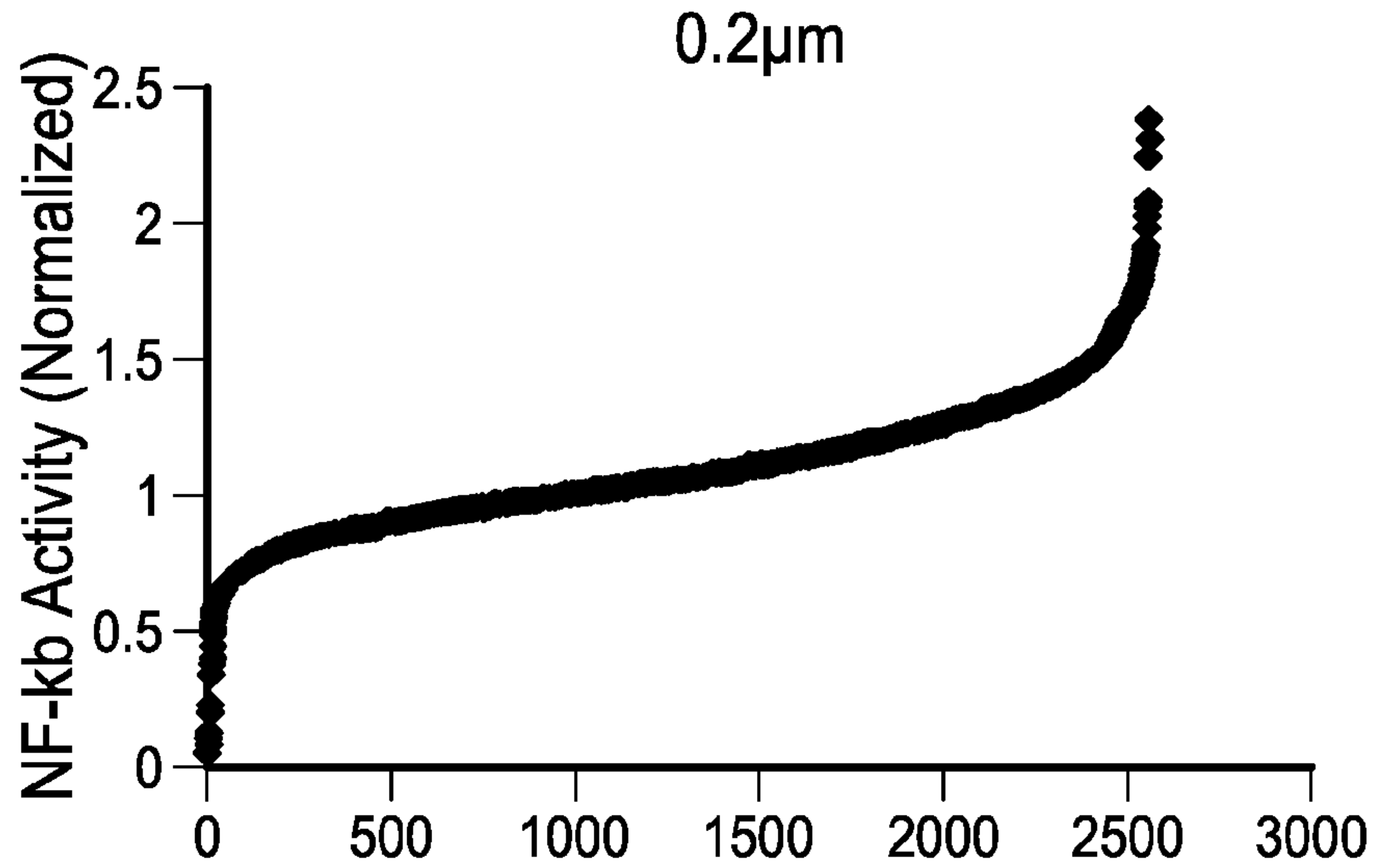
2
3
4
5
0
500
1000
1500
2000
2500
3000
Cpds


0.2μm
NF-kb Activity (Normalized)
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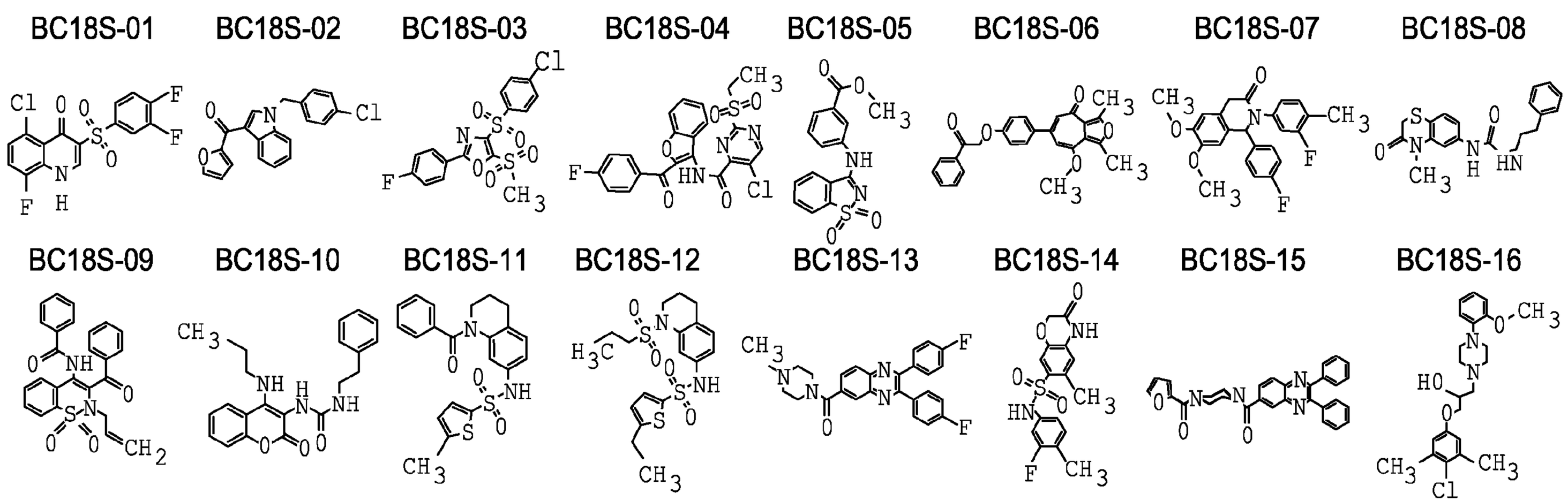
0.5
1
1.5
2
2.5
0
500
1000
1500
2000
2500
3000
Cpds


BC18S-01
BC18S-02
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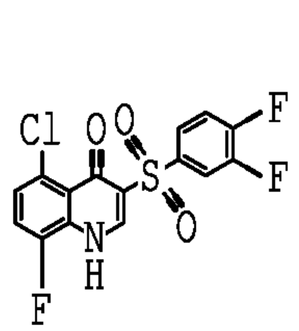
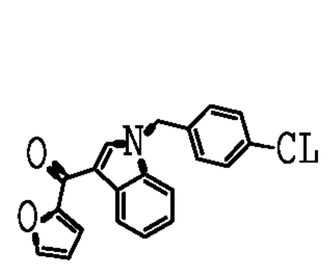
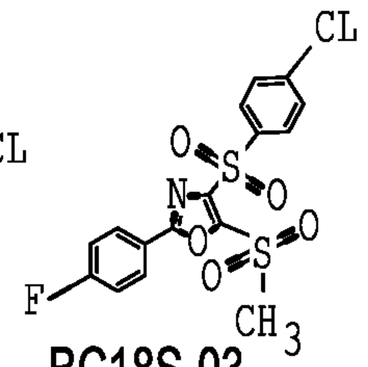
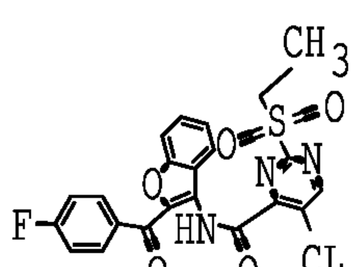
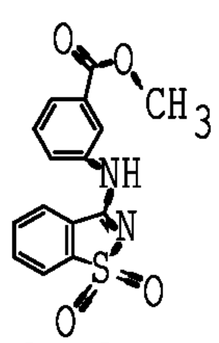
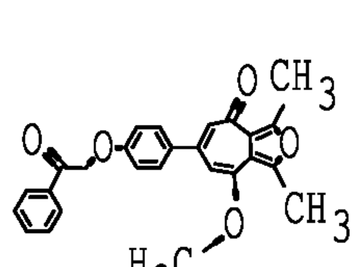
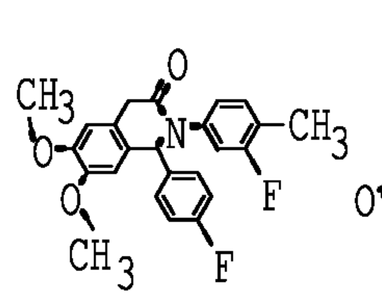
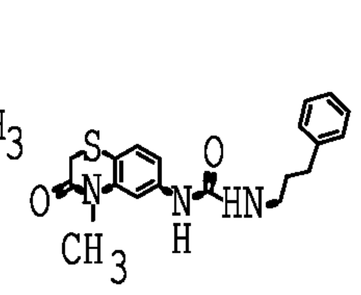
BC18S-13
BC18S-14
BC18S-15
BC18S-16

FIG. 1

BC18S-01	BC18S-02	BC18S-03	BC18S-04	BC18S-05	BC18S-06	BC18S-07	BC18S-08	LPS
380.2	4508	365.2	687.9667	394.5	10583.33	3613.667	5890.333	
1631.333	6748.333	517.5667	767.2	2625.667	12163.33	5306.667	8615.333	
1256.667	8244.667	1091.067	2667	14376.67	9715.667	7404.333	10808.67	
3584	11317.67	5898.333	8408.667	25716.67	12876.67	15716.67	12246.67	
5549.333	15303.33	11638.33	16393.33	27190	16413.33	20283.33	14683.33	
10681.67	20126.67	19506.67	23930	26110	24850	26813.33	19886.67	
16643.33	25463.33	18013.33	25840	28060	26420	26380	26123.33	
28140	28140	28140	28140	28140	28140	28140	28140	

Cpds concentration

BC18S-09	BC18S-10	BC18S-11	BC18S-12	BC18S-13	BC18S-14	BC18S-15	BC18S-16	LPS
2370	4335.333	1264.633	1830.333	537.1333	615.5	825.5333	10361.67	
6953.667	11766.67	4368.333	8077.333	501.4667	685.1333	550.2667	14003.33	
8030.667	12216.67	4896.667	10145.67	639.6667	1018.967	749.0667	14953.33	
16983.33	24210	12313.33	15906.67	2249	1866.333	1693.667	20900	
16556.67	23976.67	14390	20113.33	3542.667	2442.333	3712.333	21103.33	
22293.33	27350	24460	23406.67	8206	4579.333	8709.667	22190	
26613.33	26306.67	26956.67	24766.67	14206.67	4493	10306	20803.33	
28140	28140	28140	28140	28140	28140	28140	28140	

Cpds concentration

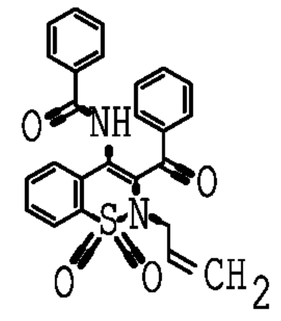
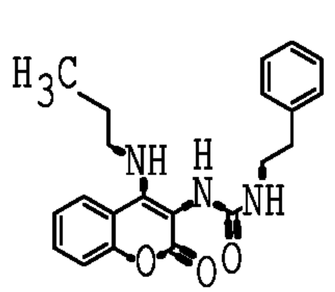
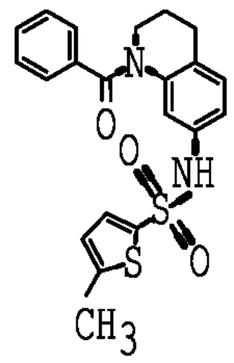
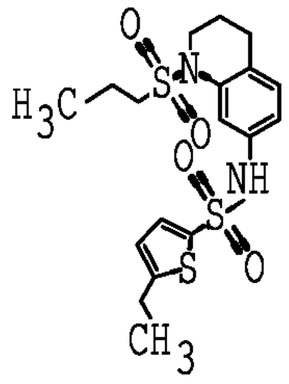
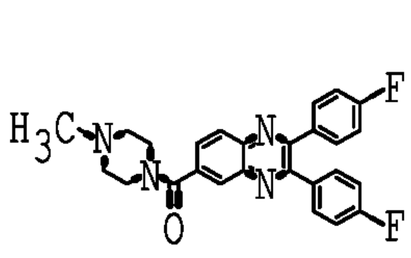
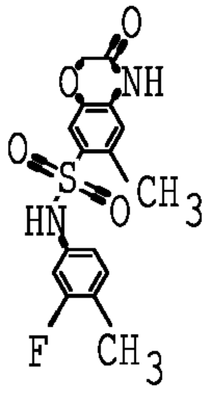
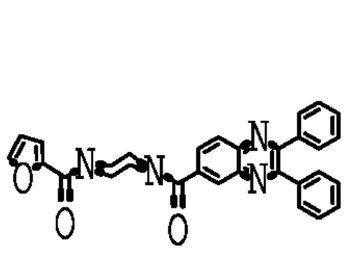
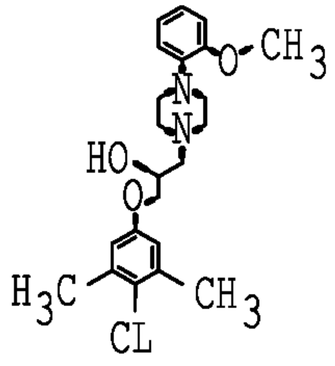
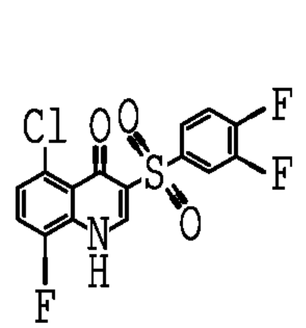
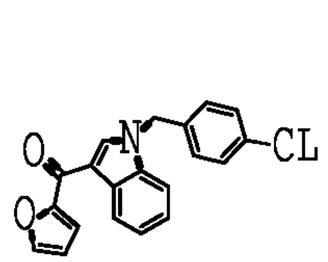
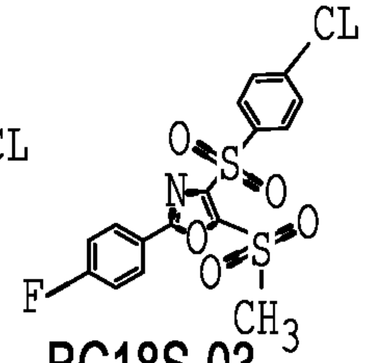
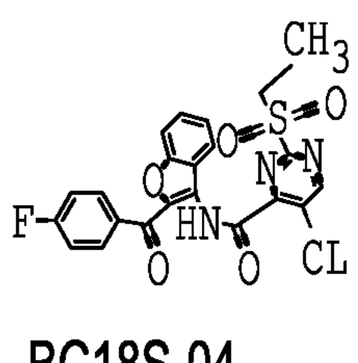
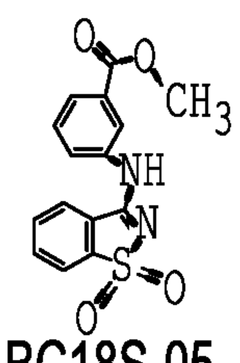
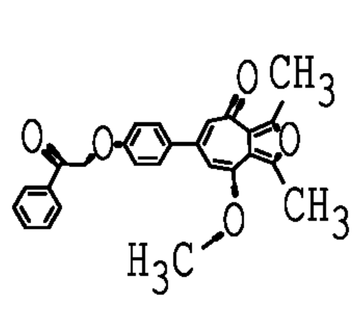
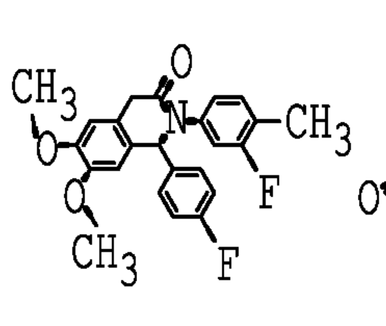
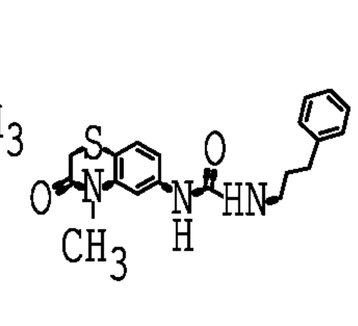









FIG. 2

BC18S-01	BC18S-02	BC18S-03	BC18S-04	BC18S-05	BC18S-06	BC18S-07	BC18S-08	PAM
311.5333	776.7667	147.5367	1077.567	333.7333	1013.867	627.4	1348.667	
484	819.6333	399.5	1168	2052.333	1151.667	1114.3	1621	
373.7333	1019.6	1127.1	1998	2271.333	1376.333	2223.667	1357	
616.5	1674.667	2450.667	2135.667	2577	2202.667	2371.667	2633	
1094.433	1914	2615.333	2659	2781.333	2259.333	2639.667	2440	
1484	3229.667	2296	2828.667	3008	2674.333	2880.667	2675.667	
2370.333	3102.667	2645	2812.333	2815.333	2817	2909	2902.333	
3022.917	3022.917	3022.917	3022.917	3022.917	3022.917	3022.917	3022.917	

Cpds concentration

BC18S-09	BC18S-10	BC18S-11	BC18S-12	BC18S-13	BC18S-14	BC18S-15	BC18S-16	PAM
234.7667	911.6667	501.9333	537.4667	119.01	223.9	242.3533	1611	
714.4667	1350.667	764.8667	1026.933	153.5367	246.9667	104.6667	1381.333	
1001.567	2175.667	942.2667	1307.067	338.8667	260.0333	265.5	1382.667	
1256.967	2522	1495.667	1492.667	557.4	515.7	451.8	1680.333	
1904	2692.667	2242.667	2156.667	1053.967	357.2667	734.1667	2213.333	
2362.333	3107.333	2700	3167	1612.667	877.9333	1082.033	2900	
2769.667	3025.667	2932	3036.667	1898	831.9667	1565	2969.667	
3022.917	3022.917	3022.917	3022.917	3022.917	3022.917	3022.917	3022.917	

Cpds concentration

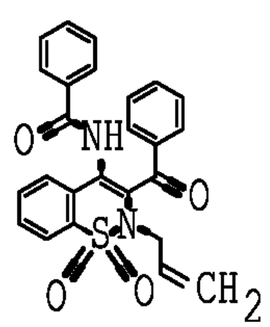
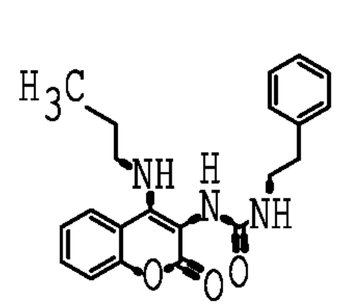
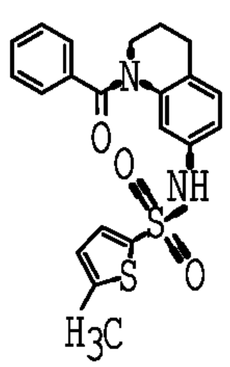
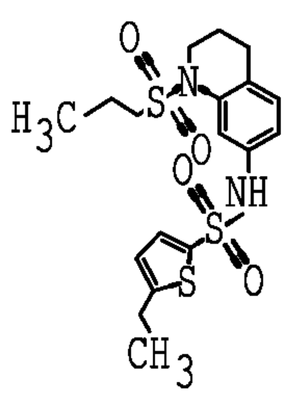
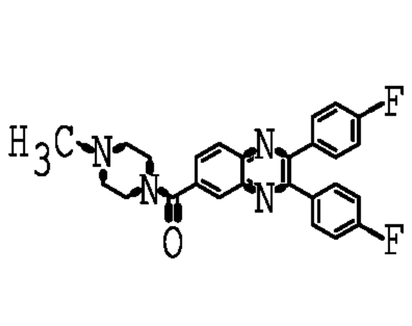
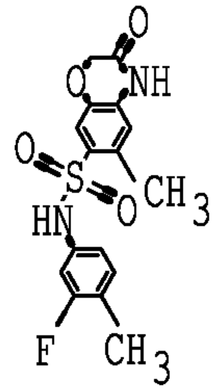
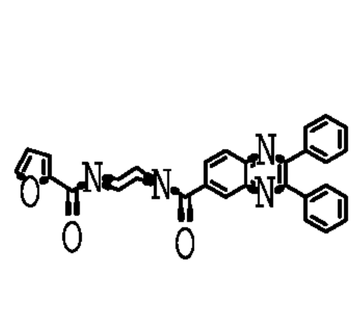
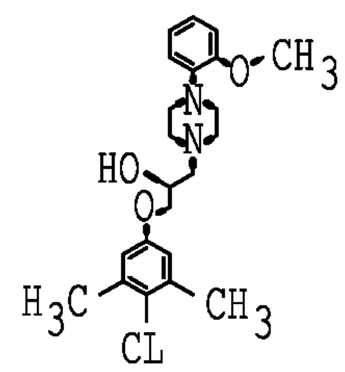
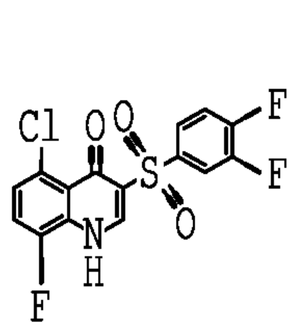
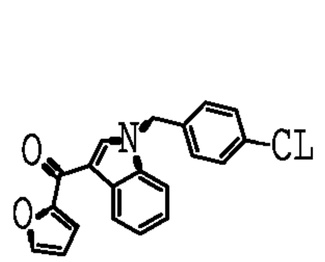
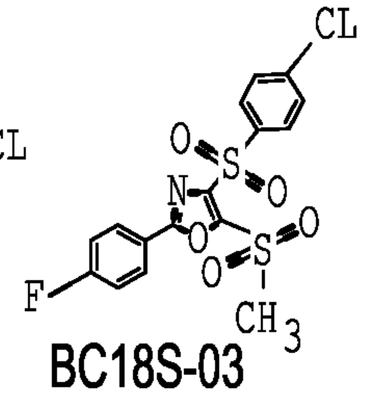
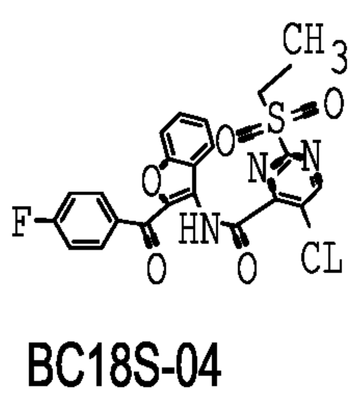
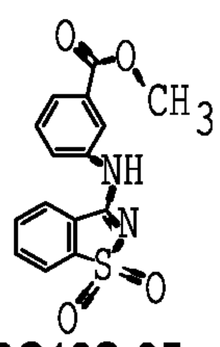
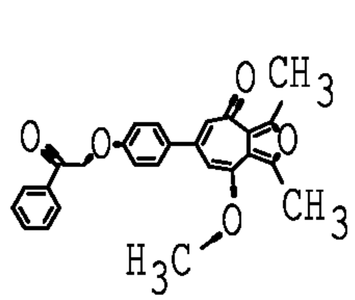
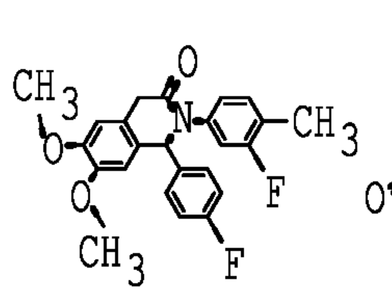
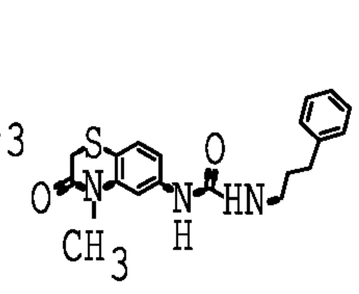









FIG. 3

BC18S-01 BC18S-02 BC18S-03 BC18S-04 BC18S-05 BC18S-06 BC18S-07 BC18S-08 R848

Cpds concentration

296.6333	1853.667	467.8667	564.1	328.7667	5624	1119.833	4146.333
454.8333	1699.033	351.5333	394.5	997.1333	5429	3748.333	3391
534.6333	2014.667	461.9333	1127.467	3719.667	5349.333	5075	5113
966.8667	3354	1984	4951.333	10077	5923.667	7395.667	8053.333
2095	3524	2586.333	8541.333	11120	10350	11273.33	9081.333
7771.667	6858.333	3955	8770.667	9106.667	10435	9512.667	10187.67
8007.333	10800	6912	10063.67	10746.67	10418.33	10723	9175
10535.02	10535.02	10535.02	10535.02	10535.02	10535.02	10535.02	10535.02

BC18S-09 BC18S-10 BC18S-11 BC18S-12 BC18S-13 BC18S-14 BC18S-15 BC18S-16 R848

Cpds concentration

735.3333	2264	874.5	610.5333	438.2	342.7667	243.6667	1113.333
1057.7	4054.667	1979.667	982.1667	313.0667	330.9	274.9667	2713
2142	5468.333	2802	2818	431.2667	269.7667	297.2667	3226
4447.667	10309.67	3907.667	4350	854.9333	623.1	741	6565.667
5921.333	12280	4516.333	5483.667	2996.333	990.7	1762	7538.333
6679.667	9486.667	6227.667	8244.333	2998.667	1146.333	4824.667	10581.33
7975	10523.33	7532.667	8096.333	4354.667	1499.067	6062.667	12070
10535.02	10535.02	10535.02	10535.02	10535.02	10535.02	10535.02	10535.02

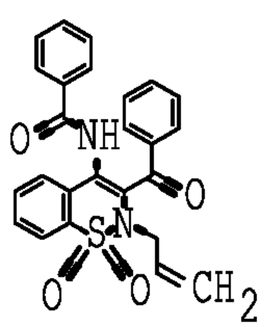
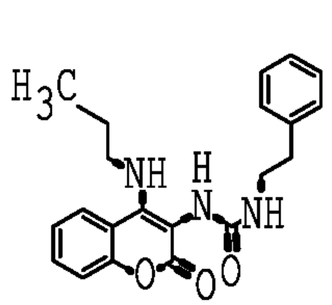
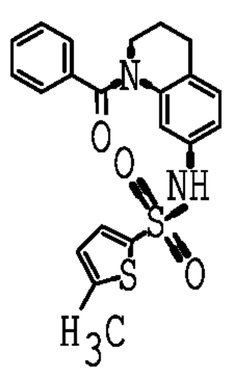
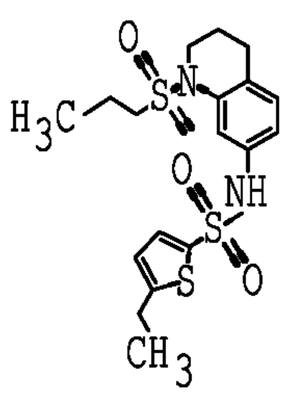
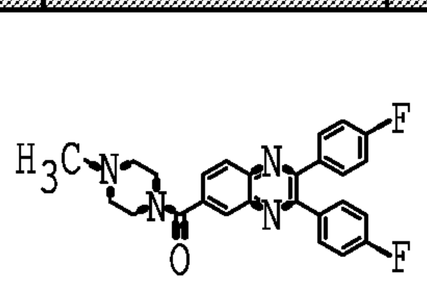
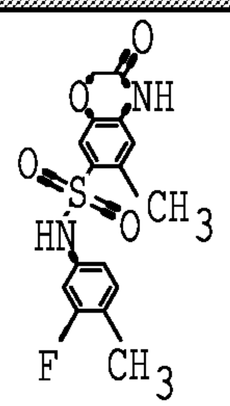
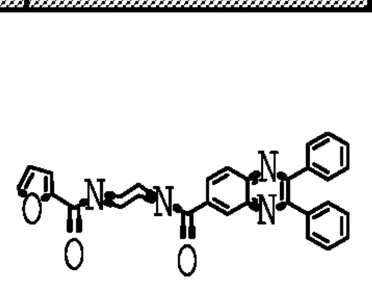
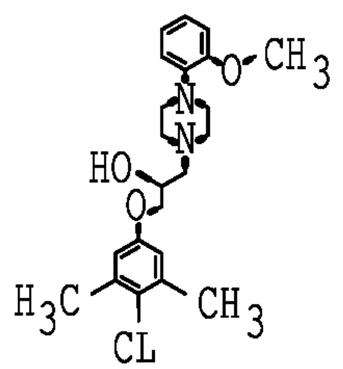









FIG. 4

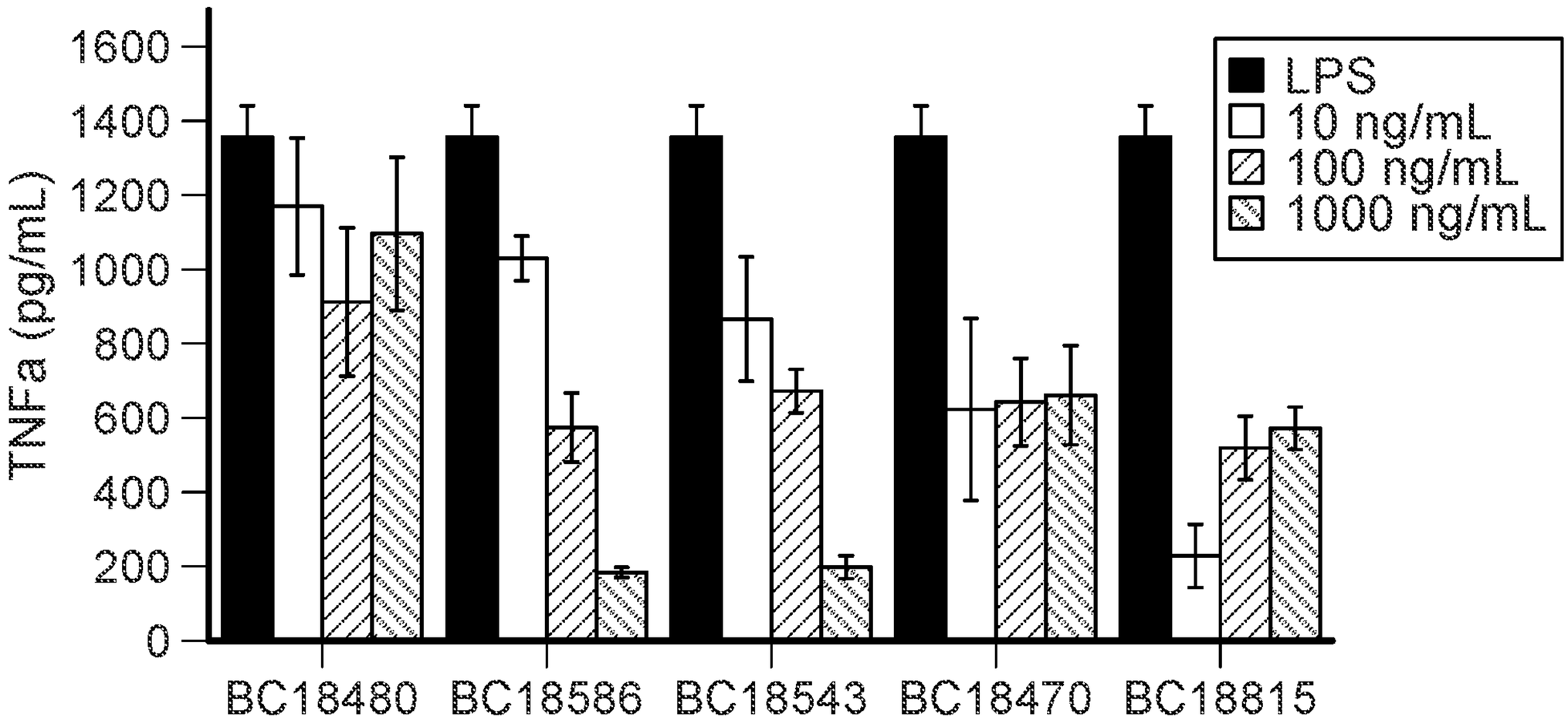

TNFa (pg/mL)
1600
1400
1200
1000
800
600
400
200
0
BC18480
BC18586
BC18543
BC18470
BC18815
LPS
10 ng/mL
100 ng/mL
1000 ng/mL

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/61670

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/4709; C07D 215/16; C07D 215/22; C07D 215/36 (2021.01)

CPC - A61K 31/4709; C07D 215/16; C07D 215/22; C07D 215/36

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2014/0073668 A1 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 13 March 2014 (13.03.2014) para [0012], [0052], Fig 8L; claim 1, claim 3, claim 5	1, 62/1, 63/1
A	US 7,557,213 B2 (MELIKIAN et al.) 07 July 2009 (07.07.2009) col 34, ln 9-22; col 208, Table 4	1, 62/1, 63/1
A	US 2014/0018384 A1 (WALLNER et al.) 16 January 2014 (16.01.2014) para [0091], pg 37, Table 4, Example 102	1, 62/1, 63/1
A	US 2017/0174704 A1 (MILLENNIUM PHARMACEUTICALS, INC.) 22 June 2017 (22.06.2017) para [0407],[0417]	1, 62/1, 63/1

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 January 2021	MAR 25 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/61670

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows:
--Please see attached sheet---

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 62/1 and 63/1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/61670

Attachment to Box.No.III:

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

Group I+: Claims 1-2, 6-9, 16-17, 31-32, 47-48 and 62-63 directed to a method for inhibiting NF-kB activity within a cell within a mammal, wherein said method comprises administering, to said mammal, an effective amount of a compound represented by Formula (Ia), (Ic), (Id), (IIa), (IIIa), or (IVa), wherein said compound is selected from any one of the compounds specified in Table Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Table 2a, 2c-2, 2d, 2d-2, 2c, 2e, Table 3a, 3b, 3b-2, Table 10, 11, 16 or Table 4a; and to a method of treating a mammal having a disease, disorder, or condition responsive to inhibiting NF-kB activity within a cell, wherein said method comprises administering said compound, or a pharmaceutically acceptable salt thereof, to said mammal.

The method for inhibiting NF-kB activity and treating a disease, disorder or condition responsive to inhibiting NF-kB activity in a mammal, will be searched to the extent that the method encompasses administering to said mammal, the first species of claim 1, represented by Formula (Ia), wherein
Y1 is C(O);
Y2 is C(O):
X1 is N; X2 is N; X3 is CR3; X4 is CR4, such that no more than two of X1-X4 are N;
each of R3, R4, R5 and R6 is H; and ring A is C6-aryl,which is unsubstituted.

It is believed that claims 1, 62/1 and 63/1 read on this first named invention, and thus these claims will be searched without fee to the extent that they encompass the method described above.
Applicant is invited to elect additional method(s) wherein each additional method elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected method. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched.
Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a method for inhibiting NF-kB activity and treating a disease, disorder or condition responsive to inhibiting NF-kB activity in a mammal, comprising administering to said mammal, the first compound specified in Table Ia [see pg 221 of the instant specification], represented by Formula (Ia), wherein
Y1 is C(O);
Y2 is S(O)2;
X1 is CR1; X2 is CR2; X3 is CR3; X4 is CR4, wherein each of R1, R3, R4, R5 and R6 is H; R2 is CN; and ring A is C6-aryl, substituted with 2 halo substituents (i.e., claims 1-2, 62/(1-2) and 63/(1-2)).

Group II+: Claims 3-5, 10-15, 18-30, 33-46 and 49-61, directed to a compound represented by Formula (Ib), (Ie), (If), (Ig), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIIc), (IIId), (IIIe), (IIIf), (IIIg-2), (IIIh), (IIIi), (IVb), (IVc), (IVd), (IVe), (IVf) or (IVg), and selected from the various structures specified in Table Id, Ie, If, Ig, Ih, Table 2c, 2c-2, 2d, 2d-2, 2e, 2f, 2h and those specified in claim 39, Table 12, 8, 9, 10, 11, 15, Table 4b, 4b-2, 4c, 4c-2, 4d, 4e, 4f, 4f-2, 4g, or Table 17, or a pharmaceutically acceptable salt thereof.
The compound will be searched to the extent that the compound encompasses the first species of claim 3, represented by Formula (Ib), wherein:
X1 s N; X2 is CR2; X3 is CR3; X4 is CR4, such that at least one of X1-X4 is N;
each of R2, R3, R4, R5 and R6 is H; and R7 and R8 are each H.
It is believed that claim 3 reads on this first named invention of Group II+, and this claim will therefore be searched upon payment of an additional fee, to the extent that it encompasses the compound described above.
Applicant is invited to elect additional compound(s), wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention of Group II+, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention of Group II+ to be searched.
Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election for Group II+ would be a compound having the first structure specified in Table Id [see pg 235 of the instant specification for structure], represented by Formula (Ib), wherein
X1 is CR1; X2 is CR2; X3 is CR3; X4 is N;
each of R1, R2, R3, R5 and R6 is H; and R7 and R8 are each halo (i.e., claims 3 and 4).

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

Special Technical Features:

Group I+ includes the technical feature of a unique method of treatment, which is not required by any other invention of Group I+, or by Group II+.

Group II+ includes the technical feature of a unique compound, not required by any other invention of Group II+.

---Continued on next sheet--

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/61670

Continuation of previous sheet:

Common technical features:

The inventions of Groups I+ share the technical features of a method for inhibiting NF-kB activity within a cell within a mammal, and a method of treating a mammal having a disease, disorder, or condition responsive to inhibiting NF-kB activity within a cell, wherein said method comprises administering, to said mammal, an effective amount of a heterobicyclic compound.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 2014/0073668 A1 to the trustees of Columbia University in the city of New York (hereinafter Columbia), which discloses a method for inhibiting NF-kB activity within a cell within a mammal (claim 1; claim 3), and a method of treating a mammal having a disease, disorder, or condition responsive to inhibiting NF-kB activity within a cell (claim 5), wherein said method comprises administering, to said mammal, an effective amount of a heterobicyclic compound (claims 1 and 5, compound 47; Fig 8L, compound 47).

The inventions of Groups I+ further share the technical features of a method for inhibiting NF-kB activity within a cell within a mammal, and a method of treating a mammal having a disease, disorder, or condition responsive to inhibiting NF-kB activity within a cell, wherein said method comprises administering, to said mammal, an effective amount of a compound represented by Formula (Ia), (Ic), (Id), (IIa), (IIIa), or (IVa), wherein said compound is selected from any one of the compounds specified in Table Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Table 2a, 2c-2, 2d, 2d-2, 2c, 2e, Table 3a, 3b, 3b-2, Table 10, 11, 16 or Table 4a.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by US 7,557,213 B2 to Melikian et al. (hereinafter Melikian), which discloses a method of treating a mammal having a disease, disorder, or condition responsive to inhibiting NF-kB activity within a cell (col 34, ln 9-22, Treating inflammation), wherein said method comprises administering, to said mammal, an effective amount of a compound (col 3, ln 14-43) represented by Formula (Ia), wherein
Y1 is C(O);
Y2 is C(O);
X1 is CR1; X2 is CR2; X3 is CR3; X4 is CR4;
each of R1, R2, R3, R4, and R6 is H;
R5 is C1-alkyl substituted with R8, where R8 is Cy1, which is C6-aryl, substituted with one Rcy1, wherein Rcy1 is halo; and wherein ring A is C6-aryl, substituted with 2-substituents selected from RA, wherein each RA is C1-alkyl (col 208, Table 4, compound No.4).
Since the compound administered in the method of Melikian fits the description of Formula (Ia) of claim 1, said compound is inherently capable of inhibiting NF-kB activity within a cell within a mammal, upon administration.

As said methods were known in the art at the time of the invention, these cannot be considered special technical features, that would otherwise unify the inventions of Groups I+.

The inventions of Groups II+ share the technical features of a compound represented by Formula (Ib), (Ie), (If), (Ig), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIIc), (IIId), (IIIe), (IIIf), (IIIg-2), (IIIh), (IIIi), (IVb), (IVc), (IVd), (IVe), (Ivf) or (IVg), and selected from the various structures specified in Table Id, Ie, If, Ig, Ih, Table 2c, 2c-2, 2d, 2d-2, 2e, 2f, 2h and those specified in claim 39, Table 12, 8, 9, 10, 11, 15, Table 4b, 4b-2, 4c, 4c-2, 4d, 4e, 4f, 4f-2, 4g, or Table 17, or a pharmaceutically acceptable salt thereof.

Groups I+ and II+ also share the technical feature of a compound selected from the various structures specified in Table Id, Ie, If, Ig, Ih, Table 2c, 2c-2, 2d, 2d-2, 2e, 2f, 2h and those specified in claim 39, Table 12, 8, 9, 10, 11, 15, Table 4b, 4b-2, 4c, 4c-2, 4d, 4e, 4f, 4f-2, 4g, or Table 17, or a pharmaceutically acceptable salt thereof.

This shared technical feature, however, does not provide a contribution over the prior art, as being anticipated by US 2017/0174704 A1 to Millennium Pharmaceuticals, Inc. (hereinafter Millennium), which discloses the first compound specified in Table 4b [see pg 416 of the instant specification for structure] (para [0407]).
As said compound was known in the art at the time of the invention, these cannot be considered special technical features, that would otherwise unify the inventions of Group II+ or those of Groups I+ and II+.

The inventions of Group I+ and II+, thus lack unity under PCT Rule 13.