BENZOPYRAN AND BENZOXEPIN PI3K INHIBITOR COMPOUNDS AND METHODS OF USE

[0001] CROSS REFERENCE TO RELATED APPLICATIONS

[0002] This application claims the benefit of U.S. Provisional Application Serial No. 61/040,827 filed on 31 March 2008 and U.S. Provisional Application Serial No. 61/102,220 filed on 2 October 2008, each of which are incorporated by reference in entirety.

[0003] FIELD OF THE INVENTION

[0004] The invention relates generally to compounds with anti-cancer activity and more specifically to compounds which inhibit PI3 kinase activity. The invention also relates to methods of using the compounds for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, or associated pathological conditions.

[0005] BACKGROUND OF THE INVENTION

[0006] Phosphatidylinositol (hereinafter abbreviated as "PI") is one of a number of phospholipids found in cell membranes. In recent years it has become clear that PI plays an important role in intracellular signal transduction. Cell signaling via 3'-phosphorylated phosphoinositides has been implicated in a variety of cellular processes, e.g., malignant transformation, growth factor signaling, inflammation, and immunity (Rameh et al (1999) J. Biol Chem, 274:8347-8350). The enzyme responsible for generating these phosphorylated signaling products, phosphatidylinositol 3-kinase (also referred to as PI 3-kinase or PI3K), was originally identified as an activity associated with viral oncoproteins and growth factor receptor tyrosine kinases that phosphorylate phosphatidylinositol (PI) and its phosphorylated derivatives at the 3'-hydroxyl of the inositol ring (Panayotou et al (1992) Trends Cell Biol 2:358-60).

[0007] Phosphoinositide 3-kinases (PI3K) are lipid kinases that phosphorylate lipids at the 3-hydroxyl residue of an inositol ring (Whitman et al (1988) Nature, 332:664). The 3-phosphorylated phospholipids (PIP3s) generated by PI3-kinases act as second messengers recruiting kinases with lipid binding domains (including plekstrin homology (PH) regions), such as Akt and phosphoinositide-dependent kinase-1 (PDK1). Binding of Akt to membrane PIP3s causes the translocation of Akt to the plasma membrane, bringing Akt into contact with PDK1, which is responsible for activating Akt. The tumor-suppressor phosphatase, PTEN, dephosphorylates PIP3 and therefore acts as a negative regulator of Akt activation. The PI3-kinases Akt and PDK1 are important in the regulation of many cellular processes including cell

cycle regulation, proliferation, survival, apoptosis and motility and are significant components of the molecular mechanisms of diseases such as cancer, diabetes and immune inflammation (Vivanco et al (2002) Nature Rev. Cancer 2:489; Phillips et al (1998) Cancer 83:41).

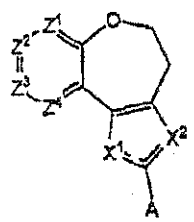
[0008] The main PI3-kinase isoform in cancer is the Class I PI3-kinase, p110 α (alpha) (US 5824492; US 5846824; US 6274327). Other isoforms are implicated in cardiovascular and immune-inflammatory disease (Workman P (2004) Biochem Soc Trans 32:393-396; Patel et al (2004) Proceedings of the American Association of Cancer Research (Abstract LB-247) 95th Annual Meeting, March 27-31, Orlando, Florida, USA; Ahmadi K and Waterfield MD (2004) Encyclopedia of Biological Chemistry (Lennarz W J, Lane M D eds) Elsevier/Academic Press).

[0009] The PI3 kinase/Akt/PTEN pathway is an attractive target for cancer drug development since such agents would be expected to inhibit proliferation, reverse the repression of apoptosis and surmount resistance to cytotoxic agents in cancer cells. PI3 kinase inhibitors have been reported (Yaguchi et al (2006) Jour. of the Nat. Cancer Inst. 98(8):545-556; US 7173029; US 7037915; US 6608056; US 6608053; US 6838457; US 6770641; US 6653320; US 6403588; US 6703414; WO 97/15658; WO 2006/046031; WO 2006/046035; WO 2006/046040; WO 2007/042806; WO 2007/042810; WO 2004/017950; US 2004/092561; WO 2004/007491; WO 2004/006916; WO 2003/037886; US 2003/149074; WO 2003/035618; WO 2003/034997; US 2003/158212; EP 1417976; US 2004/053946; JP 2001247477; JP 08175990; JP 08176070). including p110 alpha binding activity (US 2008/0207611; US 2008/0039459; US 2008/0076768; WO 2008/073785; WO 2008/070740).

[0010] SUMMARY OF THE INVENTION

[0011] Described herein are benoxepin compounds of Formula I with anti-cancer activity, and more specifically with PI3 kinase inhibitory activity. Certain hyperproliferative disorders are characterized by the modulation of PI3 kinase function, for example by mutations or overexpression of the proteins. Accordingly, the compounds described herein may be useful in the treatment of hyperproliferative disorder such as cancer. The compounds may inhibit tumor growth in mammals and may be useful for treating human cancer patients.

[0011a] In a first aspect the present invention refers to a compound selected from Formula I:



and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

Z^1 is CR^1 or N;

Z^2 is CR^2 or N;

Z^3 is CR^3 or N;

Z^4 is CR^4 or N;

where (i) X^1 is N and X^2 is S, (ii) X^1 is S and X^2 is N, (iii) X^1 is CR^7 and X^2 is S, or (iv) X^1 is S and X^2 is CR^7;

R^1, R^2, R^3, R^4, and R^7 are independently selected from H, F, Cl, Br, I, –CN, $–CF_3$, $–CH_2OR^{10}$, $–CH_2R^{10}$, $–(C_1–C_{12}$ alkylene)$NR^{10}R^{11}$, $–(C_1–C_{12}$ alkylene)$NR^{12}C(=O)R^{10}$, $–(C_1–C_{12}$ alkylene)$C(=O)OR^{10}$, $–(C_1–C_{12}$ alkylene)OR^{10}, $–CO_2R^{10}$, $–C(=O)N(R^{10})OR^{11}$, $–NO_2$, $–NR^{10}R^{11}$, $–OR^{10}$, $–S(O)_2R^{10}$, $–C(=O)NR^{10}R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene)$NR^{10}R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene)$NR^{10}C(=O)OR^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene)$NR^{10}C(=O)R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene)R^{10}, $–C(=NR^{10})NR^{10}R^{11}$, $–NR^{12}C(=O)R^{10}$, $–NR^{12}C(=O)OR^{11}$, $–NR^{12}C(=O)NR^{10}R^{11}$, $–NR^{12}C(=O)$ ($C_1–C_{12}$ alkylene)$NR^{10}R^{11}$, $–NR^{12}(C_1–C_{12}$ alkylene)$NR^{10}R^{11}$, $–NR^{12}(C_1–C_{12}$ alkylene)OR^{10}, $-NR^{12}(C_1–C_{12}$ alkylene)$C(=O)NR^{10}R^{11}$, $–C{\equiv}CR^{10}$, $–CH{=}CHR^{10}$, $C_2–C_{20}$ heterocyclyl, $C_1–C_{20}$ heteroaryl, and phenyl, where heterocyclyl, heteroaryl, phenyl and alkylene are optionally substituted with one or more groups selected from F, Cl, Br, I, $–CH_2OH$, $–(CH_2)_2OH$, $–CH_2CO_2H$, –CN, $–CH_2NH_2$, $–(CH_2)_2N(CH_3)_2$, $–CH_3$, $–C(=O)CH_3$, $–C(=O)NHCH_3$, $–CO_2H$, $–CH_2CO_2CH_3$, $–NH_2$, $–OCH_3$, $–S(O)_2CH_3$, 4-methylpiperazin-1-yl, and 4-morpholinyl;

A is selected from $–C(=O)NR^5R^6$, $C_2–C_{20}$ heterocyclyl and $C_1–C_{20}$ heteroaryl wherein $C_2–C_{20}$ heterocyclyl and $C_1–C_{20}$ heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $–CH_2OH$, $–CH_2CO_2H$, $–CH(CH_3)CH_2OCH_3$, –CN, $C_1–C_{12}$ alkyl, $–(C_1–C_{12}$ alkylene)$NR^{10}R^{11}$, $–(C_1–C_{12}$ alkylene)OR^{10}, $–CH_3$, $–C(=O)CH_3$, $–C(=O)NHCH_3$, $–C(=O)N(CH_3)_2$, $–CO_2H$, $–CO_2CH_3$, $–CH_2CO_2CH_3$, $–NH_2$, $–NHC(=O)CH_3$, $–OCH_3$, $–S(O)_2CH_3$, 1-methylpiperid-4-yl, 4-methylpiperazin-1-yl, 4-morpholinyl, isopropyl, isobutyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, triazolylmethyl, benzyl, and phenyl, where alkyl, alkylene, benzyl and phenyl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $–CF_3$, $–CH_2OH$, $–CH_2CO_2H$, –CN, $–CH_2NH_2$, $–CH_3$, $–C(=O)CH_3$, $–C(=O)NHCH_3$, $–CO_2H$, $–CH_2CO_2CH_3$, $–NH_2$, –OH, $–OCH_3$, $–S(O)_2CH_3$, 1-methylpiperid-4-yl, (4-methylpiperazin-1-yl)carboxamide, $-CH_2$(1H-1,2,4-triazol-5-yl), 4-methylpiperazin-1-yl, and 4-morpholinyl;

R^5 is selected from $C_1–C_{12}$ alkyl optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, $–CO_2H$, $–CONH_2$, $–CONHCH_3$, $–NH_2$, $–NO_2$, $–N(CH_3)_2$, $–NHCOCH_3$, $–NHS(O)_2CH_3$, –OH, $–OCH_3$, $–OCH_2CH_3$, $–S(O)_2NH_2$, and $–S(O)_2CH_3$;

R^6 is selected from C_1–C_{12} alkyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, and C_6–C_{20} aryl, each optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-C(=O)NR^{10}R^{11}$, $-NH_2$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2CH_3$, $-C(=O)NR^{10}(C_1$–C_{12} alkylene$)NR^{10}R^{11}$, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, $-C{\equiv}CR^{13}$, $-CH{=}CHR^{13}$, and $-C(=O)NR^{10}R^{11}$;

or R^5 and R^6 together with the nitrogen atom to which they are attached form morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl or S-dioxothiomorpholin-4-yl, each optionally substituted with one or more groups selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, and $-S(O)_2CH_3$;

R^{10}, R^{11} and R^{12} are independently selected from H, C_1–C_{12} alkyl, C_1–C_{12} alkylene-C_2–C_{20} heterocyclyl, C_1–C_{12} alkylene-C_6–C_{20} aryl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl, where C_1–C_{12} alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, 2-oxopyrrolidin-1-yl, $-S(O)_2NH_2$, and $-S(O)_2CH_3$;

or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a C_2–C_{20} heterocyclyl ring or C_1–C_{20} heteroaryl each optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, oxo, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, and $-S(O)_2CH_3$; and

R^{13} is selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CN$, $-CF_3$, $-CH_2N(CH_3)_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CON(CH_3)_2$, $-NO_2$, and $-S(O)_2CH_3$.

[0011b] In a second aspect the present invention refers to a the compound (4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2~yl)(3,4-dihydroquinolin-1(2H)-yl)methanone or a stereoisomer, geometric isomer, tautomer, or pharmaceutically acceptable salt thereof.

[0011c] In a three aspect the present invention refers to the compound 2-(1-(2-(trifiuoromethyl)"1H-benzo[d]imidazole—5-yl)-1H-1,2,4-1xiazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide or a stereoisomer, geometric isomer, tautomer, or pharmaceutically acceptable salt thereof.

[0011d] In a fourth aspect the present invention refers to a pharmaceutical composition comprised of a compound of the present invention and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

[0011e] In a fifth aspect the present invention refers to the use of a compound of the present invention for the manufacture of a medicament for treating cancer in a mammal comprised of administering to said mammal a therapeutically effective amount of the compound, wherein the cancer is breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, kerato acanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, pancreatic, myeloid disorders, lymphoma, hairy cells, buccal cavity, naso-pharyngeal, pharynx, lip, tongue, mouth, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's or leukemia.

[0011f] In a sixth aspect the present invention refers to a process for making a pharmaceutical composition which comprises combining of the present invention with a pharmaceutically acceptable carrier.

[0011g] In a seventh aspect the present invention refers to the use of a compound according to the present invention in the manufacture of a medicament for the prophylactic or therapeutic treatment of cancer.

[0011h] In a eighth aspect the present invention refers to an *in vitro* method for inhibiting or modulating lipid kinase activity, comprising contacting the lipid kinase with an effective inhibitory amount of a compound of the present invention.

[0011i] In a ninth aspect of the present invention refers to the use of a compound of the present invention for the manufacture of a medicament for inhibiting or modulating lipid kinase activity in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound.

[0011j] In a tenth aspect of the present invention refers to the use of a compound of the present invention for the manufacture of a medicament for use in therapy.

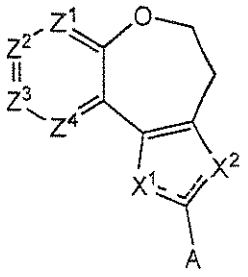
[0011k] In a eleventh aspect of the present invention refers to a kit for treating a PI3K-mediated condition, comprising:

a) a first pharmaceutical composition comprising of the present invention; and

b) instructions for use

[0012] Also described herein are methods of using the benzoxepin compounds of Formula I for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, organisms, or associated pathological conditions.

[0013] Formula I compounds include:



I

[0014] and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof. The various substituents are as defined herein.

[0015] Also described herein is a pharmaceutical composition comprising a benzoxepin compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical composition may further comprise one or more additional therapeutic agent.

[0016] Also described herein are methods of inhibiting PI3 kinase activity, comprising contacting a PI3 kinase with an effective inhibitory amount of a compound of Formula I.

[0017] Also described herein are methods of preventing or treating a hyperproliferative disease or disorder modulated by PI3 kinases, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I. Examples of such hyperproliferative disease or disorder include, but are not limited to, cancer.

[0018] Also described herein are methods of preventing or treating a hyperproliferative disorder, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, alone or in combination with one or more additional compounds having anti-hyperproliferative properties.

[0019] Also describe herein are a method of using a compound of this invention to treat a hyperproliferative disease or condition modulated by PI3 kinase in a mammal.

[0020] An additional aspect example is the use of a compound of this invention for treating cancer modulated by PI3 kinase in a mammal.

[0021] Another example describes kits comprising a compound of Formula I, a container, and optionally a package insert or label indicating a treatment.

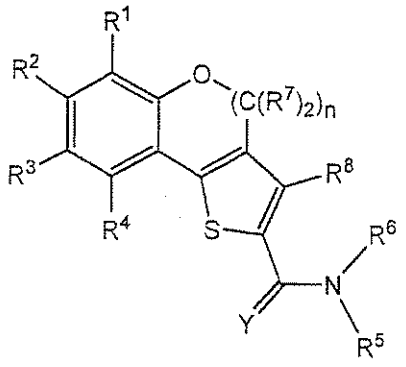
[0022] Another example includes methods of preparing, method of separating, and methods of purifying compounds of Formula I.

[0023] Another example includes novel intermediates useful for preparing Formula I compounds.

[0024] Also described herein are method of using the benzopyran and benzoxepin compounds of Formula II for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian

cells, organisms, or associated pathological conditions.

[0025] Formula II compounds include:



II

[0026] and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof. The various substituents are as defined herein.

[0027] Another example describes a pharmaceutical composition comprising a benzoxepin compound of Formula II and a pharmaceutically acceptable carrier. The pharmaceutical composition may further comprise one or more additional therapeutic agent.

[0028] Also described herein are methods of inhibiting PI3 kinase activity, comprising contacting a PI3 kinase with an effective inhibitory amount of a compound of Formula II.

[0029] Another example describes provides methods of preventing or treating a hyperproliferative disease or disorder modulated by PI3 kinases, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula II. Examples of such hyperproliferative disease or disorder include, but are not limited to, cancer.

[0030] Another example describes methods of preventing or treating a hyperproliferative disorder, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula II, alone or in combination with one or more additional compounds having anti-hyperproliferative properties.

[0031] Another example includes methods of preparing, methods of separating, and methods of purifying compounds of Formula II.

[0032] Another example includes novel intermediates useful for preparing Formula II compounds.

[0033] Additional advantages and novel features of this invention shall be set forth in part in the description that follows, and in part will become apparent to those skilled in the art upon examination of the following specification or may be learned by the practice of the invention. The advantages of the invention may be realized and attained by means of the instrumentalities, combinations, compositions, and methods particularly pointed out in the appended claims.

[0034] BRIEF DESCRIPTION OF THE DRAWINGS

[0035] Figure 1 shows a general exemplary route to 10-pyridooxepin compounds

[0036] Figure 2 shows an exemplary synthetic route to 9-pyridooxepin compounds **315** and **316**.

[0037] Figure 3 shows the mean tumor volume change over time with Taconic nude mice with MDA-MB-361.1 breast tumor cell xenografts dosed daily for 21 days with: MCT Vehicle (0.5% methycellulose/0.2% Tween 80); 50 mg/kg Compound **223**; and 100 mg/kg Compound **223**.

[0038] Figure 4 shows the mean tumor volume change over time with Taconic nude mice with MDA-MB-361.1 breast tumor cell xenografts dosed daily for 21 days with: MCT Vehicle (0.5% methycellulose/0.2% Tween 80); 25 mg/kg Compound **328**; 50 mg/kg Compound **328**; and 100 mg/kg Compound **328**.

[0039] Figure 5 shows the mean tumor volume change over time with Taconic nude mice with MDA-MB-361.1 breast tumor cell xenografts dosed daily for 21 days with: MCT Vehicle (0.5% methycellulose/0.2% Tween 80); 12.5 mg/kg Compound **345**; 25 mg/kg Compound **345**; and 50 mg/kg Compound **345**.

[0040] DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0041] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

[0042] DEFINITIONS

[0043] The term "alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms (C_1–C_{12}), wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkyl radical is one to eight carbon atoms (C_1–C_8), or one to

six carbon atoms (C_1–C_6). Examples of alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, 1-heptyl, 1-octyl, and the like.

[0044] The term "alkylene" as used herein refers to a saturated linear or branched-chain divalent hydrocarbon radical of one to twelve carbon atoms (C_1–C_{12}), wherein the alkylene radical may be optionally substituted independently with one or more substituents described below. In another embodiment, an alkylene radical is one to eight carbon atoms (C_1–C_8), or one to six carbon atoms (C_1–C_6). Examples of alkylene groups include, but are not limited to, methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), and the like.

[0045] The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include, but are not limited to, ethylenyl or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), and the like.

[0046] The term "alkenylene" refers to linear or branched-chain divalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp^2 double bond, wherein the alkenyl radical may be optionally substituted, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include, but are not limited to, ethylenylene or vinylene (-CH=CH-), allyl ($-CH_2CH=CH-$), and the like.

[0047] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally substituted independently with one

or more substituents described herein. Examples include, but are not limited to, ethynyl (-C≡CH), propynyl (propargyl, -CH_2C≡CH), and the like.

[0048] The term "alkynylene" refers to a linear or branched divalent hydrocarbon radical of two to eight carbon atoms (C_2–C_8) with at least one site of unsaturation, i.e., a carbon-carbon, sp triple bond, wherein the alkynyl radical may be optionally. Examples include, but are not limited to, ethynylene (-C≡C-), propynylene (propargylene, -CH_2C≡C-), and the like.

[0049] The terms "carbocycle", "carbocyclyl", "carbocyclic ring" and "cycloalkyl" refer to a monovalent non-aromatic, saturated or partially unsaturated ring having 3 to 12 carbon atoms (C_3–C_{12}) as a monocyclic ring or 7 to 12 carbon atoms as a bicyclic ring. Bicyclic carbocycles having 7 to 12 atoms can be arranged, for example, as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, and bicyclic carbocycles having 9 or 10 ring atoms can be arranged as a bicyclo [5,6] or [6,6] system, or as bridged systems such as bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Examples of monocyclic carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, and the like.

[0050] "Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6–C_{20}) derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Some aryl groups are represented in the exemplary structures as "Ar". Aryl includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic ring. Typical aryl groups include, but are not limited to, radicals derived from benzene (phenyl), substituted benzenes, naphthalene, anthracene, biphenyl, indenyl, indanyl, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like. Aryl groups are optionally substituted independently with one or more substituents described herein.

[0051] "Arylene" means a divalent aromatic hydrocarbon radical of 6-20 carbon atoms (C_6–C_{20}) derived by the removal of two hydrogen atom from a two carbon atoms of a parent aromatic ring system. Some arylene groups are represented in the exemplary structures as "Ar". Arylene includes bicyclic radicals comprising an aromatic ring fused to a saturated, partially unsaturated ring, or aromatic carbocyclic ring. Typical arylene groups include, but are not limited to, radicals derived from benzene (phenylene), substituted benzenes, naphthalene, anthracene, biphenylene, indenylene, indanylene, 1,2-dihydronaphthalene, 1,2,3,4-tetrahydronaphthyl, and the like. Arylene groups are optionally substituted

[0052] The terms "heterocycle," "heterocyclyl" and "heterocyclic ring" are used interchangeably herein and refer to a saturated or a partially unsaturated (i.e., having one or

more double and/or triple bonds within the ring) carbocyclic radical of 3 to about 20 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen, phosphorus and sulfur, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents described below. A heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 4 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, P, and S), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system. Heterocycles are described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. "Heterocyclyl" also includes radicals where heterocycle radicals are fused with a saturated, partially unsaturated ring, or aromatic carbocyclic or heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinylimidazolinyl, imidazolidinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 3H-indolyl quinolizinyl and N-pyridyl ureas. Spiro moieties are also included within the scope of this definition. Examples of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo (=O) moieties are pyrimidinonyl and 1,1-dioxo-thiomorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein.

[0053] The term "heteroaryl" refers to a monovalent aromatic radical of 5-, 6-, or 7-membered rings, and includes fused ring systems (at least one of which is aromatic) of 5-20 atoms, containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups are pyridinyl (including, for example, 2-hydroxypyridinyl), imidazolyl, imidazopyridinyl, pyrimidinyl (including, for example, 4-hydroxypyrimidinyl), pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxadiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl,

benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Heteroaryl groups are optionally substituted independently with one or more substituents described herein.

[0054] The heterocycle or heteroaryl groups may be carbon (carbon-linked), or nitrogen (nitrogen-linked) bonded where such is possible. By way of example and not limitation, carbon bonded heterocycles or heteroaryls are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline.

[0055] By way of example and not limitation, nitrogen bonded heterocycles or heteroaryls are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline.

[0056] The terms "treat" and "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the development or spread of cancer. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[0057] The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into

peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can be measured, for example, by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

[0058] The terms "cancer" refers to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. A "tumor" comprises one or more cancerous cells. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (*e.g.*, epithelial squamous cell cancer), lung cancer including small- cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, as well as head and neck cancer.

[0059] A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer, regardless of mechanism of action. Classes of chemotherapeutic agents include, but are not limited to: alkyating agents, antimetabolites, spindle poison plant alkaloids, cytoxic/antitumor antibiotics, topoisomerase inhibitors, antibodies, photosensitizers, and kinase inhibitors. Chemotherapeutic agents include compounds used in "targeted therapy" and conventional chemotherapy. Examples of chemotherapeutic agents include: erlotinib (TARCEVA®, Genentech/OSI Pharm.), docetaxel (TAXOTERE®, Sanofi-Aventis), 5-FU (fluorouracil, 5-fluorouracil, CAS No. 51-21-8), gemcitabine (GEMZAR®, Lilly), PD-0325901 (CAS No. 391210-10-9, Pfizer), cisplatin (cis-diamine,dichloroplatinum(II), CAS No. 15663-27-1), carboplatin (CAS No. 41575-94-4), paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.), trastuzumab (HERCEPTIN®, Genentech), temozolomide (4-methyl-5-oxo- 2,3,4,6,8-pentazabicyclo [4.3.0] nona-2,7,9-triene- 9-carboxamide, CAS No. 85622-93-1, TEMODAR®, TEMODAL®, Schering Plough), tamoxifen ((*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethylethanamine, NOLVADEX®, ISTUBAL®, VALODEX®), and doxorubicin (ADRIAMYCIN®), Akti-1/2, HPPD, and rapamycin.

[0060] More examples of chemotherapeutic agents include: oxaliplatin (ELOXATIN®, Sanofi), bortezomib (VELCADE®, Millennium Pharm.), sutent (SUNITINIB®, SU11248,

Pfizer), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®, Novartis), XL-518 (Mek inhibitor, Exelixis, WO 2007/044515), ARRY-886 (Mek inhibitor, AZD6244, Array BioPharma, Astra Zeneca), SF-1126 (PI3K inhibitor, Semafore Pharmaceuticals), BEZ-235 (PI3K inhibitor, Novartis), XL-147 (PI3K inhibitor, Exelixis), PTK787/ZK 222584 (Novartis), fulvestrant (FASLODEX®, AstraZeneca), leucovorin (folinic acid), rapamycin (sirolimus, RAPAMUNE®, Wyeth), lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), lonafarnib (SARASAR™, SCH 66336, Schering Plough), sorafenib (NEXAVAR®, BAY43-9006, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), irinotecan (CAMPTOSAR®, CPT-11, Pfizer), tipifarnib (ZARNESTRA™, Johnson & Johnson), ABRAXANE™ (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Il), vandetanib (rINN, ZD6474, ZACTIMA®, AstraZeneca), chloranmbucil, AG1478, AG1571 (SU 5271; Sugen), temsirolimus (TORISEL®, Wyeth), pazopanib (GlaxoSmithKline), canfosfamide (TELCYTA®, Telik), thiotepa and cyclosphosphamide (CYTOXAN®, NEOSAR®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, calicheamicin gamma1I, calicheamicin omegaI1 (Angew Chem. Intl. Ed. Engl. (1994) 33:183-186); dynemicin, dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, nemorubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin,

streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine (NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®, Roche); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0061] Also included in the definition of "chemotherapeutic agent" are: (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors such as MEK inhibitors (WO 2007/044515); (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant

cell proliferation, for example, PKC-alpha, Raf and H-Ras, such as oblimersen (GENASENSE®, Genta Inc.); (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN® rIL-2; topoisomerase 1 inhibitors such as LURTOTECAN®; ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[0062] Also included in the definition of "chemotherapeutic agent" are therapeutic antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG™, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixia), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG®, Wyeth).

[0063] Humanized monoclonal antibodies with therapeutic potential as chemotherapeutic agents in combination with the PI3K inhibitors of the invention include: alemtuzumab, apolizumab, aselizumab, atlizumab, bapineuzumab, bevacizumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pertuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, trastuzumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, and visilizumab.

[0064] A "metabolite" is a product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds of the invention, including compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

[0065] The term "package insert" is used to refer to instructions customarily included in

commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

[0066] The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0067] The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0068] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

[0069] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0070] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S*, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[0071] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

[0072] The phrase "pharmaceutically acceptable salt" as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the invention. Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate "mesylate", ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis(2-hydroxy-3-naphthoate)) salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion.

[0073] If the compound of the invention is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, methanesulfonic acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, trifluoroacetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

[0074] If the compound of the invention is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include, but are not limited to, organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as

piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

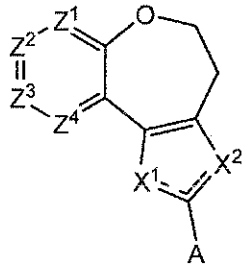
[0075] The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0076] A "solvate" refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethylacetate, acetic acid, and ethanolamine.

[0077] The terms "compound of this invention," and "compounds of the present invention" and "compounds of Formula I" include compounds of Formulas I and stereoisomers, geometric isomers, tautomers, solvates, metabolites, and pharmaceutically acceptable salts and prodrugs thereof

[0078] BENZOXEPIN COMPOUNDS

[0079] The present invention provides benzoxepin compounds, and pharmaceutical formulations thereof, which are potentially useful in the treatment of diseases, conditions and/or disorders modulated by PI3 kinases. More specifically, the present invention provides compounds of Formula I



I

[0080] and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

[0081] Z^1 is CR^1 or N;

[0082] Z^2 is CR^2 or N;

[0083] Z^3 is CR^3 or N;

[0084] Z^4 is CR^4 or N;

[0085] where (i) X^1 is N and X^2 is S, (ii) X^1 is S and X^2 is N, (iii) X^1 is CR^7 and X^2 is S, or (iv) X^1 is S and X^2 is CR^7;

[0086] R^1, R^2, R^3, R^4, and R^7 are independently selected from H, F, Cl, Br, I, –CN, –CF_3, –CH_2OR^{10}, –CH_2R^{10}, –(C_1–C_{12} alkylene)$NR^{10}R^{11}$, –(C_1–C_{12} alkylene)$NR^{12}C(=O)R^{10}$, –(C_1–C_{12} alkylene)$C(=O)OR^{10}$, –(C_1–C_{12} alkylene)OR^{10}, –CO_2R^{10}, –$C(=O)N(R^{10})OR^{11}$, –NO_2,

$-NR^{10}R^{11}$, $-OR^{10}$, $-S(O)_2R^{10}$, $-C(=O)NR^{10}R^{11}$, $-C(=O)NR^{10}(C_1-C_{12}$ alkylene)$NR^{10}R^{11}$, $-C(=O)NR^{10}(C_1-C_{12}$ alkylene)$NR^{10}C(=O)OR^{11}$, $-C(=O)NR^{10}(C_1-C_{12}$ alkylene)$NR^{10}C(=O)R^{11}$, $-C(=O)NR^{10}(C_1-C_{12}$ alkylene)R^{10}, $-C(=NR^{10})NR^{10}R^{11}$, $-NR^{12}C(=O)R^{10}$, $-NR^{12}C(=O)OR^{11}$, $-NR^{12}C(=O)NR^{10}R^{11}$, $-NR^{12}C(=O)$ (C_1-C_{12} alkylene)$NR^{10}R^{11}$, $-NR^{12}(C_1-C_{12}$ alkylene)$NR^{10}R^{11}$, $-NR^{12}(C_1-C_{12}$ alkylene)OR^{10}, $-NR^{12}(C_1-C_{12}$ alkylene)$C(=O)NR^{10}R^{11}$, $-C\equiv CR^{10}$, $-CH=CHR^{10}$, C_2-C_{20} heterocyclyl, C_1-C_{20} heteroaryl, and phenyl, where heterocyclyl, heteroaryl, phenyl and alkylene are optionally substituted with one or more groups selected from F, Cl, Br, I, $-CH_2OH$, $-(CH_2)_2OH$, $-CH_2CO_2H$, $-CN$, $-CH_2NH_2$, $-(CH_2)_2N(CH_3)_2$, $-CH_3$, $-C(=O)CH_3$, $-C(=O)NHCH_3$, $-CO_2H$, $-CH_2CO_2CH_3$, $-NH_2$, $-OCH_3$, $-S(O)_2CH_3$, 4-methylpiperazin-1-yl, and 4-morpholinyl;

[0087] A is selected from $-C(=O)NR^5R^6$, C_2-C_{20} heterocyclyl and C_1-C_{20} heteroaryl wherein C_2-C_{20} heterocyclyl and C_1-C_{20} heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2CO_2H$, $-CH(CH_3)CH_2OCH_3$, $-CN$, C_1-C_{12} alkyl, $-(C_1-C_{12}$ alkylene)$NR^{10}R^{11}$, $-(C_1-C_{12}$ alkylene)OR^{10}, $-CH_3$, $-C(=O)CH_3$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-CO_2H$, $-CO_2CH_3$, $-CH_2CO_2CH_3$, $-NH_2$, $-NHC(=O)CH_3$, $-OCH_3$, $-S(O)_2CH_3$, 1-methylpiperid-4-yl, 4-methylpiperazin-1-yl, 4-morpholinyl, isopropyl, isobutyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, triazolylmethyl, benzyl, and phenyl, where alkyl, alkylene, benzyl and phenyl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CF_3$, $-CH_2OH$, $-CH_2CO_2H$, $-CN$, $-CH_2NH_2$, $-CH_3$, $-C(=O)CH_3$, $-C(=O)NHCH_3$, $-CO_2H$, $-CH_2CO_2CH_3$, $-NH_2$, -OH, $-OCH_3$, $-S(O)_2CH_3$, 1-methylpiperid-4-yl, (4-methylpiperazin-1yl)carboxamide, $-CH_2$(1H-1,2,4-triazol-5-yl), 4-methylpiperazin-1-yl, and 4-morpholinyl;

[0088] R^5 is selected from H, C_1-C_{12} alkyl, optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CN$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NH_2$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, and $-S(O)_2CH_3$;

[0089] R^6 is selected from C_1-C_{12} alkyl, C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_1-C_{20} heteroaryl, and C_6-C_{20} aryl, each optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-C(=O)NR^{10}R^{11}$, $-NH_2$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2CH_3$, $-C(=O)NR^{10}(C_1-C_{12}$ alkylene)$NR^{10}R^{11}$, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, $-C\equiv CR^{13}$, $-CH=CHR^{13}$, and $-C(=O)NR^{10}R^{11}$;

[0090] or R^5 and R^6 together with the nitrogen atom to which they are attached form morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl or S-dioxothiomorpholin-4-yl, each optionally substituted with one or more groups selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, and $-S(O)_2CH_3$;

[0091] R^7 is selected from H and F;

[0092] R^{10}, R^{11} and R^{12} are independently selected from H, C_1–C_{12} alkyl, C_1–C_{12} alkylene-C_2–C_{20} heterocyclyl, C_1–C_{12} alkylene-C_6–C_{20} aryl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl, where C_1–C_{12} alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, 2-oxopyrrolidin-1-yl, $-S(O)_2NH_2$, and $-S(O)_2CH_3$;

[0093] or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a C_2–C_{20} heterocyclyl ring or C_1–C_{20} heteroaryl each optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, oxo, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, and $-S(O)_2CH_3$; and

[0094] R^{13} is selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CN$, $-CF_3$, $-CH_2N(CH_3)_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CON(CH_3)_2$, $-NO_2$, and $-S(O)_2CH_3$.

[0095] In addition, the present invention provides compounds of Formula I wherein:

[0096] R^1, R^2, R^3, and R^4 are independently selected from H, F, Cl, Br, I, $-CN$, $-CF_3$, $-CH_2OR^{10}$, $-CH_2R^{10}$,$-CH_2NR^{10}R^{11}$, $-(C_1$–C_{12} alkylene)$C(=O)OR^{10}$, $-(C_1$–C_{12} alkylene)OR^{10}, $-CO_2R^{10}$, $-C(=O)N(R^{10})OR^{11}$, $-NO_2$, $-NR^{10}R^{11}$, $-OR^{10}$, $-S(O)_2R^{10}$, $-C(=O)NR^{10}R^{11}$, $-C(=O)NR^{10}(C_1$–C_{12} alkylene)$NR^{10}R^{11}$, $-C(=O)NR^{10}(C_1$–C_{12} alkylene)$NR^{10}C(=O)OR^{11}$, $-C(=O)NR^{10}(C_1$–C_{12} alkylene)$NR^{10}C(=O)R^{11}$, $-C(=O)NR^{10}(C_1$–C_{12} alkylene)R^{10}, $-NR^{12}C(=O)R^{10}$, $-NR^{12}C(=O)OR^{11}$, $-NR^{12}C(=O)NR^{10}R^{11}$, $-NR^{12}(C_1$–C_{12} alkylene)$NR^{10}R^{11}$, $-NR^{12}(C_1$–C_{12} alkylene)OR^{10}, $-NR^{12}(C_1$–C_{12} alkylene)$C(=O)NR^{10}R^{11}$, $-C{\equiv}CR^{10}$, $-CH{=}CHR^{10}$, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, and phenyl, where heterocyclyl, heteroaryl, and phenyl are optionally substituted with one or more groups selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2CO_2H$, $-CN$, $-CH_2NH_2$, $-CH_3$, $-C(=O)CH_3$, $-C(=O)NHCH_3$, $-CO_2H$, $-CH_2CO_2CH_3$,

$-NH_2$, $-OCH_3$, $-S(O)_2CH_3$, 4-methylpiperazin-1-yl, and 4-morpholinyl, and where alkylene is optionally substituted with one or more F;

[0097] A is selected from $-C(=O)NR^5R^6$ and C_1-C_{20} heteroaryl optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2CO_2H$, $-CH(CH_3)CH_2OCH_3$, $-CN$, $-CH_2NH_2$, $-CH_3$, $-C(=O)CH_3$, $-C(=O)NHCH_3$, $-CO_2H$, $-CH_2CO_2CH_3$, $-NH_2$, $-OCH_3$, $-S(O)_2CH_3$, 1-methylpiperid-4-yl, 4-methylpiperazin-1-yl, 4-morpholinyl, isopropyl, isobutyl, benzyl, and phenyl, where benzyl and phenyl are optionally substituted with F, Cl, Br, I, $-CH_2OH$, $-CH_2CO_2H$, $-CN$, $-CH_2NH_2$, $-CH_3$, $-C(=O)CH_3$, $-C(=O)NHCH_3$, $-CO_2H$, $-CH_2CO_2CH_3$, $-NH_2$, $-OCH_3$, $-S(O)_2CH_3$, 1-methylpiperid-4-yl, 4-methylpiperazin-1-yl, and 4-morpholinyl;

[0098] R^5 is selected from C_1-C_{12} alkyl, optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CN$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NH_2$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, and $-S(O)_2CH_3$;

[0099] R^6 is selected from C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_1-C_{20} heteroaryl, and C_6-C_{20} aryl, each optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NH_2$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2CH_3$, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, $-C\equiv CR^{13}$, $-CH=CHR^{13}$, and $-C(=O)NR^{10}R^{11}$;

[00100] or R^5 and R^6 together with the nitrogen atom to which they are attached form morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, each optionally substituted with one or more groups selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, and $-S(O)_2CH_3$;

[00101] R^7 is selected from H and F;

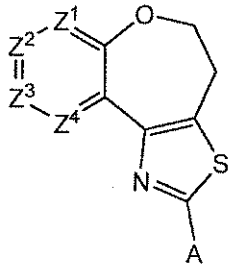
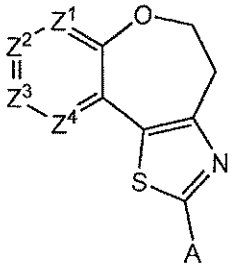
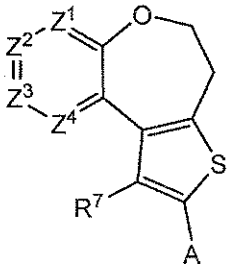
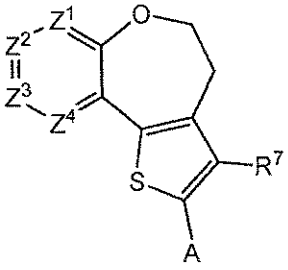
[00102] R^{10}, R^{11} and R^{12} are independently selected from H, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_6-C_{20} aryl, and C_1-C_{20} heteroaryl, where C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{12} carbocyclyl, C_2-C_{20} heterocyclyl, C_6-C_{20} aryl, and C_1-C_{20} heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$,

$-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, and $-S(O)_2CH_3$;

[00103] or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a C_2–C_{20} heterocyclyl ring, optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, and $-S(O)_2CH_3$; and

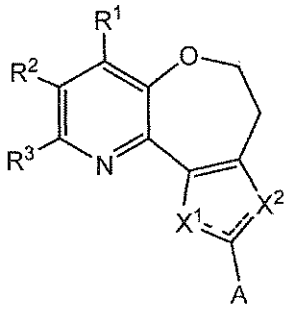
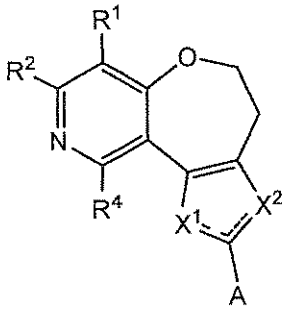
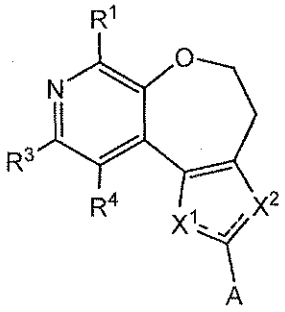
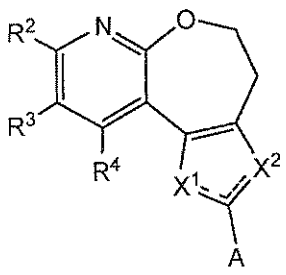
[00104] R^{13} is selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CN$, $-CF_3$, $-CH_2N(CH_3)_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CON(CH_3)_2$, $-NO_2$, and $-S(O)_2CH_3$.

[00105] Exemplary embodiments of Formula I compounds include the structures:

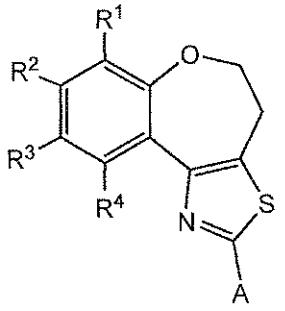
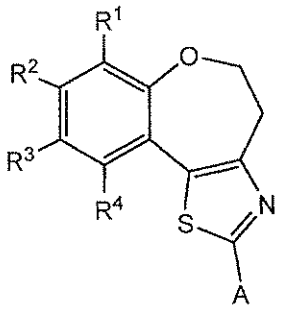
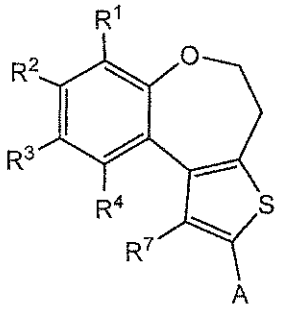
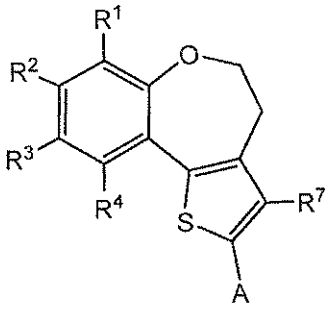





[00106] In one embodiment, each of Z^1, Z^2, Z^3, Z^4 is a substituted carbon (CR^1, CR^2, CR^3, CR^4). In another embodiment three of Z^1, Z^2, Z^3, Z^4 are substituted carbon and one of Z^1, Z^2, Z^3, Z^4 is N. Typically at least one of Z^1, Z^2, Z^3, Z^4 are substituted carbon, i.e. not all of Z^1, Z^2, Z^3, Z^4 are N.

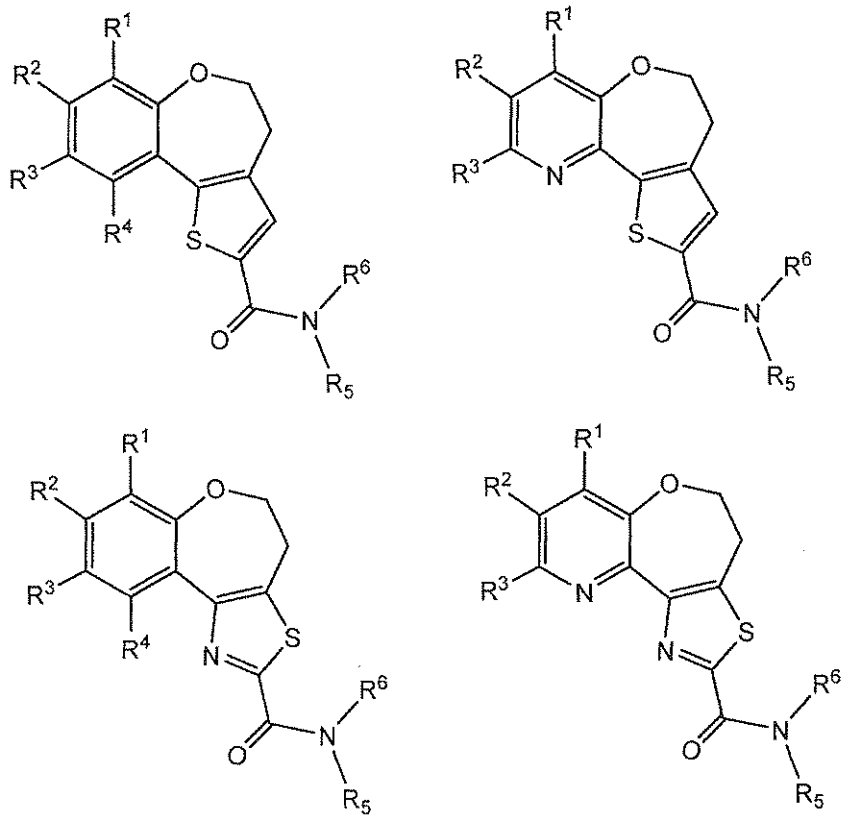
[00107] Exemplary embodiments of Formula I compounds include the structures:

[00108] Exemplary embodiments of Formula I compounds include the structures:

[00109] Exemplary embodiments of Formula I compounds include the structures:



[00110] wherein R^1, R^3, and R^4 are each H; and

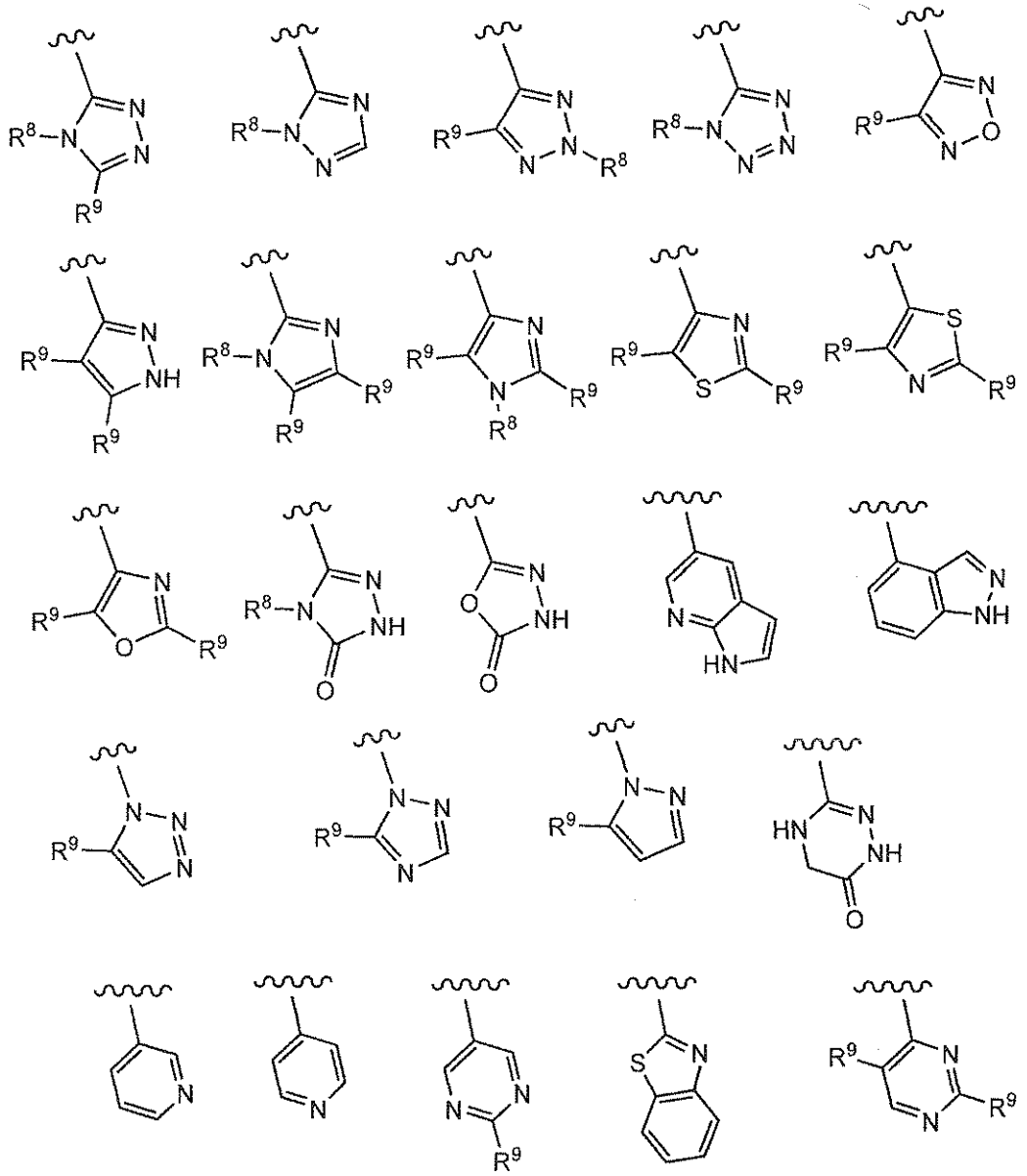
[00111] R^2 is selected from F, Cl, Br, I, –CN, $–CF_3$, $–CH_2OR^{10}$, $–CH_2R^{10}$,$–CH_2NR^{10}R^{11}$, $–(C_1–C_{12}$ alkylene$)C(=O)OR^{10}$, $–(C_1–C_{12}$ alkylene$)OR^{10}$, $–CO_2R^{10}$, $–C(=O)N(R^{10})OR^{11}$, $–NO_2$, $–NR^{10}R^{11}$, $–OR^{10}$, $–S(O)_2R^{10}$, $–C(=O)NR^{10}R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}C(=O)OR^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}C(=O)R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)R^{10}$, $–NR^{12}C(=O)R^{10}$, $–NR^{12}C(=O)OR^{11}$, $–NR^{12}C(=O)NR^{10}R^{11}$, $–NR^{12}(C_1–C_{12}$ alkylene$)NR^{10}R^{11}$, $–NR^{12}(C_1–C_{12}$ alkylene$)OR^{10}$, $-NR^{12}(C_1–C_{12}$ alkylene$)C(=O)NR^{10}R^{11}$, $-C{\equiv}CR^{10}$, $-CH=CHR^{10}$, $C_2–C_{20}$ heterocyclyl, $C_1–C_{20}$ heteroaryl, and phenyl, where heterocyclyl, heteroaryl, phenyl and alkylene are optionally substituted with one or more groups selected from F, Cl, Br, I, $–CH_2OH$, $–CH_2CO_2H$, –CN, $–CH_2NH_2$, $–CH_3$, $–C(=O)CH_3$, $–C(=O)NHCH_3$, $–CO_2H$, $–CH_2CO_2CH_3$; $–NH_2$, $–OCH_3$, $–S(O)_2CH_3$, 4-methylpiperazin-1-yl, and 4-morpholinyl.

[00112] Exemplary embodiments include wherein R^5 is CH_3.

[00113] Exemplary embodiments include wherein R^6 is phenyl substituted with one or more groups independently selected from F, Cl, Br, I, $–CH_2OH$, $–CH_2C_6H_5$, –CN, $–CF_3$, $–CO_2H$, $–CONH_2$, $–CONHCH_3$, $–NO_2$, $–N(CH_3)_2$, $–NHCOCH_3$, $–NHS(O)_2CH_3$, –OH, $–OCH_3$, $–OCH_2CH_3$, $–S(O)_2NH_2$, $–S(O)_2CH_3$, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, $-C{\equiv}CR^{13}$, and $-CH=CHR^{13}$.

[00114] Exemplary embodiments include wherein A is a C_1–C_{20} heteroaryl selected from pyridyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, thiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, oxadiazolyl, 1,3,4-oxadiazol-2(3H)-one, furanyl, thienyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,4-triazol-5(4H)-one, 4,5-dihydro-1,2,4-triazin-6(1H)-one, tetrazolyl; pyrrolo[2,3-b]pyridinyl, indazolyl, 3,4-dihydroquinolinyl, and benzo[d]thiazole.

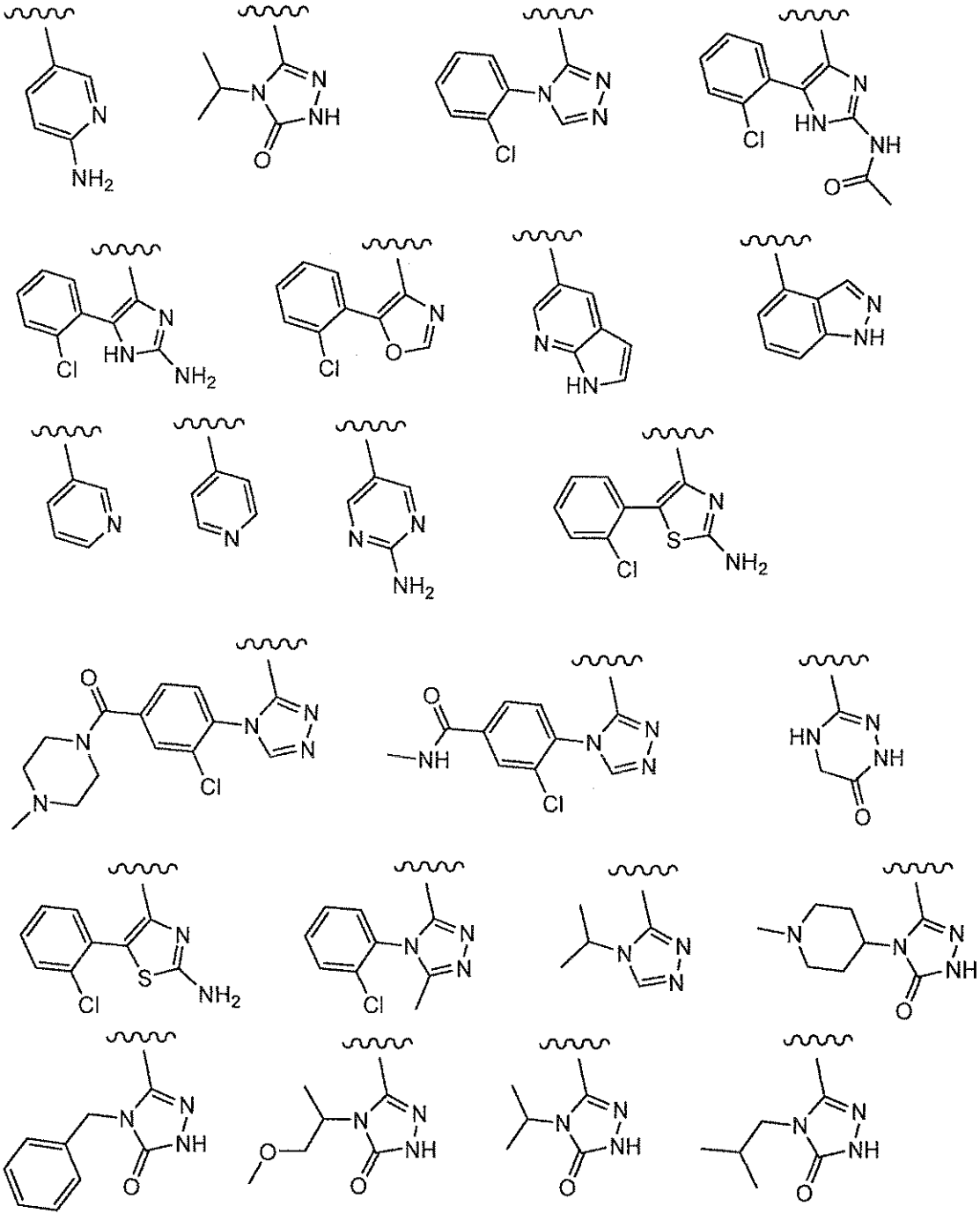
[00115] Exemplary embodiments include wherein A is selected from the heteroaryl structures:

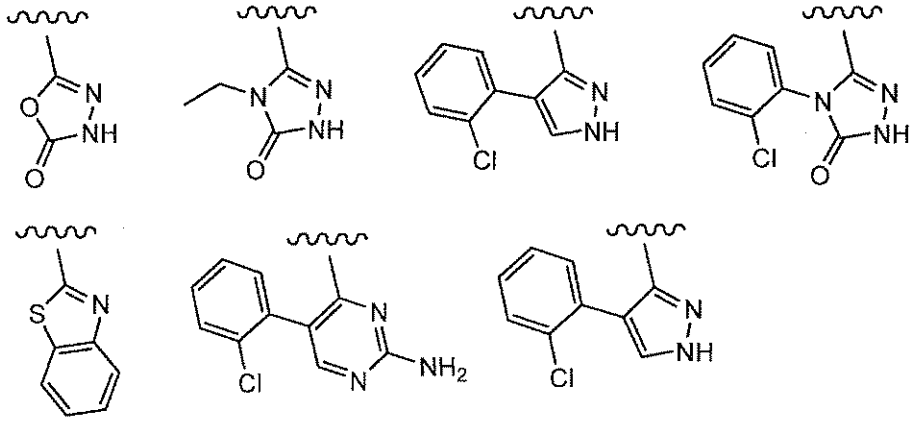


[00116] where R^8 and R^9 are independently selected from H, F, Cl, Br, I, $-CH_2OH$, $-CH_2CO_2H$, $-CH(CH_3)CH_2OCH_3$, $-CN$, $-CH_2NH_2$, $-CH_3$, $-C(=O)CH_3$, $-C(=O)NHCH_3$, $-CO_2H$, $-CH_2CO_2CH_3$, $-NH_2$, $-OCH_3$, $-S(O)_2CH_3$, 1-methylpiperid-4-yl, 4-methylpiperazin-1-yl, 4-morpholinyl, isopropyl, isobutyl, benzyl, and phenyl, where benzyl and phenyl are

optionally substituted with one or more groups selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2CO_2H$, $-CN$, $-CH_2NH_2$, $-CH_3$, $-C(=O)CH_3$, $-C(=O)NHCH_3$, $-CO_2H$, $-CH_2CO_2CH_3$, $-NH_2$, $-OCH_3$, $-S(O)_2CH_3$, 1-methylpiperid-4-yl, 4-methylpiperazin-1-yl, and 4-morpholinyl.

[00117] Exemplary embodiments include wherein A is selected from the heteroaryl structures:

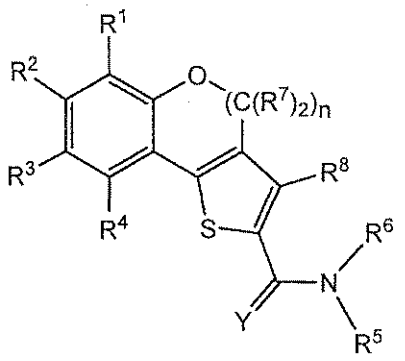




[00118] where the wavy line indicates the site of attachment.

[00119] BENZOPYRAN AND BENZOXEPIN COMPOUNDS

[00120] The present invention provides benzopyran and benzoxepin compounds, and pharmaceutical formulations thereof, which are potentially useful in the treatment of diseases, conditions and/or disorders modulated by PI3 kinases. More specifically, the present invention provides compounds of Formula II



II

[00121] and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

[00122] R^1, R^2, R^3, and R^4 are independently selected from H, F, Cl, Br, I, –CN, $–CF_3$, $–CH_2OR^{10}$, $–CH_2R^{10}$, $–CH_2NR^{10}R^{11}$, $–(C_1–C_{12}$ alkylene$)C(=O)OR^{10}$, $–CO_2R^{10}$, $–C(=O)N(R^{10})OR^{11}$, $–NO_2$, $–NR^{10}R^{11}$, $–OR^{10}$, $–S(O)_2R^{10}$, $–C(=O)NR^{10}R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}C(=O)OR^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}C(=O)R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)R^{10}$, $–NR^{12}C(=O)R^{10}$, $–NR^{12}C(=O)OR^{11}$, $–NR^{12}C(=O)NR^{10}R^{11}$, $–NR^{12}(C_1–C_{12}$ alkylene$)NR^{10}R^{11}$, $–NR^{12}(C_1–C_{12}$ alkylene$)OR^{10}$, $-NR^{12}(C_1–C_{12}$ alkylene$)C(=O)NR^{10}R^{11}$, $-C{\equiv}CR^{10}$, $-CH{=}CHR^{10}$, $C_2–C_{20}$ heterocyclyl, $C_1–C_{20}$ heteroaryl, and phenyl, where heterocyclyl, heteroaryl, and phenyl are optionally substituted with one or more groups selected from $–CH_2OH$, $–CH_2CO_2H$, –CN, $–CH_2NH_2$, $–C(=O)CH_3$, $–CO_2H$, $–CH_2CO_2CH_3$; $–NH_2$, $–S(O)_2CH_3$, 4-methylpiperazin-1-yl, and

4-morpholinyl;

[00123] R^5 is selected from C_1–C_{12} alkyl, optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, –CO_2H, –$CONH_2$, –$CONHCH_3$, –NH_2, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, –OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, and –$S(O)_2CH_3$;

[00124] R^6 is selected from C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, and C_6–C_{20} aryl, each optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CH_2OH, –$CH_2C_6H_5$, –CN, –CF_3, –CO_2H, –$CONH_2$, –$CONHCH_3$, –NH_2, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, –OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, –$S(O)_2CH_3$, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, -C≡CR^{13}, -CH=CHR^{13}, and –$C(=O)NR^{10}R^{11}$;

[00125] or R^5 and R^6 together with the nitrogen atom to which they are attached form morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, each optionally substituted with one or more groups selected from F, Cl, Br, I, –CH_2OH, –$CH_2C_6H_5$, –CN, –CF_3, –CO_2H, –$CONH_2$, –$CONHCH_3$, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, –OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, and –$S(O)_2CH_3$;

[00126] each R^7 is independently selected from H, F, Cl, Br, I, –CH_2OH, –CH_3, –CN, –CF_3, –CO_2H, –$CONH_2$, –$CONHCH_3$, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, –OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, and –$S(O)_2CH_3$; or both R^7 together are =O;

[00127] R^8 is selected from H and F;

[00128] R^{10}, R^{11} and R^{12} are independently selected from H, C_1–C_{12} alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl, where C_1–C_{12} alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CH_2OH, –$CH_2C_6H_5$, –CN, –CF_3, –CO_2H, –$CONH_2$, –$CONHCH_3$, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, –OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, and –$S(O)_2CH_3$;

[00129] or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a C_2–C_{20} heterocyclyl ring, optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CH_3, –CH_2OH, –$CH_2C_6H_5$, –CN, –CF_3, –CO_2H, –$CONH_2$, –$CONHCH_3$, –NO_2, –$N(CH_3)_2$, –$NHCOCH_3$, –$NHS(O)_2CH_3$, –OH, –OCH_3, –OCH_2CH_3, –$S(O)_2NH_2$, and –

$S(O)_2CH_3$;

[00130] R^{13} is selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CN$, $-CF_3$, $-CH_2N(CH_3)_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CON(CH_3)_2$, $-NO_2$, and $-S(O)_2CH_3$;

[00131] n is 1 or 2; and

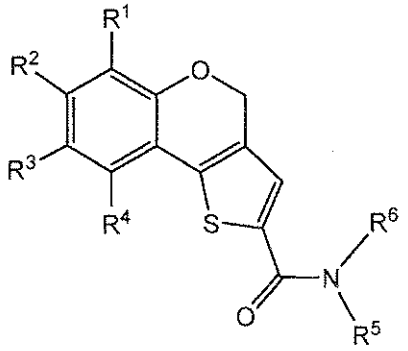
[00132] Y is O, S, N–$NR^{10}R^{11}$;

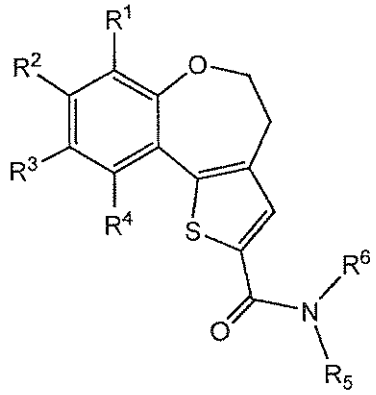
[00133] with the provisos:

[00134] when n is 1, Y is O, and R^1, R^2, R^3, R^7, R^8 are each H, then R^4 is not H or CH_3; and

[00135] when n is 1, then both R^7 together are not =O.

[00136] Exemplary embodiments include where the Formula II compound has the structures:





[00137] Exemplary embodiments include wherein R^5 is CH_3.

[00138] Exemplary embodiments include wherein R^6 is phenyl substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, $-S(O)_2CH_3$, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, $-C{\equiv}CR^{13}$, and $-CH{=}CHR^{13}$.

[00139] PREPARATION OF FORMULA I COMPOUNDS

[00140] Benzoxepin compounds of Formula I may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-23, Wiley, N.Y. (1967-2006 ed.), or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. ed. Springer-Verlag, Berlin, including

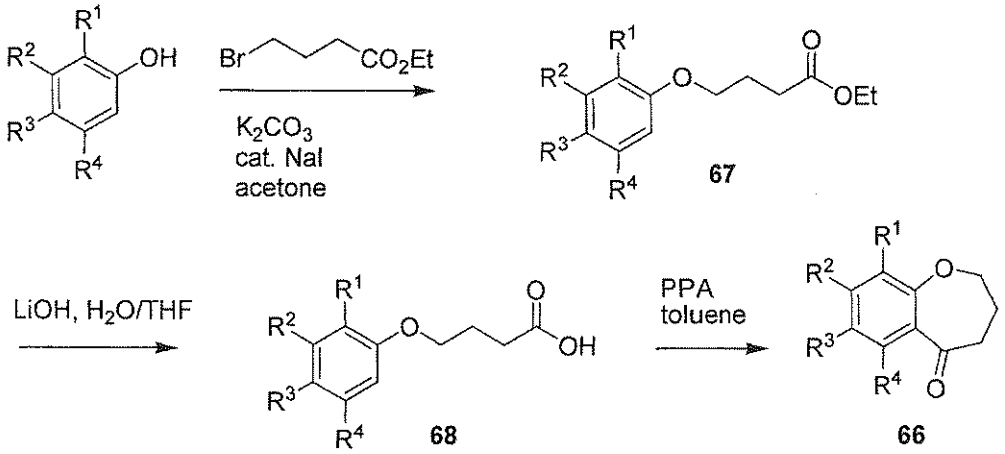
supplements (also available via the Beilstein online database).

[00141] In certain embodiments, compounds of Formula I may be readily prepared using well-known procedures to prepare benzoxepin compounds (Sekhar et al (1989) Sulfur Letters 9(6):271-277; Katsura et al (2000 J. Med. Chem. 43:3315-3321; Rueeger et al (2004) Biorganic & Med. Chem. Letters 14:2451-2457; Reiter et al (2007) Biorganic & Med. Chem. Letters 17:5447-5454; Banaszak et al (2006) Tetrahedron Letters 47:6235-6238;) and other heterocycles, which are described in: Comprehensive Heterocyclic Chemistry II, Editors Katritzky and Rees, Elsevier, 1997, e.g. Volume 3; Liebigs Annalen der Chemie, (9):1910-16, (1985); Helvetica Chimica Acta, 41:1052-60, (1958); Arzneimittel-Forschung, 40(12):1328-31, (1990).

[00142] Compounds of Formula I may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, or 10 to 100 compounds. Libraries of compounds of Formula I may be prepared by a combinatorial 'split and mix' approach or by multiple parallel syntheses using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds, or pharmaceutically acceptable salts thereof.

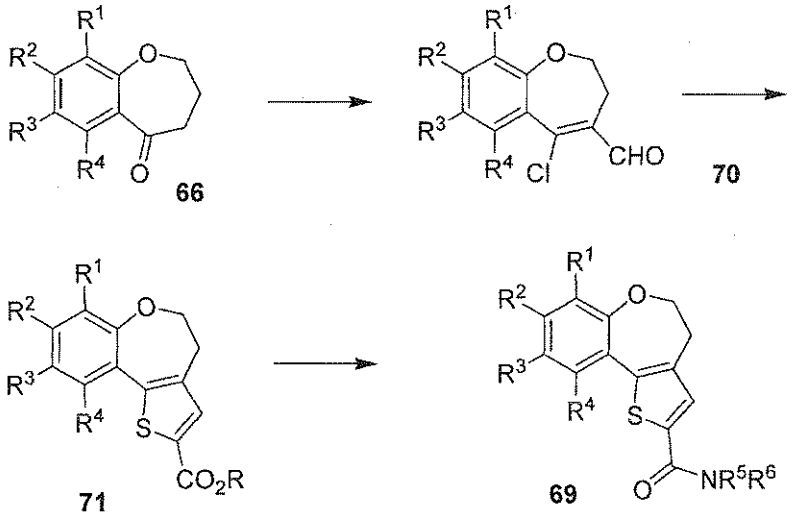
[00143] For illustrative purposes, Schemes 1-8 show general methods which may be applied for preparation of Formula I compounds, as well as key intermediates. The General Procedures and Examples sections contain more detailed description of individual reaction steps. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although certain starting materials and routes are depicted in the Schemes, General Procedures and Examples, other similar starting materials and routes can be substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

[00144] In preparing compounds of Formulas I, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, Third Ed., 1999.



Scheme 1

[00145] Scheme 1 shows a general method for preparation of 3,4-dihydrobenzo[b]oxepin-5(2H)-one intermediates **66** by O-alkylation of a phenolic compound with ethyl 4-bromobutanoate to give a ethyl 4-phenoxybutanoate intermediate **67**, followed by saponification to the carboxylic acid **68** and intramolecular cyclization under acidic conditions.



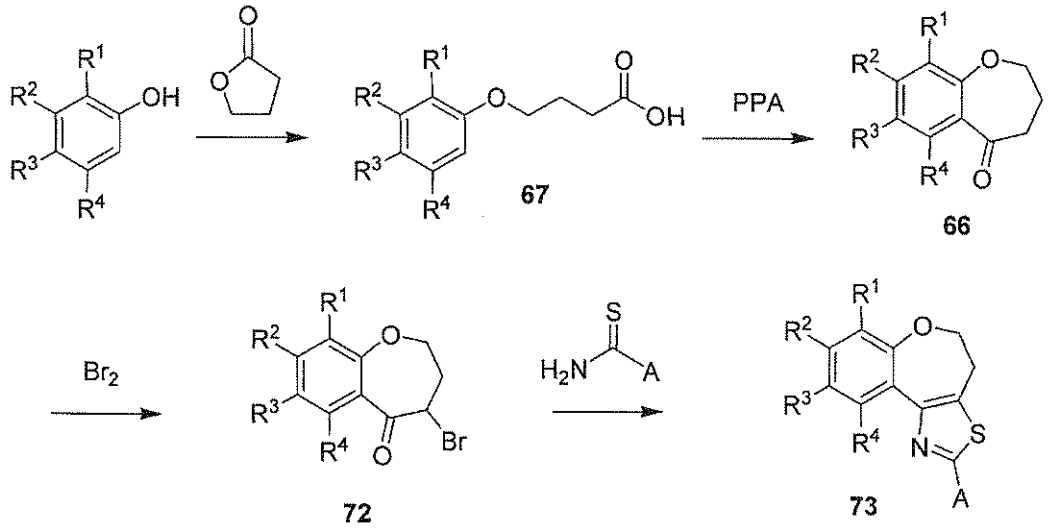
Scheme 2

[00146] Scheme 2 shows a general method of preparation of N,N-disubstituted 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide intermediates **69**. 3,4-Dihydrobenzo[b]oxepin-5(2H)-one intermediates **66** are formylated with phosphorus oxytrichloride and dimethylformamide (DMF) to give 5-chloro-2,3-dihydrobenzo[b]oxepine-4-carbaldehyde intermediate **70**. Cyclization of **70** with a mercapto acetate ester ($HSCH_2CO_2R$ where R is alkyl or aryl) in potassium carbonate and DMF gives the 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylate ester intermediate **71**. Saponification of **71** with lithium hydroxide in THF and water gives the acid (R = H) which is treated with thionyl chloride at reflux followed by a secondary amine (HNR^5R^6), such as N-methyl-2-chloroaniline, with a catalytic amount of DMAP (4,4-dimethylaminopyridine), triethylamine, and

dichloromethane to give 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide intermediates **69**. Alternatively, the acid is treated with oxalyl chloride and a catalytic amount of DMF to generate the acid chloride, followed by reaction with the amine and potassium carbonate in acetonitrile to give amides such as **69**. Where one of R^1, R^2, R^3, or R^4 is bromo, the bromine of **69**, or of another intermediate such as **66**, **70**, **71**, may be displaced by: (i) carbonylative amination to give amide ($-NR^{12}C(=O)R^{10}$, (ii) formylation (–CHO) followed by reductive amination to $-CH_2NR^{10}R^{11}$, (iii) Suzuki coupling with aryl or heteroaryl, (iv) Sonagoshira coupling to give alkynyl ($-C\equiv CR^{10}$), or (v) amination ($-NR^{10}R^{11}$).

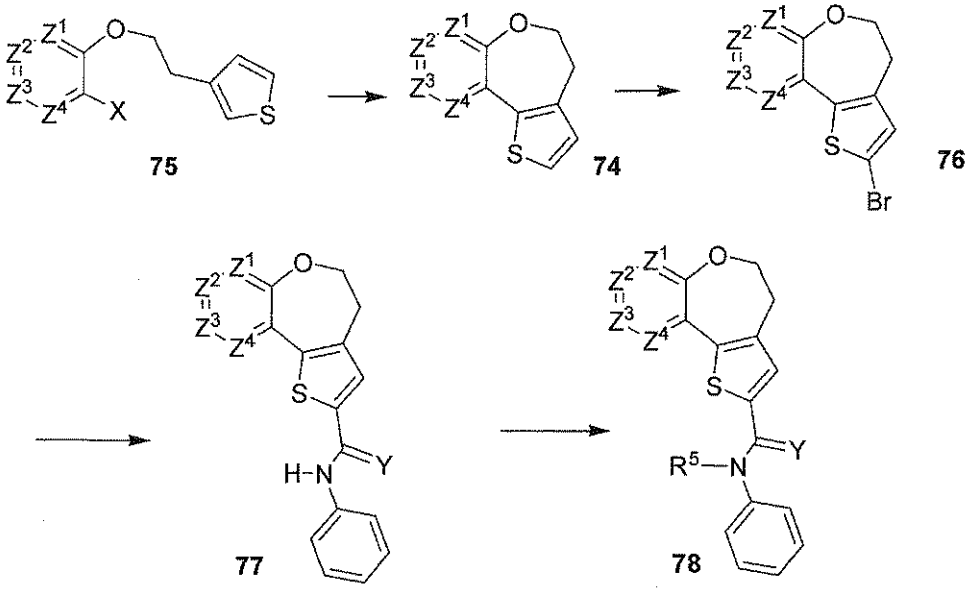
[00147] A variety of palladium catalysts can be used during the Suzuki coupling step to form compounds where R^1, R^2, R^3, or R^4 is aryl or heteroaryl. Suzuki coupling is a palladium mediated cross coupling reaction of an arylhalide, with a boronic acid or boronate esters such as pinacolato. Low valent, Pd(II) and Pd(0) catalysts may be used, including $PdCl_2(PPh_3)_2$, Pd(t-Bu)$_3$, $PdCl_2$ dppf CH_2Cl_2, $Pd(PPh_3)_4$, Pd(OAc)/PPh_3, $Cl_2Pd[(Pet_3)]_2$, $Pd(DIPHOS)_2$, $Cl_2Pd(Bipy)$, $[PdCl(Ph_2PCH_2PPh_2)]_2$, $Cl_2Pd[P(o\text{-}tol)_3]_2$, $Pd_2(dba)_3/P(o\text{-}tol)_3$, $Pd_2(dba)/P(furyl)_3$, $Cl_2Pd[P(furyl)_3]_2$, $Cl_2Pd(PMePh_2)_2$, $Cl_2Pd[P(4\text{-}F\text{-}Ph)_3]_2$, $Cl_2Pd[P(C_6F_6)_3]_2$, $Cl_2Pd[P(2\text{-}COOH\text{-}Ph)(Ph)_2]_2$, $Cl_2Pd[P(4\text{-}COOH\text{-}Ph)(Ph)_2]_2$, and encapsulated catalysts Pd EnCat™ 30, Pd EnCat™ TPP30, and Pd(II)EnCat™ BINAP30 (US 2004/0254066).

[00148] A variety of solid adsorbent palladium scavengers can be used to remove palladium after the Suzuki coupling step. Exemplary embodiments of palladium scavengers include FLORISIL® and SILIABOND® Thiourea. Other palladium scavengers include silica gel, controlled-pore glass (TosoHaas), and derivatized low crosslinked polystyrene QuadraPure™ AEA, QuadraPure™ IMDAZ, QuadraPure™ MPA, QuadraPure™ TU (Reaxa Ltd., Sigma-Aldrich Chemical Co.).



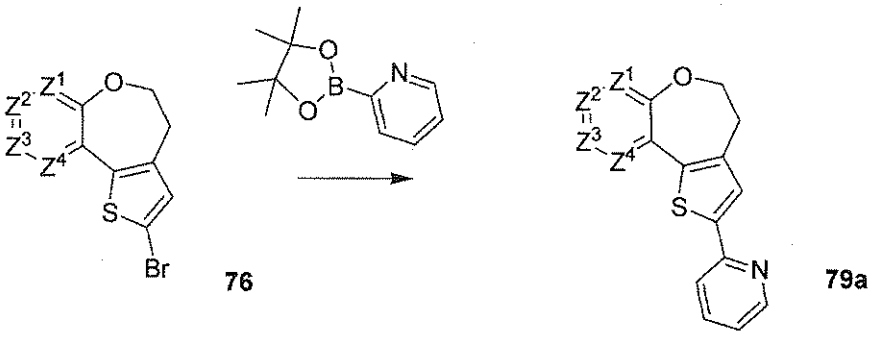
Scheme 3

[00149] Scheme 3 shows a general method of preparation of benzoxepin thiazoles **73**. Bromination of keto benzoxepin (3,4-dihydrobenzo[b]oxepin-5(2H)-one) **66** forms the 2-bromo keto benzoxepin intermediates **72**. Cyclization with thioamides form **73** (Rueeger et al (2004) Bioorganic & Med. Chem. Letters 14:2451-2457; US 2005/0277630; WO 2001/064675; US 6222040; US 6225330; US 5314889).



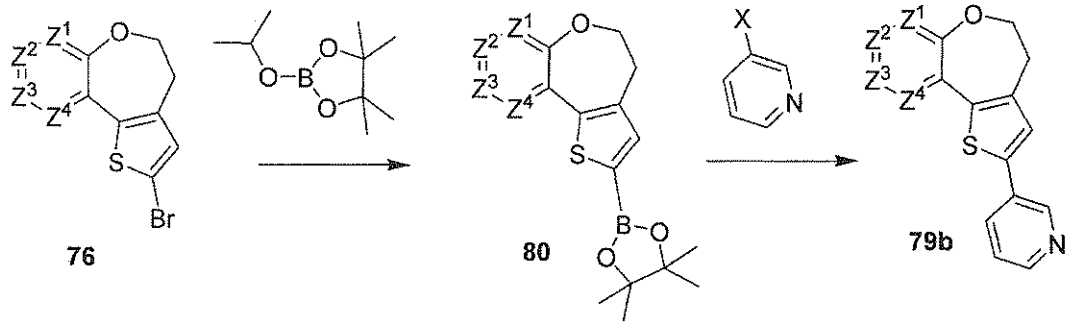
Scheme 4

[00150] Scheme 4 shows a general method of preparation of benzoxepin thiophene amides **78**. Cyclization of 3-(2-(2-halophenoxy)ethyl)thiophene intermediate **75** (X = Br, I, Cl) under palladium catalysis (see Example 8) gives 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine intermediates **74**. Bromination of the 2-position gives 2-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine intermediates **76** which can be reacted with aryl isocyanate (Ar-NCO)or aryl isoisothiocyanate (Ar-NCS) reagents to give N-phenyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide intermediates **77** (Y = O, S). The N-H group of **77** can be selectively alkylated to give **78**.



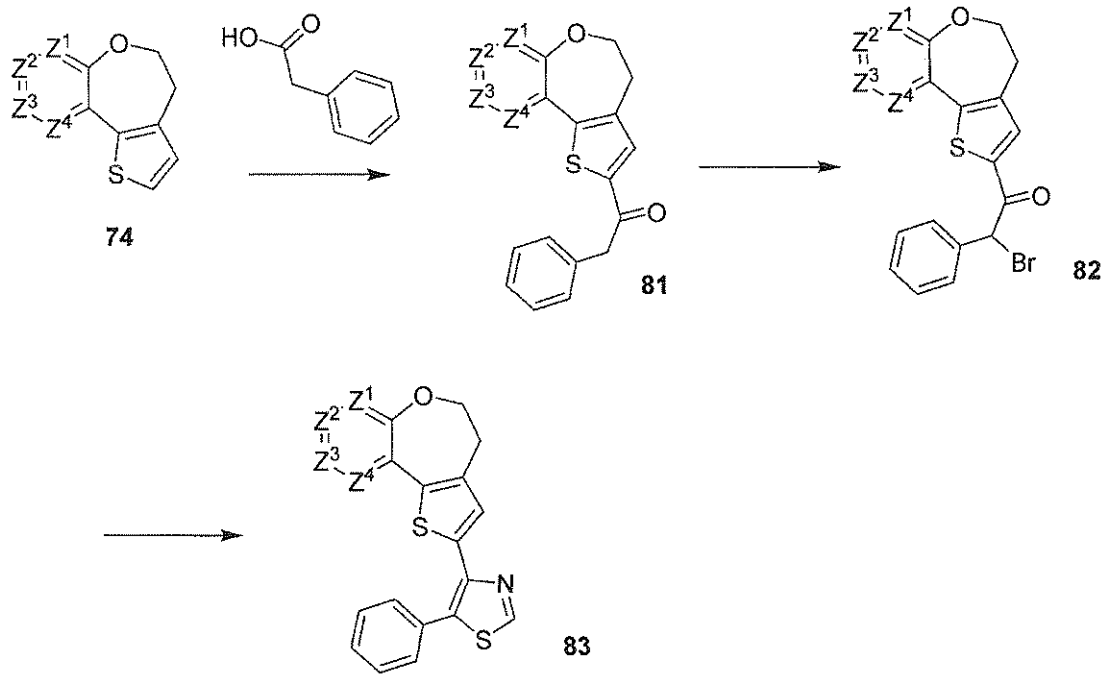
Scheme 5

[00151] Scheme 5 shows a general method of Suzuki coupling of a 2-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine intermediate **76** with a heterocyclyl boronate reagent, such as 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine to give the 2-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyridine **79a**.



Scheme 6

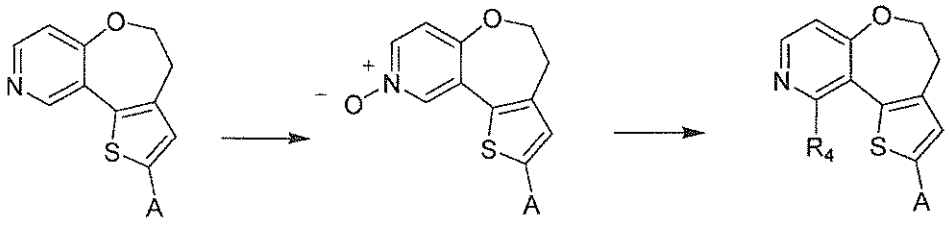
[00152] Scheme 6 shows a general method forming a thiophenyl benzoxepin boronate compound **80** by reaction of 2-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine intermediate **76** with a heterocyclyl boronate reagent, such as 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Boronate **80** undergoes Suzuki coupling with a heterocyclyl halide reagent, such as 3-iodopyridine to give 3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyridine **79b**.



Scheme 7

[00153] Scheme 7 shows a general method for substitution at the 2-position of 4,5-

dihydrobenzo[b]thieno[2,3-d]oxepine intermediates **74** by acylation with a carboxylic acid such as 2-phenylacetic acid to give 1-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-2-phenylethanone intermediate **81**. Bromination gives 2-bromo-1-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-2-phenylethanone intermediate **82**. Cyclization with a thioamide compound gives 4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-5-phenylthiazole **83**.



84 **85** **86**

Scheme 8

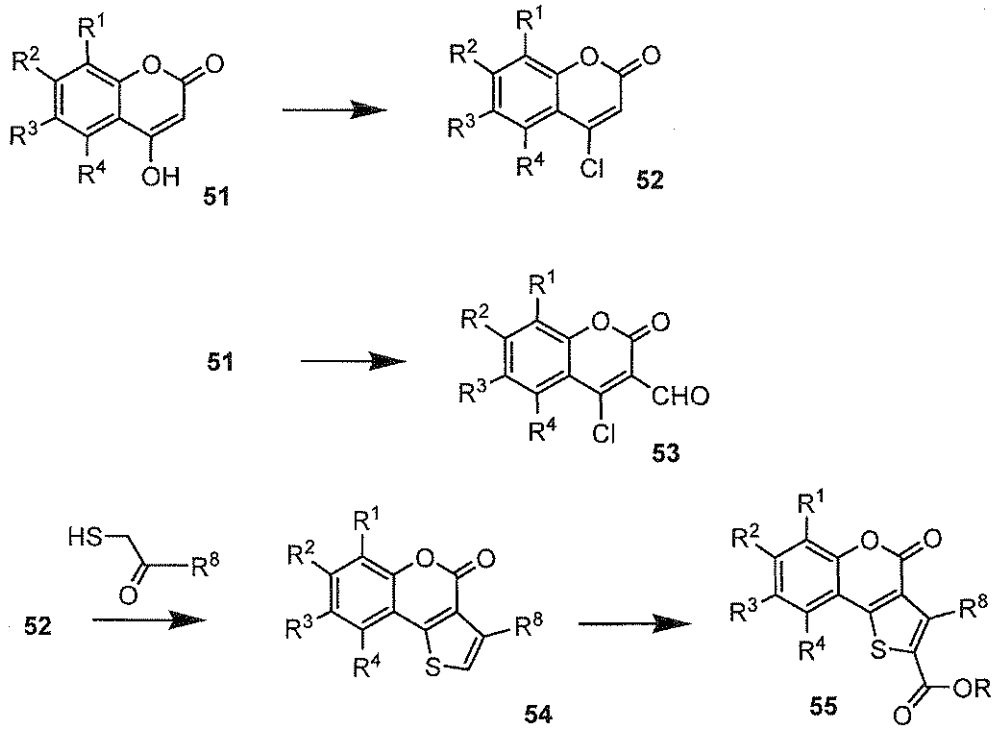
[00154] Scheme 8 shows a general method for regiospecific alkylation of 4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl intermediates **84** oxidation to form the N-oxide **85**, and alkylation to give 10-substituted 4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl **86**.

[00155] PREPARATION OF FORMULA II COMPOUNDS

[00156] In certain embodiments, compounds of Formula II may be readily prepared using well-known procedures to prepare benzopyran and benzoxepin compounds (Sekhar et al (1989) Sulfur Letters 9(6):271-277; Navarro et al (2001) Heterocycles 55(12):2369-2386; Majumdar et al (2004) Monatshefte fur Chemie 135(8):1001-1007; Potts et al (1986) Journal of the Chemical Society, Chemical Communications 7:561-3) and other heterocycles, which are described in: Comprehensive Heterocyclic Chemistry II, Editors Katritzky and Rees, Elsevier, 1997, e.g. Volume 3; Liebigs Annalen der Chemie, (9):1910-16, (1985); Helvetica Chimica Acta, 41:1052-60, (1958); Arzneimittel-Forschung, 40(12):1328-31, (1990).

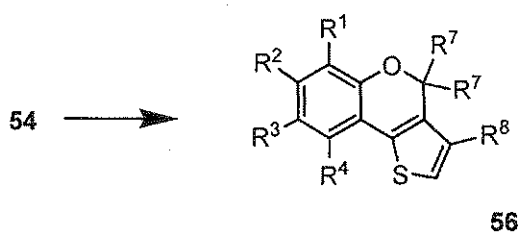
[00157] For illustrative purposes, Schemes 1bp-5bp show general methods which may be applied for preparation of benzopyran Formula I compounds, as well as key intermediates. The General Procedures and Examples sections contain more detailed description of individual reaction steps. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although certain starting materials and routes are depicted in the Schemes, General Procedures and Examples, other similar starting materials and routes can be substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

[00158] In preparing compounds of Formulas II, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, Third Ed., 1999.



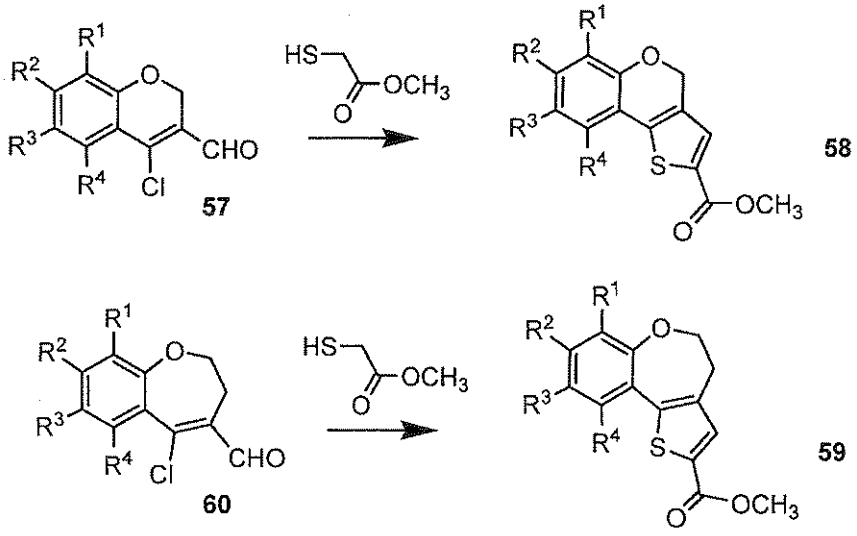
Scheme 1bp

[00159] Scheme 1bp shows a general method for preparation of 4-chloro-2H-chromen-2-one **52bp** and 4-chloro-2-oxo-2H-chromene-3-carbaldehyde **53bp** intermediates from 4-hydroxy-2H-chromen-2-one compounds **51bp** (Navarro et al (2001) Heterocycles 55(12):2369-2386). Intermediate **52bp** can be cyclized with mercapto acetyl compounds to give 3-substituted 4H-thieno[3,2-c]chromen-4-one intermediates **54bp**. Deprotonation and acylation of the 2-position of the thiophene ring of **54bp** gives 2-esterified 4H-thieno[3,2-c]chromen-4-one intermediates **55bp**.



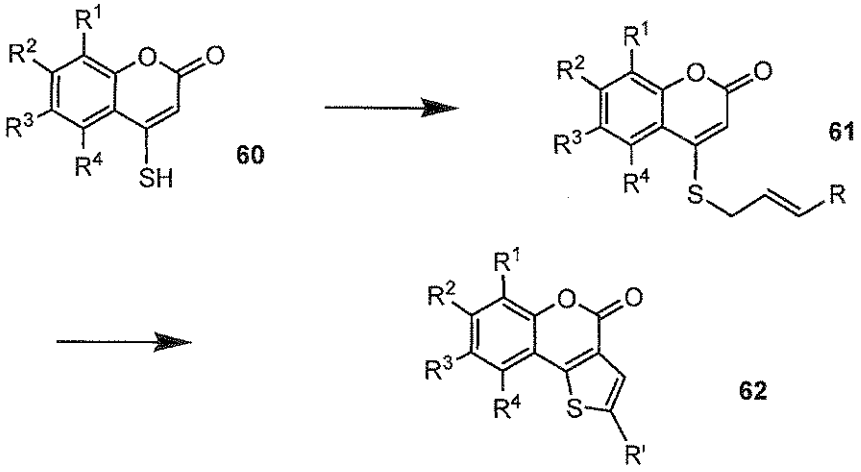
Scheme 2bp

[00160] Scheme 2bp shows gem-dialkylation of the chromene acyl group of 3-substituted 4H-thieno[3,2-c]chromen-4-one intermediates **54bp** with Grignard reagents $(R^7)_2MgI$, followed by treatment with titanium tetrachloride to give 4,4-disubstituted 4H-thieno[3,2-c]chromene intermediates **56bp** (Navarro et al (2001) Heterocycles 55(12):2369-2386).



Scheme 3bp

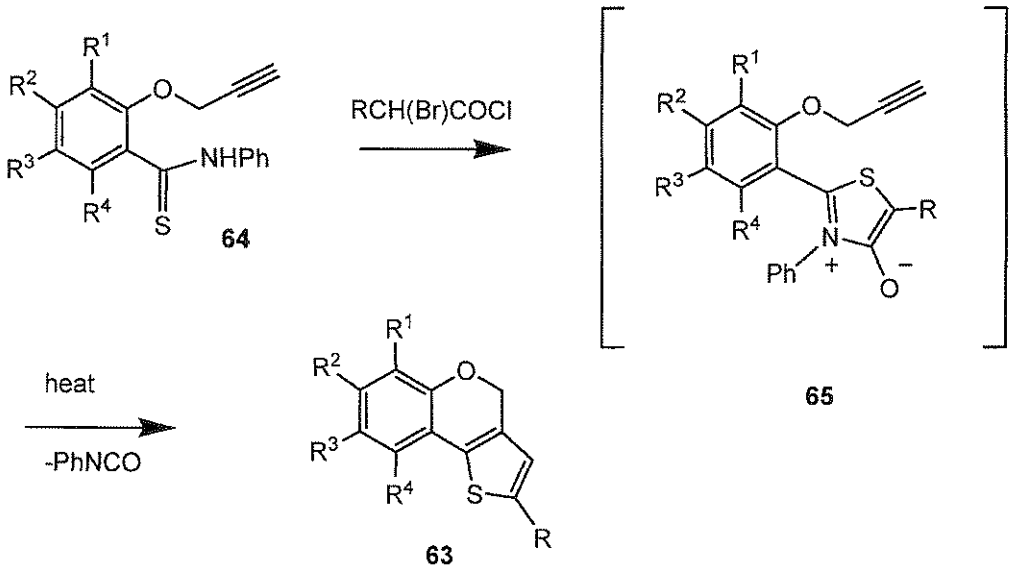
[00161] Scheme 3 shows a general method for preparation of methyl 4H-thieno[3,2-c]chromene-2-carboxylate **58bp** and methyl 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylate **59bp** intermediates from 4-chloro-2H-chromene-3-carbaldehyde **57bp** and (Z)-5-chloro-2,3-dihydrobenzo[b]oxepine-4-carbaldehyde **60bp**, respectively, by cyclization with methyl mercaptoacetate in acetonitrile and potassium carbonate (Sekhar et al (1989) Sulfur Letters 9(6):271-277).



Scheme 4bp

[00162] Scheme 4 shows a general method for preparation of 2-substituted 4H-thieno[3,2-c]chromen-4-one intermediates **62bp** from allylation of 4-mercapto-2H-chromen-2-one

intermediates **60bp** with allylic halides to give 4-(but-2-enylthio)-2H-chromen-2-one intermediates **61bp** and thermal thio-Claisen rearrangement (Majumdar et al (2004) Monatshefte fur Chemie 135(8):1001-1007).



Scheme 5bp

[00163] Scheme 5bp shows a general method for preparation of 2-substituted, 4H-thieno[3,2-c]chromene intermediates **63bp** by reaction of N-phenyl-2-(prop-2-ynyloxy)benzothioamide compounds **64bp** with an alpha-bromo acid chloride (R = alkyl or aryl) to presumably generate the thiazolium intermediate **65bp** which undergoes loss of phenylisocyanate and 1,3-dipolar cycloaddition with (Potts et al (1986) Journal of the Chemical Society, Chemical Communications 7:561-3; Potts et al (1989) J. Org. Chem. 54:1077-1088).

[00164] METHODS OF SEPARATION

[00165] In the methods of preparing the compounds of this invention, it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

[00166] Another class of separation methods involves treatment of a mixture with a

reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

[00167] Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

[00168] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC column.

[00169] A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Eliel, E. and Wilen, S. "Stereochemistry of Organic Compounds," John Wiley & Sons, Inc., New York, 1994; Lochmuller, C. H., (1975) J. Chromatogr., 113(3):283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: "Drug Stereochemistry, Analytical Methods and Pharmacology," Irving W. Wainer, Ed., Marcel Dekker, Inc., New York (1993).

[00170] Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic

functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

[00171] Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (E. and Wilen, S. "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g., (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. J. Org. Chem. (1982) 47:4165), of the racemic mixture, and analyzing the ^{1}H NMR spectrum for the presence of the two atropisomeric enantiomers or diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed., Chapman and Hall, New York; Okamoto, J. Chromatogr., (1990) 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

[00172] BIOLOGICAL EVALUATION

[00173] Determination of the PI3 kinase activity of a Formula I or Formula II compound is possible by a number of direct and indirect detection methods. Certain exemplary compounds described herein were assayed for their p110α (alpha), and other isoform, PI3K binding activity (Example 275) and *in vitro* activity against tumor cells (Example 276). The range of PI3K binding activities was less than 1 nM (nanomolar) to about 10 μM (micromolar). Certain exemplary compounds of the invention had PI3K binding activity IC_{50} values less than 10 nM. Certain compounds of the invention had tumor cell-based activity IC_{50} values less than 100 nM.

[00174] The cytotoxic or cytostatic activity of Formula I and II exemplary compounds was measured by: establishing a proliferating mammalian tumor cell line in a cell culture medium, adding a Formula I compound, culturing the cells for a period from about 6 hours to about 5 days; and measuring cell viability (Example 276). Cell-based *in vitro* assays were used

to measure viability, i.e. proliferation (IC_{50}), cytotoxicity (EC_{50}), and induction of apoptosis (caspase activation).

[00175] The *in vitro* potency of Formula I and II exemplary compounds was measured by the cell proliferation assay, CellTiter-Glo® Luminescent Cell Viability Assay, commercially available from Promega Corp., Madison, WI (Example 276). This homogeneous assay method is based on the recombinant expression of *Coleoptera* luciferase (US 5583024; US 5674713; US 5700670) and determines the number of viable cells in culture based on quantitation of the ATP present, an indicator of metabolically active cells (Crouch et al (1993) J. Immunol. Meth. 160:81-88; US 6602677). The CellTiter-Glo® Assay was conducted in 96 or 384 well format, making it amenable to automated high-throughput screening (HTS) (Cree et al (1995) AntiCancer Drugs 6:398-404). The homogeneous assay procedure involves adding the single reagent (CellTiter-Glo® Reagent) directly to cells cultured in serum-supplemented medium. Cell washing, removal of medium and multiple pipetting steps are not required. The system detects as few as 15 cells/well in a 384-well format in 10 minutes after adding reagent and mixing.

[00176] The homogeneous "add-mix-measure" format results in cell lysis and generation of a luminescent signal proportional to the amount of ATP present. The amount of ATP is directly proportional to the number of cells present in culture. The CellTiter-Glo® Assay generates a "glow-type" luminescent signal, produced by the luciferase reaction, which has a half-life generally greater than five hours, depending on cell type and medium used. Viable cells are reflected in relative luminescence units (RLU). The substrate, Beetle Luciferin, is oxidatively decarboxylated by recombinant firefly luciferase with concomitant conversion of ATP to AMP and generation of photons. The extended half-life eliminates the need to use reagent injectors and provides flexibility for continuous or batch mode processing of multiple plates. This cell proliferation assay an be used with various multiwell formats, e.g. 96 or 384 well format. Data can be recorded by luminometer or CCD camera imaging device. The luminescence output is presented as relative light units (RLU), measured over time.

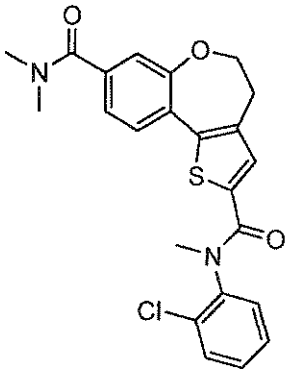
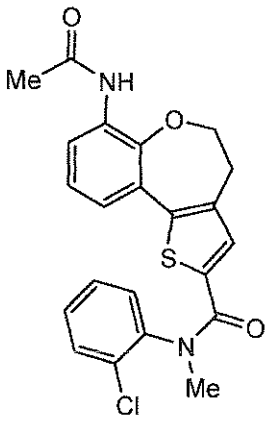
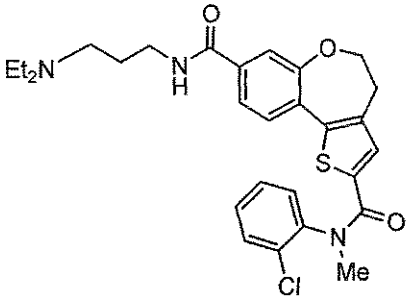
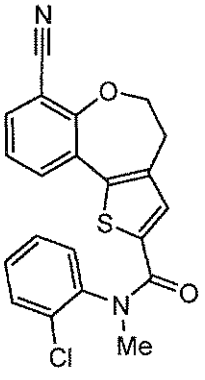
[00177] The anti-proliferative effects of Formula I and II exemplary compounds were measured by the CellTiter-Glo® Assay (Example 276) against several tumor cell lines, including PC3, Detroit 562, and MDAMB361.1. EC_{50} values were established for the tested compounds. The range of in vitro cell potency activities was about 100 nM to about 10 μM.

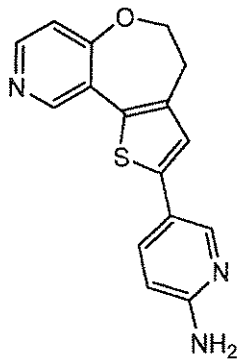
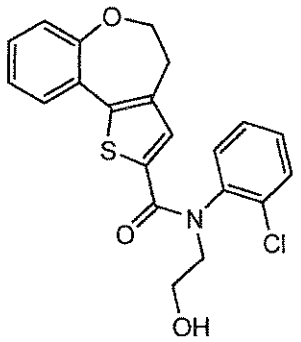
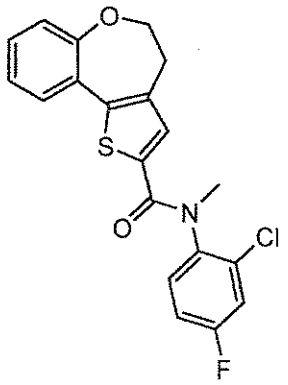
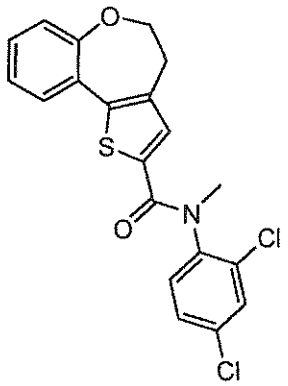
[00178] Certain ADME properties were measured for certain exemplary compounds by assays including: Caco-2 Permeability (Example 277), Hepatocyte Clearance (Example 278), Cytochrome P450 Inhibition (Example 279), Cytochrome P450 Induction (Example 280), Plasma Protein Binding (Example 281), and hERG channel blockage (Example 282).

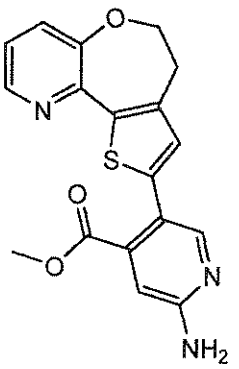
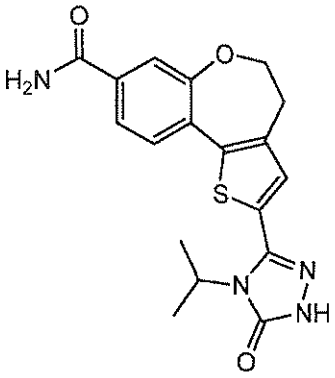
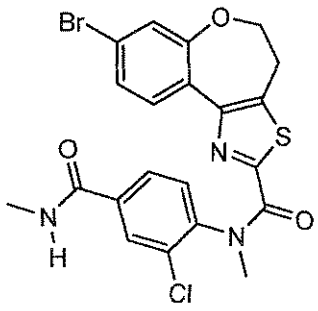
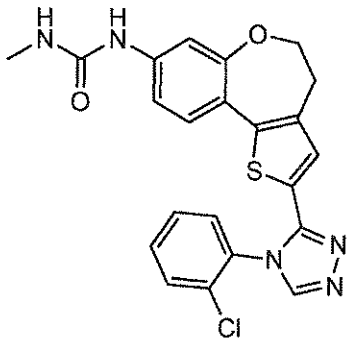
[00179] Certain exemplary compunds were tested for efficacy by a dose escalation studies by administration in tumor xenograft Taconic nude mouse models (Example 283). The breast cancer cell line MDA-MB-361.1 mouse model was administered Compound **223** along with Vehicle (MCT, negative control). The tumor growth delay was measured when dosed orally daily for 21 days at 50 and 100 mg/kg (Figure 3). Body weight change over the course of treatment was measured as an indicator of safety. The body weights of the group administered Compound **223** at 50 and 100 mg/kg did not significantly differ from the group administered Vehicle. Treatment of the MDA-MB-361.1 mouse model with Compound **328** caused tumor growth inhibition when dosed orally daily for 21 days at 25, 50 and 100 mg/kg (Figure 4). At least one of the 10 mice treated at 25 mg/kg showed a partial response. The body weights of the group administered Compound **328** at 50 and 100 mg/kg did not significantly differ from the group administered Vehicle. Treatment of the MDA-MB-361.1 mouse model with Compound **345** caused tumor growth inhibition when dosed orally daily for 21 days at 12.5, 25 and 50 mg/kg (Figure 5). The body weights of the group administered Compound **345** at 12.5, 25, and 50 mg/kg did not significantly differ from the group administered Vehicle. In each study, Compounds **223**, **328**, and **345** suppressed pAkt (phospho-Akt), a potential biomarker of PI3K signal transduction disruption (Example 284).

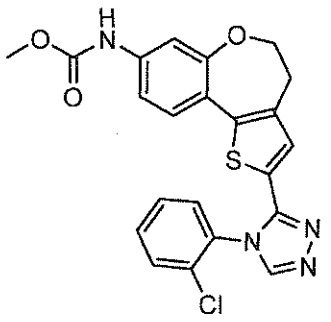
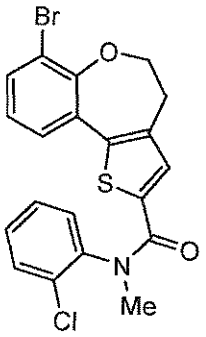
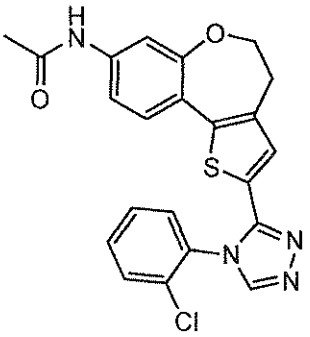
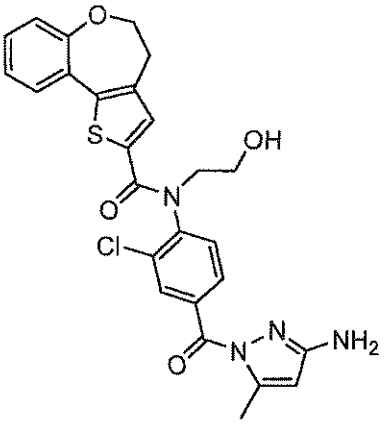
[00180] Exemplary Formula I compounds No. 101-533 in Table 1, were made, characterized, and tested for PI3K activity according to the methods of this invention, and have the following structures and corresponding names (ChemDraw Ultra, Version 9.0.1, CambridgeSoft Corp., Cambridge MA).

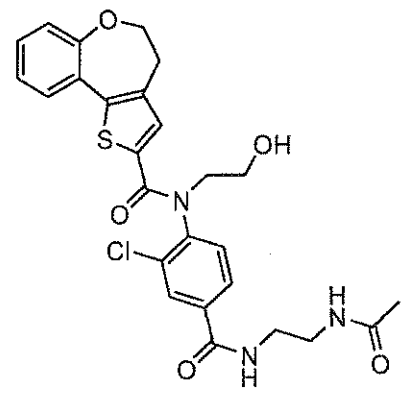
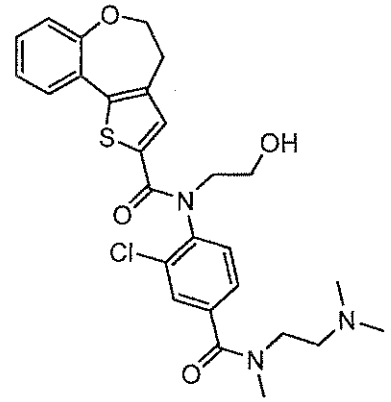
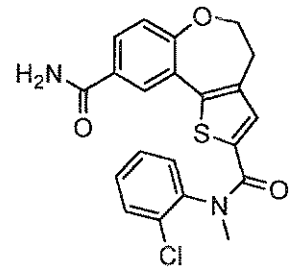
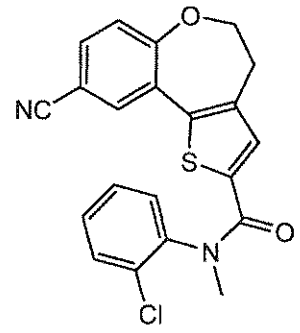
[00181] Table 1.

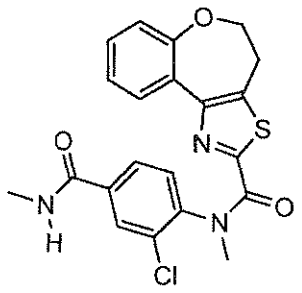
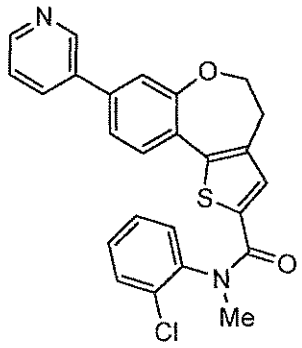
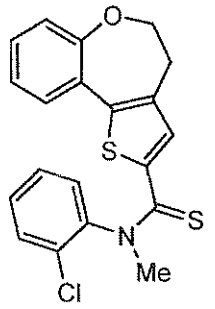
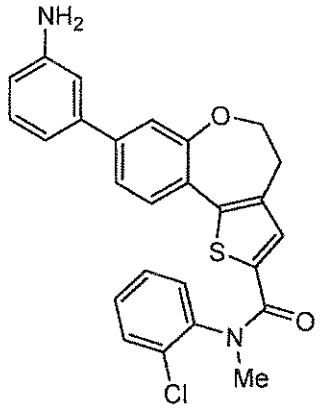
No.	Structure	Name
101		N2-(2-chlorophenyl)-N2,N8,N8-trimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
102		7-acetamido-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
103		N2-(2-chlorophenyl)-N8-(3-(diethylamino)propyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
104		N-(2-chlorophenyl)-7-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

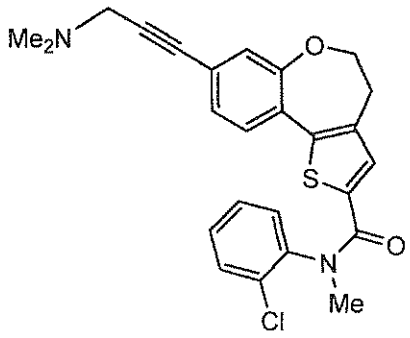
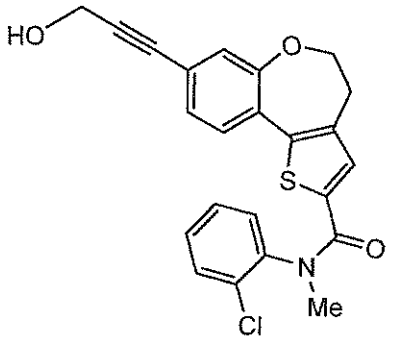
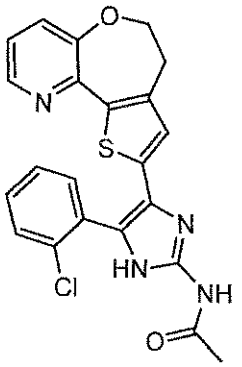
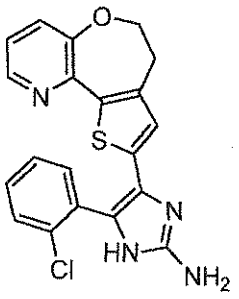
105		5-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)pyridin-2-amine
106		N-(2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
107		N-(2-chloro-4-fluorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
108		N-(2,4-dichlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

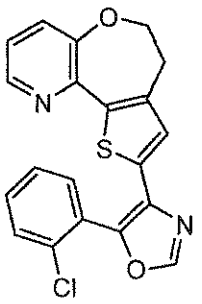
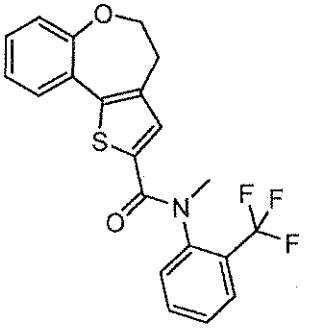
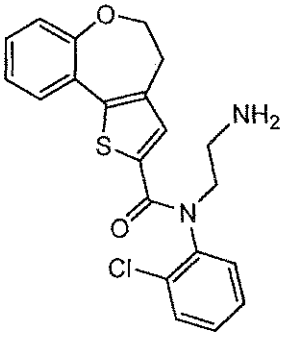
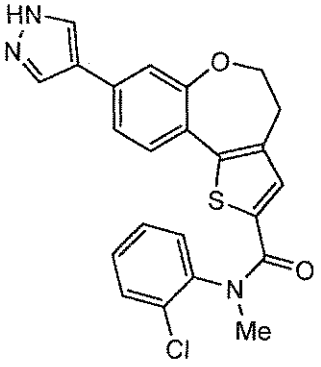
109		methyl 5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)2-aminoisonicotinate
110		2-(4-isopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
111		8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-4-methylcarbamoyl-phenyl)-methyl-amide
112		1-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-3-methylurea

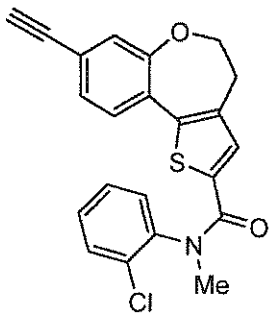
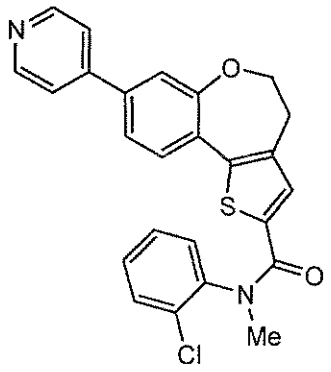
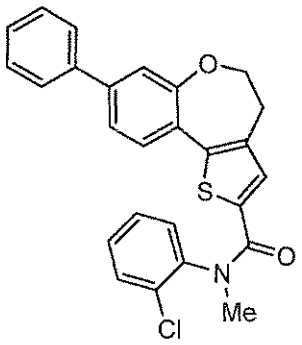
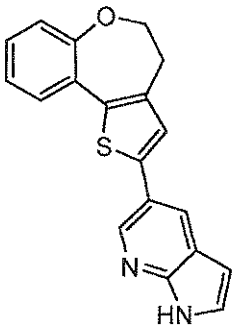
113		methyl 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-ylcarbamate
114		7-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
115		N-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)acetamide
116		N-(4-(3-amino-5-methyl-1H-pyrazole-1-carbonyl)-2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

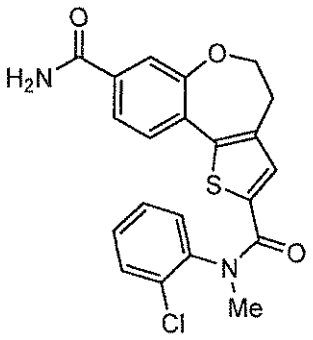
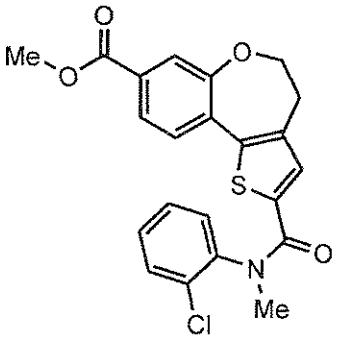
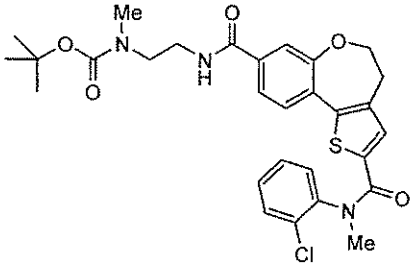
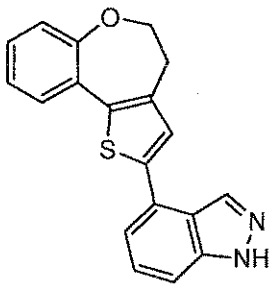
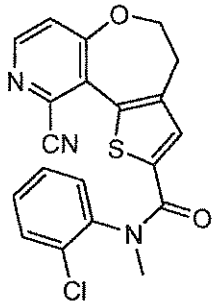
117		N-(4-(2-acetamidoethylcarbamoyl)-2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
118		N-(2-chloro-4-((2-(dimethylamino)ethyl)(methyl)carbamoyl)phenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
119		N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide
120		N-(2-chlorophenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

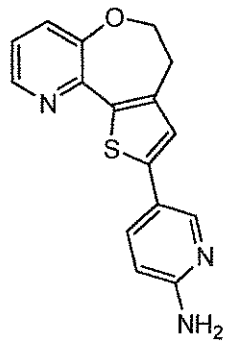
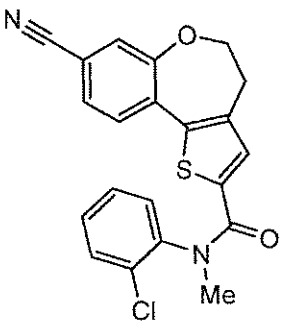
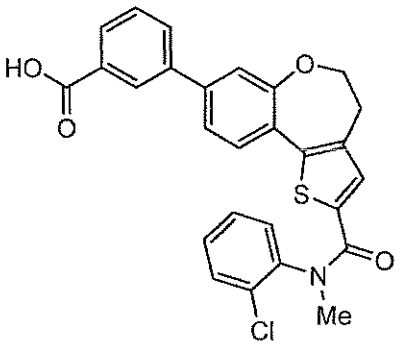
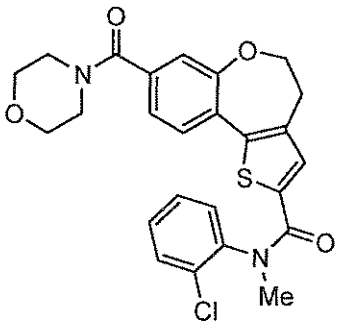
121		4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-4-methylcarbamoyl-phenyl)-methyl-amide
122		N-(2-chlorophenyl)-N-methyl-8-(pyridin-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
123		N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbothioamide
124		8-(3-aminophenyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

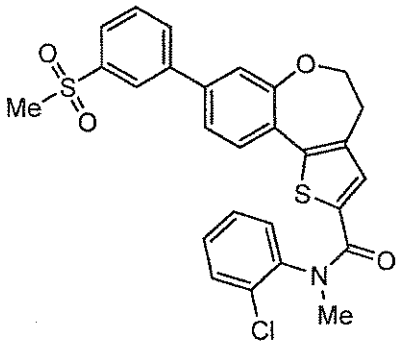
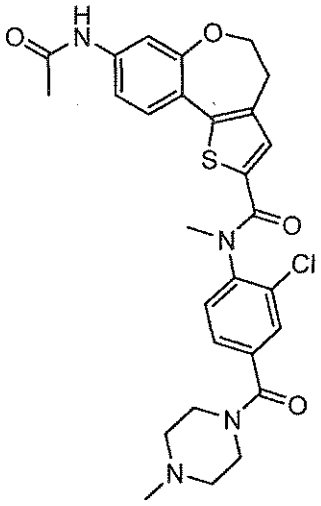
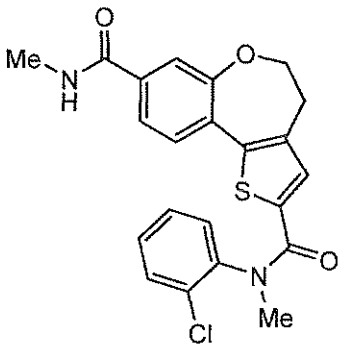
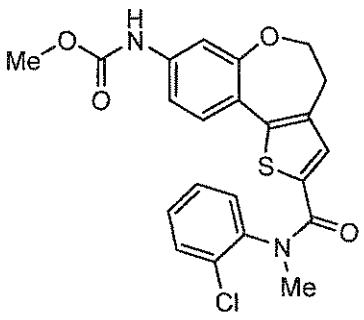
125		N-(2-chlorophenyl)-8-(3-(dimethylamino)prop-1-ynyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
126		N-(2-chlorophenyl)-8-(3-hydroxyprop-1-ynyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
127		4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(2-chlorophenyl)-2-acetamino-1H-imidazole
128		4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(2-chlorophenyl)-2-amino-1H-imidazole

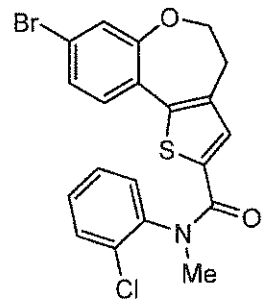
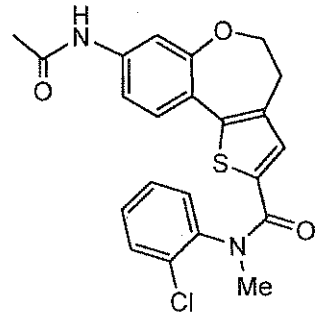
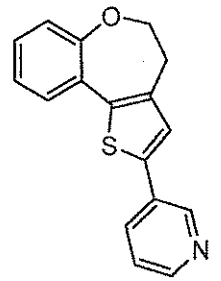
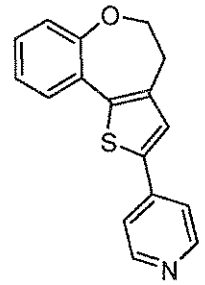
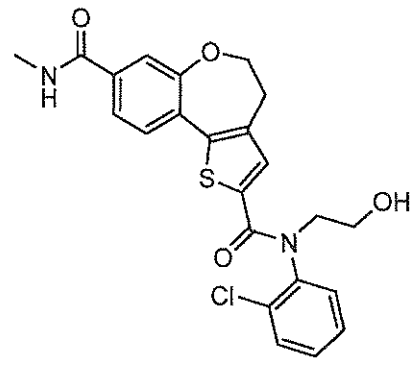
129		4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(5-(2-chlorophenyl))-oxazole
130		N-methyl-N-(2-(trifluoromethyl)phenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
131		N-(2-aminoethyl)-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
132		N-(2-chlorophenyl)-N-methyl-8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

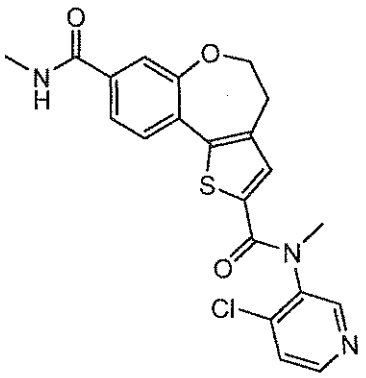
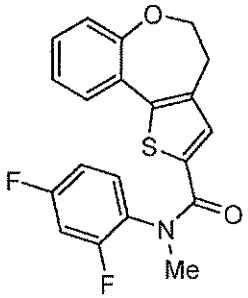
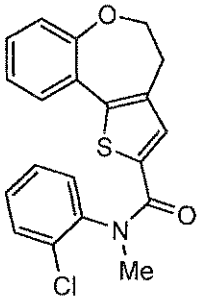
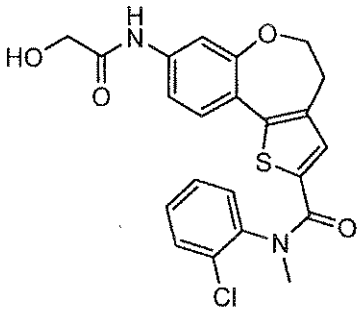
133		N-(2-chlorophenyl)-8-ethynyl-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
134		N-(2-chlorophenyl)-N-methyl-8-(pyridin-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
135		N-(2-chlorophenyl)-N-methyl-8-phenyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
136		5-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-pyrrolo[2,3-b]pyridine

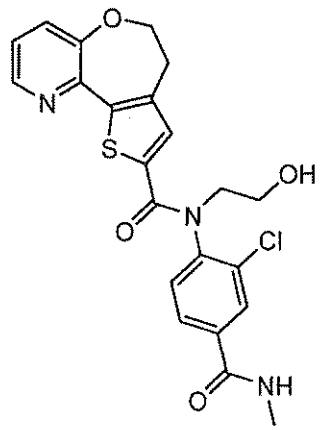
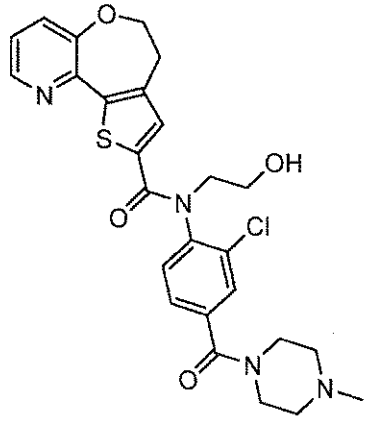
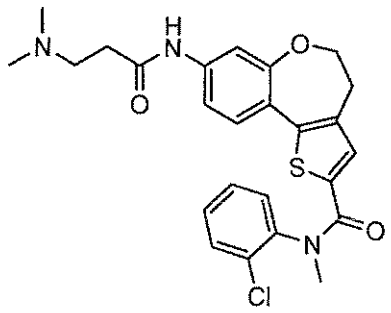
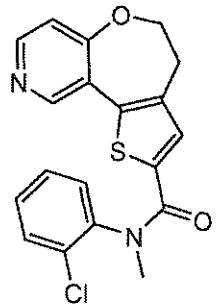
137		N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
138		methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate
139		tert-butyl 2-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamido)ethyl(methyl)carbamate
140		4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-indazole
141		N-(2-chlorophenyl)-N-methyl-(10-cyano-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide

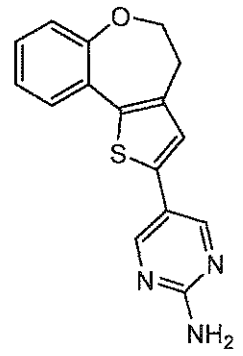
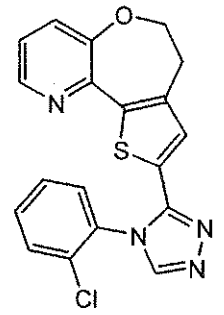
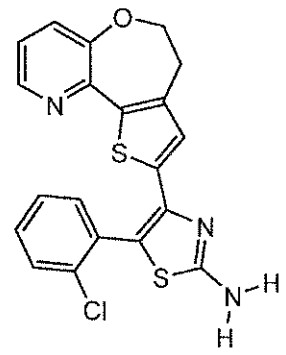
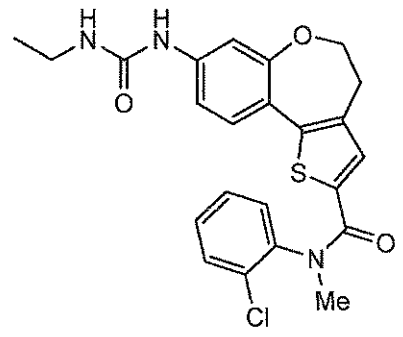
142		5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-amine
143		N-(2-chlorophenyl)-8-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
144		3-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)benzoic acid
145		N-(2-chlorophenyl)-N-methyl-8-(morpholine-4-carbonyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

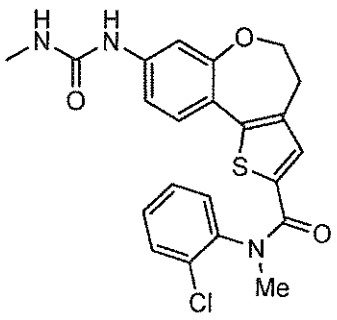
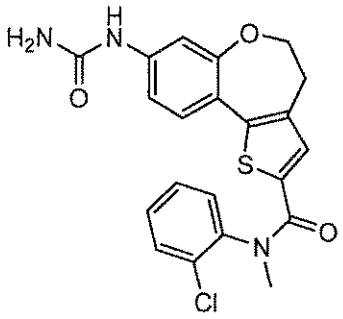
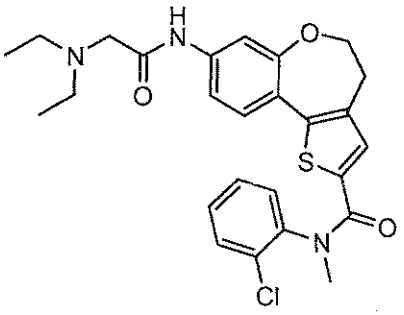
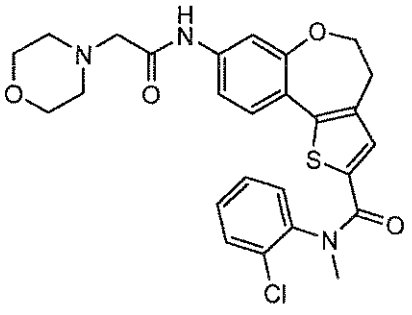
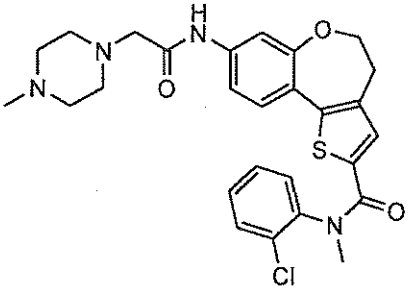
146		N-(2-chlorophenyl)-N-methyl-8-(3-(methylsulfonyl)phenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
147		8-acetamido-N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
148		N2-(2-chlorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
149		methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-ylcarbamate

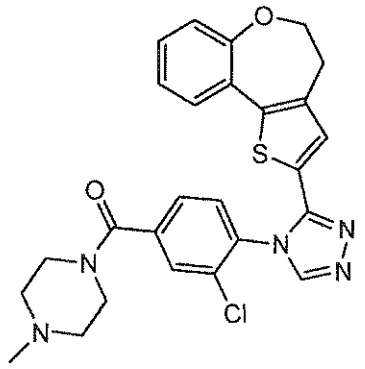
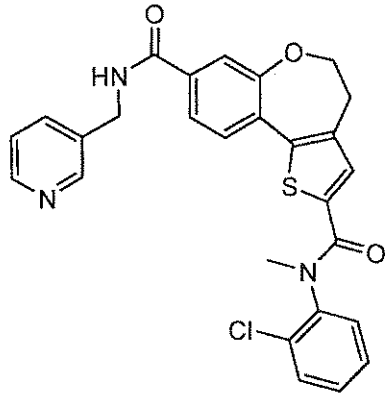
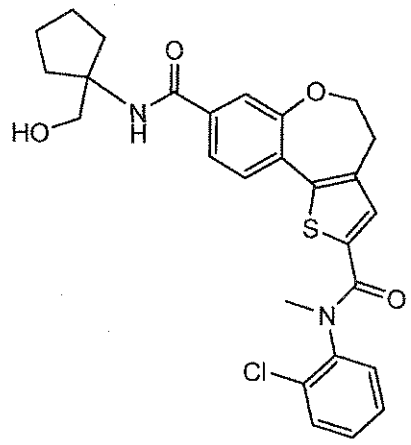
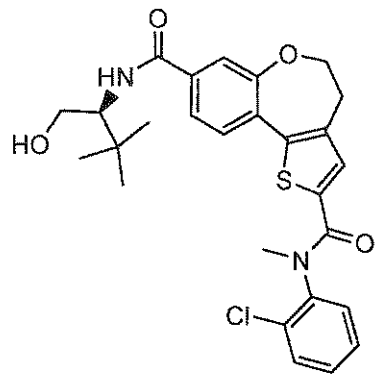
150		8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
151		8-acetamido-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
152		3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyridine
153		4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyridine
154		N2-(2-chlorophenyl)-N2-(2-hydroxyethyl)-N8-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide

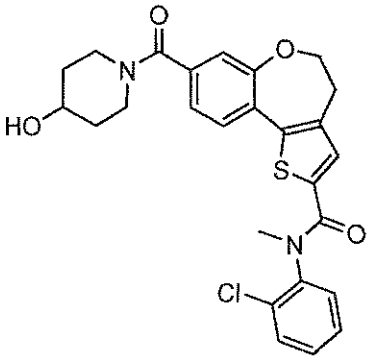
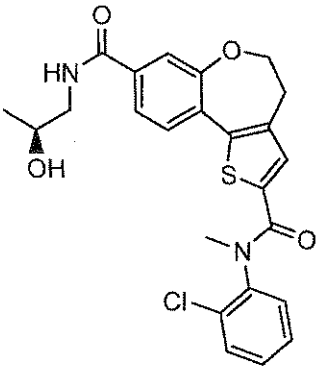
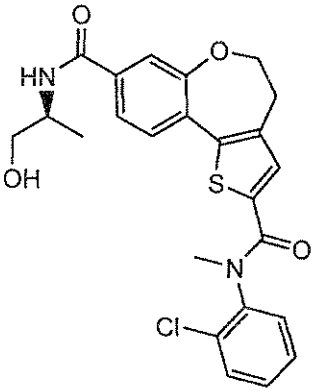
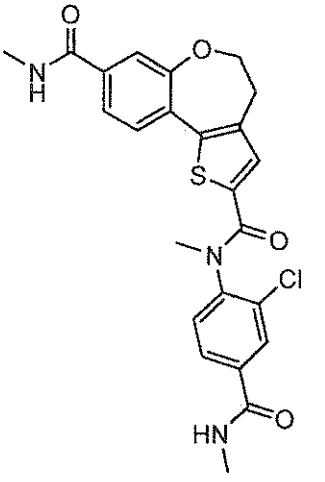
155		N2-(4-chloropyridin-3-yl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
156		N-(2,4-difluorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
157		N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
158		N-(2-chlorophenyl)-8-(2-hydroxyacetamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

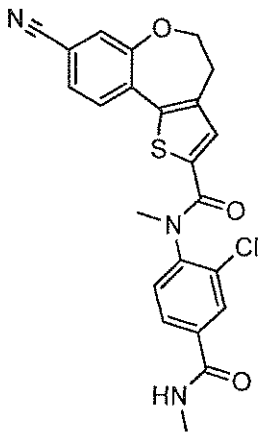
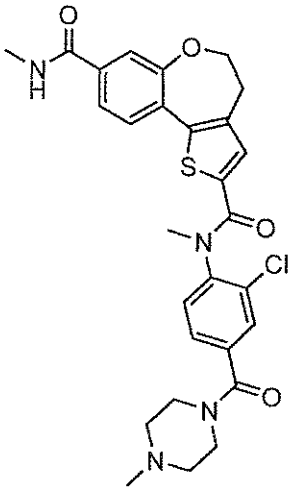
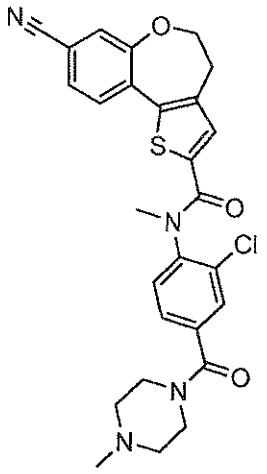
159		N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-(2-hydroxyethyl)-10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
160		N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-(2-hydroxyethyl)-10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
161		N-(2-chlorophenyl)-8-(3-(dimethylamino)propanamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
162		N-(2-chlorophenyl)-N-methyl-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-carboxamide

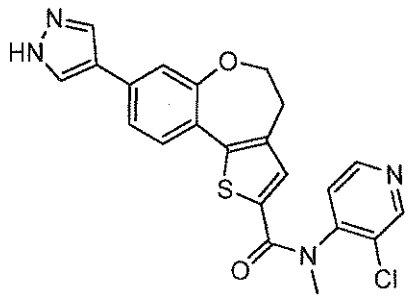
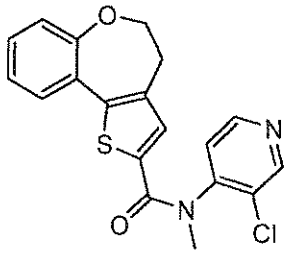
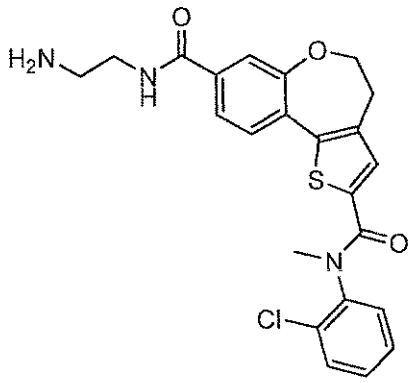
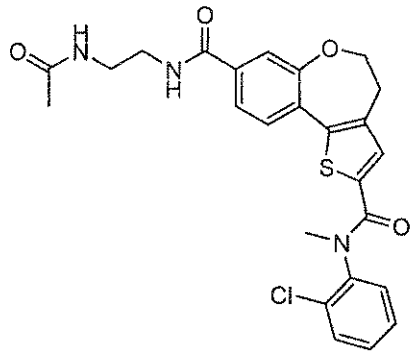
163		5-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyrimidin-2-amine
164		3-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole
165		4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(5-(2-chlorophenyl))-thiazol-2-amine
166		N-(2-chlorophenyl)-8-(3-ethylureido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

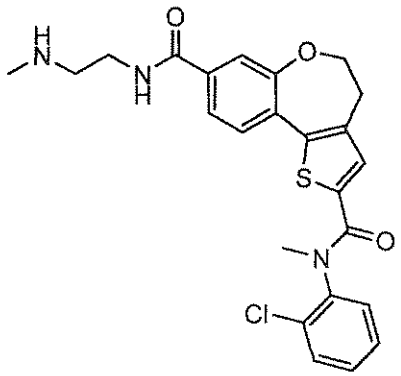
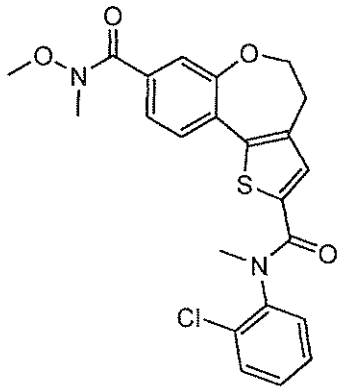
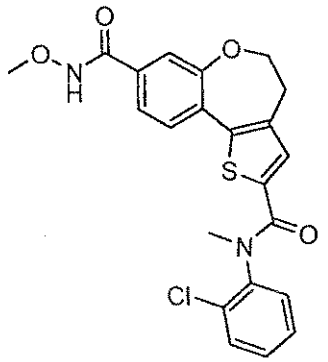
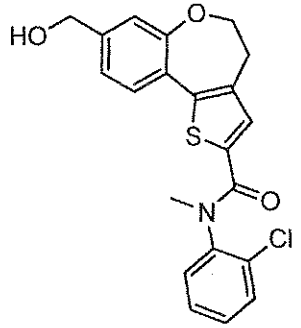
167		N-(2-chlorophenyl)-N-methyl-8-(3-methylureido)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
168		N-(2-chlorophenyl)-N-methyl-8-ureido-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
169		N-(2-chlorophenyl)-8-(2-(diethylamino)acetamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
170		N-(2-chlorophenyl)-N-methyl-8-(2-morpholinoacetamido)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
171		N-(2-chlorophenyl)-N-methyl-8-(2-(4-methylpiperazin-1-yl)acetamido)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

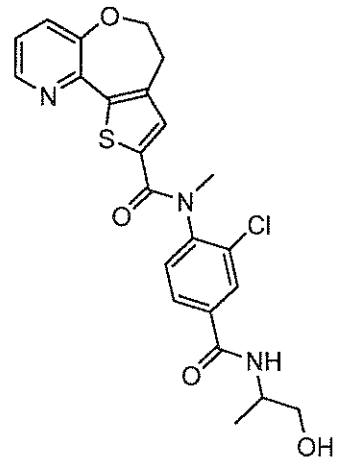
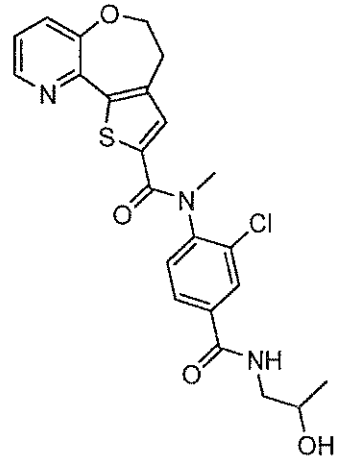
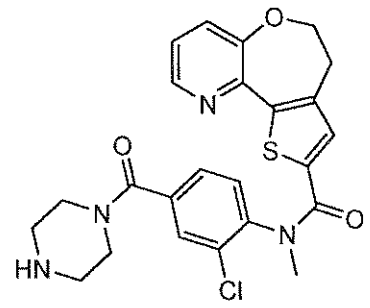
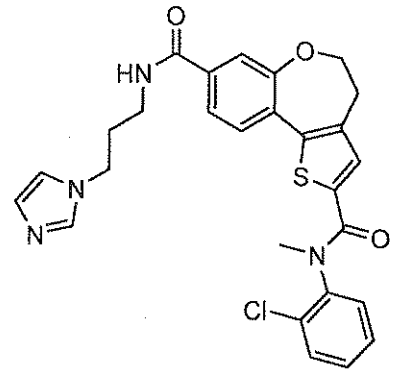
172		(3-chloro-4-(3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4H-1,2,4-triazol-4-yl)phenyl)(4-methylpiperazin-1-yl)methanone
173		N2-(2-chlorophenyl)-N2-methyl-N8-(pyridin-3-ylmethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
174		N2-(2-chlorophenyl)-N8-(1-(hydroxymethyl)cyclopentyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
175		N2-(2-chlorophenyl)-N8-((S)-1-hydroxy-3,3-dimethylbutan-2-yl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide

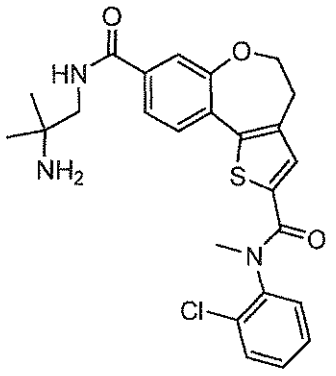
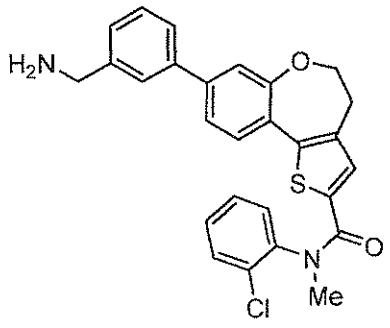
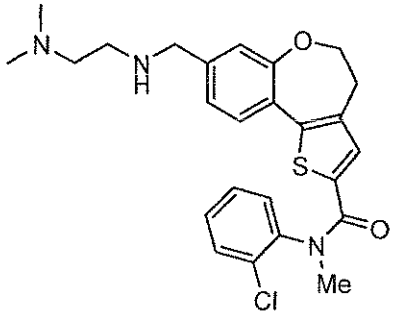
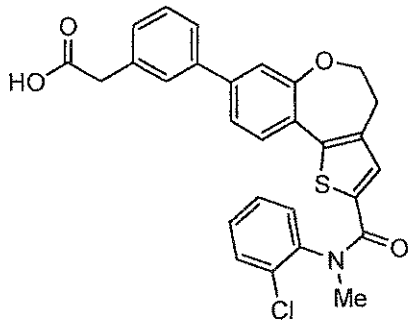
176		N-(2-chlorophenyl)-8-(4-hydroxypiperidine-1-carbonyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
177		N2-(2-chlorophenyl)-N8-((S)-2-hydroxypropyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
178		N2-(2-chlorophenyl)-N8-((S)-1-hydroxypropan-2-yl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
179		N2-(2-chloro-4-(methylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide

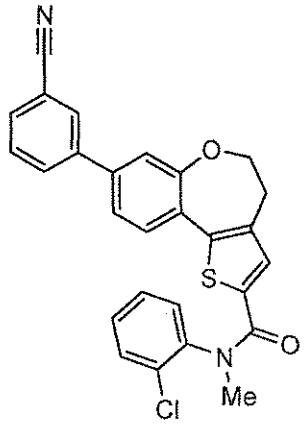
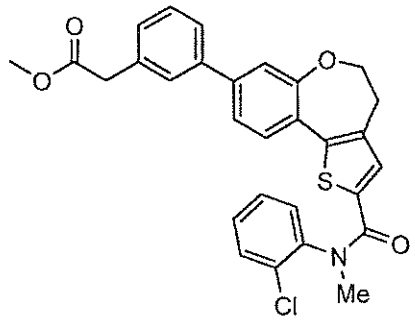
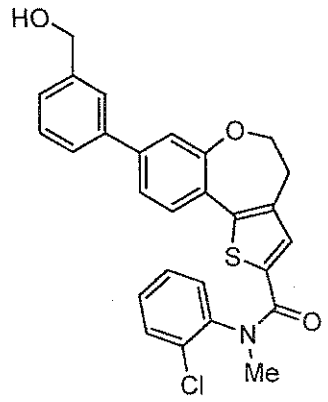
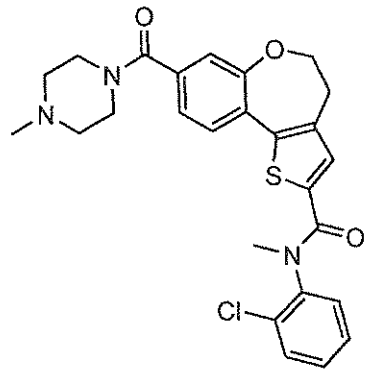
180		N-(2-chloro-4-(methylcarbamoyl)phenyl)-8-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
181		N2-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
182		N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-8-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

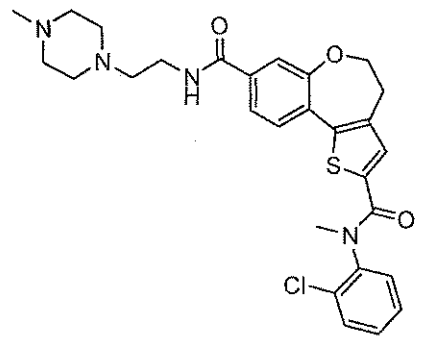
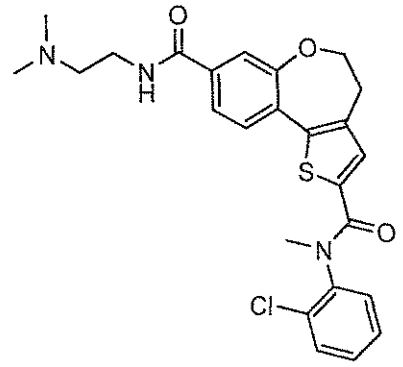
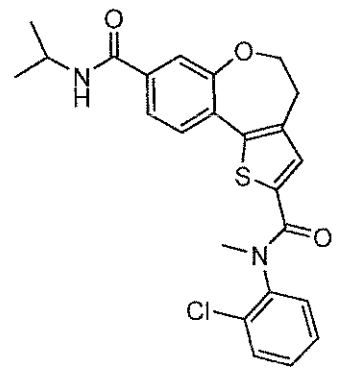
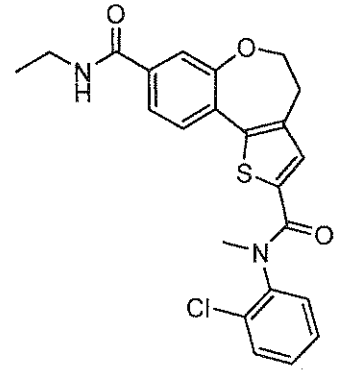
183		N-(3-chloropyridin-4-yl)-N-methyl-8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
184		N-(3-chloropyridin-4-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
185		N8-(2-aminoethyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
186		N8-(2-acetamidoethyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide

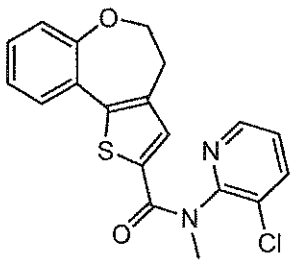
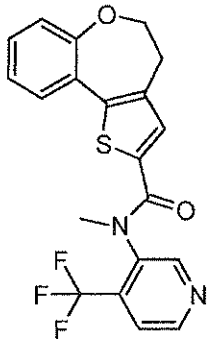
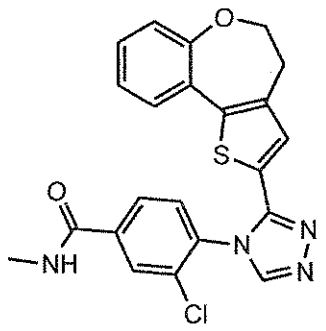
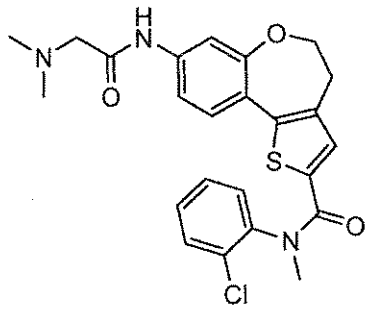
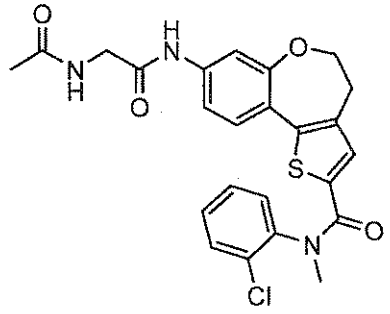
187		N2-(2-chlorophenyl)-N2-methyl-N8-(2-(methylamino)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
188		N2-(2-chlorophenyl)-N8-methoxy-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
189		N2-(2-chlorophenyl)-N8-methoxy-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
190		N-(2-chlorophenyl)-8-(hydroxymethyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

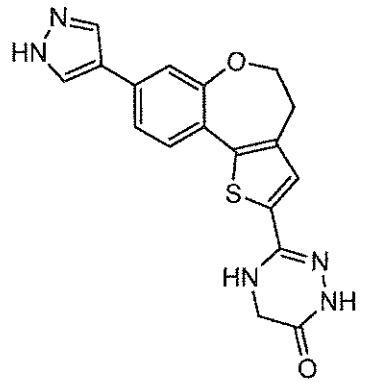
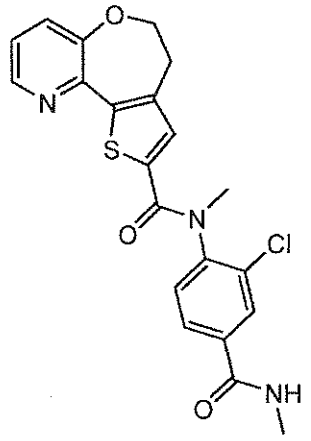
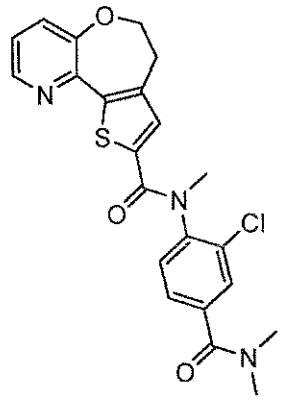
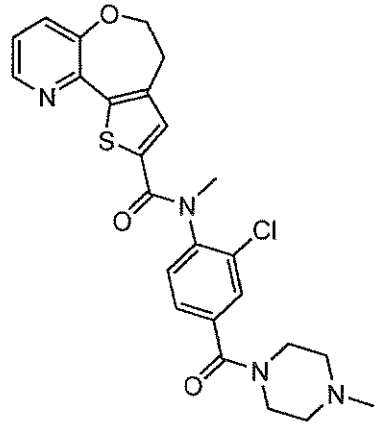
191		N-(2-chloro-4-(1-hydroxypropan-2-ylcarbamoyl)phenyl)-N,10-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
192		N-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-N-methyl(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide
193		N-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N-methyl(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide
194		N8-(3-(1H-imidazol-1-yl)propyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide

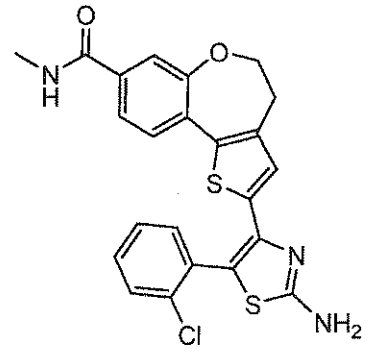
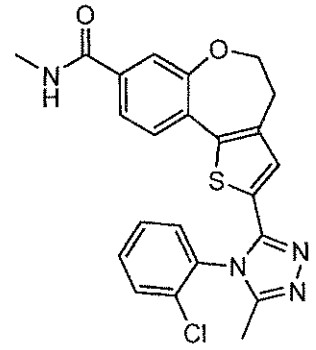
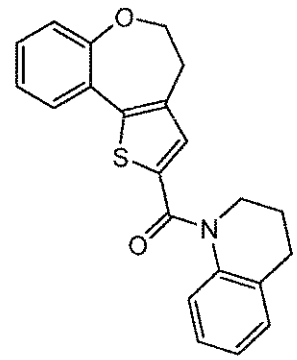
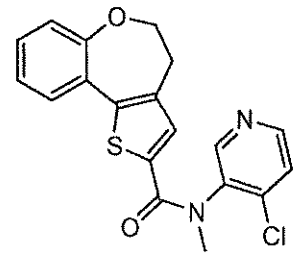
195		N8-(2-amino-2-methylpropyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
196		8-(3-(aminomethyl)phenyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
197		N-(2-chlorophenyl)-8-((2-(dimethylamino)ethylamino)methyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
198		2-(3-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)phenyl)acetic acid

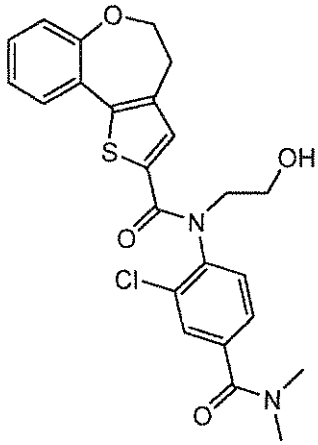
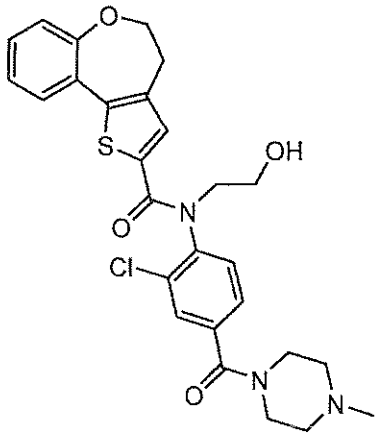
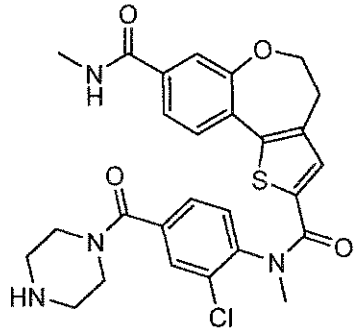
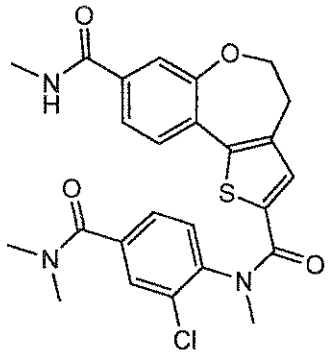
199		N-(2-chlorophenyl)-8-(3-cyanophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
200		methyl 2-(3-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)phenyl)acetate
201		N-(2-chlorophenyl)-8-(3-(hydroxymethyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
202		N-(2-chlorophenyl)-N-methyl-8-(4-methylpiperazine-1-carbonyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

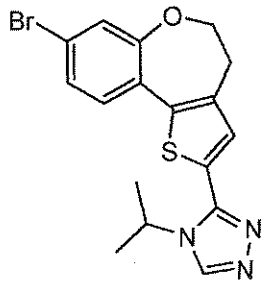
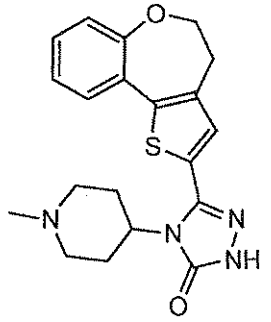
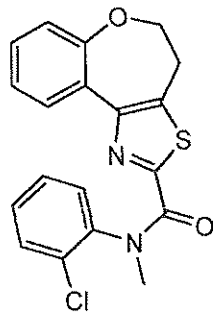
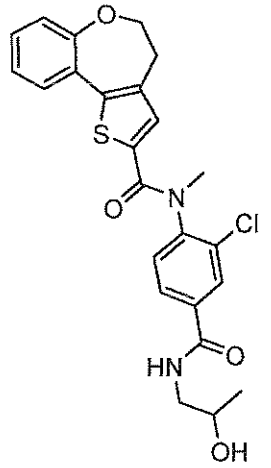
203		N2-(2-chlorophenyl)-N2-methyl-N8-(2-(4-methylpiperazin-1-yl)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
204		N2-(2-chlorophenyl)-N8-(2-(dimethylamino)ethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
205		N2-(2-chlorophenyl)-N8-isopropyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
206		N2-(2-chlorophenyl)-N8-ethyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide

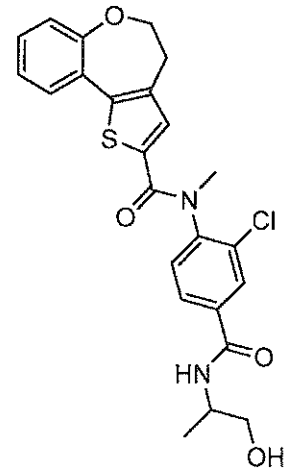
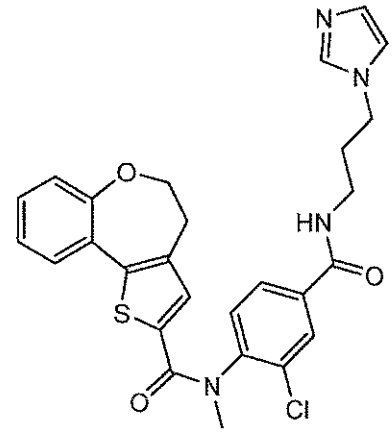
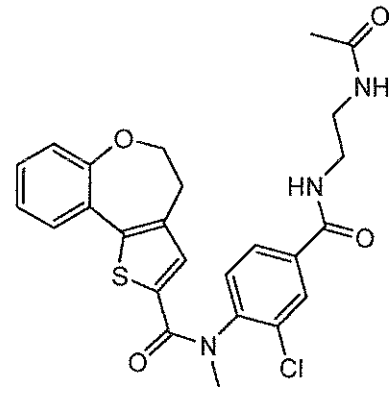
207		N-(3-chloropyridin-2-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
208		N-methyl-N-(4-(trifluoromethyl)pyridin-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
209		3-chloro-4-(3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4H-1,2,4-triazol-4-yl)-N-methylbenzamide
210		N-(2-chlorophenyl)-8-(2-(dimethylamino)acetamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
211		8-(2-acetamidoacetamido)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

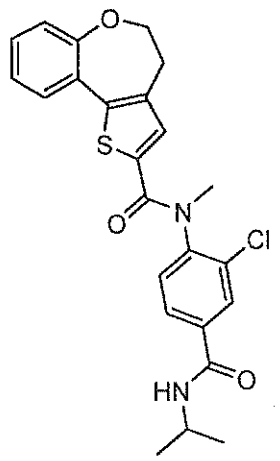
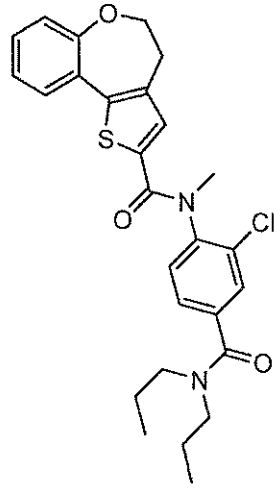
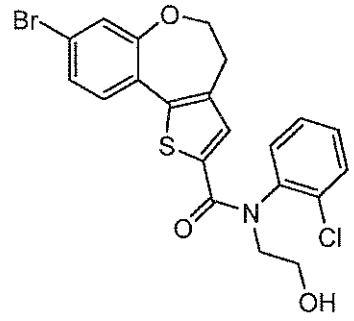
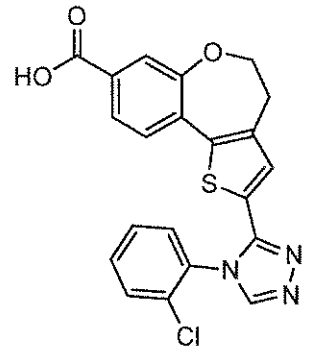
212		3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4,5-dihydro-1,2,4-triazin-6(1H)-one
213		N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-methyl(10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
214		N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl(10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide
215		N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide

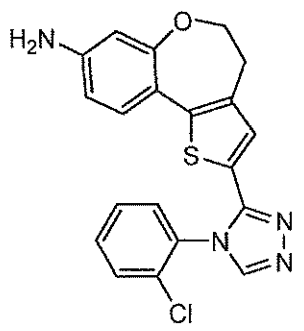
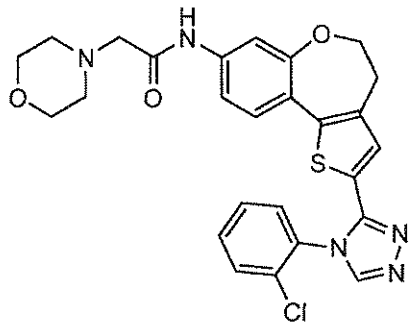
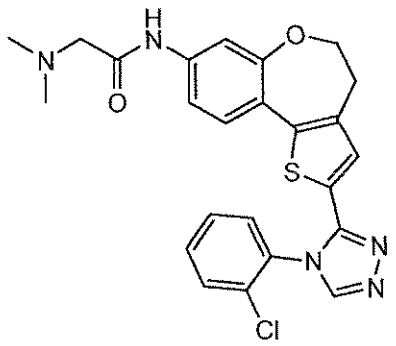
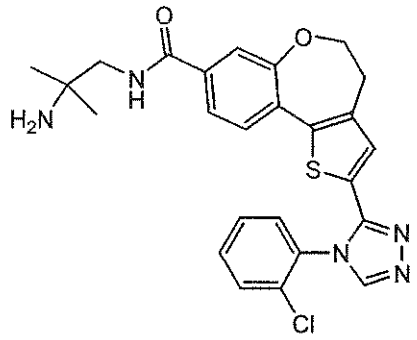
216		2-(2-amino-5-(2-chlorophenyl)thiazol-4-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
217		2-(4-(2-chlorophenyl)-5-methyl-4H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
218		(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone
219		N-(4-chloropyridin-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

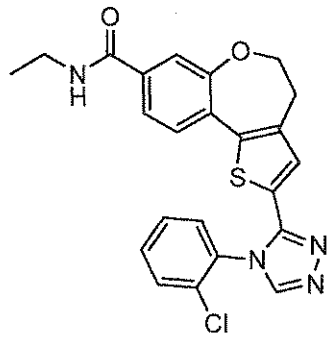
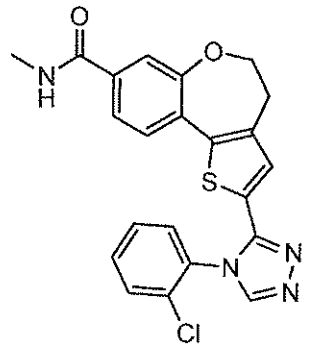
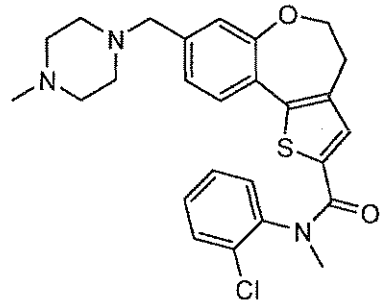
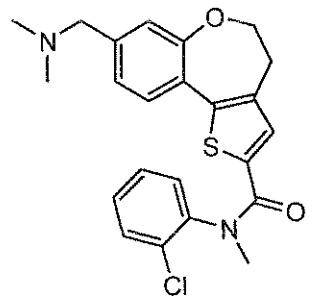
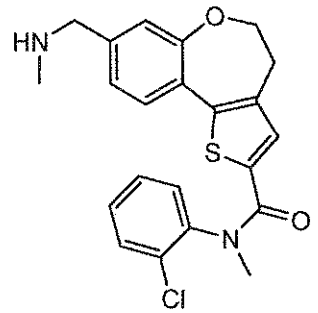
220		N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
221		N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
222		N2-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
223		N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide

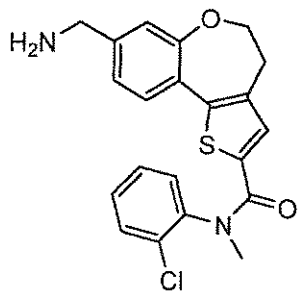
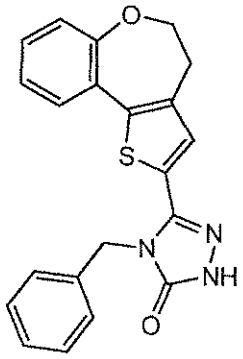
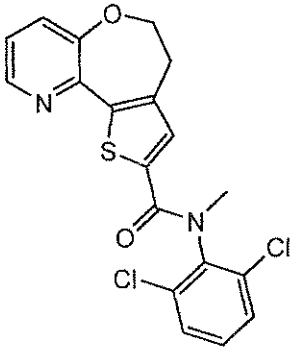
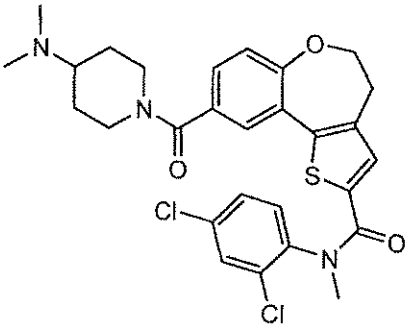
224		3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isopropyl-4H-1,2,4-triazole
225		3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(1-methylpiperidin-4-yl)-1H-1,2,4-triazol-5(4H)-one
226		4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-phenyl)-methyl-amide
227		N-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

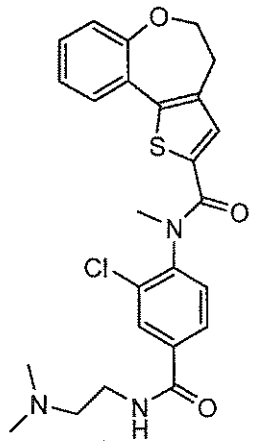
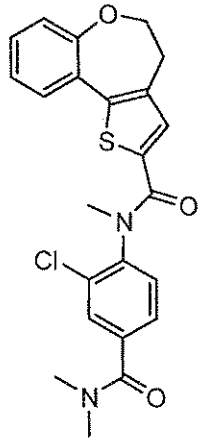
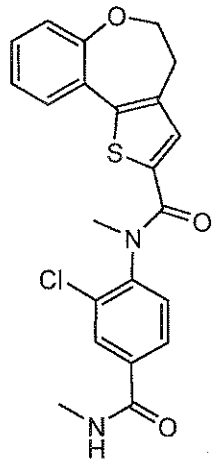
228		N-(2-chloro-4-(1-hydroxypropan-2-ylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
229		N-(4-(3-(1H-imidazol-1-yl)propylcarbamoyl)-2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
230		N-(4-(2-acetamidoethylcarbamoyl)-2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

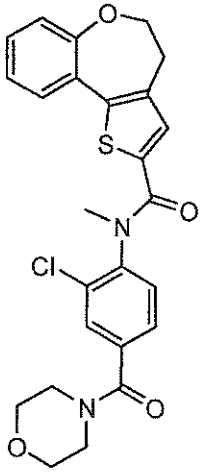
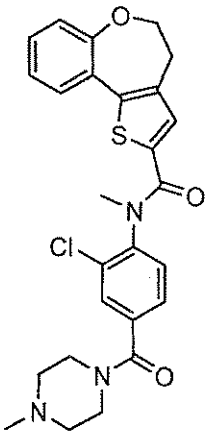
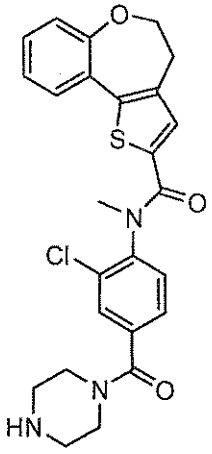
231		N-(2-chloro-4-(isopropylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
232		N-(2-chloro-4-(dipropylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
233		8-bromo-N-(2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
234		2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid

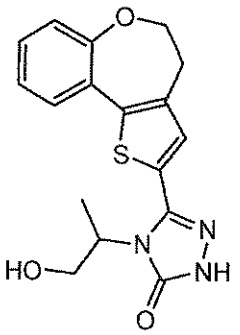
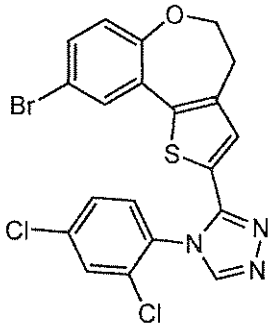
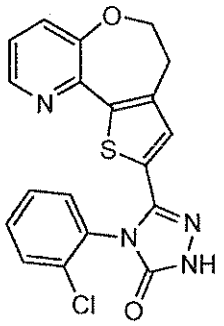
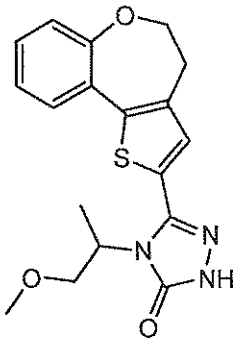
235		2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-amine
236		N-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-2-morpholinoacetamide
237		N-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-2-(dimethylamino)acetamide
238		N-(2-amino-2-methylpropyl)-2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

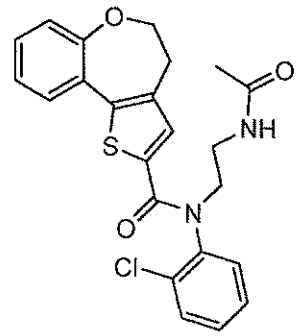
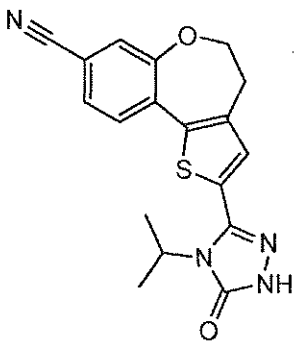
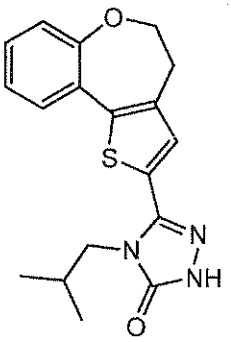
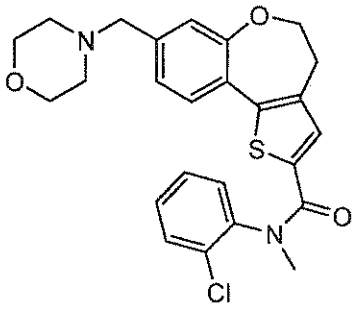
239		2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-ethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
240		2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
241		N-(2-chlorophenyl)-N-methyl-8-((4-methylpiperazin-1-yl)methyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
242		N-(2-chlorophenyl)-8-((dimethylamino)methyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
243		N-(2-chlorophenyl)-N-methyl-8-((methylamino)methyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

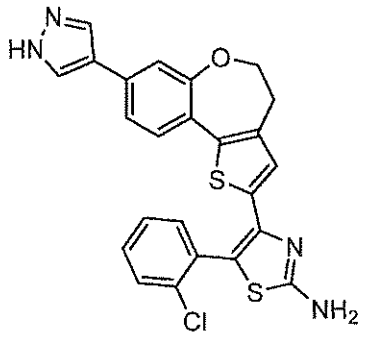
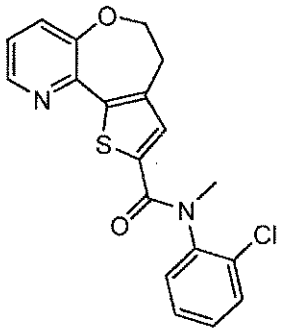
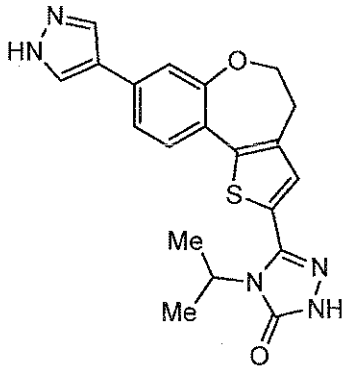
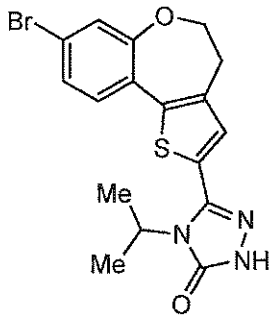
244		8-(aminomethyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
245		4-benzyl-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-5(4H)-one
246		N-(2,6-dichlorophenyl)-N-methyl-(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
247		N-(2,4-dichlorophenyl)-9-(4-(dimethylamino)piperidine-1-carbonyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

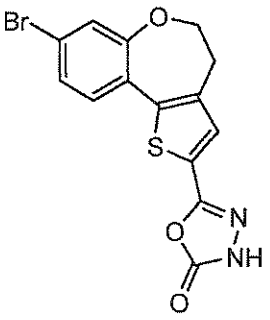
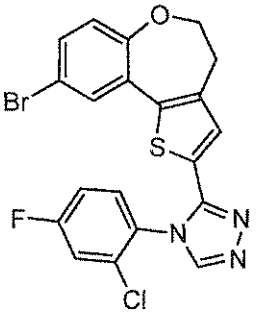
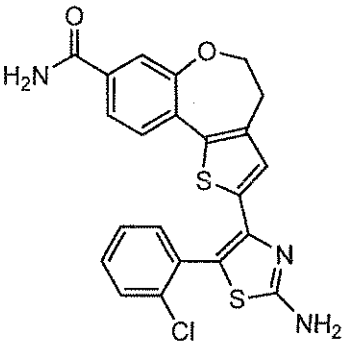
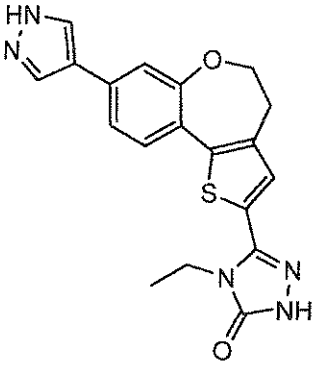
248		N-(2-chloro-4-(2-(dimethylamino)ethylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
249		N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
250		N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

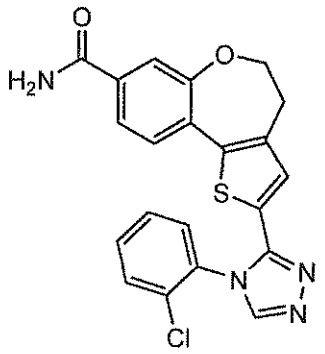
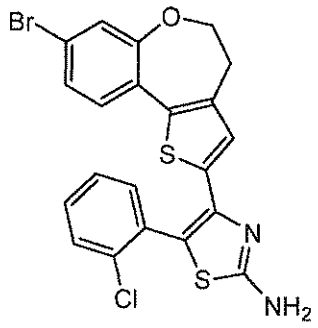
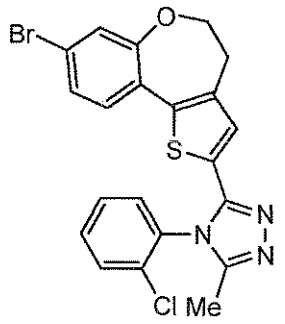
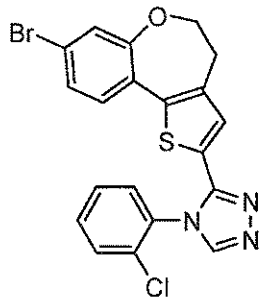
251		N-(2-chloro-4-(morpholine-4-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
252		N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
253		N-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

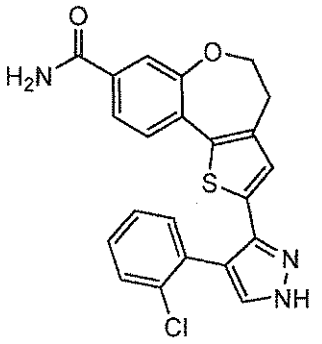
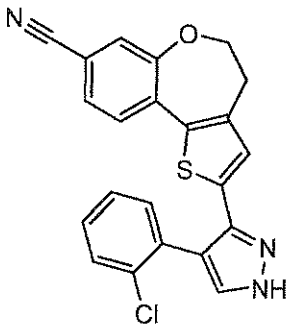
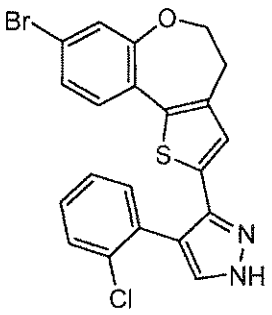
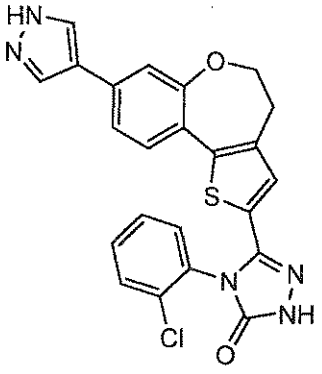
254		3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(1-hydroxypropan-2-yl)-1H-1,2,4-triazol-5(4H)-one
255		3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2,4-dichlorophenyl)-4H-1,2,4-triazole
256		4-(2-chlorophenyl)-3-(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-5(4H)-one
257		3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(1-methoxypropan-2-yl)-1H-1,2,4-triazol-5(4H)-one

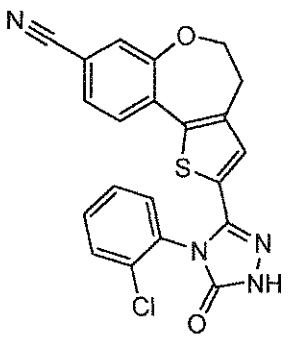
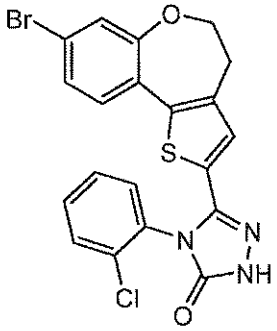
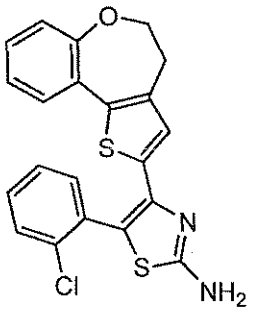
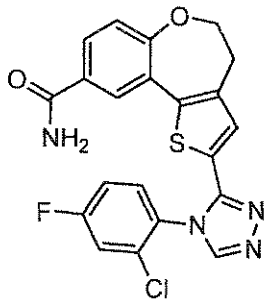
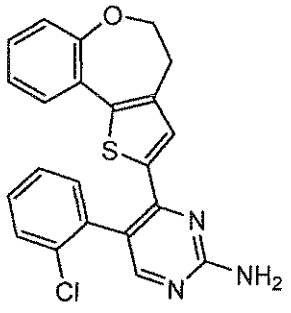
258		N-(2-acetamidoethyl)-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
259		2-(4-isopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile
260		3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isobutyl-1H-1,2,4-triazol-5(4H)-one
261		N-(2-chlorophenyl)-N-methyl-8-(morpholinomethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

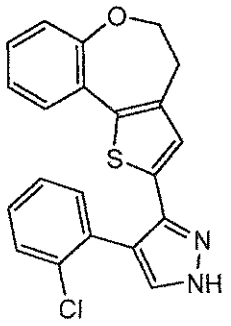
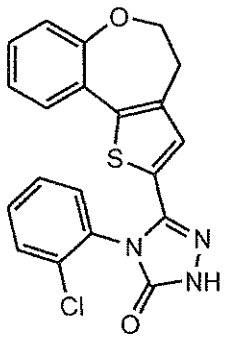
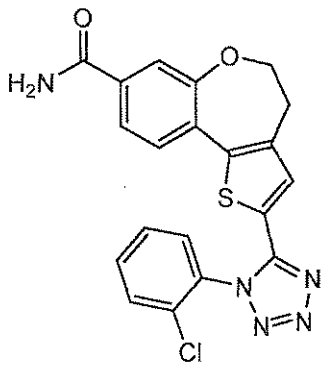
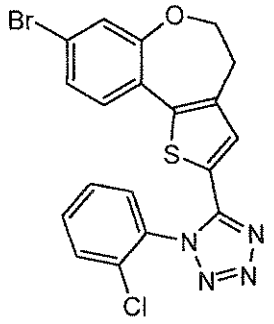
262		4-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-5-(2-chlorophenyl)thiazol-2-amine
263		N-(2-chlorophenyl)-N-methyl-(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
264		3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isopropyl-1H-1,2,4-triazol-5(4H)-one
265		3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isopropyl-1H-1,2,4-triazol-5(4H)-one

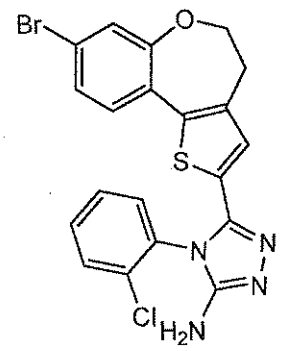
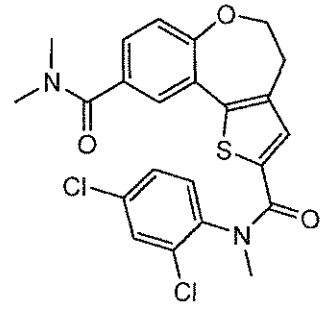
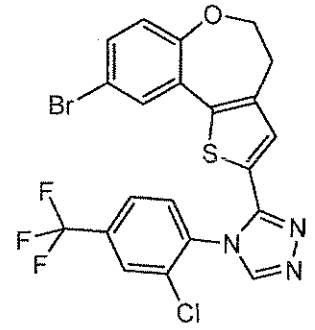
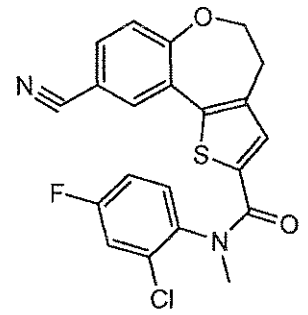
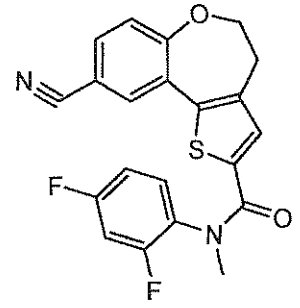
266		5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1,3,4-oxadiazol-2(3H)-one
267		3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chloro-4-fluorophenyl)-4H-1,2,4-triazole
268		2-(2-amino-5-(2-chlorophenyl)thiazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
269		3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-ethyl-1H-1,2,4-triazol-5(4H)-one

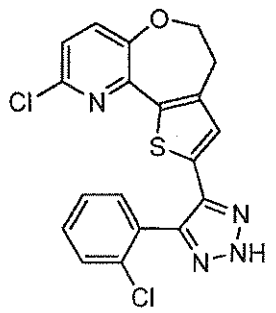
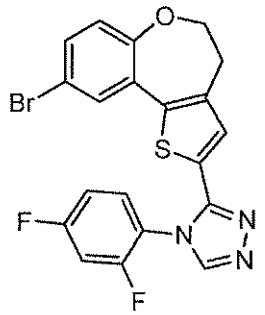
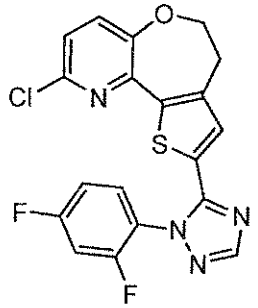
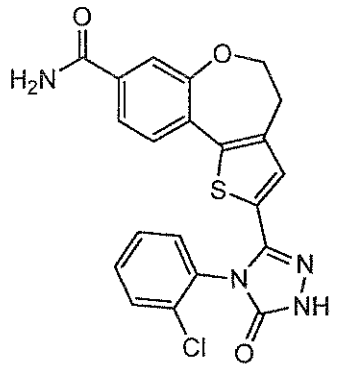
270		2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
271		4-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-5-(2-chlorophenyl)thiazol-2-amine
272		3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-5-methyl-4H-1,2,4-triazole
273		3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole

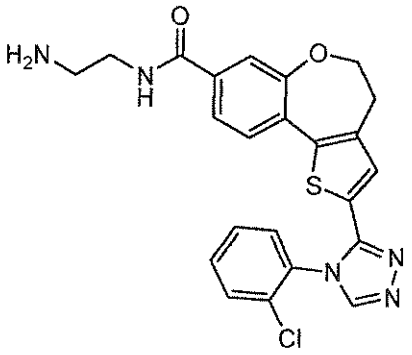
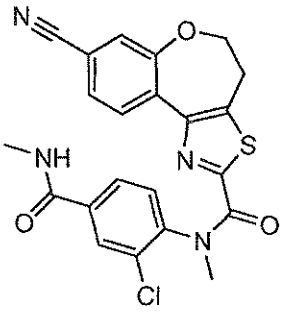
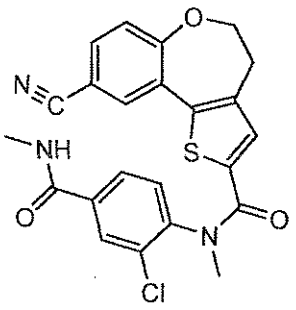
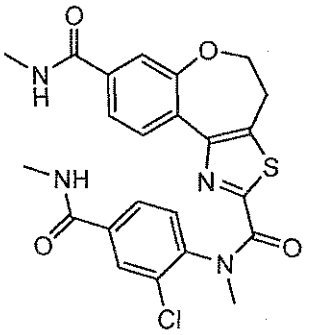
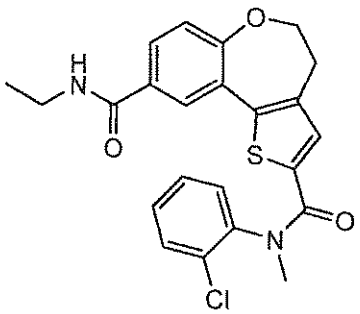
274		2-(4-(2-chlorophenyl)-1H-pyrazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
275		2-(4-(2-chlorophenyl)-1H-pyrazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile
276		3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-pyrazole
277		3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one

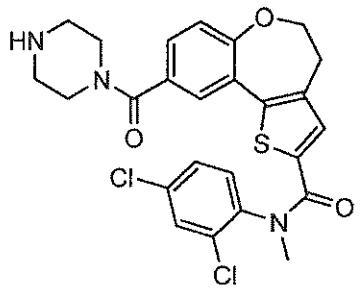
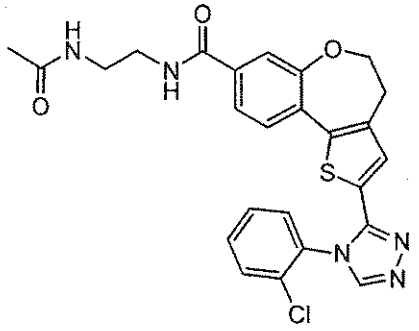
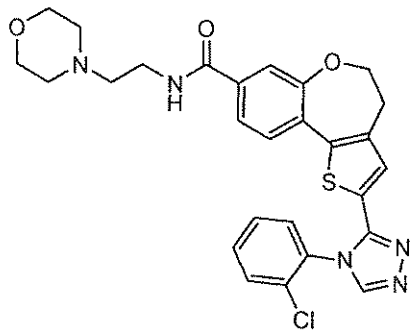
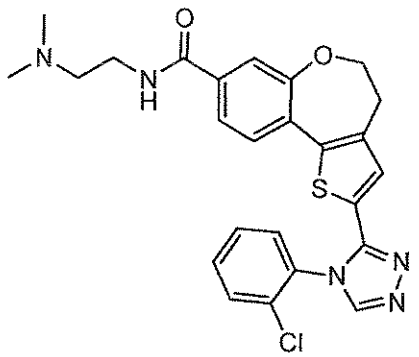
278		2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile
279		3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one
280		5-(2-chlorophenyl)-4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)thiazol-2-amine
281		2-(4-(2-chloro-4-fluorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide
282		5-(2-chlorophenyl)-4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyrimidin-2-amine

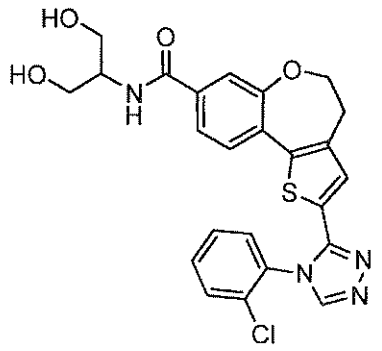
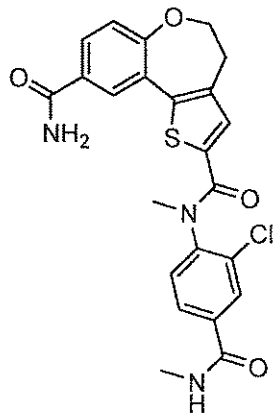
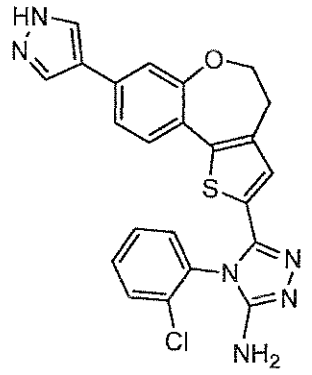
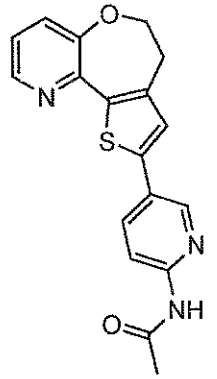
283		4-(2-chlorophenyl)-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-pyrazole
284		4-(2-chlorophenyl)-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-5(4H)-one
285		2-(1-(2-chlorophenyl)-1H-tetrazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
286		5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2-chlorophenyl)-1H-tetrazole

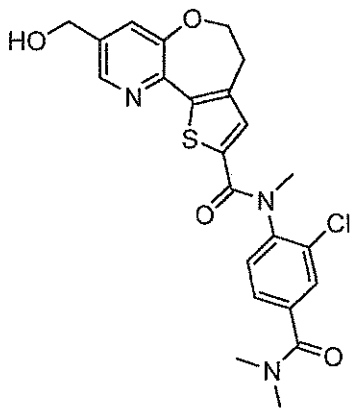
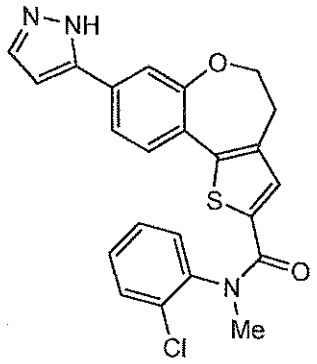
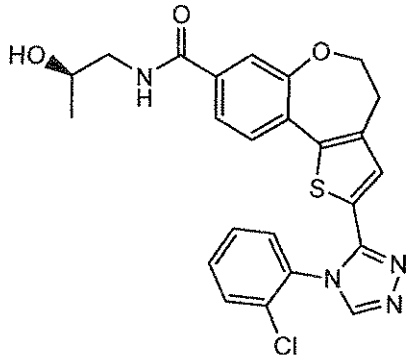
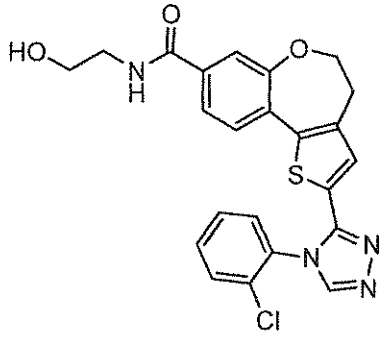
287		5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazol-3-amine
288		N2-(2,4-dichlorophenyl)-N2,N9,N9-trimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide
289		3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chloro-4-(trifluoromethyl)phenyl)-4H-1,2,4-triazole
290		N-(2-chloro-4-fluorophenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
291		9-cyano-N-(2,4-difluorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

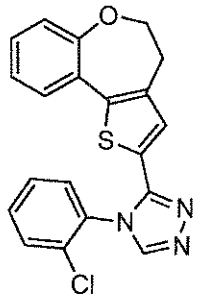
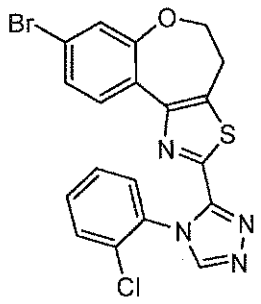
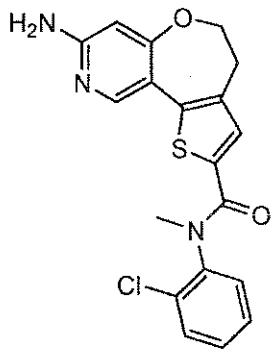
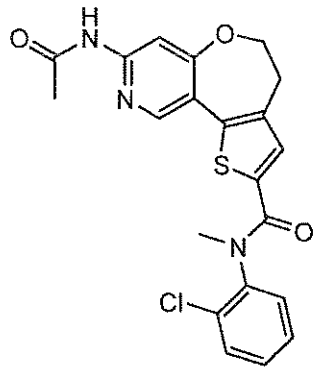
292		4-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2-chlorophenyl)-2H-1,2,3-triazole
293		3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole
294		5-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1,2,4-triazole
295		2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

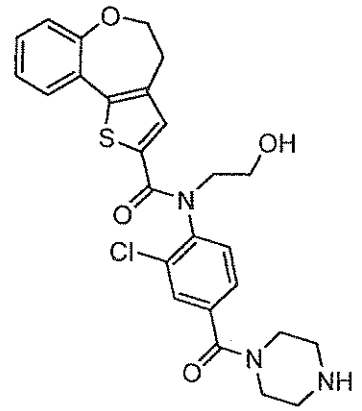
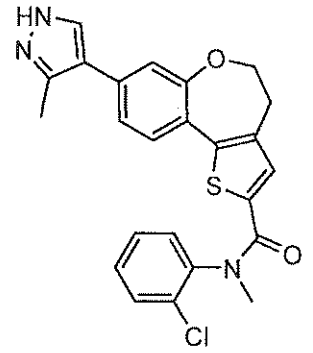
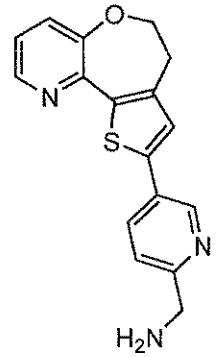
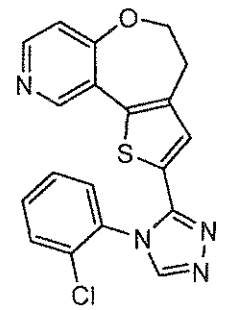
296		N-(2-aminoethyl)-2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
297		8-cyano-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene-2-carboxylic acid (2-chloro-(4-methylcarbamoyl)phenyl)-methyl-amide
298		N-(2-chloro-4-(methylcarbamoyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
299		8-methylcarbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene-2-carboxylic acid (2-chloro-(4-methylcarbamoyl)phenyl)-methyl-amide
300		N2-(2-chlorophenyl)-N9-ethyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide

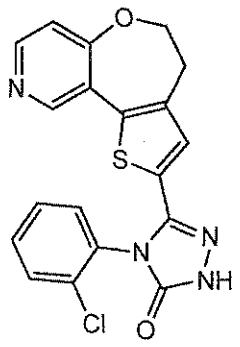
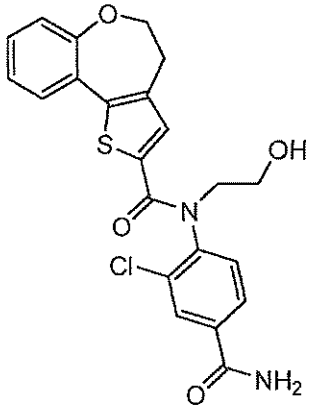
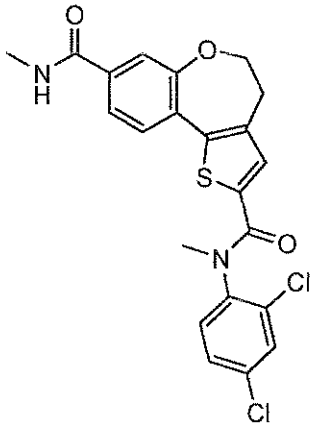
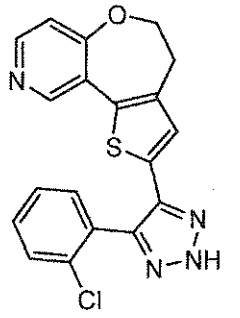
301		N-(2,4-dichlorophenyl)-N-methyl-9-(piperazine-1-carbonyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
302		N-(2-acetamidoethyl)-2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
303		2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-morpholinoethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
304		2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-(dimethylamino)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

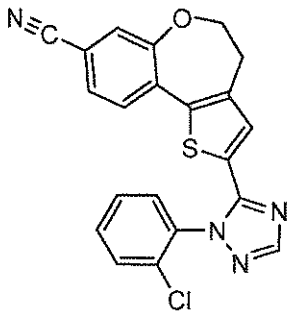
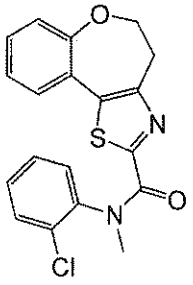
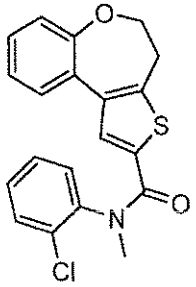
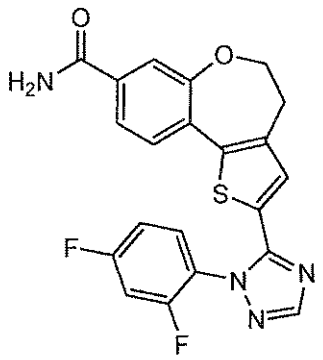
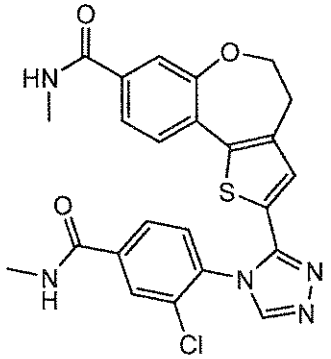
305		2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(1,3-dihydroxypropan-2-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
306		N2-(2-chloro-4-(methylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide
307		5-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazol-3-amine
308		5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-2-acetaminopyridine

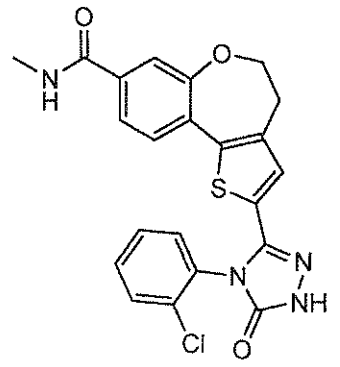
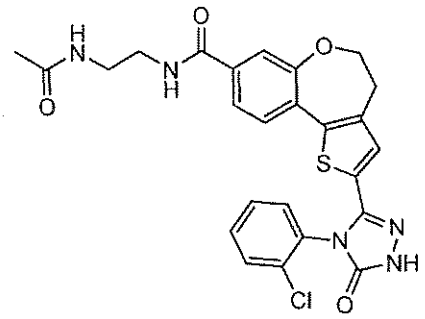
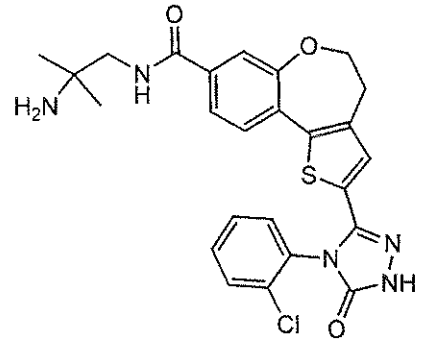
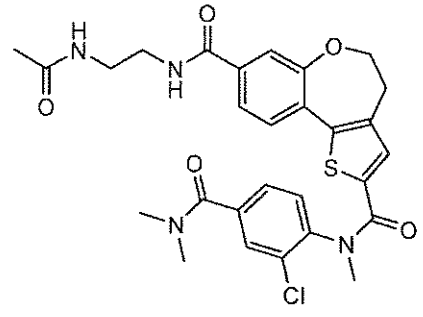
309		N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-(3-hydroxymethyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide
310		N-(2-chlorophenyl)-N-methyl-8-(1H-pyrazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
311		2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-((R)-2-hydroxypropyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
312		2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

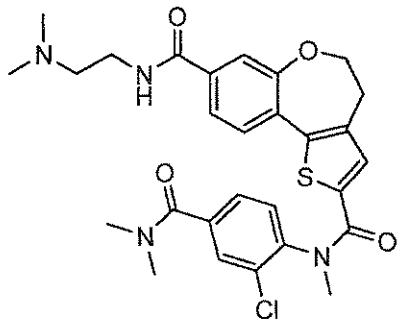
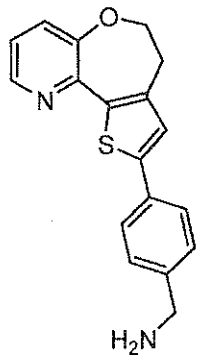
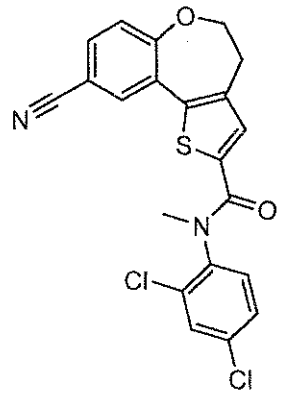
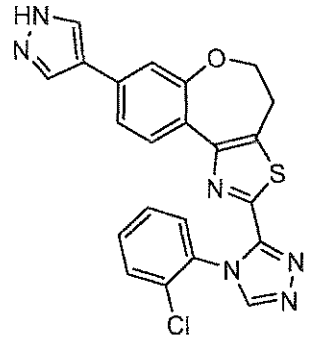
313		4-(2-chlorophenyl)-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4H-1,2,4-triazole
314		8-bromo-2-[4-(2-chloro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
315		N-(2-chlorophenyl)-N-methyl-(8-amino-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide
316		N-(2-chlorophenyl)-N-methyl-(8-acetamino-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide

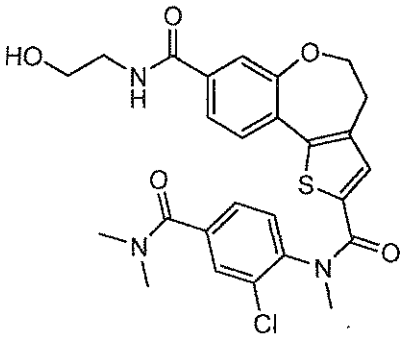
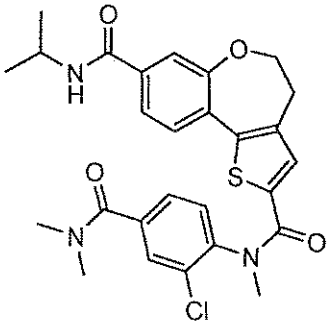
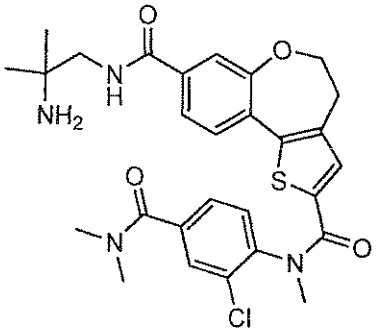
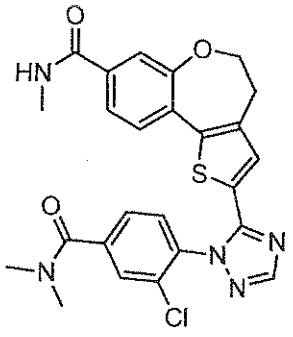
317		N-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
318		N-(2-chlorophenyl)-N-methyl-8-(3-methyl-1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
319		5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-methylamine
320		3-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole

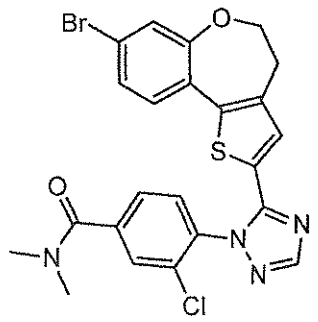
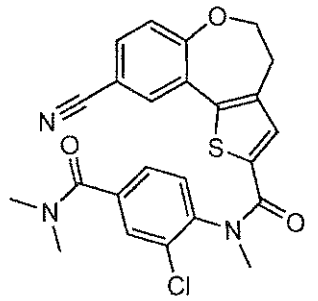
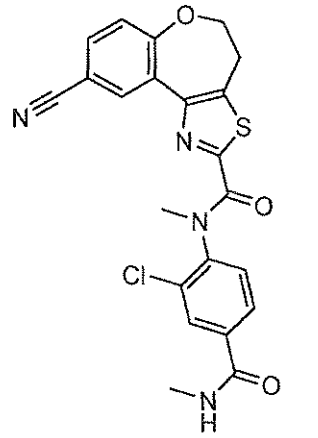
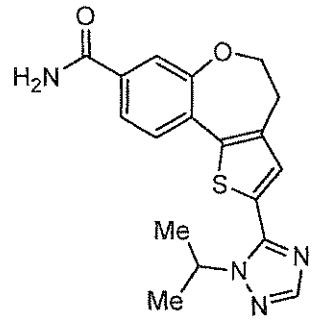
321		3-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one
322		N-(4-carbamoyl-2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
323		N2-(2,4-dichlorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
324		4-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)-5-(2-chlorophenyl)-2H-1,2,3-triazole

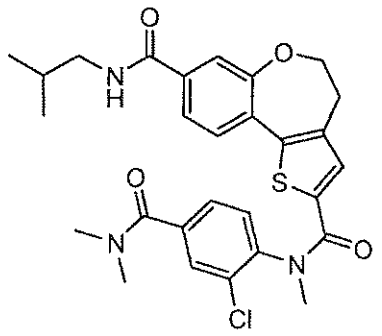
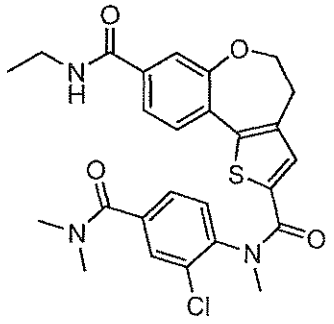
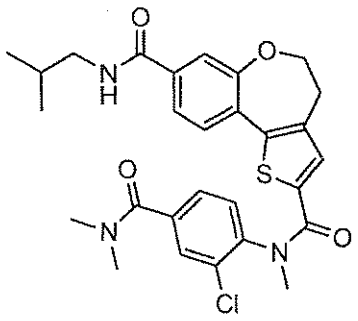
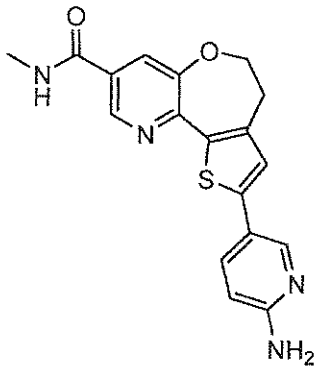
325		2-(1-(2-chlorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile
326		4,5-dihydro-6-oxa-1-thia-3-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-phenyl)-methyl-amide
327		N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[3,2-d]oxepine-2-carboxamide
328		2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
329		2-(4-(2-chloro-4-(methylcarbamoyl)phenyl)-4H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

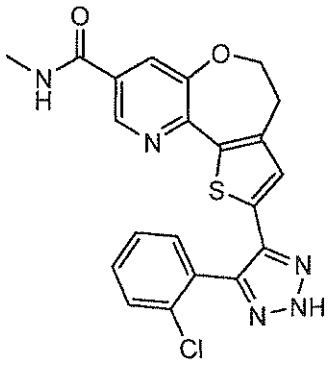
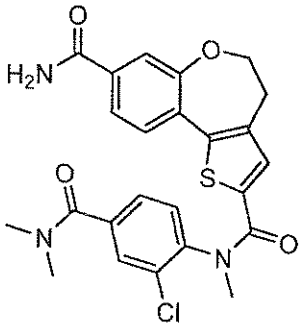
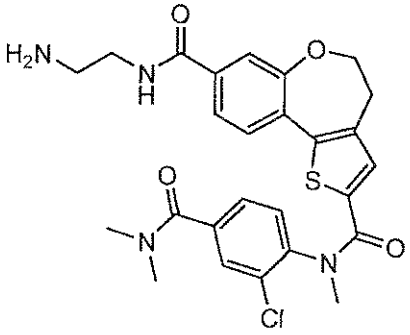
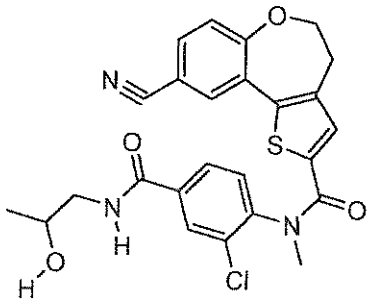
330		2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
331		N-(2-acetamidoethyl)-2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
332		N-(2-amino-2-methylpropyl)-2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
333		N8-(2-acetamidoethyl)-N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide

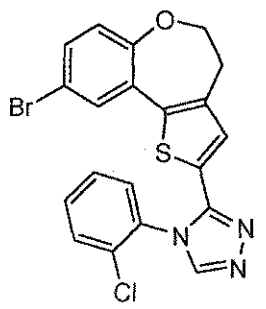
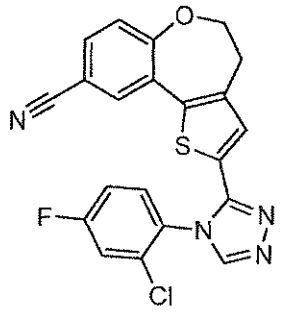
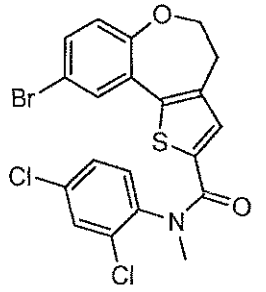
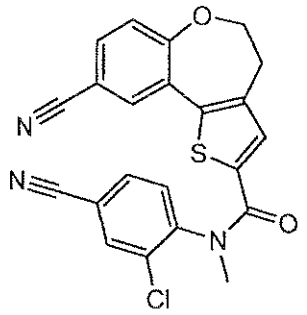
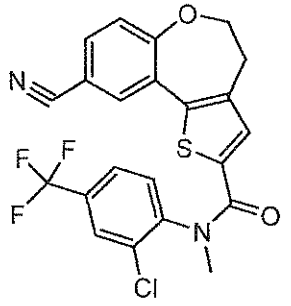
334		N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-(2-(dimethylamino)ethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
335		5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)benzen-2-methylamine
336		9-cyano-N-(2,4-dichlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
337		3-(8-(pyrazol-4-yl)-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole

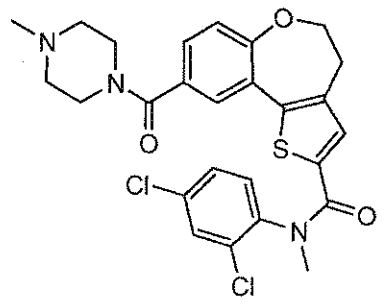
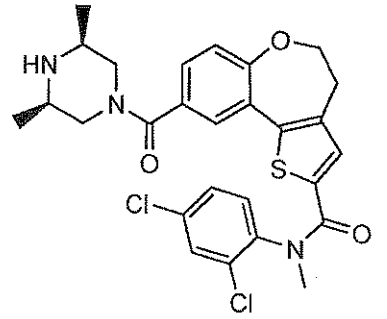
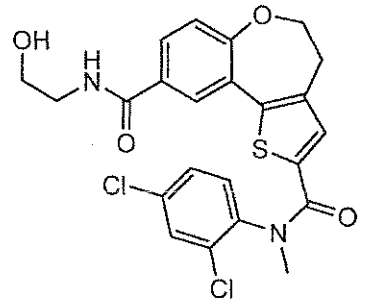
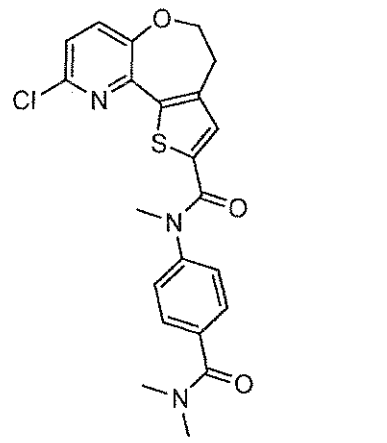
338		N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-(2-hydroxyethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
339		N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-isopropyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
340		N8-(2-amino-2-methylpropyl)-N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
341		2-(1-(2-chloro-4-(dimethylcarbamoyl)phenyl)-1H-1,2,4-triazol-5-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

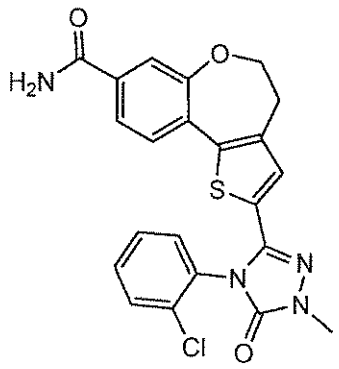
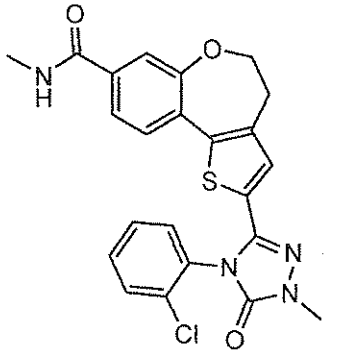
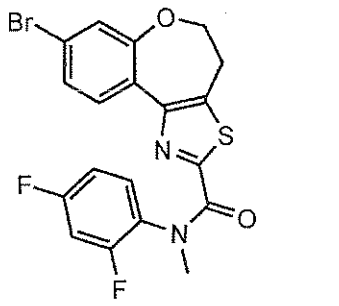
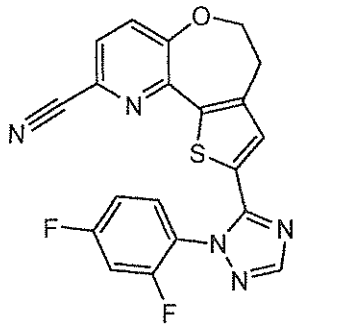
342		4-(5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-1-yl)-3-chloro-N,N-dimethylbenzamide
343		N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
344		2-(9-cyano-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene)-N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-methyl-carboxamide
345		2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

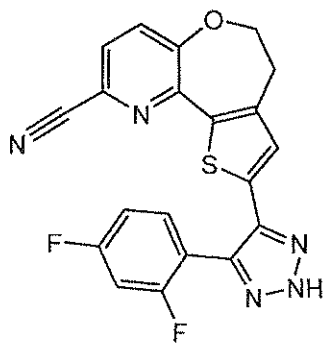
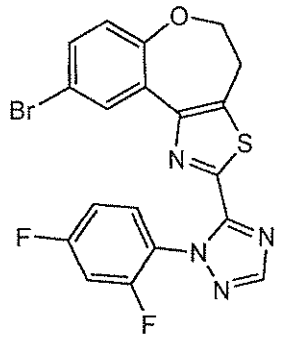
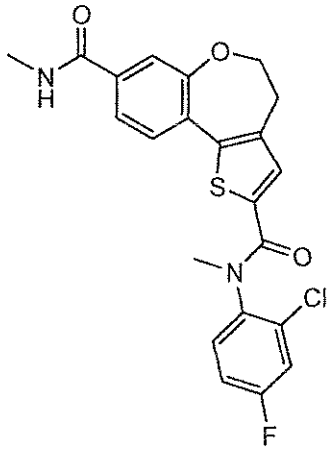
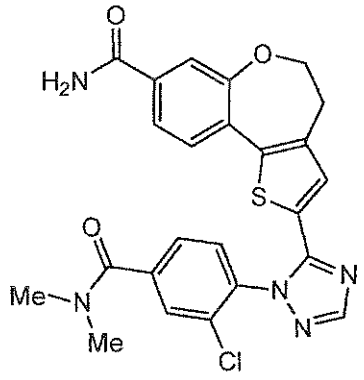
346		N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-isobutyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
347		N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-ethyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
348		N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-isobutyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
349		5-(3-methylcarbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-amine

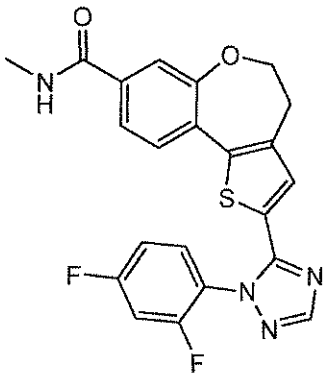
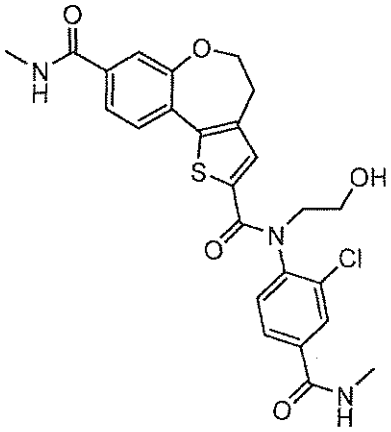
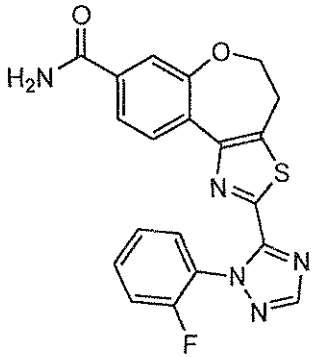
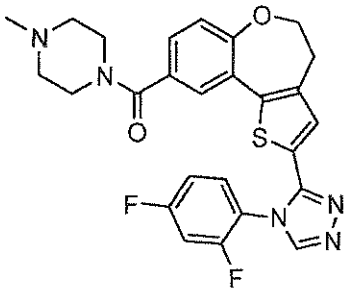
350		4-(3-methylcarbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2-chlorophenyl)-2H-1,2,3-triazole
351		N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
352		N8-(2-aminoethyl)-N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
353		N-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

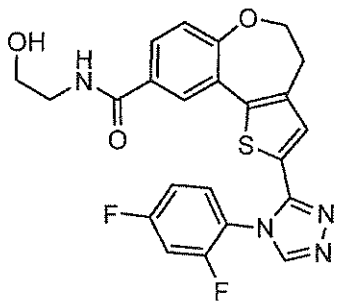
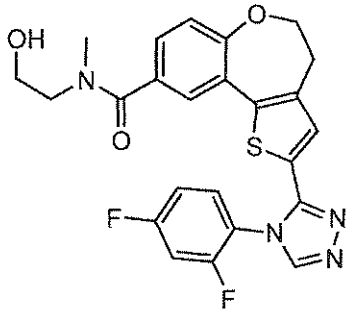
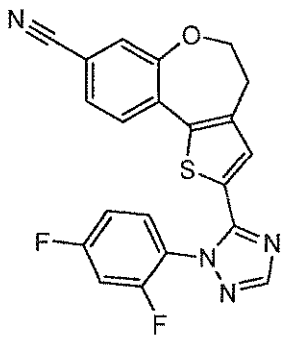
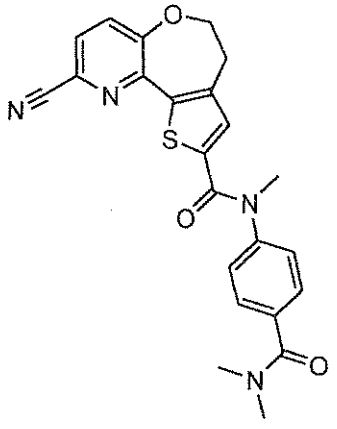
354		3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole
355		2-(4-(2-chloro-4-fluorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carbonitrile
356		9-bromo-N-(2,4-dichlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
357		N-(2-chloro-4-cyanophenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
358		N-(2-chloro-4-(trifluoromethyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

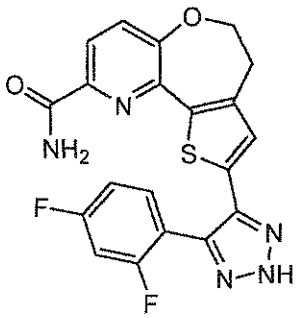
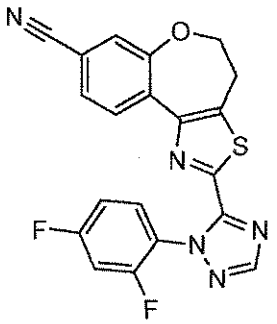
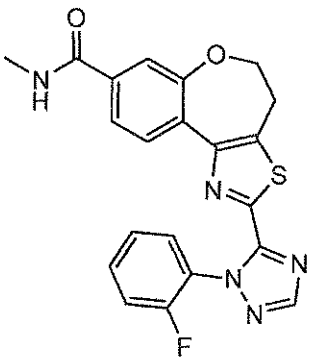
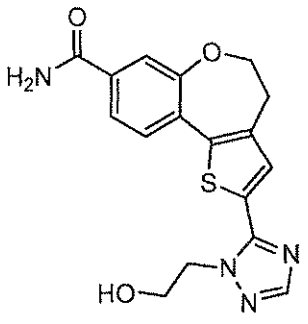
359		N-(2,4-dichlorophenyl)-N-methyl-9-(4-methylpiperazine-1-carbonyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
360		N-(2,4-dichlorophenyl)-9-((3S,5R)-3,5-dimethylpiperazine-1-carbonyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
361		N2-(2,4-dichlorophenyl)-N9-(2-hydroxyethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide
362		N-(4-(dimethylcarbamoyl)phenyl)-N-methyl-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide

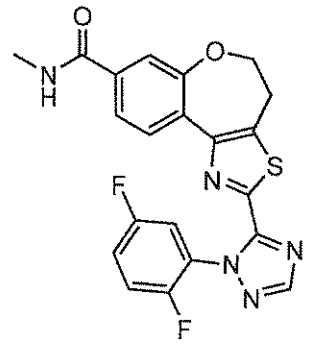
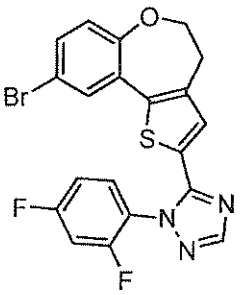
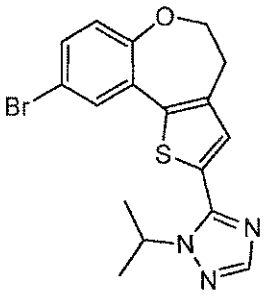
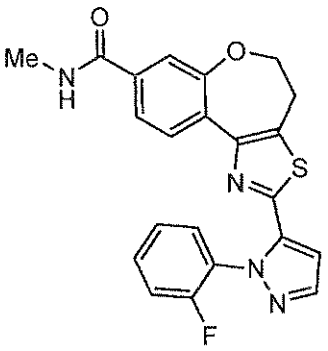
363		2-(4-(2-chlorophenyl)-1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
364		2-(4-(2-chlorophenyl)-1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
365		2-(8-bromo-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene)-N-(2,4-difluoro)phenyl)-N-methyl-carboxamide
366		3-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-2-(2,4-difluorophenyl)-2H-1,2,4-triazole

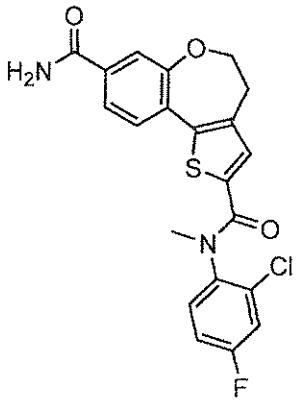
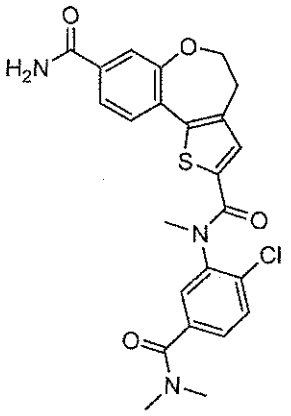
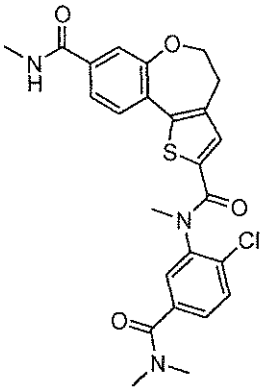
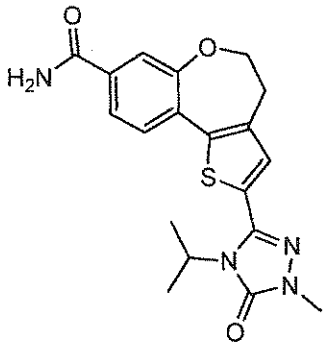
367		4-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2,4-difluorophenyl)-2H-1,2,3-triazole
368		3-(9-bromo-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole
369		N2-(2-chloro-4-fluorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
370		2-(1-(2-chloro-4-(dimethylcarbamoyl)phenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

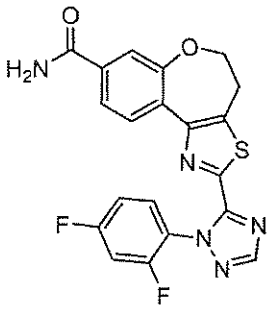
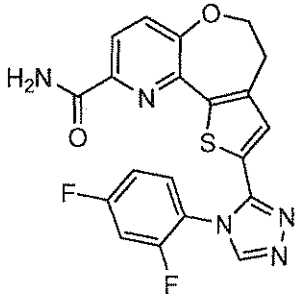
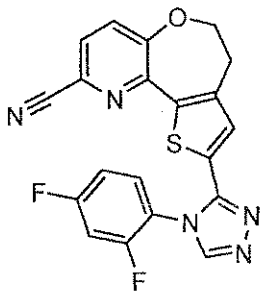
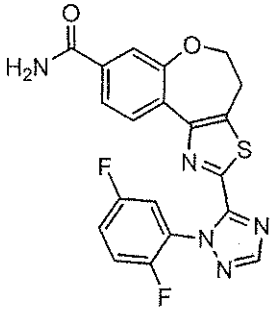
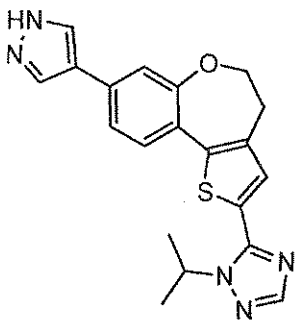
371		2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
372		N2-(2-chloro-4-(methylcarbamoyl)phenyl)-N2-(2-hydroxyethyl)-N8-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
373		3-(8-carbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-4-(2-fluorophenyl)-4H-1,2,4-triazole
374		(2-(4-(2,4-difluorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(4-methylpiperazin-1-yl)methanone

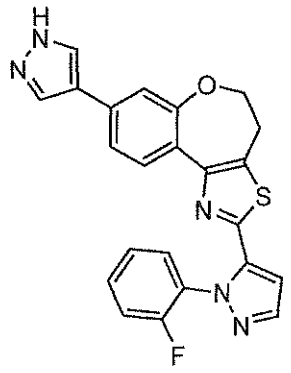
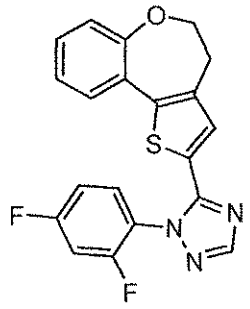
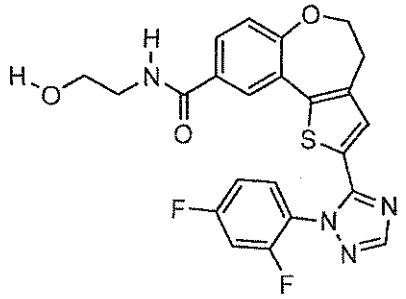
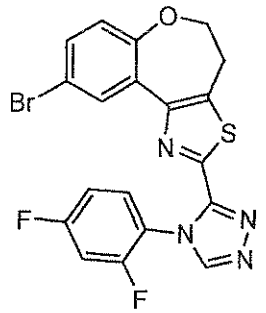
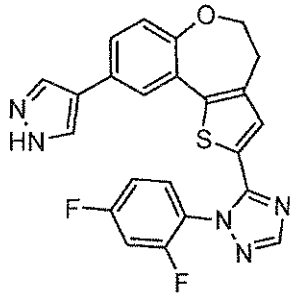
375		2-(4-(2,4-difluorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide
376		2-(4-(2,4-difluorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-hydroxyethyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide
377		2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile
378		N-(4-(dimethylcarbamoyl)phenyl)-N-methyl-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide

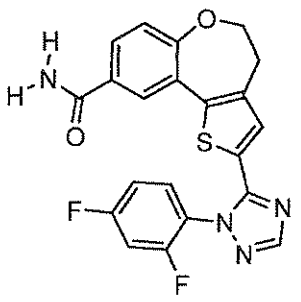
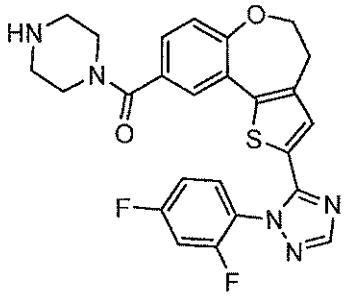
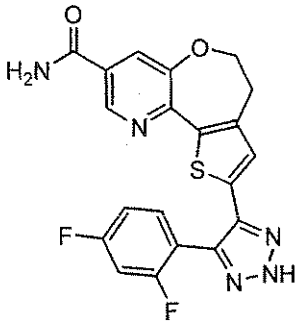
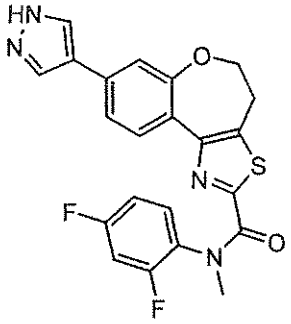
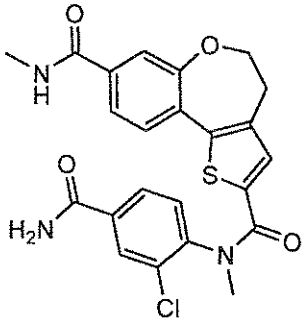
379		4-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2,4-difluorophenyl)-2H-1,2,3-triazole
380		3-(8-cyano-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole
381		3-(8-methylcarbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-4-(2-fluorophenyl)-4H-1,2,4-triazole
382		2-(1-(2-hydroxyethyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

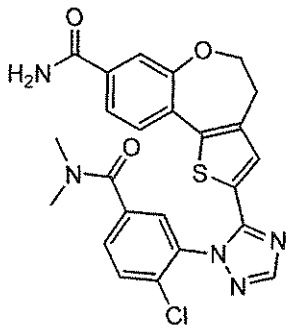
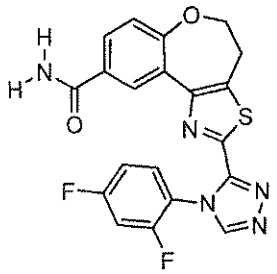
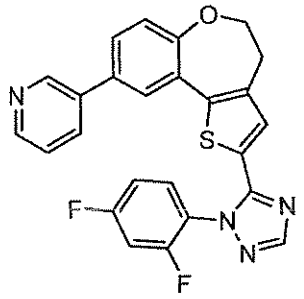
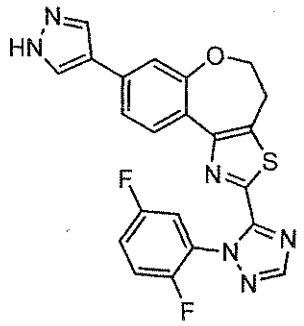
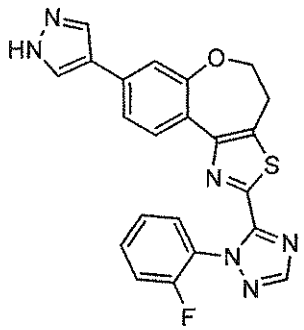
383		3-(8-methylcarbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-2-(2,5-difluorophenyl)-2H-1,2,4-triazole
384		5-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
385		5-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-isopropyl-1H-1,2,4-triazole
386		3-(8-methylcarbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-2-(2-fluorophenyl)-2H-pyrazole

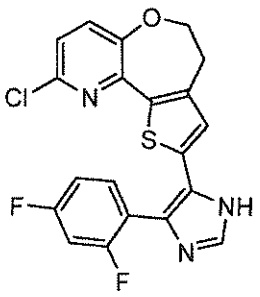
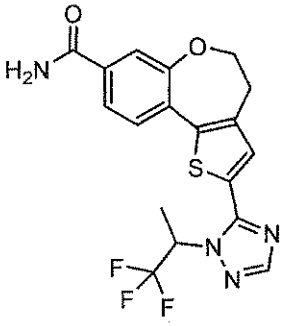
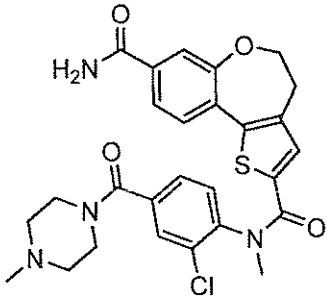
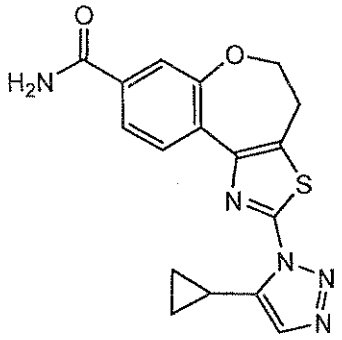
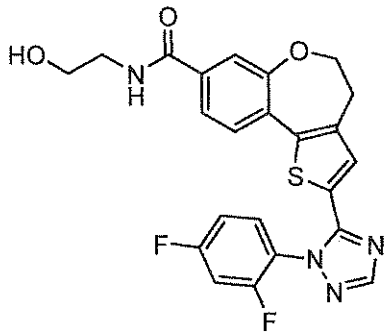
387		N2-(2-chloro-4-fluorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
388		N2-(2-chloro-5-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
389		N2-(2-chloro-5-(dimethylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
390		2-(4-isopropyl-1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

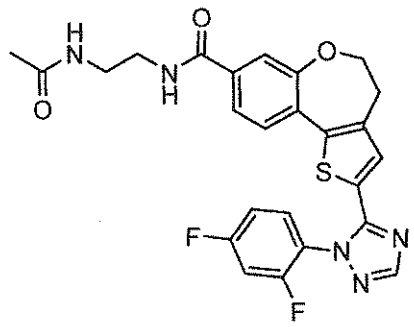
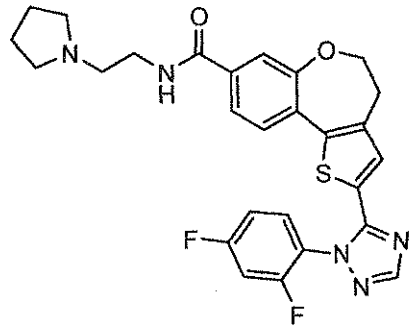
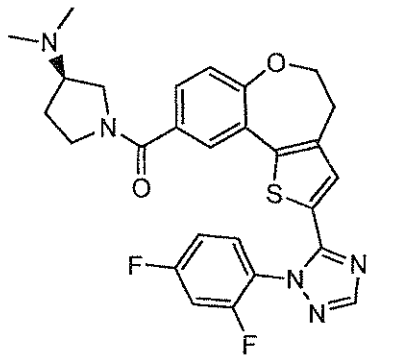
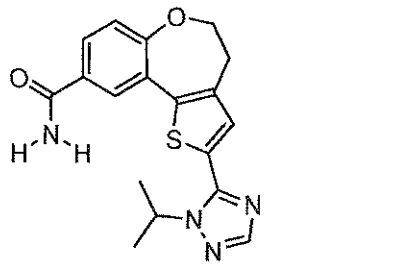
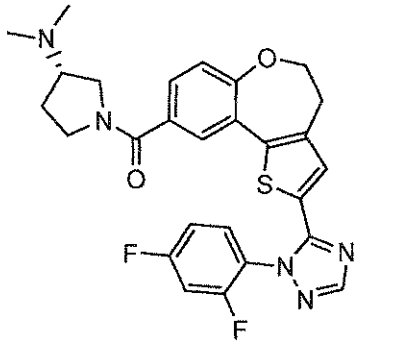
391		3-(8-carbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-2-(2,4-difluorophenyl)-2H-1,2,4-triazole
392		3-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole
393		3-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole
394		3-(8-carbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-2-(2,5-difluorophenyl)-2H-1,2,4-triazole
395		5-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-isopropyl-1H-1,2,4-triazole

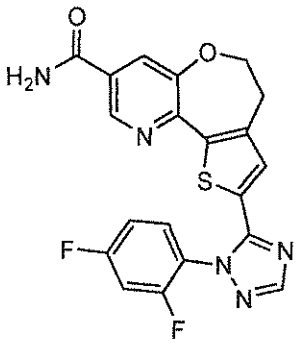
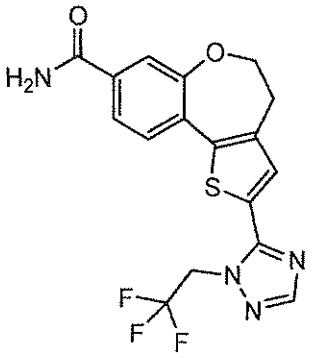
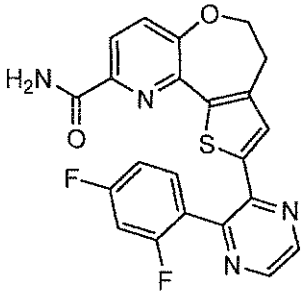
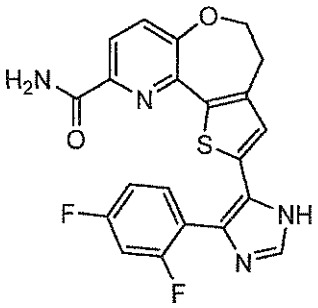
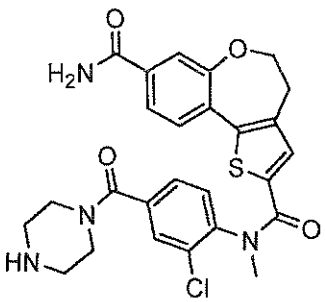
396		3-(8-(1H-pyrazol-4-yl)-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-2-(2-fluorophenyl)-2H-pyrazole
397		1-(2,4-difluorophenyl)-5-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazole
398		2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide
399		9-bromo-2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
400		5-(9-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole

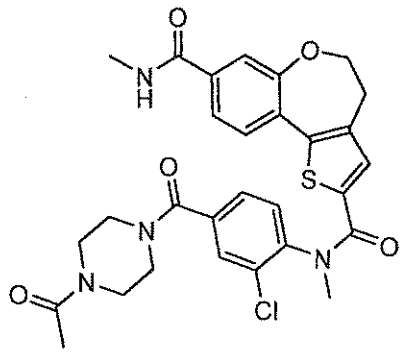
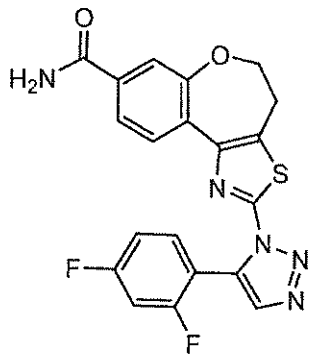
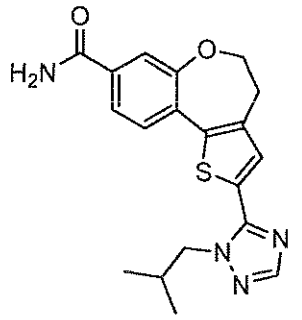
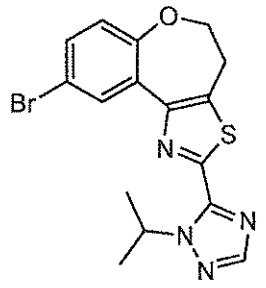
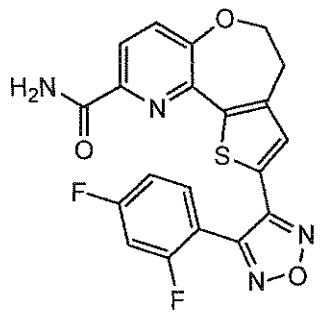
401		2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide
402		(2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(piperazin-1-yl)methanone
403		4-(3-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2,4-difluorophenyl)-2H-1,2,3-triazole
404		8-(1H-pyrazol-4-yl)-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene-2-carboxylic acid-N-(2,4-difluorophenyl)-N-methyl-amide
405		N2-(4-carbamoyl-2-chlorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide

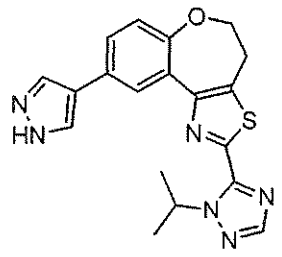
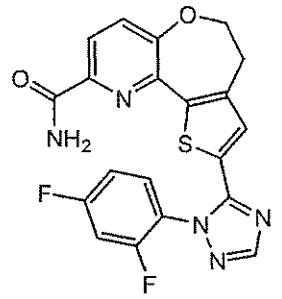
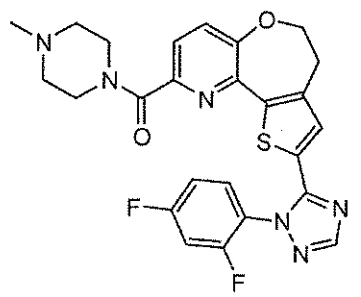
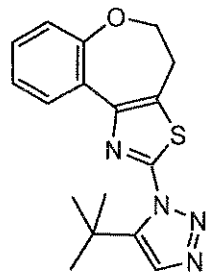
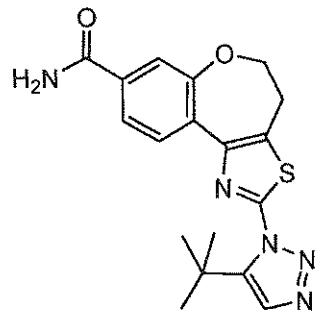
406		2-(1-(2-chloro-5-(dimethylcarbamoyl)phenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
407		2-[4-(2,4-Difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-9-carboxylic acid amide
408		3-(2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)pyridine
409		8-(1H-pyrazol-4-yl)-2-[2-(2,5-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
410		8-(1H-pyrazol-4-yl)-2-[2-(2-fluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

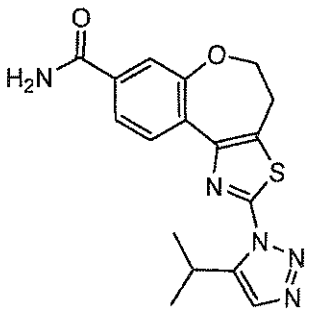
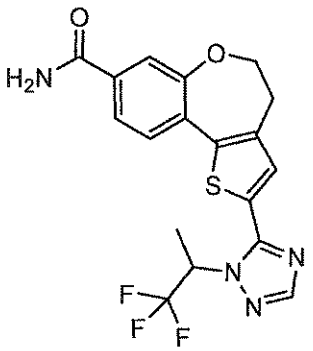
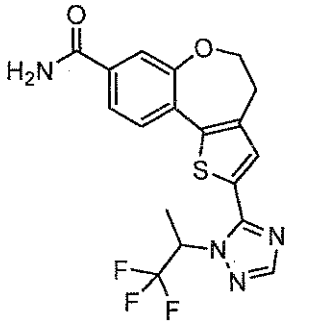
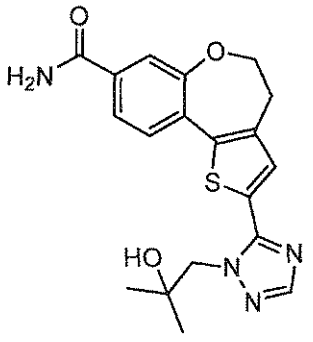
411		5-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2,4-difluorophenyl)-1H-imidazole
412		2-(1-(1,1,1-trifluoropropan-2-yl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
413		N2-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
414		2-(5-cyclopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide
415		2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

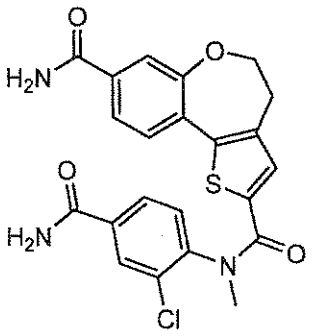
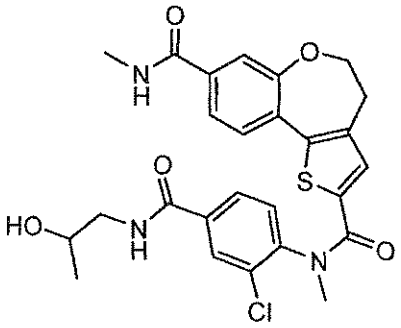
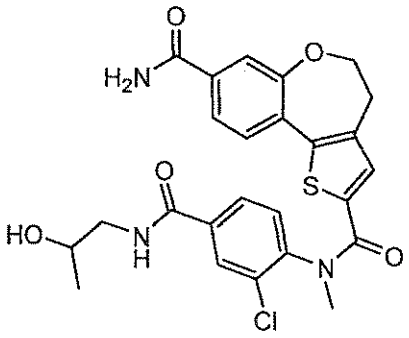
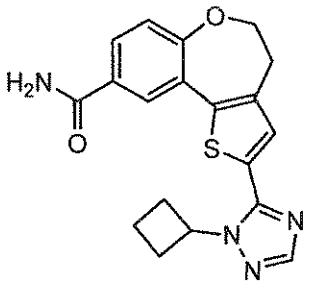
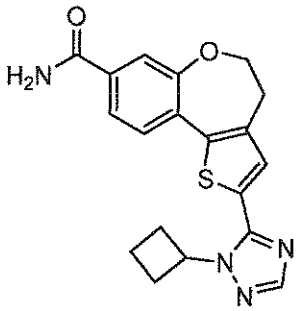
416		N-(2-acetamidoethyl)-2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
417		2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-N-(2-(pyrrolidin-1-yl)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
418		(2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)((R)-3-(dimethylamino)pyrrolidin-1-yl)methanone
419		2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide
420		(2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)((S)-3-(dimethylamino)pyrrolidin-1-yl)methanone

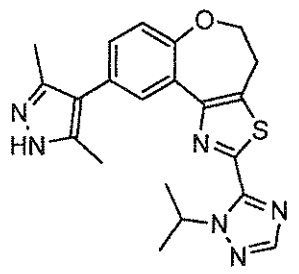
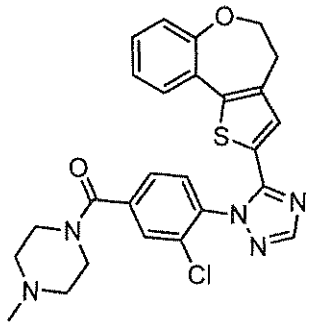
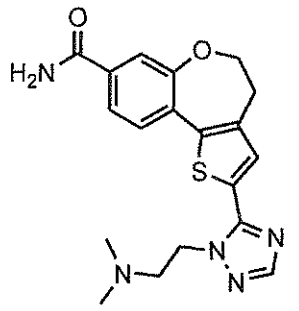
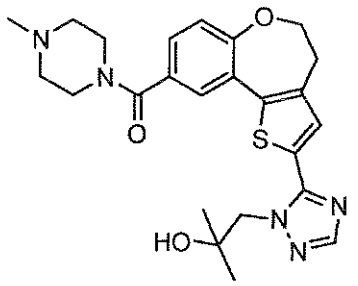
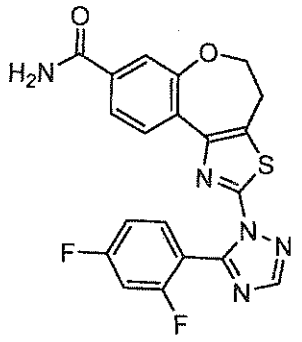
421		5-(3-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
422		2-(1-(2,2,2-trifluoroethyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
423		2-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-3-(2,4-difluorophenyl)-pyrazine
424		5-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2,4-difluorophenyl)-1H-imidazole
425		N2-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide

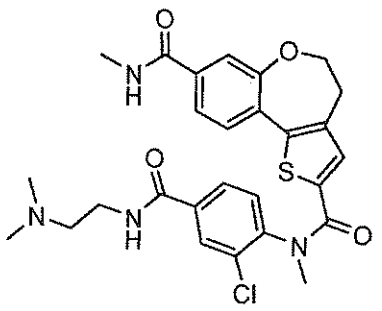
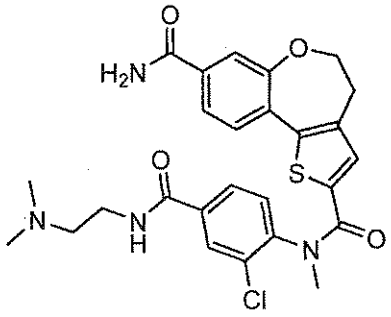
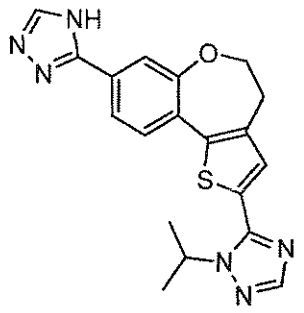
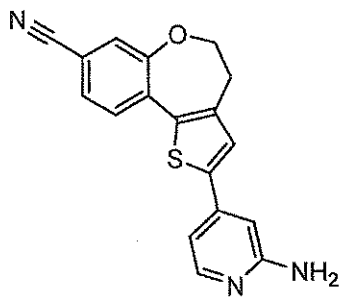
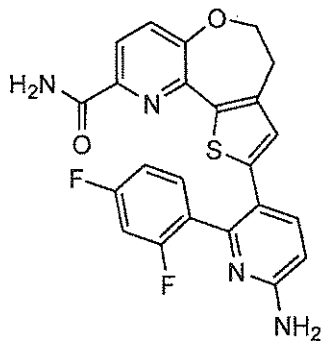
426		N2-(4-(4-acetylpiperazine-1-carbonyl)-2-chlorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
427		2-[5-(2,4-Difluoro-phenyl)-[1,2,3]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide
428		2-(1-isobutyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
429		9-bromo-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
430		4-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-3-(2,4-difluorophenyl)-1,2,5-oxadiazole

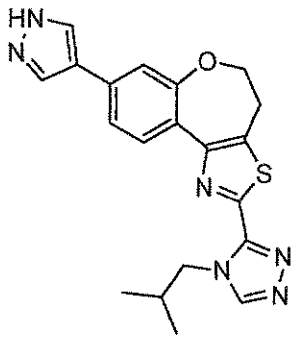
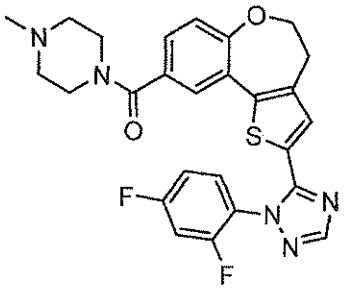
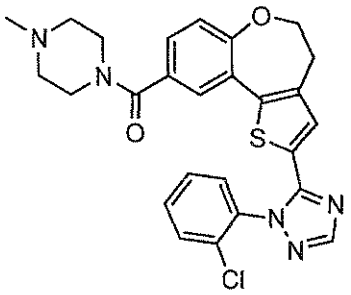
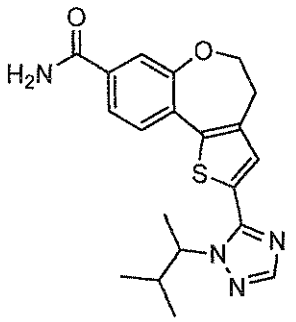
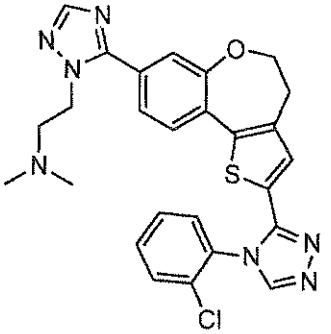
431		9-(1H-pyrazol-4-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
432		5-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
433		(9-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-2-yl)(4-methylpiperazin-1-yl)methanone
434		2-(5-tert-Butyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
435		2-(5-tert-Butyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide

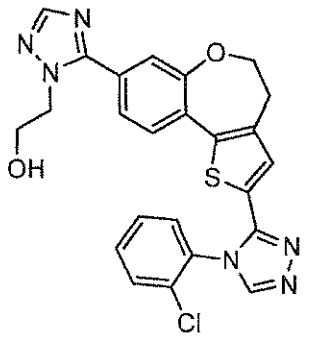
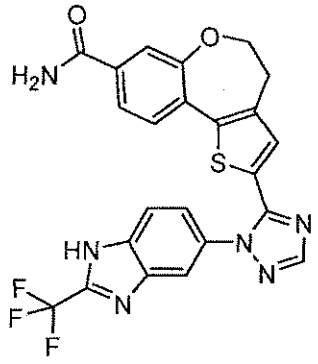
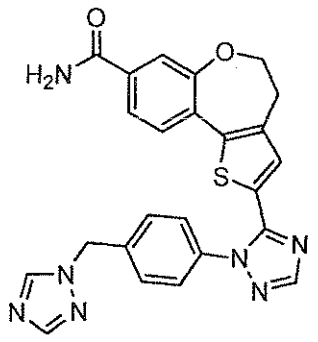
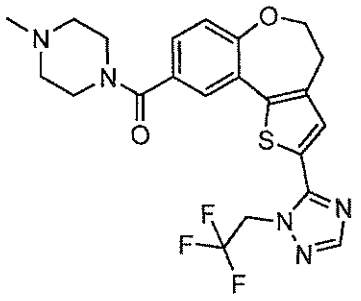
436		2-(5-Isopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide
437		2-(1-(1,1,1-trifluoropropan-2-yl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
438		2-(1-(1,1,1-trifluoropropan-2-yl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
439		2-(1-(2-hydroxy-2-methylpropyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

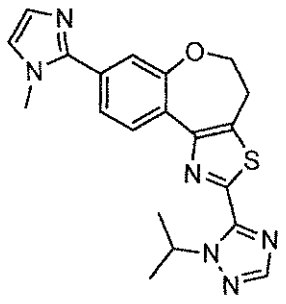
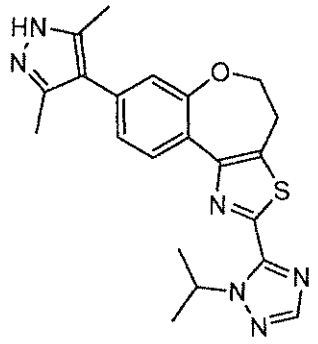
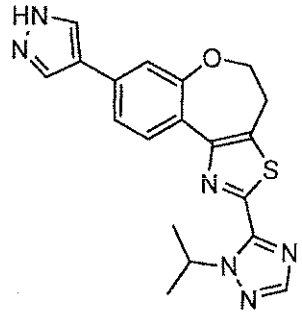
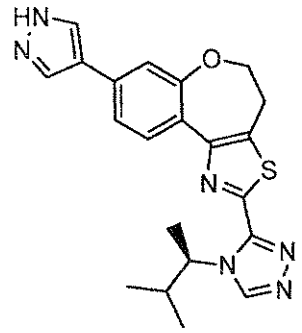
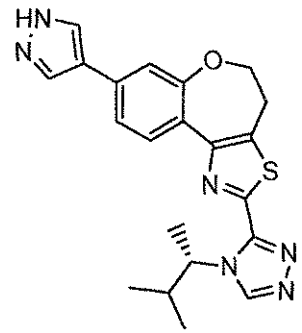
440		N2-(4-carbamoyl-2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
441		N2-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
442		N2-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
443		2-(1-cyclobutyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide
444		2-(1-cyclobutyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

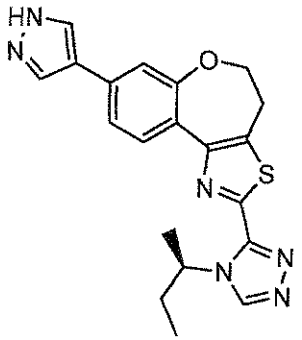
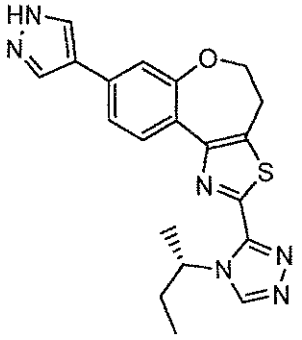
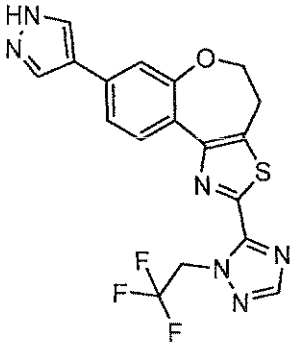
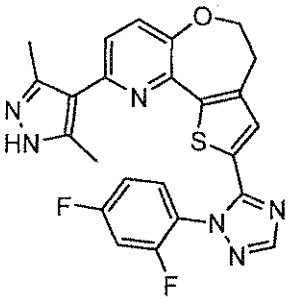
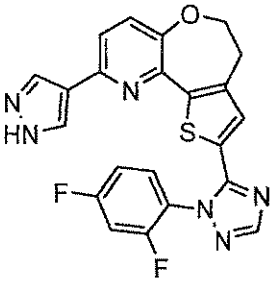
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446		(3-chloro-4-(5-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-1-yl)phenyl)(4-methylpiperazin-1-yl)methanone
447		2-(1-(2-(dimethylamino)ethyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
448		(2-(1-(2-hydroxy-2-methylpropyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(4-methylpiperazin-1-yl)methanone
449		2-[5-(2,4-Difluoro-phenyl)-[1,2,4]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide

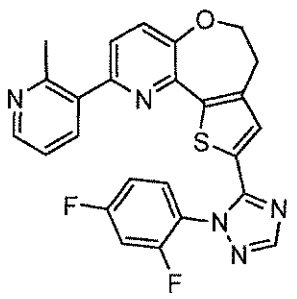
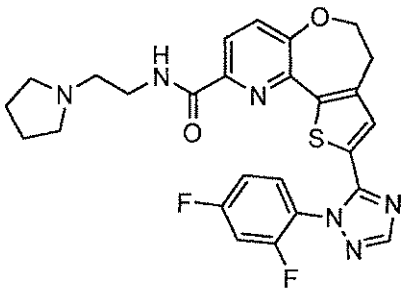
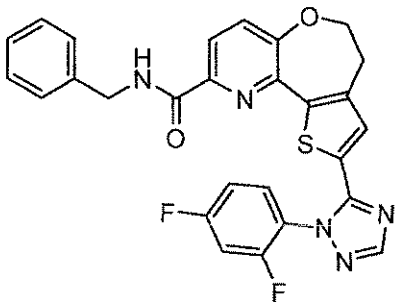
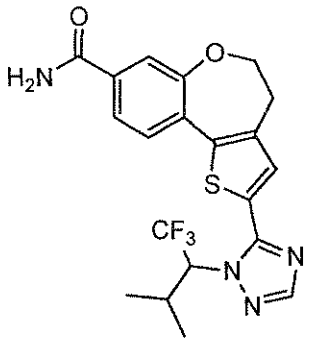
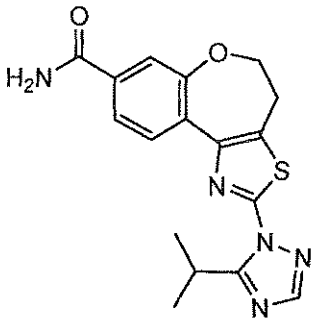
450		N2-(2-chloro-4-(2-(dimethylamino)ethylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
451		N2-(2-chloro-4-(2-(dimethylamino)ethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide
452		5-(8-(4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-isopropyl-1H-1,2,4-triazole
453		2-(2-aminopyridin-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile
454		5-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-6-(2,4-difluorophenyl)pyridin-2-amine

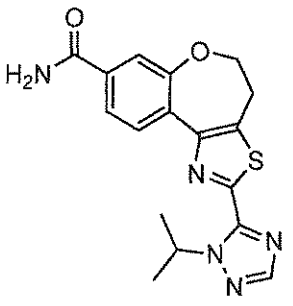
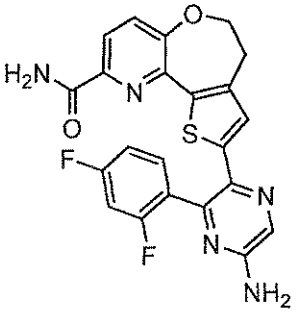
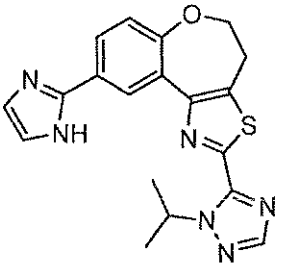
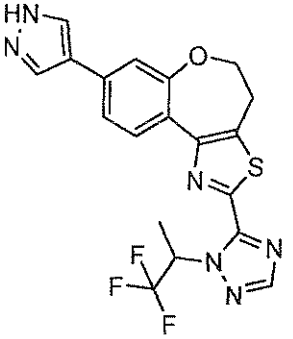
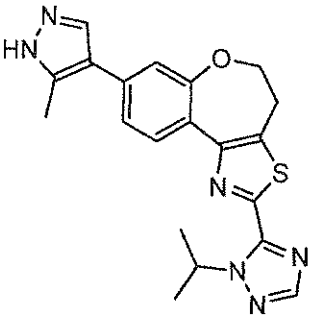
455		8-(1H-pyrazol-4-yl)-(4H-4-isobutyl-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
456		(2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(4-methylpiperazin-1-yl)methanone
457		(2-(1-(2-chlorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(4-methylpiperazin-1-yl)methanone
458		2-(1-(3-methylbutan-2-yl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
459		2-(5-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-1H-1,2,4-triazol-1-yl)-N,N-dimethylethanamine

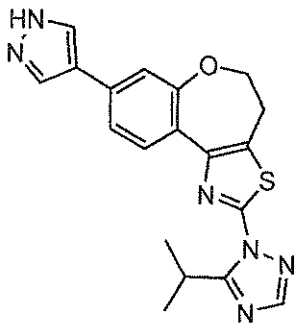
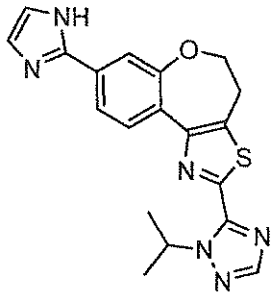
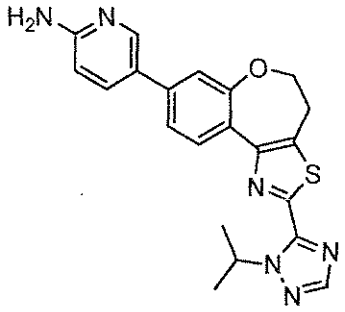
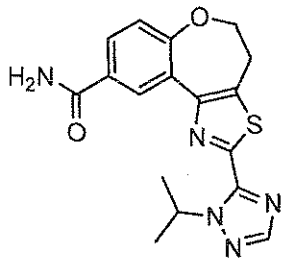
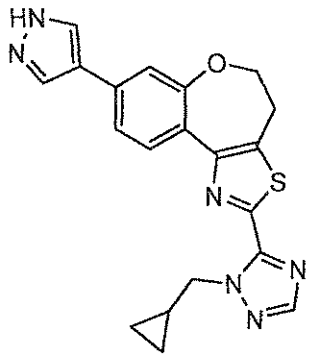
460		2-(5-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-1H-1,2,4-triazol-1-yl)ethanol
461		2-(1-(2-(trifluoromethyl)-1H-benzo[d]imidazol-5-yl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
462		2-(1-(4-((1H-1,2,4-triazol-1-yl)methyl)phenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
463		(4-methylpiperazin-1-yl)(2-(1-(2,2,2-trifluoroethyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)methanone

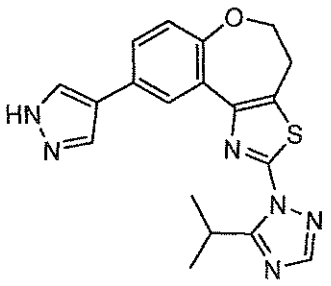
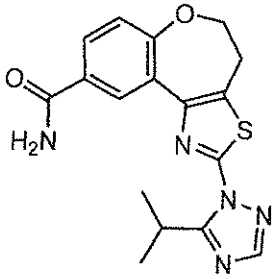
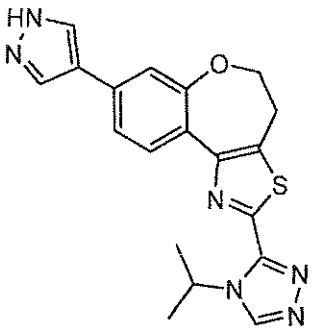
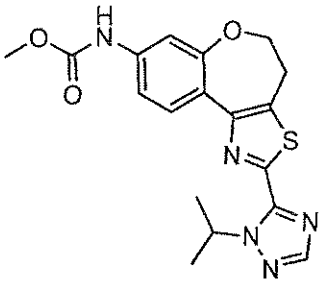
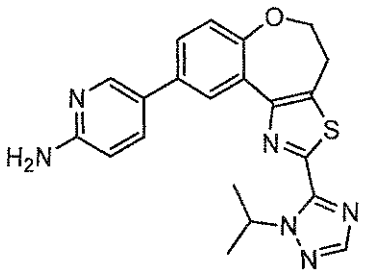
464		8-(1-methylimidazol-2-yl)-(4H-4-isopropyl-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
465		8-(1H-3,5-dimethylpyrazol-4-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
466		8-(1H-pyrazol-4-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
467		8-(1H-pyrazol-4-yl)-(4-(*R*-1-methylisobutyl-4H)-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
468		8-(1H-pyrazol-4-yl)-(4-(*S*-1-methylisobutyl-4H)-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

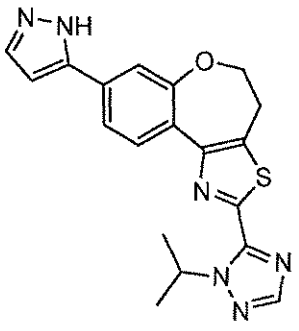
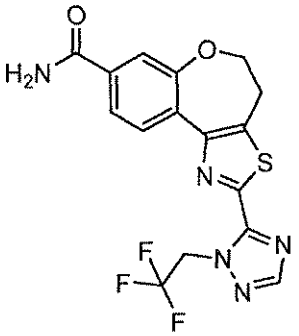
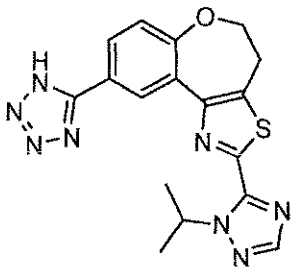
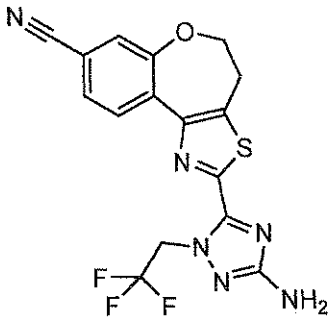
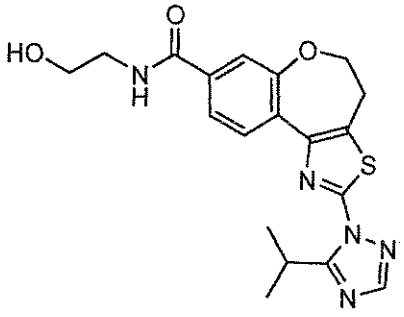
469		8-(1H-pyrazol-4-yl)-(4-(*R*-1-methylpropyl-4H)-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
470		8-(1H-pyrazol-4-yl)-(4-(*S*-1-methylpropyl-4H)-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
471		8-(1H-pyrazol-4-yl)-(2-trifluoroethyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
472		5-(2-(1H-3,5-dimethylpyrazol-4-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
473		5-(2-(1H-pyrazol-4-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole

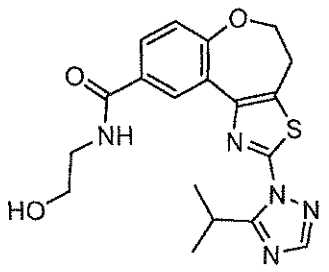
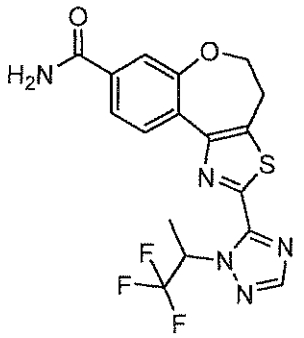
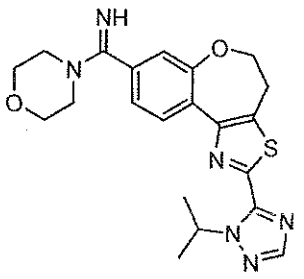
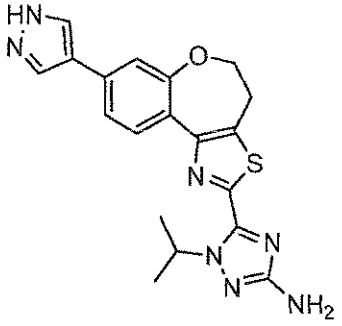
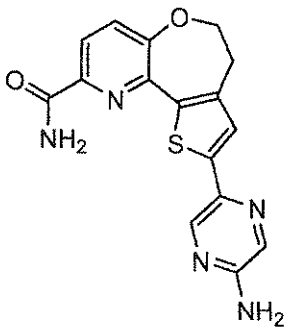
474		5-(2-(2-methylpyrid-3-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
475		5-(2-(N-2-(pyrrolidin-1-yl)ethylcarbamoyl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
476		5-((2-N-benzylcarbamoyl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
477		2-(1-(1,1,1-trifluoro-3-methylbutan-2-yl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide
478		2-(5-Isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide

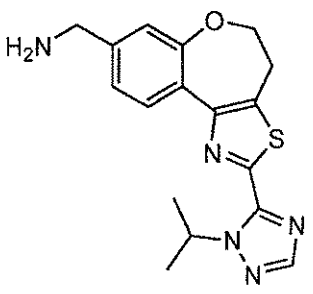
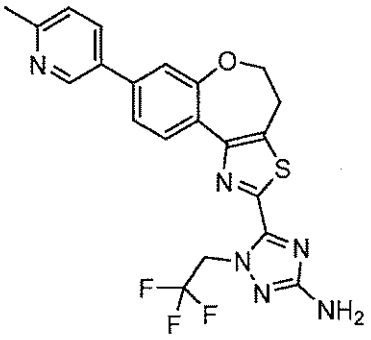
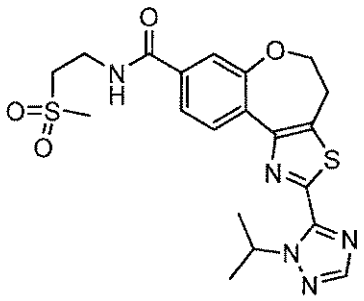
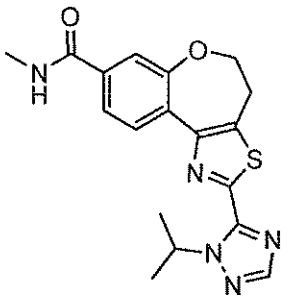
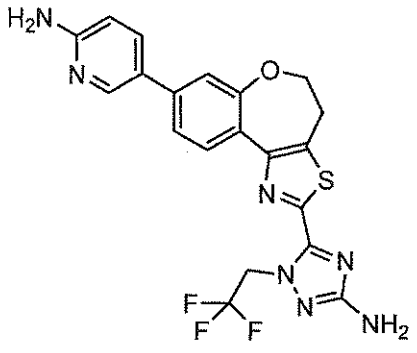
479		8-carbamoyl-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
480		2-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-3-(2,4-difluorophenyl)-5-aminopyrazine
481		9-(imidazo-2-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
482		8-(1H-pyrazol-4-yl)-((1,1,1-trifluoropropan-2-yl)-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
483		8-(1H-5-methyl-pyrazol-4-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

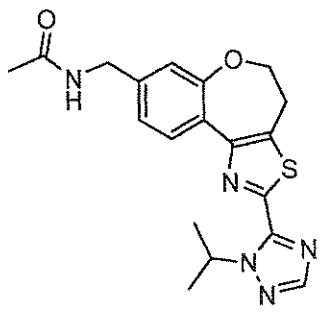
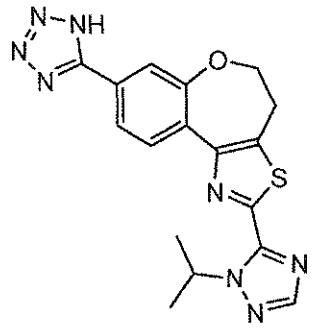
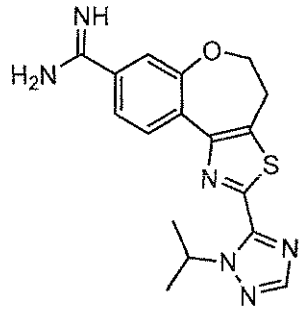
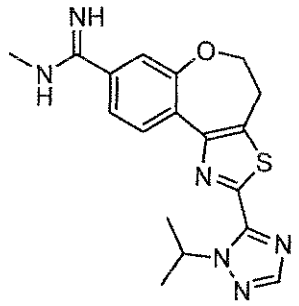
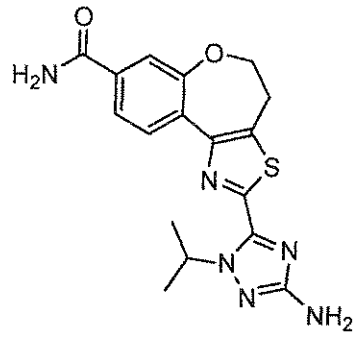
484		2-(5-Isopropyl-[1,2,4]triazol-1-yl)-8-(1*H*-pyrazol-4-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
485		8-(imidazo-2-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
486		8-(2-amino-pyrid-5-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
487		9-(carbamoyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
488		8-(1H-pyrazol-4-yl)-(1-cyclopropylmethyl-1H-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

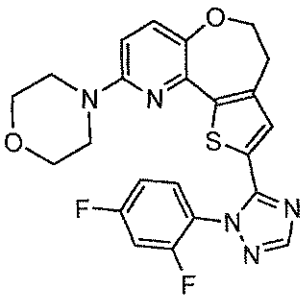
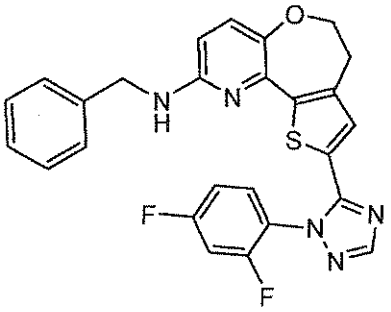
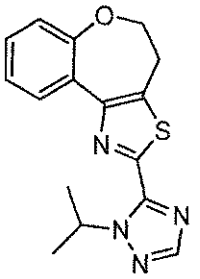
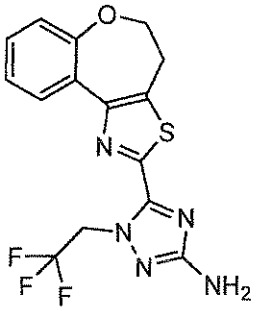
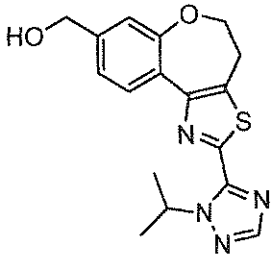
489		2-(5-Isopropyl-[1,2,4]triazol-1-yl)-9-(1*H*-pyrazol-4-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
490		2-(5-Isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-9-carboxylic acid amide
491		8-(1H-pyrazol-4-yl)-(4-isopropyl-4H-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
492		8-(methylcarbamate)-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
493		9-(2-amino-pyrid-5-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

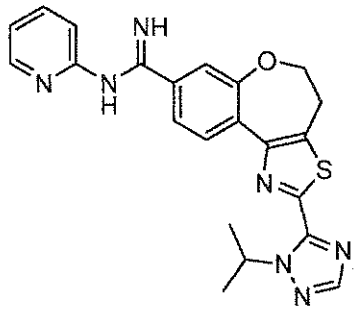
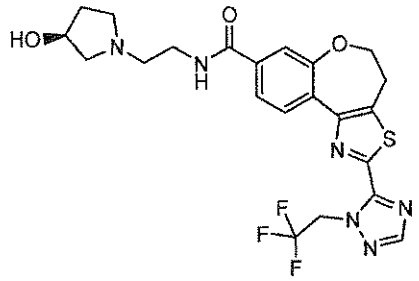
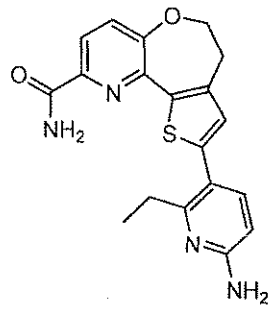
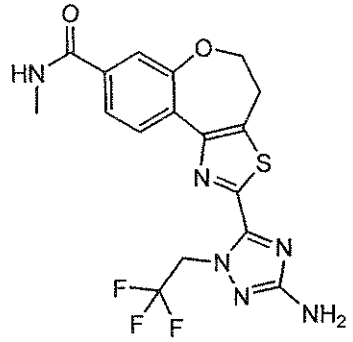
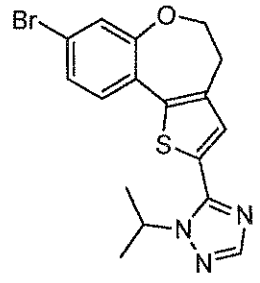
494		8-(1H-pyrazol-5-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
495		8-(carbamoyl)-(2-trifluoroethyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
496		9-(tetrazol-5-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
497		8-(cyano)-(2-trifluoroethyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
498		2-(5-isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid (2-hydroxy-ethyl)-amide

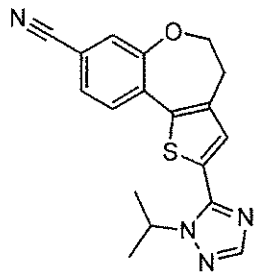
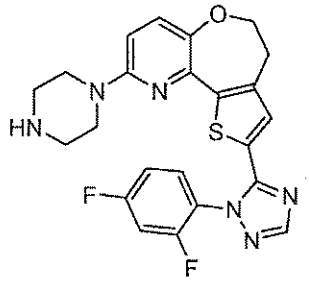
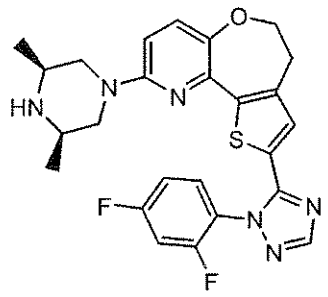
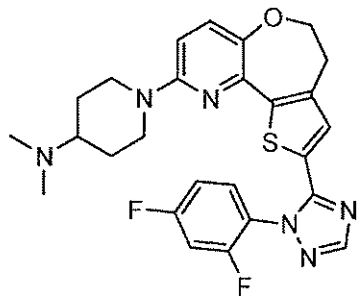
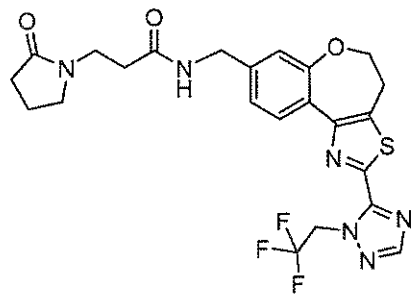
499		2-(5-Isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-9-carboxylic acid (2-hydroxy-ethyl)-amide
500		8-(carbamoyl)-((1,1,1-trifluoropropan-2-yl)-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
501		8-(morpholinomethanimine)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
502		8-(1H-pyrazol-4-yl)-(2-isopropyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
503		2-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-aminopyrazine

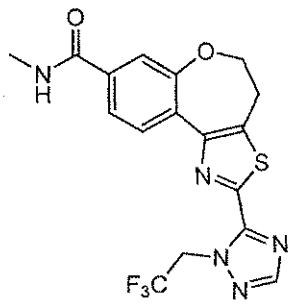
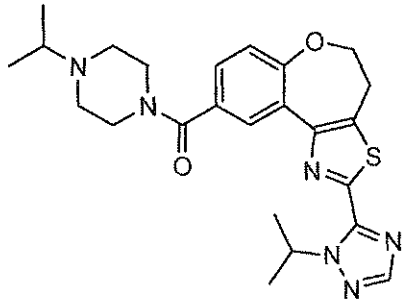
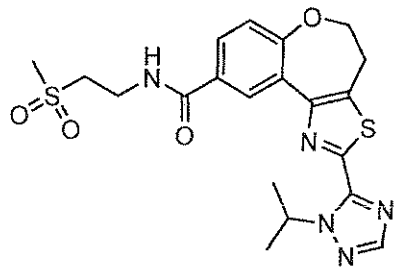
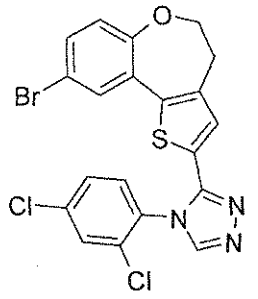
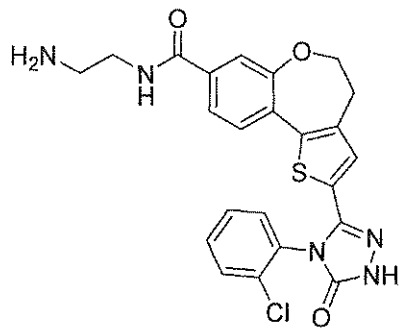
504		8-(aminomethyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
505		8-(6-methylpyrid-3-yl)-(2-trifluoroethyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
506		8-((2-methylsulfonylethyl)-amide)-(4-isopropyl-4H-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
507		8-(methylcarbamoyl)-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
508		8-(2-aminopyrid-5-yl)-(2-trifluoroethyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

509		8-(acetamidomethyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
510		8-(tetrazol-5-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
511		8-(formamidinyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
512		8-(methylformamidinyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
513		8-(carbamoyl)-(2-isopropyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

514		5-(2-(morpholin-4-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
515	76858 	5-(2-(N-benzylamino)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
516		(2-isopropyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
517		(2-trifluoroethyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
518		8-(hydroxymethyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

519		8-(N-(pyrid-2-yl)formamidinyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
520		8-(N-2-(*S*-3-hydroxypyrrolidin-1-yl)ethylcarbamoyl)-(2-trifluoroethyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
521		5-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-2-amino-6-ethylpyridine
522		8-(methylcarbamoyl)-(2-trifluoroethyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
523		5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-isopropyl-1H-1,2,4-triazole

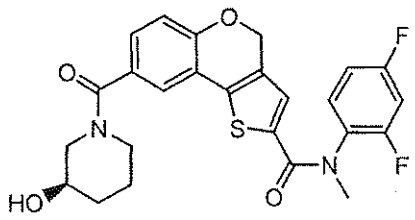
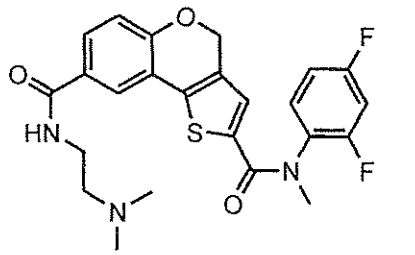
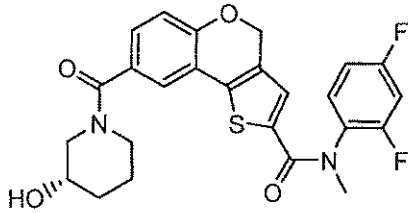
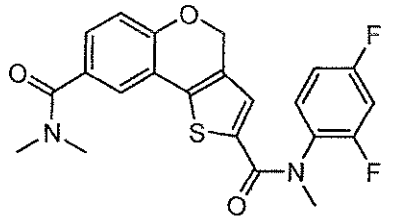
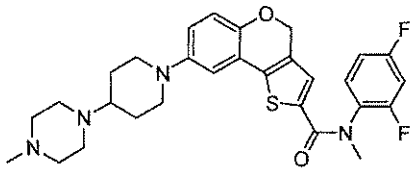
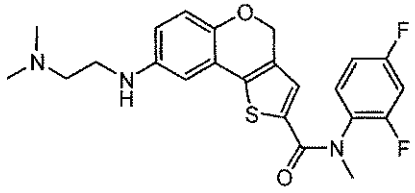
524		2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile
525		5-(2-(N-piperazinyl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
526		5-(2-(3R,5S-dimethylpiperazin-1-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
527		5-((2-(4-dimethylamino)piperidin-1-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole
528		8-(3-(2-oxopyrrolidin-1-yl)propanamidomethyl)-(2-trifluoroethyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

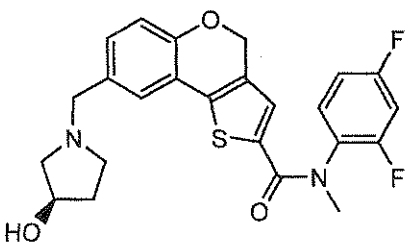
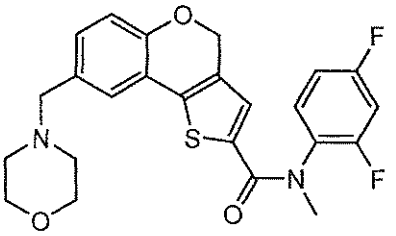
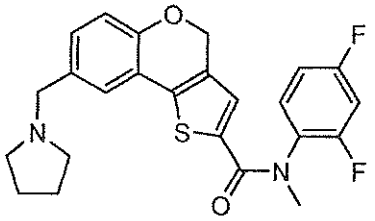
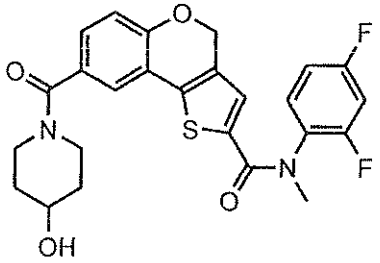
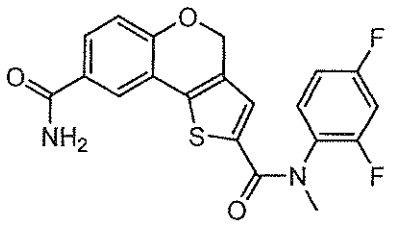
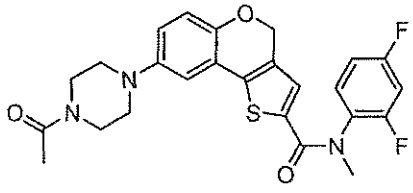
529		8-(methylcarbamoyl)-(2-trifluoroethyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
530		(2-(2-isopropyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-9-yl)(4-isopropylpiperazin-1-yl)methanone
531		9-((2-methylsulfonylethyl)-amide)-(4-isopropyl-4H-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene
532		3-(9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-4-(2,4-dichloro-phenyl)-4H-[1,2,4]triazole
533		N-(2-aminoethyl)-2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide

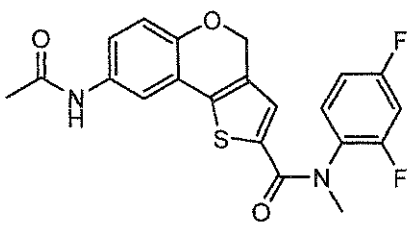
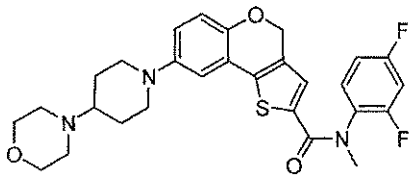
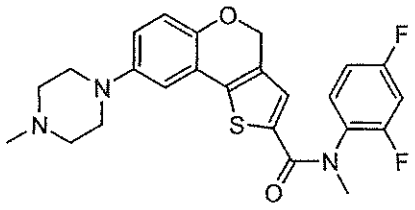
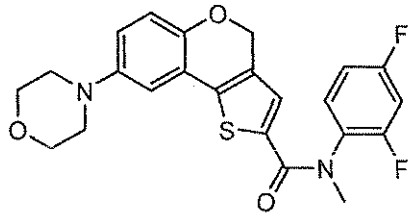
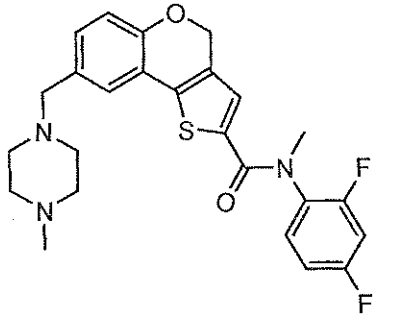
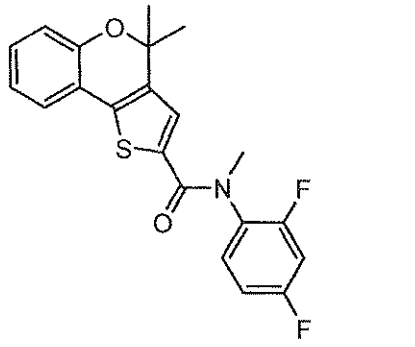
[00182] Exemplary Formula II compounds in Table 2, were made, characterized, and tested for PI3K activity according to the methods of this invention, and have the following

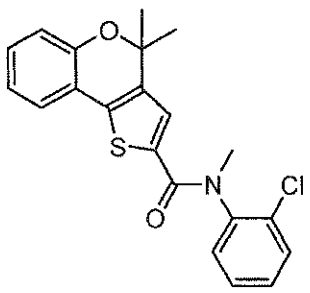
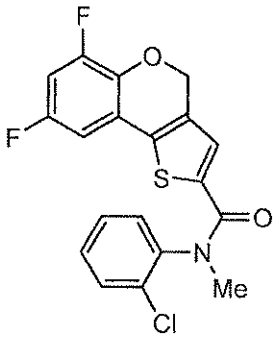
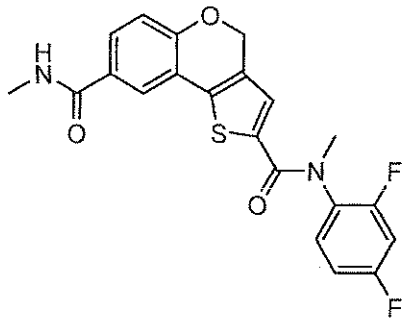
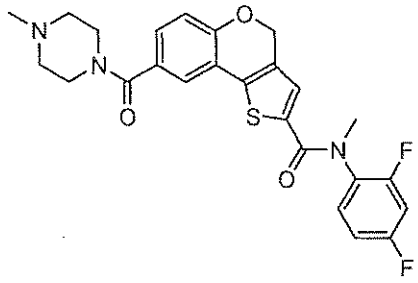
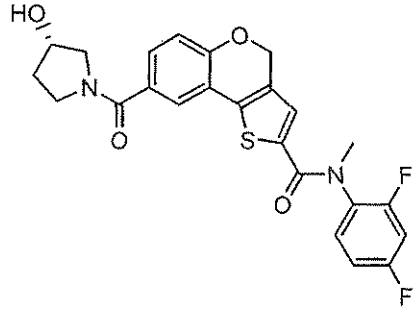
structures and corresponding names (ChemDraw Ultra, Version 9.0.1, CambridgeSoft Corp., Cambridge MA).

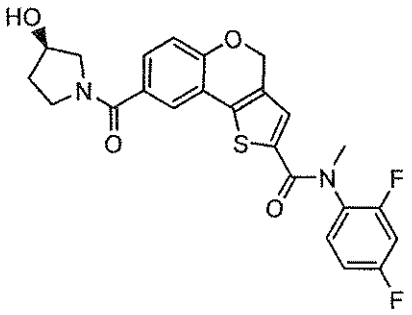
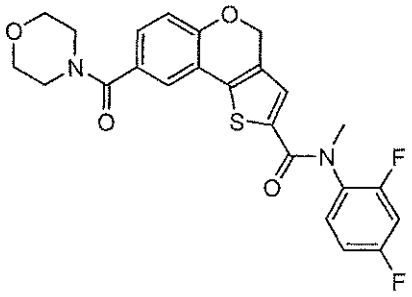
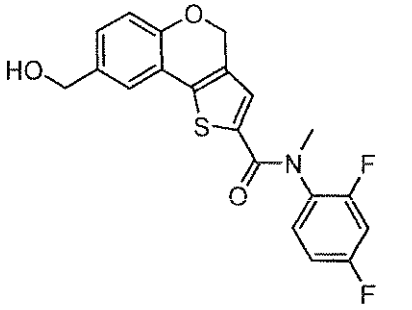
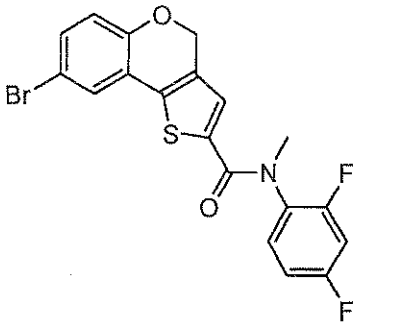
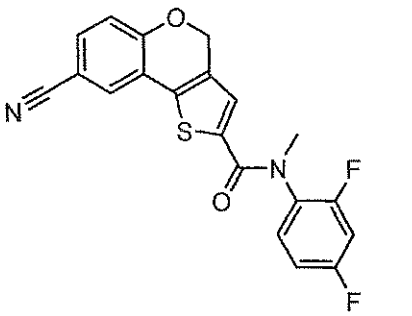
[00183] Table 2.

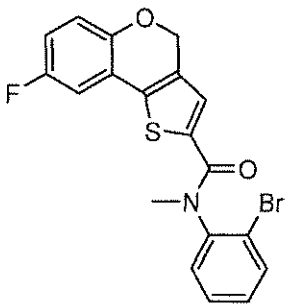
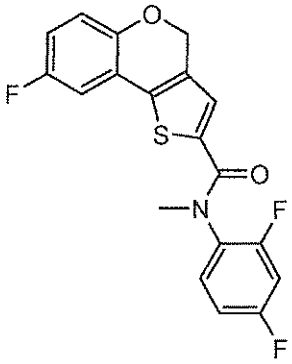
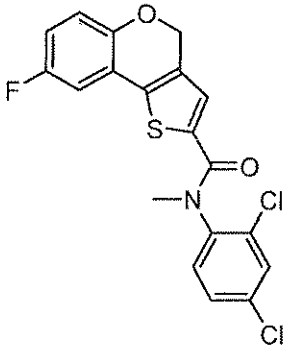
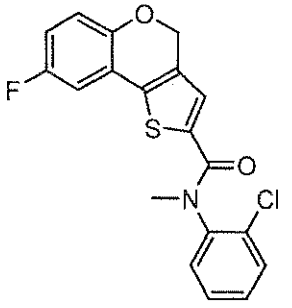
No.	Structure	Name
105bp		(R)-N-(2,4-difluorophenyl)-8-(3-hydroxypiperidine-1-carbonyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
109bp		N2-(2,4-difluorophenyl)-N8-(2-(dimethylamino)ethyl)-N2-methyl-4H-thieno[3,2-c]chromene-2,8-dicarboxamide
110bp		(S)-N-(2,4-difluorophenyl)-8-(3-hydroxypiperidine-1-carbonyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
111bp		N2-(2,4-difluorophenyl)-N2,N8,N8-trimethyl-4H-thieno[3,2-c]chromene-2,8-dicarboxamide
112bp		N-(2,4-difluorophenyl)-N-methyl-8-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)-4H-thieno[3,2-c]chromene-2-carboxamide
113bp		N-(2,4-difluorophenyl)-8-(2-(dimethylamino)ethylamino)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide

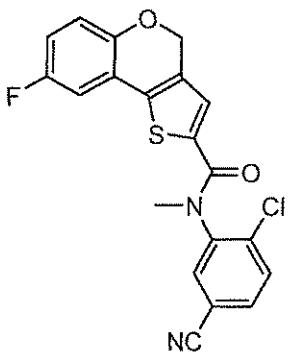
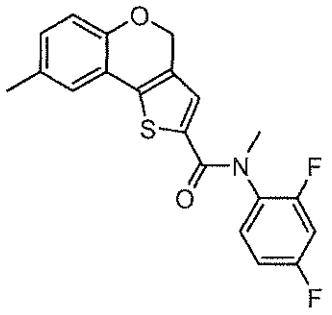
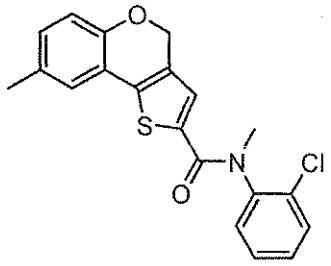
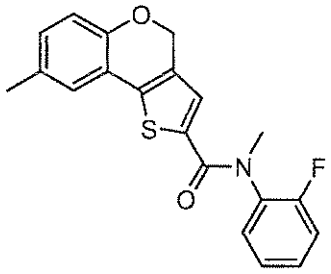
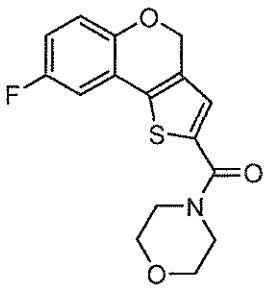
115bp		(R)-N-(2,4-difluorophenyl)-8-((3-hydroxypyrrolidin-1-yl)methyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
116bp		N-(2,4-difluorophenyl)-N-methyl-8-(morpholinomethyl)-4H-thieno[3,2-c]chromene-2-carboxamide
117bp		N-(2,4-difluorophenyl)-N-methyl-8-(pyrrolidin-1-ylmethyl)-4H-thieno[3,2-c]chromene-2-carboxamide
118bp		N-(2,4-difluorophenyl)-8-(4-hydroxypiperidine-1-carbonyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
119bp		N2-(2,4-difluorophenyl)-N2-methyl-4H-thieno[3,2-c]chromene-2,8-dicarboxamide
120bp		8-(4-acetylpiperazin-1-yl)-N-(2,4-difluorophenyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide

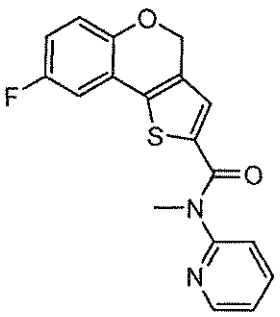
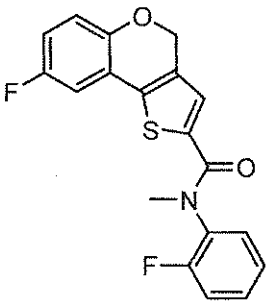
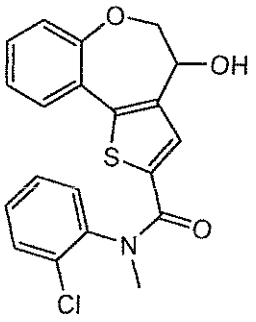
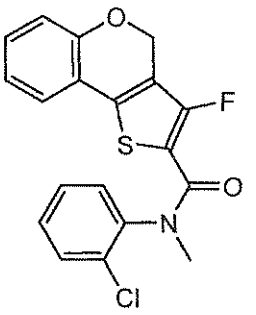
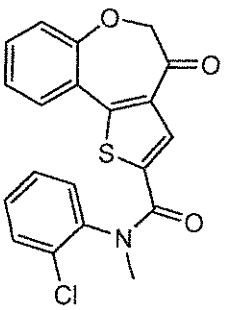
121bp		8-acetamido-N-(2,4-difluorophenyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
127bp		N-(2,4-difluorophenyl)-N-methyl-8-(4-morpholinopiperidin-1-yl)-4H-thieno[3,2-c]chromene-2-carboxamide
128bp		N-(2,4-difluorophenyl)-N-methyl-8-(4-methylpiperazin-1-yl)-4H-thieno[3,2-c]chromene-2-carboxamide
129bp		N-(2,4-difluorophenyl)-N-methyl-8-morpholino-4H-thieno[3,2-c]chromene-2-carboxamide
136bp		N-(2,4-difluorophenyl)-N-methyl-8-((4-methylpiperazin-1-yl)methyl)-4H-thieno[3,2-c]chromene-2-carboxamide
140bp		N-(2,4-difluorophenyl)-N,4,4-trimethyl-4H-thieno[3,2-c]chromene-2-carboxamide

141bp		N-(2-chlorophenyl)-N,4,4-trimethyl-4H-thieno[3,2-c]chromene-2-carboxamide
142bp		N-(2-chlorophenyl)-6,8-difluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
152bp		N2-(2,4-difluorophenyl)-N2,N8-dimethyl-4H-thieno[3,2-c]chromene-2,8-dicarboxamide
153bp		N-(2,4-difluorophenyl)-N-methyl-8-(4-methylpiperazine-1-carbonyl)-4H-thieno[3,2-c]chromene-2-carboxamide
154bp		(S)-N-(2,4-difluorophenyl)-8-(3-hydroxypyrrolidine-1-carbonyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide

155bp		(R)-N-(2,4-difluorophenyl)-8-(3-hydroxypyrrolidine-1-carbonyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
158bp		N-(2,4-difluorophenyl)-N-methyl-8-(morpholine-4-carbonyl)-4H-thieno[3,2-c]chromene-2-carboxamide
159bp		N-(2,4-difluorophenyl)-8-(hydroxymethyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
160bp		8-bromo-N-(2,4-difluorophenyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
161bp		8-cyano-N-(2,4-difluorophenyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide

162bp		N-(2-bromophenyl)-8-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
163bp		N-(2,4-difluorophenyl)-8-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
164bp		N-(2,4-dichlorophenyl)-8-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
165bp		N-(2-chlorophenyl)-8-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide

166bp		N-(2-chloro-5-cyanophenyl)-8-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
167bp		N-(2,4-difluorophenyl)-N,8-dimethyl-4H-thieno[3,2-c]chromene-2-carboxamide
168bp		N-(2-chlorophenyl)-N,8-dimethyl-4H-thieno[3,2-c]chromene-2-carboxamide
169bp		N-(2-fluorophenyl)-N,8-dimethyl-4H-thieno[3,2-c]chromene-2-carboxamide
170bp		(8-fluoro-4H-thieno[3,2-c]chromen-2-yl)(morpholino)methanone

171bp		8-fluoro-N-methyl-N-(pyridin-2-yl)-4*H*-thieno[3,2-c]chromene-2-carboxamide
172bp		8-fluoro-N-(2-fluorophenyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
191bz		N-(2-chlorophenyl)-4-hydroxy-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide
192bp		N-(2-chlorophenyl)-3-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide
193bz		N-(2-chlorophenyl)-N-methyl-4-oxo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide

[00184] ADMINISTRATION OF COMPOUNDS OF FORMULA I and II

[00185] The Formula I and II compounds of the invention may be administered by any route appropriate to the condition to be treated. Suitable routes include oral, parenteral (including subcutaneous, intramuscular, intravenous, intraarterial, intradermal, intrathecal and epidural), transdermal, rectal, nasal, topical (including buccal and sublingual), vaginal, intraperitoneal, intrapulmonary and intranasal. For local immunosuppressive treatment, the compounds may be administered by intralesional administration, including perfusing or otherwise contacting the graft with the inhibitor before transplantation. It will be appreciated that the preferred route may vary with for example the condition of the recipient. Where the compound is administered orally, it may be formulated as a pill, capsule, tablet, etc. with a pharmaceutically acceptable carrier or excipient. Where the compound is administered parenterally, it may be formulated with a pharmaceutically acceptable parenteral vehicle and in a unit dosage injectable form, as detailed below.

[00186] A dose to treat human patients may range from about 10 mg to about 1000 mg of Formula I or II compound. A typical dose may be about 100 mg to about 300 mg of the compound. A dose may be administered once a day (QID), twice per day (BID), or more frequently, depending on the pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. In addition, toxicity factors may influence the dosage and administration regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less frequently for a specified period of time. The regimen may be repeated for a number of cycles of therapy.

[00187] METHODS OF TREATMENT WITH FORMULA I and II COMPOUNDS

[00188] Compounds of the present invention are useful for treating hyperproliferative diseases, conditions and/or disorders including, but not limited to, those characterized by over expression of lipid kinases, e.g. PI3 kinase. Accordingly, another aspect of this invention includes methods of treating or preventing diseases or conditions that can be treated or prevented by inhibiting lipid kinases, including PI3. In one embodiment, the method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of Formula I, or a stereoisomer, geometric isomer, tautomer, or pharmaceutically acceptable salt thereof. In one embodiment, a human patient is treated with a compound of Formula I and a pharmaceutically acceptable carrier, adjuvant, or vehicle, wherein said compound of Formula I is present in an amount to detectably inhibit PI3 kinase activity.

[00189] Cancers which can be treated according to the methods of this invention include, but are not limited to, breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid

carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's and leukemia.

[00190] Another aspect of this invention provides a compound of this invention for use in the treatment of the diseases or conditions described herein in a mammal, for example, a human, suffering from such disease or condition. Also provided is the use of a compound of this invention in the preparation of a medicament for the treatment of the diseases and conditions described herein in a warm-blooded animal, such as a mammal, for example a human, suffering from such disorder.

[00191] PHARMACEUTICAL FORMULATIONS

[00192] In order to use a compound of this invention for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. According to this aspect of the invention there is provided a pharmaceutical composition comprising a compound of this invention in association with a pharmaceutically acceptable diluent or carrier.

[00193] A typical formulation is prepared by mixing a compound of the present invention and a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG 400, PEG 300), etc. and mixtures thereof. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

[00194] The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to enable patient compliance with the prescribed regimen.

[00195] The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

[00196] Pharmaceutical formulations of the compounds of the present invention may be prepared for various routes and types of administration. For example, a compound of Formula I having the desired degree of purity may optionally be mixed with pharmaceutically acceptable diluents, carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences (1980) 16th edition, Osol, A. Ed.), in the form of a lyophilized formulation, milled powder, or an aqueous solution. Formulation may be conducted by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed. The pH of the formulation depends mainly on the particular use and the concentration of compound, but may range from about 3 to about 8. Formulation in an acetate buffer at pH 5 is a suitable embodiment.

[00197] The compound of this invention for use herein is preferably sterile. In particular, formulations to be used for *in vivo* administration must be sterile. Such sterilization is readily accomplished by filtration through sterile filtration membranes.

[00198] The compound ordinarily can be stored as a solid composition, a lyophilized formulation or as an aqueous solution.

[00199] The pharmaceutical compositions of the invention will be formulated, dosed and administered in a fashion, i.e., amounts, concentrations, schedules, course, vehicles and route of administration, consistent with good medical practice. Factors for consideration in this context

include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "therapeutically effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to prevent, ameliorate, or treat the coagulation factor mediated disorder. Such amount is preferably below the amount that is toxic to the host or renders the host significantly more susceptible to bleeding.

[00200] As a general proposition, the initial pharmaceutically effective amount of the inhibitor administered parenterally per dose will be in the range of about 0.01-100 mg/kg, namely about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day.

[00201] Acceptable diluents, carriers, excipients and stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG). The active pharmaceutical ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

[00202] Sustained-release preparations of compounds of Formula I and II may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a compound of Formula I or II, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or

poly(vinyl alcohol)), polylactides (U.S. Patent No. 3,773,919), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate) and poly-D-(-)-3-hydroxybutyric acid.

[00203] The formulations include those suitable for the administration routes detailed herein. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[00204] Formulations of a compound of Formula I or II suitable for oral administration may be prepared as discrete units such as pills, capsules, cachets or tablets each containing a predetermined amount of a compound of Formula I or II.

[00205] Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

[00206] Tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, e.g., gelatin capsules, syrups or elixirs may be prepared for oral use. Formulations of compounds of Formula I and II intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating

agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[00207] For treatment of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

[00208] If desired, the aqueous phase of the cream base may include a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulfoxide and related analogs.

[00209] The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

[00210] Aqueous suspensions of Formula I or II compounds contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, croscarmellose, povidone, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of

ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

[00211] The pharmaceutical compositions of compounds of Formula I may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[00212] The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

[00213] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

[00214] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of about 0.5 to 20% w/w, for example about 0.5 to 10% w/w, for example about 1.5% w/w.

[00215] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[00216] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[00217] Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis disorders as described below.

[00218] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[00219] The formulations may be packaged in unit-dose or multi-dose containers, for example sealed ampoules 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 injection immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

[00220] The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefore. Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered parenterally, orally or by any other desired route.

[00221] COMBINATION THERAPY

[00222] The compounds of Formula I and II may be employed alone or in combination

with other therapeutic agents for the treatment of a disease or disorder described herein, such as a hyperproliferative disorder (e.g., cancer). In certain embodiments, a compound of Formula I or II is combined in a pharmaceutical combination formulation, or dosing regimen as combination therapy, with a second compound that has anti-hyperproliferative properties or that is useful for treating a hyperproliferative disorder (e.g., cancer). The second compound of the pharmaceutical combination formulation or dosing regimen preferably has complementary activities to the compound of Formula I such that they do not adversely affect each other. Such compounds are suitably present in combination in amounts that are effective for the purpose intended. In one embodiment, a composition of this invention comprises a compound of Formula I or II, in combination with a chemotherapeutic agent such as described herein.

[00223] The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes coadministration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities.

[00224] Suitable dosages for any of the above coadministered agents are those presently used and may be lowered due to the combined action (synergy) of the newly identified agent and other chemotherapeutic agents or treatments.

[00225] The combination therapy may provide "synergy" and prove "synergistic", i.e., the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined, unit dosage formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., by different injections in separate syringes, separate pills or capsules, or separate infusions. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e., serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

[00226] In a particular embodiment of anti-cancer therapy, a compound of Formula I, or a stereoisomer, geometric isomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, may be combined with other chemotherapeutic, hormonal or antibody agents such as those described herein, as well as combined with surgical therapy and radiotherapy. Combination therapies according to the present invention thus comprise the

administration of at least one compound of Formula I, or a stereoisomer, geometric isomer, tautomer, solvate, metabolite, or pharmaceutically acceptable salt or prodrug thereof, and the use of at least one other cancer treatment method. The amounts of the compound(s) of Formula I and the other pharmaceutically active chemotherapeutic agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

[00227] METABOLITES OF COMPOUNDS OF FORMULA I and II

[00228] Also falling within the scope of this invention are the *in vivo* metabolic products of Formula I and II described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds of Formula I and II, including compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

[00229] Metabolite products typically are identified by preparing a radiolabelled (e.g., ^{14}C or ^{3}H) isotope of a compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS, LC/MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well known to those skilled in the art. The metabolite products, so long as they are not otherwise found *in vivo*, may be useful in diagnostic assays for therapeutic dosing of the compounds of the invention.

[00230] ARTICLES OF MANUFACTURE

[00231] In another embodiment of the invention, an article of manufacture, or "kit", containing materials useful for the treatment of the diseases and disorders described above is provided. The kit comprises a container comprising a compound of Formula I or II. The kit may further comprise a label or package insert, on or associated with the container. The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. Suitable containers include, for example, bottles, vials, syringes, blister pack, etc. The container may be formed from a variety of materials such as glass or plastic. The container

may hold a compound of Formula I or II or a formulation thereof which is effective for treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a compound of Formula I or II. The label or package insert indicates that the composition is used for treating the condition of choice, such as cancer. In addition, the label or package insert may indicate that the patient to be treated is one having a disorder such as a hyperproliferative disorder, neurodegeneration, cardiac hypertrophy, pain, migraine or a neurotraumatic disease or event. In one embodiment, the label or package inserts indicates that the composition comprising a compound of Formula I or II can be used to treat a disorder resulting from abnormal cell growth. The label or package insert may also indicate that the composition can be used to treat other disorders. Alternatively, or additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[00232] The kit may further comprise directions for the administration of the compound of Formula I or II and, if present, the second pharmaceutical formulation. For example, if the kit comprises a first composition comprising a compound of Formula I or II, and a second pharmaceutical formulation, the kit may further comprise directions for the simultaneous, sequential or separate administration of the first and second pharmaceutical compositions to a patient in need thereof.

[00233] In another embodiment, the kits are suitable for the delivery of solid oral forms of a compound of Formula I or II, such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered.

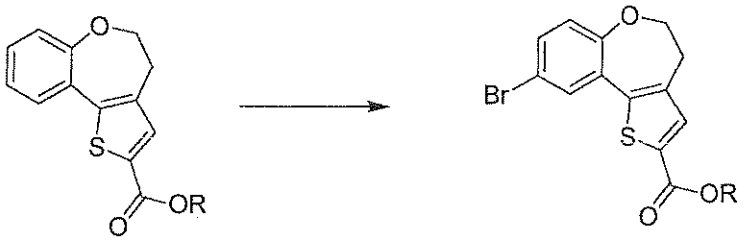
[00234] According to one embodiment, a kit may comprise (a) a first container with a compound of Formula I or II contained therein; and optionally (b) a second container with a second pharmaceutical formulation contained therein, wherein the second pharmaceutical formulation comprises a second compound with anti-hyperproliferative activity. Alternatively, or additionally, the kit may further comprise a third container comprising a pharmaceutically-

acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[00235] In certain other embodiments wherein the kit comprises a composition of Formula I and a second therapeutic agent, the kit may comprise a container for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically, the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

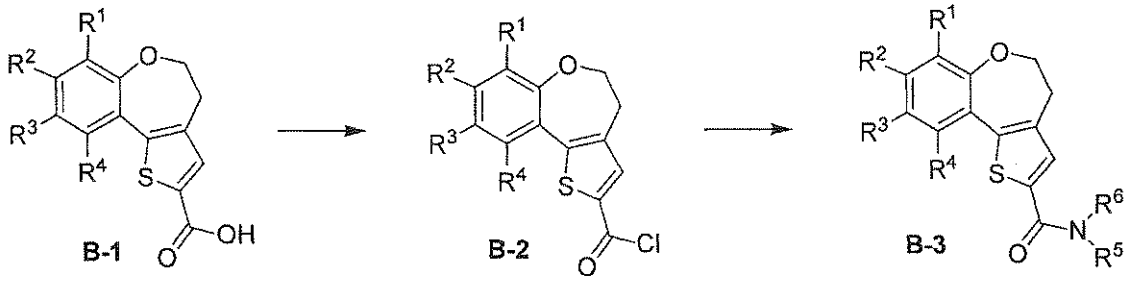
[00236] GENERAL PREPARATIVE PROCEDURES

[00237] General Procedure A



[00238] Benzoxepin intermediates, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylate esters, **A-1** can be selectively brominated with N-bromosuccinimide (NBS) in DMF to give 9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylate esters **A-2**.

[00239] General Procedure B



[00240] Benzoxepin carboxylic acid intermediates **B-1** are converted to the acid chloride **B-2** and reacted with primary or secondary amines with triethylamine, DMAP, and solvent such

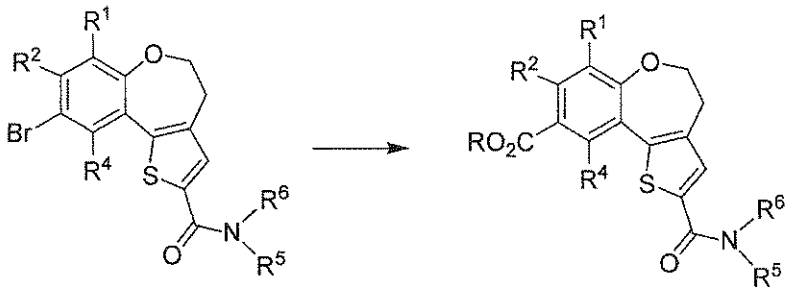
as dichloromethane. Reaction with a primary amine may be followed by N-alkylation, for example with methyl iodide and sodium hydride, to generate 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **B-3**.

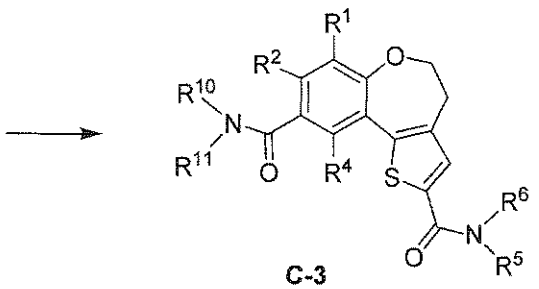
[00241] For example, to a suspension of carboxylic acid (0.4 mmol) in anhydrous dichloromethane, is added oxalyl chloride (0.7mmol) and one drop of dimethyl formamide. After 30 minutes, concentrate *in-vacuo*. Residue is dissolved in acetonitrile, and potassium carbonate (0.9 mmol) and an amine, e.g. aniline (0.48 mmol) are added. Reaction mixture is stirred overnight at room temperature before diluting with water and ethylacetate. Organic phase is dried ($MgSO_4$) and concentrated *in-vacuo*.

[00242] Alternatively, other active esters of benzoxepin carboxylic acid intermediates **B-1** can be formed as anhydrides, acyl imidazolides, acyl azides, and NHS esters to react with amines. Also, benzoxepin carboxylic acid intermediates **B-1** can be coupled with amines by in situ formation of active ester intermediates under the broad array of known peptide coupling reagents and methodology.

[00243] For example, to a solution of the carboxylic acid (1 eq) in DMF (6 mL) is added the amine (1.3 eq), HATU (1.3 eq) and diisopropylethyl amine (1.3 eq + 1.3 eq for each HCl salt of the amine) and the reaction stirred at room temperature for 16 h. The mixture is partitioned between ethyl acetate and water. The organic layer was washed with brine (3 x), dried ($MgSO_4$), reduced in vacuo and purified on silica to give the final amide.

[00244] General Procedure C

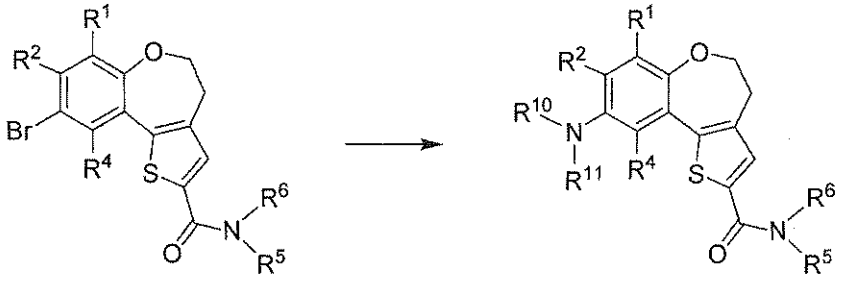




[00245] 9-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide intermediates **C-1** are carbonylated with carbon monoxide under high pressure with palladium catalysis, such as $Pd(OAc)_2$, and an alcohol, such as methanol to give the carboxamide intermediate **C-2**. Saponification with lithium hydroxide, sodium hydroxide or other aqueous base to the 8-carboxylic acid intermediate, followed by coupling of a primary or secondary amine with a coupling reagent, such as HATU or DCC gives the 9-carboxamide intermediate **C-3**.

[00246] Alternatively, intermediate **C-3** may be prepared directly from bromo intermediate **C-1** by aminocarbonylation, following the procedures of Wannberg et al (2003) J. Org. Chem. 68:5750–5753.

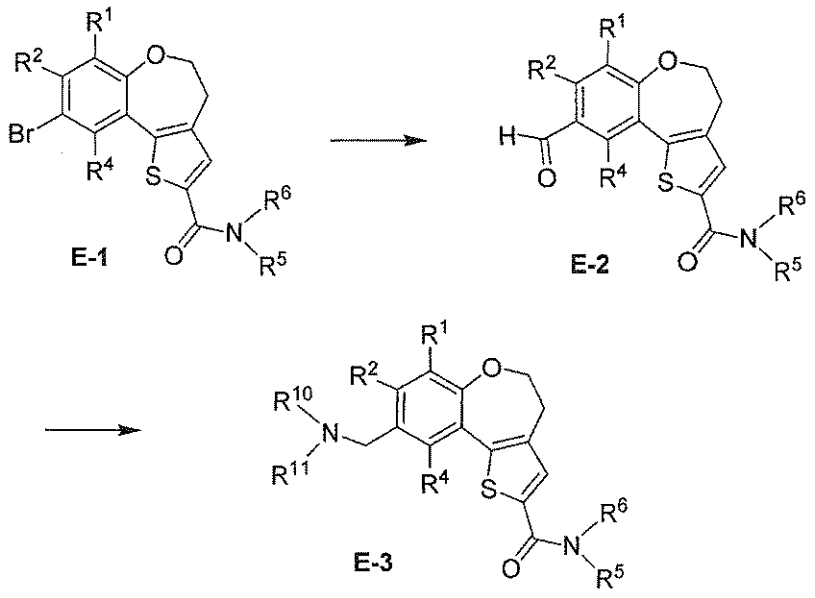
[00247] General Procedure D



D-1 **D-2**

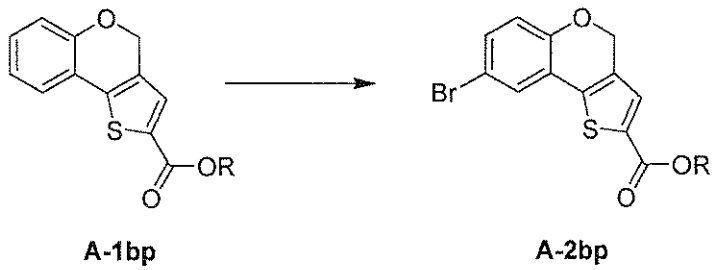
[00248] 9-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide intermediates **D-1** are aminated with primary or secondary amines ($HNR^{10}R^{11}$) or amides ($H_2NC(=O)R^{10}$), palladium complexes such as $Pd_2(dba)_3$, catalysts such as xantphos and BINAP, alkoxides such as NaOt-Bu or carbonates such as cesium carbonate, in toluene or dioxane, and heating to give aminated products **D-2**.

[00249] General Procedure E



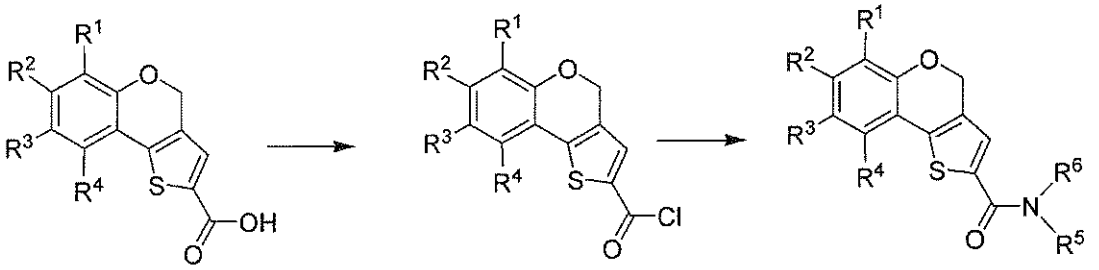
[00250] 8-Bromo-4H-thieno[3,2-c]chromene-2-carboxamide intermediates **E-1** are formylated with butyl lithium and dimethylformamide (DMF) to give **E-2** which is reductively aminated with a hydride such as sodium acetoxyborohydride and a primary or secondary amine ($HNR^{10}R^{11}$).

[00251] General Procedure A-bp



[00252] Benzopyran intermediates **A-1bp** can be selectively brominated with N-bromosuccinimide (NBS) in DMF to give 8-bromo-4H-thieno[3,2-c]chromene-2-carboxylate esters **A-2bp**.

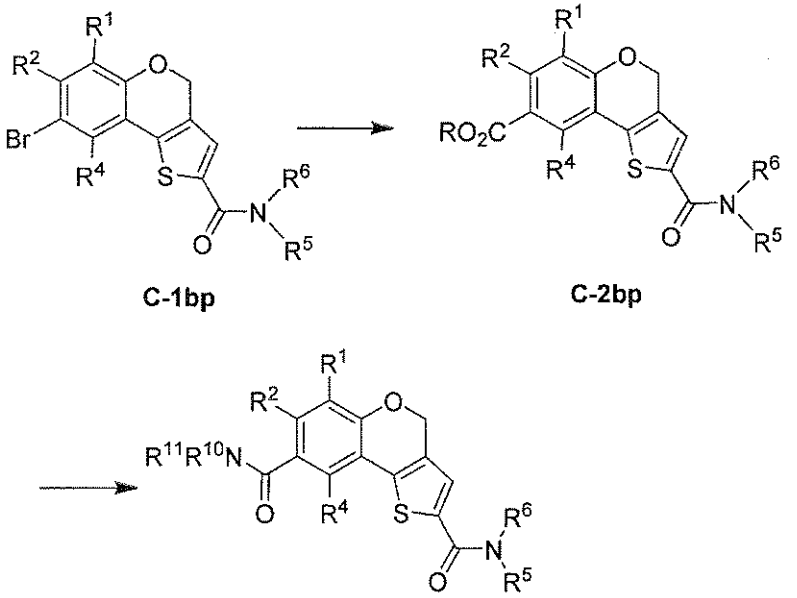
[00253] General Procedure B-bp



B-1bp B-2bp B-3bp

[00254] Benzopyran carboxylic acid intermediates **B-1bp** are converted to the acid chloride **B-2bp** and reacted with primary or secondary amines with triethylamine, DMAP, and solvent such as dichloromethane. Reaction with a primary amine may be followed by N-alkylation, for example with methyl iodide and sodium hydride, to generate carboxamide **B-3bp**.

[00255] General Procedure C-bp



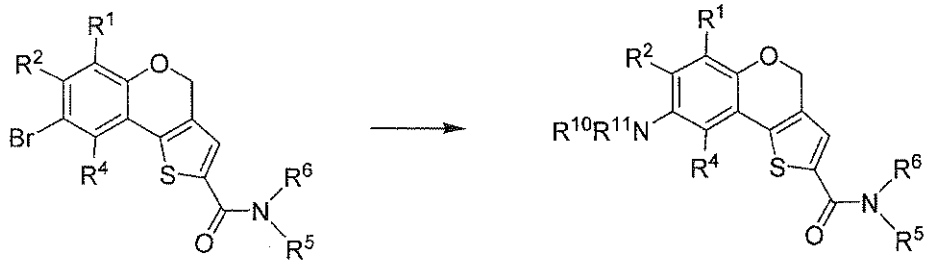
C-1bp C-2bp

C-3bp

[00256] 8-Bromo-4H-thieno[3,2-c]chromene-2-carboxamide intermediates **C-1bp** are carbonylated with carbon monoxide under high pressure with palladium catalysis, such as $Pd(OAc)_2$, and an alcohol, such as methanol to give the 8-carboxylate ester 4H-thieno[3,2-c]chromene-2-carboxamide intermediate **C-2bp**. Saponification with lithium hydroxide, sodium hydroxide or other aqueous base to the 8-carboxylic acid intermediate, followed by coupling of a primary or secondary amine with a coupling reagent, such as HATU or DCC gives the 8-carboxamide 4H-thieno[3,2-c]chromene-2-carboxamide intermediate **C-3bp**.

[00257] Alternatively, intermediate **C-3bp** may be prepared directly from bromo intermediate **C-1bp** by aminocarbonylation, following the procedures of Wannberg et al (2003) J. Org. Chem. 68:5750–5753.

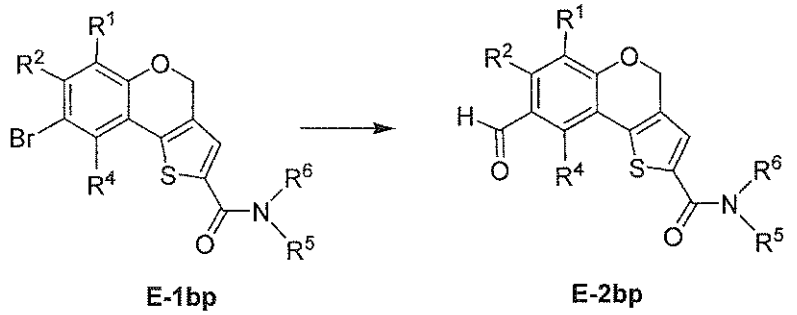
[00258] General Procedure D-bp



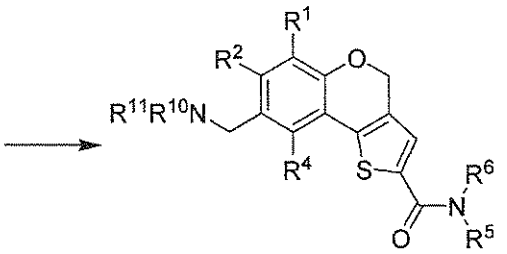
D-1bp **D-2bp**

[00259] 8-Bromo-4H-thieno[3,2-c]chromene-2-carboxamide intermediates **D-1bp** are aminated with primary or secondary amines ($HNR^{10}R^{11}$) or amides ($H_2NC(=O)R^{10}$), palladium complexes such as $Pd_2(dba)_3$, catalysts such as xantphos and BINAP, alkoxides such as NaOt-Bu or carbonates such as cesium carbonate, in toluene or dioxane, and heating to give aminated products **D-2bp**.

[00260] General Procedure E-bp



E-1bp **E-2bp**



E-3bp

[00261] 8-Bromo-4H-thieno[3,2-c]chromene-2-carboxamide intermediates **E-1bp** are formylated with butyl lithium and dimethylformamide (DMF) to give **E-2bp** which are

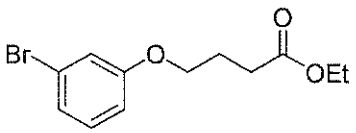
reductively aminated with a hydride such as sodium acetoxyborohydride and a primary or secondary amine ($HNR^{10}R^{11}$) to give **E-3bp**.

[00262] EXAMPLES

[00263] The chemical reactions described in the Examples may be readily adapted to prepare a number of other PI3K inhibitors of the invention, and alternative methods for preparing the compounds of this invention are deemed to be within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

[00264] In the Examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Sigma Aldrich Chemical Company, and were used without further purification unless otherwise indicated. The reactions set forth below were conducted generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. Column chromatography was conducted on a Biotage system (Manufacturer: Dyax Corporation) having a silica gel column or on a silica SEP PAK® cartridge (Waters). ^1H NMR spectra were obtained at 400 MHz in deuterated $CDCl_3$, d_6-DMSO, CH_3OD or d_6-acetone solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm). When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

[00265] Example 1 ethyl 4-(3-bromophenoxy)butanoate **6**

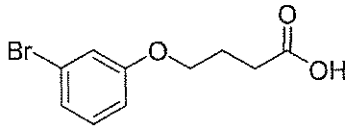


6

[00266] Solid 3-bromophenol (10.0 g, 58 mmol) was added portion wise to a stirred suspension of K_2CO_3 in acetone (100 mL) at room temperature. Sodium iodide (NaI, 1.0 g) was added, followed by ethyl-4-bromobutyrate (9.2 mL, 64 mmol). The reaction mixture was heated

at 80 °C overnight, cooled to room temperature, diluted with water and extracted with ethylacetate to give ethyl 4-(3-bromophenoxy)butanoate **6**.

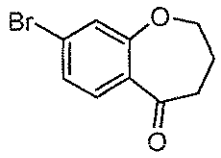
[00267] Example 2 4-(3-bromophenoxy)butanoic acid **7**



7

[00268] Ethyl 4-(3-bromophenoxy)butanoate **6** from Example 5 was taken up in 100 mL THF and 50 mL water and treated with lithium hydroxide LiOH (hydrate, 4.9 g). The whole was heated at 50 °C for 2 days. The mixture was cooled to room temperature and acidified to pH 1 with 2N HCl. The aqueous was extracted with ethylacetate. The combined organics were washed with brine and dried over sodium sulfate to give crude 4-(3-Bromophenoxy)butanoic acid **7** as a sticky solid. ^{1}H NMR (DMSO-d_6, 500 MHz) 7.24 (m, 1H), 7.13 (m, 1H), 7.11 (m, 1H), 6.95 (m, 1H), 3.99 (m, 2H), 2.37 (m, 2H), 1.94 (m, 2H).

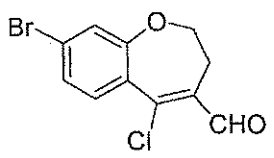
[00269] Example 3 8-bromo-3,4-dihydrobenzo[b]oxepin-5(2H)-one **8**



8

[00270] To a stirred suspension of polyphosphoric acid (PPA, ca. 60 g) and celite (ca. 40 g) in 100 mL toluene was added crude 4-(3-bromophenoxy)butanoic acid **7** (ca. 58 mmol) in one portion, 10 mL toluene rinse. The resultant suspension was heated at 110 °C for 5 hr. The toluene was decanted through a plug of celite and the remaining slurry was washed repeatedly with toluene and ethylacetate. The eluent was concentrated and purified by flash column chromatography (4:1 hex:EtOAc) to give 8-bromo-3,4-dihydrobenzo[b]oxepin-5(2H)-one (7 g, ca. 50% y) **8**. ^{1}H NMR (DMSO-d_6, 500 MHz) 7.55 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.35 (dd, J = 8.5, 1.5 Hz, 1H), 4.24 (t, J = 6.5 Hz, 2H), 2.79 (t, J = 7.0 Hz, 2H), 2.14 (m, 2H).

[00271] Example 4 (Z)-8-bromo-5-chloro-2,3-dihydrobenzo[b]oxepine-4-carbaldehyde **9**

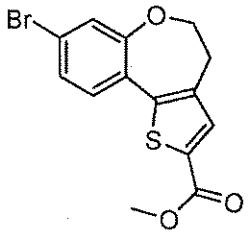


9

[00272] Phosphorus oxychloride, $POCl_3$ (1.88 mL, 20.8 mmol) was added dropwise to DMF (5 mL) at 0°C. After 30 min a solution of 8-bromo-3,4-dihydrobenzo[b]oxepin-5(2H)-one **8** (2.0 g, 8. 3 mmol) in 8 mL DMF was added dropwise. The reaction mixture was allowed to

reach room temperature to stir 2 hr, then poured slowly over rapidly stirred ice water. The aqueous phase was extracted with ethylacetate and the combined organics were washed with brine, dried over sodium sulfate and concentrated to give **9**.

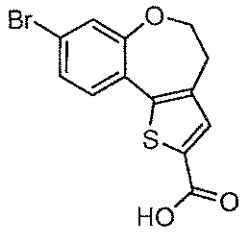
[00273] Example 5 methyl 8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylate **10**



10

[00274] (Z)-8-Bromo-5-chloro-2,3-dihydrobenzo[b]oxepine-4-carbaldehyde **9** was dissolved in 10 mL DMF and treated sequentially with potassium carbonate (2.20 g, 16.6 mmol) and methyl thioglycolate (0.83 mL). The whole was heated at 50 °C overnight, cooled to room temperature, diluted with water and extracted with ethylacetate. The combined organics were washed with brine, dried over sodium sulfate and concentrated. The crude residue was purified by flash column chromatography (20-50% ethylacetate in hexanes) to give 2.20 g (78% yield) **10** as a colorless solid. ^{1}H NMR (DMSO-d_6, 500 MHz) 7.70 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.31-7.28 (m, 2H), 4.32 (t, J = 5.0 Hz, 2H), 3.84 (s, 3H), 3.21 (t, J = 5.0 Hz, 2H).

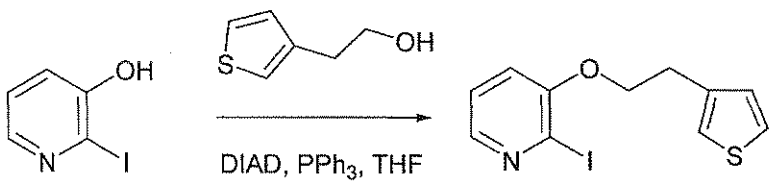
[00275] Example 6 8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid **11**



11

[00276] Methyl 8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylate **10** was treated with lithium hydroxide in water and tetrahydrofuran (THF) to give **11**.

[00277] Example 7 2-Iodo-3-(2-thiophen-3yl-ethoxy)-pyridine **13**

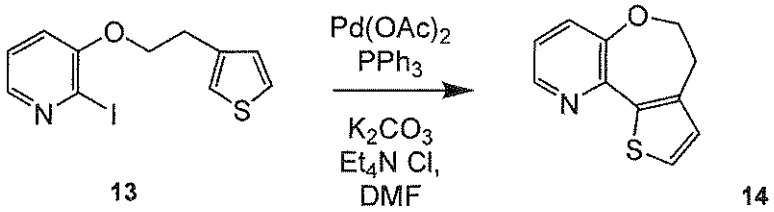


12 **13**

[00278] To a solution containing 2-iodo-3-hydroxypyridine **12** (1.85 g, 8.37 mmol), 2-(3-thienyl)ethanol (1.20 mL, 10.9 mmol), and triphenylphosphine (2.85 g, 10.9 mmol) in

tetrahydrofuran (46.2 mL, 5.70 mmol) was added diisopropyl azodicarboxylate (2.14 mL, 10.9 mmol) dropwise. The reaction mixture was stirred at room temperature for 18h. The reaction mixture was concentrated and purified by flash chromatography EtOAc/Hex (0-100%) eluted at 30% to give **13** (yield 90%). MS: (ESI+) 332.2

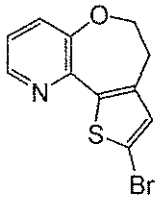
[00279] Example 8 10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine **14**



13 14

[00280] To a solution of 2-iodo-3-(2-thiophen-3yl-ethoxy)-pyridine **13** (1.15 g, 4.05 mmol) in N,N-dimethylformamide (60.9 mL, 787 mmol) was added potassium carbonate (2.80 g, 20.2 mmol), triphenylphosphine (212 mg, 0.809 mmol), tetraethylammonium chloride (4.05 mmol) and palladium acetate (90.8 mg, 0.405 mmol). The reaction mixture was stirred at 90 °C 8h. The reaction mixture was diluted with DCM then filtered through celite. The filtrate was concentrated and wash water. The crude product was purified by flash chromatography EtOAc/Hex (0-100%) product eluted at 30% to give **14** (yield 60%). MS: (ESI+) 204.3

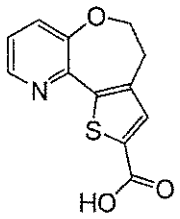
[00281] Example 9 2-bromo-(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine) **15**



15

[00282] 10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine **14** (1.73 g, 8.51 mmol) was dissolved in methylene chloride (20 mL, 400 mmol) and acetic acid (20 mL, 400 mmol) and cooled to 0 °C. N-Bromosuccinimide (1.67 g, 9.36 mmol) was added portionwise to the mixture. The reaction was stirred for 18 hours. Solvents were rotary evaporated, the residue partitioned between ethyl acetate and sat. sodium carbonate aqueous solution. The organic layer was washed with water, brine and dried over sodium sulfate. After rotary evaporation the crude product was chromatographed on Isco (hexane-EtOAc gradient, 0-100%) eluted 20% EtOAc to give **15**. MS: (ESI+) 283.2

[00283] Example 10 10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid **16**

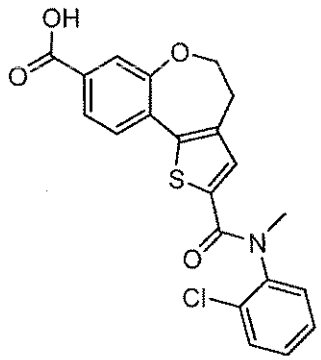


16

[00284] To a solution of 2-bromo-(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine) **15** (0.700 g, 2.48 mmol) in tetrahydrofuran (25.0 mL, 308 mmol) was added 2.50 M of n-butyllithium in hexane (1.19 mL) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 1h. The mixture was added to a slurry of dry ice in THF (15ml) then stirred 2h. The reaction mixture was quenched with water then slightly basified and extracted EtOAc (2x). The aqueous layer was acidified to pH 2 then extracted with DCM (2x). The organic layers were combined and concentrated to give **16** (yield 62%). MS: (ESI+) 248.3

[00285] Example 11 N2-(2-chlorophenyl)-N2,N8,N8-trimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **101**

[00286] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and dimethylamine gave **101**. MS: (ESI+) 441.1.



[00287] Alternatively, a solution of 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid (100 mg, 0.24 mmol) in 2 mL of $SOCl_2$ was heated at 80 °C for 2h. After removal of the solvent, the residue was co-evaporated with toluene to give the crude acid chloride 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine- 8-carbonyl chloride. To a solution of $(CH_3)_2NH$ HCl salt(118 mg, 1.412 mmol) and pyridine (0.2 mL) in 5mL of THF was slowly added 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2, 3-d]oxepine-8-carbonyl chloride (417 mg, 0.966 mmol) in 20 mL of THF. The mixture was stirred at room temperature overnight, concentrated in vacuo, dissolved in ethyl acetate, washed with water and brine, dried over Na_2SO_4, and concentrated to give **101** (350 mg, yield: 82 %). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.67- 7.59 (m, 8H), 4.16 (t, J= 4.8 Hz, 2H), 3.33 (s, 1H), 2.95- 2.97 (m, 8H). MS (ESI): 441.1

[00288] Example 12 7-acetamido-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **102**

[00289] Following Example 61 and General Procedure C, 7-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid and acetamide were reacted to give **102**. MS: (ESI+) 427.1

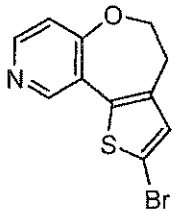
[00290] Example 13 N2-(2-chlorophenyl)-N8-(3-(diethylamino)propyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **103**

[00291] A suspension of 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** (100 mg, 0.22 mmol), $Mo(CO)_6$ (58 mg), Hermann's palladacycle (trans-Di(mu-acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium (II), 31 mg), and N,N-diethyl-1,3-propanediamine (58 mg) in THF (2.0 mL) in a 10 mL microwave vial was treated with DBU (0.02 mL, 0.5 equiv) and immediately sealed. The whole was heated in a microwave at 150°C for 25 min, cooled to room temperature and diluted with ethylacetate. The crude suspension was filtered through celite and the eluent concentrated to give a residue that was purified by flash column chromatography (1-10% methanol in dichloromethane) to give **103** as a colorless solid. MS: (ESI+) = 526.2. ^{1}H NMR (DMSO-d_6) δ 8.53 (m, 1H), 7.66 (m, 2H), 7.55-7.44 (m, 4H), 6.55 (m, 1H), 4.20 (m, 2H), ca. 3.2 (m, 2H, obstructed by water), 3.24 (s, 3H, obstructed by water), 2.97 (m, 2H), 2.67-2.56 (m, 6H), 1.69 (m, 2H), 0.99 (m, 6H)

[00292] Example 14 7-acetamido-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **104**

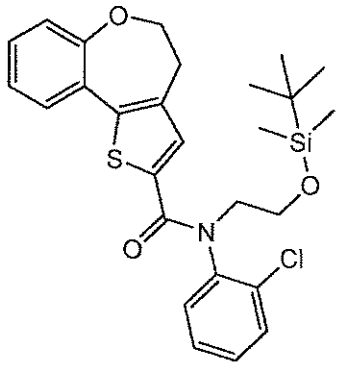
[00293] Following Example 53, 7-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid and CuCN were reacted to give **104**. MS: (ESI+) 395.1

[00294] Example 15 5-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)pyridin-2-amine **105**



[00295] Following Example 52, 2-bromo-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine and 2-aminopyridine-5-boronic acid, pinacol ester were reacted to give **105**. ^{1}H NMR (400 MHz, DMSO) δ 8.79 (s, 1H), 8.27 (d, J = 2.2, 1H), 8.22 (d, J = 5.5, 1H), 7.67 (dd, J = 2.6, 8.6, 1H), 7.22 (s, 1H), 6.99 (d, J = 5.4, 1H), 6.51 (d, J = 8.6, 1H), 6.25 (s, 2H), 4.37 (t, J = 4.8, 2H), 3.20 (t, J = 4.8, 2H). MS: (ESI+) 296.1

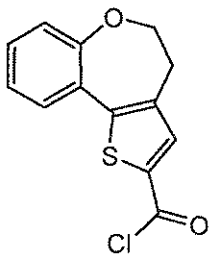
[00296] Example 16 N-(2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **106**



[00297] To a solution of N-(2-(tert-butyldimethylsilyloxy)ethyl)-2-chloroaniline (0.145 g, 0.508 mmol) and triethylamine (0.113 mL, 0.812 mmol) in tetrahydrofuran (1 mL, 10 mmol) was added a solution of 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbonyl chloride (0.107 g, 0.406 mmol) in tetrahydrofuran (4 mL). The reaction was stirred overnight and concentrated in vacuo. Aqueous work up gave a yellow solid which was purified on silica by MPLC to give 150 mg of N-(2-(tert-butyldimethylsilyloxy)ethyl)-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide.

[00298] To a solution of N-(2-(tert-butyldimethylsilyloxy)ethyl)-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (0.030 g, 0.058 mmol) in acetic acid (0.0033 mL, 0.058 mmol) and tetrahydrofuran (0.3 mL, 4 mmol) was added 1 M of tetrabutylammonium fluoride hydrate in tetrahydrofuran (0.058 mL). The reaction was stirred at room temperature w/TLC and LC/MS monitor. Deprotection was complete after overnight stirring. The reaction mixture was concentrated in vacuo, taken into ethylacetate and washed with water/saline and concentrated to a glassy residue, which was purified by MPLC, eluting with ethylacetate/hexanes, gradient 0-50% B to give 22.4 mg of **106** (yield 40%). MS: (ESI+) 401

[00299] Example 17 N-(2-chloro-4-fluorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **107**



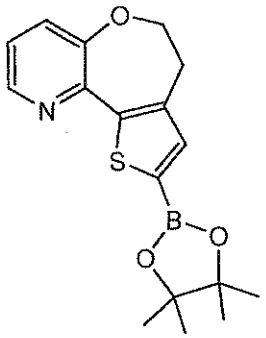
[00300] To a solution of 2-chloro-4-fluoroaniline (0.110 g, 0.755 mmol) and triethylamine (0.105 mL, 0.755 mmol) in tetrahydrofuran (1.5 mL, 18 mmol) was added portion wise as a solid 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbonyl chloride (0.100 g, 0.378

mmol). Reaction mix was stirred at room temperature with monitor for formation of desired product. The reaction was stirred overnight. The mixture containing the alkylated product was concentrated in vacuo to a solid residue, then taken into N,N-dimethylformamide (1.5 mL, 19 mmol) and treated with sodium hydride (0.0181 g, 0.755 mmol) followed by the addition of methyl iodide (0.0470 mL, 0.755 mmol). Reaction stirred at room temperature for about 1 hr with complete conversion to desired N-methyl derivative. After aqueous work up, the crude was taken into DMF at 100mg/1mL and purified by preparative RP-HPLC to give **107**. Yield = 22% of theoretical. MS: (ESI+) 375

[00301] Example 18 N-(2,4-dichlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **108**

[00302] To a solution of N-methyl-2,4-dichloroaniline (0.133 g, 0.755 mmol) and triethylamine (0.105 mL, 0.755 mmol) in tetrahydrofuran (1.5 mL, 18 mmol) was added 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbonyl chloride (0.100 g, 0.378 mmol) portion wise as a solid. Reaction was stirred at room temperature with monitor for formation of desired product. The reaction was stirred overnight. After aqueous workup, the crude was taken into DMF at a concentrated of 100 mg/ml and purified by preparative RP-HPLC to give **108**. Yield = 30% of theoretical. MS: (ESI+) 405.5

[00303] Example 19 methyl 5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)2-aminoisonicotinate **109**



[00304] n-Butyllithium in hexane (0.7833 mL, 1.6 M) was added dropwise to a solution of 9-bromo-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine (0.282 g, 1.00 mmol) in tetrahydrofuran (7.46 mL, 91.9 mmol) at -75 °C. The dark brown mixture was stirred at -78 °C for 20 min. 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.31 mL, 1.5 mmol) in 2 ml of tetrahydrofuran was added dropwise and the mixture was kept at -78 °C for 20 min gradually warming up to -30 °C. sat. aq.NH_4Cl (10 ml) was added and the mixture was poured into 25 ml of water, extracted with ethylacetate , the organic layer was washed with water, brine and dried over MgSO4. The solution was rotary evaporated and the residue purified on silicagel column

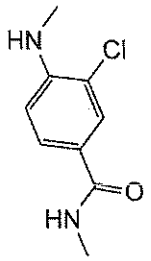
eluting with 18% of ethyl acetate in hexane to give 9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine (yield 0.224 g, 68%). MS: (ESI+) 330.1

[00305] Following Example 52, 9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine and 2-amino-5-bromo-isonicotinic acid methyl ester were reacted to give **109**. ^{1}H NMR (400 MHz, DMSO) δ 8.22 (dd, J = 1.4, 4.5, 1H), 8.14 (s, 1H), 7.40 (dd, J = 1.4, 8.1, 1H), 7.19 (dd, J = 4.5, 8.1, 1H), 6.87 (s, 1H), 6.64 (s, 1H), 6.52 (s, 2H), 4.33 (t, J = 4.8, 2H), 3.76 (s, 3H), 3.20 (t, J = 4.8, 2H). MS: (ESI+) 354.1

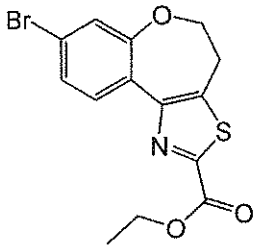
[00306] Example 20 2-(4-isopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **110**

[00307] 2-(4-Isopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile was treated with potassium carbonate in DMSO, then hydrogen peroxide to give **110**. MS: (ESI+) 371.1

[00308] Example 21 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-4-methylcarbamoyl-phenyl)-methyl-amide **111**



[00309] A solution of 3-chloro-4-fluorobenzonitrile (1.0 g), methylamine (16 mL of a 2 M solution in methanol) and diisopropylethylamine was reacted in the microwave at 120 °C for 15 min. The mixture was then partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with brine (30 mL), dried ($MgSO_4$) and reduced in vacuo to give 3-chloro-4-methylamino-benzonitrile. A suspension of 3-chloro-4-methylamino-benzonitrile (900 mg) in 2 M aqueous sodium hydroxide solution (30 mL) was heated at reflux for 3 h. After cooling to room temperature, the solution was acidified with 2 M aqueous hydrochloric acid and the resulting solid collected by filtration and air-dried to give 3-chloro-4-methylamino-benzoic acid. To a solution of 3-chloro-4-methylamino-benzoic acid (860 mg) in DMF (20 mL) was added carbonyl diimidazole (630 mg) and the reaction stirred at room temperature for 1 h. Then, methylamine hydrochloride (262 mg) and triethylamine (1.62 mL) were added and the reaction stirred at room temperature for 16 h. The reaction was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with brine (3 x 40 mL), dried (MgSO4), reduced in vacuo and purified on silica to give 3-chloro-N-methyl-4-methylamino-benzamide.

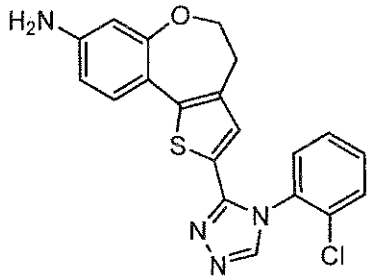


[00310] 8-Bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid ethyl ester was prepared from 3-bromophenol according to Example 136 for **226**, and hydrolyzed to the corresponding acid using General Procedure B. To a suspension of 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (373mg) in dry dichloromethane (20mL) was added oxalyl chloride (170μL) and DMF (1 drop). After 2 hours the solvent was removed in vacuo and to the residue was added acetonitrile (20 mL), 3-chloro-N-methyl-4-methylamino-benzamide (250 mg) and sodium bicarbonate (105 mg). After 3 hours, water was added to the reaction mixture and the resulting precipitate was collected by filtration. The solid was recrystallized form ethyl acetate/methanol/hexane to yield **111** (307mg). NMR: (CDCl3): 3.04 (3H,d), 3.31 (2H,t), 3.48 (3H,s), 4.28-4.31 (2H,m), 6.05 (1H,sbr.), 6.91-6.93 (2H,m), 7.15 (1H,s), 7.45 (1H,d), 7.72 (1H,dd), 7.91 (1H,s). MS: (ESI+) MH+ 508

[00311] Example 22 1-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-3-methylurea **112**

[00312] Following the procedures of Example 76, 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-amine was reacted with methyl isocyanate to give **112**. MS: (ESI+) 452.1

[00313] Example 23 methyl 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-ylcarbamate **113**



[00314] To a solution of 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydro - benzo[b]thieno [2,3-d]oxepin-8-amine HCl salt (0.2 g, 0.464 mmol) in 10 ml of dried DCM was added TEA (0.32 mL, 2.3 mmol). The mixture was stirred at 0 °C for 20 min and 0.2 ml of methyl chloroformate was added. The reaction mixture was stirred for 10 min and the solution was quenched with water and evaporated to the crude product, which was purified by preparative HPLC to give **113** (81 mg, 38%). ^{1}HNMR (DMSO-d_6, 400 MHz): δ 9.78 (s, 1H),

8.81 (s, 1H), 7.79- 7.12 (m, 7H), 6.53 (s, 1H), 4.15 (t, J= 5.2 Hz, 2H), 3.63 (s, 3H), 2.93 (t, J= 5.2 Hz, 2H). MS: (ESI+) 453.1

[00315] Example 24 7-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **114**

[00316] Following Example 70 and General Procedure B, **114** was prepared from 7-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid and 2-chloro-N-methylaniline. MS: (ESI+) 450.0

[00317] Example 25 N-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)acetamide **115**

[00318] To a solution of 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydro - benzo[b]thieno [2,3-d]oxepin-8-amine HCl salt (0.2 g, 0.464 mmol) in 10 ml of dried DCM was added TEA (0.32 mL, 2.3 mmol). The mixture was stirred at 0 °C for 20 min and 0.2 ml of acetic anhydride was added. After stirred for 10 min, the solution was quenched with water and evaporated to the crude product, which was purified by preparative TLC to give **115** (80 mg, 39%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.02 (s, 1H), 8.81 (s, 1H), 7.79- 7.15 (m, 7H), 6.54 (s, 1H), 4.16 (t, J= 4.8 Hz, 2H), 2.95 (t, J= 4.8 Hz, 2H), 1.99 (s, 3H). MS: (ESI+) 437.1

[00319] Example 26 N-(4-(3-amino-5-methyl-1H-pyrazole-1-carbonyl)-2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **116**

[00320] Following Example 91, 3-chloro-4-(N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and 3-amino-5-methylpyrazole were reacted to give **116**. Yield 25% of theoretical. MS: (ESI+) 523.1

[00321] Example 27 N-(4-(2-acetamidoethylcarbamoyl)-2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **117**

[00322] Following Example 91, 3-chloro-4-(N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and N-(2-aminoethyl)acetamide were reacted to give **118**. Yield 35% of theoretical. MS: (ESI+) 528.2

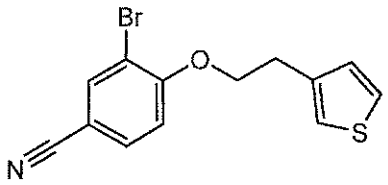
[00323] Example 28 N-(2-chloro-4-((2-(dimethylamino)ethyl)(methyl)carbamoyl)phenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **118**

[00324] Following Example 91, 3-chloro-4-(N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and N1,N1,N2-trimethylethane-1,2-diamine were reacted to give **118** (yield 35% of theoretical). MS: (ESI+) 528.2

[00325] Example 29 N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide **119**

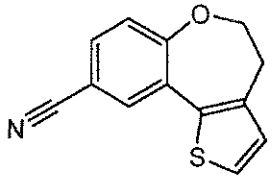
[00326] To a mixture of N-(2-chlorophenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **120** (120 mg) and K_2CO_3 (49 mg) in dry DMSO (2 mL) was added 33% hydrogen peroxide (40 μL). The resultant was stirred overnight at room temperature. Ice was added to the resulting solution and the solid formed was collected, washed with water and dried to give **119**. NMR: (CDCl3): 3.04 (t, 2H, CH2, J = 5.02Hz), 3.42 (s, 3H, CH3), 4.28 (t, 2H, CH2, J = 5.06Hz), 5.75 (sbr, 2H, NH2), 6.71 (s, H, ArH), 7.03 (d, H, ArH, J = 8.44Hz), 7.39-7.45 (m, 3H, 3 x ArH), 7.55-7.60 (m, 2H, 2 x ArH), 7.99 (d, H, ArH, J = 1.81Hz). MS: (ESI+) MH+ 413.14

[00327] Example 30 N-(2-chlorophenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **120**

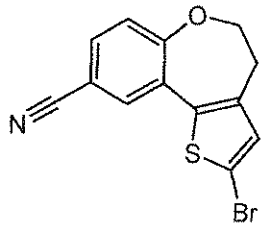


[00328] To a solution of 3-bromo-4-hydroxybenzonitrile (15.0 g) in THF (100 mL) was added 2-(3-thienyl)ethanol (7.94 mL) and triphenyl phosphine (19.84 g). The reaction was cooled to 0 °C and diethylazodicarboxylate (11.92 mL) was added dropwise. The reaction was stirred at room temperature for 16 h. The solvent was then reduced in vacuo and the residue redissolved in diethyl ether (100 mL). The mixture was stirred at 0 °C for 10 min and then filtered. The filtrate was washed with aqueous sodium carbonate solution (80 mL), 1 M aqueous hydrochloric acid (80 mL) and brine (80 mL), dried ($MgSO_4$), reduced in vacuo and purified on silica to give 3-bromo-4-(2-thiophen-3-yl-ethoxy)-benzonitrile.

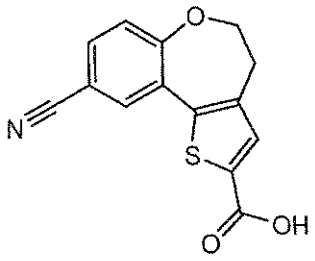
[00329] To a solution of 3-bromo-4-(2-thiophen-3-yl-ethoxy)-benzonitrile (4.50 g) in DMF (20 mL) was added palladium acetate (327 mg), triphenylphosphine (766 mg) and potassium carbonate (4.03 g) and the reaction heated at 90 °C for 16 h. After cooling to room temperature the mixture was diluted with ethyl acetate (60 ml) and filtered. The filtrate was washed with brine (80 mL), dried ($MgSO_4$), reduced in vacuo and purified on silica to give 4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carbonitrile.



[00330] To a solution of 4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carbonitrile (4.58 g) in dichloromethane (30 mL) and acetic acid (30 mL) was added N-bromosuccinimide (3.95 g) and the reaction stirred at room temperature for 16 h. Water (100 mL) was then added and the solid collected by filtration and air-dried to give 2-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carbonitrile.



[00331] To a solution of 2-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carbonitrile (3.0 g) in THF (80 mL) at -78 °C was added n-butyllithium (4.31 mL) and the reaction allowed to warm to -10 °C over 1 h. The reaction was then recooled to -78 ° and carbon dioxide was bubbled through the solution for 15 min. The reaction was then allowed to warm to room temperature over 4 h. The reaction was quenched with water (10 mL) and the product extracted into aqueous sodium carbonate solution (100 mL). The aqueous layer was washed with ethyl acetate (100 mL) and then acidified to pH 2-3 with 2 M aqueous hydrochloric acid. The product was then extracted into ethyl acetate (2 x 100 mL) and the organic layers were dried ($MgSO_4$) and reduced in vacuo to give 9-cyano-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid.



[00332] To a solution of 9-cyano-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid (300 mg) in dichloromethane (10 mL) was added DMF (1 drop) and oxalyl chloride (0.165 mL) and the reaction stirred at room temperature for 30 min. The solvent was then reduced in vacuo and the residue redissolved in acetonitrile (10 mL). To this solution was added 2-chloro-N-methylaniline (0.165 mL) and potassium carbonate (308 mg) and the reaction stirred at room temperature for 16 h. The mixture was partitioned between water (40 mL) and ethyl acetate (30 mL). The organic layer was dried (Na_2SO_4), reduced in vacuo and purified on silica to give **120**. NMR: (CDCl3): 3.08 (t, 2H, CH2, J = 5.00Hz), 3.41 (s, 3H, CH3), 4.29 (t, 2H, CH2, J = 5.02Hz), 6.92 (s, H, ArH), 7.03 (d, H, ArH, J = 8.43Hz), 7.38-7.47 (m, 4H, 4 x ArH), 7.57 (m, H, ArH), 7.72 (d, H, ArH, J = 1.65Hz). MS: (ESI+) MH+ 395

[00333] Example 31 4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-4-methylcarbamoyl-phenyl)-methyl-amide **121**

[00334] 4,5-Dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid ethyl ester was prepared according to Example 136 for **226**, and hydrolyzed to the corresponding acid using General Procedure B. To a suspension of 4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (130 mg) in dry dichloromethane (10 mL) was added oxalyl chloride (78 μL) and DMF (1 drop). After 1 hour the solvent was reduced in vacuo and the residue was dissolved in acetonitrile (10mL) and to this was added 3-chloro-N-methyl-4-methylamino-benzamide from Example 21 (116 mg) and sodium bicarbonate (49 mg). The reaction mixture was warmed to 60 °C. After 3 hours the reaction mixture was cooled, diluted with dichloromethane, washed with water, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was recrystallized form ethyl acetate/methanol/hexane to yield **121** (132mg). NMR: (CDCl3): 3.04 (3H,d), 3.31 (2H,t), 3.48 (3H,s), 4.28-4.31 (2H,m), 6.05 (1H,sbr.), 6.81-6.83 (1H,m), 6.96 (1H,d), 7.05-7.15 (2H,m), 7.48 (1H,d), 7.78 (1H,dd), 7.93 (1H,s). MS: (ESI+) MH+ 428

[00335] Example 32 N-(2-chlorophenyl)-N-methyl-8-(pyridin-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **122**

[00336] Following Examples 44 and 60 and General Procedure C, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and 3-pyridylboronic acid were reacted to give **122**. MS: (ESI+) 447.1

[00337] Example 33 N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbothioamide **123**

[00338] To a suspension of N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **157** (60 mg, 0.16 mmol) in dry toluene (2 mL) in a 20 mL scintillation vial was added Lawesson's reagent (4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, 49 mg, 0.12 mmol, 0.75 equiv). The vial was sealed and heated at 90 °C for 36 hr. The mixture was cooled to room temperature, concentrated and purified by reverse phase HPLC to give **123** as a yellow solid. ^1H NMR ($CDCl_3$) δ 7.57 (m, 1H), 7.48 (m, 1H), 7.35-7.27 (m, 4H), 7.14 (m, 1H), 6.96 (m, 1H), 6.52 (s, 1H), 4.19 (m, 2H), 3.80 (s, 3H), 2.92 (m, 2H). MS: (ESI+) 386.1

[00339] Example 34 8-(3-aminophenyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **124**

[00340] Following Examples 44 and 60 and General Procedure C, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and 3-aminophenyl boronic acid were reacted to give **124**. MS: (ESI+) 461.1

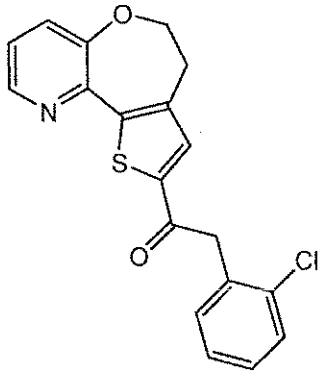
[00341] Example 35 N-(2-chlorophenyl)-8-(3-(dimethylamino)prop-1-ynyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **125**

[00342] Following Examples 43 and 60, Sonagoshira coupling of 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and N,N-dimethylpropargyl amine gave **125**.

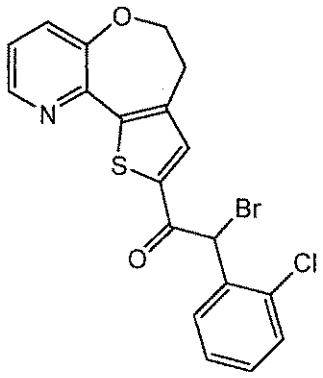
[00343] Example 36 N-(2-chlorophenyl)-8-(3-hydroxyprop-1-ynyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **126**

[00344] Following Examples 43 and 60, Sonagoshira coupling of 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and 3-propargyl alcohol gave **126**. MS: (ESI+) 424.1

[00345] Example 37 4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(2-chlorophenyl)-2-acetamino-1H-imidazole **127**



[00346] A stirred mixture of 6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine (1016 mg, 5.000 mmol) and (2-chlorophenyl)-acetic acid (1134 mg, 6.650 mmol) in polyphosphoric acid (30 g, 300 mmol) was heated for 4 hours at 110 °C . Ice (200 g) was added and the mixture was shaken until a homogeneous suspension formed.. The precipitate was filtered out, washed with water, ethyl acetate and dried in air. Recrystallized from 100 ml of hot dioxane gave 6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl-(2-chlorophenyl)ethanone (1.34 g, 70%). ^{1}H NMR (400 MHz, DMSO) δ 8.30 (d, J = 3.8, 1H), 8.03 (s, 1H), 7.50 – 7.44 (m, 2H), 7.41 (dt, J = 3.7, 7.5, 1H), 7.37 – 7.30 (m, 3H), 4.48 (s, 2H), 4.39 (t, J = 4.7, 2H), 3.28 (t, J = 4.7, 2H). MS (ESI+) 356.0



[00347] To a solution of 6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl-(2-chlorophenyl)ethanone (142 mg, 0.400 mmol) in hot 1,4-dioxane (4 mL, 60 mmol), copper(II) bromide (139 mg, 0.622 mmol) was added and the mixture was heated for 3 hours at 110 °C. The mixture was then cooled to room temperature and partitioned between ethylacetate and water. The suspension was filtered through celite, the organic layer separated, washed with water and brine, dried over $MgSO_4$, and evaporated to dryness. The crude product was purified on silica gel column eluting with 20% ethylacetate in hexane to give 6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl-(2-chlorophenyl)-2-bromoethanone (yield 100 mg, 57%). ^{1}H NMR (400 MHz, CDCl3) δ 8.30 (d, J = 4.4, 1H), 7.75 (dd, J = 2.0, 7.4, 1H), 7.60 (s, 1H), 7.44 – 7.38 (m, 1H), 7.30 (ddd, J = 1.7, 7.8, 9.6, 3H), 7.16 (dd, J = 4.4, 8.2, 1H), 6.72 (s, 1H), 4.41 – 4.31 (m, 2H), 3.25 (d, J = 3.0, 2H). MS(ESI+) 434.0

[00348] 6,7-Dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl-(2-chlorophenyl)-2-bromoethanone (87.0 mg, 0.200 mmol) and N-acetyl-guanidine (101 mg, 1.00 mmol) were mixed in acetonitrile (2 mL, 50 mmol). The reaction was microwaved on 300 watts at 120 °C for 20 minutes. The mixture was kept at room temperature for 18 hours, the crystalline product was filtered out, washed with cold acetonitrile and purified on silicagel column eluting with 2% of methanol in methylene chloride to give **127** (yield 34 mg, 39%). MS(ESI+) 437.1.

[00349] Example 38 4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(2-chlorophenyl)-2-amino-1H-imidazole **128**

[00350] From Example 37, 4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(2-chlorophenyl)-2-amino-1H-imidazole **127** (27 mg, 0.062 mmol) was added to ethanol (2 mL, 30 mmol) containing 1 ml of 10% aqueous sulfuric acid. The reaction was microwaved on 300 watts at 100 °C for 15 minutes. The reaction mixture was mixed with 10 ml of 1 M aq Na_2CO_3 and extracted with ethyl acetate twice. The organic layer was washed with brine and dried over K_2CO_3. The solvent was evaporated to afford **128**. (18 mg, 74%). MS(ESI+) 395.1

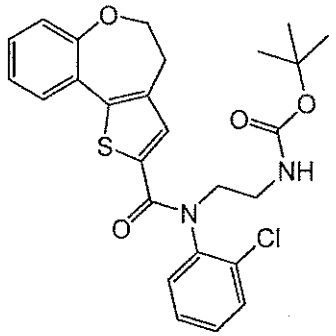
[00351] Example 39 4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(5-(2-chlorophenyl))-oxazole **129**

[00352] 6,7-Dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl-(2-chlorophenyl)-2-bromoethanone from Example 37 (65.0 mg, 0.150 mmol) was suspended in formamide (2 mL, 50 mmol). The reaction was microwaved on 300 watts at 130 °C for 20 minutes. Water was added and the product was extracted with ethylacetate. The organic layer was washed with water twice and brine, dried over MgSO4, and evaporated to dryness. The crude product was purified on silica gel column, eluting with 25% of ethylacetate in hexane to give **129** (yield 10 mg, 18%). MS(ESI+) 381.1

[00353] Example 40 N-methyl-N-(2-(trifluoromethyl)phenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **130**

[00354] To a solution of 2-(trifluoromethyl)aniline (0.122 g, 0.755 mmol) and triethylamine (0.105 mL, 0.756 mmol) in tetrahydrofuran (1.5 mL, 18 mmol) was added portion wise as a solid 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbonyl chloride (0.100 g, 0.378 mmol). The reaction mixture was stirred at room temperature with LC/MS monitor for formation of the alkylated product and noted complete after 2 hours. After aqueous work up, the reaction mixture was concentrated in vacuo, taken into DMF and treated with sodium hydride (0.03 g, 1 mmol) at room temperature for several minutes. Methyl iodide (0.06 g, 0.4 mmol) was added and the reaction was stirred at room temperature for several hours, then concentrated in vacuo. The residue was taken into EtOAc and washed with water and saline, concentrated to a solid residue, taken into DMF at a concentration of 100 mg/ml and purified by preparative RP-HPLC to give **130**. Yield = 25% of theoretical. MS: (ESI+) 404.1

[00355] Example 41 N-(2-aminoethyl)-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **131**



[00356] To a solution of room temperature tert-butyl 2-(2-chlorophenylamino)ethylcarbamate (0.145 g, 0.508 mmol) and triethylamine (0.113 mL, 0.812 mmol) in tetrahydrofuran (1 mL, 10 mmol) was added a solution of 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbonylchloride in tetrahydrofuran (4 mL). The reaction mixture was stirred overnight and measured complete by LC/MS. Reaction concentrated in vacuo, and aqueous work up gave a yellow solid which was purified by MPLC

to give 150 mg N-(2-(tert-butyldimethylsilyloxy)ethyl)-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide.

[00357] To a solution of tert-butyl 2-(N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)ethylcarbamate (0.022 g, 0.36 mmol) /in DCM (0.400 mL, 4.93 mmol) was added a solution of 95% TFA/5% water. The reaction was monitored by LC/MS for desired product. Reaction mix concentrated in vacuo, taken into EA and washed with H_20, dried (Na_2SO_4), concentrated and crude purified by preparative RP-HLPC to give **131** (yield = 98% of theoretical). MS: (ESI+) 400.1

[00358] Example 42 N-(2-chlorophenyl)-N-methyl-8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **132**

[00359] Following Examples 44 and 60, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and pyrazole-4-boronic acid pinacol ester were reacted to give **132**. MS: (ESI+) 436.1

[00360] Example 43 N-(2-chlorophenyl)-8-ethynyl-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **133**

[00361] A solution of 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** (50 mg, 0.11 mmol) in triethylamine (2 mL) containing CuI (2.1 mg, 0.011 mmol) was degassed with bubbling nitrogen for 10 min. $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) was added followed by trimethylsilylacetylene (5 equiv). The reaction vessel was sealed and heated in the microwave at 130 °C for 30 min. The cooled mixture was diluted with water and extracted with ethylacetate. The combined organics were concentrated and the residue dissolved in 2 mL methanol. The solution was treated with potassium carbonate (100 mg) and the suspension stirred for 2 hr at room temperature. The reaction mixture was concentrated, diluted with water and extracted with ethylacetate. The combined organics were concentrated and the residue purified by reverse phase HPLC to give **133**. MS: (ESI+) 394.1.

[00362] Example 44 N-(2-chlorophenyl)-N-methyl-8-(pyridin-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **134**

[00363] A suspension of 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** (50 mg, 0.11 mmol) in 1.0 mL MeCN and 1.0 mL 1M KOAc in water in a 10 mL microwave vial was degassed with bubbling nitrogen for approximately 10 min. 4-pyridineboronic acid (16 mg) was added followed by $Pd(PPh_3)_4$ (13 mg). The vessel was sealed and heated in a microwave at 140 °C for 30 min. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethylacetate. The combined organics were concentrated and the residue purified by reverse phase HPLC to

give **134**. ^{1}H NMR (DMSO-d_6) δ 8.77 (m, 2H), 8.05 (m, 2H), 7.70-7.53 (m, 7H), 6.65 (br s, 1H), 4.25 (m, 2H), 3.31 (s, 3H), 3.02 (m, 2H). MS: (ESI+) 447.1

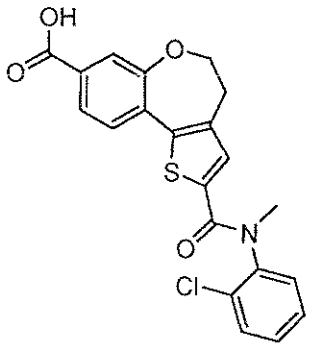
[00364] Example 45 N-(2-chlorophenyl)-N-methyl-8-phenyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **135**

[00365] Following Examples 44 and 60, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and phenyl boronic acid were reacted to give **135**. MS: (ESI+) 446.1

[00366] Example 46 5-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-pyrrolo[2,3-b]pyridine **136**

[00367] 2-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine from Example 73 was reacted with 7-azaindole-5-boronic acid pinacol ester using standard Suzuki coupling procedure. Purification on prep HPLC gave **136**. 1H NMR (400MHz, CDCl3): 3.30 (2H, t), 4.40 (2H, t), 6.56-6.58 (1H, m), 7.05-7.07 (2H, m), 7.15-7.18 (2H, m), 7.36 (1H, t), 7.75 (1H, d), 8.16 (1H, d), 8.63 (1H, d). MS: (ESI+) 318

[00368] Example 47 N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **137**



[00369] To a solution of methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** (45 mg, 0.11 mmol) in 1.0 mL THF and 1.0 mL water in a 20 mL scintillation vial was added LiOH (monohydrate, 200 mg). The vessel was sealed and heated at 50 °C over night. The reaction mixture was cooled to room temperature, acidified to pH 2 with 2N HCl, and extracted with ethylacetate. The combined organic extracts were dried over Na_2SO_4 and concentrated to give the crude 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid. To a solution of this acid in 2 mL DMF was added DIPEA (0.15 mL) and HATU, (N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate, 75 mg) followed by ammonium chloride (34 mg). The whole was stirred at room temperature for 2 hours, diluted with water and extracted with ethylacetate. The combined organics were concentrated and the residue purified by reverse phase HPLC to give **137** as a colorless solid. ^{1}H NMR (500 MHz,

DMSO-d_6) δ 7.94 (br s, 1H), 7.66 (m, 2H), 7.54-7.46 (m, 4H), 7.35 (m, 1H), 6.59 (m, 1H), 4.21 (m, 2H), 3.26 (m, 3H, obstructed by water), 2.98 (m, 2H). MS: (ESI+) 413.1

[00370] Example 48 methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138**

[00371] The mixture of 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]- oxepine-2-carboxamide (10 g, 0.022 mol), $Pd(OAc)_2$ (2.47 g, 0.011 mmol), dppf (10 g, 0.018 mol), TEA(4.45 g, 0.044 mol) in DMF (50 mL) and MeOH (100 mL) was stirred under CO (50 psi) atmosphere at 70 °C for 2 days. After filtration over celite, the mixture was concentrated to give the crude product, which was purified by flash column chromatography (hexanes:EtOAc / 5:1) to give **138**. (6.59 g, yield: 69 %). MS (ESI): 428.1

[00372] Alternatively, a suspension of 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** (113 mg, 0.25 mmol), $Mo(CO)_6$ (66 mg, 0.25 mmol), Hermann's palladacycle (trans-di(mu-acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium (II), 23 mg) and tri-tert-butylphosphonium tetrafluoroborate (15 mg) in methanol (0.8 mL) and THF (0.8 mL) in a 10 mL microwave vial was treated with DBU (0.11 mL, 0.75 mmol) and immediately sealed. The whole was heated in a microwave at 110 °C for 20 min, cooled to room temperature and diluted with ethylacetate. The crude suspension was filtered through celite and the eluent concentrated to give a residue that was purified by flash column chromatography (10-100% ethylacetate in hexanes) to give **138** as a colorless solid. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.69-7.49 (m, 7H), 6.57 (m, 1H), 4.22 (m, 2H), 3.85 (s, 3H), 3.23 (s, 3H, obstructed by water), 3.02 (m, 2H). MS: (ESI+) 428.1

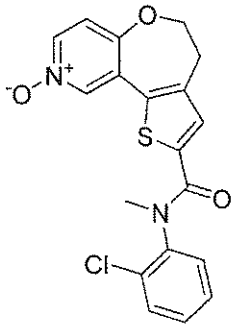
[00373] Example 49 tert-butyl 2-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamido)ethyl(methyl)carbamate **139**

[00374] Following the procedure of Example 13 and General Procedure C, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and N-Boc-N-methyl-ethylenediamine (tert-butyl 2-aminoethyl(methyl)carbamate) were reacted to give **139**. MS: (ESI+) 470.2.

[00375] Example 50 4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-indazole **140**

[00376] 2-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine from Example 73 was reacted with indazole 4-boronic acid pinacol ester using standard Suzuki coupling procedure. Purification on prep HPLC and triturating with hexanes gave **140**. 1H NMR (400 MHz, CDCl3): 3.34 (2H, t), 4.42 (2H, t), 7.07-7.11 (2H, m), 7.18-7.22 (1H, m), 7.35 (1H, s), 7.42-7.49 (3H, m), 7.79 (1H, dd), 8.50 (1H, s). MS: (ESI+) 319

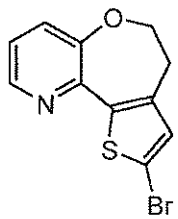
[00377] Example 51 N-(2-chlorophenyl)-N-methyl-(10-cyano-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide **141**



[00378] m-Chloroperbenzoic acid (88.0 mg, 0.36 mmol) was added to a solution of N-(2-chlorophenyl)-N-methyl-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine-2-carboxamide **162** (100 mg, 0.27 mmol) in 20 ml of methylene chloride. The reaction mixture was stirred for 18 hours. The solvent was removed under vacuum and the residue partitioned between 0.1 N aq. Na2CO3 and ethyl acetate. The organic layer was washed with water and brine, and dried over Na2SO4. Concentration under vacuum gave almost pure N-(2-chlorophenyl)-N-methyl-(9-oxo-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide (0.112 g, 90%). MS(ESI+) 387.0.

[00379] N,N-Dimethylcarbamoyl chloride (40 uL, 0.4 mmol) was added to a solution of N-(2-chlorophenyl)-N-methyl-(9-oxo-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide (56 mg, 0.14 mmol) and triethylamine (24 uL, 0.17 mmol) in 2 ml of acetonitrile. After stirring for 5 minutes, trimethylsilyl cyanide (96 uL, 0.72 mmol) was added and the mixture was kept for 4 hours. The mixture was concentrated under vacuum and the residue partitioned between ethyl acetate and 1 M aq Na2CO3. The organic layer was washed with water and brine, and dried over MgSO4. After concentration, the residue was purified on a silica gel column, eluting with 45% of ethyl acetate in hexane to give **141** (yield 27.2 mg, 47%). ^{1}H NMR (400 MHz, DMSO) δ 8.51 (d, J = 5.3, 1H), 7.72 – 7.61 (m, 2H), 7.58–7.47 (m, 2H), 7.41 (d, J = 5.3, 1H), 6.82 (s, 1H), 4.48 (t, J = 5.8, 2H), 3.30 (s, 3H), 2.93 (t, J = 5.7, 2H). MS(ESI+) 396.1

[00380] Example 52 5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-amine **142**



[00381] A mixture of 9-bromo-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine (113 mg, 0.400 mmol), 2-aminopyridine-5-boronic acid, pinacol ester (96.8 mg, 0.440 mmol) and bis(triphenylphosphine)palladium(II) chloride (14.0 mg, 0.0200 mmol) in 1.0 M of sodium carbonate in water (0.500 mL) and acetonitrile (3 mL, 60 mmol) was degassed and microwaved

on 300 watts at 140 °C for 20 minutes. The reaction mixture was partitioned between ethyl acetate and water and filtered from inorganic salts. The organic layer was washed with water, brine, dried over MgSO4 and evaporated to dryness. The crude residue was purified on silicagel column, eluting with 50% of ethyl acetate in methylene chloride to give **142** (yield 43 mg, 36%). 1H NMR (400 MHz, DMSO- d6) δ 8.27 (d, J = 2.3, 1H), 8.21 (dd, J = 1.4, 4.5, 1H), 7.68 (dd, J = 2.5, 8.6, 1H), 7.38 (dd, J = 1.4, 8.1, 1H), 7.21 (s, 1H), 7.17 (dd, J = 4.5, 8.1, 1H), 6.50 (d, J = 8.7, 1H), 6.21 (s, 2H), 4.32 (t, J = 4.8, 2H), 3.19 (t, J = 4.8, 2H). MS: (ESI+) 296.1

[00382] Example 53 N-(2-chlorophenyl)-8-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **143**

[00383] To a solution of 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** (50 mg, 0.11 mmol) in 1 mL of DMF in a 10 mL microwave vial was added CuCN (30 mg). The reaction vessel was sealed and heated to 250 °C in a microwave for 20 min. The whole was cooled to room temperature, diluted with saturated aqueous ammonium chloride and extracted with ethylacetate. The combined organic extracts were concentrated and the crude residue purified by reverse phase HPLC to give **143**. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.65 (m, 2H), 7.58-7.46 (m, 5H), 6.64 (s, 1H), 4.22 (m, 2H), 3.28 (s, 3H), 3.00 (m, 2H). MS: (ESI+) 395.1

[00384] Example 54 3-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)benzoic acid **144**

[00385] Following Examples 44 and 60 and General Procedure C, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and 3-carboxyphenyl boronic acid were reacted to give **144**. MS: (ESI+) 490.1

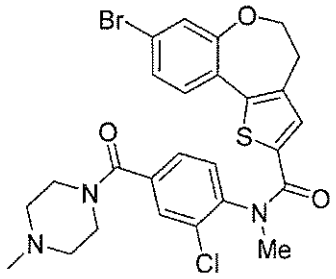
[00386] Example 55 N-(2-chlorophenyl)-N-methyl-8-(morpholine-4-carbonyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **145**

[00387] Following the procedure of Example 13 and General Procedure C, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and morpholine were reacted to give **145**. MS: (ESI+) 483.1

[00388] Example 56 N-(2-chlorophenyl)-N-methyl-8-(3-(methylsulfonyl)phenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **146**

[00389] Following the procedure of Examples 44 and 60 and General Procedure C, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and 3-methylsulfonylphenyl boronic acid were reacted to give **146**. MS: (ESI+) 524.1

[00390] Example 57 8-acetamido-N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **147**



[00391] Following the procedure of Example 91, to a solution containing 8-bromo-N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (0.095 g, 0.16 mmol) in 1,4-dioxane (2.00 mL, 25.6 mmol;) was added 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos, 9.6 mg, 0.016 mmol;), acetamide (15 mg, 0.25 mmol;), and cesium carbonate (120 mg, 0.36 mmol) then degassed with nitrogen gas for 15 min. To the reaction mixture was added tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 7.6 mg, 0.0083 mmol;). The reaction mixture was heat at 100 °C for 18h. The crude product was submitted for rHPLC to give **147** (5.5%). MS: (ESI+) 553.2

[00392] Example 58 N2-(2-chlorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **148**

[00393] Following the procedure of Example 13 and General Procedure C, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and methylamine were reacted to give **148**. MS: (ESI+) 427.1

[00394] Example 59 methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-ylcarbamate **149**

[00395] Following the procedure of Example 61, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and methyl carbamate were coupled to give **149**. MS: (ESI+) 443.1

[00396] Example 60 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150**

[00397] Following Example 10 and General Procedure C, **150** is prepared from 8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid **11** and 2-chloro-N-methylaniline. MS: (ESI+) 449.9.

[00398] Example 61 8-acetamido-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **151**

[00399] To a suspension of 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** (100 mg, 0.22 mmol), Cs_2CO_3 (158 mg), acetamide (20 mg), and xantphos (13 mg) in dry 1,4-dioxane (2 mL) was degassed with

bubbling N_2. Pd_2dba_3 was added and the 10 mL tube was sealed and heated at 110 °C for 8 hr. After cooling to room temp., the mixture was diluted with water and extracted with ethylacetate. The combined organics were concentrated and the crude residue obtained purified by reverse phase HPLC to give **151**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.03 (s, 1H), 7.65 (m, 2H), 7.62 (m, 2H), 7.35 (m, 2H), 7.17 (m, 1H), 6.51 (br s, 1H), 4.15 (m, 2H), 3.29 (s, 3H), 2.91 (m, 2H), 2.03 (s, 3H) MS: (ESI+) 427.1

[00400] Example 62 3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyridine **152** 2-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine from Example 73 was reacted with 3-pyridine boronic acid pinacol ester using standard Suzuki coupling procedure. Purification on silica gave **152**. 1H NMR (400MHz, CDCl3): 3.29 (2H, t), 4.39 (2H, t), 7.05-7.10 (2H, m), 7.18-7.22 (2H, m), 7.32-7.35 (1H, m), 7.74 (1H, dd), 7.89 (1H, dt), 8.55 (1H, dd), 8.91 (1H, s). MS: (ESI+) 280

[00401] Example 63 4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyridine **153**

[00402] 2-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine from Example 73 was reacted with 4-pyridine boronic acid pinacol ester using standard Suzuki coupling procedure. Purification on silica gave **153**. 1H NMR (400MHz, CDCl3): 3.29 (2H, t), 4.39 (2H, t), 7.06-7.11 (2H, m), 7.22 (1H, dt), 7.28 (1H, s), 7.49 (2H, dd), 7.75 (1H, dd), 8.62 (2H, dd). MS: (ESI+) 280

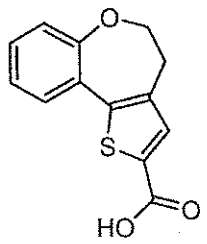
[00403] Example 64 N2-(2-chlorophenyl)-N2-(2-hydroxyethyl)-N8-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **154**

[00404] Under ambient conditions a sealable reaction vessel was charged with 8-bromo-N-(2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (0.08g, 0.17 mmol), molybdenum hexacarbonyl (0.044g, 0.167 mmol) in methanol (0.5 ml, 10 mmol)/THF 1 ml, 10 mmol), followed by the addition of 2M methylamine in THF (0.251 ml), / trans-D(mu-acetato)bis[di-o-tolylphosphino)benzyl]dipalladium(II) (32.3 mg, 0.0334 mmol). Finally, DBU (0.025 ml, 0.167 mmol) was added and the reaction vial was quickly sealed. The charged reaction vial was flash heated on a Biotage Emrys Optimizer microwave at 150 °C for 20 minutes. The cooled reaction mixture was diluted with ethyl acetate and filtered through a bed of Celite. The filtrate was concentrated to a solid and purified by MPLC on silica to give 3.2 mg **154** (yield = 4.3% of theoretical). MS: (ESI+) 458.2

[00405] Example 65 N2-(4-chloropyridin-3-yl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **155**

[00406] Following the procedure of Example 64, 8-bromo-*N*-(4-chloropyridin-3-yl)-*N*-methyl-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamide and methylamine gave **155**. Yield = 2.5% of theoretical. MS: (ESI+) 429.1

[00407] Example 66 N-(2,4-difluorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **156**

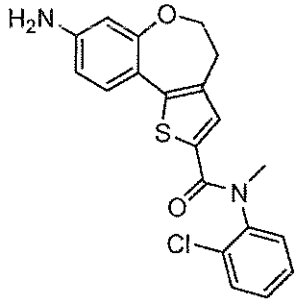


[00408] Following General Procedure C, **156** is prepared from 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid and 2,4-difluoro-N-methylaniline. MS: (ESI+) 371.9

[00409] Example 67 N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **157**

[00410] Following General Procedure C, **157** is prepared from 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid and 2-chloro-N-methylaniline. MS: (ESI+) 370.1

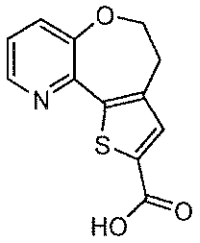
[00411] Example 68 N-(2-chlorophenyl)-8-(2-hydroxyacetamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **158**



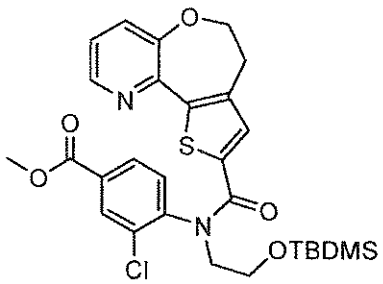
[00412] To a mixture of 8-amino-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide HCl salt (1.0 g, 2.37 mmol) in 30 mL of DCM (dichloromethane, methylene chloride) was added triethylamine (1 mL, 7.12 mmol). The mixture was stirred at 0 °C for 10 min and $BnOCH_2COCl$ (0.53 g, 2.85 mmol) was added dropwise. After the addition was completed, the reaction mixture was raised to room temperature and stirred for another 2 hours. The mixture was quenched by water and extracted with EtOAc. The organic phases were combined, dried over Na_2SO_4 and evaporated to about 0.9 g of the crude product, which was used for the next step without further purification. A mixture of 8-(2-(benzyloxy)acetamido)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo [b]thieno[2,3-d]oxepine-2-carboxamide (0.6 g, 1.13 mmol) in TFA(5 mL) and CF_3SO_3H (2 mL) was stirred at 60 °C overnight. After removal of the solvent, the crude product was purified by prep. TLC to give about 320 mg of **158** (isolated yield: 64%). ^1H NMR (DMSO-d_6, 400 MHz): δ 9.77 (s,

1H), 7.63- 7.35 (m, 7H), 6.47 (s, 1H), 5.64 (s, 1H), 4.11 (s, 2H), 3.94 (d, *J*= 5.2 Hz, 2H), 3.23 (s, 3H), 2.88 (d, *J*= 5.2 Hz, 2H). MS: (ESI+) 443.0

[00413] Example 69 N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-(2-hydroxyethyl)-10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **159**

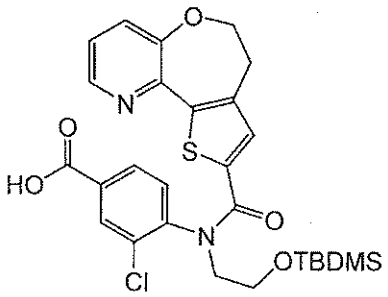


[00414] To a solution containing 10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid (0.175 g, 0.708 mmol;) in methylene chloride (1.84 mL, 28.7 mmol;) was added thionyl chloride (0.155 mL, 2.12 mmol;). The mixture was stirred at 80 °C for 2h, cooled and concentrated in vacuo. To the crude product acid chloride (0.400 g, 1.16 mmol) in tetrahydrofuran (5.22 mL, 64.4 mmol) was added 1.00 M of sodium bis(trimethylsilyl)amide in tetrahydrofuran (1.16 mL). The reaction mixture was stirred at room temperature 1h then methyl 4-(2-(tert-butyldimethylsilyloxy)ethylamino)-3-chlorobenzoate was added at 0 °C . The reaction mixture was stirred overnight, quenched with sat. NH_4Cl, and extracted with DCM (2x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography EtOAc/Hex (0-100%), eluted at 70% EtOAc, to give methyl 4-(N-(2-(tert-butyldimethylsilyloxy)ethyl)-10-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoate (yield 58%). MS: (ESI+) 573.2



[00415] To a solution of methyl 4-(N-(2-(tert-butyldimethylsilyloxy)ethyl)-10-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoate (0.250 g, 0.436 mmol) in tetrahydrofuran (10.2 mL, 126 mmol;) and water (10.2 mL, 566 mmol) was added lithium hydroxide, monohydrate (0.0732 g, 1.74 mmol) . The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated, acidified with 1M HCl, and extracted with DCM (3X). The combined organics were dried (Na_2SO_4), filtered and concentrated to give 4-(N-(2-(tert-butyldimethylsilyloxy)ethyl)-10-methyl-4,5-

dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoic acid (yield 60%). MS: (ESI+) 559.1



[00416] To a solution of 4-(N-(2-(tert-butyldimethylsilyloxy)ethyl)-10-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoic acid (0.0710 g, 0.127 mmol) in methylene chloride (1.8 mL, 28 mmol) was added methylamine (0.254 mmol) and N,N-diisopropylethylamine (0.221 mL, 1.27 mmol), and then N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU, 0.0966 g, 0.254 mmol). The mixture was stirred at room temperature for 2h. LCMS indicated the reaction was complete. The reaction was quenched with sat. NH_4Cl and extracted with DCM (2x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude TBDMS-amide product was purified by flash chromatography (MeOH/DCM, eluted at 5%MeOH) and dissolved in tetrahydrofuran (5.00 ml) and acetic acid (0.007 mL, 0.127 mmol). Tetra-n-butylammonium fluoride in tetrahydrofuran (0.127 mL, 1.00 M, 0.127 mmol) was added. The reaction mixture was stirred at room temperature for 14h. The reaction mixture was diluted with ethyl acetate and washed with water. The crude product was purified by rHPLC to give **159** (yield 22%). MS: (ESI+) 558.1

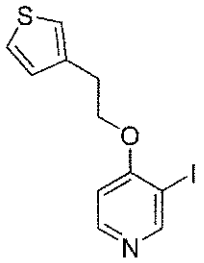
[00417] Example 70 **160**

[00418] Following the procedure of Example 69 to prepare **159**, 4-(N-(2-(tert-butyldimethylsilyloxy)ethyl)-10-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoic acid and 1-methylpiperazine were reacted to give **160**, following fluoride treatment to remove the TBDMS group. MS: (ESI+) 527.2

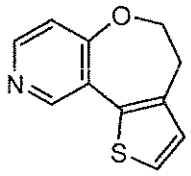
[00419] Example 71 N-(2-chlorophenyl)-8-(3-(dimethylamino)propanamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **161**

[00420] Following the procedure of Example 68 for **158**, 8-amino-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide HCl salt and acryloyl chloride reacted to give 8-acrylamido-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide which was treated with dimethylamine to give **161**. MS: (ESI+) 484.1

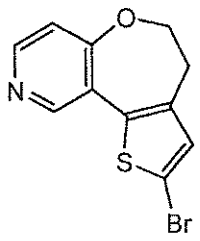
[00421] Example 72 N-(2-chlorophenyl)-N-methyl-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-carboxamide **162**



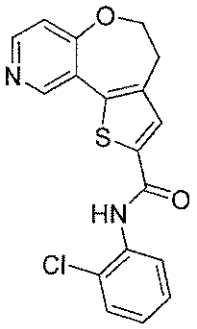
[00422] To a solution of 4-chloro-3-iodo-pyridine (4.79 g, 20.0 mmol) and 2-(3-thienyl)ethanol (2.43 mL, 22.0 mmol) in a mixture of tetrahydrofuran (60 mL, 700 mmol) and N,N-dimethylformamide (20 mL, 200 mmol) was added sodium hydride, 60% dispersion in mineral oil (0.960 g, 24.0 mmol) portionwise over 30 min. The mixture was stirred for 2 hours, poured carefully into 200 ml of cold water and extracted with diethylether twice. The organic extract was washed with water and brine, and dried over $MgSO_4$. After concentration under vacuum, the crude residue was purified on silica gel column, eluting with 50% ethyl acetate in hexane to give 3-iodo-4-(2-(thiophen-3-yl)ethoxy)pyridine (yield 5.34 g, 81%). ^{1}H NMR (400 MHz, CDCl3) δ 8.75 (s, 1H), 8.35 (d, J = 5.6, 1H), 7.29 (dd, J = 3.0, 4.8, 1H), 7.19 (s, 1H), 7.12 (d, J = 4.9, 1H), 6.70 (d, J = 5.6, 1H), 4.26 (t, J = 6.5, 2H), 3.21 (t, J = 6.5, 2H). MS(ESI+) 332.0, 221.9.



[00423] 3-Iodo-4-(2-(thiophen-3-yl)ethoxy)pyridine (1.66 g, 5.00 mmol), palladium acetate (112 mg, 0.500 mmol), triphenylphosphine (262 mg, 1.00 mmol) and potassium carbonate (1.38 g, 10.0 mmol) in N,N-dimethylformamide (80 mL, 1000 mmol) were heated at 115 °C for 2 hours. The reaction mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with water and brine, and dried over MgSO4. The crude product was purified on a silica gel column eluting with 50% ethyl acetate in hexane to give 4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine (yield 0.86 g, 85%). ^{1}H NMR (400 MHz, CDCl3) δ 8.93 (s, 1H), 8.25 (d, J = 5.5, 1H), 7.23 (d, J = 5.2, 1H), 6.89 (dd, J = 3.6, 5.3, 2H), 4.43 – 4.33 (m, 2H), 3.29 – 3.20 (m, 2H). MS(ESI+) 204.0



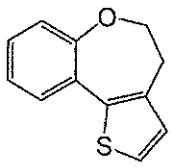
[00424] N-Bromosuccinimide (0.237 g, 1.33 mmol) in dimethylformamide (4 mL) was added dropwise to a solution of 4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine (0.250 g, 1.23 mmol) in dimethylformamide (4 mL, 100 mmol) at 0 °C. The reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was mixed with 40 ml of water and extracted with 20 ml of ethylacetate twice. Combined organic extracts were washed with water and brine, and dried over $MgSO_4$. The solvent was evaporated affording 2-bromo-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine (0.227 g, 63%). 1H NMR (500 MHz, CDCl3) δ 8.76 (s, 1H), 8.26 (d, J = 5.4, 1H), 6.90 (d, J = 5.5, 1H), 6.88 (s, 1H), 4.36 (t, J = 4.7, 2H), 3.19 (t, J = 4.8, 2H). MS(ESI+) 282.0



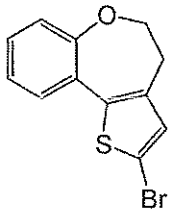
[00425] 1.6 M of n-Butyllithium in hexane (0.6302 mL) was added dropwise to a solution of 2-bromo-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine (0.227 g, 0.804 mmol) in tetrahydrofuran (6.00 mL, 74.0 mmol) at -75 °C. The dark brown mixture was stirred at -78 °C for 20 min. 1-Chloro-2-isocyanato-benzene (0.1421 g, 0.9252 mmol) in 2 ml of tetrahydrofuran was added dropwise and the mixture was kept at -78 °C for 20 min. 4N aq. HCl (1 ml) was added and the mixture was poured into 50 ml of sat. aq $NaHCO_3$. The mixture was extracted twice with methylene chloride, combined, and washed with water and brine, and dried over MgSO4. After concentrating under vacuum, the residue was triturated with ethyl acetate. The collected precipitate was N-(2-chlorophenyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-carboxamide (0.19 g, 66% yield). MS(ESI+) 357.0.

[00426] Sodium hydride, 60% dispersion in mineral oil (80 mg, 2.0 mmol) was added to a solution of N-(2-chlorophenyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-carboxamide (71.4 mg, 0.2 mmol) in 10 ml of tetrahydrofuran. The mixture was stirred for 30 min and mixed with methyl iodide (0.12 mL, 2.0 mmol). The reaction mixture was stirred for 1 hour. The mixture was mixed with 50 ml of iced water and extracted with ethyl acetate twice. The combined ethyl acetate solution was washed with brine, dried over MgSO4, concentrated in vacuo, and purified on silica gel column eluting with 25% of ethylacetate in methylene chloride to give **162** (yield 50 mg, 67%). ^{1}H NMR (400 MHz, DMSO) δ 8.57 (s, 1H), 8.25 (d, J = 5.5, 1H), 7.68 (t, J = 5.9, 2H), 7.60 – 7.50 (m, 2H), 6.98 (d, J = 5.5, 1H), 6.64 (s, 1H), 4.27 (m, 2H), 3.28 (s, 3H), 2.99 (m, 2H). MS(ESI+) 371.1

[00427] Example 73 5-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyrimidin-2-amine **163**



[00428] To a stirred solution of 2-iodophenol (6.7 g, 30.6 mmol), 2-(3-thienyl)ethanol (3.57 g, 27.8 mol) and triphenylphosphene (8.00 g, 30.6 mmol) in THF, was slowly added a solution of DEAD (4.8 ml, 30.6 mmol). Reaction mixture was stirred at room temperature for 3 hours. Purification on silica gave 3-[2-(2-iodo-phenoxy)-ethyl]-thiophene. A mixture of 3-[2-(2-iodo-phenoxy)-ethyl]-thiophene (1.55 g, 4.69 mmol), palladium(II) acetate (105 mg, 0.47 mmol), potassium carbonate (3.2 g, 23.45 mmol), triphenylphosphene (246 mg, 0.94 mmol) and tetraethylammonium chloride (1.3g, 4.69mmol) in DMF was microwaved at 100 °C for 1hour. The reaction was diluted with dichloromethane and filtered through celite. The filtrate was washed with water, dried ($MgSO_4$), and concentrated *in-vacuo*. Purification on silica gave 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine.



[00429] To a stirred solution of 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine (440 mg, 2.2 mmol) and acetic acid (10 ml) in dichloromethane (10 ml) at 0 °C, was added N-bromosuccinimide in portions. Reaction mixture was stirred for 18 hours, allowing solution to raise to room temperature before being concentrated *in-vacuo*. Residue was dissolved in ethyl acetate and sat. sodium carbonate solution. Organic phase was washed with water and brine, dried (Na_2SO_4) and concentrated *in-vacuo* to give 2-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine.

[00430] 2-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine was reacted with 2-aminopyrimidine-5-boronic acid pinacol ester using standard Suzuki coupling procedure. Purification on silica and triturating with diethyl ether gave **163**. 1H NMR (400MHz, CDCl3), 3.26 (2H, t, J=5.14), 4.37 (2H, t, J=5.18), 5.16 (2H, Broad s), 7.02-7.09 (3H, m), 7.16-7.22 (1H, m), 7.70 (1H, d, J=7.91), 8.56 (2H, s). MS: (ESI+) 396

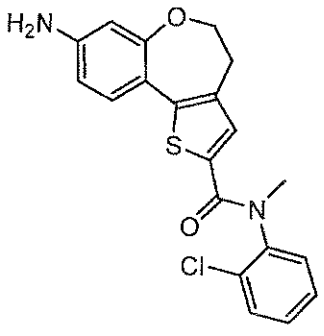
[00431] Example 74 3-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole **164**

[00432] Following the procedure of Example 166 to prepare **256**, N-(2-chlorophenyl)-10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (0.167 g, 0.504 mmol) was dissolved in 1,4-dioxane (6.2 mL). 2,4-Bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (Lawesson's reagent, 0.153 g, 0.378 mmol) was added. The reaction mixture was stirred at 85 °C for overnight. The reaction mixture was concentrated to give the crude thioamide intermediate. To a solution containing crude thioamide intermediate in methanol (7.3 mL) was added hydrazine (1.180 mL, 37 mmol). The reaction mixture was stirred at room temperature, concentrated, diluted with methylene chloride, washed with water and brine, and concentrated to give crude hydrazine intermediate. The crude hydrazine intermediate was sealed in a vial with ethyl chloroformate (2.33 mL, 0.014 mol) at 95 °C for 1 day, cooled to room temperature and concentrated. The crude product was purified by flash chromatograph (50-100% EtOAc/Hex) to give **164** (yield 14%). MS: (ESI+) 381.1

[00433] Example 75 4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(5-(2-chlorophenyl))-thiazol-2-amine **165**

[00434] 6,7-Dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl-(2-chlorophenyl)-2-bromoethanone from Example 37 (100.0 mg, 0.230 mmol) and thiourea (20.14 mg, 0.264 mmol) were heated in ethanol (5 mL, 80 mmol) for 1 hour. The solvent was evaporated to half of the volume, whereupon the product crystallized upon standing. The product **165** was collected by filtration and washed with cold ethanol (yield 43 mg, 45%). ^{1}H NMR (400 MHz, DMSO) δ 8.15 (d, J = 3.2, 1H), 7.66 (d, J = 8.2, 1H), 7.54 (t, J = 7.6, 2H), 7.47 (t, J = 7.4, 1H), 7.36 (d, J = 8.1, 1H), 7.16 (dd, J = 4.5, 8.1, 1H), 6.73 (s, 1H), 5.80–4.90 (m, 2H), 4.24 (t, J = 4.7, 2H), 3.04 (t, J = 4.7, 2H). MS(ESI+) 412.1

[00435] Example 76 N-(2-chlorophenyl)-8-(3-ethylureido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **166**



[00436] Solid $Pd_2(dba)_3$ (101 mg, 0.11 mmol) and BINAP (205 mg, 0.33 mmol) was added to a 10 mL flask and the whole purged with nitrogen. To the flask was added 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5- dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (500 mg, 1.11 mmol), benzophenone imine (303 mg, 1.67 mmol), NaO^{t}Bu (213 mg, 2.22 mmol) and

toluene (30 mL). The mixture was heated to 80 °C with stirring until the starting material had been consumed (determined by TLC analysis). The mixture was cooled to room temperature, diluted with EtOAc, filtered and concentrated. The crude product was purified by column chromatography (5:1 hexanes:ethyl acetate) to give N-(2-chlorophenyl)-8-(diphenylmethyleneamino)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide as a yellow solid (400 mg, yield 65 %). N-(2-chlorophenyl)-8-(diphenylmethyleneamino)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (4.9 g, 8.92 mmol) was dissolved in 10 mL of MeOH. To the solution was added 6 mL of CH_3COCl in MeOH (1: 10). The mixture was stirred at room temperature for 15 min before concentrated under vacuum. The residue was washed with EtOAc to give 8-amino-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide as a white solid (3.6 g, yield 95 %). ^{1}H NMR (MeOD, 400 MHz): δ 7.59- 6.60 (m, 8H), 4.21 (t, J= 5.2 Hz, 2H), 3.31 (s, 3H), 2.96 (t, J = 4.8 Hz, 2H).

[00437] To a solution of 8-amino-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide HCl salt (0.25 g, 0.593 mmol) in anhydrous THF (15 mL) was added DIPEA (0.52 mL, 2.97 mmol) and ethyl isocyanate (0.1 g, 1.4 mmol). The solution was stirred at 40 °C overnight. The reaction mixture was poured into ammonium chloride aqueous solution and extracted with EtOAc. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated to the crude product, which was purified by preparative TLC to afford about 0.113 g of **166** (isolated yield: 42%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.56 (s, 1H), 7.64- 7.58 (m, 2H), 7.49 (t, J = 3.6 Hz, 2H), 7.22 (d, J= 4.4 Hz, 1H), 7.15 (d, J = 2.4 Hz, 1H), 6.92 (dd, J= 2.0, 8.4 Hz, 1H), 6.44 (s, 1H), 6.13 (t, J = 5.6 Hz,1H), 4.09 (d, J= 4.4 Hz, 2H), 3.22 (s, 3H), 3.06 (dd, J = 6.0, 7.2 Hz, 2H), 2.85 (s, 2H), 1.01 (t, J= 7.2 Hz, 3H). MS: (ESI+) 456.1

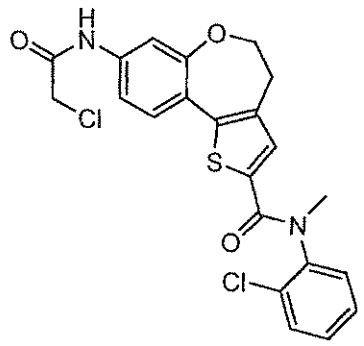
[00438] Example 77 N-(2-chlorophenyl)-N-methyl-8-(3-methylureido)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **167**

[00439] Following the procedures of Example 76, 8-amino-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide and methyl isocyanate gave **167**. MS: (ESI+) 442.1

[00440] Example 78 N-(2-chlorophenyl)-N-methyl-8-ureido-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **168**

[00441] Following the procedures of Example 76, 8-amino-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide was reacted with carbonyl diimidazole and ammonium chloride to give **168**. MS: (ESI+) 428.1

[00442] Example 79 N-(2-chlorophenyl)-8-(2-(diethylamino)acetamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **169**



[00443] Following the procedure in Example 147 for **237**, 8-(2-chloroacetamido)-N-(2-chlorophenyl)-N-methyl-4,5- dihydro -benzo[b]thieno[2,3-d]oxepine-2-carboxamide and diethyl amine were reacted to give **169**. MS: (ESI+) 498.2

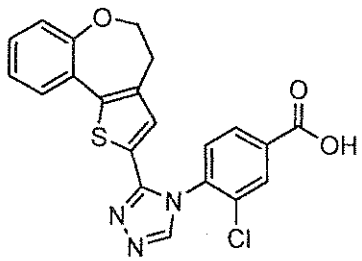
[00444] Example 80 N-(2-chlorophenyl)-N-methyl-8-(2-morpholinoacetamido)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **170**

[00445] Following the procedure in Example 147 for **237**, 8-(2-chloroacetamido)-N-(2-chlorophenyl)-N-methyl-4,5- dihydro -benzo[b]thieno[2,3-d]oxepine-2-carboxamide and morpholine were reacted to give **170**. MS: (ESI+) 512.2

[00446] Example 81 N-(2-chlorophenyl)-N-methyl-8-(2-(4-methylpiperazin-1-yl)acetamido)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **171**

[00447] Following the procedure in Example 147 for **237**, 8-(2-chloroacetamido)-N-(2-chlorophenyl)-N-methyl-4,5- dihydro -benzo[b]thieno[2,3-d]oxepine-2-carboxamide and N-methylpiperazine were reacted to give **171**. MS: (ESI+) 525.3

[00448] Example 82 (3-chloro-4-(3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4H-1,2,4-triazol-4-yl)phenyl)(4-methylpiperazin-1-yl)methanone **172**



[00449] 3-Chloro-4-(3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4H-1,2,4-triazol-4-yl)benzoic acid N-methylpiperazine were reacted by a procedure similar to that to prepare **137** in Example 47 to give **172**. MS: (ESI+) 506.2

[00450] Example 83 N2-(2-chlorophenyl)-N2-methyl-N8-(pyridin-3-ylmethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **173**

[00451] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and 3-aminomethylpyridine gave **173**. MS: (ESI+) 504.0

[00452] Example 84 N2-(2-chlorophenyl)-N8-(1-(hydroxymethyl)cyclopentyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **174**

[00453] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and 1-amino-1-cyclopentanemethanol gave **174**. MS: (ESI+) 511.0

[00454] Example 85 N2-(2-chlorophenyl)-N8-((S)-1-hydroxy-3,3-dimethylbutan-2-yl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **175**

[00455] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and L-valinol gave **175**. MS: (ESI+) 513.2

[00456] Example 86 N-(2-chlorophenyl)-8-(4-hydroxypiperidine-1-carbonyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **176**

[00457] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and 4-hydroxypiperidine gave **176**. MS: (ESI+) 497.2

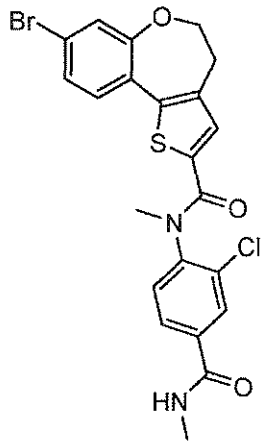
[00458] Example 87 N2-(2-chlorophenyl)-N8-((S)-2-hydroxypropyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **177**

[00459] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and (S)-(+)-1-amino-2-propanol gave **177**. MS: (ESI+) 471.0

[00460] Example 88 N2-(2-chlorophenyl)-N8-((S)-1-hydroxypropan-2-yl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **178**

[00461] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and L-alaninol gave **178**. MS: (ESI+) 471.1

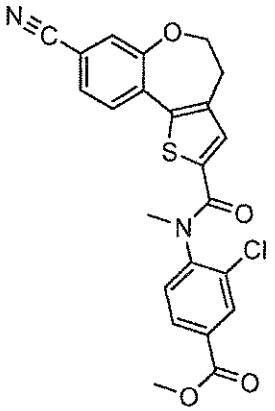
[00462] Example 89 N2-(2-chloro-4-(methylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **179**



[00463] Following Example 91, to a solution of methyl 4-(8-bromo-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoate in tetrahydrofuran and water was added lithium hydroxide, monohydrate to give 4-(8-bromo-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoic acid, which was coupled with methylamine, HBTU, and DIEA in dichloromethane to give 8-bromo-N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide.

[00464] To a solution containing 8-bromo-N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide and methylamine in tetrahydrofuran was added molybdenumhexacarbonyl, trans-di(mu-acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium (II). Then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added and capped quickly to prevent CO gas from escaping. The reaction mixture was heated in a microwave, then diluted with EtOAc then filtered thru celite. The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude was submitted for RP HPLC to give **179**. MS: (ESI+) 484.1

[00465] Example 90 N-(2-chloro-4-(methylcarbamoyl)phenyl)-8-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **180**

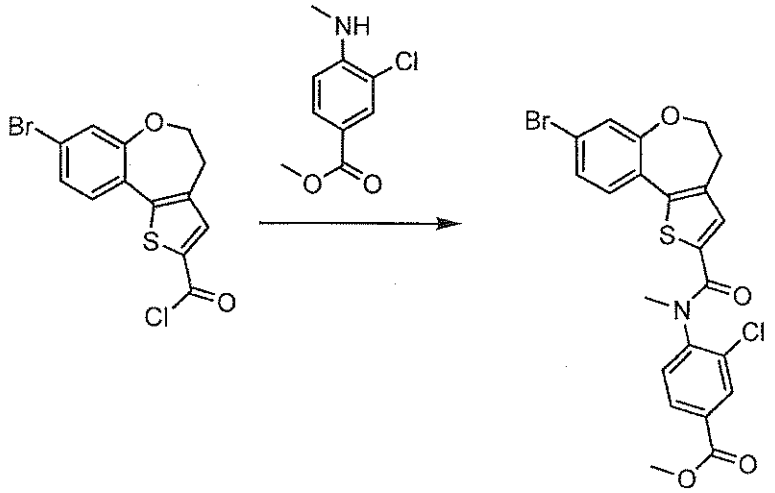


[00466] Following Example 53, methyl 4-(8-bromo-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoate and CuCN gave methyl

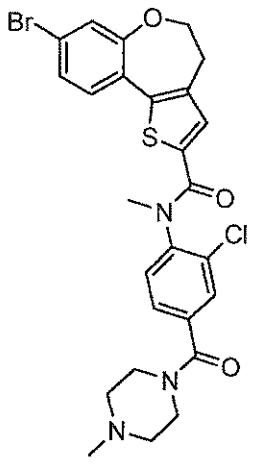
3-chloro-4-(8-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoate.

[00467] Following Example 91, methyl 3-chloro-4-(8-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoate was saponified with lithium hydroxide in THF and water, then the carboxylic acid was coupled with methylamine, HBTU, DIEA in dichloromethane to give **180**. MS: (ESI+) 452.1

[00468] Example 91 N2-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **181**



[00469] To a solution containing methyl 3-chloro-4-(methylamino)benzoate (0.184 g, 0.922 mmol) in N,N-dimethylformamide (11.0 mL, 142 mmol) was added sodium hydride (0.0369 g, 0.922 mmol). The mixture was stirred at room temperature 30 min then 8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbonyl chloride (0.288 g, 0.838 mmol) was added. The reaction mixture was stirred for 16 hr. The reaction mixture was quenched with sat. NH4Cl, extracted with DCM (2x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography EtOAc/Hex (0-100%) to give methyl 4-(8-bromo-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoate (yield 65%). MS: (ESI+) 508.2



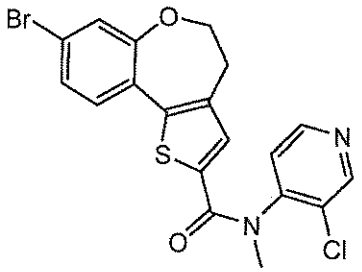
[00470] To a solution of methyl 4-(8-bromo-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoate (0.180 g, 0.355 mmol) in tetrahydrofuran (6.00 mL, 74.0 mmol) and water (6.00 mL, 333 mmol) was added lithium hydroxide, monohydrate (0.0596 g, 1.42 mmol) . The reaction mixture was stirred at room temp. overnight. The reaction mixture was concentrated. The reaction mixture was acidified with 1M HCl then extracted with DCM (3X). The combined organics were dried (Na_2SO_4), filtered and concentrated to give 4-(8-bromo-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoic acid. To a solution of 4-(8-bromo-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoic acid (175 mg, 0.355 mmol;) in methylene chloride (5.1 mL, 79 mmol) was added 1-methyl-piperazine, (0.047 mL, 0.43 mmol), N,N-diisopropylethylamine (0.618 mL, 3.55 mmol) then O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.269 g, 0.710 mmol). The mixture was stirred at room temp. for 2hr. LCMS indicated the reaction was complete. The reaction was quenched with sat. NH_4Cl, extracted with DCM (2x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography (5%MeOH/DCM) to give 8-bromo-N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (yield 82%). MS: (ESI+) 576.4

[00471] To a solution containing 8-bromo-N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (0.075 g, 0.13 mmol) in tetrahydrofuran (1.50 mL, 18.5 mmol), 2.00 M of methylamine in tetrahydrofuran (0.196 mL) was added molybdenumhexacarbonyl (34.4 mg, 0.130 mmol), , trans-di(mu-acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium (II) (18.3 mg, 0.0196 mmol) then 1,8-diazabicyclo[5.4.0]undec-7-ene (9.75 uL, 0.0652 mmol) and capped quickly to prevent CO gas from escaping. The reaction mixture was heated in a microwave at 150 °C for 20 min. The reaction mixture was diluted with EtOAc then filtered thru celite. The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude was submitted for RP HPLC to give **181** (yield 32%). MS: (ESI+) 553.2

[00472] Example 92 N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-8-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **182**

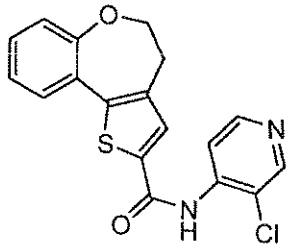
[00473] Following Examples 53 and 91, 8-bromo-N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide and CuCN gave **182**. MS: (ESI+) 521.2

[00474] Example 93 N-(3-chloropyridin-4-yl)-N-methyl-8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **183**



[00475] A solution of 8-bromo-N-methyl-(3-chloropyridin-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide, (0,050 g, 0.100 mmol), 4,4,5,5,-tetramethyl-2-(1H-pyrazoyl-4-yl)-1,3,2-dioxaborane (0.033 g, 0.173 mmol), tetrakis(triphenylphosphine)palladium(0) 0.0133 g, 0.0115 mmol), and 1 M of sodium carbonate in water (0.2 mL, 0.2 mmol) in 1 mL of DMF was flash heated on Emry Optimizer microwave at 150 °C for 10 minutes. The reaction mix was then diluted with EtOAc and washed with water and saline, and concentrated to a solid residue, which was taken into DMF at a concentration of 100 mg/ml and purified by preparative RP-HPLC to give **183** (yield = 25% of theoretical). MS: (ESI+) 437.1

[00476] Example 94 N-(3-chloropyridin-4-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **184**



[00477] Following Example 17, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbonylchloride and 4-amino-3-chloropyridine were reacted to give N-(3-chloropyridin-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide. To a solution of N-(3-chloropyridin-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (0.340 g, 0.953 mmol) in DMF (5 mL, 60 mmol) was added sodium hydride (0.0381 g, 0.953 mmol). The reaction mixture was stirred at room temperature for about 10 min. followed by the addition of methyl iodide (65.25 uL, 1.048 mmol) and stirred at room temperature for another 1 hr. An aliquot was analyzed by LC/MS showing clean conversion to desired product. The reaction mix was diluted with EtOAc and washed with water/saline, dried (Na_2SO_4) then concentrated to a residue which was analyzed by LC/MS and1H NMR. The crude product was taken into DMF at about 100 mg/mL, but was not totally soluble. Soluble material was purified by preparative RP-HPLC to give **184** (yield 30% of theoretical). MS: (ESI+) 372.2

[00478] Example 95 N8-(2-aminoethyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **185**

[00479] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and ethanediamine gave **185**. MS: (ESI+) 456.0

[00480] Alternatively, 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine- 8-carbonyl chloride and ethylene diamine gave **185**. MS (ESI) 456.0

[00481] Example 96 N8-(2-acetamidoethyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **186**

[00482] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and N-acetylethanediamine gave **186**. MS: (ESI+) 498.0

[00483] Alternatively, 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine- 8-carbonyl chloride and N-(2-aminoethyl)acetamide gave **186**. MS (ESI) 498.0

[00484] Example 97 N2-(2-chlorophenyl)-N2-methyl-N8-(2-(methylamino)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **187**

[00485] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and N-methylethanediamine gave **187**. MS: (ESI+) 470.1

[00486] Alternatively, 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine- 8-carbonyl chloride and N1-methylethane-1,2-diamine gave **187**. MS (ESI): 470.1

[00487] Example 98 N2-(2-chlorophenyl)-N8-methoxy-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **188**

[00488] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and N,O-dimethylhydroxylamine gave **188**. MS: (ESI+) 457.0

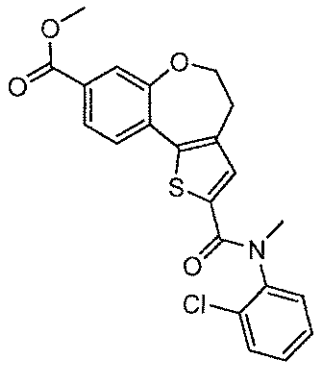
[00489] Alternatively, 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine- 8-carbonyl chloride and N,O-dimethylhydroxylamine hydrochloride gave **188**. MS (ESI) 457.0

[00490] Example 99 N2-(2-chlorophenyl)-N8-methoxy-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **189**

[00491] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and O-methylhydroxylamine gave **189**. MS: (ESI+) 443.1

[00492] Alternatively, 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine- 8-carbonyl chloride and O-methylhydroxylamine hydrochloride gave **189**. MS (ESI) 443.1

[00493] Example 100 N-(2-chlorophenyl)-8-(hydroxymethyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **190**



[00494] To a solution of 2-[(2-chloro-phenyl)- methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-8-carboxylic acid methyl ester (1 g, 2.3 mmol) in dry THF (30 mL) was added lithium aluminum hydride (174 mg, 4.6 mmol) by portion at 0 °C. The resulting mixture was stirred under nitrogen atmosphere for 30 minutes. The reaction was monitored by LC-MS. When the starting material was disappeared, the reaction mixture was quenched by the slow addition of water and 10% NaOH aqueous solution. After filtered, the filtrate was concentrated to the crude product, which was recrystallized from MeOH to give **190** as a yellow solid (450 mg, yield 48.9 %). MS (ESI) 399.8

[00495] Example 101 N-(2-chloro-4-(1-hydroxypropan-2-ylcarbamoyl)phenyl)-N-methyl(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide **191**

[00496] Following the procedure in Example 124 for **214**, methyl 3-chloro-4-(N-methyl, 10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoate and 2-aminopropan-1-ol were reacted to give **191**. MS: (ESI+) 472.1

[00497] Example 102 N-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-N-methyl(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide **192**

[00498] Following the procedure in Example 124 for **214**, methyl 3-chloro-4-(N-methyl, 10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoate and 1-aminopropan-2-ol were reacted to give **192**. MS: (ESI+) 472.1

[00499] Example 103 N-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N-methyl(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide **193**

[00500] Following the procedure in Example 124 for **214**, methyl 3-chloro-4-(N-methyl, 10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoate and piperazine were reacted to give **193**. MS: (ESI+) 483.2

[00501] Example 104 N8-(3-(1H-imidazol-1-yl)propyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **194**

[00502] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and 2-(imidazol-1-yl)-ethylamine gave **194**. MS: (ESI+) 520.8

[00503] Alternatively, 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine- 8-carbonyl chloride and 3-(1H-imidazol-1-yl)propan-1-amine gave **194**. MS (ESI) 520.8

[00504] Example 105 N8-(2-amino-2-methylpropyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **195**

[00505] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and 3-methyl-1,3-butanediamine gave **195**. MS: (ESI+) 484.1

[00506] Alternatively, 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine- 8-carbonyl chloride and 2-methylpropane-1,2-diamine gave **195**. MS (ESI): 484.1

[00507] Example 106 8-(3-(aminomethyl)phenyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **196**

[00508] Following the procedure of Example 93, Suzuki coupling of 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and (3-aminophenyl)boronic acid gave **196.**

[00509] Example 107 N-(2-chlorophenyl)-8-((2-(dimethylamino)ethylamino)methyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **197**

[00510] 8-(Bromomethyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide was reacted with N1,N1-dimethylethane-1,2-diamine using the procedure of Example 153 to give **197**.

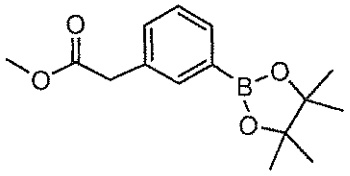
[00511] Example 108 2-(3-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)phenyl)acetic acid **198**

[00512] Methyl 2-(3-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)phenyl)acetate **200** was treated with lithium hydroxide in THF and water to give **198**. MS: (ESI+) 503.7

[00513] Example 109 N-(2-chlorophenyl)-8-(3-cyanophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **199**

[00514] Following the procedure of Example 93, Suzuki coupling of 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and 3-cyanophenylboronic acid gave **199**. MS: (ESI+) 471.1

[00515] Example 110 methyl 2-(3-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)phenyl)acetate **200**



[00516] Following the procedure of Example 93, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150**, methyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate, potassium acetate, and $Pd(dppf)Cl_2$ in acetonitrile and DMSO were heated at 80 °C overnight to give **200**. MS: (ESI+) 518.2

[00517] Example 111 N-(2-chlorophenyl)-8-(3-(hydroxymethyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **201**

[00518] Following the procedure of Example 93, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **150** and 3-hydroxymethylphenylboronic acid were reacted to give **201**. MS: (ESI+) 476.16

[00519] Example 112 N-(2-chlorophenyl)-N-methyl-8-(4-methylpiperazine-1-carbonyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **202**

[00520] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and N-methylpiperazine gave **202**. MS: (ESI+) 496.2

[00521] Alternatively, 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine-8-carbonyl chloride and 1-methylpiperazine gave **202**. MS (ESI) 496.2

[00522] Example 113 N2-(2-chlorophenyl)-N2-methyl-N8-(2-(4-methylpiperazin-1-yl)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **203**

[00523] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and 1-(N-aminoethyl)-4-methyl piperazine gave **203**. MS: (ESI+) 539.2

[00524] Alternatively, 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine-8-carbonyl chloride and 2-(4-methylpiperazin-1-yl)ethanamine gave **203**. MS (ESI) 539.2

[00525] Example 114 N2-(2-chlorophenyl)-N8-(2-(dimethylamino)ethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **204**

[00526] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and N,N'-dimethylethanediamine gave **204**. MS: (ESI+) 484.0

[00527] Alternatively, 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine-8-carbonyl chloride and N1,N1-dimethylethane-1,2-diamine gave **204**. MS (ESI) 484.0

[00528] Example 115 N2-(2-chlorophenyl)-N8-isopropyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **205**

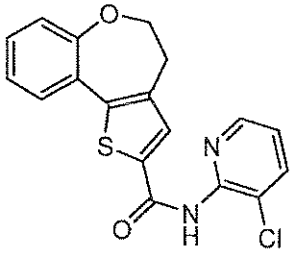
[00529] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and isopropylamine gave **205**. MS: (ESI+) 455.0

[00530] Alternatively, 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno [2,3-d]oxepine-8-carbonyl chloride and isopropylamine gave **205**. MS (ESI) 455.0

[00531] Example 116 N2-(2-chlorophenyl)-N8-ethyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **206**

[00532] Following Example 47 and General Procedure C, methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate **138** and ethylamine gave **206**. MS: (ESI+) 441.0

[00533] Example 117 N-(3-chloropyridin-2-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **207**



[00534] An ice water cooled solution of 2-amino-3-chloropyridine (0.200 g, 0.755 mmol) in tetrahydrofuran (1.5 mL, 18 mmol) was reacted with a THF solution of 1 M sodium hexamethyldisilazane to give a clear solution. This reaction mix was stirred at cooled temperature for 30 minutes. Next, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbonylchloride (0.100 g, 0.378 mmol) was added portionwise as a solid. Reaction mix was stirred at room temperature with monitor for formation of desired product and concentrated in vacuo to a solid residue. This residue was taken into ethyl acetate and the organic was washed with water, then saline and dried (Na_2SO_4). The crude material was purified by MPLC on silica, eluting with 10% to 80% ethyl acetate / hexanes to give 128 mg N-(3-chloropyridin-2-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide, 34% of theoretical yield.

[00535] To a solution of N-(3-chloropyridin-2-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide in acetonitrile (0.702 ml) was added hexamethyldisilazane (0.029 ml, 0.140 mmol) and heated at reflux for 3 hours. Chloro(chloromethyl)dimethylsilane (0.029 ml, 0.224 mmol) was added to the refluxing solution drop-wise and the reaction mixture was refluxed overnight. Next, the reaction mixture was equilibrated to room temperature and concentrated to a solid residue. This solid was taken into diglyme (2 ml, 10 mmol) and treated with cesium fluoride (0.21g, 1.4 mmol) at reflux for 3 hours. The reaction mixture was cooled to room temperature and diluted with water and ethyl acetate. The organic was separated from the aqueous in a separatory funnel. The organic was washed with saline, dried (Na_2SO_4) and concentrated to a solid. This crude material was taken into methanol at 100 mg/ml and purified by RP-HPLC to give 24 mg of **207**, 29% of theoretical yield.. MS: (ESI+) 371.1

[00536] Example 118 N-methyl-N-(4-(trifluoromethyl)pyridin-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **208**

[00537] Following Example X to prepare **207**, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbonylchloride and 3-amino-4-trifluoromethylpyridine were reacted, followed by methylation to give **208** (yield 8% of theoretical). MS: (ESI+) 344.1

[00538] Example 119 3-chloro-4-(3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4H-1,2,4-triazol-4-yl)-N-methylbenzamide **209**

[00539] 3-Chloro-4-(3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4H-1,2,4-triazol-4-yl)benzoic acid and methylamine were reacted by a procedure similar to that to prepare **137** in Example 47 to give **209**. MS: (ESI+) 437.1

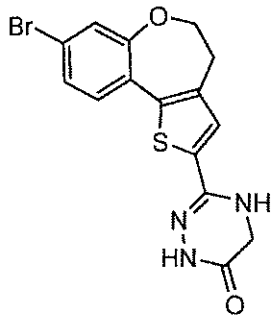
[00540] Example 120 N-(2-chlorophenyl)-8-(2-(dimethylamino)acetamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **210**

[00541] Following the procedure in Example 147 for the synthesis of **237**, 8-(2-chloroacetamido)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide was reacted with dimethylamine to give **210**. MS: (ESI+) 470.2

[00542] Example 121 8-(2-acetamidoacetamido)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **211**

[00543] Following the procedure in Example 147 for **237**, 8-(2-chloroacetamido)-N-(2-chlorophenyl)-N-methyl-4,5-dihydro-benzo[b]thieno[2,3-d]oxepine-2-carboxamide and acetamide were reacted to give **211**. MS: (ESI+) 484.1

[00544] Example 122 3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4,5-dihydro-1,2,4-triazin-6(1H)-one **212**

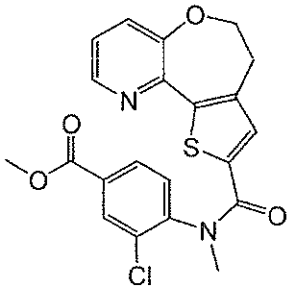


[00545] Following the procedure in Example 44 for **134**, 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4,5-dihydro-1,2,4-triazin-6(1H)-one and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole were reacted to give **212**. MS: (ESI+) 366.2

[00546] Example 123 N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-methyl(10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **213**

[00547] Following the procedure in Example 124 for **214**, methyl 3-chloro-4-(N-methyl, 10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoate and methylamine were reacted to give **213**. MS: (ESI+) 428.1

[00548] Example 124 N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl(10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide **214**



[00549] To a solution of 10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid **16** from Example 10 (0.350 g, 1.42 mmol;) in methylene chloride (3.68 mL, 57.4 mmol) was added thionyl chloride (0.310 mL, 4.25 mmol;). The mixture was stirred at 80 °C for 2h. The reaction mixture was concentrated in vacuo. The crude acid chloride (0.424 g, 2.12 mmol) was dissolved in tetrahydrofuran (10.4 mL, 129 mmol;) and 1.00 M of sodium bis(trimethylsilyl)amide in tetrahydrofuran (2.12 mL) was added. The reaction mixture was stirred at room temperature 1h then methyl 3-chloro-4-(methylamino)benzoate was added at 0 °C . The reaction mixture was stirred overnight, quenched with sat. NH_4Cl, and extracted with DCM (2x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography EtOAc/Hex (0-100%) (eluted 70% EtOAc) to give methyl 3-chloro-4-(N-methyl, 10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoate (yield 77%). MS: (ESI+) 430.0

[00550] The methyl ester of methyl 3-chloro-4-(N-methyl, 10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoate was hydrolyzed and the resulting acid (53.0 mg, 0.128 mmol;) was dissolved in methylene chloride (1.8 mL, 28 mmol). Dimethylamine hydrochloride (0.0208 g, 0.256 mmol), N,N-diisopropylethylamine (0.222 mL, 1.28 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.0972 g, 0.256 mmol) were added. The mixture was stirred at room temperature for 2h whereupon LCMS indicated the reaction was complete. The reaction was quenched with sat. NH_4Cl and extracted with DCM (2x). The combined organics were dried (Na2SO4), filtered and concentrated. The crude product was purified by flash chromatography (MeOH/DCM) (eluted at 5%MeOH) to give **214** (yield 88%). MS: (ESI+) 442.1

[00551] Example 125 N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide **215**

[00552] Following the procedure in Example 124 for **214**, methyl 3-chloro-4-(N-methyl, 10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoate and 1-methypiperazine were reacted to give **215**. MS: (ESI+) 497.2

[00553] Example 126 2-(2-amino-5-(2-chlorophenyl)thiazol-4-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **216**

[00554] Following the procedure of Example 13 and General Procedure C, 4-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-5-(2-chlorophenyl)thiazol-2-amine **271** and methylamine (1.0 M in tetrahydrofuran) gave **216**. MS: (ESI+) 468.1

[00555] Example 127 2-(4-(2-chlorophenyl)-5-methyl-4H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **217**

[00556] Following the procedure of Example 13 and General Procedure C, 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-5-methyl-4H-1,2,4-triazole and methylamine (1.0 M in tetrahydrofuran) gave **217**. MS: (ESI+) 451.1

[00557] Example 128 (4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone **218**

[00558] To a solution of 1,2,3,4-tetrahydroquinoline (0.755 mmol) and triethylamine (0.105 mL, 0.755 mmol) in tetrahydrofuran (1.5 mL, 18 mmol) was added 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbonylchloride (0.100 g, 0.378 mmol) portionwise as a solid. Reaction was stirred at room temperature with monitor for formation of desired product. The reaction was stirred overnight. After aqueous workup, the crude was taken into DMF at a concentrated of 100 mg/ml and purified by preparative RP-HPLC to give **218** (yield 80% of theoretical). MS: (ESI+) 362.2

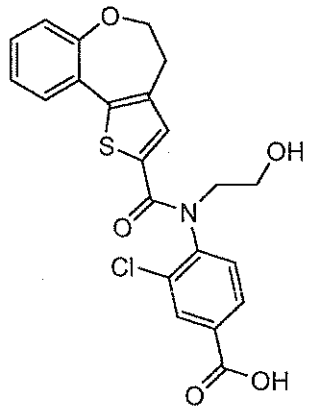
[00559] Example 129 N-methyl-N-(4-(trifluoromethyl)pyridin-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **219**

[00560] Following Example 117 to prepare **207**, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbonylchloride and 3-amino-4-chloropyridine were reacted, followed by methylation to give **219** (yield 29% of theoretical). MS: (ESI+) 371.2

[00561] Example 130 N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **220**

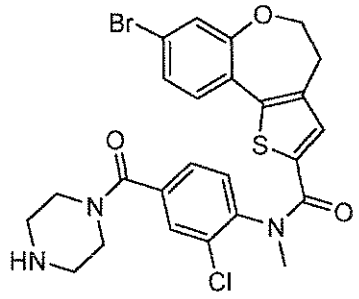
[00562] Following the procedure of Example 91, 3-chloro-4-(*N*-(2-hydroxyethyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamido)benzoic acid and dimethylamine were reacted to give **220** (yield 50%). MS: (ESI+) 471.1

[00563] Example 131 N-methyl-N-(4-(trifluoromethyl)pyridin-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **221**



[00564] Following Example 91, 3-chloro-4-(N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and 1-methylpiperazine were reacted to give **221** (yield 30%). MS: (ESI+) 526.2

[00565] Example 132 N2-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **222**

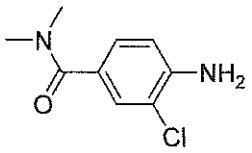


[00566] Following the procedure of Example 91 to prepare **181**, 8-bromo-N-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide and methylamine were reacted to give **222**. MS: (ESI+) 539.2

[00567] Example 133 N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **223**

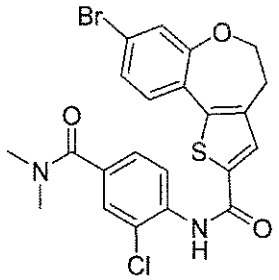
[00568] Following the procedure of Example 91 to prepare **181**, 8-bromo-N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide, methylamine, and molybdenumhexacarbonyl under palladium catalysis were reacted to give **223**. MS: (ESI+) 498.1.

[00569] Step 1: Preparation of 4-amino-3-chloro-N,N-dimethylbenzamide



[00570] DIPEA (116 mL, 699.5 mmol) was added into a suspension of dimethylamine hydrochloride (28.51 g, 349.6 mmol) in THF (600 mL). The mixture was stirred at room temperature for 0.5 h. Then 4-amino-3-chlorobenzoic acid (30.00 g, 174.8 mmol) and HATU (86.41 g, 227.2 mmol) were added into the above suspension separately. The reaction mixture was continued to be stirred for 1.5 h. Then it was concentrated and the residue was partitioned between EtOAc (300 mL) and water (150 mL). The separated organic phase was washed with water, dried over Na_2SO_4 and evaporated in vacuum. The crude product was purified by silica gel chromatography, eluted with Hexanes: EtOAc = 1: 1 to afford 4-amino-3-chloro-N,N-dimethylbenzamide (34.72 g, yield: 89%). ESI-MS: 199.06. ^{1}H NMR ($CDCl_3$, 400 MHz): δ7.39 (s, 1H, ArH), 7.19 (d, J= 8.4 Hz, 1H, ArH), 6.74 (d, J= 8.4 Hz, 1H, ArH), 4.24 (br, 2H, NH_2), 3.05 (s, 6H, $2CH_3$).

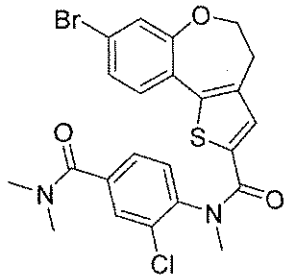
[00571] Step 2: Preparation of 8-bromo-N-(2-chloro-4-(dimethylcarbamoyl)phenyl)- 4,5-dihydro-benzo [b]thieno[2,3-d]oxepine-2-carboxamide



[00572] A solution of 8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid (25.00 g, 76.9 mmol) in $SOCl_2$ (200 mL) was heated at 90-100 °C for 3 h. Concentration of the reaction mixture gave the crude acid chloride. A suspension of the acid chloride in THF (600 mL) was treated with a solution of 4-amino-3-chloro-N,N-dimethylbenzamide (18.23 g, 92.3 mmol) and pyridine (14 mL) in THF (200 mL) at 0 °C. The mixture was allowed to reach room temperature and stirred overnight. After concentration, water (200 mL) was added into the

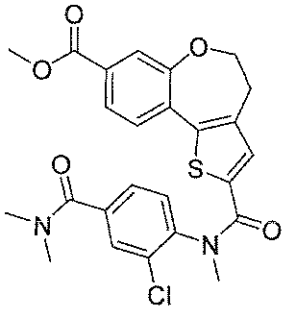
mixture. The resulting precipitate was collected by filtration, washed with water and dried to give 8-bromo-N-(2-chloro-4-(dimethylcarbamoyl)phenyl)- 4,5-dihydro-benzo [b]thieno[2,3-d]oxepine-2-carboxamide (29.88 g, yield: 77%). ESI-MS: 504.99. ^{1}H NMR (DMSO-d_6, 400 MHz): δ10.14 (s, 1H, NH), 7.86 (s, 1H, ArH), 7.67- 7.57 (m, 3H, ArH), 7.40- 7.25 (m, 3H, ArH), 4.32 (t, J= 5.2 Hz, 2H, CH_2), 3.21 (t, J= 5.2 Hz, 2H, CH_2), 2.95 (s, 3H, CH_3), 2.92 (s, 3H, CH_3).

[00573] Step 3: Preparation of 8-bromo-N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-4, 5-dihydrobenzo [b]thieno[2,3-d]oxepine-2-carboxamide (5)



[00574] To solution of 8-bromo-N-(2-chloro-4-(dimethylcarbamoyl)phenyl)- 4,5-dihydro-benzo [b]thieno[2,3-d]oxepine-2-carboxamide (29.0 g, 57.3 mmol), Cs_2CO_3 (37.40 g, 114.7 mmol) in DMF (600 mL), CH_3I (30 mL, 479.8 mmol) was slowly added. The reaction mixture was stirred at room temperature overnight. Concentration removed about 200 mL of DMF, and then water (100 mL) was added to the mixture. The resulting precipitate was filtered, washed with water, dried to give 8-bromo-N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-4, 5-dihydrobenzo [b]thieno[2,3-d]oxepine-2-carboxamide (29.50 g, yield: 99%). ESI-MS: 519.4. ^{1}H NMR (DMSO- d_6, 400 MHz): δ7.72- 7.68 (m, 2H, ArH), 7.52- 7.49 (m, 1H, ArH), 7.30- 7.20 (m, 3H, ArH), 6.76 (s, 1H, =CH), 4.19 (s, 2H, CH_2), 3.29 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 2.96 (s, 2H, CH_2), 2.93 (s, 3H, CH_3).

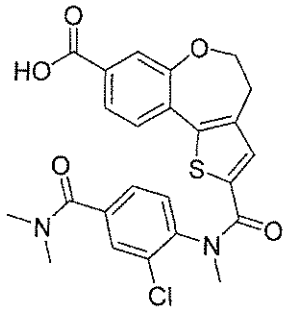
[00575] Step 4: Preparation of methyl 2-((2-chloro-4-(dimethylcarbamoyl)phenyl) (methyl)-carbamoyl) -4,5-dihydrobenzo[b] thieno[2,3-d] oxepine-8-carboxylate



[00576] The mixture of 8-bromo-N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-4, 5-dihydrobenzo [b]thieno[2,3-d]oxepine-2-carboxamide (27.0 g, 51.9 mmol), dppf (23.20 g, 41.9 mmol), $Pd(OAc)_2$ (5.8 g, 25.8 mmol), TEA (27 mL), in DMF (270 mL) and MeOH (400

mL) was stirred under CO (50 psi) atmosphere at 70 °C for 2 days. The reaction mixture was filtrated and the filtrate was concentrated. The crude product was purified by silica gel chromatography eluted with Hexanes: EtOAc = 1: 1 to give methyl 2-((2-chloro-4-(dimethylcarbamoyl)phenyl) (methyl)-carbamoyl) -4,5-dihydrobenzo[b] thieno[2,3-d] oxepine-8-carboxylate (23.00 g, 89%). ESI-MS: 499.1. ^{1}H NMR (DMSO- d_6, 400 MHz): δ7.74- 7.69 (m, 2H, ArH), 7.58- 7.47 (m, 4H, ArH), 6.79 (s, 1H, =CH), 4.23 (t, J= 4.8 Hz, 2H, CH_2), 3.83 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 3.01 (br, 5H, CH_2, CH_3), 2.94 (s, 3H, CH_3).

[00577] Step 5: Preparation of 2-((2-chloro-4-(dimethylcarbamoyl)phenyl)(methyl) carbamoyl)-4, 5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid



[00578] Methyl 2-((2-chloro-4-(dimethylcarbamoyl)phenyl) (methyl)-carbamoyl) -4,5-dihydrobenzo[b] thieno[2,3-d] oxepine-8-carboxylate (25.00 g, 50.1 mmol) was dissolved in THF (50 mL) and water (50 mL). The solution was treated with LiOH·H_2O (5.26 g, 125.3 mmol). The reaction mixture was stirred at room temperature for 2 h. Concentrated to remove the solvent THF and the mixture was acidified by 2N HCl. The resulting precipitate was filtrated, washed by water, dried to give 2-((2-chloro-4-(dimethylcarbamoyl)phenyl)(methyl) carbamoyl)-4, 5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid (20.00 g, 82%). ESI-MS: 485.1. ^{1}H NMR ($CDCl_3$, 400 MHz): δ7.66- 7.60 (m, 3H, ArH), 7.46- 7.42 (m, 3H, ArH), 6.99 (s, 1H, =CH), 4.23 (t, J= 5.0 Hz, 2H, CH_2), 3.39 (s, 3H, CH_3), 3.14 (s, 3H, CH_3), 3.07 (t, J = 5.0 Hz, 2H, CH_2), 3.02 (s, 3H, CH_3).

[00579] Step 6: Preparation of N^2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N^2,N^8-imethyl- 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **223**

[00580] DIPEA (16.83 g, 130.2 mmol) was added to a suspension of H_2NMe·HCl (5.02 g, 74.4 mmol) in THF (180 mL) and stirred at room temperature for 0.5 h. 2-((2-Chloro-4-(dimethylcarbamoyl)phenyl)(methyl) carbamoyl)-4, 5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic aci (9.00 g, 18.6 mmol) and HATU (21.22 g, 55.8 mmol) were added into the suspension separately. The reaction mixture was stirred at room temperature for 2 h. Concentrated to remove solvent, the resulting mixture was dissolved in CH_2Cl_2 (200 mL), washed by 2N HCl (200 mL), water (100 mL), and dried over Na_2SO_4. The crude product was purified by silica gel chromatography eluted with CH_2Cl_2 : MeOH = 10: 1 (3.70 g, 40%) to

furnish **223**. ESI-MS: 498. ^{1}H NMR ($CDCl_3$, 400 MHz): δ7.58 (s, 1H, ArH), 7.42- 7.29 (m, 4H, ArH), 6.92 (s, 1H, ArH), 6.34 (d, J= 4.0 Hz, 1H, NH), 4.20 (t, J= 5.0 Hz, 2H, CH_2), 3.37 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 3.04- 2.98 (m, 8H, CH_2, $2CH_3$).

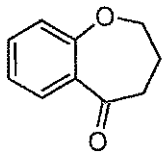
[00581] Example 134 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isopropyl-4H-1,2,4-triazole **224**

[00582] To a solution of in 8-bromo-N-isopropyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (180 mg, 0.49 mmol) in 5 mL toluene was added phosphorus pentachloride (0.184 g, 0.88 mmol) under nitrogen and the reaction mixture was heated at 80 °C for 2 h. The mixture was cooled and carefully concentrated. The crude residue was dissolved in 10 mL THF and treated sequentially with formyl hydrazine (118 mg, 2.0 mmol) and potassium carbonate (0.340 g, 2.46 mmol). The mixture was stirred overnight at room temperature, diluted with water and extracted with ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate and concentrated. The crude residue was dissolved in toluene (10 mL) and treated with p-toluenesulfonic acid (15 mg, 0.087 mmol). The whole was sealed and heated at 90 °C for 15 min. The reaction mixture was cooled to room temperature, concentrated, diluted with ethyl acetate and washed with water, sodium bicarbonate and brine. The organics were dried over sodium sulfate and concentrated to give **224** as the crude product which could be used without purification in subsequent operations. A small amount was purified by reverse-phase HPLC for analytical purposes. 1H NMR (dmso-d_6, 400 MHz) δ 11.9 8.84 (s, 1H), 7.65 (d, 1H), 7.45 (s, 1H), 7.32-7.27 (m, 2H), 4.75 (m, 1H), 4.34 (t, 2H), 3.25 (t, 2H), 1.48 (d, 6H). MS (ESI) 392.1

[00583] Example 135 3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(1-methylpiperidin-4-yl)-1H-1,2,4-triazol-5(4H)-one **225**

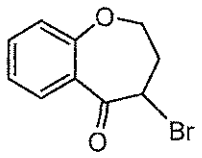
[00584] Prepared from N-(1-methylpiperidin-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide to give **225** using a procedure similar to that described in Example 175. MS (ESI) 383.2

[00585] Example 136 4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-phenyl)-methyl-amide **226**

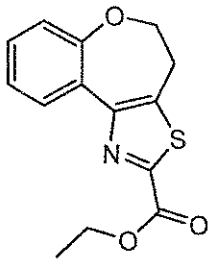


[00586] To a solution of phenol (3.16 g, 33.6 mmol) in acetonitrile, was added ethyl 4-bromobutyrate (4.8 ml, 33.6 mmol), potassium carbonate (4.64 g, 33.6 mmol) and tetrabutylammonium iodide (370 mg, 1mmol). The reaction mixture was stirred vigorously and heated to reflux for 2 days before being cooled, filtered, dried ($MgSO_4$) and concentrated *in-*

vacuo to yield 4-phenoxy-butyric acid ethyl ester. 4-Phenoxy-butyric acid ethyl ester was hydrolyzed to its corresponding carboxylic acid using sodium hydroxide mediated hydrolysis to yield 4-phenoxy-butyric acid. To a solution of 4-phenoxy-butyric acid (7.67 g, 29.6 mmol) in anhydrous dichloromethane was added oxalyl chloride (4.4 ml, 50.3 mmol) and one drop of dimethyl formamide and the reaction mixture stirred at room temperature for 30 minutes. Reaction mixture was concentrated *in-vacuo* and the residue dissolved in 1,2-dichloroethane (90 ml). This solution was added drop wise to a suspension of aluminum trichloride (4.73 g, 35. 5mmol) in 1,2-dichloroethane (50 ml) at 0 °C. Reaction mixture was left stirring in ice bath which rose to room temperature overnight. The reaction mixture was poured over conc. hydrochloric acid (30 ml) stirred into 10 0g ice, and then stirred for a further 90 minutes until the ice fully melted. The aqueous phase was washed with dichloromethane 3 times, before the organics were combined, dried (Na_2SO_4) and concentrated *in-vacuo*. Purification by triturating with diethyl ether gave 3,4-dihydro-2H-benzo[b]oxepin-5-one.



[00587] To a solution of 3,4-dihydro-2H-benzo[b]oxepin-5-one (3.10 g, 12.8 mmol) in diethyl ether at 0°C, bromine (625 µl, 12.2mmol) was added and stirred for 2.5 hours, gradually raising the temperature to room temperature. Purification on silica and triturating using diethyl ether and hexanes gave 4-bromo-3,4-dihydro-2H-benzo[b]oxepin-5-one.



[00588] To a solution of 4-bromo-3,4-dihydro-2H-benzo[b]oxepin-5-one (4.0 g, 12.4mmol) in ethanol, was added ethyl thiooxamate (5.0 g, 37.4 mmol) and the reaction mixture was heated to reflux for 3 days. Purification on silica gave 4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid ethyl ester, which was hydrolyzed to the carboxylic acid, 4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid, in THF, sodium hydroxide, and water. 4,5-Dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid was coupled with 2-chloro-N-methylaniline using General Procedure B. Purification on silica gave **226**. 1H NMR (400MHz, CDCl3): 3.24 (2H, t), 3.37 (3H, s), 4.17-4.25 (2H, m), 6.74-6.79 (1H, m), 6.85 (1H,

dd), 7.02-7.07 (1H, m), 7.11 (1H, dd), 7.27-7.33 (3H, m), 7.42-7.45 (1H, m). MS: (ESI+) MH 371

[00589] Example 137 N-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **227**

[00590] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and 1-aminopropan-2-ol were reacted by a procedure similar to that to prepare **137** in Example 47 to give **227**. MS: (ESI+) 471.1

[00591] Example 138 N-(2-chloro-4-(1-hydroxypropan-2-ylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **228**

[00592] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and 2-aminopropan-1-ol were reacted by a procedure similar to that to prepare **137** in Example 47 to give **228**. MS: (ESI+) 471.0

[00593] Example 139 N-(4-(3-(1H-imidazol-1-yl)propylcarbamoyl)-2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **229**

[00594] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and 3-(1H-imidazol-1-yl)propan-1-amine were reacted by a procedure similar to that to prepare **137** in Example 47 to give **229**. MS: (ESI+) 521.1

[00595] Example 140 N-(4-(2-acetamidoethylcarbamoyl)-2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **230**

[00596] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and N-(2-aminoethyl)acetamide were reacted by a procedure similar to that to prepare **137** in Example 47 to give **230**. MS: (ESI+) 498.1

[00597] Example 141 N-(2-chloro-4-(isopropylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **231**

[00598] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and isopropylamine were reacted by a procedure similar to that to prepare **137** in Example 47 to give **231**. MS: (ESI+) 455.1

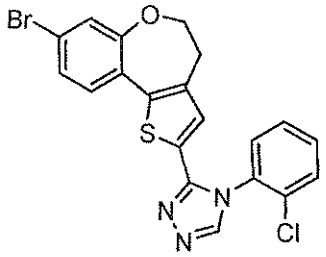
[00599] Example 142 N-(2-chloro-4-(dipropylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **232**

[00600] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and diethylamine were reacted by a procedure similar to that to prepare **137** in Example 47 to give **232**. MS: (ESI+) 497.0

[00601] Example 143 8-bromo-N-(2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **233**

[00602] Following Example 16, 8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylic acid was converted to the acid chloride and reacted with N-(2-(tert-butyldimethylsilyloxy)ethyl)-2-chloroaniline. Desilylation gave **233** (yield 25%). MS: (ESI+) 480

[00603] Example 144 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid **234**

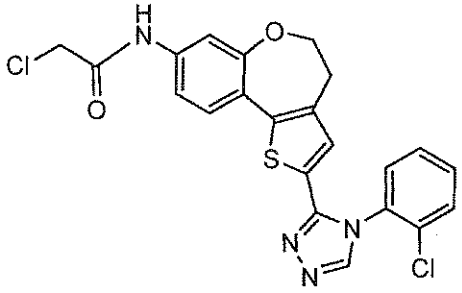


[00604] Following the procedures to prepare **138**, 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole was methoxycarbonylated to give methyl 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate which was treated with LiOH in THF and water at 50 °C for 2h, cooled and acidified with 2N HCl. The precipitate was collected and dried to give **234**. MS (ESI): 424.0

[00605] Example 145 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-amine **235**

[00606] Following the procedure of Example 76, 3-(8-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole was converted to **235**. MS: (ESI+) 395.2

[00607] Example 146 N-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-2-morpholinoacetamide **236**

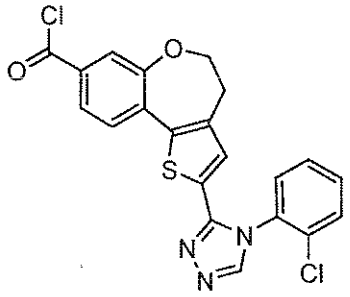


[00608] Following the procedure in Example 147 for **237**, 2-chloro-N-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)acetamide was reacted with morpholine to give **236**. MS: (ESI+) 522.3

[00609] Example 147 N-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-2-(dimethylamino)acetamide **237**

[00610] To a solution of 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b] thieno [2,3-d]oxepin-8-amine HCl salt (0.5 g, 1.16 mmol) in dried DCM (30 mL) was added DIPEA (0.61 mL, 3.48 mmol). The solution was stirred at 0 °C for 20 min and 2-chloro- acetyl chloride (0.2 g, 1.74 mmol) was added dropwise. The mixture was allowed to reach room temperature and stirred for a further 2 hours. The reaction solution was poured into ice water and extracted with EtOAc. The organics were combined, dried over Na_2SO_4 and evaporated in vacuum to afford the crude product (0.45 g, yield: 82%). 2-chloro-N-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)acetamide (0.2 g, 0.424 mmol) was mixed with HCl salt of $NH(CH_3)_2$ (0.172 g, 2.12 mmol) and NEt_3 (0.3 mL, 2.12 mmol) in 15 mL of DCM. The solution was stirred at room temperature for 4 hours and quenched with ice water. Extraction with EtOAc and evaporation of the organics gave the crude product. It was purified by preparative TLC to afford **237** (40 mg, isolated yield: 20%). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.81 (s, 1H), 8.81 (s, 1H), 7.79- 7.38 (m, 7H), 6.55 (s, 1H), 4.16 (t, J= 5.2 Hz, 2H), 3.02 (s, 3H), 2.96 (t, J= 5.2 Hz, 2H), 2.21 (s, 6H). MS: (ESI+) 480.1

[00611] Example 148 N-(2-amino-2-methylpropyl)-2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **238**



[00612] 2-(4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride and 2-methylpropane-1,2-diamine gave **238**. MS (ESI) 494.1

[00613] Example 149 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-ethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **239**

[00614] 2-(4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride and ethylamine gave **239**. MS (ESI) 450.9

[00615] Example 150 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **240**

[00616] 2-(4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride and methylamine gave **240**. MS (ESI) 436.9

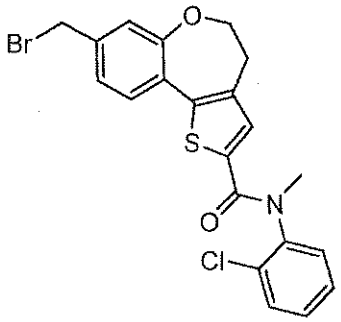
[00617] Example 151 N-(2-chlorophenyl)-N-methyl-8-((4-methylpiperazin-1-yl)methyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **241**

[00618] 8-(Bromomethyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide was reacted with N-methylpiperazine using the procedure of Example 153 for **243** to give **241**. MS: (ESI+) 482.0

[00619] Example 152 N-(2-chlorophenyl)-8-((dimethylamino)methyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **242**

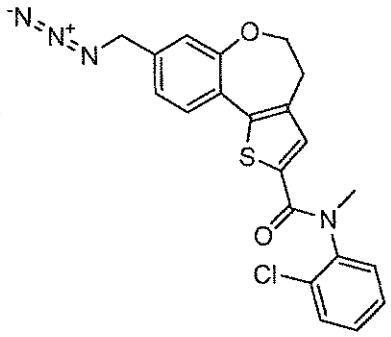
[00620] 8-(Bromomethyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide was reacted with dimethylamine using the procedure of Example 153 for **243** to give **242**. MS: (ESI+) 427.0

[00621] Example 153 N-(2-chlorophenyl)-N-methyl-8-((methylamino)methyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **243**



[00622] To a solution of CH_3NH_2 in EtOH (0.25 mL) was added TEA(0.5 mL) and 8-(bromomethyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (250 mg). The reaction mixture was stirred for 2h at 60 °C before added water. The mixture was extracted with EtOAc (20 mLx3), dried over Na_2SO_4 and filtered. The filtrate was concentrated to give the crude product, which was purified by preparative TLC (CH_2Cl_2 : MeOH = 10 : 1) to afford **243** as a light yellow solid (95.6 mg, 42.8%). MS: (ESI+) 412.9

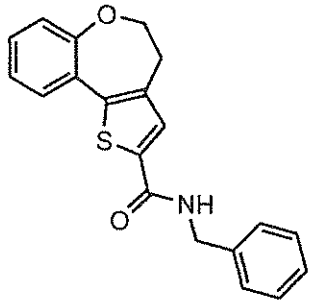
[00623] Example 154 8-(aminomethyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **244**



[00624] 8-(Azidomethyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (100 mg, 0.23 mmol) was dissolved in 10 mL of MeOH. To the solution was added Pd/C (10 mg) and charged with H_2. The mixture was stirred at 40 °C for 3h. Filtered and concentrated in vacuo to obtain **244** (54.1 mg, yield 59%). ^1H NMR ($CDCl_3$, 400

MHz) δ 8.48-8.52 (m, $2H_2$), 6.55-7.47 (m, 8H), 4.15 (t, J = 4.8 Hz, 2H), 3.91-3.95 (m, 2H), 3.28 (s, 3H), 2.94 (t, J= 4.8Hz, 2H). MS: (ESI+) 382.1

[00625] Example 155 4-benzyl-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-5(4H)-one **245**



[00626] Prepared from N-benzyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide to give **245** using a procedure similar to that described for **265** in Example 175. Removal of the acetoxy group is spontaneous under conditions for cyclization (potassium carbonate, ethanol and water). MS (ESI) 376.2

[00627] Example 156 N-(2,6-dichlorophenyl)-N-methyl-(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **246**

[00628] Following the procedures of Example 166, 2-bromo-10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine (0.112 g, 0.397 mmol) was dissolved in tetrahydrofuran (6.03 mL). n-Butyllithium in hexane (2.50 M, 0.190 mL) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 1h. 2, 6-Dichlorophenyl isocyanate (0.149 g, 0.794 mmol;) was added to the mixture at -78 °C then let stirred overnight. The reaction mixture was quenched with sat. NaHCO3 then extracted EtOAc (2x). The combined organic layers was dried Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (0-100% EtOAc/Hex) (eluted 40%) to give the amide intermediate which was dissolved in DMF (5.00 mL) at 0 °C. Sodium hydride (19.0 mg, 0.794 mmol) was added. The reaction mixture was stirred 30 min then methyl iodide (0.113 g, 0.794 mmol) was added and stirred 2h. The reaction mixture was quenched 5 mL water then extracted DCM (3x5 mL). The organic layers were combined, concentrated, and purified by rHPLC to give **246** (yield 30%). MS: (ESI+) 405.1

[00629] Example 157 N-(2,4-dichlorophenyl)-9-(4-(dimethylamino)piperidine-1-carbonyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **247**

[00630] 2-[(2,4-Dichloro-phenyl)-methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid and 4-(dimethylamino)piperidine were reacted by General Procedure B to give **247**. NMR: ($CDCl_3$): 1.45-1.62 (2 H, br m), 1.88-2.01 (2 H, br, m), 2.39 (6 H, s, Me), 2.50-2.61 (1 H, br m), 2.82-3.10 (2 H, br m), 3.07-3.09 (2 H, m), 3.38 (3 H, s, Me), 3.80-4.01 (1 H, br m), 4.26-4.29 (2 H, m), 4.58-4.79 (1 H, br m), 6.85 (1 H, s, Ar), 7.02 (1 H, d,

J 8.3, Ar), 7.25 (1 H, dd, J 8.2 and 2.0, Ar), 7.28-7.32 (1 H, m, Ar), 7.37-7.39 (1 H, m, Ar), 7.55 (1 H, s, Ar) and 7.60 (1 H, s, Ar). MS: (ESI+) MH+ = 558.14

[00631] Example 158 N-(2-chloro-4-(2-(dimethylamino)ethylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **248**

[00632] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and N1,N1-dimethylethane-1,2-diamine were reacted by a procedure similar to that to prepare **137** in Example 47 to give **248**. MS: (ESI+) 484.3

[00633] Example 159 N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **249**

[00634] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and dimethylamine hydrochloride were reacted by a procedure similar to Example 47 to give **249**. MS: (ESI+) 441.0

[00635] Example 160 N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **250**

[00636] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and methylamine were reacted by a procedure similar to Example 47 to give **250**. MS: (ESI+) 427.2

[00637] Example 161 N-(2-chloro-4-(morpholine-4-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **251**

[00638] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and morpholine were reacted by a procedure similar to Example 47 to give **251**. MS: (ESI+) 483.1

[00639] Example 162 N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **252**

[00640] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and N-methylpiperazine were reacted by a procedure similar to Example 47 to give **252**. MS: (ESI+) 496.2

[00641] Example 163 N-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **253**

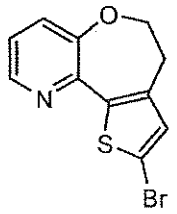
[00642] 3-Chloro-4-(N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid and piperazine were reacted by a procedure similar to Example 47 to give **253**. MS: (ESI+) 482.1

[00643] Example 164 3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(1-hydroxypropan-2-yl)-1H-1,2,4-triazol-5(4H)-one **254**

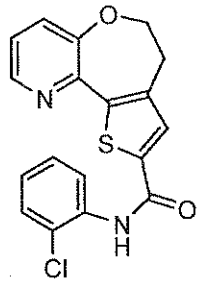
[00644] Prepared from 2-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)propyl acetate to give **254** using a procedure similar to Example 175. MS (ESI) 344.2

[00645] Example 165 3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2,4-dichlorophenyl)-4H-1,2,4-triazole **255**

[00646] Example 166 4-(2-chlorophenyl)-3-(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-5(4H)-one **256**



[00647] To a solution of 2-bromo-10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine (0.405 g, 1.44 mmol) in tetrahydrofuran (21.8 mL, 269 mmol) was added 2.50 M of n-butyllithium in hexane (0.689 mL) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 1h. 1-Chloro-2-isocyanatobenzene (2-chlorophenyl isocyanate 0.346 mL, 2.87 mmol) was added to the mixture at -78 °C then let stir overnight. The reaction mixture was quenched with sat. $NaHCO_3$ then extracted EtOAc (2x). The combined organic layers was dried Na2SO4, concentrated. The crude product was purified by flash chromatography (0-100% EtOAc/Hex) (eluted 40%) to give N-(2-chlorophenyl)-10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (yield 82%). MS: (ESI+) 357.8



[00648] To a solution of N-(2-chlorophenyl)-10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (0.180 g, 0.504 mmol;) in 1,4-dioxane (4.50 mL, 57.7 mmol) was added 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (Lawesson's reagent, 0.153 g, 0.378 mmol). The reaction mixture was stirred at 85 °C for 3h. The reaction mixture was concentrated to give the crude thioamide intermediate. To a solution containing crude thioamide intermediate in methanol (10.0 mL, 247 mmol) was added hydrazine (0.80 mL, 25 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated to give crude hydrazine intermediate which was dissolved in THF. N,N-Carbonyldiimidazole (0.164 g, 1.01 mmol) was added and the reaction mixture was stirred

rapidly at room temperature for 4h. The reaction mixture was concentrated and purified by rHPLC to give **256** (yield 10%). MS: (ESI+) 397.1

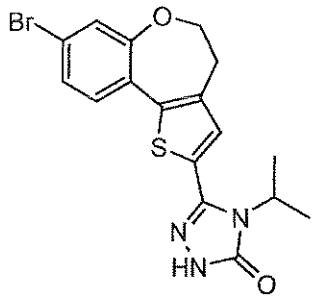
[00649] Example 167 3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(1-methoxypropan-2-yl)-1H-1,2,4-triazol-5(4H)-one **257**

[00650] Prepared from N-(1-methoxypropan-2-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide to give **257** using a procedure similar to Example 175. MS (ESI) 358.2. The enantiomers of the racemic mixture were separated by preparative chiral chromatography.

[00651] Example 168 N-(2-acetamidoethyl)-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **258**

[00652] To a solution of N-(2-aminoethyl)-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **131** (0.300 g, 0.6 mmol) in methylene chloride (1.5 ml) was added DIEA (0.262 ml, 1,5 mmol). The reaction mixture was cooled with an ice water bath and and acetyl chloride (0.0944 g, 1.2 mmol) was added drop-wise via syringe. The reaction mixture was stirred at cool temperature for 30 minutes and equilibrated to room temperature. The reaction mixture was washed with water, then saline and concentrated to a solid. The crude solid was taken into DMF and purified by RP-HPLC to give 46 mg of **258** (yield 18% of theoretical). MS: (ESI+) 441.1

[00653] Example 169 2-(4-isopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile **259**



[00654] Following the procedure of Example 53, 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isopropyl-1H-1,2,4-triazol-5(4H)-one and CuCN were reacted to give **259**. MS: (ESI+) 353.1

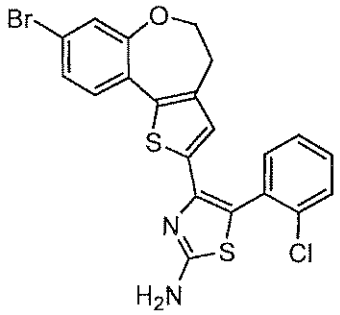
[00655] Example 170 3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isobutyl-1H-1,2,4-triazol-5(4H)-one **260**

[00656] Prepared from N-isobutyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide to give **260** using a procedure similar to Example 175. MS (ESI) 342.2

[00657] Example 171 N-(2-chlorophenyl)-N-methyl-8-(morpholinomethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **261**

[00658] Following the procedure in Example 153 for the synthesis of **243**, 8-(bromomethyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide was reacted with morpholine to give **261**. MS: (ESI+) 469.0

[00659] Example 172 4-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-5-(2-chlorophenyl)thiazol-2-amine **262**

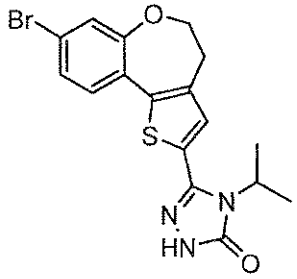


[00660] Following the procedure of Example 44, 4-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-5-(2-chlorophenyl)thiazol-2-amine and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole were reacted to give **262**. MS: (ESI+) 477.1

[00661] Example 173 N-(2-chlorophenyl)-N-methyl-(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **263**

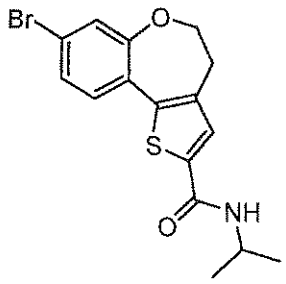
[00662] Following the procedures of Examples 156 and 166, N-(2-chlorophenyl)-10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide, was methylated to give **263**. MS: (ESI+) 371.1

[00663] Example 174 3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isopropyl-1H-1,2,4-triazol-5(4H)-one **264**



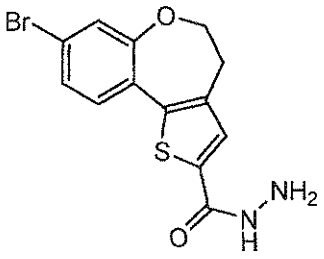
[00664] Following the procedure of Example 44, 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isopropyl-1H-1,2,4-triazol-5(4H)-one and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole were reacted to give **264**. MS: (ESI+) 394.2

[00665] Example 175 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isopropyl-1H-1,2,4-triazol-5(4H)-one **265**



[00666] A solution of 8-bromo-N-isopropyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (200 mg, 0.5 mmol) in toluene (5 mL, 0.05 mol) under nitrogen atmosphere was treated with phosphorus pentachloride (0.182 g, 0.87 mmol) in one portion. The flask was sealed and heated at 80 °C for 2 h, cooled to room temperature and the solvent concentrated under reduced pressure with care to avoid atmospheric exposure. The crude residue was taken up in methylene chloride (8 mL, 0.1 mol) and treated with methyl hydrazinecarboxylate (0.123 g, 1.36 mmol). The resulting suspension was stirred at room temperature for 2 h. The reaction mixture was diluted with saturated sodium bicarbonate and extracted with methylene chloride. The combined organics were washed with brine, dried over sodium sulfate and concentrated. The crude residue was dissolved in ethanol (5 mL) and potassium carbonate (0.2264 g, 1.64 mmol) was added. The reaction mixture was stirred at 80 °C for 2 h. 0.5 mL water was added and the heating continued overnight. The mixture was concentrated, diluted with water and extracted with ethyl acetate. The organics were washed with brine, concentrated, and the resultant residue purified by flash column chromatography to give **265** (75 mg). ^{1}H NMR (dmso-d_6, 500 MHz) δ 11.9 (s, 1H), 7.60 (m, 1H), 7.30-7.23 (m, 3H), 4.44 (pentet, 1H), 4.32 (t, 2H), 3.22 (t, 2H), 1.46 (d, 6H). MS (ESI) 408.1

[00667] Example 176 5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1,3,4-oxadiazol-2(3H)-one **266**



[00668] 8-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbohydrazide (150 mg, 0.44 mmol) was suspended in tetrahydrofuran (5.0 mL) and triethylamine (0.12 mL, 0.88 mmol) was added. N,N-Carbonyldiimidazole (108 mg, 0.66 mmol) was added and the whole stirred at room temperature for 1 h. No reaction was observed. The whole was sealed and heat at 80 °C for 2 h. More N,N-carbonyldiimidazole (150 mg, 0.92 mmol) was added and the whole heated at 85 °C for 10 min. LCMS indicated clean conversion to the desired product. The

reaction mixture was cooled to room temperature, diluted with saturated sodium bicarbonate and extracted with ethyl acetate. The organics were dried over sodium sulfate. Concentration gave 125 mg colorless solid. A small amount was purified by reverse phase HPLC to give **266** as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (br s, 1H), 7.70 - 7.00 (overlapping m, 4H), 4.23 (t, 2H), 3.21 (t, 2H). MS: (ESI+) 367.0

[00669] Example 177 3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chloro-4-fluorophenyl)-4H-1,2,4-triazole **267**

[00670] To a stirred solution of 5-bromo-2-hydroxyacetophenone (15.29 g; 71 mmol) in 2-butanone (150 ml) was added K_2CO_3 (21 g; 152 mmol) then 1,2-dibromoethane (30 ml; 350 mmol). The reaction mixture was heated at reflux temperature overnight (17 h), cooled, filtered (acetone washing) and the solvent evaporated. The residue was treated with a mixture of Et_2O/EtOAc (4:1; 250 ml) and the resulting solid removed by filtration. The filtrate was washed with 2M NaOH (150 ml), dried ($MgSO_4$) and concentrated to give 1-[5-bromo-2-(2-bromo-ethoxy)-phenyl]-ethanone as an off-white crystalline solid (15.99 g). This solid was dissolved in anhydrous THF (300 ml), cooled to 0 °C and treated with NaH (2.11 g of a 60 wt% suspension in mineral oil; 53 mmol). The reaction mixture was carefully heated to reflux and heating continued overnight (17 h). The reaction mixture was cooled, quenched with 2M HCl (50 ml) and partitioned between brine (300 ml) and EtOAc (200 ml). The organic layer was dried ($MgSO_4$), concentrated and purified by ISCO (hexanes/EtOAc) to give 7-bromo-3,4-dihydro-2*H*-benzo[b]oxepin-5-one as a pale yellow oil (9.84 g; 57%). δ_H (400 MHz, $CDCl_3$) 2.24 (quintet, J = 6.8, 2H), 2.91 (t, J = 6.8, 2H), 4.25 (t, J = 6.8, 2H), 6.98 (d, J = 8.8, 1H), 7.52 (dd, J = 8.8 and 2.8, 1H), 7.90 (d, J = 2.8, 1H).

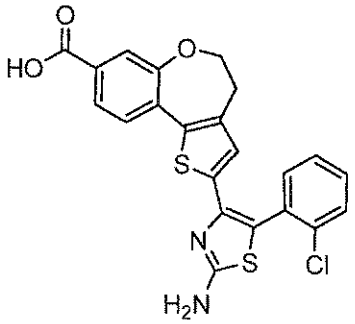
[00671] To a stirred solution of 7-bromo-3,4-dihydro-2H-benzo[b]oxepin-5-one (9.84 g; 41 mmol) in DMF (50 ml) at 0 °C was added $POCl_3$ (10 ml; 107 mmol) dropwise over 10 min. The reaction mixture was stirred whilst allowing to warm to room temperature overnight (16 h) upon which time it was quenched by pouring into well-stirred ice/water (500 ml). The resulting solid was extracted into EtOAc (2 400 ml), the combined organics were dried ($MgSO_4$) and concentrated to give a yellow solid (7-bromo-5-chloro-2,3-dihydro-benzo[b]oxepine-4-carbaldehyde). This solid was dissolved in DMF (50 ml) and treated successively with K_2CO_3 (7 g; 51 mmol) then ethyl mercaptoacetate (5.5 ml; 50 mmol). The reaction mixture was heated at 70 °C for 4h upon which time it was cooled and poured into well-stirred ice/water (500 ml). The resulting solid was collected by filtration and dried to give 9-Bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid ethyl ester as an off-white solid (13.69 g; 95 %). δ_H (400 MHz, d_6-DMSO) 1.31 (t, J = 7.2, 3H), 3.23 (t, J = 5.2, 2H), 4.27-4.35 (m, 4H), 7.03 (d, J = 8.8, 1H), 7.42 (dd, J = 8.8 and 2.4, 1H), 7.70 (s, 1H), 7.80 (d, J = 2.4, 1H).

[00672] To a stirred suspension of 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid ethyl ester (4.24 g; 12 mmol) in THF (40 ml) at room temperature was added a solution of NaOH (0.96 g; 24 mmol) in water (20 ml) followed by EtOH (20 ml). The reaction mixture was stirred at room temperature for 4 h (now a clear solution) upon which time it was quenched with 2M HCl (20 ml) and diluted with water (50 ml). The resulting solid was collected by filtration, washed with water and dried to give 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid as a white solid (3.64 g; 93 %). δ_H (400 MHz, d_6-DMSO) 3.22 (t, J = 5.2, 2H), 4.31 (t, J = 5.2, 2H), 7.02 (d, J = 8.4, 1H), 7.43 (dd, J = 8.4 and 2.4, 1H), 7.62 (s, 1H), 7.78 (d, J = 2.4, 1H).

[00673] A stirred solution of 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid ethyl ester (7.43 g; 21 mmol) and $N_2H_4 \cdot H_2O$ (5.1 ml; 105 mmol) in EtOH was heated at reflux temperature overnight (18 h) and the resulting solid was collected by filtration (3.68 g). A further crop (2.88 g) of the intermediate hydrazide was obtained by treating the filtrate with more $N_2H_4 \cdot H_2O$ (20 ml) and refluxing overnight to obtain 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid hydrazide as white needles (6.56 g; 92%). The intermediate hydrazide was heated in a microwave (performed in 4 batches) with p-TsOH (10 mol%) and $CH(OMe)_3$ (5 ml per 1 g of hydrazide) at 140 °C for 1 h. The batches were combined, the mixture diluted with MeOH and filtered to give the 2-(9-Bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-[1,3,4]oxadiazole as light yellow needles (4.39 g; 65 %). δ_H (400 MHz, $CDCl_3$) 3.30 (t, J = 5.2, 2H), 4.37 (t, J = 5.2, 2H), 6.96 (d, J = 8.8, 1H), 7.33 (dd, J = 8.8 and 2.4, 1H), 7.61 (s, 1H), 7.84 (d, J = 2.4, 1H), 8.44 (s, 1H).

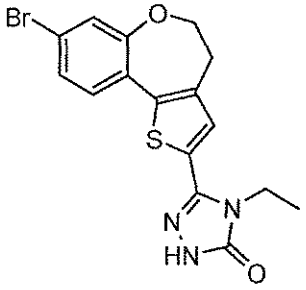
[00674] A microwave tube was charged with 2-(9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-[1,3,4]oxadiazole (0.64 g; 1.83 mmol), 2-chloro-4-fluoroaniline (0.44 ml; 3.68 mmol), TFA (0.27 ml; 3.63 mmol) and toluene (5 ml). The mixture was heated in a microwave at 160 °C for 30 min., diluted with EtOAc (150 ml) and washed with satd. $NaHCO_3$. The organic layer was dried ($MgSO_4$), concentrated and purified by ISCO to give **267** as a cream-coloured solid (0.59 g; 68 %). δ_H (400 MHz, $CDCl_3$) 3.14 (t, J = 5.2, 2H), 4.29 (t, J = 5.2, 2H), 6.91 (d, J = 8.4, 1H), 6.93 (s, 1H), 7.22-7.27 (m, 2H), 7.43-7.51 (m, 2H), 7.65 (d, J = 2.4, 1H), 8.22 (s, 1H). $[M+H]^+$: 478

[00675] Example 178 2-(2-amino-5-(2-chlorophenyl)thiazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **268**



[00676] Following Example 47, 2-(2-amino-5-(2-chlorophenyl)thiazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid and ammonium chloride were coupled with HATU and DIPEA in DMF to give **268**.

[00677] Example 179 3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-ethyl-1H-1,2,4-triazol-5(4H)-one **269**

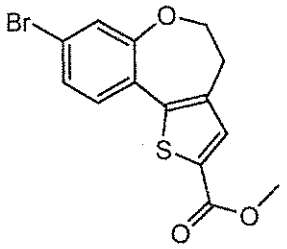


[00678] Following the procedure of Example 44, 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-ethyl-1H-1,2,4-triazol-5(4H)-one and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole were reacted to give **269**. MS: (ESI+) 380.2

[00679] Example 180 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **270**

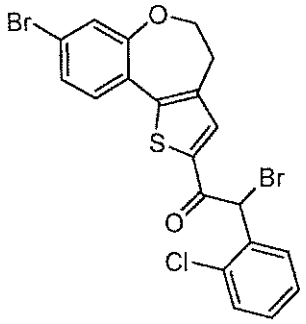
[00680] 2-(4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride and ammonium chloride gave **270**. (ESI) 423.1.

[00681] Example 181 4-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-5-(2-chlorophenyl)thiazol-2-amine **271**



[00682] 1-(8-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-2-(2-chlorophenyl)ethanone (1.0 g, 2.3 mmol) was prepared by reaction of 2-chlorophenylacetic acid with methyl 8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxylate. A solution of 1-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-2-(2-chlorophenyl)ethanone in ethyl

acetate (60 mL) was treated with copper(II) bromide (1.3 g, 5.8 mmol) in one portion in 100 mL rb flask. Acetic acid (2 mL) was added, and the flask sealed and heated at 85 °C. After 8 hr, the reaction was removed from heat and allowed to stand overnight. The reaction mixture was concentrated to dryness, diluted with 100 mL diethyl ether and filtered through celite (ether wash). The eluent was re-filtered through the same celite pad, and concentration gave 2-bromo-1-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-2-(2-chlorophenyl)ethanone as a crude solid used without purification.



[00683] 2-Bromo-1-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-2-(2-chlorophenyl)ethanone (ca. 2.3 mmol) was suspended in acetone (15 mL, 0.20 mol) and treated with thiourea (0.26 g, 0.0034 mol;). The mixture was sealed and heated at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated, suspended in water and the solid was collected by filtration. The solid was rinsed with water to give 953 mg of **271** as a light yellow solid. ^{1}H NMR (dmso-d_6, 500 MHz) δ 7.64 (m, 1H), 7.53 (m, 2H), 7.45 (m, 1H), 7.35 (m, 1H), 7.23 (m, 1H), 7.17 (m, 1H), 6.47 (s, 1H), 4.19 (t, 2H), 2.95 (t, 2H). MS (ESI) 491.0

[00684] Example 182 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-5-methyl-4H-1,2,4-triazole **272**

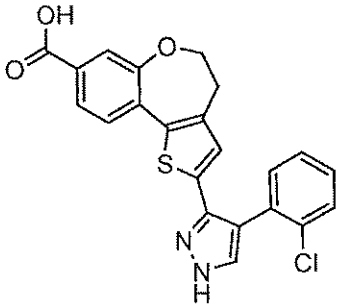
[00685] A solution of crude 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbohydrazonamide (150 mg) was heated in a sealed vessel with triethyl orthoacetate at 90 °C for 3 h. The mixture was cooled to room temperature and concentrated to give a crude residue that was purified by flash column chromatography (10-100% ethyl acetate in hexanes) to give **272**. ^{1}H NMR (dmso-d_6, 400 MHz) δ 7.86 (m, 2H), 7.48 (m, 1H), 7.69 (m, 1H), 7.44 (m, 1H), 7.28-7.23 (m, 2H), 6.57 (s, 1H), 4.22 (t, 2H), 3.00 (t, 2H), 2.18 (s, 3H). MS (ESI) 474.0

[00686] Example 183 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole **273**

[00687] A solution of crude 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbohydrazonamide (150 mg) was heated in a sealed vessel with methyl orthoformate at 90 °C for 3 h. The mixture was cooled to room temperature and concentrated to

give a crude residue that was purified by flash column chromatography (10-100% ethyl acetate in hexanes) to give **273**. ^{1}H NMR (dmso-d_6, 400 MHz) δ 8.89 (s, 1H), 7.84 (m, 2H), 7.75 (m, 1H), 7.66 (m, 1H), 7.46 (m, 2H), 7.28-7.23 (m, 2H), 6.66 (s, 1H), 4.23 (t, 2H), 3.02 (t, 2H). MS (ESI) 460.0

[00688] Example 184 2-(4-(2-chlorophenyl)-1H-pyrazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **274**

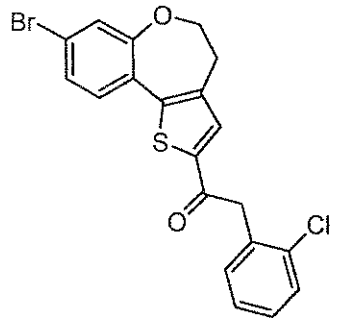


[00689] Following Example 47, 2-(4-(2-chlorophenyl)-1H-pyrazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid and ammonium chloride were coupled with HATU and DIPEA in DMF to give **274**.

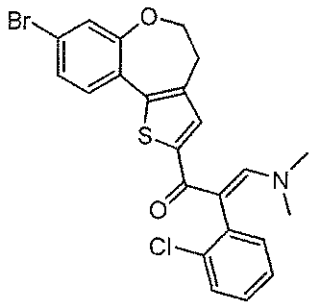
[00690] Example 185 2-(4-(2-chlorophenyl)-1H-pyrazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile **275**

[00691] Following the procedure of Example 53, 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-pyrazole and CuCN gave **275**. MS: (ESI+) 404.1

[00692] Example 186 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-pyrazole **276**

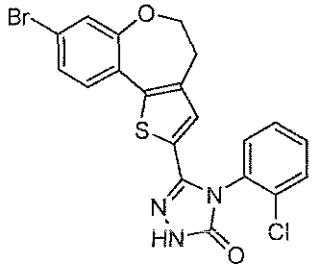


[00693] To a solution of 1-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-2-(2-chlorophenyl)ethanone (500 mg, 1.15 mmol) in dry toluene (10 mL) was added 1,1-dimethoxy-N,N-dimethylmethanamine (1.22 mL). The whole vessel was sealed and heated at 90°C overnight, cooled to room temperature and concentrated. The obtained compound, 1-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-2-(2-chlorophenyl)-3-(dimethylamino)prop-2-en-1-one, could be used crude without purification in subsequent reactions.



[00694] Crude 1-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-2-(2-chlorophenyl)-3-(dimethylamino)prop-2-en-1-one was suspended in methanol (5 mL) and treated with hydrazine (ca. 1 mL). After 2 h, the mixture was concentrated and the residue purified by flash column chromatography to give **276** as colorless solid (527 mg). MS (ESI): 459.0

[00695] Example 187 3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one **277**



[00696] Following the procedure of Example 44, 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole were reacted to give **277**. MS: (ESI+) 462.1

[00697] Example 188 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile **278**

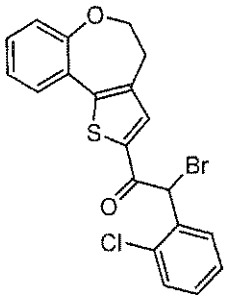
[00698] Following the procedure of Example 53, (8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one and CuCN gave **278**. MS: (ESI+) 421.1

[00699] Example 189 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one **279**

[00700] To a solution of crude 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbohydrazonamide (about 1.15 mmol) in dry THF (10 mL) was added carbonyl diimidazole (373 mg, 2.3 mmol). The reaction mixture was stirred at room temperature until completion judged by LCMS. Aqueous sodium bicarbonate was added and the mixture extracted with ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate, concentrated and the residue purified by flash column

chromatography (10-100% ethyl acetate in hexanes) to give **279** as a colorless solid (308 mg). ^{1}H NMR (dmso-d_6, 400 MHz) δ 12.32 (s, 1H), 7.75-7.59 (m, 4H), 7.42 (m, 1H), 7.27-7.21 (m, 2H), 6.53 (s, 1H), 4.21 (t, 2H), 2.97 (t, 2H). MS (ESI) 476.0.

[00701] Example 190 5-(2-chlorophenyl)-4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)thiazol-2-amine **280**

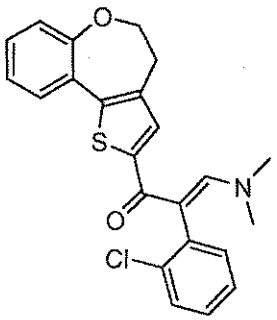


[00702] A solution of crude 2-bromo-2-(2-chlorophenyl)-1-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)ethanone (0.21 mmol) in 2 mL acetone was treated with thiourea (48 mg) and the resultant suspension was heated at 80 °C overnight. The reaction mixture was cooled to room temperature and concentrated. The crude residue was purified by reverse phase HPLC to give **280** as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (m, 1H), 7.55 - 7.53 (m, 2H), 7.47 - 7.43 (m, 2H), 7.29 (br s, 2H), 7.14 (m, 1H), 7.02 (m, 1H), 6.45 (s, 1H), 4.17 (t, 2H), 2.95 (t, 2H). MS: (ESI+) 411.1

[00703] Example 191 2-(4-(2-chloro-4-fluorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide **281**

[00704] To a stirred solution of 2-[4-(2-chloro-4-fluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carbonitrile (90 mg; 0.21 mmol) in DMSO (3 ml) and MeOH (5 ml) was added K_2CO_3 (36 mg; 0.26 mmol) then H_2O_2 (30 µl of a 30 % aqueous soln.). The reaction mixture was stirred at room temperature overnight (16 h) upon which time the methanol was removed on a rotary evaporator and the residue was diluted with water (40 ml). The resulting solid was collected by filtration, washed with water and dried to give **281** as a white solid (82 mg; 89 %). δ_H (400 MHz, $CDCl_3$) 3.15 (t, J = 5.2, 2H), 4.34 (t, J = 5.2, 2H), 5.50-6.30 (br s, 2H), 6.88 (s, 1H), 7.07 (d, J = 8.4, 1H), 7.22-7.27 (m, 1H), 7.42-7.63 (m, 3H), 8.06 (d, J = 2.0, 1H), 8.22 (s, 1H). $[M+H]^+$: 441

[00705] Example 192 5-(2-chlorophenyl)-4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyrimidin-2-amine **282**

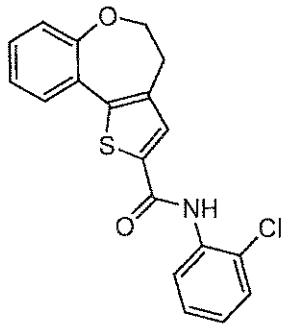


[00706] To a solution of crude 2-(2-chlorophenyl)-1-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-3-(dimethylamino)prop-2-en-1-one (ca. 0.22 mmol) in ethanol (2 mL) was added potassium carbonate (87 mg, 0.63 mmol) and then guanidine hydrochloride (40 mg, 0.42 mmol). The whole was sealed and heated at 90°C for 8 h, cooled to room temperature and concentrated. The residue was diluted with water and extracted with ethyl acetate. The combined organics were purified by reverse phase HPLC to give **282**. MS (ESI) 406.2

[00707] Example 193 4-(2-chlorophenyl)-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-pyrazole **283**

[00708] 2-(2-Chlorophenyl)-1-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-3-(dimethylamino)prop-2-en-1-one was treated with hydrazine in methanol to give **283**. MS (ESI) 379.1

[00709] Example 194 4-(2-chlorophenyl)-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-5(4H)-one **284**

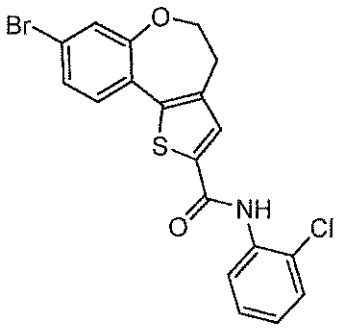


[00710] Prepared starting from N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide to give **284** using procedures similar to those described in Examples 196 and 189. MS (ESI) 396.1

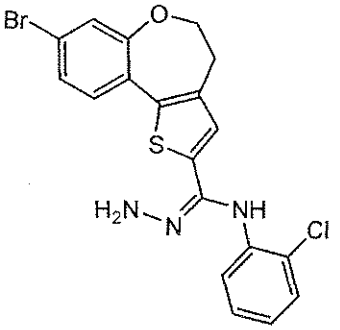
[00711] Example 195 2-(1-(2-chlorophenyl)-1H-tetrazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **285**

[00712] 8-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2-chlorophenyl)-1H-tetrazole **286** was converted to **285** using procedures similar to those in Examples 205 and 53. MS: (ESI+) 424.0

[00713] Example 196 5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2-chlorophenyl)-1H-tetrazole **286**



[00714] To a solution of 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide in dry 1,4-dioxane was added Lawesson's reagent. The 50 mL round-bottom was sealed and heated at 80°C for 3 h. The reaction mixture was cooled to room temperature and concentrated to give the crude thioamide. The bright yellow crude solid thus obtained was taken up in methanol and methylene chloride and treated with hydrazine. Reaction progress was monitored by LCMS. Upon completion, the mixture was diluted with saturated sodium bicarbonate and extracted with ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate and concentrated to give crude 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbohydrazonamide as a yellow solid.



[00715] A solution of crude 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbohydrazonamide (150 mg, 0.334 mmol) in acetic acid (0.5 mL) was treated with a solution of sodium nitrite (115 mg, 1.6 mmol) in water (0.5 mL) at 0°C. After 30 min, an additional 50 mg of sodium nitrite was added. After 10 min, 3 mL of 10% aqueous sodium hydroxide was added. The mixture was extracted with ethyl acetate and the organics dried over sodium sulfate and concentrated. The crude residue was purified by flash column chromatography to give **286** as a colorless solid (111 mg). ^{1}H NMR (dmso-d_6, 400 MHz) δ 8.00 (m, 1H), 7.98 (m, 1H), 7.85 (m, 1H), 7.56 (m, 1H), 7.46 (m, 1H), 7.26 (m, 2H), 7.13 (m, 1H), 4.27 (t, 2H), 3.11 (t, 2H). MS (ESI) 461.1

[00716] Example 197 5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazol-3-amine **287**

[00717] A solution of crude 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbohydrazonamide (195, 0.434) in methanol (5 mL) was treated with a solution of cyanogen bromide (115 mg, 1.1 mmol) in methanol (1 mL) at room temperature. The reaction vessel was sealed and heated at 45°C for 2 h, cooled to room temperature, quenched upon addition of saturated sodium bicarbonate and extracted with ethylacetate. The combined organics were dried over sodium sulfate and concentrated and the residue purified by flash column chromatography (1-10% MeOH in methylene chloride to give **287** (43 mg, 21 % yield). MS (ESI): 475.0

[00718] Example 198 N2-(2,4-dichlorophenyl)-N2,N9,N9-trimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide **288**

[00719] 2-[(2,4-Dichloro-phenyl)-methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid and dimethylamine hydrochloride salt were reacted in the general amide coupling procedure to give **288**. NMR: ($CDCl_3$): 2.73-3.04 (6 H, br m), 2.95-3.00 (2 H, m), 3.29 (3 H, s, Me), 4.17-4.20 (2 H, m), 6.79 (1 H, s, Ar), 6.93 (1 H, d, J 8.3, Ar), 7.19-7.29 (3 H, m, Ar) and 7.47-7.48 (2 H, m, Ar). MS: (ESI+) MH+ = 475.04

[00720] Example 199 3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chloro-4-(trifluoromethyl)phenyl)-4H-1,2,4-triazole **289**

[00721] A microwave tube charged with 2-(9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-[1,3,4]oxadiazole (200 mg; 0.57 mmol), 2-chloro-4-trifluoromethylaniline (0.12 ml; 0.86 mmol), TFA (64 µl; 0.86 mmol) and toluene (1.5 ml) was heated in a microwave at 160 °C for 30 min. The reaction mixture was basified with DIPEA (0.2 ml), volatiles removed in vacuo and the residue purified by prep. LCMS to give **289** as a white solid (109 mg; 36 %). δ_H (400 MHz, $CDCl_3$) 3.13 (t, J = 5.2, 2H), 4.29 (t, J = 5.2, 2H), 6.89-6.93 (m, 2H), 7.24-7.28 (m, 1H), 7.62-7.67 (m, 2H), 7.80-7.83 (m, 1H), 7.98 (s, 1H), 8.26 (s, 1H). $[M+H]^+$: 527

[00722] Example 200 N-(2-chloro-4-fluorophenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **290**

[00723] Compound **290** was prepared using the standard amide coupling conditions to give a white solid (198 mg, 82%). δ_H (400 MHz, $CDCl_3$) 3.11 (t, 2H), 3.39 (s, 3H), 4.31 (t, 2H), 6.93 (s, 1H), 7.06 (d, 1H), 7.13 (m, 1H), 7.32 (dd, 1H), 7.39 (m, 1H), 7.44 (dd, 1H), 7.77 (s, 1H). $[M + H]^+$ (453.97).

[00724] Example 201 9-cyano-N-(2,4-difluorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **291**

[00725] Compound **291** was prepared using the standard amide coupling conditions to give a white solid (151 mg, 65 %). δ_H (400 MHz, $CDCl_3$) 3.11 (t, 2H), 3.42 (s, 3H), 4.32 (t, 2H),

6.94 (s, 1H), 7.00 (t, 2H), 7.07 (d, 1H), 7.33 (m, 1H), 7.43 (dd, 1H), 7.78 (s, 1H). $[M + H]^+$ (438.05).

[00726] Example 202 4-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2-chlorophenyl)-2H-1,2,3-triazole **292**

[00727] Example 203 3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole **293**

[00728] To a suspension of 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid (described previously, 396 mg) in dichloromethane (10mL) was added oxalyl chloride (0.18 mL) and N,N-dimethylformamide (1 drop). After ~1 hour the reaction mixture was reduced in vacuo and to this was added ammonia in methanol (7N, 10mL). After stirring overnight water was added, and 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid amide was collected by filtration (340 mg).

[00729] A mixture of 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid amide (340mg), dimethylformamide dimethyl acetal (3ml) and toluene (2.5mL) was heated to 100°C for 16 hours. The solvent was then reduced in vacuo and dissolved in acetic acid (3ml) and water (0.3 mL) and to this was added 2,4-difluorophenylhydrazine hydrochloride (265mg). The reaction mixture was heated to 100 °C for 3 hours. The reaction mixture was then cooled, and then diluted with dichloromethane, washed with sodium carbonate solution, dried ($MgSO_4$) and the solvent removed in vacuo. Purification using flash chromatography yielded **293**. NMR: (CDCl3): 3.15 (2H, t), 4.31 (2H, t), 6.82 (1H, d), 6.86 (1H, s), 7.08-7.13 (2H, m), one proton under chloroform peak, 7.72 (1H, s), 8.10 (1H, s)

[00730] Example 204 5-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1,2,4-triazole **294**

[00731] Example 205 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **295**

[00732] A solution of 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile **278** in DMSO was treated with potassium carbonate and the resultant yellow suspension cooled to 0 °C. The reaction mixture was treated dropwise with hydrogen peroxide (30% wt. in water). The whole was warmed to room temperature and the reaction quenched with sat. $NaHSO_3$. Extraction with ethylacetate and concentration gave a residue that was purified by reverse phase HPLC to give **295** as a colorless solid.

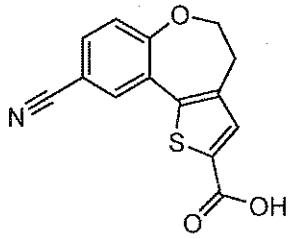
[00733] Example 206 N-(2-aminoethyl)-2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **296**

[00734] 2-(4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride and 1,2-diaminoethane gave **296**. MS (ESI) 465.9

[00735] Example 207 8-cyano-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene-2-carboxylic acid (2-chloro-(4-methylcarbamoyl)phenyl)-methyl-amide **297**

[00736] To a solution of 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-4-methylcarbamoyl-phenyl)-methyl-amide **111** (100 mg) in DMF (6 mL) was added copper cyanide (18 mg) and the reaction mixture was heated at 110 °C overnight. The reaction mixture was then cooled, diluted with ethyl acetate, washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo and the residue purified using prep LCMS to yield **297**. (400 MHz, CDCl3), 3.00 (3 H, d, J 4.9, NMe), 3.27-3.29 (2 H, m), 3.38 (3 H, s, Me), 4.20-4.24 (2 H, m), 5.92-5.94 (1 H, m, NH), 7.01-7.07 (2 H, m, Ar), 7.14 (1 H, s, Ar), 7.37 (1 H, d, J 8.1, Ar), 7.67-7.70 (1 H, m, Ar) and 7.84 (1 H, d, J 1.8, Ar)

[00737] Example 208 N-(2-chloro-4-(methylcarbamoyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **298**



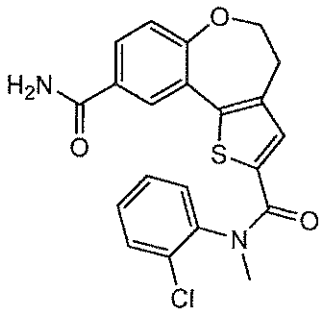
[00738] To a solution of 9-cyano-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid (300 mg) in toluene (10 mL) was added thionyl chloride (2 mL) and the reaction heated at 80 °C for 2 h. After cooling to room temperature, the solvent was reduced in vacuo and the residue redissolved in acetonitrile (10 mL). Potassium carbonate (306 mg) and 3-chloro-N-methyl-4-methylamino-benzamide from Example 21 (263 mg) were added and the reaction stirred at room temperature for 16 h. Water (20 mL) was added and the product extracted into ethyl acetate (2 x 20 mL). The organics were dried ($MgSO_4$), reduced in vacuo and purified on silica to give **298**. NMR: (CDCl3): 2.95-2.98 (5 H, m), 3.31 (3 H, s, Me), 4.19-4.21 (2 H, m), 6.10 (1 H, s, NH), .76 (1 H, s, Ar), 6.96 (1 H, d, J 8.4, Ar), 7.31-7.36 (2 H, m, Ar), 7.64-7.67 (2 H, m, Ar) and 7.87 (1 H, d, J 1.8, Ar). MS: (ESI+) MH+ 451.25

[00739] Example 209 8-methylcarbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene-2-carboxylic acid (2-chloro-(4-methylcarbamoyl)phenyl)-methyl-amide **299**

[00740] A mixture of 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-4-methylcarbamoyl-phenyl)-methyl-amide **111** (60mg), molybdenum hexacarbonyl (31 mg), Hermann's catalyst (22 mg), methylamine (2.0M solution in THF, 0.20 mL) and diazabicycloundecane (DBU, 8.8 μL) was reacted in a microwave at 150 °C for 20

minutes. The reaction mixture was then cooled, diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), solvent removed in vacuo, and the residue purified using flash chromatography to yield **299**. (400 MHz, CDCl3): 2.92 (3H,d,J 4.8), 2.98 (3H,d,J 4.8), 3.24-3.26 (2H,m), 3.38 (3H,s,Me), 4.18-4.21 (2H,m), 6.12 (2H,s,NH), 7.04-7.10 (2H,m,Ar), 7.19 (1H,s,Ar), 7.36 (1H,d,J 8.1,Ar), 7.62-7.64 (1H,m,Ar) and 7.83 (1H,d,J 1.9,Ar)

[00741] Example 210 N2-(2-chlorophenyl)-N9-ethyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide **300**



[00742] A mixture of N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide **119** (70 mg), TFA (37.5 μL), triethylsilane (80 μL)and acetaldehyde (28 μL) in dry MeCN (Dube et al (1999) Tet. Letters 40(12):2295-2298) was stirred at room temperature overnight then concentrated *in vacuo*. Purification on silica yielded **300**. NMR: ($CDCl_3$ δ 7.19ppm): 1.21 (t, 3H, CH3, J = 7.28Hz), 2.93 (t, 2H, CH2, J = 5.07Hz), 3.32 (s, 3H, CH3), 3.43 (m, 2H, CH2), 4.17 (t, 2H, CH2, J = 5.10Hz), 5.94 (m, H, NH), 6.59 (s, H, ArH), 6.91 (d, H, ArH, J = 8.41Hz), 7.29-7.36 (m, 3H, 3 x ArH), 7.44-7.47 (m, 2H, 2 x ArH), 7.81 (m, H, ArH). MS: (ESI+) MH+ 482.15

[00743] Example 211 N-(2-chlorophenyl)-N-methyl-8-(3-(pyridin-2-ylamino)propanamido)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **301**

[00744] 2-[(2,4-Dichloro-phenyl)-methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid and 1-butyl-1-piperazine carboxylate were reacted in the general amide coupling procedure to give 4-{2-[(2,4-dichloro-phenyl)-methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carbonyl}-piperazine-1-carboxylic acid tert-butyl ester.

[00745] To a solution of 4-{2-[(2,4-dichloro-phenyl)-methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carbonyl}-piperazine-1-carboxylic acid tert-butyl ester in THF was added hydrochloric acid (2 eq of a 2 M in diethyl ether solution) and the reaction stirred at room temperature for 16 h. The mixture was then quenched with aqueous sodium hydrogen carbonate solution and extracted into ethyl acetate. The organic layer was dried (MgSO4), reduced in vacuo and purified on silica to give the title compound. NMR: ($CDCl_3$): 2.72-2.95 (4 H, br m), 2.98-3.01 (2 H, m), 3.29 (3 H, s, Me), 3.38-3.75 (4 H, br m), 4.17-4.20 (2 H, m), 6.81 (1 H, s, Ar), 6.94 (1 H, d, J 8.3, Ar), 7.16 (1 H, dd, J 8.9 and 1.3, Ar), 7.23 (1 H, d, J 8.5, Ar),

7.28 (1 H, dd, J 8.4 and 2.1, Ar), 7.44 (1 H, s, Ar) and 7.58 (1 H, d, J 2.2, Ar). MS: (ESI+) MH+ = 557.13

[00746] Example 212 N-(2-acetamidoethyl)-2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **302**

[00747] 2-(4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride and N-(2-aminoethyl)acetamide gave **302**. MS (ESI) 508.1

[00748] Example 213 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-morpholinoethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **303**

[00749] 2-(4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride and 2-morpholinoethanamine gave **303**. MS (ESI) 536.2

[00750] Example 214 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-(dimethylamino)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **304**

[00751] 2-(4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride and N1,N1-dimethylethane-1,2-diamine gave **304**. MS (ESI) 494.2

[00752] Example 215 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(1,3-dihydroxypropan-2-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **305**

[00753] 2-(4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride and 2-aminopropane-1,3-diol gave **305**. MS (ESI) 497.3

[00754] Example 216 N2-(2-chloro-4-(methylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide **306**

[00755] To a solution of N-(2-chloro-4-(methylcarbamoyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **298** (100 mg) and potassium carbonate (37 mg) in DMSO (3 mL) at 0 °C was added hydrogen peroxide (30 μL of a 33% solution in water). The reaction was stirred at room temperature for 16 h. Water was then added and the resulting solid collected by filtration and air-dried to give **306**. NMR: (DMSO): 2.81 (3 H, d, J 4.5, Me), 2.91-2.93 (2 H, m), 3.68 (3 H, s, Me), 4.19-4.22 (2 H, m), 6.41 (1 H, s, NH), 7.03 (1 H, d, J 8.4, Ar), 7.35 (1 H, s), 7.71-7.77 (2 H, m, Ar), 7.92 (1 H, dd, J 8.3 and 2.0, Ar), 8.03-8.05 (3 H, m) and 8.65-8.67 (1 H, m). MS: (ESI+) MH+ 469.35

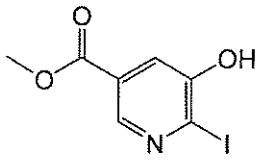
[00756] Example 217 5-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazol-3-amine **307**

[00757] Following the procedure in Example 93, 5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazol-3-amine was coupled with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give **307**. MS (ESI) 461.1

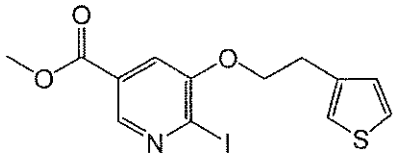
[00758] Example 218 5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-2-acetaminopyridine **308**

[00759] 5-(6,7-Dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-amine **142** (60 mg, 0.2 mmol) was heated in 1 ml of acetic anhydride at 85 ^{0}C for 60 min. The reaction mixture was then cooled to room temperature, the precipitate filtered out, washed with cold ethanol and dried in high vacuum to yield **308** (44 mg, 60%). MS: (ESI+) 338.1

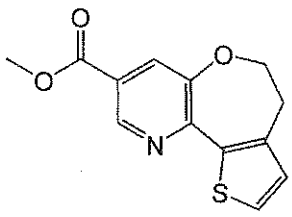
[00760] Example 219 N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-(3-hydroxymethyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide **309**



[00761] To solution of 5-hydroxy-nicotinic acid methyl ester (2.50 g, 16.3 mmol) in tetrahydrofuran (50.0 mL, 616 mmol)/ water (50.0 mL, 2780 mmol) was added sodium carbonate (5.19 g, 49.0 mmol) and iodine (10.4 g, 40.8 mmol). The reaction mixture was stirred at room temperature 4h. The aqueous layer containing product was separated and wash with hexane. The organic layer was neutralized to pH 7 with HCl, extracted EtOAc 4x. The combined organic layers was dried Na_2SO_4, concentrated. The crude product was purified by flash chromatography (EtOAc/DCM) (eluted at 40 EtOAc) to give methyl 5-hydroxy-6-iodonicotinate (81.2%). MS: (ESI+) 280.0

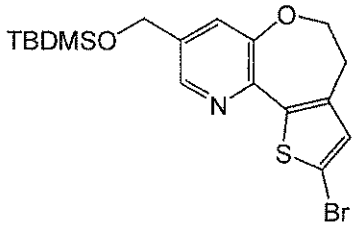


[00762] To a solution containing 5-hydroxy-6-iodonicotinate (3.70 g, 13.3 mmol;), 2-(3-thienyl)ethanol (1.90 mL, 17.2 mmol), and triphenylphosphine (4.52 g, 17.2 mmol;) in tetrahydrofuran (73.3 mL, 903 mmol;) was added Diisopropyl azodicarboxylate (3.39 mL, 17.2 mmol;) dropwise. The reaction mixture was stirred at RT o/n. The reaction mixture was concentrated and purified by flash chromatography EtOAc/Hex (0-100%) (eluted at 30%) to give methyl 6-iodo-5-(2-(thiophen-3-yl)ethoxy)nicotinate (93.2 % yield). MS: (ESI+) 390.1

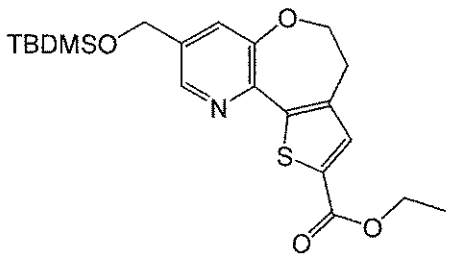


[00763] To a solution of 6-Iodo-5-(2-thiophen-3-yl-ethoxy)-nicotinic acid methyl ester (4.40 g, 11.3 mmol) in N,N-Dimethylformamide (176 mL, 2270 mmol) was added potassium

carbonate (9.37 g, 67.8 mmol), triphenylphosphine (1.19 g, 4.52 mmol) and palladium acetate (508 mg, 2.26 mmol). The reaction mixture was stirred at 90 °C 8 h. The reaction mixture was diluted with MeOH then filtered through celite. The filtrate was concentrated. The crude product was purified by flash chromatography EtOAc/Hex (0-100%) (product eluted at 30%) to give 3-methylcarboxy-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine (52.8 %). MS: (ESI+) 262.0

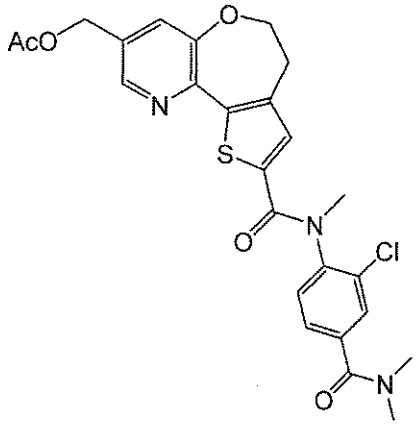


[00764] To a solution of 1.00 M of diisobutylaluminum hydride in toluene (4.02 mL) at 0 °C was added 3-methylcarboxy-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine (0.420 g, 1.61 mmol) in toluene (17.8 mL, 167 mmol) . The reaction mixture was stirred at 0 °C 2h . The reaction is diluted with EtOAc then quenched with 1M HCl. The organic layer was dried Na2SO4, concentrated to give 3-hydroxymethyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine which was dissolved in triethylamine (0.336 mL, 2.41 mmol) and N,N-dimethylformamide (10.5 mL, 136 mmol). Tert-butyldimethylsilyl chloride (0.291 g, 1.93 mmol) was added. The reaction was stirred at room temperature 20 min. The reaction was diluted with EtOAc then wash with water and brine, dried and concentrated to give 3-tert-butyldimethylsilyloxymethyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine which was dissolved in DCM/Acetic acid at 0 °C. N-Bromosuccinimide (315 mg, 1.77 mmol) was added. The reaction was stirred overnight at room temperature. The reaction was concentrated and purified by flash chromatography (EtOAc/Hex) (eluted 10%) to give 3-tert-butyldimethylsilyloxymethyl-9-bromo-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine (61.3% yield). MS: (ESI+) 426.1



[00765] To a solution of 3-tert-butyldimethylsilyloxymethyl-9-bromo-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine (0.0500 g, 0.117 mmol;) in tetrahydrofuran (1.78 mL, 22.0 mmol) was added 1.60 M of n-butyllithium in hexane (0.0806 mL) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 1h. Ethyl chloroformate (0.0336 mL, 0.352 mmol;) was added to the mixture at -78 °C then let stirred 2h. The reaction mixture was quenched with sat.NaHCO3 then extracted EtOAc (2x). The combined organic layers was dried

Na_2SO_4, concentrated. The crude product was purified by flash chromatography (0-50% EtOAc/Hex) (eluted 15%) to give 3-tert-butyldimethylsilyloxymethyl-9-ethylcarboxy-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine (36% yield). MS: (ESI+) 420.1



[00766] To a solution of 3-tert-butyldimethylsilyloxymethyl-9-ethylcarboxy-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine (0.100 g, 0.238 mmol) in tetrahydrofuran (0.715 mL, 8.82 mmol) and water (0.715 mL, 39.7 mmol) was added 1.00 M of lithium hydroxide in water (0.715 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was acidified with 1M HCl then extracted with EtOAc (3X). The combined organics were dried (Na_2SO_4), filtered and concentrated to give 3-tert-butyldimethylsilyloxymethyl-9-carboxy-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine to which was added 5ml DCM, triethylamine (0.166 mL, 1.19 mmol) and acetic anhydride (0.112 mL, 1.19 mmol). The reaction was stirred at room temperature 1h. The reaction was quenched with $NaHCO_3$ washed with EtOAc. The organic layer was acidified 1M HCl extracted EtOAc (3X). The combined organics were dried (Na2SO4), filtered and concentrated to give 3-acetoxymethyl-9-carboxy-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine which was dissolved in 5 ml DCM. A solution of 2.0 M oxalyl chloride in methylene chloride (DCM, 0.357 mL) and 1 drop of DMF was added. The reaction was stirred at room temperature 2h. The reaction was concentrated to give 3-acetoxymethyl-9-chlorocarbonyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine which was dissolved in 5 ml acetonitrile. 3-Chloro-N,N-dimethyl-4-(methylamino)benzamide (0.101 g, 0.477 mmol;) and sodium bicarbonate (0.040 g, 0.47 mmol) were added. The reaction was stirred at room temperature overnight. The reaction was quenched water, extracted three times with ethyl acetate, and concentrated. The crude product was purified by flash chromatography (50-100% EtOAc/Hex) (product eluted at 100% EtOAc, sm at 75% EtOAc) to give N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-(3-acetoxymethyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide (41%). MS: (ESI+) 514.3

[00767] To a solution of N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-(3-acetoxymethyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide (0.050 g, 0.097

mmol;) in tetrahydrofuran (2.28 mL, 28.0 mmol) and water (2.28 mL, 126 mmol) was added lithium hydroxide, monohydrate (0.0163 g, 0.389 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated and acidified with 1M HCl then extracted with DCM (3X). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography EtOAc/Hex (0-100%) (eluted at 80%) to give **309** (87%). MS: (ESI+) 472.1

[00768] Example 220 N-(2-chlorophenyl)-N-methyl-8-(1H-pyrazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **310**

[00769] Following the procedure in Example 93, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide was coupled with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give **310**. MS (ESI) 436.1

[00770] Example 221 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-((R)-2-hydroxypropyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **311**

[00771] 2-(4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride and(R)-1-aminopropan-2-ol gave **311**. MS (ESI) 481.3

[00772] Example 222 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **312**

[00773] 2-(4-(2-Chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride and 2-aminoethanol gave **312**. MS (ESI) 467.3

[00774] Example 223 4-(2-chlorophenyl)-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4H-1,2,4-triazole **313**

[00775] Hydrogenation of 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole using 5% Pd on carbon in ethanol under 1 atmosphere of hydrogen gave **313** after filtration, concentration and purification by reverse-phase HPLC. MS (ESI) 380.1

[00776] Example 224 8-bromo-2-[4-(2-chloro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene **314**

[00777] To a solution of 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid ethyl ester from Example 21 (518 mg) in tetrahydrofuran (10 ml) was added a solution of sodium hydroxide (117 mg) in water (2 mL). Methanol (5 mL) was also added to aid dissolution. After 2 hours, the reaction mixture was acidified with HCl (2M) and the reaction mixture was then extracted with dichloromethane, dried ($MgSO_4$) and the solvent removed in vacuo to yield 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid.

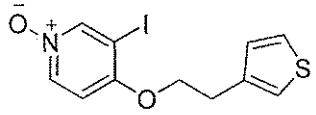
[00778] To a suspension of 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (396 mg) in dry dichloromethane (20 mL) was added oxalyl chloride (180 μL)

and DMF (1 drop). After 3 hours the solvent was removed in vacuo and to the residue was added acetonitrile (20 mL), 2-chloroaniline (140 μL) and sodium bicarbonate (111 mg). After 3 hours, water was added to the reaction mixture and the resulting precipitate was collected by filtration to yield 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-phenyl)-amide (467 mg).

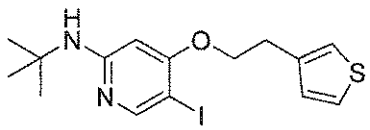
[00779] A mixture of 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-phenyl)-amide (260 mg), Lawesson's reagent (193 mg) and toluene (10 mL) was heated to reflux. After 5 hours, the reaction mixture was cooled and the precipitate was collected by filtration to yield the corresponding thioamide, 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carbothioic acid (2-chloro-phenyl)-amide (160 mg).

[00780] A mixture of 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carbothioic acid (2-chloro-phenyl)-amide (160 mg) , methanol (10 mL) and hydrazine hydrate (170 μL) was heated to reflux for 6 hours. The reaction mixture was then cooled and the solid collected by filtration. A mixture of this solid (144 mg) and triethyl orthoformate (5mL) was heated to 90 °C for 2 hours and then to 130 °C for 2 hours. The reaction mixture was then cooled and the solvent removed in vacuo and the residue purified using flash chromatography to yield **314** (55mg). NMR: (CDCl3): 3.32 (2H,t), 4.36 (2H, t), 6.96 (1H, dd), 7.11-7.16 (2H,m), 7.49-7.68 (4H,m), 8.30 (1H, s). MS: (ESI+) MH+ 461

[00781] Example 225 N-(2-chlorophenyl)-N-methyl-(8-amino-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide **315**

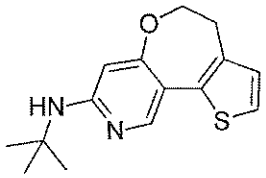


[00782] m-Chloroperbenzoic acid (1.55 g, 6.29 mmol) was added portionwise to a solution of 1.0 g (3.02 mmol) of 3-iodo-4-(2-(thiophen-3-yl)ethoxy)pyridine in 150 ml of methylene chloride. The mixture was stirred for 18 hours then mixed with 100 ml of 1 M aqueous sodium carbonate. The organic layer was separated and the aqueous one was extracted 2 times with 10 ml of methylene chloride. Combined organic extracts were washed with brine and dried over sodium sulfate. The solution was concentrated in vacuum to give 3-iodo-4-(2-(thiophen-3-yl)ethoxy)pyridine 1-oxide (1.01 g, 92%). MS: (ESI+) 348.0

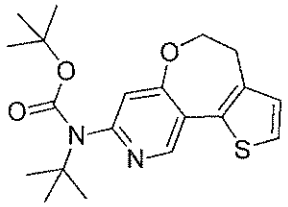


[00783] A solution of p-toluenesulfonic anhydride (1.47 g, 4.49 mmol) in 15 ml of chloroform was added dropwise to a stirred mixture of 0.78 g (2.25 mmol) of 3-iodo-4-(2-(thiophen-3-yl)ethoxy)pyridine 1-oxide and 1.18 ml (11.2 mmol) of tert-butylamine in 15 ml of

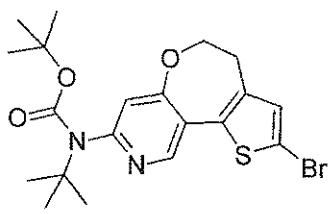
chloroform at 0 ^{0}C. After 30 minutes, the addition of the same quantities of p-toluenesulfonic anhydride and tert-butylamine was repeated to complete the reaction. The reaction mixture was concentrated and partitioned between 100 ml of diethylether and 1 M aqueous sodium carbonate. The aqueous layer was extracted with 50 ml of diethylether again and combined organic extracts were washed with water, brine, dried over sodium sulfate and concentrated in vacuum. The residue was purified by flash chromatography eluting with 10% of ethyl acetate in hexane to give N-tert-butyl-5-iodo-4-(2-(thiophen-3-yl)ethoxy)pyridin-2-amine (0.473 g (52%). ^{1}H NMR (400 MHz, CDCl3) δ 8.15 (s, 1H), 7.28 (dd, *J* = 3.0, 4.8, 1H), 7.18 (s, 1H), 7.12 (d, *J* = 4.9, 1H), 5.85 (s, 1H), 4.44 (s, 1H), 4.15 (t, *J* = 6.5, 2H), 3.18 (t, *J* = 6.5, 2H), 1.39 (s, 9H). MS: (ESI+) 403.2



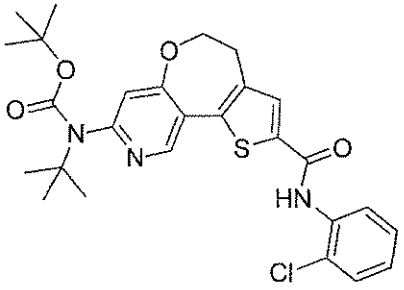
[00784] Following Scheme 4, N-tert-butyl-5-iodo-4-(2-(thiophen-3-yl)ethoxy)pyridin-2-amine was cyclized in the presence of palladium (II) acetate and triphenylphosphine to give N-tert-butyl-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-8-amine (42%). ^{1}H NMR (400 MHz, CDCl3) δ 8.44 (s, 1H), 7.04 (d, *J* = 5.2, 1H), 6.81 (d, *J* = 5.2, 1H), 6.07 (s, 1H), 4.59 (s, 1H), 4.35 – 4.29 (m, 2H), 3.21-3.07 (m, 2H), 1.42 (s, 9H). MS: (ESI+) 275.1



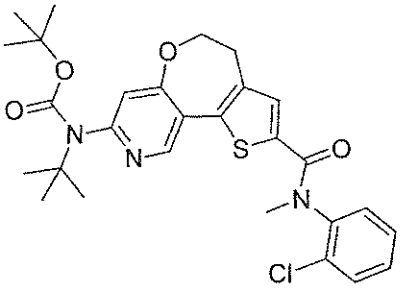
[00785] A mixture of N-tert-butyl-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-8-amine (115 mg, 0.42 mmol) and di-tertbutyldicarbonate (275 mg, 1.26 mmol) in 3 ml of tert-butyl alcohol was heated at 80 ^{0}C for 4 hours. The mixture was concentrated in vacuum, and the residue was purified by flash chromatography eluting with 10% ethyl acetate in hexane to give tert-butyl tert-butyl(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-8-yl)carbamate (120 mg, 76%). ^{1}H NMR (500 MHz, CDCl3) δ 8.80 (s, 1H), 7.26 (s, 1H), 7.23 (d, *J* = 5.1, 1H), 6.90 (d, *J* = 5.2, 1H), 6.69 (s, 1H), 4.39 (t, *J* = 4.8, 2H), 3.25 (t, *J* = 4.8, 2H), 1.40 (s, 9H), 1.37 (s, 9H). MS: (ESI+) 375.4



[00786] A solution of N-bromosuccinimide (59 mg, 0.33 mmol) in 1 ml of dimethylformamide was added dropwise to a solution of tert-butyl tert-butyl(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-8-yl)carbamate (120 mg, 0.32 mmol) in 2 ml of dimethylformamide (DMF). The reaction mixture was stirred for 18 hours, concentrated in vacuum and partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulfate and concentrated in vacuum to give tert-butyl 2-bromo-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-8-yl(tert-butyl)carbamate which was used in the next step without further purification. MS: (ESI+) 453.2



[00787] Following Scheme 4, tert-butyl 2-bromo-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-8-yl(tert-butyl)carbamate and 2-chlorophenylisocyanate were reacted to give tert-Butyl tert-butyl(2-(2-chlorophenylcarbamoyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-8-yl)carbamate (61%). MS: (ESI+) 528.2



[00788] Following Scheme 4, tert-butyl tert-butyl(2-(2-chlorophenylcarbamoyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-8-yl)carbamate, methyl iodide and sodium hydride were reacted to give tert-butyl tert-butyl(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-8-yl)carbamate (78%). MS: (ESI+) 542.3

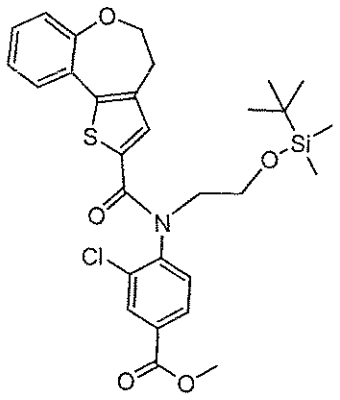
[00789] A solution of 0.10 g (0.185 mmol) of tert-butyl tert-butyl(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-8-yl)carbamate in 3 ml of trifluoroacetic acid was stirred at room temperature for 30 min and then heated at 70 ^{0}C for 45 min. The mixture was concentrated in vacuum the residue triturated with ethyl ether, the precipitate filtered out and washed with ethyl ether. The resulting trifluoroacetate salt was converted to a free base by partitioning between saturated aqueous sodium bicarbonate solution and ethyl acetate. Ethyl acetate extract was washed with water, brine , dried over sodium sulfate and concentrated to give **315** (46 mg, 63%). ^{1}H NMR (500 MHz, DMSO) δ 8.01 (s, 1H), 7.67

(d, J = 9.4, 1H), 7.63 (d, J = 8.6, 1H), 7.56 – 7.48 (m, 2H), 6.47 (s, 1H), 6.21 (s, 2H), 5.94 (s, 1H), 4.14 (s, 2H), 3.26 (s, 3H), 2.87 (s, 2H). MS: (ESI+) 386.1

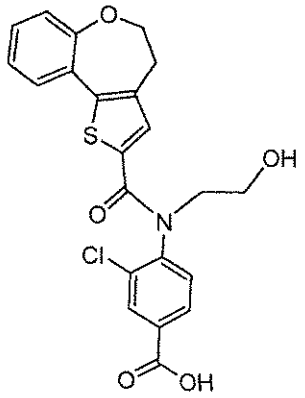
[00790] Example 226 N-(2-chlorophenyl)-N-methyl-(8-acetamino-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide **316**

[00791] A mixture of N-(2-chlorophenyl)-N-methyl-(8-amino-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide **315** (18 mg, 0.047 mmol) in 3 ml of acetic anhydride was heated at 75 ^{0}C for 45 min. The mixture was concentrated in vacuum, the residue redissolved in 3 ml of methanol and mixed with 0.3 ml of 28% aqueous ammonia. In 5 min the mixture was poured in 5 ml of water and extracted with ethyl acetate. The organic extract was washed with water, brine, dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography eluting with 50% ethyl acetate in hexane to give **316** (13 mg, 65%). ^{1}H NMR (500 MHz, DMSO) δ 10.59 (s, 1H), 8.35 (s, 1H), 7.71 – 7.62 (m, 3H), 7.58 – 7.49 (m, 2H), 6.42 (s, 1H), 4.25 (s, 2H), 3.27 (s, 3H), 2.93 (s, 2H), 2.08 (s, 3H). MS: (ESI+) 428.1

[00792] Example 227 N-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **317**



[00793] To a soln. of methyl 3-chloro-4-(2-(*tert*-butyldimethylsilyloxy)ethylamino)benzoate (1.3 g 3.78mmol) pretreated with 1M of sodium hexamethyldisilazine in THF (3.46 ml) in tetrahydofuran (12.2 ml) was added at room temperature 4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carbonyl chloride (1.00g, 3.79 mmol) portion-wise. The reaction mixture was stirred at room temperature under nitrogen for 1 hour. The reaction mixture was concentrated in vacuo and the residue taken into ethyl acetate and washed with water, then saline and dried (Na2SO4) to give 1.37 grams of crude methyl 4-(N-(2-(tert-butyldimethylsilyloxy)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoate. MS: (ESI+) = 572.1



[00794] A solution of methyl 4-(N-(2-(tert-butyldimethylsilyloxy)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)-3-chlorobenzoate (1.37 grams, 2.39 mmol) and lithium hydroxide (0.229 g, 0.68 mmol) in 5 mL of water and 20 mL of THF was stirred at room temperature to give the expected carboxylic acid as determined by LC/MS (59025-71). The reaction mixture was stripped of THF and diluted with water, and acidified with conc. HCl. This aqueous solution was extracted with ethyl acetate and the organics washed with water, washed with saline and concentrated in vacuo to a solid. This solid material was taken into 20 mL of THF and acetic acid was added (0.135 mL, 2. 4 mmol). Next, 1M TBAF in THF was added to the reaction mixture via syringe and the solution was stirred overnight at room temperature. The reaction mixture was then diluted with a large volume of ethyl acetate. This solution was washed with water, then saline and dried (Na2SO4), then concentrated in vacuo to a solid. The crude material was purified by MPLC on a 120 g silica column, eluting with 20–90% ethyl acetate/hexanes to 1 gram of 3-chloro-4-(N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid. Yield = 90% of theoretical. MS: (ESI+) = 443.1

[00795] To a solution of 3-chloro-4-(N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamido)benzoic acid (0.100 g, 0.225 mmol) in 1 mL of THF was added as a whole HATU (0.094 g, 0.248 mmol) and DIEA (0.078 mL, 0.450 mmol). This reaction mixture was allowed to stir at room temperature for 30 minutes. Next, *tert*-butyl piperazine-1-carboxylate (0.12 g, 0.22 mmol) was added to the reaction mixture and stirred at room temperature for 1 hour. The reaction mixture was taken into a large volume of ethyl acetate, washed with water, then saline and dried (Na_2SO_4). The organic was then conc. in vacuo to a solid residue and purified by RP-HPLC to give *tert*-butyl 4-(3-chloro-4-(*N*-(2-hydroxyethyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamido)benzoyl)piperazine-1-carboxylate.

[00796] A solution of *tert*-butyl 4-(3-chloro-4-(*N*-(2-hydroxyethyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamido)benzoyl)piperazine-1-carboxylate (0.04 g, 0.6 mmol) in 0.500 ml of DCM was treated with TFA (0.1 g, 1mmol) at room temperature with

TLC monitor for loss of starting material. The reaction was complete after 1 hour. The reaction mixture was conc. in vacuo to **317** as a solid, purified by RP-HPLC, Yield = 22% of theoretical. MS: (ESI+) = 512.5

[00797] Example 228 N-(2-chlorophenyl)-N-methyl-8-(3-methyl-1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **318**

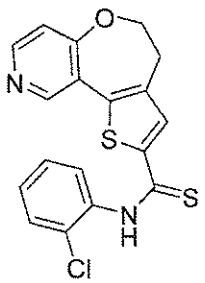
[00798] Following the procedure in Example 93, 8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide was coupled with 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give **318**. MS (ESI) 450.1

[00799] Example 229 5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-methylamine **319**

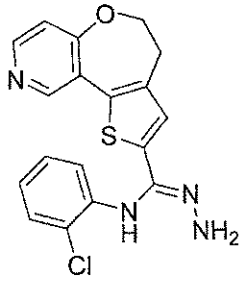
[00800] A mixture of 80 mg (0.3 mmol) of 9-bromo-6,7-dihydro-pyrido[3,2-b]thieno[2,3-d]oxepine, 78.3 (0.34 mmol), 2-cyanopyridine-5-boronic acid pinacole ester, and 10 mg (0.014 mmol) of bis(triphenylphosphine)palladium (II) chloride in 0.35 ml (0.35 mmol) of aqueous 1 M solution of sodium carbonate and 4 ml of acetonitrile was degassed and microwaved on 200 Wt at 140^{0}C for 30 min. the reaction mixture was filtered through celite and partitioned between ethyl acetate and water. The organic layer was washed with water, brine dried over sodium sulfate and concentrated in vacuum. The residue was purified on a 4 g silica column eluting with 10% of methanol in dichloromethane to give 5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-nitrile. Yield 27 mg (30%). MS: (ESI+) 306.1

[00801] A solution of 25 mg (0.082 mmol) of 5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-nitrile in 3 ml of acetic acid and 3 ml of tetrahydrofuran was subjected to hydrogenation over 40 mg of 5% palladium on charcoal for 4 hours. The catalyst was filtered off, the mother liquor was concentrated in vacuum. The residue was triturated with ethyl ether afforded a precipitate which was collected and dried in vacuum to give **319**. Yield 24 mg (79%). MS: (ESI+) 310.0. ^{1}H NMR (400 MHz, DMSO) δ 8.82 (s, 1H), 8.25 (dd, J = 4.4, 1.1, 1H), 8.06 (dd, J = 8.1, 1.9, 1H), 7.50 (d, J = 9.9, 2H), 7.42 (dd, J = 8.1, 1.1, 1H), 7.23 (dd, J = 8.1, 4.5, 1H), 4.35 (t, J = 4.6, 1H), 3.86 (s, 2H), 3.24 (t, J = 4.6, 2H).

[00802] Example 230 3-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole **320**



[00803] Following Scheme 4, 2-bromo-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin and 2-chlorophenylisothiocyanate were reacted to give N-(2-chlorophenyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine-2-carbothioamide (66%). MS: (ESI+) 357.0



[00804] Hydrazine (0.32 ml, 10 mmol) was added to a suspension of N-(2-chlorophenyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine-2-carbothioamide (90 mg, 0.2 mmol) in 3 ml of methanol and the reaction mixture was stirred for 24 hour . The precipitate was filtered, washed with methanol and dried in vacuum to give N-(2-chlorophenyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine-2-carbohydrazonamide (94 mg, 90%). MS: (ESI+) =371.1

[00805] A mixture of N-(2-chlorophenyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine-2-carbohydrazonamide (44 mg, 0.12 mmol) and 3 ml of triethylorthoformate was heated at 85 ^{0}C for 4 hours. The mixture was concentrated in vacuum and triturated with diethylether. The precipitate was collected, washed with diethylether and purified by flash chromatography eluting with 60% of ethyl acetate in hexane to give **320** (17 mg, 38%). MS: (ESI+) 381.1

[00806] Example 231 3-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one **321**

[00807] A mixture of N-(2-chlorophenyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine-2-carbohydrazonamide (42 mg, 0.11 mmol) from Example 230 and 92 mg (0.57 mmol) of N,N-carbonyldiimidazole in 3 ml of dimethylformamide was heated at 65 ^{0}C for 18 hours. The mixture was concentrated in vacuum and triturated with diethylether. The precipitate was collected, washed with ethyl ether and purified by flash chromatography eluting with 5% of methanol in methylene chloride to give **321** (14 mg, 31%). MS: (ESI+) 397.0

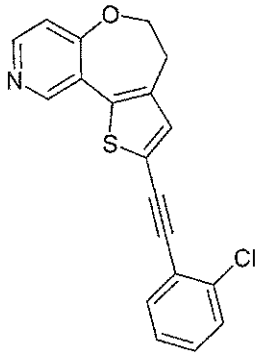
[00808] Example 232 N-(4-carbamoyl-2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **322**

[00809] To a solution of 3-chloro-4-(*N*-(2-hydroxyethyl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-2-carboxamido)benzoic acid, from Example 227, (0.08g, 0.20 mmol) in 72 mL of THF was added as a whole HATU (0.082 g, 0.22 mmol) and DIEA (0.12 mL, 0.72 mmol). This reaction mixture was allowed to stir at room temperature for 30 minutes. Next, ammonium chloride (0.12 g, 0.22 mmol) was added to the reaction mixture and stirred at room temperature for 1 hour. The reaction mixture was taken into a large volume of ethyl acetate, washed with

water, then saline and dried (Na2SO4). The organic was then concentrated in vacuo to give **322** as a solid residue, purified by RP-HPLC. Yield = 25% of theoretical. MS: (ESI+) = 442.1

[00810] Example 233 N2-(2,4-dichlorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **323**

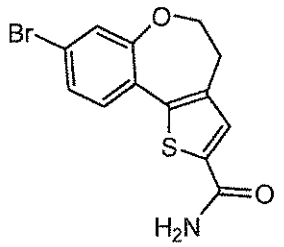
[00811] Example 234 4-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)-5-(2-chlorophenyl)-2H-1,2,3-triazole **324**



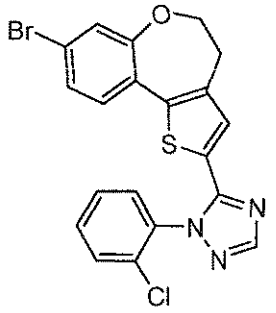
[00812] A mixture of 2-bromo-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine (140 mg, 0.5 mmol) from Example 72, 1-chloro-2-ethynylbenzene, 18 mg (0.025 mmol) of bistriphenylphosphinepalladium(II) chloride and 1 ml (7.17 mmol) of triethylamine in 4 ml of acetonitrile was degassed. Copper (I) iodide (2.4 mg, 0.012 mmol) was then added and the mixture was heated at 85 ^{0}C for 3 hours. The mixture was mixed with 20 ml of water and extracted with 10 ml of ethyl acetate twice. The combined extracts were washed with 1% aqueous ammonia, water, brine and dried over sodium sulfate. The solution was concentrated in vacuum, the residue purified by flash chromatography eluting with 30% ethyl acetate in hexane to give 2-((2-chlorophenyl)ethynyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine (137 mg, 81%). MS: (ESI+) 338.1

[00813] A mixture of 68 mg (0.2 mmol) of 2-((2-chlorophenyl)ethynyl)-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepine and 52 mg (0.8 mmol) of sodium azide in 4 ml of dimethylsulfoxide was heated at 90 ^{0}C for 36 hours. Water (20 ml) was added to the mixture and extracted 6 times with 10 ml of ethyl acetate. The combined organic extracts were washed with water, brine and dried over sodium sulfate. The solvent was removed in vacuum and the crude product was recrystallized from ethyl acetate to give **324** (14 mg, 18%). ^{1}H NMR (400 MHz, DMSO) δ 8.68 (s, 1H), 8.24 (d, J = 5.5, 1H), 7.73 – 7.46 (m, 4H), 6.98 (d, J = 5.5, 1H), 6.77 (s, 1H), 4.31 (t, J = 4.7, 2H), 3.08 (t, J = 4.7, 2H). MS: (ESI+) 381.1

[00814] Example 235 2-(1-(2-chlorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile **325**

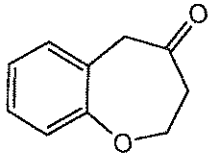


[00815] 8-Bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide was suspended in dry toluene and the reaction mixture treated with dimethylformamide dimethylacetal. The whole was heated at 90 °C for about 8 h, cooled to room temperature and concentrated. Crude 1H NMR indicated clean conversion to the anticipated acylamidine intermediate. (2-Chlorophenyl)hydrazine in acetic acid and water was added to the crude residue in one portion. The whole was sealed and heated at 95 °C to give a bright yellow suspension. LCMS at 8 h indicated significant product formation. The reaction mixture was concentrated, diluted with dichloromethane and saturated sodium bicarbonate and extract with dichloromethane. The combined organics were washed with brine, dried over sodium sulfate, concentrated and the crude residue purified by flash column chromatography to give 5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2-chlorophenyl)-1H-1,2,4-triazole.



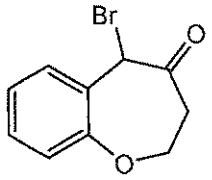
[00816] Following the procedure in Example 53, 5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2-chlorophenyl)-1H-1,2,4-triazole was reacted with CuCN in DMF to give **325** as a colorless solid after purification by reverse phase HPLC. MS: (ESI+) 405.1

[00817] Example 236 4,5-dihydro-6-oxa-1-thia-3-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-phenyl)-methyl-amide **326**

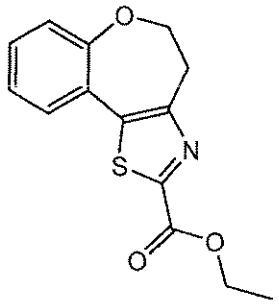


[00818] To a solution of 4-chromanone (1 eq, 16.8 mmol, 2.5g) in anhydrous diethyl ether (70 ml) at 0°C, boron trifluoride diethyl etherate (1.1 eq, 18.6 mmol, 2.4 ml) was added added dropwise followed by the dropwise addition of 2M TMS diazomethane in ether (1.1 eq, 18.6

mmol, 9.2 ml), and stirred at 0°C under N_2 for 1hr. Saturated $NaHCO_3$ aq was carefully added (100ml) and the reaction extracted into diethyl ether, the organic layer was then washed with water before drying over $MgSO_4$, filtering and absorbing onto silica. The crude material was then purified on the ISCO companion system running a gradient from 0% ethyl acetate/petrol to 20% ethyl acetate/petrol. This gave 2,3-dihydro-5H-benzo[b]oxepin-4-one as a yellow oil (1.15g, yield 42%).



[00819] To a solution of 2,3-dihydro-5H-benzo[b]oxepin-4-one (1 eq, 1.6 mmol, 260 mg,), in anhydrous diethyl ether (10ml), bromine was added dropwise (1.1 eq, 1.76 mmol, 90ul), and the reaction allowed to stir for an hour. The reaction was absorbed onto silica and purified on the ISCO companion running a gradient from 0% ethyl acetate/petrol to 15% ethyl acetate/petrol, with the product seen at 9% ethyl acetate. This gave 5-bromo-2,3-dihydro-5H-benzo[b]oxepin-4-one as an oil (270 mg, yield 70%).



[00820] A solution of 5-bromo-2,3-dihydro-5H-benzo[b]oxepin-4-one (1 eq, 4.1 mmol, 1g), and ethyl thiooxamate (1.5 eq, 6.15 mmol, 818 mg), in ethanol was refluxed for 16hrs. Reaction cooled and absorbed onto silica and purified on the ISCO companion running a gradient from 0% ethyl acetate/petrol to 40% ethyl acetate/petrol, to give 4,5-dihydro-6-oxa-1-thia-3-aza-benzo[e]azulene-2-carboxylic acid ethyl ester as an oil (530 mg, yield 47%).

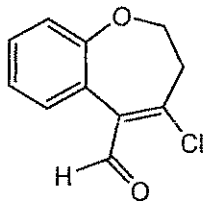
[00821] A solution of 4,5-dihydro-6-oxa-1-thia-3-aza-benzo[e]azulene-2-carboxylic acid ethyl ester (1 eq, 1.9 mmol, 530 mg), and sodium hydroxide (5 eq, 9.6 mmol, 385 mg), in THF (5 ml) and water (5ml) was allowed to stir at RT for 3hrs. Reaction concentrated in vacuo and the solid washed with water to give 4,5-dihydro-6-oxa-1-thia-3-aza-benzo[e]azulene-2-carboxylic acid (290 mg, yield 58%).

[00822] To a suspension of 4,5-dihydro-6-oxa-1-thia-3-aza-benzo[e]azulene-2-carboxylic acid (1 eq, 0.38 mmol, 101 mg) in anhydrous DCM (3 ml), 1 drop of DMF was added, followed by 2M oxalyl chloride in DCM (1.7 eq, 0.65 mmol, 330 ul) dropwise. Effervescence was seen

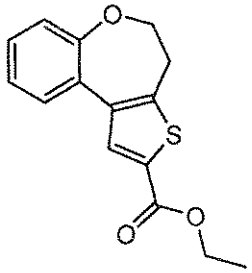
and the reaction was stirred at room temperature for 40 mins before evaporating in vacuo. The crude material was dissolved in DCM (3 ml) and 2-chloro-N-methyl aniline (2 eq, 0.76 mmol, 94 ul) was added. The reaction was stirred at room temperature for 16hr and extracted into DCM, washed with aq K_2CO_3, the organic layer dried over MgSO4, filtered, and purified on silica (ISCO, gradient 0% ethyl acetate/petrol to 25% ethyl acetate/petrol) to give **326** as a white solid (42 mg, yield 30%). 1H NMR DMSO, 2.89-2.92 (2H, m), 3.43 (3H, s), 4.23 (2H, br. m), 7.02 (1H, d, J = 8.4), 7.08 (1H, t, J = 7.6), 7.26 (1H, t, J = 8), 7.38-7.41 (2H, m), 7.48-7.51 (2H, m), 7.58 (1H, d, J = 8.4). MS: (ESI+): MH+ 371, purity > 95%.

[00823] Example 237 N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[3,2-d]oxepine-2-carboxamide **327**

[00824] To a solution of 4-chromanone (9.54 g, 64.3 mmol) in diethyl ether at 0 °C was slowly added boron trifluoride diethyl etherate (16.3ml, 128.6mmol), followed by the dropwise addition of 2M $TMSCHN_2$ in diethyl ether. The mixture was allowed to stir for 1 hour at 0 °C before diluting with sat. sodium bicarbonate solution and diethyl ether. The organic phase was dried, concentrated, and purified on silica to give 2,3-dihydro-5H-benzo[b]oxepin-4-one.



[00825] Phosphorus oxychloride (1.4 ml, 15.2 mmol) was added dropwise to anhydrous DMF (5 ml) at 0 °C. After 30 minutes a solution of 2,3-dihydro-5H-benzo[b]oxepin-4-one (980 mg, 6.04 mmol) in anhydrous DMF (5ml) was added dropwise and this was allowed to stir at room temperature for 2 days. The reaction mixture was then added to ice water, and the ice allowed to melt before extracting into ethyl acetate and washing with water and brine to give 4-chloro-2,3-dihydro-benzo[b]oxepine-5-carbaldehyde.

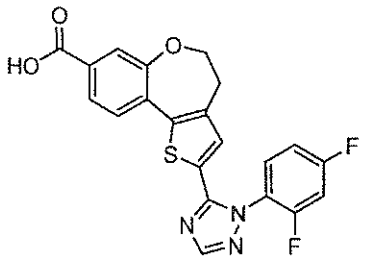


[00826] To a solution of 4-chloro-2,3-dihydro-benzo[b]oxepine-5-carbaldehyde (605 mg, 5.8 mmol) in dimethyl formamide (8 ml) at 0 °C, was added ethyl 2-mercaptoacetate (640 µl, 5.8 mmol) and potassium carbonate (800 mg, 5.8 mmol). The reaction mixture was stirred at room temperature for 30 minutes and then at 70 °C for 2 hours. The reaction mixture was cooled and

diluted with water and ethyl acetate, and the organic phase was washed with brine, dried ($MgSO_4$), and concentrated *in-vacuo*. Purification on silica gave 4,5-dihydro-6-oxa-3-thia-benzo[e]azulene-2-carboxylic acid ethyl ester.

[00827] 4,5-Dihydro-6-oxa-3-thia-benzo[e]azulene-2-carboxylic acid ethyl ester was hydrolyzed to its corresponding carboxylic acid to give 4,5-dihydro-6-oxa-3-thia-benzo[e]azulene-2-carboxylic acid, which was coupled with 2-chloro-N-methylaniline. Purification of the crude product on silica gave **327**. 1H NMR (400MHz, CDCl3): 3.12 (2H, t), 3.33 (3H, s), 4.22 (2H, t), 9.91-6.96 (2H, m), 7.05-7.09 (1H, m), 7.19-7.24 (1H, m). 7.31-7.36 (3H, m), 7.45-7.49 (1H, m). MS: (ESI+) MH 370

[00828] Example 238 2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **328**



[00829] Following the procedures in Examples 47 and 235, 2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid was reacted with ammonium chloride, HATU and DIPEA in THF to give **328** as a colorless solid after reverse phase HPLC. MS: (ESI+) 425.0

[00830] Example 239 2-(4-(2-chloro-4-(methylcarbamoyl)phenyl)-4H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **329**

[00831] Following the procedures in Examples 47 and 235, 2-(4-(4-carboxy-2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid was reacted with excess methylamine, HATU and DIPEA in THF to give **329** as a colorless solid after reverse phase HPLC. MS: (ESI+) 494.1

[00832] Example 240 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **330**

[00833] Following the procedures in Examples 47 and 235, 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid was reacted with methylamine, HATU and DIPEA in THF to give **330** as a colorless solid after reverse phase HPLC. MS: (ESI+) 453.0

[00834] Example 241 N-(2-acetamidoethyl)-2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **331**

[00835] Following the procedures in Examples 47 and 235, 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid was reacted with N-(2-aminoethyl)acetamide, HATU and DIPEA in THF to give **331** as a colorless solid after reverse phase HPLC. MS: (ESI+) 524.0

[00836] Example 242 N-(2-amino-2-methylpropyl)-2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **332**

[00837] Following the procedures in Examples 47 and 235, 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid was reacted with 2-methylpropane-1,2-diamine, HATU and DIPEA in THF to give **332** as a colorless solid after reverse phase HPLC. MS: (ESI+) 510.0

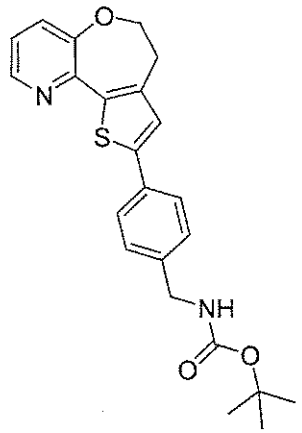
[00838] Example 243 N8-(2-acetamidoethyl)-N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **333**

[00839] Following the procedures in Examples 47 and 235, 2-((2-chloro-4-(dimethylcarbamoyl)phenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid was reacted with N-(2-aminoethyl)acetamide, HATU and DIPEA in THF to give **333** as a colorless solid after reverse phase HPLC. MS: (ESI+) 569.1

[00840] Example 244 N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-(2-(dimethylamino)ethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **334**

[00841] Following the procedures in Examples 47 and 235, 2-((2-chloro-4-(dimethylcarbamoyl)phenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid was reacted with N1,N1-dimethylethane-1,2-diamine, HATU and DIPEA in THF to give **334** as a colorless solid after reverse phase HPLC. MS: (ESI+) 555.2

[00842] Example 245 5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)benzen-2-methylamine **335**



[00843] Following Scheme 5, 2-bromo-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine and 4-(N-Boc-aminomethyl)-phenylboronic acid were reacted to give tert-butyl 4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)benzylcarbamate. MS: (ESI+) = 409.1. Hydrogen chloride in dioxane (4 ml, 4 N) was added to a solution of 67 mg (0.16 mmol) of tert-butyl 4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)benzylcarbamate in 6 ml of methylene chloride and the mixture was stirred for 2 hours. The precipitate was collected, washed with methylene chloride and ethyl ether and dried in vacuum to give **335** (34 mg, 55%). MS: (ESI+) 309.1.

[00844] Example 246 9-cyano-N-(2,4-dichlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **336**

[00845] To a solution of 9-cyano-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid (300 mg) in dichloromethane (10 mL) was added DMF (1 drop) and oxalyl chloride (0.165 mL) and the reaction stirred at room temperature for 30 min. The solvent was then reduced in vacuo and the residue redissolved in acetonitrile (10mL). To this solution was added 2,4-dichloro-N-methylaniline (0.16 mL) and potassium carbonate (308 mg) and the reaction stirred at room temperature for 16 h. The mixture was partitioned between water (40 mL) and ethyl acetate (30 mL). The organic layer was dried (Na_2SO_4), reduced in vacuo and purified on silica to give **336**. (CDCl3): 3.11 (2H, t), 3.39 (3H, s), 4.32 (2H, t), 6.91 (1H, s), 7.07 (1H, d), 7.32 (1H, d), 7.37-7.44 (2H, m), 7.58 (1H, s), 7.79 (1H, s). MH+ 429:431:433 (3:2:1)

[00846] Example 247 3-(8-(pyrazol-4-yl)-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole **337**

[00847] A mixture of 8-bromo-2-[4-(2-chloro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene **314** was reacted with 4,4,5,5-tetramethyl-2-(1H-pyrazol-4-yl)-1,3,2-dioxoborolane using Suzuki coupling reaction conditions to yield **337**. NMR: (CDCl3): 3.38(2H,t), 4.39(2H, t), 6.96 (1H, dd), 7.18 (1H, d), 7.28 (1H, d), 7.51-7.54 (2H,m), 7.61-7.66 (2H, m), 7.85 (2H, s), 8.30 (1H, s). MS: (ESI+) MH+ 447

[00848] Example 248 N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-(2-hydroxyethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **338**

[00849] Following the procedures in Examples 47 and 235, 2-((2-chloro-4-(dimethylcarbamoyl)phenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid was reacted with 2-aminoethanol, HATU and DIPEA in THF to give **338** as a colorless solid after reverse phase HPLC. MS: (ESI+) 528.0

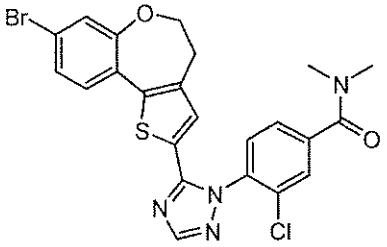
[00850] Example 249 N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-isopropyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **339**

[00851] Following the procedures in Examples 47 and 235, 2-((2-chloro-4-(dimethylcarbamoyl)phenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid was reacted with isopropylamine, HATU and DIPEA in THF to give **339** as a colorless solid after reverse phase HPLC. MS: (ESI+) 526.1

[00852] Example 250 N8-(2-amino-2-methylpropyl)-N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **340**

[00853] Following the procedures in Examples 47 and 235, 2-((2-chloro-4-(dimethylcarbamoyl)phenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid was reacted with 2-methylpropane-1,2-diamine, HATU and DIPEA in THF to give **340** as a colorless solid after reverse phase HPLC. MS: (ESI+) 555.3

[00854] Example 251 2-(1-(2-chloro-4-(dimethylcarbamoyl)phenyl)-1H-1,2,4-triazol-5-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **341**



[00855] Following the procedure in Example 89 for carbonylative amination, 4-(5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-1-yl)-3-chloro-N,N-dimethylbenzamide was reacted with methylamine and molybdenum hexacarbonyl to give **341** after reverse phase HPLC. MS: (ESI+) 508.1

[00856] Example 252 4-(5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-1-yl)-3-chloro-N,N-dimethylbenzamide **342**

[00857] Following the procedure from Example 235, 8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide was reacted with 3-chloro-4-hydrazinyl-N,N-dimethylbenzamide in acetic acid to give **342** as a colorless solid after purification by flash column chromatography (50-100% ethyl acetate in hexanes). MS: (ESI+) 531.0

[00858] Example 253 N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **343**

[00859] 3-Chloro-4-methylamino-benzonitrile was prepared by bubbling a stream of methylamine gas was bubbled through a solution of 3-chloro-4-fluorobenzonitrile in acetonitrile. A mixture of 3-chloro-4-methylamino-benzonitrile (1.29g) was heated to reflux in 2M sodium hydroxide solution (43mL). After 4 hours the reaction mixture was cooled, and then acidified

(HCl, 2N) carefully to pH 5, resulting in a white precipitate which was collected by filtration to yield 3-chloro-4-methylamino-benzoic acid (1.10g)

[00860] To 3-chloro-4-methylamino-benzoic acid (387mg) in dry N. N-dimethylformamide (10mL) was added carbonyl diimidazole (440mg). After one hour, dimethylamine. HCl (221mg) and triethylamine (0.38 mL) were added. The reaction mixture was stirred overnight, then diluted with ethyl acetate, washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. Purification using flash chromatography yielded 3-chloro-N,N-dimethyl-4-methylamino-benzamide.

[00861] Compound **343** was prepared from the corresponding acid (described previously) and 3-chloro-N,N-dimethyl-4-methylamino-benzamide using General Procedure B. NMR: (CDCl3): 3.10-3.20 (8H, m), 3.39 (3H,s), 4.31 (2H, t), 7.02 (1H, d), 7.19 (1H, s), 7.42 (1H,d), 7.47 (2H, s), 7.63 (2H, s). MS ESI+ 420 (MH+)

[00862] Example 254 2-(9-cyano-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene)-N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-methyl-carboxamide **344**

[00863] To a solution of 7-bromo-3,4-dihydro-2H-benzo[b]oxepin-5-one (700 mg) in diethyl ether (20 mL) at 0 °C was added bromine (0.14 mL) dropwise and the reaction was stirred at room temperature for 16 h. The reaction was then quenched with aqueous sodium thiosulfate solution (30 mL) and the product extracted into diethyl ether (2 x 30 mL). The combined organics were dried ($MgSO_4$), reduced in vacuo and purified on silica to give 4,7-dibromo-3,4-dihydro-2H-benzo[b]oxepin-5-one.

[00864] To a solution of 4,7-dibromo-3,4-dihydro-2H-benzo[b]oxepin-5-one (852 mg) in ethanol (20 mL) was added ethyl thiooxamate (1.06 g) and the reaction heated at reflux for 4 days. After cooling to room temperature, the solid was filtered, washed with diethyl ether and air-dried to give 9-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid ethyl ester.

[00865] A mixture of 9-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid ethyl ester (500 mg), potassium ferrocyanide (dried, 104 mg), copper (I) iodide (27 mg) and 1-butylimidazole (0.37 mL) in toluene (3 mL) was reacted in the microwave at 160 °C for 4 h. The mixture was then partitioned between dichloromethane (30 mL) and water (20 mL). The organic layer was dried ($MgSO_4$), reduced in vacuo and purified on silica to give 9-cyano-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid ethyl ester.

[00866] To a suspension of 9-cyano-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid ethyl ester (80 mg) in THF (6 mL) and ethanol (3 mL) was added sodium hydroxide solution (18 mg in 3mL of water) and the reaction stirred at room temperature for 16 h. The reaction was then acidified with 2M hydrochloric acid and the resulting solid was filtered

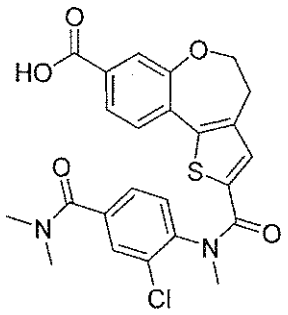
and air-dried to give 9-cyano-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid.

[00867] To a solution of 9-cyano-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (72 mg) in dichloromethane (10 mL) and DMF (1 drop) was added oxalyl chloride (0.04 mL) and the reaction stirred at room temperature for 3 h. The solvent was then reduced in vacuo and the residue redissolved in acetonitrile (10 mL). Sodium hydrogen carbonate (24 mg) and 3-chloro-N-methyl-4-methylamino-benzamide (58 mg) were added and the reaction stirred at room temperature for 16 h. Water (20 mL) was added and the product extracted into ethyl acetate (2 x 20 mL). The organics were dried ($MgSO_4$), reduced in vacuo and purified on silica to give **344**. NMR: ($CDCl_3$): 2.95 (3 H, d, J 4.8, Me), 3.26-3.29 (2 H, m), 3.42 (3 H, s, Me), 4.21-4.36 (2 H, m), 6.85-6.86 (1 H, m, NH), 6.94 (1 H, d, J 8.4, Ar), 7.29 (1 H, dd, J 8.4 and 2.1, Ar), 7.43 (1 H, d, J 8.1, Ar), 7.54 (1 H, d, J 2.0, Ar), 7.76 (1 H, dd, J 8.1 and 1.8, Ar) and 7.93 (1 H, d, J 1.7, Ar)

[00868] Example 255 2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **345**

[00869] Example 256 N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-isobutyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **346**

[00870] Example 257 N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-ethyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **347**



[00871] 2-((2-Chloro-4-(dimethylcarbamoyl)phenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid (0.15 g, 0.31 mmol) was dissolved in $SOCl_2$ (10 mL). The solution was heated at 90-100 °C for 3 hours. Removal of the rest $SOCl_2$ gave the crude product. A solution of the crude acid chloride in THF (12 mL) was treated with a solution of ethanamine (0.14 g, 3.1 mmol) and Pyridine (0.3 mL) in THF (8 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and stirred overnight. Concentrated to remove THF to afford the crude product, it was purified by preparative TLC to obtain **347** (48.5 mg, 31%). ESI-MS: 512. ^1H NMR ($CDCl_3$, 400 MHz) : δ7.59 (s, 1H, ArH), 7.44- 7.32 (m, 5H, ArH), 6.95 (s, 1H, =CH), 6.12 (s, 1H, NH), 4.23 (t, J= 5.0 Hz, 2H, CH_2), 3.51- 3.44 (m, 2H,

CH_2), 3.39 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 3.05 (t, J= 5.0 Hz, 2H, CH_2), 3.02 (s, 3H, CH_3), 1.24 (t, J= 7.2 Hz, 3H, CH_3).

[00872] Example 258 N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-isobutyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **348**

[00873] Following Example 133, compound **348** was prepared with isobutylamine. Yield: 25%. ESI-MS: 540. ^{1}H NMR ($CDCl_3$, 400 MHz): δ7.59 (s, 1H, NH), 7.45- 7.26 (m, 5H, ArH), 6.94 (s, 1H, ArH), 6.17 (d, J= 4.0 Hz, 1H, ArH), 4.24 (t, J= 4.8 Hz, 2H, CH_2), 3.39 (s, 3H, CH_3), 3.28 (t, J= 6.0 Hz, 2H, CH_2), 3.13 (s, 3H, CH_3), 3.06- 3.02 (m, 5H, CH_2, CH_3), 1.91- 1.85 (m, 1H, CH), 0.97 (d, J= 2.8 Hz, 6H, $C(CH_3)_2$)

[00874] Example 259 5-(3-methylcarbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-amine **349**

[00875] Following the procedures for **454**, compound **349** was prepared with 9-bromo-6,7-dihydro-pyrido[3,2-b]thieno[2,3-d]oxepine-3-carboxylic acid methylamide and 2-aminopyridine-5-boronic acid pinacole ester. MS: (ESI+) 353.0

[00876] Example 260 4-(3-methylcarbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2-chlorophenyl)-2H-1,2,3-triazole **350**

[00877] Example 261 N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **351**

[00878] Following Example 257, the acid chloride of 2-((2-Chloro-4-(dimethylcarbamoyl)phenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid and ammonia gave **351**. Yield: 31%. ESI-MS: 484. ^{1}H NMR ($CDCl_3$, 400 MHz) : δ7.60 (s, 1H, NH), 7.47- 7.37 (m, 5H, ArH), 6.94 (s, 1H, ArH), 6.10 (br, 1H, 0.5 NH_2), 5.62 (br, 1H, 0.5 NH_2), 4.24 (s, 2H, CH_2), 3.39 (s, 3H, CH_3), 3.13- 3.02 (m , 8H, CH_2, $2CH_3$).

[00879] Example 262 N8-(2-aminoethyl)-N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide **352**

[00880] Following Example 133, compound **352** was prepared with 1,2-diaminoethane. Yield: 28%. ESI-MS: 527. ^{1}H NMR ($CDCl_3$, 400 MHz): δ7.66- 7.56 (m, 2H, 2NH), 7.40- 7.26 (m, 5H, ArH), 6.80 (s, 1H, =CH), 4.10 (s, 2H, CH_2), 3.58 (s, 3H, CH_3), 3.38- 2.93 (m, 13H, $2CH_2$, $3CH_3$)

[00881] Example 263 N-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **353**

[00882] Compound **353** was prepared using the standard amide coupling conditions to give a pale yellow solid (80 mg, 10 %). δ_H (400 MHz, $CDCl_3$) 1.30 (d, J = 6.2, 3H), 2.37 (m, 1H), 3.11 (t, J = 4.7, 2H) 3.28 (m, 1H), 3.42 (s, 3H), 3.78 (m, 1H), 4.09 (m, 1H), 4.31 (t, J =

4.9H, 2H), 6.69 (m, 1H), 7.06 (m, 2H), 7.41 (dd, 1H), 7.47 (d, J = 8.02, 1H), 7.68 (s, 1H), 7.80 (m, 1H), 8.02 (m, 1H). $[M + H]^+$ (406.07).

[00883] Example 264 3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole **354**

[00884] Reaction of 2-chloroaniline with 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carbonyl chloride (prepared from the corresponding carboxylic acid using oxalyl chloride with catalytic N, N-dimethylformamide) yielded 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid (2-chloro-phenyl)-amide.

[00885] A mixture of 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid (2-chloro-phenyl)-amide (235 mg) and Lawesson's reagent (175 mg) was heated to reflux in o-xylene (10 mL). After heating overnight the reaction mixture was cooled, and ether and hexane were added carefully resulting in the corresponding thioamide precipitating as an orange solid which was collected by filtration (196 mg). A mixture of 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carbothioic acid (2-chloro-phenyl)-amide (196mg), methanol (10mL) and hydrazine hydrate (0.21mL) was heated to reflux. After 5 hours the reaction mixture was cooled, and the resulting precipitate was collected by filtration. The precipitate (99mg) was then heated to 90°C in trimethylorthoformate (5mL). After 22 hours the reaction mixture was cooled, the volatiles were removed in vacuo and the residue was purified using flash chromatography to yield **354**. NMR: (CDCl3): 3.10 (2H,t), 4.30 (2H, t), 6.85-6.90 (2H, d), 7.25 (1H,dd), 7.46-7.72 (5H,m), 8.25 (1H,s). MS. ESI+ 460 (MH+)

[00886] Example 265 2-(4-(2-chloro-4-fluorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carbonitrile **355**

[00887] A microwave tube was charged with 3-(9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-4-(2-chloro-4-fluoro-phenyl)-4H-[1,2,4]triazole (0.57 g; 1.2 mmol), $K_4[Fe(CN)_6]$ (101 mg; 0.24 mmol), CuI (23 mg; 0.12 mmol), 1-butylimidazole (0.32 ml; 2.4 mmol) and toluene (5 ml). The mixture was flushed with argon and heated in a microwave at 160 °C for 4 h. LCMS shows approx. 40 % conversion so the same amount of $K_4[Fe(CN)_6]$, CuI and 1-butylimidazole was added again and reaction mixture heated in a microwave at 170 °C for a further 4 h. The reaction mixture was partitioned between CH_2Cl_2 and water, the organic layer was dried (Na_2SO_4) and purified by ISCO then prep. LCMS to give **355** as a white solid (154 mg; 30 %). δ_H (400 MHz, $CDCl_3$) 3.19 (t, J = 5.2, 2H), 4.36 (t, J = 5.2, 2H), 7.08-7.11 (m, 2H), 7.23-7.32 (m, 1H), 7.43-7.52 (m, 3H), 7.81 (d, J = 2.0, 1H), 8.23 (s, 1H). $[M+H]^+$: 423

[00888] Example 266 9-bromo-N-(2,4-dichlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **356**

[00889] To a solution of 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid (911 mg) in dichloromethane (20 mL) and DMF (1 drop) was added oxalyl chloride (0.42 mL) and the reaction stirred at room temperature for 3 h. The solvent was then reduced in vacuo and the residue redissolved in acetonitrile. Sodium hydrogen carbonate (259 mg) and 2,4-dichloro-N-methylaniline (546 mg) were added and the reaction stirred at room temperature for 16h. Water (20 mL) was added and the product extracted into ethyl acetate (2 x 20 mL). The organics were dried ($MgSO_4$), reduced in vacuo and purified on silica to give **356**. NMR: ($CDCl_3$): 2.95-2.98 (2 H, m), 3.29 (3 H, s, Me), 4.13-4.16 (2 H, m), 6.72 (1 H, s, Ar), 6.78 (1 H, d, J 8.6, Ar), 7.16 (1 H, dd, J 8.6 and 2.3, Ar), 7.22 (1 H, d, J 8.5, Ar), 7.29 (1 H, dd, J 8.4 and 2.2, Ar) and 7.48-7.52 (1 H, m, Ar)

[00890] Example 267 N-(2-chloro-4-cyanophenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **357**

[00891] 3-Chloro-4-methylamino-benzonitrile was prepared by bubbling a stream of methylamine gas was bubbled through a solution of 3-chloro-4-fluorobenzonitrile in acetonitrile. Compound **357** was prepared from the corresponding acid (described previously) and 3-chloro-4-methylamino-benzonitrile using General Procedure B. NMR:(CDCl3): 3.05 (2H, t), 3.39 (3H,s), 4.31 (2H, t), 6.80 (1H, s), 7.05(1H, d), 7.42-7.51 (2H, m), 7.70 (1H, dd), 7.80 (1H, s), 7.88 (1H, s). Analytical trace shows MH+ 420

[00892] Example 268 N-(2-chloro-4-(trifluoromethyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **358**

[00893] Compound **358** was prepared using the standard amide coupling conditions to give an off-white solid (94 mg, 37 %). δ_H (400 MHz, $CDCl_3$) 3.08 (t, 2H), 3.43 (s, 3H), 4.31 (t, 2H), 8.84 (s, 1H), 7.06 (d, 1H), 7.43 (dd, 1H), 7.52 (d, 1H), 7.67 (d, 1H), 7.77 (s, 1H), 7.84 (s, 1H). $[M + H]^+$ (504.00).

[00894] Example 269 N-(2,4-dichlorophenyl)-N-methyl-9-(4-methylpiperazine-1-carbonyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **359**

[00895] A mixture of 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid (2,4-dichloro-phenyl)-methyl-amide (1.0 g), molybdenum hexacarbonyl (550 mg), Cataxium C (190 mg), tributylphosphine tetrafluoroborate (120 mg) and 1,8-diazabicycloundec-7-ene (0.90 mL) in methanol (6 mL) and THF (6 mL) was reacted in the microwave at 130 °C for 30 minutes. The mixture was then partitioned between dichloromethane (40 mL) and water (40 mL). The organic layer was dried ($MgSO_4$), reduced in vacuo and purified on silica to give 2-[(2,4-dichloro-phenyl)-methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid methyl ester.

[00896] To a solution of 2-[(2,4-dichloro-phenyl)-methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid methyl ester (700 mg) in THF (8 mL) and ethanol (4 mL) was added sodium hydroxide solution (121 mg in 4 mL of water) and the reaction stirred at room temperature for 16 h. The reaction was then acidified with 2 M hydrochloric acid and the resulting solid was filtered and air-dried to give 2-(2,4-dichloro-phenyl)-methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid.

[00897] 2-[(2,4-dichloro-phenyl)-methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid and N-methylpiperazine were reacted by General Procedure B to give **359**. NMR: ($CDCl_3$): 2.40 (3 H, s, Me), 2.49-2.58 (4 H, br m), 3.06-3.09 (2 H, m), 3.38 (3 H, s, Me), 3.49-3.90 (4 H, br m), 4.26-4.29 (2 H, m), 6.83 (1 H, s, Ar), 7.02 (1 H, d, J 8.2, Ar), 7.25 (1 H, dd, J 8.3 and 1.9, Ar), 7.31 (1 H, d, J 8.4, Ar), 7.37 (1 H, dd, J 8.4 and 2.2, Ar) and 7.55-7.57 (2 H, m, Ar). MS: (ESI+) MH+ = 530.13

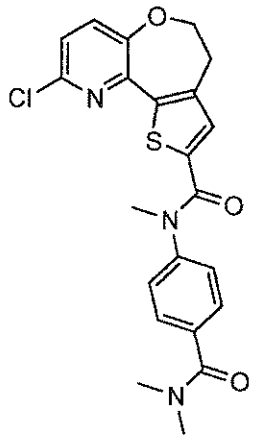
[00898] Example 270 N-(2,4-dichlorophenyl)-9-((3S,5R)-3,5-dimethylpiperazine-1-carbonyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **360**

[00899] 2-[(2,4-Dichloro-phenyl)-methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid and 2,6-dimethylpiperazine were reacted by General Procedure B to give **360**. NMR: ($CDCl_3$): 1.01-1.20 (6 H, br m, Me), 2.40-2.62 (2 H, br, m), 2.73 (2 H, s), 2.82-2.87 (1 H, br, m), 2.98-3.00 (2 H, m), 3.29 (3 H, s, Me), 3.52-3.60 (1 H, br m), 4.18-4.21 (2 H, m), 4.45-4.55 (1 H, br, s, NH), 6.76 (1 H, s, Ar), 6.94 (1 H, d, J 8.3, Ar), 7.15 (1 H, dd, J 8.3 and 1.9, Ar), 7.23 (1 H, d, J 8.4, Ar), 7.28 (1 H, dd, J 8.5 and 2.2, Ar) and 7.44-7.48 (2 H, m, Ar). MS: (ESI+) MH+ = 544.11

[00900] Example 271 N2-(2,4-dichlorophenyl)-N9-(2-hydroxyethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide **361**

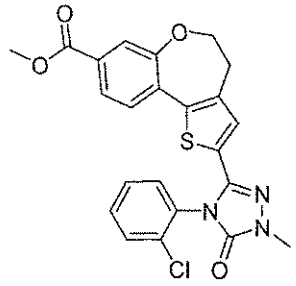
[00901] 2-[(2,4-Dichloro-phenyl)-methyl-carbamoyl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid and ethanolamine were reacted by General Procedure B to give **361**. NMR: ($CDCl_3$): 2.70-2.73 (1 H, m, OH), 3.04-3.07 (2 H, m), 3.38 (3 H, s, Me), 3.66-3.70 (2 H, m), 3.89-3.91 (2 H, m), 4.26-4.29 (2 H, m), 6.48-6.51 (1 H, m, NH), 6.73 (1 H, s, Ar), 7.02 (1 H, d, J 8.4, Ar), 7.32 (1 H, d, 8.4, Ar), 7.38 (1 H, dd, J 8.4 and 2.2, Ar), 7.56-7.61 (2 H, m, Ar) and 7.94 (1 H, s, Ar). MS: (ESI+) MH+ = 532.08

[00902] Example 272 N-(4-(dimethylcarbamoyl)phenyl)-N-methyl-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide **362**



[00903] To a solution of N-(4-carboxyphenyl)-N-methyl-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide (0.082 g, 0.20 mmol;) in methylene chloride (2.8 mL, 44 mmol;) was added dimethylamine hydrochloride (0.0322 g, 0.395 mmol;), N,N-diisopropylethylamine (0.344 mL, 1.98 mmol;) then N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.150 g, 0.395 mmol). The mixture was stirred at room temperature for 2h. LCMS indicated the reaction was complete. The reaction was quenched with sat. NH4Cl, extracted with DCM (2x). The combined organics were dried (Na2SO4), filtered and concentrated. The crude product was purified by flash chromatography (MeOH/DCM) (eluted at 5%MeOH) to give **362** (61% yield). MS: (ESI+) = 442.2

[00904] Example 273 2-(4-(2-chlorophenyl)-1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **363**



[00905] To a mixture of 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1*H*- 1,2,4-triazol-3-yl)-4,5- dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-8-carboxylic acid (1.50 g, 3.41 mmol), Cs_2CO_3 (3.33 g, 10.23 mmol) and DMF (30 mL) was added CH_3I (0.5 mL). The whole was stirred at room temperature overnight. Diluted with water, the solids were washed with water and dried in vacuum to give methyl 2-(4-(2-chlorophenyl)-1-methyl-5-oxo -4,5-dihydro- 1*H*- 1,2,4-triazol-3-yl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-8-carboxylate (1.45 g, yield 91%). ESI-MS: 468.07.

[00906] Methyl 2-(4-(2-chlorophenyl)-1-methyl-5-oxo -4,5-dihydro- 1*H*- 1,2,4-triazol-3-yl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-8-carboxylate (1.45 g, 3.10 mmol) was dissolved in 20 mL of THF and 20 mL of water and treated with LiOH (0.325 g, mono-hydrate). The

whole was heated at 50 °C for 2 h, cooled to room temperature and acidified. The resulting precipitate was filtered and washed with water. The filter cake was dried to a constant weight under vacuum (1.30 g, yield 92%). ESI-MS: 454.4. ^{1}H NMR (DMSO-d_6, 400 MHz): δ13.09 (s, 1H, OH), 7.79- 7.46 (m, 7H, ArH), 6.53 (s, 1H, =CH), 4.22 (t, J= 5.2 Hz, 2H, CH_2), 3.60 (s, 1H, CH_3), 3.01 (t, J= 5.2 Hz, 2H, CH_2).

[00907] A solution of 2-(4-(2-chlorophenyl)-1-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3 -yl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-8-carboxylic acid (300 mg, 0.66 mmol) in 10 mL of $SOCl_2$ was heated at 80 °C for 3 h. Concentration gave the crude acid chloride, 2-(4-(2-chlorophenyl)-1-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4- triazol-3-yl)-4,5-dihydrobenzo[*b*]thieno[2,3-*d*]oxepine-8-carbonyl chloride which was slowly added (ca.312 mg, ca.0.66 mmol in 10 mL of THF), to a solution of NH_3 (saturated solution in THF) and pyridine (0.5 mL) in 5 mL of THF at 0 °C. The mixture was stirred at room temperature overnight, Diluted with water, the solids were washed with water and dried in vacuum. The crude product was purified by HPLC separation, gave 160.1 mg of **363**, isolated yield: 54%. ESI-MS: 453. ^{1}H NMR (DMSO- d_6, 400 MHz): δ 7.98- 7.41 (m, 9H, ArH, NH_2), 6.49 (s, 1H, =CH), 4.20 (s, 2H, CH_2), 3.49 (s, 3H, CH_3), 2.99 (s, 2H, CH_2).

[00908] Example 274 2-(4-(2-chlorophenyl)-1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **364**

[00909] Following Example 273, compound **364** was prepared with methylamine. Yield: 52%. ESI-MS: 467. ^{1}H NMR (DMSO- d_6, 400 MHz): δ8.46 (t, J= 4.4 Hz, 1H, NH), 7.79- 7.45 (m, 7H, ArH), 6.49 (s, 1H, =CH), 4.22 (t, J= 5.2 Hz, 2H, CH_2), 3.50 (s, 3H, CH_3), 3.01 (t, J= 5.2 Hz, 2H, CH_2), 2.76 (d, J= 4.4 Hz, 3H, NCH_3)

[00910] Example 275 p110α (alpha) PI3K Binding Assay

[00911] Binding Assays: Initial polarization experiments were performed on an Analyst HT 96-384 (Molecular Devices Corp, Sunnyvale, CA.). Samples for fluorescence polarization affinity measurements were prepared by addition of 1:3 serial dilutions of p110 alpha PI3K (Upstate Cell Signaling Solutions, Charlottesville, VA) starting at a final concentration of 20ug/mL in polarization buffer (10 mM tris pH 7.5, 50 mM NaCl, 4mM $MgCl_2$, 0.05%Chaps, and 1 mM DTT) to 10mM PIP_2 (Echelon-Inc., Salt Lake City, UT.) final concentration. After an incubation time of 30 minutes at room temperature, the reactions were stopped by the addition of GRP-1 and PIP3-TAMRA probe (Echelon-Inc., Salt Lake City, UT.) 100 nM and 5 nM final concentrations respectively. Read with standard cut-off filters for the rhodamine fluorophore (λex = 530 nm; λem = 590 nm) in 384-well black low volume Proxiplates (PerkinElmer, Wellesley, MA.) Fluorescence polarization values were plotted as a function of the protein concentration, and the EC_{50} values were obtained by fitting the data to a 4-parameter

equation using KaleidaGraph software (Synergy software, Reading, PA). This experiment also establishes the appropriate protein concentration to use in subsequent competition experiments with inhibitors.

[00912] Inhibitor IC_{50} values were determined by addition of the 0.04 mg/mL p110 alpha PI3K (final concentration) combined with PIP_2 (10mM final concentration) to wells containing 1:3 serial dilutions of the antagonists in a final concentration of 25mM ATP (Cell Signaling Technology, Inc., Danvers, MA) in the polarization buffer. After an incubation time of 30 minutes at room temperature, the reactions were stopped by the addition of GRP-1 and PIP3-TAMRA probe (Echelon-Inc., Salt Lake City, UT.) 100 nM and 5 nM final concentrations respectively. Read with standard cut-off filters for the rhodamine fluorophore (λex = 530 nm; λem = 590 nm) in 384-well black low volume proxi plates (PerkinElmer, Wellesley, MA.) Fluorescence polarization values were plotted as a function of the antagonist concentration, and the IC_{50} values were obtained by fitting the data to a 4-parameter equation in Assay Explorer software (MDL, San Ramon, CA.).

[00913] Alternatively, inhibition of PI3K was determined in a radiometric assay using purified, recombinant enzyme and ATP at a concentration of 1uM. The Formula I compound was serially diluted in 100% DMSO. The kinase reaction was incubated for 1 hr at room temperature, and the reaction was terminated by the addition of PBS. IC_{50} values were subsequently determined using sigmoidal dose-response curve fit (variable slope).

[00914] Example 276 In vitro cell proliferation assay

[00915] Efficacy of Formula I compounds were measured by a cell proliferation assay employing the following protocol (Promega Corp. Technical Bulletin TB288; Mendoza et al (2002) Cancer Res. 62:5485-5488):

[00916] 1. An aliquot of 100 µl of cell culture containing about 10^4 cells (PC3, Detroit562, or MDAMB361.1) in medium was deposited in each well of a 384-well, opaque-walled plate.

[00917] 2. Control wells were prepared containing medium and without cells.

[00918] 3. The compound was added to the experimental wells and incubated for 3-5 days.

[00919] 4. The plates were equilibrated to room temperature for approximately 30 minutes.

[00920] 5. A volume of CellTiter-Glo Reagent equal to the volume of cell culture medium present in each well was added.

[00921] 6. The contents were mixed for 2 minutes on an orbital shaker to induce cell lysis.

[00922] 7. The plate was incubated at room temperature for 10 minutes to stabilize the luminescence signal.

[00923] 8. Luminescence was recorded and reported in graphs as RLU = relative luminescence units.

[00924] Alternatively, cells were seeded at optimal density in a 96 well plate and incubated for 4 days in the presence of test compound. Alamar Blue™ was subsequently added to the assay medium, and cells were incubated for 6 hr before reading at 544 nm excitation, 590 nm emission. EC_{50} values were calculated using a sigmoidal dose response curve fit.

[00925] Example 277 Caco-2 Permeability

[00926] Caco-2 cells are seeded onto Millipore Multiscreen plates at 1 x 10^5 cells/cm^2, and cultured for 20 days. Assessment of compound permeability is subsequently conducted. The compounds are applied to the apical surface (A) of cell monolayers and compound permeation into the basolateral (B) compartment was measured. This is performed in the reverse direction (B-A) to investigate active transport. A permeability coefficient value, P_{app}, for each compound, a measure of the rate of permeation of the compound across the membrane, is calculated. Compounds are grouped into low (P_{app} </= 1.0 x 10^6cm/s) or high (P_{app} >/= 1.0 x 10^6cm/s) absorption potential based on comparison with control compounds with established human absorption.

[00927] For assessment of a compound's ability to undergo active efflux, the ratio of basolateral (B) to apical (A) transport compared with A to B was determined. Values of B-A/A-B >/= 1.0 indicate the occurrence of active cellular efflux.

[00928] Example 278 Hepatocyte Clearance

[00929] Suspensions of cryopreserved human hepatocytes are used. Incubations are performed at compound concentration of 1mM or 3μM at a cell density of 0.5 x 10^6 viable cells/mL. The final DMSO concentration in the incubation is about 0.25%. Control incubations are also performed in the absence of cells to reveal any non-enzymatic degradation. Duplicate samples (50μL) are removed from the incubation mixture at 0, 5, 10, 20, 40 and 60 minutes (control sample at 60 minutes only) and added to methanol containing internal standard (100μL) - to terminate the reaction. Tolbutamide, 7-hydroxycoumarin, and testosterone may be used as control compounds. Samples are centrifuged and the supernatants at each time point pooled for analysis by LC-MSMS. From a plot of ln peak area ratio (parent compound peak area / internal standard peak area) against time, intrinsic clearance (CL_{int}) is calculated as follows: CL_{int} (μl/min/million cells) = V x k, where k is the elimination rate constant, obtained from the gradient of ln concentration plotted against time; V is a volume term derived from the incubation volume and is expressed as uL 10^6 $cells^{-1}$.

[00930] Example 279 Cytochrome P450 Inhibition

[00931] Formula I compounds may be screened against CYP450 targets (1A2, 2C9, 2C19, 2D6, 3A4) at about 10 concentrations in duplicate, with a top concentration of about 100uM. Standard inhibitors (furafylline, sulfaphenazole, tranylcypromine, quinidine, ketoconazole) may be used as controls. Plates may be read using a BMG LabTechnologies PolarStar in fluorescence mode.

[00932] Example 280 Cytochrome P450 Induction

[00933] Freshly isolated human hepatocytes from a single donor may be cultured for about 48 hr prior to addition of Formula I compound at three concentrations and incubated for 72 hr. Probe substrates for CYP3A4 and CYP1A2 are added for 30 minutes and 1 hr before the end of the incubation. At 72 hr, cells and media are removed and the extent of metabolism of each probe substrate quantified by LC-MS/MS. The experiment is controlled by using inducers of the individual P450s incubated at one concentration in triplicate.

[00934] Example 281 Plasma Protein Binding

[00935] Solutions of Formula I compound (5um, 0.5% final DMSO concentration) are prepared in buffer and 10% plasma (v/v in buffer). A 96 well HT dialysis plate is assembled so that each well is divided in two by a semi-permeable cellulose membrane. The buffer solution is added to one side of the membrane and the plasma solution to the other side; incubations are then conducted at 37 °C over 2 hr in triplicate. The cells are subsequently emptied, and the solutions for each batch of compounds are combined into two groups (plasma-free and plasma-containing) then analyzed by LC-MSMS using two sets of calibration standards for plasma-free (6 points) and plasma-containing solutions (7 points). The fraction unbound value for the compound is calculated.

[00936] Example 282 hERG channel blockage

[00937] Formula I compounds are evaluated for ability to modulate rubidium efflux from HEK-294 cells stably expressing hERG potassium channels using established flux methodology. Cells are prepared in medium containing RbCl, plated into 96-well plates and grown overnight to form monolayers. The efflux experiment is initiated by aspirating the media and washing each well with 3 x 100μL of pre-incubation buffer (containing low [K^+]) at room temperature. Following the final aspiration, 50 μL of working stock (2x) compound is added to each well and incubated at room temperature for 10 minutes. Stimulation buffer 50μL (containing high [K+]) is then added to each well giving the final test compound concentrations. Cell plates are then incubated at room temperature for a further 10 minutes. Supernatant 80μL from each well is then transferred to equivalent wells of a 96-well plate and analyzed via atomic emission

spectroscopy. The compound is screened as 10pt duplicate IC_{50} curves, n=2, from a top concentration of 100 μM.

[00938] Example 283 In Vivo Tumor Xenograft

[00939] Animals suitable for transgenic experiments can be obtained from standard commercial sources. Groups of Taconic nude mice (were implanted subcutaneously in the hind flank with MDA-MB-361.1 (PI3K mutant) breast cancer cells. Mouse xenografts were dosed daily for 21 days with drug or vehicle. Tumor sizes were recorded twice weekly over the course of the study. Mouse body weights were also recorded twice weekly, and the mice were observed regularly. Tumor volume was measured in two dimensions (length and width) using Ultra Cal-IV calipers (Model 54-10-111; Fred V. Fowler Co., Inc.; Newton, MA) and analyzed using Excel v.11.2 (Microsoft Corporation; Redmond, WA). Tumor inhibition graphs were plotted using KaleidaGraph, Version 3.6 (Synergy Software; Reading, PA). The tumor volume was calculated with formula: Tumor size (mm^3) = (longer measurement x shorter measurement^2) x 0.5

[00940] Animal body weights were measured using an Adventurera Pro AV812 scale (Ohaus Corporation; Pine Brook, NJ). Graphs were generated using KaleidaGraph Version 3.6. Percent weight change was calculated using formula: Group percent weight change = (1-(initial weight / new weight)) x 100.

[00941] Mice whose tumor volume exceeded 2000 mm^3 or whose body weight loss was > 20% of their starting weight were promptly euthanized according to regulatory guidance.

[00942] The percent tumor growth inhibition (% INH) at the end of study (EOS) was calculated using formula: % INH = 100 x (EOS mean volume of tumors in animals given vehicle – EOS mean volume of tumors in animals given the drug)/EOS mean volume of tumors in animals given vehicle.

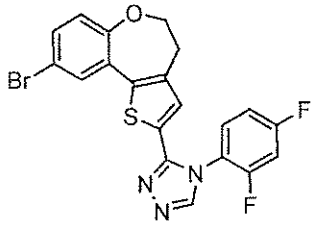
[00943] Tumor incidence (TI) was determined based on the number of measurable tumors remaining in each group at the end of the study. A partial response (PR) was defined as a > 50% but ≤100% reduction in tumor volume, compared with the starting tumor volume, observed on any day of the study. A complete response (CR) was defined as a 100% reduction in tumor volume, compared with the initial tumor volume, observed on any day of the study. Data were analyzed and p-values were determined using the Dunnett's test with JMP statistical software, version 5.1.2 (SAS Institute; Cary, NC). Individual tumor volumes at end of study and mean tumor volume ± SEM values were calculated using JMP statistical software, version 5.1.2. Body weight data were graphed based on the mean percentage of change from initial body weights ± SEM.

[00944] Example 284 phospho AKT induction assay.

[00945] In a 6-well tissue culture plate cells were seeded at 5 x 10^5 cells per well

overnight. Cells were treated with an EC_{80} of the Formula I or Formula II compound, including **223**, **328**, and **345**. Following treatment, cells were washed once with cold PBS and lysed in 1X Cell Extraction Buffer from Biosource (Carlsbad, CA) supplemented with protease inhibitors (Roche, Mannheim, Germany), 1mM PMSF, and Phosphatase Inhibitor Cocktails 1 and 2 from Sigma (St. Louis, MO). Determination of protein concentration was performed using the Pierce BCA Protein Assay Kit (Rockford, IL). Levels of pAkt (Ser^{473}) and total Akt were assessed using bead kits from Biosource (Carlsbad, CA) and the Luminex Bio-Plex system (Bio-Rad, Hercules, CA).

[00946] Example 285 (2-(4-(2,4-difluorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(4-methylpiperazin-1-yl)methanone **374**



[00947] A mixture of 3-(9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-4-(2,4-difluoro-phenyl)-4H-[1,2,4]triazole (600 mg), molybdenum hexacarbonyl (344 mg), Cataxium C (122 mg), tributylphosphine tetrafluoroborate (76 mg) and 1,8-diazabicycloundec-7-ene (0.58 mL) in methanol (5 mL) and THF (5 mL) was reacted in the microwave at 130 °C for 30 minutes. The mixture was then partitioned between dichloromethane (30 mL) and water (30 mL). The organic layer was dried ($MgSO_4$), reduced in vacuo and purified on silica to give 2-[4-(2,4-difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid methyl ester.

[00948] To a solution of 2-[4-(2,4-difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid methyl ester (210 mg) in THF (4 mL) and ethanol (2 mL) was added sodium hydroxide solution (38 mg in 2 mL of water) and the reaction stirred at room temperature for 16 h. The reaction was then acidified with 2 M hydrochloric acid and the resulting solid was filtered and air-dried to give 2-[4-(2,4-difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid.

[00949] 2-[4-(2,4-Difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid and N-methylpiperazine were reacted in the general amide coupling procedure to give **374**. NMR: ($CDCl_3$): 2.37 (3 H, s, Me), 2.37-2.51 (4 H, m), 3.13-3.17 (2 H, m), 3.51-3.78 (4 H, m), 4.32-4.35 (2 H, m), 6.98 (1 H, s, Ar), 7.05 (1 H, d, J 8.3, Ar), 7.12-7.17 (2 H, m, Ar), 7.24-7.27 (1 H, m, Ar), 7.42-7.48 (1 H, m, Ar), 7.61-7.62 (1 H, m, Ar) and 8.24 (1 H, s, Ar). MS: (ESI+) MH+ = 508.22

[00950] Example 286 2-(4-(2,4-difluorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide **375**

[00951] 2-[4-(2,4-Difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid and ethanolamine were reacted in the general amide coupling procedure to give **375**. NMR: ($CDCl_3$): 2.72 (1 H, s, OH), 3.01-3.04 (2 H, m), 3.57-3.61 (2 H, m), 3.72-3.81 (2 H, m), 4.20-4.23 (2 H, m), 6.68-6.72 (1 H, m, NH), 6.79 (1 H, s, Ar), 6.94 (1 H, d, J 8.4, Ar), 7.02-7.06 (2 H, m, Ar), 7.33-7.40 (1 H, m, Ar), 7.50-7.53 (1 H, m, Ar), 7.89-7.90 (1 H, m, Ar) and 8.16 (1 H, s, Ar). MS: (ESI+) MH+ = 469.04

[00952] Example 287 2-(4-(2,4-difluorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-hydroxyethyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide **376**

[00953] 2-[4-(2,4-Difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid and 2-(methylamino)ethanol were reacted in the general amide coupling procedure to give **376**. NMR: ($CDCl_3$): (400 MHz, CDCl3): 3.13 (3 H, s, Me), 3.13-3.16 (2 H, m), 3.74-3.78 (2 H, m), 3.90-3.95 (2 H, m), 4.31-4.34 (2 H, m), 6.93 (1 H, s, Ar), 7.05 (1 H, d, J 8.3, Ar), 7.12-7.16 (2 H, m, Ar), 7.31-7.33 (1 H, m, Ar), 7.43-7.48 (1 H, m, Ar), 7.69-7.70 (1 H, m, Ar) and 8.24 (1 H, s, Ar). MS: (ESI+) MH+ = 483.08

[00954] Example 288 5-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole **384**

[00955] A microwave tube charged with 2-(9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-[1,3,4]oxadiazole (200 mg; 0.57 mmol), 2,4-difluoroaniline (0.11 ml; 1.1 mmol), TFA (82 µl; 1.1 mmol) and toluene (1.5 ml) was heated in a microwave at 140 °C for 30 min. The reaction mixture was diluted with CH_2Cl_2 (20 ml) and washed with satd. $NaHCO_3$ (20 ml), the organic layer was separated (hydrophobic frit), concentrated and purified by ISCO to give **384** as a pale yellow solid (191 mg; 70 %). δ_H (400 MHz, $CDCl_3$) 3.15 (t, J = 5.2, 2H), 4.30 (t, J = 5.2, 2H), 6.91 (d, J = 8.8, 1H), 6.97 (s, 1H), 7.02-7.18 (m, 2H), 7.25-7.28 (m, 1H), 7.43-7.49 (m, 1H), 7.66 (d, J = 2.4, 1H), 8.25 (s, 1H). $[M+H]^+$: 461

[00956] Example 289 5-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-isopropyl-1H-1,2,4-triazole **385**

[00957] A mixture of 9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-2-carboxylic acid amide (1.01 g), dimethylformamide dimethyl acetal (9 ml) and toluene (7.5 mL) was heated to 100 °C for 16 hours. The solvent was then reduced in vacuo and dissolved in acetic acid (9 ml) and water (1mL) and to this was added isopropyl hydrazide hydrochloride (482 mg). The reaction mixture was heated to 100 °C for 7 hours. The reaction mixture was then cooled, and then diluted with ethyl acetate, washed with sodium carbonate solution, dried ($MgSO_4$) and the solvent removed in vacuo. Purification using flash chromatography yielded **385**. NMR:

(CDCl3): 1.61 (6H, d), 3.25 (2H, t), 4.33 (2H, t), 4.99 (1H, septet), 6.90 (1H, d), 7.28-7.31 (2H, m), 7.85 (1H, s), 7.92 (1H, s). MS. ESI+ 432 (MH^+ + MeCN)

[00958] Example 290 1-(2,4-difluorophenyl)-5-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazole **397**

[00959] Compound **397** was prepared according to the procedures herein. NMR: (CDCl3): 3.13 (2H, t), 4.31 (2H, t), 6.99-7.21 (6H, m), 7.51-7.58 (2H, m), 8.01 (1H, s). MS. ESI+ 423 (MH^+ + MeCN)

[00960] Example 291 2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide **398**

[00961] A mixture of 5-(9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-1-(2,4-difluoro-phenyl)-1H-[1,2,4]triazole (847 mg), molybdenum hexacarbonyl (485mg), Herman's catalyst (173mg), tributyl phosphine tetrafluoroborate (106mg), methanol (8ml), THF (8ml), and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.82mL) was heated in the microwave at 130°C for 30 minutes. The reaction mixture was cooled, and then diluted with dichloromethane, washed with water, dried ($MgSO_4$) and the solvent removed in vacuo. Purification using flash chromatography yielded the corresponding methyl ester, 2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid methyl ester. Standard hydrolysis using sodium hydroxide in methanol/THF/water yielded the corresponding carboxylic acid, 2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid.

[00962] A mixture of 2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid (53mg), HATU (61mg) and diisopropylethylamine (0.028mL) and ethanolamine was stirred in N, N-dimethylformamide (3ml). The reaction mixture was stirred overnight, and then diluted with ethyl acetate, washed with water, dried ($MgSO_4$) and the solvent removed in vacuo. Purification using flash chromatography yielded **398** (24mg). NMR: (CDCl3): 2.30 (1H, t, br.), 3.05 (2H, t), 3.51-3.55 (2H, m), 3.7-3.75 (2H, m), 4.31 (2H, t), 6.40 (1H, br.), 6.80 (1H, s), 6.99 (1H, d), 7.05-7.12 (2H, m), 7.42-7.52 (2H, m), 7.90 (1H, s), 8.01 (1H, s). MS. ESI+ 510 (MH^+ + MeCN)

[00963] Example 292 9-Bromo-2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene **399**

[00964] To a stirred suspension of 9-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (3.75 g; 11.5 mmol) in CH_2Cl_2 (80 ml) at room temperature was added $(COCl)_2$ (2.6 ml; 30 mmol) then DMF (3 drops). The reaction mixture was stirred at room temperature for 3 h upon which time all volatiles were removed in vacuo. The resulting residue was slurried in THF (60 ml) cooled to 0 °C and treated with NH_3 (10 ml of a 7M MeOH

soln.; 70 mmol). The reaction mixture was stirred whilst allowing to warm to room temperature over 1.5 h. The reaction mixture was diluted with water (200 ml) and the resulting solid collected by filtration to obtain 9-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid amide as a white solid (3.09 g; 83 %). δ_H (400 MHz, d_6-DMSO) 3.30 (t, J = 5.2, 2H), 4.29 (t, J = 5.2, 2H), 6.98 (d, J = 8.8, 1H), 7.39 (dd, J = 8.8 and 2.4, 1H), 7.42 (br s, 1H), 7.62 (s, 1H), 7.71 (d, J = 2.4, 1H), 7.96 (br s, 1H).

[00965] A stirred suspension of 9-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid amide (0.70 g; 2.2 mmol) and dimethylformamide dimethylacetal (DMF·DMA, 6 ml) in toluene (5 ml) was heated at 100 °C overnight (16 h) upon which time the reaction mixture was concentrated. To the resulting residue was added AcOH (5 ml), water (0.5ml) and 2,4-difluorophenylhydrazine hydrochloride (0.56 g; 3.1 mmol) and the resulting solution heated at 100 °C for 3 h. The reaction mixture was concentrated, the residue was dissolved in CH_2Cl_2 (50 ml) and washed with satd. $NaHCO_3$ (50 ml). The organic layer was separated (hydrophobic frit), concentrated and purified by ISCO to give **399** as a cream-coloured solid (0.31 g; 31 %). δ_H (400 MHz, $CDCl_3$) 3.41 (t, J = 5.2, 2H), 4.36 (t, J = 5.2, 2H), 6.89 (d, J = 8.8, 1H), 7.14-7.20 (m, 2H), 7.27-7.30 (m ,1H), 7.55-7.61 (m, 1H), 7.69 (d, J = 2.8, 1H), 8.16 (s, 1H). $[M+H]^+$: 462

[00966] Alternatively, t o a suspension of 9-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid ethyl ester (4.55 g) in ethanol (50 mL) was added hydrazine monohydrate (5 mL) and the reaction heated at reflux for 16 h. After cooling to room temperature, the solid was filtered, washed with diethyl ether and air-dried to give 9-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid hydrazide.

[00967] To a solution of 9-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid hydrazide (400 mg) in trimethyl orthoformate (10 mL) was added p-toluenesulfonic acid (100 mg) and the reaction heated at 100 °C for 16 h. After cooling to room temperature, the solvent was reduced in vacuo and diethyl ether (10 mL) was added. The resulting solid was filtered and air-dried to give 9-bromo-2-[1,3,4]oxadiazol-2-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene.

[00968] A mixture of 9-bromo-2-[1,3,4]oxadiazol-2-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (250 mg), 2,4-difluoroaniline (0.15 mL) and trifluoroacetic acid (0.11 mL) in toluene (5 mL) was reacted in the microwave at 110 °C for 20 minutes. The mixture was then partitioned between dichloromethane (20 mL) and aqueous sodium hydrogen carbonate solution (20 mL). The organic layer was dried (MgSO4), reduced in vacuo and purified on silica to give **399**. NMR: ($CDCl_3$): 3.38-3.41 (2 H, m), 4.33-4.36 (2 H, m), 6.89 (1 H, d, J 8.6, Ar), 7.15-7.21

(2 H, m, Ar), 7.25-7.28 (1 H, m, Ar), 7.47-7.53 (1 H, m, Ar), 7.61 (1 H, d, J 2.4, Ar) and 8.32 (1 H, s, Ar). MS: (ESI+) MH+ = 460.97

[00969] Example 293 5-(9-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole **400**

[00970] 5-(9-Bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-1-(2,4-difluoro-phenyl)-1H-[1,2,4]triazole was treated with 4-pyrazoleboronic acid pinacol ester using standard Suzuki condition to yield **400**. NMR: (CDCl3): 3.15 (2H, t), 4.31 (2H, t), 6.82 (1H, s), 7.01 (1H, d), 7.08-7.18 (2H, m), 7.31 (1H, d), 7.51-7.55 (1H, m), 7.72 (1H, s), 7.90 (2H, s, br.), 8.18 (1H, s). MS. ESI+ 489 (MH^+ + MeCN)

[00971] Example 294 2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide **401**

[00972] The corresponding carboxylic acid was reacted with ammonium chloride to give **401**. NMR: (DMSO): 3.15 (2H, t), 4.31 (2H, t), 6.80 (1H, s), 7.01 (1H, d), 7.25 (1H, s, br.), 7.37-7.40 (1H, m), 7.65-7.75 (2H, m), 7.90 (1H, m), 7.99 (1H, s, br.), 8.05 (1H, s), 8.28 (1H, s). MS. ESI+ 466 (MH^+ + MeCN)

[00973] Example 295 (2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(piperazin-1-yl)methanone **402**

[00974] The corresponding carboxylic acid was reacted with 1-BOC-piperazine. The BOC group was cleaved using HCl in ether to yield **402** as the hydrochloride salt. MS. ESI+ 493 (MH^+)

[00975] Example 296 2-[4-(2,4-Difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-9-carboxylic acid amide **407**

[00976] To a solution of 9-bromo-2-[4-(2,4-difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (250 mg) in methanol (0.50 mL) was added palladium acetate (6 mg), XANTPHOS (31 mg) and triethylamine (2 mL) and the reaction heated at 70 °C under a balloon of carbon monoxide for 16 h. After cooling to room temperature, the mixture was filtered through Celite, washing with ethyl acetate. The filtrate was reduced in vacuo and redissolved in THF (8 mL) and ethanol (4 mL). Sodium hydroxide solution (43 mg in 4 mL of water) was added and the reaction stirred at room temperature for 16 h. The reaction was then acidified with 2 M hydrochloric acid and the resulting solid was filtered and air-dried to give 2-[4-(2,4-difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-9-carboxylic acid.

[00977] 2-[4-(2,4-Difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-9-carboxylic acid and ammonium chloride were reacted in the general amide coupling procedure to give **407**. NMR: ($CDCl_3$): 3.32-3.35 (2 H, m), 4.32-4.30 (2 H, m),

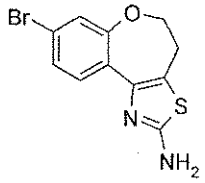
6.96-6.99 (1 H, m, Ar), 7.09-7.14 (1 H, m, Ar), 7.48-7.50 (1 H, m, Ar), 7.54-7.58 (1 H, m, Ar), 8.09-8.11 (1 H, m, Ar) and 8.35 (1 H, s, Ar). MS: (ESI+) MH+ = 425.95

[00978] Example 297 3-(2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)pyridine **408**

[00979] 5-(9-Bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-1-(2,4-difluoro-phenyl)-1H-[1,2,4]triazole was treated with 3-pyridineboronic acid pinacol ester using standard Suzuki condition to yield **408**. NMR: (CDCl3): 3.15 (2H, t), 4.31 (2H, t), 6.82 (1H, s), 7.03-7.18 (3H, m), 7.32-7.38 (2H, m), 7.51-7.55 (1H, m), 7.72 (1H, s), 7.82 (1H, d), 8.05 (1H, s), 8.55 (1H, d), 8.80 (1H,s). MS. ESI+ 500 (MH^+ + MeCN)

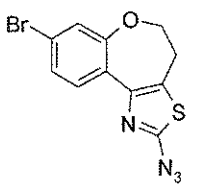
[00980] Example 298 2-(5-Cyclopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide **414**

[00981] Step 1: 8-Bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-ylamine



[00982] To a solution of 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (12.5 g, 38.3 mmol) in *tert*-butanol (250 mL) were added triethylamine (5.5 mL, 40 mmol) and diphenylphosphoryl-azide (8.6 mL, 40 mmol). The reaction mixture was stirred at 95°C for 16h, then allowed to cool down to RT, and concentrated *in vacuo*. The resultant residue was dissolved in ethyl acetate, washed successively with water, aqueous saturated sodium bicarbonate solution and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resultant residue was dissolved in DCM (150 mL) and treated with trifluoroacetic acid (50 mL). The reaction mixture was stirred at RT for 3h then concentrated *in vacuo*. The resulting residue was triturated with 20% ethyl acetate/cyclohexane and filtered to afford the title compound as an off-white solid (7.94 g, 70%). LCMS (Method A): R_T = 3.13 min, $[M+H]^+$ = 297 and 299. ^1H NMR (DMSO-d_6): 8.01 (1 H, d, J = 8.6 Hz), 7.30-7.25 (1 H, d, J = 8.6, 2.1 Hz), 7.19 (1 H, d, J = 2.1 Hz), 4.27 (2 H, t, J = 5.1 Hz), 3.08 (2 H, t, J = 5.1 Hz).

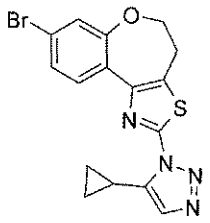
[00983] Step 2: 2-Azido-8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene



[00984] To a suspension of 8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-ylamine (2.38 g, 8 mmol) in acetonitrile at 0°C was added *tert*-butyl nitrite (1.43 mL, 12 mmol)

followed by trimethylsilyl azide (1.26 mL, 9.6 mmol) dropwise. The reaction mixture was stirred at 0°C for 90 mins, allowed to warm up to RT and concentrated in vacuo. The resulting residue was purified by flash chromatography (SiO_2, 10% ethyl acetate in cyclohexane) to yield the title compound as a red oil which solidified upon standing (956 mg, 37%). ^{1}H NMR ($CDCl_3$): 8.21 (1 H, d, J = 8.6 Hz), 7.24 (1 H, dd, J = 8.6, 2.1 Hz), 7.20 (1 H, d, J = 2.1 Hz), 4.34 (2 H, t, J = 5.1 Hz), 3.21 (2 H, t, J = 5.1 Hz).

[00985] Step 3: 8-Bromo-2-(5-cyclopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene



To a 1M solution of ethylmagnesium bromide in THF (1.3 mL, 1.3 mmol) under a nitrogen atmosphere, was added dropwise cyclopropylethyne (70% in toluene, 0.154 mL, 1.3 mmol). The reaction mixture was heated at 50°C for 15 mins then allowed to cool down to RT. A solution of 2-azido-8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (425 mg, 1.3 mmol) in THF (1.5 mL) was then added dropwise. The reaction mixture was stirred at RT for 2h, quenched with aqueous saturated ammonium chloride and diluted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resultant residue was triturated with 20% ethyl acetate/cyclohexane and filtered to afford the title compound as a pale yellow solid (373 mg, 64%). LCMS 110142391 (Method B): R_T = 4.40 min, $[M+H]^+$ = 390. ^{1}H NMR (DMSO-d_6): 8.20 (1 H, d, J = 8.6 Hz), 7.71 (1 H, d, J = 0.7 Hz), 7.36 (1 H, dd, J = 8.6, 2.1 Hz), 7.30 (1 H, d, J = 2.1 Hz), 4.40 (2 H, t, J = 5.0 Hz), 3.41 (2 H, t, J = 5.0 Hz), 2.70-2.63 (1 H, m), 1.21-1.15 (2 H, m), 0.91-0.86 (2 H, m).

[00986] Step 4: 2-(5-Cyclopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide

[00987] To a suspension of 8-bromo-2-(5-cyclopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (224 mg, 0.58 mmol), hydroxylamine hydrochloride (81 mg, 1.16 mmol), molybdenum hexacarbonyl (77 mg, 0.29 mmol), tri-tert-butylphosphine tetrafluoroborate (17 mg, 0.058 mmol), trans-di-μ-acetatobis[2-(di-o-tolylphosphino)benzyl]dipalladium(II) (27 mg, 0.029 mmol) in dioxane (7 mL) were added 1,8-diazabicyclo[5.4.0]undec-7-ene (86 μL, 0.58 mmol) and DIPEA (197 μL, 1.16 mmol). The reaction mixture was heated at 150°C under microwave irradiation for 30 mins, and diluted with ethyl acetate. The organic layer was washed successively with water, aqueous saturated

ammonium chloride, aqueous saturated sodium bicarbonate solution and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (SiO_2, 3% MeOH in DCM) to give an off-white solid, which was dissolved in DMSO/water. The mixture was left to stand at RT for 7 days, filtered, and the filtrate was diluted with ethyl acetate and water. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give **414** as an off-white solid (42 mg, 21%). LCMS (Method C): R_T = 8.65 min, $[M+H]^+$ = 354. ^1H NMR (DMSO-d_6): 8.32 (1 H, d, J = 8.3 Hz), 7.99 (1 H, bs), 7.72 (1 H, d, J = 0.7 Hz), 7.66 (1 H, dd, J = 8.3, 1.8 Hz), 7.57 (1 H, d, J = 1.8 Hz), 7.40 (1 H, bs), 4.41 (2 H, t, J = 5.0 Hz), 3.45 (2 H, t, J = 5.0 Hz), 2.74-2.66 (1 H, m), 1.23-1.15 (2 H, m), 0.93-0.87 (2 H, m).

[00988] Example 299 (2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)((R)-3-(dimethylamino)pyrrolidin-1-yl)methanone **418**

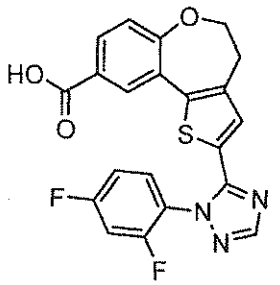
[00989] To a stirred solution of 2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid (82 mg; 0.19 mmol) in DMF (5 ml) was added HATU (103 mg; 0.27 mmol), DIPEA (50 µl; 0.27 mmol) and (*R*)-(+)-3-(dimethylamino)pyrrolidine (50 µl; 0.38 mmol). The reaction mixture was stirred at room temperature for 4 h upon which time it was diluted with EtOAc (20 ml) and washed successively with satd. $NaHCO_3$ (20 ml) and brine (2 20 ml). The organic layer was dried (Na_2SO_4), concentrated and purified by prep. LCMS to give **418** as an off-white solid (53 mg; 53 %). δ_H (400 MHz, $CDCl_3$) 1.80-1.95 (m, 1H), 2.03-2.15 (br m, 1H), 2.24 (br s, 3H), 2.35 (br s, 3H), 2.62-2.85 (br m, 1H), 3.16 (br s, 2H), 3.30-4.00 (m, 4H), 4.33 (br s, 2H), 6.92-7.20 (m, 4H), 7.40 (br s, 1H), 7.51-7.61 (m, 1H), 7.77 (s, 1H), 8.11 (s, 1H). $[M+H]^+$: 522

[00990] Example 300 2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide **419**

[00991] A mixture of 5-(9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-1-isopropyl-1H-[1,2,4]triazole (290 mg), molybdenum hexacarbonyl (196 mg), Herman's catalyst (70 mg), tributyl phosphonic tetrafluoroborate (43 mg) , methanol (3 mL), THF (3 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.33 ml) was heated in the microwave at 130 °C for 30 minutes. The reaction mixture was cooled, and then diluted with dichloromethane, washed with water, dried ($MgSO_4$) and the solvent removed in vacuo to yield 2-(2-isopropyl-2H-[1,2,4]triazol-3-yl)-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid methyl ester. This was hydrolyzed using sodium hydroxide in water/methanol/THF to yield the corresponding acid. Treatment with HATU, diisopropylethylamine and ammonium chloride in dry DMF yielded **419**. NMR: (DMSO): 1.51 (6H, d), 3.25 (2H, t), 4.38 (2H, t), 5.09 (1H, septet), 7.02

(1H, d), 7.33 (1H,br,s), 7.51 (1H, s), 7.75 (1H, dd), 8.00 (1H, s), 8.04 (1H, s, br.), 8.18 (1H, s). MS. ESI+ 3396 (MH^+ + MeCN)

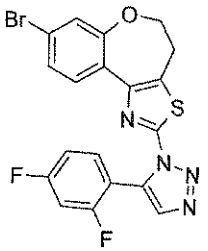
[00992] Example 301 ((2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)((S)-3-(dimethylamino)pyrrolidin-1-yl)methanone **420**



[00993] To a stirred solution of 2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-1-thia-benzo[e]azulene-9-carboxylic acid (70 mg; 0.16 mmol) in DMF (5 ml) was added HATU (103 mg; 0.27 mmol), DIPEA (50 µl; 0.27 mmol) and (*S*)-(-)-3-(dimethylamino)pyrrolidine (50 µl; 0.38 mmol). The reaction mixture was stirred at r.t. for 4 h upon which time it was diluted with EtOAc (20 ml) and washed successively with satd. $NaHCO_3$ (20 ml) and brine (2 20 ml). The organic layer was dried (Na_2SO_4), concentrated and purified by prep. LCMS to give **420** as an off-white solid (50 mg; 58 %). δ_H (400 MHz, $CDCl_3$) 1.77-1.92 (br m, 1H), 2.06-2.17 (m, 1H), 2.24 (br s, 3H), 2.35 (br s, 3H), 2.60-2.83 (m, 1H), 3.16 (br s, 2H), 3.29-3.98 (m, 4H), 4.33 (br s, 2H), 6.94-7.20 (m, 4H), 7.32-7.39 (m, 1H), 7.50-7.60 (m, 1H), 7.77 (s, 1H), 8.11 (s, 1H). $[M+H]^+$: 522

[00994] Example 302 2-[5-(2,4-Difluoro-phenyl)-[1,2,3]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide **427**

[00995] Step 1: 8-Bromo-2-[5-(2,4-difluoro-phenyl)-[1,2,3]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene



[00996]

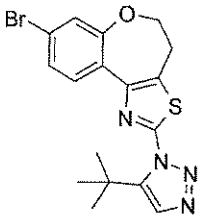
[00997] Following the procedure for **414**, Step 3, 2-azido-8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with 1-ethylnyl-2,4-difluorobenzene to afford the title compound as a beige solid. ^1H NMR (DMSO-d_6): 8.26 (1 H, s), 7.73 (1 H, m), 7.58-7.52 (1 H, m), 7.36-7.30 (2 H, m), 7.24 (1 H, d, J = 2.0 Hz), 7.18-7.10 (1 H, m), 4.35 (2 H, t, J = 5.0 Hz), 3.38 (2 H, t, J = 5.0 Hz).

[00998] Step 2: 2-[5-(2,4-Difluoro-phenyl)-[1,2,3]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide

[00999] Following the procedure for **414**, Step 4, 8-bromo-2-[5-(2,4-difluoro-phenyl)-[1,2,3]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with hydroxylamine hydrochloride to afford **427** as a white solid. LCMS (Method C): R_T = 9.67 min, $[M+H]^+$ = 426. ^1H NMR (DMSO-d_6): 8.27 (1 H, s), 7.99 (1 H, bs), 7.75 (1 H, td, J = 8.5, 6.4 Hz), 7.59-7.51 (2 H, m), 7.46-7.31 (4 H, m), 4.36 (2 H, t, J = 5.0 Hz), 3.41 (2 H, t, J = 5.0 Hz).

[001000] Example 303 2-(5-tert-Butyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene **434**

[001001] Step 1: 8-Bromo-2-(5-tert-butyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

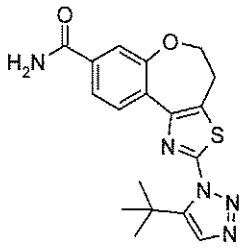


[001002] Following the procedure for **414**, Step 3, 2-azido-8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with 3,3-dimethyl-1-butyne to afford the title compound as a pale yellow solid. LCMS (Method A): R_T = 4.95 min, $[M+H]^+$ = 405 and 407. ^1H NMR ($CDCl_3$): 8.16 (1 H, dd, J = 8.1, 0.9 Hz), 7.55 (1 H, s), 7.28 (2 H, m), 4.42 (2 H, t, J = 5.1 Hz), 3.37 (2 H, t, J = 5.1 Hz), 1.54 (9 H, s).

[001003] Step 2: 2-(5-tert-Butyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

[001004] A suspension of 8-bromo-2-(5-tert-butyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (101 mg, 0.25 mmol) and 10% Pd/C (250 mg) in MeOH (5 mL) was stirred at RT under a hydrogen atmosphere for 16h. The reaction mixture was flushed with nitrogen, filtered through Celite, washed with ethyl acetate and concentrated in vacuo. The resulting residue was purified by flash chromatography (SiO_2, 20% ethyl acetate in cyclohexane) to give **434** as a white solid (54 mg, 66%). LCMS (Method C): R_T = 13.19 min, $[M+H]^+$ = 327. ^1H NMR ($CDCl_3$): 8.30 (1 H, dd, J = 7.9, 1.8 Hz), 7.55 (1 H, s), 7.29 (1 H, m), 7.17-7.12 (1 H, m), 7.08 (1 H, dd, J = 8.0, 1.4 Hz), 4.43 (2 H, t, J = 5.1 Hz), 3.39 (2 H, t, J = 5.1 Hz), 1.55 (9 H, s).

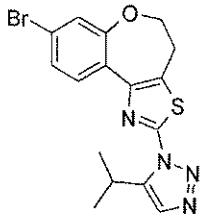
[001005] Example 304 2-(5-tert-Butyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide **435**



[001006] Following the procedure for **414**, Step 4, 8-bromo-2-(5-tert-butyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with hydroxylamine hydrochloride to afford **435** as a pale yellow solid. LCMS (Method C): R_T = 9.29 min, $[M+H]^+$ = 370. ^1H NMR (DMSO-d_6): 8.25 (1 H, d, J = 8.3 Hz), 8.00 (1 H, bs), 7.83 (1 H, s), 7.67 (1 H, dd, J = 8.3, 1.8 Hz), 7.59 (1 H, d, J = 1.8 Hz), 7.42 (1 H, bs), 4.43 (2 H, t, J = 5.0 Hz), 3.48 (2 H, t, J = 5.0 Hz), 1.48 (9 H, s).

[001007] Example 305 2-(5-Isopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide **436**

[001008] Step 1: 8-Bromo-2-(5-isopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene



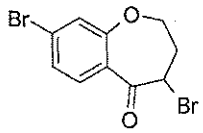
[001009] Following the procedure for **414**, Step 3, 2-azido-8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with 3-methyl-1-butyne to afford the title compound as a beige solid. LCMS (Method A): R_T = 4.88 min, $[M+H]^+$ = 391 and 393. ^1H NMR ($CDCl_3$): 8.12 (1 H, d, J = 8.5 Hz), 7.59 (1 H, s), 7.30-7.25 (2 H, m), 4.41 (2 H, t, J = 5.0 Hz), 3.98-3.90 (1 H, m), 3.36 (2 H, t, J = 5.0 Hz), 1.44 (3 H, s), 1.42 (3 H, s).

[001010] Step 2: 2-(5-Isopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide

[001011] Following the procedure for **414**, Step 4, 8-bromo-2-(5-isopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with hydroxylamine hydrochloride to afford **436** as a pale yellow solid. LCMS (Method C): R_T = 9.07 min, $[M+H]^+$ = 356. ^1H NMR (DMSO-d_6): 8.26 (1 H, d, J = 8.3 Hz), 8.00 (1 H, bs), 7.91 (1 H, d, J = 0.7 Hz), 7.68 (1 H, dd, J = 8.3, 1.8 Hz), 7.58 (1 H, d, J = 1.8 Hz), 7.41 (1 H, bs), 4.41 (2 H, t, J = 5.0 Hz), 3.91-3.82 (1 H, sept, J = 6.8 Hz), 3.44 (2 H, t, J = 5.0 Hz), 1.39 (3 H, s), 1.38 (3 H, s).

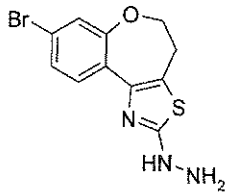
[001012] Example 306 2-[5-(2,4-Difluoro-phenyl)-[1,2,4]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide **449**

[001013] Step 1: 4,8-Dibromo-3,4-dihydro-2*H*-benzo[b]oxepin-5-one



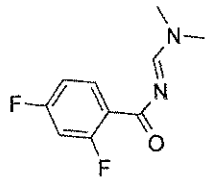
[001014] To a solution of 8-bromo-3,4-dihydro-2*H*-benzo[b]oxepin-5-one (1.2g, 5 mmol) in diethyl ether (20 mL) at 0°C was added bromine (257 μL, 5 mmol) dropwise under nitrogen. The reaction mixture was stirred at 0°C for 1h, allowed to warm up to RT and stirred for 3h. Further bromine (50 μL, 0.97 mmol) was added and stirring was pursued for 16h. The solvent was removed *in vacuo* and the resultant residue was purified by flash chromatography (SiO_2, 10% ethyl acetate in cyclohexane) to give the title compound as a white solid (1.55 g, 97%). ^{1}H NMR ($CDCl_3$): 7.62 (1 H, m), 7.26 (2 H, m), 4.94 (1 H, dd, J = 7.7, 6.7 Hz), 4.43 (1 H, ddd, J = 12.7, 5.6, 4.8 Hz), 4.25-4.15 (1 H, m), 2.97-2.86 (1 H, m), 2.51 (1 H, ddt, J = 14.7, 7.7, 4.6 Hz).

[001015] Step 2: (8-Bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl)-hydrazine



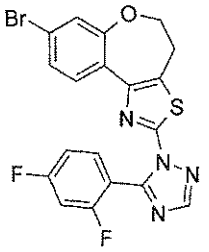
[001016] A solution of 4,8-dibromo-3,4-dihydro-2*H*-benzo[b]oxepin-5-one (1.5 g, 4.7 mmol) and thiosemicarbazide (455 mg, 5 mmol) in IMS (15 mL) was stirred at 85°C for 2h, allowed to cool down to RT and filtered to give the title compound as a beige solid (1.03 g, 70%). LCMS (Method B): R_T = 3.06 min, $[M+H]^+$ = 312 and 314. ^{1}H NMR (DMSO-d_6): 10.10 (2 H, bs), 9.80 (1 H, bs), 8.27 (1 H, d, J = 8.6 Hz), 7.34 (1 H, dd, J = 8.6, 2.1 Hz), 7.22 (1 H, d, J = 2.1 Hz), 4.31 (2 H, t, J = 5.0 Hz), 3.19 (2 H, t, J = 5.0 Hz).

[001017] Step 3: *N*-[1-Dimethylamino-meth-(*E*)-ylidene]-2,4-difluoro-benzamide



[001018] A suspension of 2,4-difluorobenzamide (5 g, 32 mmol) in DMF-DMA (10 mL) was heated at 120°C for 2.5h, allowed to cool down to RT and filtered to afford the title compound as a white solid (6.16 g, 91%). ^{1}H NMR ($CDCl_3$): 8.60 (1 H, s), 8.19-8.12 (1 H, m), 6.91-6.79 (2 H, m), 3.19 (6 H, m).

[001019] Step 4: 8-Bromo-2-[5-(2,4-difluoro-phenyl)-[1,2,4]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

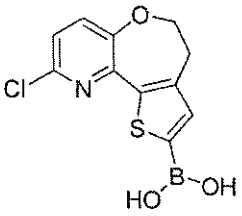


[001020] A suspension of (8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl)-hydrazine (312 mg, 1 mmol) and *N*-[1-dimethylamino-meth-(*E*)-ylidene]-2,4-difluoro-benzamide (232 mg, 1.1 mmol) in acetic acid (6 mL) was heated at 90°C for 3h, allowed to cool down to RT and filtered. The precipitate was washed with diethyl ether and dried to afford the title compound as a beige solid (300 mg, 65%). LCMS (Method B): R_T = 4.51 min, $[M+H]^+$ = 461 and 463. ^{1}H NMR (DMSO-d_6): 8.50 (1 H, s), 7.82 (1 H, td, J = 8.4, 6.4 Hz), 7.57 (1 H, ddd, J = 10.4, 9.4, 2.5 Hz), 7.39-7.30 (2 H, m), 7.23 (1 H, d, J = 2.0 Hz), 7.13 (1 H, dd, J = 8.6, 2.0 Hz), 4.33 (2 H, t, J = 5.0 Hz), 3.34 (2 H, t, J = 5.0 Hz).

[001021] Step 5: 2-[5-(2,4-Difluoro-phenyl)-[1,2,4]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide

[001022] Following the procedure for **414**, Step 4, 8-bromo-2-[5-(2,4-difluoro-phenyl)-[1,2,4]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with hydroxylamine hydrochloride to afford **449** as a white solid. LCMS (Method C): R_T = 9.22 min, $[M+H]^+$ = 426. ^{1}H NMR (DMSO-d_6): 8.51 (1 H, m), 7.98 (1 H, bs), 7.88-7.80 (1 H, m), 7.60-7.53 (1 H, m), 7.51 (1 H, d, J = 1.7 Hz), 7.46-7.34 (4 H, m), 4.34 (2 H, t, J = 5.0 Hz), 3.38 (2 H, t, J = 5.0 Hz).

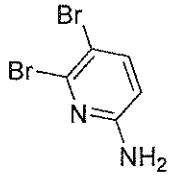
[001023] Example 307 5-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-6-(2,4-difluorophenyl)pyridin-2-amine **454**



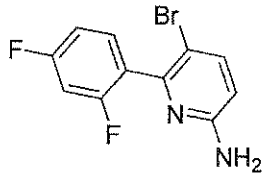
[001024] Step 1: 2-Chloro-6,7-dihydro-pyrido[3,2-b]thieno[2,3-d]oxepine-9-boronic acid

[001025] 4.77 ml (12 mmol) of 2.5 M n-Butyl lithium in hexane was added dropwise to a solution of 3166 mg(10.0 mmol) of 2-chloro-6,7-dihydro-9-bromopyrido[3,2-b]thieno[2,3-d]oxepine in 100 ml of tetrahydrofuran at -76^{0}C. After stirring for 10 min, 3.21 ml (14.0 mmol) of triisopropylborate was added. The mixture was kept at -76^{0}C for 20 min, then 10 ml of saturated aqueous ammonium chloride were added and the mixture was mixed with 360 ml of water. The product was extracted with 150 ml of ethyl acetate. The organic layer was washed

with 100 ml of water, 100 ml of brine and dried over anhydrous sodium sulfate. The solution was filtered and concentrated in vacuum to afford a residue which was then triturated with a mixture of hexane and ethyl ether (1:1). A precipitate was filtered, washed with cold ethyl ether, hexane and dried in vacuum to give 2-Chloro-6,7-dihydro-pyrido[3,2-b]thieno[2,3-d]oxepine-9-boronic acid. Yield 2.20 g (78%). MS: (ESI+) = 282.1.

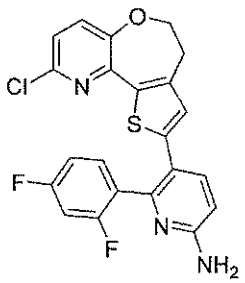


[001026] 5,6-Dibromopyridin-2-amine was synthesized following a procedure in WO 2005/100353.



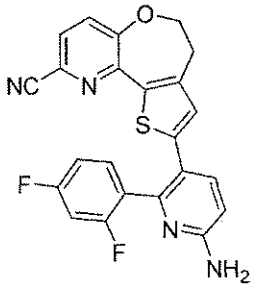
[001027] Step 2: 5-Bromo-6-(2,4-difluorophenyl)pyridin-2-amine.

[001028] A mixture of 5,6-dibromopyridin-2-amine (315 mg, 1.25 mmol), 2,4-difluorophenylboronic acidboronic acid, pinacol ester (197 mg, 1.25 mmol;) and bis(triphenylphosphine)palladium(II) chloride (44.0 mg, 0.063 mmol;) in 1.0 M of Sodium carbonate in water (1.5 mL, 1.5 mmol)) and 4 ml of Acetonitrile was degassed and microwaved on 200 watts at 130°C for 30 minutes. The reaction mixture was partitioned between ethyl acetate and water and filtered from inorganic salts. The organic layer was washed with water, brine, dried over MgSO4 and evaporated to dryness. The crude residue was purified on silicagel column, eluting the product with 0.4% of methanol in methylene chloride. Yield 150 mg (42%). MS: (ESI+) = 285.0.

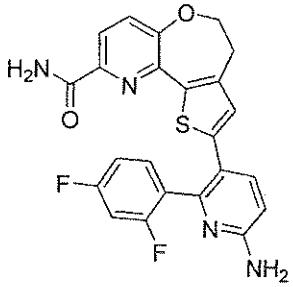


[001029] A mixture of 140 mg (0.49 mmol) of 5-bromo-6-(2,4-difluorophenyl)pyridin-2-amine, 146 mg (0.52 mmol) of 2-chloro-6,7-dihydro-pyrido[3,2-b]thieno[2,3-d]oxepine-9-boronic acid and 20 mg (0.0025mmol) of [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II), complex with dichloromethane (1:1) in 0.86 ml (0.86 mmol) of 1 M aqueous sodium carbonate and 4 ml of dioxane was degassed microwaved on 200 watts at

130°C for 30 minutes. The reaction mixture was partitioned between dichloromethane and water and filtered from inorganic salts. The organic layer was washed with water, brine, dried over MgSO4 and evaporated to dryness. The crude residue was purified on silica gel column, eluting the product with 35-40% of ethyl acetate. Yield 110 mg (51%). MS: (ESI+) 442.2



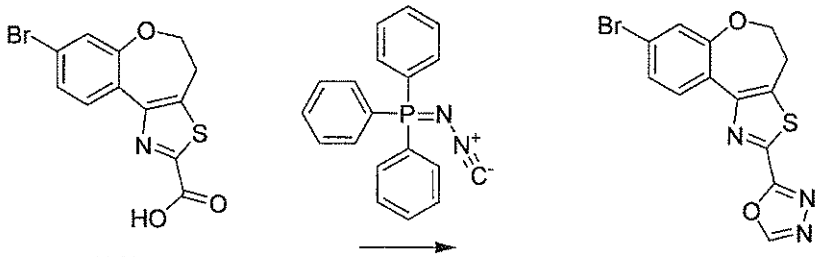
[001030] A suspension of 75 mg (0.168 mmol) of the above product, 59 mg (0.5 mmol) of zinc cyanide, 33 mg (0.5 mmol) of zinc and 20 mg (0.02 mmol) of[1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II), complex with dichloromethane (1:1), in 3 ml of dimethylformamide was degassed and microwaved on 200 watts at 180^{0}C for 30 min. The reaction mixture was mixed with 30 ml of 3% ammonium hydroxide in water and extracted with 20 ml of ethyl acetate three times. The combined organic extract was washed with water, brine, dried over anhydrous sodium sulfate and concentrated in vacuum. The residue was triturated with dichloromethane producing a precipitate, which was collected, washed with cold dichloromethane and dried in vacuum. Yield 47 mg (64%). MS: (ESI+) 432.2



[001031] A mixture of 47 mg (0.11 mmol) of the above nitrile, 61 mg (0.44 mmol) of potassium carbonate and 27 uL (0.44 mmol) of 50% hydrogen peroxide was stirred for 4 hours. Another portion of 27 uM of hydrogen peroxide was added and the mixture was continued to stir for 2 hours. The reaction mixture was mixed with 30 ml of water and extracted with 30 ml of ethyl acetate three times. The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulfate and concentrated in vacuum. The residue was purified by reverse phase HPLC (acetonitrile gradient) to give **454**. Yield 19 mg (38%). MS: (ESI+) 451.1 ^{1}H NMR (400 MHz, DMSO) δ 8.19 (s, 1H), 7.74 (d, J = 8.2, 6H), 7.51 – 7.41 (m, 4H), 7.29 – 7.19 (m, 4H), 7.14 (td, J = 8.5, 2.4, 2H), 6.66 (s, 2H), 6.57 (d, J = 8.6, 2H), 6.42 (s, 4H), 4.31 (t, J = 4.6, 4H), 3.06 (t, J = 4.6, 5H).

[001032] Example 308 8-(1H-pyrazol-4-yl)-(4H-4-isobutyl-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene **455**

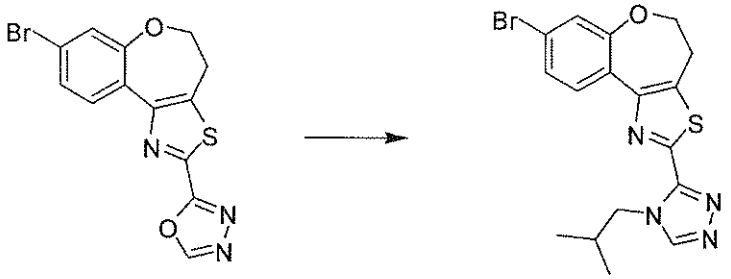
[001033] Step 1: Preparation of (**1B**).



(1A) (1B)

[001034] To (**1A**) (2.5 g, 7.7 mmol) was added DCM (20 mL). To this mixture was added (isocyanoimino)triphenylphosphorane (2.3 g, 7.7 mmol) dissolved in DCM (20 mL) dropwise over 20 minutes. The reaction was allowed to stir 5 hours at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed sequentially with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel eluting with 60% EtOAc in hexanes to provide 0.66 g (25%) of the desired product (**1B**): LC/MS (APCI): m/z 352.0 (M+H).

[001035] Step 2: Preparation of (**1C**).



(1B) (1C)

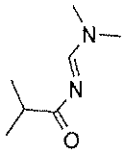
[001036] To (**1B**) (0.236 g, 0.674 mmol) and isobutylamine (0.2 mL, 2 mmol) was added toluene (2 mL) and TFA (0.3 mL) and allowed to stir and heat at 65 °C in a sealed vial for 24 hours. The reaction was monitored by LCMS. To the reaction mixture was added isobutylamine (0.2 mL, 2 mmol) and TFA (0.3 mL) and allowed to stir and heat at 65 °C in a sealed vial for 24 hours. Allowed to cool to room temperature, added EtOAc, filtered, and concentrated the filtrate under reduced pressure to provide 0.273 g (quantitative yield) of the desired product 8-bromo-(4H-4-isobutyl-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (**1C**): LC/MS (APCI): m/z 405.0 (M+H).

[001037] Step 3: Preparation of **455**.

[001038] To 8-bromo-(4H-4-isobutyl-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (**1C**) (0.273 g, 0.674 mmol), 4-pyrazole boronic acid (0.060 g, 0.808 mmol), potassium acetate (0.264 g, 2.69 mmol) and tetrakis(triphenylphosphine)palladium(0) (39 mg, 0.03 mmol) was added DMF (10 mL) and water (1 mL). Nitrogen was bubbled through the reaction mixture for 5 minutes. The reaction mixture was allowed to stir and heat at 105 °C for 24 hours. The reaction mixture was concentrated under reduced pressure and purified by reverse phase HPLC provide 0.023 g (9%) of **455**: LC/MS (APCI): m/z 393.1 (M+H).

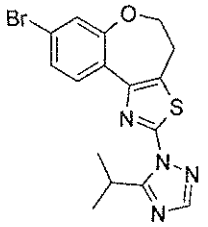
[001039] Example 309 2-(5-Isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide **478**

[001040] Step 1: [1-Dimethylamino-meth-(*E*)-ylidene]-isobutyramide



[001041] Following the procedure for **449**, Step 3, isobutyramide was reacted with DMF-DMA to afford the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$): 8.39 (1 H, s), 3.10 (3 H, m), 3.07 (3 H, d, J = 0.67 Hz), 2.68-2.56 (1 H, m), 1.17 (3 H, s), 1.18-1.11 (3 H, s).

[001042] Step 2: 8-Bromo-2-(5-isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene



[001043] Following the procedure for **449**, Step 4, (8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl)-hydrazine was reacted with [1-dimethylamino-meth-(*E*)-ylidene]-isobutyramide to afford the title compound as a beige solid. LCMS (Method D): R_T = 5.09 min, $[M+H]^+$ = 391 and 393. ^{1}H NMR ($CDCl_3$): 8.14 (1 H, d, J = 8.5 Hz), 7.89 (1 H, s), 7.31-7.24 (2 H, m), 4.40 (2 H, t, J = 5.0 Hz), 4.15-4.07 (1 H, m), 3.33 (2 H, t, J = 5.0 Hz), 1.50 (3 H, s), 1.48 (3 H, s).

[001044] Step 3: 2-(5-Isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide

[001045] Following the procedure for **414**, Step 4, 8-bromo-2-(5-isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with hydroxylamine hydrochloride to afford **478** as a white solid. LCMS (Method C): R_T = 8.56 min, $[M+H]^+$ = 356. ^{1}H NMR (DMSO-d_6): 8.26 (1 H, d, J = 8.3 Hz), 8.17 (1 H, s), 7.99 (1 H, bs), 7.69 (1 H, dd, J =

8.3, 1.8 Hz), 7.57 (1 H, d, J = 1.8 Hz), 7.41 (1 H, bs), 4.39 (2 H, t, J = 5.0 Hz), 4.10-4.00 (1 H, m), 3.41 (2 H, t, J = 5.0 Hz), 1.42 (3 H, s), 1.41 (3 H, s).

[001046] Example 310 2-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-3-(2,4-difluorophenyl)-5-aminopyrazine **480**

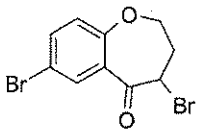
[001047] Following the procedures for **454**, compound **480** was prepared. MS: (ESI+) 452.0. ^{1}H NMR (400 MHz, DMSO) δ 8.49 (d, 1H), 7.99 (s, 2H), 7.77 (d, *J* = 8.3, 5H), 7.57 (dd, *J* = 15.0, 8.5, 4H), 7.49 (d, *J* = 8.3, 2H), 7.38 (d, *J* = 12.1, 4H), 7.27 (t, *J* = 9.9, 3H), 6.96 (s, 4H), 6.34 (s, 2H), 4.30 (t, *J* = 4.6, 3H), 3.00 (t, *J* = 4.4, 3H)

[001048] Example 311 2-(5-Isopropyl-[1,2,4]triazol-1-yl)-8-(1*H*-pyrazol-4-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene **484**

[001049] A suspension of 8-bromo-2-(5-isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (84 mg, 0.21 mmol), 4,4,5,5-tetramethyl-2-(1*H*-pyrazol-4-yl)-1,3,2-dioxaborolane (62 mg, 0.32 mmol), tetrakis(triphenylphosphine) palladium (0) (24 mg, 0.021 mmol) and sodium carbonate (45 mg, 0.42 mmol) in acetonitrile (6 mL) and water (3 mL) under nitrogen was heated at 140°C for 25 mins under microwave irradiation. More tetrakis(triphenylphosphine) palladium (0) (24 mg, 0.021 mmol) was added, and heating was pursued for 30 mins at 150°C. The reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with brine, dried (Na_2SO_4), concentrated *in vacuo* and purified twice by flash chromatography (SiO_2, gradient 50 to 75 % ethyl acetate in cyclohexane, then 60% ethyl acetate in cyclohexane) to afford **484** as an off-white solid (16 mg, 20%). LCMS (Method C): R_T = 10.30 min, $[M+H]^+$ = 379. ^{1}H NMR (DMSO-d_6): 12.98 (1 H, bs), 8.28 (1 H, bs), 8.18 (1 H, d, J = 8.3 Hz), 8.16 (1 H, s), 7.99 (1 H, bs), 7.46 (1 H, dd, J = 8.3, 1.8 Hz), 7.34 (1 H, d, J = 1.8 Hz), 4.38 (2 H, t, J = 5.0 Hz), 4.13-4.01 (1 H, m), 3.37 (2 H, t, J = 5.0 Hz), 1.43 (3 H, s), 1.41 (3 H, s).

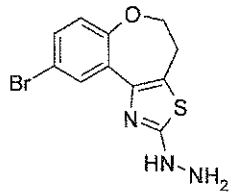
[001050] Example 312 2-(5-Isopropyl-[1,2,4]triazol-1-yl)-9-(1*H*-pyrazol-4-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene **489**

[001051] Step 1: 4,7-Dibromo-3,4-dihydro-2*H*-benzo[b]oxepin-5-one



[001052] Following the procedure for **449**, Step 1, 7-bromo-3,4-dihydro-2*H*-benzo[b]oxepin-5-one was reacted with bromine to afford the title compound as a white solid. ^{1}H NMR ($CDCl_3$): 7.86 (1 H, d, J = 2.6 Hz), 7.53 (1 H, dd, J = 8.7, 2.6 Hz), 6.96 (1 H, d, J = 8.7 Hz), 4.94 (1 H, dd, J = 7.6, 6.7 Hz), 4.43 (1 H, ddd, J = 12.7, 5.6, 4.7 Hz), 4.18 (1 H, ddd, J = 12.7, 9.7, 4.4 Hz), 2.97-2.87 (1 H, m), 2.51 (1 H, ddt, J = 14.7, 7.6, 4.6 Hz).

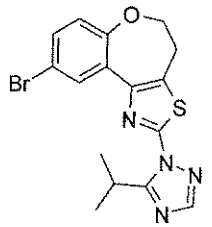
[001053] Step 2: (9-Bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl)-hydrazine



[001054]

[001055] Following the procedure for **449**, Step 2, 4,7-dibromo-3,4-dihydro-2*H*-benzo[b]oxepin-5-one was reacted with thiosemicarbazide to afford the title compound as a beige solid. LCMS (Method E): R_T = 3.85 min, $[M+H]^+$ = 312 and 314. ^1H NMR (DMSO-d_6): 10.13 (2 H, bs), 9.80 (1 H, bs), 8.49 (1 H, d, J = 2.6 Hz), 7.37 (1 H, dd, J = 8.6, 2.6 Hz), 6.97 (1 H, d, J = 8.6 Hz), 4.29 (2 H, t, J = 5.0 Hz), 3.21 (2 H, t, J = 5.0 Hz).

[001056] Step 3: 9-Bromo-2-(5-isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene



[001057] Following the procedure for **449**, Step 4, (9-Bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulen-2-yl)-hydrazine was reacted with [1-dimethylamino-meth-(*E*)-ylidene]-isobutyramide to afford the title compound as a beige solid. LCMS (Method E): R_T = 5.22 min, $[M+H]^+$ = 391 and 393. ^1H NMR (DMSO-d_6): 8.32 (1 H, d, J = 2.6 Hz), 8.17 (1 H, s), 7.44 (1 H, dd, J = 8.6, 2.6 Hz), 7.04 (1 H, d, J = 8.6 Hz), 4.37 (2 H, t, J = 5.0 Hz), 4.01-3.93 (1 H, m), 3.38 (2 H, t, J = 5.0 Hz), 1.43 (3 H, s), 1.41 (3 H, s).

[001058] Step 4: 2-(5-Isopropyl-[1,2,4]triazol-1-yl)-9-(1*H*-pyrazol-4-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene

[001059] Following the procedure for **484**, Step 4, 9-bromo-2-(5-isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1*H*-pyrazole to afford **489** as a white solid. LCMS (Method C): R_T = 10.17 min, $[M+H]^+$ = 379. ^1H NMR (DMSO-d_6): 12.95 (1 H, bs), 8.42 (1 H, d, J = 2.3 Hz), 8.18 (1 H, s), 8.07 (1 H, bs), 7.81 (1 H, bs), 7.51 (1 H, dd, J = 8.3, 2.3 Hz), 7.06 (1 H, d, J = 8.3 Hz), 4.36 (2 H, t, J = 5.0 Hz), 4.12-4.04 (1 H, m), 3.38 (2 H, t, J = 5.0 Hz), 1.47 (3 H, s), 1.46 (3 H, s).

[001060] Example 313 2-(5-Isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-9-carboxylic acid amide **490**

[001061] Following the procedure for **414**, Step 4, 9-bromo-2-(5-isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with hydroxylamine hydrochloride to afford **490** as a white solid. LCMS (Method C): R_T = 8.44 min, $[M+H]^+$ = 356. ^1H NMR (DMSO-d_6): 8.82 (1 H, d, J = 2.3 Hz), 8.17 (1 H, s), 7.91 (1 H, bs), 7.75 (1 H, dd, J = 8.4, 2.3 Hz), 7.24 (1 H, bs), 7.09 (1 H, d, J = 8.4 Hz), 4.40 (2 H, t, J = 5.0 Hz), 4.10-4.02 (1 H, m), 3.39 (2 H, t, J = 5.0 Hz), 1.43 (3 H, s), 1.41 (3 H, s).

[001062] Example 314 2-(5-Isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid (2-hydroxy-ethyl)-amide **498**

[001063] Following the procedure for **414**, Step 4, 8-bromo-2-(5-isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with 2-aminoethanol to afford **498** as an off-white solid. LCMS (Method C): R_T = 8.12 min, $[M+H]^+$ = 400. ^1H NMR (DMSO-d_6): 8.45 (1 H, t, J = 5.6 Hz), 8.27 (1 H, d, J = 8.3 Hz), 8.17 (1 H, s), 7.67 (1 H, dd, J = 8.3, 1.8 Hz), 7.56 (1 H, d, J = 1.8 Hz), 4.71 (1 H, t, J = 5.6 Hz), 4.39 (2 H, t, J = 5.0 Hz), 4.10-4.02 (1 H, m), 3.51 (2 H, q, J = 6.0 Hz), 3.41 (2 H, t, J = 5.0 Hz), 3.34 (2 H, q, J = 6.0 Hz), 1.42 (3 H, s), 1.40 (3 H, s).

[001064] Example 315 2-(5-Isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-9-carboxylic acid (2-hydroxy-ethyl)-amide **499**

[001065] Following the procedure for **414**, Step 4, 9-bromo-2-(5-isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene was reacted with 2-aminoethanol to afford **499** as an off-white solid. LCMS (Method C): R_T = 8.02 min, $[M+H]^+$ = 400. H NMR (DMSO-d_6): 8.81 (1 H, d, J = 2.3 Hz), 8.35 (1 H, t, J = 5.6 Hz), 8.17 (1 H, s), 7.75 (1 H, dd, J = 8.4, 2.3 Hz), 7.11 (1 H, d, J = 8.4 Hz), 4.71 (1 H, t, J = 5.6 Hz), 4.40 (2 H, t, J = 4.9 Hz), 4.11-4.01 (1 H, m), 3.52 (2 H, q, J = 6.0 Hz), 3.40 (2 H, t, J = 4.9 Hz), 3.34 (2 H, q, J = 6.1 Hz), 1.44 (3 H, s), 1.42 (3 H, s).

[001066] Example 316 8-(morpholinomethanimine)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene **501**

[001067] Prepared as for **512**, 8-methylthioamide-(2-isopropyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (162 mg, 0.42 mmoles) was reacted in a round-bottom flask equipped with a magnetic stir-bar, with morpholine (73.3 μL, 0.84 mmoles, 2 equiv.), acetic acid (48.1 μL, 0.84 mmoles, 2 equiv.) and methanol (2.1 mL) and stirred at room temperature for 2 hours. The mixture was concentrated to dryness and purified by reverse-phase HPLC to obtain 119.8 mg 67 % yield of **501** as a colorless solid.

[001068] Example 317 2-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-aminopyrazine **503**

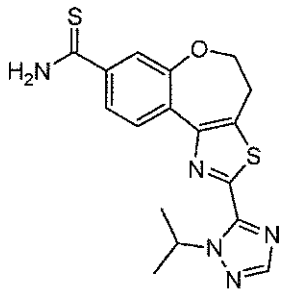
[001069] Following the procedures for **454**, compound **503** was prepared. MS: (ESI+) 340.0. ^{1}H NMR (400 MHz, DMSO) δ 8.50 (d, J = 1.2, 1H), 7.89 (d, J = 1.3, 1H), 7.79 (d, J = 8.3, 1H), 7.68 (s, 1H), 7.56 (s, 1H), 7.51 (d, J = 8.3, 1H), 7.48 (s, 1H), 6.70 (s, 2H), 4.40 (t, J = 4.5, 2H), 3.24 (t, J = 4.6, 2H).

[001070] Example 318 8-(morpholinomethanimine)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene **511**

[001071] Prepared as for **512**, 8-methylthioamide-(2-isopropyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (150 mg, 0.39 mmoles) was reacted in a round-bottom flask equipped with a magnetic stir-bar with ammonium acetate (749.8 mg, 9.73 mmoles, 25 equiv.) and methanol (1.95 mL). The reaction mixture was stirred at room temperature for 4 hours. Saturated Na_2CO_3 was added and the reaction mixture was extracted with methylene chloride (3x). The organic phases were combined, dried with $MgSO_4$, and concentrated. The product was purified by reverse phase HPLC to obtain 11.5 mg (8.3 % yield) of **511** as a colorless solid.

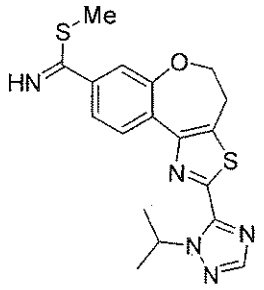
[001072] Example 319 8-(methylformamidinyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene **512**

[001073] 8-Bromo-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (330 mg, 0.84 mmol) and degassed dimethylformamide (4.2 mL) were added to a CEM microwave vial. The mixture was thoroughly purged with nitrogen. Zinc cyanide (99.0 mg, 0.84 mmol, 1.0 equiv.) and $Pd(PPh_3)_4$ (48.7 mg, 0.04 mmol, 0.05 equiv.) were added to the reaction mixture in one portion and the vial was sealed immediately. The reaction was submitted to MW irradiation at 60W for 15 minutes (T = 175 °C). The mixture was diluted with methylene chloride, filtered through celite, and washed with saturated NH_4Cl. The organic layers were combined, dried with $MgSO_4$ and concentrated. The crude mixture was loaded onto silica gel and purified by flash chromatography (0-100% EtOAc in hexanes) to give 202 mg (71.3 % yield) of 8-cyano-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene a yellow solid.



[001074] In a round-bottom flask equipped with a magnetic stir-bar, hydrogen sulfide was bubbled through a solution of 8-cyano-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-

thia-1-aza-benzo[e]azulene (750 mg, 2.22 mmoles) in pyridine (10.0 mL) and triethylamine (1.11 mL) for 20 minutes. The reaction mixture was stirred at room temperature overnight, concentrated, and partitioned between 5% methanol in methylene chloride and H_2O. The combined organics were washed with brine, dried over $MgSO_4$, and concentrated to give 8-thioamide-(2-isopropyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene. LCMS showed clean conversion to product – product was carried forward crude without further purification (obtained as a yellow solid).



[001075] To a solution of 8-thioamide-(2-isopropyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene (820 mg, 2.21 mmoles) in acetone (5.52 mL) in a round bottom flask equipped with a magnetic stir-bar was added methyl iodide (0.69 mL, 11.04 mmoles, 5 equiv.) via syringe. The mixture was stirred at room temperature overnight. LCMS showed clean conversion to 8-methylthioamide-(2-isopropyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene. The solution was concentrated to dryness and used crude in a round-bottom flask equipped with a magnetic stir-bar, monomethylamine (2M in methanol, 0.39 mL, 0.78 mmoles, 2 equiv.) and acetic acid (45 μL, 0.78 mmoles, 2 equiv.) in methanol (1.95 mL). The mixture was added to the thiomethyl imidate (150 mg, 0.39 mmoles) and stirred at room temperature for 4 hours. The mixture was concentrated to dryness and purified by reverse-phase HPLC to obtain **512**, 32.8 mg (22.9 % yield) of a colorless solid.

[001076] Example 320 5-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-2-amino-6-ethylpyridine **521**

[001077] Following the procedures for **454**, compound **521** was prepared. MS: (ESI+) 367.0. ^{1}H NMR (400 MHz, DMSO) δ 7.79 (d, J = 8.3, 1H), 7.65 (s, 1H), 7.52 (d, J = 8.4, 2H), 7.40 (d, J = 8.4, 1H), 6.94 (s, 1H), 6.34 (d, J = 8.4, 1H), 6.09 (s, 2H), 4.40 (t, J = 4.5, 2H), 3.25 (t, J = 4.5, 2H), 2.73 (q, J = 7.5, 2H), 1.17 (t, J = 7.5, 3H).

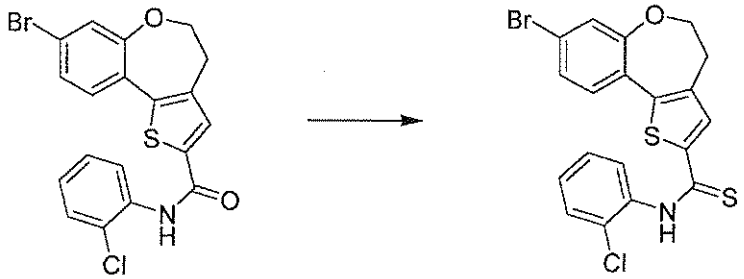
[001078] Example 321 3-(9-Bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-4-(2,4-dichloro-phenyl)-4H-[1,2,4]triazole **532**

[001079] A microwave tube charged with 2-(9-bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azulen-2-yl)-[1,3,4]oxadiazole (200 mg; 0.57 mmol), 2,4-dichloroaniline (139 mg; 0.86 mmol), TFA (64 μl; 0.86 mmol) and toluene (1.5 ml) was heated in a microwave at 160 °C for

30 min. The reaction mixture was basified with DIPEA (0.2 ml), volatiles removed in vacuo and the residue purified by prep. LCMS to give **532** as a pale yellow solid (129 mg; 46 %). δ_H (400 MHz, $CDCl_3$) 3.14 (t, J = 5.2, 2H), 4.29 (t, J = 5.2, 2H), 6.89-6.92 (m, 2H), 7.25-7.28 (m ,1H), 7.42 (d, J = 8.4, 1H), 7.52 (dd, J = 8.4 and 2.4, 1H), 7.66 (d, J = 2.4, 1H), 7.71 (d, J = 2.0, 1H), 8.22 (s, 1H). $[M+H]^+$: 493

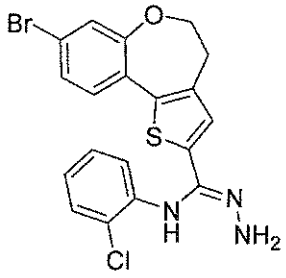
[001080] Example 322 N-(2-aminoethyl)-2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide **533**

[001081] Step 1: Preparation of 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbothioamide



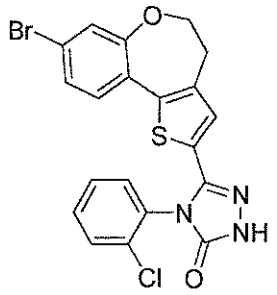
[001082] A solution of 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (10 g, 0.023 mol) in anhydrous 1,4-dioxane (400 mL) was treated with Lawesson's reagent (7.44 g, 0.018 mol) and heated at 85 °C for 4 h. The orange solution was cooled to room temperature and concentrated in vacuo. The crude product was washed with CH_2Cl_2 and then dried to give 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbothioamide as a yellow solid (9.41 g, yield 91 %). ESI-MS: 449.9.

[001083] Step 2: Preparation of 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbohydrazonamide



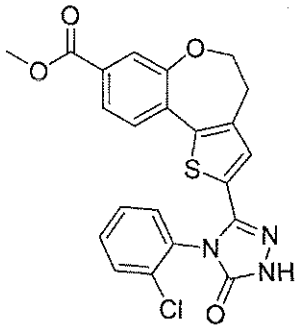
[001084] 8-Bromo-4,5-dihydro-6-oxa-1-thia-benzo[e]azuene-2-carbothiolic acid (2-chloro-phenyl)–methyl-amide (9 g, 19.96 mmol) was suspended in ethanol (150 mL), mixed with 85% hydrazine aqueous solution (30 mL) and heated under reflux for 3 h. At this time, it was observed that the suspension was decolored. After cooling to room temperature, the solid was filtered and washed with ethanol, concentrated under vacuum to give 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbohydrazonamide as a yellow solid (7.41 g, yield 83 %). ESI-MS: 447.98

[001085] Step 3: Preparation of 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one



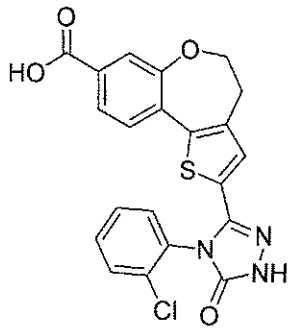
[001086] A solution of 8-bromo-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbohydrazonamide (200 mg, 0.45 mmol) in anhydrous THF (8 mL) was treated with CDI (145 mg, 0.89 mmol) and stirred at room temperature overnight, diluted with water. The solid was washed with water and dried in vacuum to give 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one (195 mg, yield: 92%). ESI-MS: 473.96

[001087] Step 4: Preparation of methyl 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate



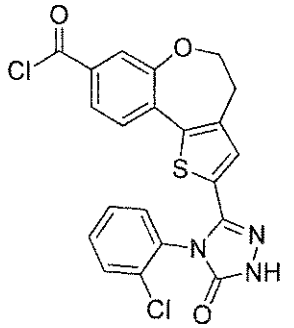
[001088] The mixture of 3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one (6.5 g, 13.7 mmol), $Pd(OAc)_2$ (1.54 g, 6.85 mmol), dppf (6.1 g, 11.0 mmol), TEA(3.8 mL) in DMF (30 mL) and MeOH (60 mL) was stirred under CO(50 psi) atmosphere at 70 °C for 2 days. Filtered and concentrated, the crude product was purified by column chromatography (Hexanes: EtOAc =2: 1~1: 1) to give methyl 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate (5.83 g, yield 94 %). ESI-MS: 454.2.

[001089] Step 5: Preparation of 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid



[001090] Methyl 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate (5.83 g, 12.8 mmol) was dissolved in 25 mL of THF and 25 mL of water and treated with LiOH (1.35 g, mono-hydrate). The whole was heated at 50 °C for 3 h, cooled to room temperature and acidified. The resulting precipitate was filtered and washed with water. The filter cake was dried to a constant weight under vacuum to give 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid (5.47 g, yield 97 %). ESI-MS: 440.2. ^{1}H NMR (DMSO-d_6, 400 MHz): δ12.34 (s, 1H, NH), 7.74- 7.42 (m, 7H, ArH), 6.50 (s, 1H, =CH), 4.18 (t, J= 5.2 Hz, 2H, CH_2), 2.98 (t, J= 5.2 Hz, 2H, CH_2).

[001091] Step 6: Preparation of 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride



[001092] A solution of 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5- dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate acid (400 mg, 0.91 mmol) in 20 mL of $SOCl_2$ was heated at 80 °C for 3 h. Concentration gave 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride.

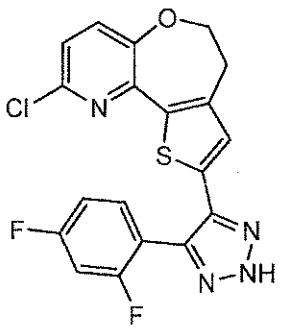
[001093] To a solution of ethane-1,2-diamine (82 mg, 1.36 mmol) and pyridine (0.5 mL) in 5 mL of THF was slowly added 2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonyl chloride (ca.417 mg, ca.0.91 mmol) in 20 mL of THF at 0 °C. The mixture was stirred at room temperature overnight, diluted with water and purified by preparative HPLC to afford 66 mg of **533**, isolated yield: 20%. ESI-MS: 482. ^{1}H NMR (DMSO- d_6, 400 MHz): δ 8.74 (s, 1H, NH), 8.37 (s, 1H, NH), 7.74- 7.47 (m, 7H,

ArH), 6.47 (s, 1H, =CH), 4.19 (t, J= 4.8 Hz, 2H, CH_2), 3.40- 3.36 (m, 4H, $2CH_2$), 2.98 (t, *J*= 5.2 Hz, 2H, CH_2), 2.86 (t, *J*= 6.0 Hz, 2H, CH_2).

[001094] Example 323 3-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-2-(2,4-difluorophenyl)-2H-1,2,4-triazole **366**

[001095] To solution containing 3-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-2-(2,4-difluorophenyl)-2H-1,2,4-triazole (0.030 g, 0.072 mmol), zinc cyanide (16.9 mg, 0.144 mmol), and tetrakis(triphenylphosphine)palladium(0) (4.16 mg, 0.00360 mmol) in N,N-dimethylformamide (1.00 mL, 12.9 mmol) was evacuated then back-filled with nitrogen. The reaction mixture was heated in microwave to 200 °C for 10min. The reaction mixture was quenched with sat.NH4Cl then extracted EtOAc (3X). The crude product was purified by column chromatography (EtOAc/Hex) (eluted 50% EtOAc) to give **366** (60% yield). MS: (ESI+) = 408.0

[001096] Example 324 4-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2,4-difluorophenyl)-2H-1,2,3-triazole **367**



[001097] To solution containing 4-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2,4-difluorophenyl)-2H-1,2,3-triazole (0.085 g, 0.20 mmol), zinc cyanide (47.9 mg, 0.408 mmol;), and tetrakis(triphenylphosphine)palladium(0) (11.8 mg, 0.0102 mmol;) in N,N-dimethylformamide (2.83 mL, 36.6 mmol;) was evacuated then back-filled with nitrogen. The reaction mixture was heated in microwave to 200 °C for 10min. The reaction mixture was quenched with sat.NH4Cl then extracted EtOAc (3X). The crude product was purified by column chromatography (EtOAc/Hex) to give **367** (84% yield). MS: (ESI+) = 408.2

[001098] Example 325 N-(4-(dimethylcarbamoyl)phenyl)-N-methyl-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide **378**

[001099] Following the procedure for **366**, compound **362**, zinc cyanide, and tetrakis(triphenylphosphine)palladium(0) in N,N-dimethylformamide were reacted to give **378**. Yield 38% MS: (ESI+) = 433.2

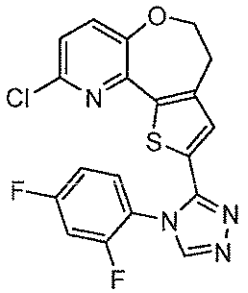
[001100] Example 326 4-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2,4-difluorophenyl)-2H-1,2,3-triazole **379**

[001101] To a solution of **367** (70.0 mg, 0.172 mmol) in dimethyl sulfoxide (0.439 mL, 6.18 mmol) and treated with a solution of potassium carbonate (65.5 mg, 0.474 mmol;) in water (0.433 mL, 24.0 mmol;). After cooling at 0 °C, hydrogen peroxide (0.540 mL, 7.04 mmol) was added slowly. The reaction was complete by LCMS at 15 min. Saturated sodium bisulfite (0.894 g, 8.59 mmol) was added and the reaction mixture extracted into ethyl acetate. The organics were washed with brine, dried over sodium sulfate and concentrated to give crude C which was submitted to reverse-phase HPLC to give **379** (27% yield). MS: (ESI+) = 426.1

[001102] Example 327 3-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole **392**

[001103] Following the procedure to prepare **379**, compound **393**, hydrogen peroxide, potassium carbonate in water and DMSO were reacted to give **392**. Yield 38% MS: (ESI+) = 426.2

[001104] Example 328 3-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole **393**

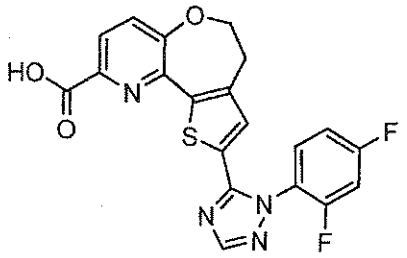


[001105] Following the procedure to give **366**, 4-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2,4-difluorophenyl)-2H-1,2,3-triazole, 3-(2-chlro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole, zinc cyanide, and tetrakis(triphenylphosphine)palladium(0) in N,N-dimethylformamide were reacted to give **393**. Yield 80% MS: (ESI+) = 408.0

[001106] Example 329 5-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole **432**

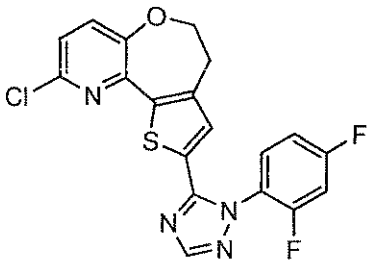
[001107] Following the procedure to prepare **379**, compound **366**, hydrogen peroxide, potassium carbonate in water and DMSO were reacted to give **432**. Yield 38% MS: (ESI+) = 426.1

[001108] Example 330 (9-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-2-yl)(4-methylpiperazin-1-yl)methanone **433**



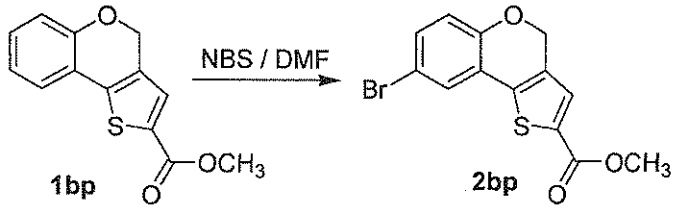
[001109] 5-(2-Carboxy-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole (0.052 g, 0.12 mmol) was dissolved in N,N-dimethylformamide (0.904 mL, 0.0117 mol) and treated sequentially with N,N-diisopropylethylamine (0.127 mL, 0.732 mmol) 1-methyl-piperazine, (0.0541 mL, 0.488 mmol), then N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU, 0.0556 g, 0.146 mmol). The reaction was stirred at room temperature overnight. Saturated sodium bicarbonate was added and extracted with ethyl acetate. Organics were dried over sodium sulfate and concentrated. The crude product was submitted HPLC purification to give **433** (32% yield). MS: (ESI+) = 509.3

[001110] Example 331 5-(2-(2-methylpyrid-3-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole **474**



[001111] 5-(2-(Chloro)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole (50 mg, 0.1 mmol) was dissolved in 1 ml acetonitrile and 1 ml water, with potassium acetate (39.9 mg, 0.406 mmol). The solution was degassed by bubbling with nitrogen for 5 min. 2-Methylpyridin-3-ylboronic acid (21.4 mg, 0.156 mmol) was added, then tetrakis(triphenylphosphine)palladium(0) (19 mg, 0.016 mmol). The reaction was microwaved at 300 watts, 140°C for 20 minutes, cooled to room temperature, and extracted with ethyl acetate. The combined organics were concentrated and purified by reverse phase HPLC to give **474** (70% yield). MS: (ESI+) = 474.0

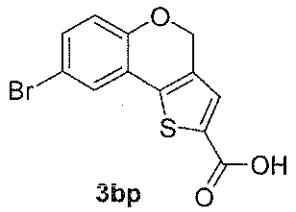
[001112] Example 2bp Methyl 8-bromo-4H-thieno[3,2-c]chromene-2-carboxylate **2bp**



1bp 2bp

[001113] To a solution of methyl 4H-thieno[3,2-c]chromene-2-carboxylate **1bp** (Sigma Aldrich, CAS Reg. 126522-01-8; Sekhar et al (1989) Sulfur Letters 9(6):271-7; 2.00 g, 8.12 mmol, 1 equiv) in *N*,*N*-dimethylformamide (31 mL) was added *N*-bromosuccinimide (1.91 g, 10.7 mmol, 1.32 equiv) at 24 °C over 5 min, as in General Procedure A. After 20 hr, the reaction mixture was diluted with water (100 mL). The resulting suspension was filtered through a Buchner funnel. The resulting tan solid was air dried to yield **2bp** (2.77 g). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.52 (s, 1 H), 7.45 (d, J = 2.3 Hz, 1 H), 7.29 (dd, J = 8.6, 2.3 Hz, 1 H), 6.83 (d, J = 8.6 Hz, 1 H), 5.26 (s, 2 H), 3.91 (s, 3 H).

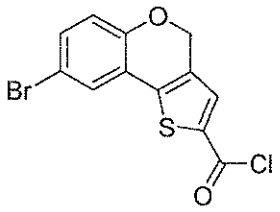
[001114] Example 3bp 8-Bromo-4H-thieno[3,2-c]chromene-2-carboxylic acid **3bp**



3bp

[001115] To a suspension of methyl 8-bromo-4H-thieno[3,2-c]chromene-2-carboxylate **2** (2.64 g, 8.12 mmol, 1 equiv) in 4:1 tetrahydrofuran / water (80 mL) was added aqueous potassium hydroxide (24 mL, 24 mmol, 3.0 equiv, 1.0 M solution in water) at 24 °C. After 15 hr, the tetrahydrofuran was removed in vacuo (<20 mm Hg). The resulting aqueous suspension was diluted with water until all the solids were dissolved. To the resulting solution was added concentrated hydrochloric acid until the solution reached pH = 1. The resulting solids were collected by filtration and dried in vacuo (<1 mm Hg) to afford **3bp** as a yellow solid (2.36 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 13.28 (br s, 1 H), 7.64 (d, J = 2.4 Hz, 1 H), 7.60 (s, 1 H), 7.40 (dd, J = 8.7, 2.4 Hz, 1 H), 6.94 (d, J = 8.7 Hz, 1 H), 5.30 (s, 3 H).

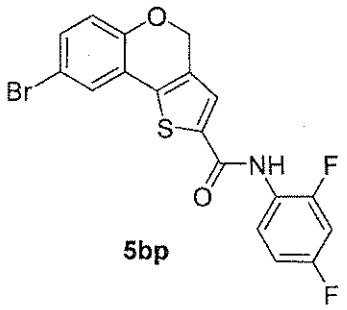
[001116] Example 4bp 8-bromo-4H-thieno[3,2-c]chromene-2-carbonyl chloride **4bp**



4bp

[001117] To a suspension of 8-bromo-4H-thieno[3,2-c]chromene-2-carboxylic acid **3bp** (1.50 g, 4.82 mmol, 1 equiv) in dichloromethane (45 mL) at 24 °C was sequentially added oxalyl chloride (3.1 mL, 6.3 mmol, 1.3 equiv, 2.0 M in dichloromethane) and *N,N*-dimethylformamide (56 μL, 0.72 mmol, 0.15 equiv), as in General Procedure B. After 2 hr, the clear yellow solution was concentrated in vacuo (~20 mm Hg) to afford crude **4bp**.

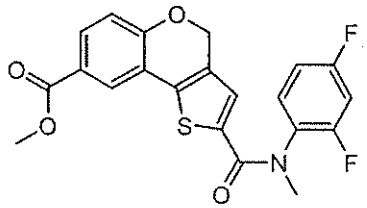
[001118] Example 5bp 8-Bromo-N-(2,4-difluorophenyl)-4H-thieno[3,2-c]chromene-2-carboxamide **5bp**



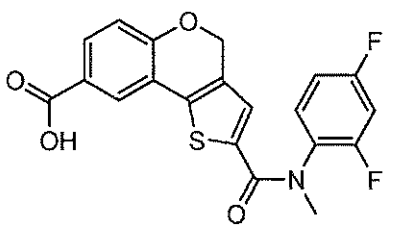
5bp

[001119] 8-Bromo-4H-thieno[3,2-c]chromene-2-carbonyl chloride **4bp** is reacted with 2,4-difluoroaniline to give **5bp**, as in General Procedure B-bp.

[001120] Example 6bp (R)-N-(2,4-difluorophenyl)-8-(3-hydroxypiperidine-1-carbonyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **105bp**



[001121] A solution of 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** (3.0 g, 6.9 mmol), palladium (II) acetate (1.5 g, 6.9 mmol), dppf (7.6 g, 13.8 mmol), and triethylamine (1.38 g, 13.8 mmol) in *N,N*-dimethylformamide (50 mL) and methanol (50 mL) was stirred at 70 °C for 48 hr under a carbon monoxide atmosphere. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The resulting black residue was purified by flash column chromatography to afford 1.2 g of methyl 2-((2,4-difluorophenyl)(methyl)carbamoyl)-4H-thieno[3,2-c]chromene-8-carboxylate. LCMS (ESI) *m/z*: 416.



[001122] A solution of methyl 2-((2,4-difluorophenyl)(methyl)carbamoyl)-4H-thieno[3,2-c]chromene-8-carboxylate, sodium hydroxide (115 mg, 2.9 mmol) in ethanol (20 mL), tetrahydrofuran (20 mL) and water (20 mL) was stirred at room temperature for 16 hr. The reaction mixture was acidified to pH=2 with concentrated hydrochloric acid, and the organic solvents were removed in vacuo. The resulting aqueous solution was extracted with ethylacetate. The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated to afford 2-((2,4-difluorophenyl)(methyl)carbamoyl)-4H-thieno[3,2-c]chromene-8-carboxylic acid (1.0 g). LCMS (ESI) *m/z*: 402.

[001123] A solution of 2-((2,4-difluorophenyl)(methyl)carbamoyl)-4H-thieno[3,2-c]chromene-8-carboxylic acid (0.100 g, 0.250 mmol), (*R*)-3-hydroxypiperidine (50.5mg, 0.500 mmol), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (114 mg, 0.3 mmol), *N,N*-diisopropylethylamine (39 mg, 0.3 mmol) in *N,N*-dimethylformamide (2 mL) was stirred at room temperature overnight. The reaction mixture was diluted with ethylacetate, and the resulting solution was washed with water. The collected organic was concentrated. Purification by preparative thin layer chromatography (3:1 petroleum ether / ethylacetate) afforded **105bp** (50 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.24 (m, 2H), 7.14–7.17 (m, 1H), 6.88–6.92 (m, 2H), 6.78–6.82 (m, 2H),5.08 (s, 1H), 3.70–3.9 (br s, 1H), 3.26–3.5 (br s, 5H), 1.75–1.94 (m, 2H), 1.46–1.68 (m, 4H). LCMS (ESI) *m/z*: 485.0

[001124] Example 7bp N2-(2,4-difluorophenyl)-N8-(2-(dimethylamino)ethyl)-N2-methyl-4H-thieno[3,2-c]chromene-2,8-dicarboxamide **109bp**

[001125] Following the procedure of Example 15 and General Procedure C, 2-((2,4-difluorophenyl)(methyl)carbamoyl)-4H-thieno[3,2-c]chromene-8-carboxylic acid and *N1,N1*-dimethyl-1,2-ethanediamine were coupled to give **109bp**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br s, 1 H), 7.67 (s, 1 H), 7.56 (m, 1 H), 7.25 (m, 1 H), 6.88 (m, 2 H), 6.78 (m, 1 H), 6.69 (s, 1 H), 5.07 (s, 2 H), 3.78 (m, 2 H), 3.31 (s, 3 H), 3.27 (m, 2 H), 2.84 (s, 6 H). LCMS (ESI) *m/z*: 472.2

[001126] Example 8bp (S)-N-(2,4-difluorophenyl)-8-(3-hydroxypiperidine-1-carbonyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **110bp**

[001127] Following the procedure of Example 15 and General Procedure C, 2-((2,4-difluorophenyl)(methyl)carbamoyl)-4H-thieno[3,2-c]chromene-8-carboxylic acid and (*S*)-3-hydroxypiperidine were coupled to give **110bp**. LCMS (ESI) *m/z*: 485.0

[001128] Example 9bp N2-(2,4-difluorophenyl)-N2,N8,N8-trimethyl-4H-thieno[3,2-c]chromene-2,8-dicarboxamide **111bp**

[001129] Following the procedure of Example 15 and General Procedure C, 2-((2,4-difluorophenyl)(methyl)carbamoyl)-4H-thieno[3,2-c]chromene-8-carboxylic acid and

dimethylamine were coupled to give **111bp**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15–7.31 (m, 3 H), 6.82–7.00 (m, 4 H), 5.13 (s, 2 H), 3.33 (m, 3 H), 2.94–3.13 (m, 6 H). LCMS (ESI) *m/z*: 429.1.

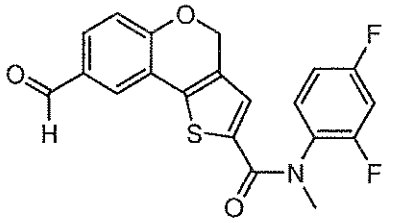
[001130] Example 10bp N-(2,4-difluorophenyl)-N-methyl-8-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)-4H-thieno[3,2-c]chromene-2-carboxamide **112bp**

[001131] A solution of 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** (250 mg, 0.57 mmol), 1-methyl-4-(4-piperidinyl)piperazine (157 mg, 0.86 mmol), sodium *tert*-butoxide (82 mg, 0.86 mmol), tris(dibenzylidineacetone)dipalladium (0) (25 mg, 0.3 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (1.14 mmol, 2.00 equiv) in toluene (10 mL) was refluxed under nitrogen for 1 hr. The reaction mixture was cooled to room temperature and filtered through silica gel, and the filtrate was concentrated. Purification by flash column chromatography followed by HPLC afforded **112bp** (100 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 1 H), 6.90–6.93 (m, 2 H), 6.78–6.88 (m, 3 H), 6.63 (m, 1 H), 4.97 (s, 2 H), 3.51–3.57 (m, 2 H), 3.40–3.56 (m, 8 H), 3.32 (s, 3 H), 2.71–2.85 (m, 6 H), 2.12–2.16 (m, 2 H), 1.96–2.01(m, 2 H). LCMS (ESI) *m/z*: 539.3.

[001132] Example 11bp N-(2,4-difluorophenyl)-8-(2-(dimethylamino)ethylamino)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **113bp**

[001133] Following Example 70 and General Procedure C, 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** and *N1,N1*-dimethyl-1,2-ethanediamine were reacted to give **113bp**. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.23 (m, 1 H), 6.87–6.92 (m, 2 H), 6.67–6.74 (m, 2 H), 6.47–6.54 (m, 2 H), 4.93 (s, 2 H), 3.84 (m, 2 H), 3.31–3.39 (m, 5 H), 2.86 (s, 6 H). LCMS (ESI) *m/z*: 444.0

[001134] Example 12bp (R)-N-(2,4-difluorophenyl)-8-((3-hydroxypyrrolidin-1-yl)methyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **115bp**



[001135] To the solution of 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide (1.0 g, 2.3 mmol) in tetrahydrofuran (20 mL) at –78 °C was added n-BuLi (2.2 mL, 5.5 mmol, 2.5 M in hexane) under a nitrogen atmosphere. After 3 hr, *N,N*-dimethylformamide (2 mL) was added. The solution was then warmed to –60 °C. After 3 hr, aqueous ammonium chloride solution (1 mL, 10%) was added to the reaction mixture, and the resulting solution was extracted with dichloromethane. The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated to yield crude aldehyde, N-(2,4-

difluorophenyl)-8-formyl-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide (800 mg), LCMS (ESI) *m/z*: 386.

[001136] A solution of crude aldehyde, N-(2,4-difluorophenyl)-8-formyl-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide (0.20 g, 0.52 mmol), (3*R*)-hydroxypyrrolidine (1.04 mmol), and acetic acid (37.4 mg, 0.62 mmol) in 1,2-dichloroethane (15 mL) was stirred for 3 hours. Sodium triacetoxyborohydride (0.50 g, 2.3 mmol) was added, the resulting suspension was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo. Sequential purification by preparative thin layer chromatography and HPLC afforded **115bp** (25 mg). ^{1}H NMR (* denotes minor rotamer peaks, 400 MHz, $CDCl_3$), δ: 7.71* (m, 1 H), 7.51 (m, 1 H), 7.31–7.38* (m, 3 H), 7.11–7.19 (m, 3 H), 6.84–6.93 (m, 3 H), 5.09 (s, 2 H), 4.52 (m, 1 H), 4.45 (m, 2 H), 4.33 (m, 2 H), 3.44* (s, 3 H), 3.40 (s, 3 H), 2.20 (m, 1 H), 2.00 (m, 1 H). LCMS (ESI) *m/z*: 457.2.

[001137] Example 13bp N-(2,4-difluorophenyl)-N-methyl-8-(morpholinomethyl)-4H-thieno[3,2-c]chromene-2-carboxamide **116bp**

[001138] Following Examples 25 and 70 and General Procedure E, reductive amination of N-(2,4-difluorophenyl)-8-formyl-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide and morpholine gave **116bp**. ^{1}H NMR (* denotes minor rotamer peaks, 400 MHz, $CDCl_3$), δ: 7.69* (m, 1 H), 7.53 (m, 1 H), 7.31–7.39* (m, 3 H), 7.12–7.23 (m, 3 H), 6.99–7.05* (m, 2 H), 6.88–6.93 (m, 2 H), 6.83 (s, 1 H), 5.10 (s, 2 H), 4.23* (m, 4 H), 3.82 (m, 4 H), 3.67* (m, 4 H), 3.48* (s, 3 H), 3.42 (s, 3 H), 3.00 (m, 4 H). LCMS (ESI) *m/z*: 458.2.

[001139] Example 14bp N-(2,4-difluorophenyl)-N-methyl-8-(pyrrolidin-1-ylmethyl)-4H-thieno[3,2-c]chromene-2-carboxamide **117bp**

[001140] Following Example 25 and 70 and General Procedure E, reductive amination of N-(2,4-difluorophenyl)-8-formyl-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide and pyrrolidine gave **117bp**. ^{1}H NMR (* denotes minor rotamer peaks, 400 MHz, $CDCl_3$), δ: 7.65* (m, 1 H), 7.45 (m, 1 H), 7.28–7.30* (m, 3 H), 7.04–7.24 (m, 3 H), 6.89–6.96* (m, 3 H), 6.80–6.87 (m, 3 H), 5.04 (s, 2 H), 4.27 (m, 2 H), 3.65 (m, 2 H), 3.40* (s, 3 H), 3.38 (s, 3 H), 2.62* (m, 4 H), 1.96 (m, 4 H). LCMS (ESI) *m/z*: 441.2

[001141] Example 15bp N-(2,4-difluorophenyl)-8-(4-hydroxypiperidine-1-carbonyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **118bp**

[001142] Following the procedure of Example 15 and General Procedure C, 2-((2,4-difluorophenyl)(methyl)carbamoyl)-4H-thieno[3,2-c]chromene-8-carboxylic acid and 4-hydroxypiperidine were coupled to give **118bp**. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.68 (m, 1 H), 7.46 (m, 1 H), 7.21–7.25 (m, 3 H), 6.93 (m, 1 H), 6.69 (m, 1 H), 5.16 (s, 2 H), 3.65 (m, 3 H), 3.29 (s, 3 H), 3.17 (m, 2 H), 1.73 (m, 2 H), 1.36 (m, 2 H). LCMS (ESI) *m/z*: 485.1

[001143] Example 16bp N2-(2,4-difluorophenyl)-N2-methyl-4H-thieno[3,2-c]chromene-2,8-dicarboxamide **119bp**

[001144] Following the procedure of Example 15 and General Procedure C, 2-((2,4-difluorophenyl)(methyl)carbamoyl)-4H-thieno[3,2-c]chromene-8-carboxylic acid and ammonium chloride were coupled to give **119bp**. LCMS (ESI) *m/z*: 401.1

[001145] Example 17bp 8-(4-acetylpiperazin-1-yl)-N-(2,4-difluorophenyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **120bp**

[001146] Following Example 70 and General Procedure D, 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** and 1-acetylpiperazine were reacted to give **120bp**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 1 H), 6.82–6.93 (m, 5 H), 5.99 (s, 1 H), 5.01 (s, 2 H), 3.86 (m, 2 H), 3.73 (m, 2 H), 3.32 (s, 3 H), 3.21 (m, 2 H), 3.16 (m, 2 H), 2.13 (s, 3 H). LCMS (ESI) *m/z*: 484.1

[001147] Example 18bp 8-acetamido-N-(2,4-difluorophenyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **121bp**

[001148] Following Example 70 and General Procedure D, 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** and acetamide were reacted to give **121bp**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84–7.31 (m, 6 H), 6.76 (s, 1 H), 5.05 (s, 2 H), 3.40 (s, 3 H), 2.16 (s, 3 H). LCMS (ESI) *m/z*: 414.9

[001149] Example 19bp N-(2,4-difluorophenyl)-N-methyl-8-(4-morpholinopiperidin-1-yl)-4H-thieno[3,2-c]chromene-2-carboxamide **127bp**

[001150] Following Example 70 and General Procedure D, 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** and 4-(4-piperidinyl)morpholine were reacted to give **127bp**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 1 H), 7.05–7.10 (m, 2 H), 6.84–6.93 (m, 3 H), 6.74 (m, 1 H), 5.05 (s, 2 H), 4.00 (m, 4 H), 3.63–3.68 (m, 3 H), 3.29–3.50 (m, 5 H), 3.18 (m, 2 H), 3.05 (m, 2 H), 2.47 (m, 2 H), 2.21 (m, 2 H). LCMS (ESI) *m/z*: 526.1

[001151] Example 20bp N-(2,4-difluorophenyl)-N-methyl-8-(4-methylpiperazin-1-yl)-4H-thieno[3,2-c]chromene-2-carboxamide **128bp**

[001152] Following Example 70 and General Procedure D, 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** and *N*-methylpiperazine were reacted to give **128bp**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 1 H), 6.94–7.00 (m, 2 H), 6.85 (m, 1 H), 6.75–6.82 (m, 2 H), 6.68 (s, 1 H), 5.03 (s, 2 H), 3.69 (m, 2 H), 3.46 (m, 2 H), 3.39 (s, 3 H), 3.30 (m, 2 H), 3.07 (m, 2 H), 2.90 (s, 3 H). LCMS (ESI) *m/z*: 456.2.

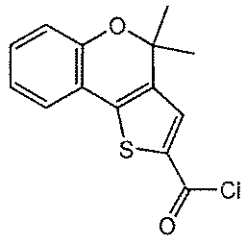
[001153] Example 21bp N-(2,4-difluorophenyl)-N-methyl-8-morpholino-4H-thieno[3,2-c]chromene-2-carboxamide **129bp**

[001154] Following Example 70 and General Procedure D, 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** and morpholine were reacted to give **129bp**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (m, 1 H), 7.11–7.14 (m, 2 H), 6.90–6.98 (m, 3 H), 6.75 (s, 1 H), 5.09 (s, 2 H), 4.04 (m, 2 H), 3.38 (s, 3 H), 3.32 (m, 2 H). LCMS (ESI) *m/z*: 442.9

[001155] Example 22bp N-(2,4-difluorophenyl)-N-methyl-8-((4-methylpiperazin-1-yl)methyl)-4H-thieno[3,2-c]chromene-2-carboxamide **136bp**

[001156] Following the procedure of Examples 25 and70 and General Procedure E, 2-((2,4-difluorophenyl)(methyl)carbamoyl)-4H-thieno[3,2-c]chromene-8-carboxylic acid and 1-methylpiperazine were coupled to give **136bp**.

[001157] Example 23bp N-(2-chlorophenyl)-N,4,4-trimethyl-4H-thieno[3,2-c]chromene-2-carboxamide **140bp**



[001158] To a solution of 2,4-difluoroaniline (0.03936 g, 0.2750 mmol) in 1.2 M of Pyridine in methylene chloride (0.8333 mL) was added a catalytic amount of DMAP, followed by the addition of 4,4-dimethyl-4H-thieno[3,2-c]chromene-2-carbonyl chloride (70.2 mg, 0.250 mmol). The reaction was stirred at room temperature under N_2 with LC/MS monitor. The crude product was purified on silica to give 38 mg **140bp**. Yield = 40% of theoretical. MS: (ESI+) = 386

[001159] Example 24bp N-(2-chlorophenyl)-N,4,4-trimethyl-4H-thieno[3,2-c]chromene-2-carboxamide **141bp**

[001160] To a solution of 2-chloro-N-methylaniline (32.10 uL, 0.2750 mmol) in 1.2 M of Pyridine in methylene chloride (0.8333 mL) was added a pinch of DMAP, followed by the addition of 4,4-dimethyl-4H-thieno[3,2-c]chromene-2-carbonyl chloride (70.2 mg, 0.250 mmol). The reaction was stirred at room temperature under N_2 with LC/MS monitor. The crude product was purified on silica to give 30 mg **141bp**. Yield = 31% of theoretical. MS: (ESI+) = 385

[001161] Example 25bp N-(2-chlorophenyl)-6,8-difluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **142bp**

[001162] Following the procedure of Example 70 and General Procedure B, **142bp** was prepared from 6,8-difluoro-4H-thieno[3,2-c]chromene-2-carboxylic acid and 2-chloro-N-methylaniline. MS: (ESI+) = 392.1

[001163] Example 26bp N2-(2,4-difluorophenyl)-N2,N8-dimethyl-4H-thieno[3,2-c]chromene-2,8-dicarboxamide **152bp**

[001164] To a microwave reaction vessel charged with 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** (0.100 g, 0.229 mmol, 1 equiv), methylamine (0.34 mL, 0.68 mmol, 3.0 equiv, 2.0 M in tetrahydrofuran), molybdenumhexacarbonyl (60.5 mg, 0.229 mmol, 1.00 equiv), and trans-di(mu-acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium (II) (0.15 equiv) in tetrahydrofuran (1 mL) at 24 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (15.4 μL, 0.103 mmol, 0.450 equiv), following the procedures of Wannberg et al (2003) J. Org. Chem. 68:5750–5753. The reaction mixture was heated in the microwave at 150 °C for 15 min, and filtered through Celite. The resulting filtrate was concentrated in vacuo. Purification by flash column chromatography (95:5 dichloromethane / methanol) afforded **152bp** (58 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.62 (d, J = 2.1 Hz, 1 H), 7.50 (dd, J = 8.4, 2.2 Hz, 1 H), 7.30 (m, 1 H), 6.95–6.99 (m, 2 H), 6.88 (d, J = 8.4 Hz, 1 H), 6.84 (br s, 1 H), 6.08 (br s, 1 H), 5.16 (s, 2 H), 3.38 (s, 3 H), 3.00 (d, J = 4.8 Hz, 3 H). LCMS (ESI) *m/z*: 415.2

[001165] Example 27bp N-(2,4-difluorophenyl)-N-methyl-8-(4-methylpiperazine-1-carbonyl)-4H-thieno[3,2-c]chromene-2-carboxamide **153bp**

[001166] Following Example 62, 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** and 1-methylpiperidine gave **153bp**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 1 H), 7.26 (m, 1 H), 7.18 (dd, J = 8.3, 2.0 Hz, 1 H), 6.95–6.98 (m, 2 H), 6.87 (d, J = 8.3 Hz, 1 H), 6.86 (s, 1 H), 5.14 (s, 2 H), 3.65 (br s, 4 H), 3.38 (s, 3 H), 2.42 (br s, 4 H), 2.33 (s, 3 H). LCMS (ESI) *m/z*: 484.2.

[001167] Example 28bp (S)-N-(2,4-difluorophenyl)-8-(3-hydroxypyrrolidine-1-carbonyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **154bp**

[001168] Following Example 62, 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** and *S*-3-hydroxypyrrolidine gave **154bp**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (m, 1 H), 7.47 (m, 1 H), 7.38–7.40 (m, 2 H), 7.25 (m, 1 H), 6.94 (d, J = 8.6 Hz, 1 H), 6.71 (br s, 1 H), 5.18 (s, 2 H), 4.95 (m, 1 H), 4.27 (m, 1 H), 3.20–3.61 (m, 3 H), 3.30 (s, 3 H), 1.90 (m, 1 H), 1.79 (m, 1 H).

[001169] Example 29bp (R)-N-(2,4-difluorophenyl)-8-(3-hydroxypyrrolidine-1-carbonyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **155bp**

[001170] Following Example 62, 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** and *R*-3-hydroxypyrrolidine gave **155bp**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (m, 1 H), 7.47 (m, 1 H), 7.38–7.40 (m, 2 H), 7.25 (m, 1 H), 6.94 (d, J = 8.6 Hz, 1 H), 6.71 (br s, 1 H), 5.18 (s, 2 H), 4.95 (m, 1 H), 4.27 (m, 1 H), 3.20–3.61 (m, 3 H), 3.30 (s, 3 H), 1.90 (m, 1 H), 1.79 (m, 1 H). LCMS (ESI) *m/z*: 471.2.

[001171] Example 30bp N-(2,4-difluorophenyl)-N-methyl-8-(morpholine-4-carbonyl)-4H-thieno[3,2-c]chromene-2-carboxamide **158bp**

[001172] Following Example 62, 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** and morpholine gave **158bp**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (m, 1 H), 7.47 (m, 1 H), 7.23–7.30 (m, 2 H), 6.96 (d, J = 8.3 Hz, 1 H), 6.71 (br s, 1 H), 5.17 (s, 2 H), 3.59 (m, 4 H), 3.48 (m, 4 H), 3.30 (s, 3 H). LCMS (ESI) *m/z*: 471.0.

[001173] Example 31bp N-(2,4-difluorophenyl)-8-(hydroxymethyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **159bp**

[001174] To a solution of 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** (19.6 mg, 0.0449 mmol, 1 equiv) in tetrahydrofuran (1 mL) at –78 °C was added *n*-butyllithium (54 μL, 0.14 mmol, 3.0 equiv, 2.5 M in hexanes) dropwise. After 15 min, *N*,*N*-dimethylformamide (35 μL, 0.45 mmol, 10 equiv) was added. After 40 min, the reaction mixture was warmed to 24 °C for 50 min. Saturated aqueous ammonium chloride solution (5 mL) was added to the reaction mixture, and the resulting solution was extracted with ethylacetate (3 x 3 mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated to afford the corresponding aldehyde, N-(2,4-difluorophenyl)-8-formyl-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide. LCMS (ESI) *m/z*: 386.

[001175] To an ice-cooled solution of N-(2,4-difluorophenyl)-8-formyl-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide in ethanol (1 mL) was added sodium borohydride (10 mg, 0.3 mmol, 6 equiv). After 3 hr, excess sodium borohydride was quenched with saturated aqueous ammonium chloride solution (3 mL). The ethanol was removed in vacuo, and the resulting aqueous solution was extracted with ethylacetate (3 x 3 mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by flash column chromatography (3:2 hexanes/ethylacetate) provided **159bp** (5.2 mg, 30%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 1 H), 7.15 (m, 1 H), 7.05 (m, 1 H), 6.86–6.93 (m, 4 H), 5.25 (s, 2 H), 4.55 (d, J = 6.7 Hz, 2 H), 4.06 (m, 1 H), 3.40 (s, 3 H). LCMS (ESI) *m/z*: 388.1.

[001176] Example 32bp 8-bromo-N-(2,4-difluorophenyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp**

[001177] To a solution of crude 8-bromo-4H-thieno[3,2-c]chromene-2-carbonyl chloride **4** (~4.82 mmol), *N*-methyl-2,4-difluoroaniline (1.03 g, 7.23 mmol, 1.50 equiv), and triethylamine (3.36 mL, 24.1 mmol, 5.00 equiv) in dichloromethane (46 mL) was added *N*,*N*-dimethyl-4-aminopyridine (118 mg, 0.964 mmol, 0.200 equiv) at 24 °C. The reaction mixture became a yellow/orange suspension within 5 min of *N*,*N*-dimethyl-4-aminopyridine addition. After 22 hr, the reaction mixture was diluted with dichloromethane (50 mL), and the resulting solution was washed with saturated aqueous sodium bicarbonate (30 mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by flash column chromatography (5:2 hexanes / ethylacetate) provided **160bp** as a yellow solid (1.59 g, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 1 H), 7.26 (m, 1 H), 7.23 (dd, J = 8.6, 2.4, 1 H), 6.95–7.00 (m, 2 H), 6.81 (s, 1 H), 6.76 (d, J = 8.6 Hz, 1 H), 5.10 (s, 2 H), 3.39 (s, 3 H). LCMS (ESI) *m/z*: 436.

[001178] Alternatively, **160bp** may be prepared by methylation of 8-bromo-N-(2,4-difluorophenyl)-4H-thieno[3,2-c]chromene-2-carboxamide **5** with methyl iodide and sodium hydride.

[001179] Example 33bp 8-Cyano-N-(2,4-difluorophenyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **161bp**

[001180] A solution of 8-bromo-*N*-(2,4-difluorophenyl)-*N*-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **160bp** (33.7 mg, 0.0772 mmol, 1 equiv) and copper cyanide (22 mg, 0.24 mmol, 3.2 equiv) in *N*,*N*-dimethylformamide (1 mL) was heated at 250 °C in the microwave for 30 min. The reaction mixture was diluted with 9:1 saturated aqueous ammonium chloride solution / ammonium hydroxide (10 mL). The resulting mixture was extracted with dichloromethane (3 x 5 mL). The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by flash column chromatography (11:4 / hexanes:ethylacetate) provided **161bp** as a white solid (23.4 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.42 (m, 2 H), 7.32 (m, 1 H), 6.99 (t, J = 8.1 Hz, 1 H), 6.92 (m, 1 H), 6.88 (s, 1 H), 5.23 (s, 2 H), 3.40 (s, 3 H). LCMS (ESI) *m/z*: 383.1

[001181] Example 34bp N-(2-bromophenyl)-8-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **162bp**

[001182] To a reaction vial charged with 8-fluoro-4H-thieno[3,2-c]chromene-2-carbonyl chloride (0.05 g, 0.2 mmol) and 2-bromo-N-methylaniline (0.044 g, 0.24 mmol) was added a catalytic amount of DMAP. Pyridine in methylene chloride (1.2 M, 0.66 mL) was added and the reaction was stirred at room temperature with LC/MS monitor. The reaction was complete in a couple hours. After aqueous work up, the reaction mixture was concentrated in vacuo, taken

into DMF at 100mg/ml and purified by preparative RP-HPLC to give **162bp**. Yield = 24% of theoretical. MS: (ESI+) = 419.5

[001183] Example 35bp N-(2,4-difluorophenyl)-8-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **163bp**

[001184] To a reaction vial charged with 8-fluoro-4H-thieno[3,2-c]chromene-2-carbonyl chloride (0.120 g, 0.447 mmol) and 2,4-difluoroaniline (0.0959 g, 0.670 mmol) was added a catalytic amount of DMAP. Pyridine in methylene chloride (1.2 M, 1.49 mL) was added. The reaction was stirred at room temperature with LC/MS monitor. The reaction was complete in a couple hours. After aqueous work up, the reaction was concentrated in vacuo, taken into DMF at a concentrated of 100mg/ml and purified by preparative RP-HPLC to give **163bp**. Yield = 31% of theoretical. MS: (ESI+) = 376.4

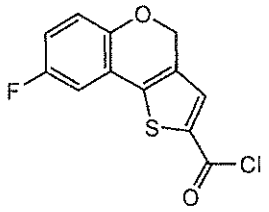
[001185] Example 36bp N-(2,4-dichlorophenyl)-8-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **164bp**

[001186] Following Example 75, 8-fluoro-4H-thieno[3,2-c]chromene-2-carbonyl chloride and 2,4-dichloro-N-methylaniline gave **164bp**. MS: (ESI+) = 408.0

[001187] Example 37bp N-(2-chlorophenyl)-8-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **165bp**

[001188] To a reaction vial charged with 8-fluoro-4H-thieno[3,2-c]chromene-2-carbonyl chloride (0.05 g, 0.2 mmol) and 2-chloro-N-methylaniline (0.034 g, 0.24 mmol) was added a catalytic amount of DMAP. Pyridine in methylene chloride (1.2 M, 0.66 mL) was added and the reaction was stirred at room temperature with LC/MS monitor. The reaction was complete in a couple hours. After aqueous work up, the reaction was concentrated in vacuo, taken into DMF at 100mg/ml and purified by preparative RP-HPLC to give **165bp**. Yield = 28% of theoretical. MS: (ESI+) = 374.8

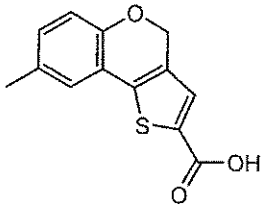
[001189] Example 38bp N-(2-chloro-5-cyanophenyl)-8-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **166bp**



[001190] To a reaction vial charged with 8-fluoro-4H-thieno[3,2-c]chromene-2-carbonyl chloride (0.08 g, 0.3 mmol) and 3-chloro-2-aminobenzonitrile (0.054 g, 0.36 mmol) was added a catalytic amount of DMAP. Pyridine in methylene chloride (1.2 M, 1 mL) was added and the reaction was stirred at room temperature with LC/MS monitor. The reaction was complete in a couple hours. After aqueous work up, the reaction mixture was concentrated in vacuo, taken

into DMF and treated with Sodium hydride (0.03 g, 1 mmol) for several minutes at room temperature. This was followed by the addition of methyl iodide (0.06 g, 0.4 mmol) 100 mg/ml. The reaction mixture was stirred at room temperature for several hours, then concentrated in vacuo and after 2nd aqueous work up, purified by preparative RP-HPLC to give **166bp**. Yield = 32% of theoretical. MS: (ESI+) = 385.8

[001191] Example 39bp N-(2,4-difluorophenyl)-N,8-dimethyl-4H-thieno[3,2-c]chromene-2-carboxamide **167bp**



[001192] 8-Methyl-4H-thieno[3,2-c]chromene-2-carboxylic acid was converted to the acid chloride as in Example 3, then treated with *N*-methyl-2,4-difluoroaniline (1.5 equiv), and triethylamine (5 equiv) in dichloromethane and *N*,*N*-dimethyl-4-aminopyridine (0.2 equiv) at 24 °C. After about 24 hr, the reaction mixture was diluted with dichloromethane, and the resulting solution was washed with saturated aqueous sodium bicarbonate. The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by flash column chromatography (5:2 hexanes / ethylacetate) provided **167bp**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 1 H), 6.95–6.98 (m, 4 H), 6.78 (d, J = 8.2 Hz, 1 H), 5.04 (s, 2 H), 3.39 (s, 3 H), 2.27 (s, 3 H). LCMS (ESI) *m/z*: 372.1.

[001193] Example 40bp N-(2-chlorophenyl)-N,8-dimethyl-4H-thieno[3,2-c]chromene-2-carboxamide **168bp**

[001194] 8-Methyl-4H-thieno[3,2-c]chromene-2-carboxylic acid was converted to the acid chloride as in Example 3, then treated with *N*-methyl-2-chloroaniline (1.5 equiv), and triethylamine (5 equiv) in dichloromethane and *N*,*N*-dimethyl-4-aminopyridine (0.2 equiv) at 24 °C. After about 24 hr, the reaction mixture was diluted with dichloromethane, and the resulting solution was washed with saturated aqueous sodium bicarbonate. The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by flash column chromatography (5:2 hexanes / ethylacetate) provided **168bp**. ^{1}H (500 MHz, $CDCl_3$) δ 7.53 (d, J = 7.7 Hz, 1 H), 7.35–7.41 (m, 3 H), 6.97 (s, 1 H), 6.94 (d, J = 8.2 Hz, 1 H), 6.76 (d, J = 8.2 Hz, 1 H), 6.56 (s, 1 H), 5.00 (s, 2 H), 3.39 (s, 3 H), 2.26 (s, 3 H). LCMS (ESI) *m/z*: 370.1

[001195] Example 41bp N-(2-fluorophenyl)-N,8-dimethyl-4H-thieno[3,2-c]chromene-2-carboxamide **169bp**

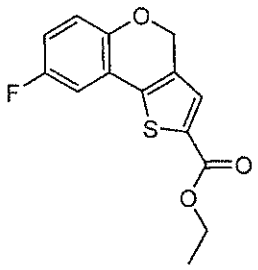
[001196] 8-Methyl-4H-thieno[3,2-c]chromene-2-carboxylic acid was converted to the acid chloride as in Example 3, then treated with *N*-methyl-2-fluoroaniline (1.5 equiv), and

triethylamine (5 equiv) in dichloromethane and *N,N*-dimethyl-4-aminopyridine (0.2 equiv) at 24 °C. After about 24 hr, the reaction mixture was diluted with dichloromethane, and the resulting solution was washed with saturated aqueous sodium bicarbonate. The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by flash column chromatography (5:2 / hexanes:ethylacetate) provided **169bp**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 1 H), 7.31 (m, 1 H), 7.18–7.22 (m, 2 H), 6.80 (s, 1 H), 6.94 (d, J = 8.3 Hz, 1 H), 6.77 (d, J = 8.2 Hz, 1 H), 6.60 (s, 1 H), 5.00 (s, 2 H), 3.42 (s, 3 H), 2.26 (s, 3 H). LCMS (ESI) *m/z*: 354.1

[001197] Example 42bp (8-fluoro-4H-thieno[3,2-c]chromen-2-yl)(morpholino)methanone **170bp**

[001198] To a cooled solution (ice/H_20) of morpholine in DCE was added slowly dropwise 2 equiv. of dimethylaluminum chloride. This reaction was stirred for greater than 30 minutes until reaching ambient temperature. Next the reaction was again cooled (ice/H_20) and 8-fluoro-4H-thieno[3,2-c]chromene-2-carboxylate was added as a solid portion wise. The reaction was allowed to equilibrate to ambient temp and monitored by LC/MS. The completed reaction was quenched with an aqueous solution of Na, K-tartrate (20% wt/wt). This mixture was extracted with EtOAc and the organic was washed with saline and dried (MgSO4). The dried org. was concentrated in vacuo to a residue. This residue was not soluble in DMF and **170bp** as a white solid was collected by vacuum filtration, Yield = 40% of theoretical. MS: (ESI+) = 320.5

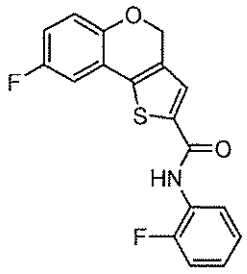
[001199] Example 43bp 8-fluoro-N-methyl-N-(pyridin-2-yl)-4H-thieno[3,2-c]chromene-2-carboxamide **171bp**



[001200] To a cooled solution (ice/H_20) of 2-fluoroaniline in DCE was added slowly dropwise 2 equiv. of dimethylaluminum chloride. The reaction was then stirred for greater than 30 minutes until reaching ambient temperature. Next the reaction was again cooled (ice/H20) and ethyl 8-fluoro-4H-thieno[3,2-c]chromene-2-carboxylate was added as a solid portion wise. The reaction was allowed to equilibrate to ambient temp and monitored by LC/MS. Reaction was quenched with an aqueous solution of Na, K-tartrate (20% wt./wt.) . This mixture was extracted with EtOAc and the organic was washed with saline and dried (MgSO4). The dried org. was concentrated in vacuo to a residue. This residue was taken into a min. of DMF and

filtered, and purified by preparative RP-HPLC to give 98 mg of **171bp** as the TFA salt. Yield = 40% of theoretical. MS: (ESI+) = 341.4

[001201] Example 44bp 8-fluoro-N-(2-fluorophenyl)-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **172bp**

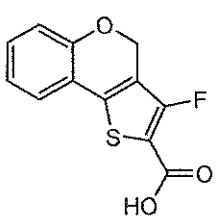


[001202] N-(2-fluororophenyl)-7-fluoro-4H-thieno[3,2-c]chromene-2-carboxamide (0.200 g, 0.582 mmol) was taken into dichloromethane (DCM) and placed under nitrogen (N2). Cesium carbonate was added as a solid and stirred into solution for several minutes. This solution was cooled (ice/H20) and methyl iodide (MeI) was added slowly dropwise. The cooling bath was immediately removed and reaction was monitored by LC/MS for loss of starting material. The completed reaction was diluted with EtOAc and the organic phase was washed with water x 2, followed by saline x 1, then dried ($MgSO_4$). The dried organic phase was concentrated in vacuo and the resulting residue was taken into DMF at a concentration of 100 mg/mL, and purified by preparative RP-HPLC to give **172bp**. MS: Yield = 25% of theoretical. (ESI+) = 358.4

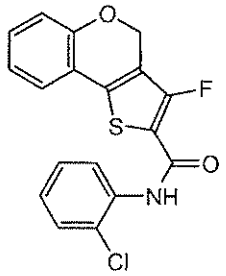
[001203] Example 45bzOH N-(2-chlorophenyl)-4-hydroxy-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **191bzOH**

[001204] Sodium borohydride (8 mg, 0.2 mmol) was added to a solution of N-(2-chlorophenyl)-N-methyl-4-oxo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **193bzO** (38 mg, 0.1 mmol) in 2 ml of methanol. The mixture was stirred for 30 min, poured into 4 ml of water and extracted with 3 ml of ethylacetate. The ethylacetate layer was washed with water, brine and dried over magnesium sulfate. The crude product was purified by normal phase column chromatography using dichloromethane/ethylacetate mobile phase (ethylacetate gradient 0-20%) to yield **191bzOH** (0.022 g, 57%). MS: (ESI+) MH+ = 386.1

[001205] Example 46bp N-(2-chlorophenyl)-3-fluoro-N-methyl-4H-thieno[3,2-c]chromene-2-carboxamide **192bp**



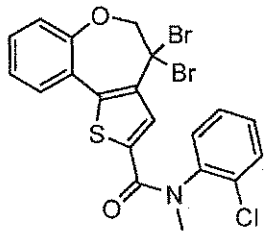
[001206] To 4H-thieno[3,2-c]chromene-2-carboxylic acid (1.65 g, 7.10 mmol) in THF (70 mL) at -78 °C was added a 1.5 M solution of tert-butyllithium in pentane (15 mL). The resulting solution stirred 1 hr at -78 °C. N-fluoro-N-(phenylsulfonyl)benzenesulfonamide (7.2 g, 23 mmol) was added and the reaction warmed to room temperature over 2 hr. The reaction was quenched by the addition of 1 M HCl to effect pH 3. The aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield 3-fluoro-4H-thieno[3,2-c]chromene-2-carboxylic acid, which contained less than 40% 4H-thieno[3,2-c]chromene-2-carboxylic acid, which was utilized in the next step without purification (1.0 g). MS (Q1) 249 (M)+



[001207] To 3-fluoro-4H-thieno[3,2-c]chromene-2-carboxylic acid (1.0 g, >60% purity) in CH_2Cl_2 (17 mL) was added thionyl chloride (0.6 mL) followed by a few drops of DMF. The reaction was heated to reflux for several hours. The crude reaction mixture was concentrated *in vacuo*. To the residue was added CH_2Cl_2 (50 mL), 2-chloroaniline (1.1 mL), and a catalytic amount of 4-dimethylaminopyridine. Next, pyridine (5 mL) and the reaction stirred at room temperature. After 4 hr the reaction was concentrated *in vacuo* and partially purified by silica gel chromatography (hexane/ethylacetate as eluent) to provide N-(2-chlorophenyl)-3-fluoro-4H-thieno[3,2-c]chromene-2-carboxamide along with an unidentified by-product. MS (Q1) 360 (M)+

[001208] To N-(2-chlorophenyl)-3-fluoro-4H-thieno[3,2-c]chromene-2-carboxamide in DMF was added sodium hydride (0.16 g) then methyl iodide (0.37 mL). The resulting solution stirred 45 min at room temperature. The reaction was quenched by pouring into ice water. The aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. After partial purification by silica gel chromatography (CH_2Cl_2/EtOAc) the product was purified by reverse phase HPLC to afford **192bp** (18 mg). MS (Q1) 374 (M)+

[001209] Example 47bzO N-(2-chlorophenyl)-N-methyl-4-oxo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide **193bzO**



[001210] N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide, N-bromosuccinimide (157 mg, 0.88 mmol) and benzoyl peroxide (2 mg, 0.008 mmol) was heated at 90 °C for 6 hours. The mixture was filtered, the solvent evaporated to dryness, and the residue partitioned between 10 ml of ethylacetate and 20 ml of water. The organic layer was washed with water, brine and dried over magnesium sulfate. The crude product was purified by normal phase column chromatography using dichloromethane – ethylacetate mixture (ethylacetate gradient 0-20%) to yield 0.16 g 4,4-dibromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (76%). MS: (ESI+) MH+ = 525.9

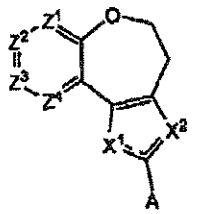
[001211] A mixture of 4,4-dibromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide (0.16 g, 0.3 mmol) and silver acetate (0.15 g, 0.9 mmol) in toluene was heated at 60 °C for 14 hours. The mixture was filtered and evaporated to dryness. The residue was dissolved in 10 ml of methanol and 1 ml 0.5% aqueous sodium hydroxide was added. The mixture was stirred for 10 min and neutralized by addition of 1 N aqueous hydrogen chloride. The solvents were evaporated in vacuo, the residue was purified by normal phase column chromatography using dichloromethane/ethylacetate mobile phase (ethylacetate gradient 0-20%) to yield **193bzO** (0.064 g, 42%). MS: (ESI+) MH+ = 384.1

[001212] The foregoing description is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will be readily apparent to those skilled in the art, the invention is not limited to the exact examples shown as described above. Accordingly, all suitable modifications and equivalents may be considered to fall within the scope of the invention as defined by the claims that follow.

[001213] The words "comprise," "comprising," "include," "including," and "includes" when used in this specification and in the following claims are intended to specify the presence of stated features, integers, components, or steps, but they do not preclude the presence or addition of one or more other features, integers, components, steps, or groups thereof.

What is claimed is:

1. A compound selected from Formula I:



and stereoisomers, geometric isomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

Z^1 is CR^1 or N;

Z^2 is CR^2 or N;

Z^3 is CR^3 or N;

Z^4 is CR^4 or N;

where (i) X^1 is N and X^2 is S, (ii) X^1 is S and X^2 is N, (iii) X^1 is CR^7 and X^2 is S, or (iv) X^1 is S and X^2 is CR^7;

R^1, R^2, R^3, R^4, and R^7 are independently selected from H, F, Cl, Br, I, –CN, $–CF_3$, $–CH_2OR^{10}$, $–CH_2R^{10}$, $–(C_1–C_{12}$ alkylene$)NR^{10}R^{11}$, $–(C_1–C_{12}$ alkylene$)NR^{12}C(=O)R^{10}$, $–(C_1–C_{12}$ alkylene$)C(=O)OR^{10}$, $–(C_1–C_{12}$ alkylene$)OR^{10}$, $–CO_2R^{10}$, $–C(=O)N(R^{10})OR^{11}$, $–NO_2$, $–NR^{10}R^{11}$, $–OR^{10}$, $–S(O)_2R^{10}$, $–C(=O)NR^{10}R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}C(=O)OR^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}C(=O)R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)R^{10}$, $–C(=NR^{10})NR^{10}R^{11}$, $–NR^{12}C(=O)R^{10}$, $–NR^{12}C(=O)OR^{11}$, $–NR^{12}C(=O)NR^{10}R^{11}$, $–NR^{12}C(=O)(C_1–C_{12}$ alkylene$)NR^{10}R^{11}$, $–NR^{12}(C_1–C_{12}$ alkylene$)NR^{10}R^{11}$, $–NR^{12}(C_1–C_{12}$ alkylene$)OR^{10}$, $–NR^{12}(C_1–C_{12}$ alkylene$)C(=O)NR^{10}R^{11}$, $–C{\equiv}CR^{10}$, $–CH{=}CHR^{10}$, $C_2–C_{20}$ heterocyclyl, $C_1–C_{20}$ heteroaryl, and phenyl, where heterocyclyl, heteroaryl, phenyl and alkylene are optionally substituted with one or more groups selected from F, Cl, Br, I, $–CH_2OH$, $–(CH_2)_2OH$, $–CH_2CO_2H$, –CN, $–CH_2NH_2$, $–(CH_2)_2N(CH_3)_2$, $–CH_3$, $–C(=O)CH_3$, $–C(=O)NHCH_3$, $–CO_2H$, $–CH_2CO_2CH_3$, $–NH_2$, $–OCH_3$, $–S(O)_2CH_3$, 4-methylpiperazin-1-yl, and 4-morpholinyl;

A is selected from $–C(=O)NR^5R^6$, $C_2–C_{20}$ heterocyclyl and $C_1–C_{20}$ heteroaryl wherein $C_2–C_{20}$ heterocyclyl and $C_1–C_{20}$ heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $–CH_2OH$, $–CH_2CO_2H$, –

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$CH(CH_3)CH_2OCH_3$, –CN, C_1–C_{12} alkyl, –(C_1–C_{12} alkylene)$NR^{10}R^{11}$, –(C_1–C_{12} alkylene)OR^{10}, $–CH_3$, $–C(=O)CH_3$, $–C(=O)NHCH_3$, $–C(=O)N(CH_3)_2$, $–CO_2H$, $–CO_2CH_3$, $–CH_2CO_2CH_3$, $–NH_2$, $–NHC(=O)CH_3$, $–OCH_3$, $–S(O)_2CH_3$, 1-methylpiperid-4-yl, 4-methylpiperazin-1-yl, 4-morpholinyl, isopropyl, isobutyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, triazolylmethyl, benzyl, and phenyl, where alkyl, alkylene, benzyl and phenyl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $–CF_3$, $–CH_2OH$, $–CH_2CO_2H$, –CN, $–CH_2NH_2$, $–CH_3$, $–C(=O)CH_3$, $–C(=O)NHCH_3$, $–CO_2H$, $–CH_2CO_2CH_3$, $–NH_2$, –OH, $–OCH_3$, $–S(O)_2CH_3$, 1-methylpiperid-4-yl, (4-methylpiperazin-1yl)carboxamide, $-CH_2$(1H-1,2,4-triazol-5-yl), 4-methylpiperazin-1-yl, and 4-morpholinyl;

R^5 is selected from C_1–C_{12} alkyl optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, $–CO_2H$, $–CONH_2$, $–CONHCH_3$, $–NH_2$, $–NO_2$, $–N(CH_3)_2$, $–NHCOCH_3$, $–NHS(O)_2CH_3$, –OH, $–OCH_3$, $–OCH_2CH_3$, $–S(O)_2NH_2$, and $–S(O)_2CH_3$;

R^6 is selected from C_1–C_{12} alkyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, and C_6–C_{20} aryl, each optionally substituted with one or more groups independently selected from F, Cl, Br, I, $–CH_2OH$, $–CH_2C_6H_5$, –CN, $–CF_3$, $–CO_2H$, $–C(=O)NR^{10}R^{11}$, $–NH_2$, $–NO_2$, $–N(CH_3)_2$, $–NHCOCH_3$, $–NHS(O)_2CH_3$, –OH, $–OCH_3$, $–OCH_2CH_3$, $–S(O)_2NH_2$, $–S(O)_2CH_3$, $–C(=O)NR^{10}$(C_1–C_{12} alkylene)$NR^{10}R^{11}$, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, $–C{\equiv}CR^{13}$, $–CH{=}CHR^{13}$, and $–C(=O)NR^{10}R^{11}$;

or R^5 and R^6 together with the nitrogen atom to which they are attached form morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl or S-dioxothiomorpholin-4-yl, each optionally substituted with one or more groups selected from F, Cl, Br, I, $–CH_2OH$, $–CH_2C_6H_5$, –CN, $–CF_3$, $–CO_2H$, $–CONH_2$, $–CONHCH_3$, $–NO_2$, $–N(CH_3)_2$, $–NHCOCH_3$, $–NHS(O)_2CH_3$, –OH, $–OCH_3$, $–OCH_2CH_3$, $–S(O)_2NH_2$, and $–S(O)_2CH_3$;

R^{10}, R^{11} and R^{12} are independently selected from H, C_1–C_{12} alkyl, C_1–C_{12} alkylene-C_2–C_{20} heterocyclyl, C_1–C_{12} alkylene-C_6–C_{20} aryl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_6–C_{20} aryl, and C_1–C_{20} heteroaryl, where C_1–C_{12} alkyl, C_2–C_8 alkenyl, C_2–C_8 alkynyl, C_3–C_{12} carbocyclyl, C_3–C_{20} heterocyclyl, C_6–C_{20} aryl, and

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C_1–C_{20} heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, 2-oxopyrrolidin-1-yl, $-S(O)_2NH_2$, and $-S(O)_2CH_3$;

or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a C_2–C_{20} heterocyclyl ring or C_1–C_{20} heteroaryl each optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2OH$, $-CH_2C_6H_5$, $-CN$, $-CF_3$, $-CO_2H$, $-CONH_2$, $-CONHCH_3$, $-NO_2$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-OH$, oxo, $-OCH_3$, $-OCH_2CH_3$, $-S(O)_2NH_2$, and $-S(O)_2CH_3$; and

R^{13} is selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CN$, $-CF_3$, $-CH_2N(CH_3)_2$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CON(CH_3)_2$, $-NO_2$, and $-S(O)_2CH_3$.

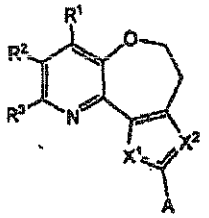
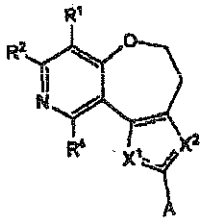
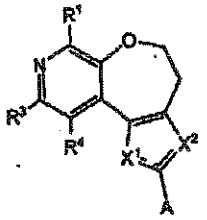
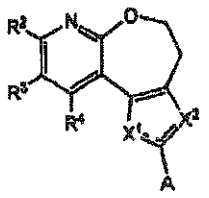
2. The compound of claim 1 wherein X^1 is N and X^2 is S.

3. The compound of claim 1 wherein X^1 is S and X^2 is N.

4. The compound of claim 1 wherein X^1 is CR^7 and X^2 is S.

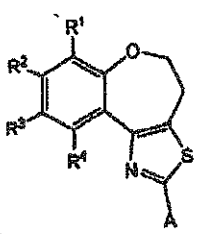
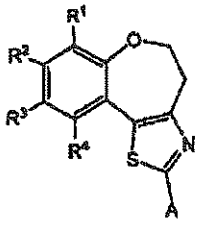
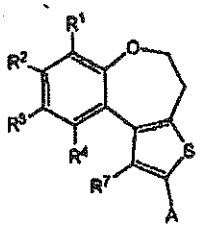
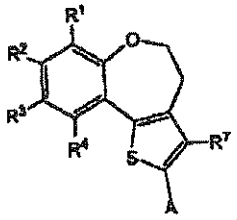
5. The compound of claim 1 wherein X^1 is S and X^2 is CR^7.

6. The compound of claim 1 selected from the structures:

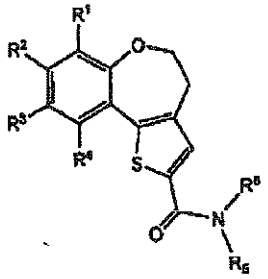
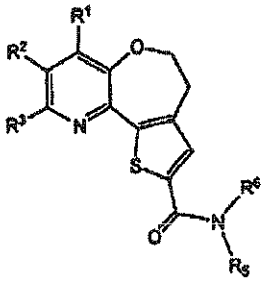
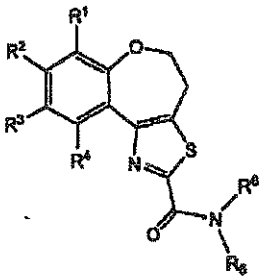
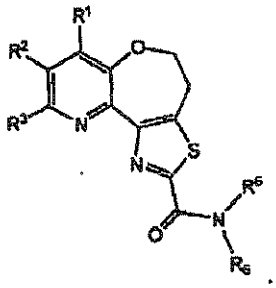





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7. The compound of claim 1 selected from the structures:

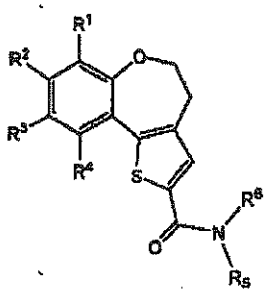
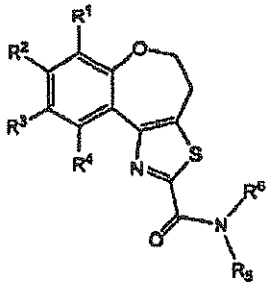





8. The compound of claim 1 is selected from the structures:

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9. The compound of claim 1 is selected from the structures:

wherein R^1, R^3, and R^4 are each H; and

R^2 is selected from F, Cl, Br, I, –CN, $–CF_3$, $–CH_2OR^{10}$, $–CH_2R^{10}$, $–CH_2NR^{10}R^{11}$, $–(C_1–C_{12}$ alkylene$)C(=O)OR^{10}$, $–(C_1–C_{12}$ alkylene$)OR^{10}$, $–CO_2R^{10}$, $–C(=O)N(R^{10})OR^{11}$, $–NO_2$, $–NR^{10}R^{11}$, $–OR^{10}$, $–S(O)_2R^{10}$, $–C(=O)NR^{10}R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}C(=O)OR^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)NR^{10}C(=O)R^{11}$, $–C(=O)NR^{10}(C_1–C_{12}$ alkylene$)R^{10}$, $–NR^{12}C(=O)R^{10}$, $–NR^{12}C(=O)OR^{11}$, $–NR^{12}C(=O)NR^{10}R^{11}$, $–NR^{12}(C_1–C_{12}$ alkylene$)NR^{10}R^{11}$, $–NR^{12}(C_1–C_{12}$ alkylene$)OR^{10}$, $–NR^{12}(C_1–C_{12}$ alkylene$)C(=O)NR^{10}R^{11}$, $–C≡CR^{10}$, $–CH=CHR^{10}$, $C_2–C_{20}$ heterocyclyl, $C_1–C_{20}$ heteroaryl, and phenyl, where heterocyclyl, heteroaryl, and phenyl are optionally substituted with one or more groups selected from F, Cl, Br, I, $–CH_2OH$, $–CH_2CO_2H$, –CN, $–CH_2NH_2$, $–CH_3$, $–C(=O)CH_3$, $–C(=O)NHCH_3$, $–CO_2H$, $–CH_2CO_2CH_3$, $–NH_2$, $–OCH_3$, $–S(O)_2CH_3$, 4-methylpiperazin-1-yl, and 4-morpholinyl, and where alkylene is optionally substituted with one or more F.

10. The compound of claim 1 wherein R^5 is CH_3.

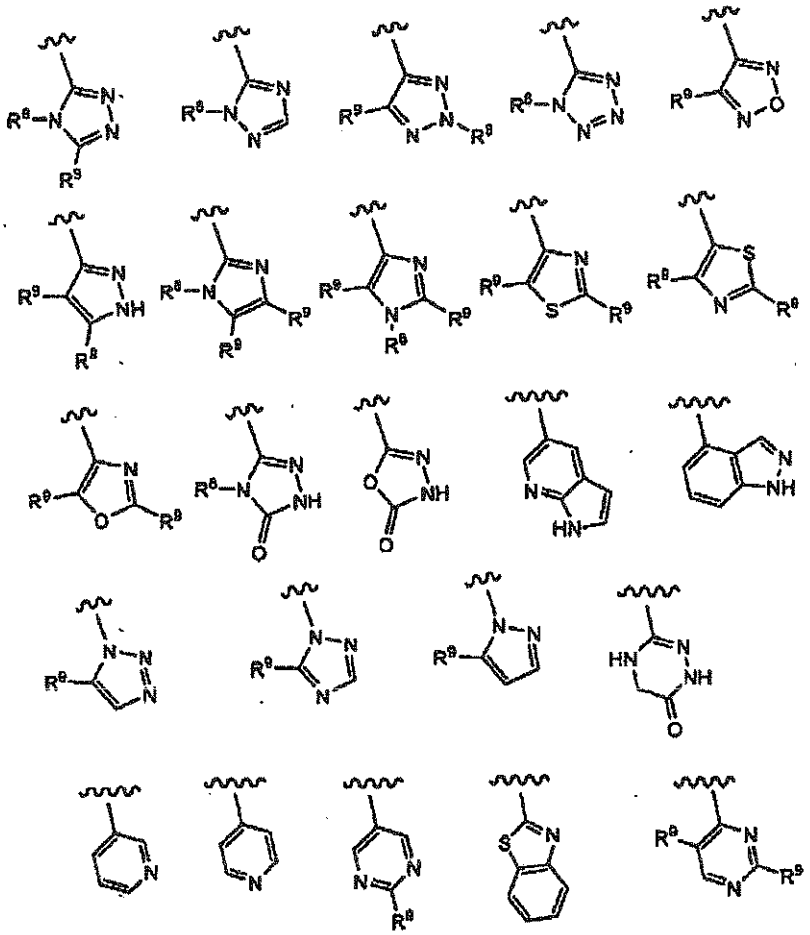
11. The compound of claim 1 wherein R^6 is phenyl substituted with one or more groups independently selected from F, Cl, Br, I, $–CH_2OH$, $–CH_2C_6H_5$, –CN, $–CF_3$, $–CO_2H$, $–CONH_2$, $–CONHCH_3$, $–NO_2$, $–N(CH_3)_2$, $–NHCOCH_3$, $–NHS(O)_2CH_3$, –OH, $–OCH_3$, $–OCH_2CH_3$, $–S(O)_2NH_2$, $–S(O)_2CH_3$, morpholin-4-yl, piperidin-1-yl, piperazinyl, piperazin-4-yl-2-one, piperazin-4-yl-3-one, pyrrolidin-1-yl, thiomorpholin-4-yl, S-dioxothiomorpholin-4-yl, $–C≡CR^{12}$, and $–CH=CHR^{13}$.

12. The compound of claim 1 wherein A is a $C_1–C_{20}$ heteroaryl selected from pyridyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, thiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, oxadiazolyl, 1,3,4-oxadiazol-2(3H)-one, furanyl, thienyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,4-triazol-5(4H)-one, 4,5-dihydro-1,2,4-triazin-6(1H)-one, tetrazolyl;

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pyrrolo[2,3-b]pyridinyl, indazolyl, 3,4-dihydroquinolinyl, and benzo[d]thiazole.

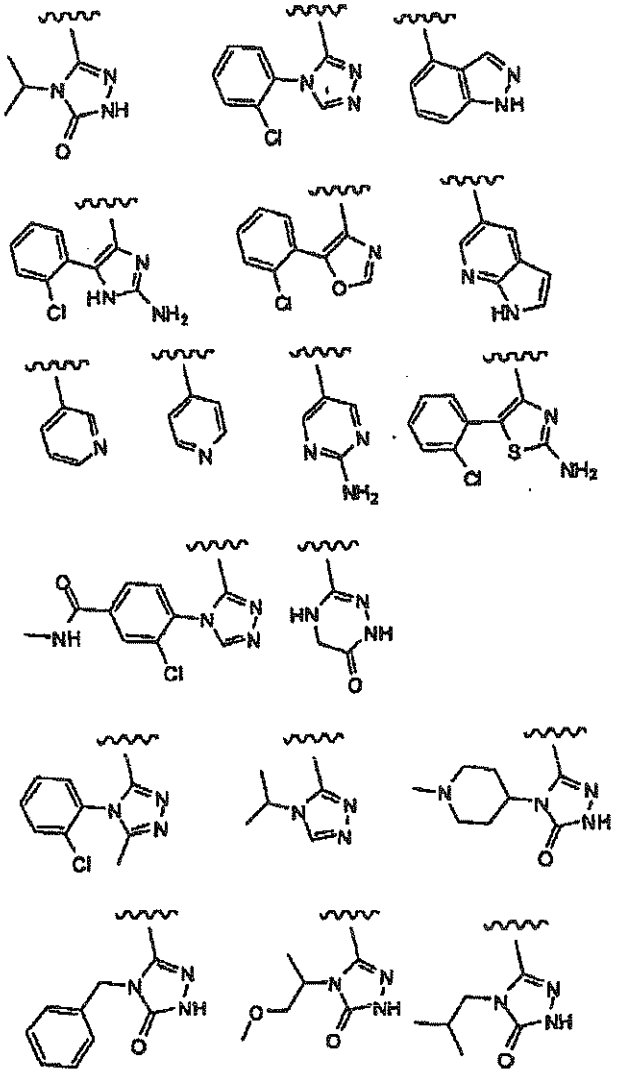
13. The compound of claim 1 wherein A is selected from the structures:



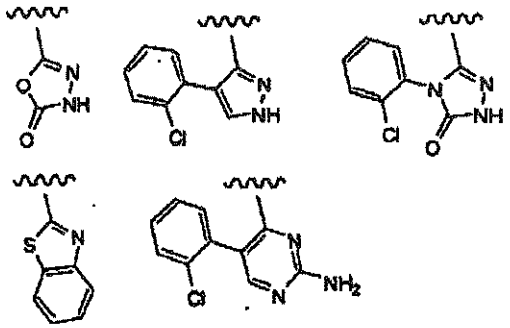
where R^8 and R^9 are independently selected from H, F, Cl, Br, I, $-CH_2OH$, $-CH_2CO_2H$, $-CH(CH_3)CH_2OCH_3$, $-CN$, $-CH_2NH_2$, $-CH_3$, $-C(=O)CH_3$, $-C(=O)NHCH_3$, $-CO_2H$, $-CH_2CO_2CH_3$, $-NH_2$, $-OCH_3$, $-S(O)_2CH_3$, 1-methylpiperid-4-yl, 4-methylpiperazin-1-yl, 4-morpholinyl, isopropyl, isobutyl, benzyl, and phenyl, where benzyl and phenyl are optionally substituted with one or more groups selected from F, Cl, Br, I, $-CH_2OH$, $-CH_2CO_2H$, $-CN$, $-CH_2NH_2$, $-CH_3$, $-C(=O)CH_3$, $-C(=O)NHCH_3$, $-CO_2H$, $-CH_2CO_2CH_3$, $-NH_2$, $-OCH_3$, $-S(O)_2CH_3$, 1-methylpiperid-4-yl, 4-methylpiperazin-1-yl, and 4-morpholinyl.

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14. The compound of claim 13 wherein A is selected from the structures:



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where the wavy line indicates the site of attachment.

15. A compound of claim 1 selected from:

N2-(2-chlorophenyl)-N2,N8,N8-trimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

7-acetamido-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N2-(2-chlorophenyl)-N8-(3-(diethylamino)propyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N-(2-chlorophenyl)-7-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

5-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)pyridin-2-amine;

N-(2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-fluorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2,4-dichlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

methyl 5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)2-aminoisonicotinate;

2-(4-isopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

8-bromo-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-4-methylcarbamoyl-phenyl)-methyl-amide;

1-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-3-methylurea;

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methyl 2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-ylcarbamate;

7-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)acetamide;

N-(4-(3-amino-5-methyl-1H-pyrazole-1-carbonyl)-2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(4-(2-acetamidoethylcarbamoyl)-2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-((2-(dimethylamino)ethyl)(methyl)carbamoyl)phenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide;

N-(2-chlorophenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-4-methylcarbamoyl-phenyl)-methyl-amide;

N-(2-chlorophenyl)-N-methyl-8-(pyridin-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carbothioamide;

8-(3-aminophenyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-8-(3-(dimethylamino)prop-1-ynyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-8-(3-hydroxyprop-1-ynyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(2-chlorophenyl)-2-acetamino-1H-imidazole;

4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(2-chlorophenyl)-2-amino-1H-imidazole;

4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(5-(2-chlorophenyl))-oxazole;

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N-methyl-N-(2-(trifluoromethyl)phenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-aminoethyl)-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-8-ethynyl-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-(pyridin-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-phenyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

5-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-pyrrolo[2,3-b]pyridine;

N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate;

tert-butyl 2-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamido)ethyl(methyl)carbamate;

4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-indazole;

N-(2-chlorophenyl)-N-methyl-(10-cyano-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide;

5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-amine;

N-(2-chlorophenyl)-8-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

3-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)benzoic acid;

N-(2-chlorophenyl)-N-methyl-8-(morpholine-4-carbonyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-(3-(methylsulfonyl)phenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

8-acetamido-N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

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N2-(2-chlorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

methyl 2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-ylcarbamate;

8-bromo-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

8-acetamido-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyridine;

4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyridine;

N2-(2-chlorophenyl)-N2-(2-hydroxyethyl)-N8-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(4-chloropyridin-3-yl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N-(2,4-difluorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-8-(2-hydroxyacetamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-(2-hydroxyethyl)-10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-(2-hydroxyethyl)-10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-8-(3-(dimethylamino)propanamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-carboxamide;

5-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyrimidin-2-amine;

3-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole;

4-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-(5-(2-chlorophenyl))-thiazol-2-amine;

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N-(2-chlorophenyl)-8-(3-ethylureido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-(3-methylureido)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-ureido-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-8-(2-(diethylamino)acetamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-(2-morpholinoacetamido)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-(2-(4-methylpiperazin-1-yl)acetamido)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

(3-chloro-4-(3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4H-1,2,4-triazol-4-yl)phenyl)(4-methylpiperazin-1-yl)methanone;

N2-(2-chlorophenyl)-N2-methyl-N8-(pyridin-3-ylmethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chlorophenyl)-N8-(1-(hydroxymethyl)cyclopentyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chlorophenyl)-N8-((S)-1-hydroxy-3,3-dimethylbutan-2-yl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N-(2-chlorophenyl)-8-(4-hydroxypiperidine-1-carbonyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N2-(2-chlorophenyl)-N8-((S)-2-hydroxypropyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chlorophenyl)-N8-((S)-1-hydroxypropan-2-yl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chloro-4-(methylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N-(2-chloro-4-(methylcarbamoyl)phenyl)-8-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N2-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-8-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

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N-(3-chloropyridin-4-yl)-N-methyl-8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(3-chloropyridin-4-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N8-(2-aminoethyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N8-(2-acetamidoethyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chlorophenyl)-N2-methyl-N8-(2-(methylamino)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chlorophenyl)-N8-methoxy-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chlorophenyl)-N8-methoxy-N2-methyl-4,5-dihydrobenzp[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N-(2-chlorophenyl)-8-(hydroxymethyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(1-hydroxypropan-2-ylcarbamoyl)phenyl)-N,10-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-N-methyl(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide;

N-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N-methyl(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide;

N8-(3-(1H-imidazol-1-yl)propyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N8-(2-amino-2-methylpropyl)-N2-(2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

8-(3-(aminomethyl)phenyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-8-((2-(dimethylamino)ethylamino)methyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

2-(3-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)phenyl)acetic acid;

N-(2-chlorophenyl)-8-(3-cyanophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

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methyl 2-(3-(2-((2-chlorophenyl)(methyl)carbamoyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)phenyl)acetate;

N-(2-chlorophenyl)-8-(3-(hydroxymethyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-(4-methylpiperazine-1-carbonyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N2-(2-chlorophenyl)-N2-methyl-N8-(2-(4-methylpiperazin-1-yl)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chlorophenyl)-N8-(2-(dimethylamino)ethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chlorophenyl)-N8-isopropyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chlorophenyl)-N8-ethyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N-(3-chloropyridin-2-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-methyl-N-(4-(trifluoromethyl)pyridin-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

3-chloro-4-(3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4H-1,2,4-triazol-4-yl)-N-methylbenzamide;

N-(2-chlorophenyl)-8-(2-(dimethylamino)acetamido)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

8-(2-acetamidoacetamido)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4,5-dihydro-1,2,4-triazin-6(1H)-one;

N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-methyl(10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl(10-aza, 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide;

N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine)-2-carboxamide;

2-(2-amino-5-(2-chlorophenyl)thiazol-4-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

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2-(4-(2-chlorophenyl)-5-methyl-4H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

N-(4-chloropyridin-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N2-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isopropyl-4H-1,2,4-triazole;

3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(1-methylpiperidin-4-yl)-1H-1,2,4-triazol-5(4H)-one;

4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-phenyl)-methyl-amide;

N-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(1-hydroxypropan-2-ylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(4-(3-(1H-imidazol-1-yl)propylcarbamoyl)-2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(4-(2-acetamidoethylcarbamoyl)-2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(isopropylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(dipropylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

8-bromo-N-(2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylic acid;

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2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-amine;

N-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-2-morpholinoacetamide;

N-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-2-(dimethylamino)acetamide;

N-(2-amino-2-methylpropyl)-2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-ethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-((4-methylpiperazin-1-yl)methyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-8-((dimethylamino)methyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-((methylamino)methyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

8-(aminomethyl)-N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

4-benzyl-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-5(4H)-one;

N-(2,6-dichlorophenyl)-N-methyl-(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2,4-dichlorophenyl)-9-(4-(dimethylamino)piperidine-1-carbonyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(2-(dimethylamino)ethylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(morpholine-4-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

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N-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(1-hydroxypropan-2-yl)-1H-1,2,4-triazol-5(4H)-one;

3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2,4-dichlorophenyl)-4H-1,2,4-triazole;

4-(2-chlorophenyl)-3-(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-5(4H)-one;

3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(1-methoxypropan-2-yl)-1H-1,2,4-triazol-5(4H)-one;

N-(2-acetamidoethyl)-N-(2-chlorophenyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

2-(4-isopropyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile;

3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isobutyl-1H-1,2,4-triazol-5(4H)-one;

N-(2-chlorophenyl)-N-methyl-8-(morpholinomethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

4-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-5-(2-chlorophenyl)thiazol-2-amine;

N-(2-chlorophenyl)-N-methyl-(10-aza-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isopropyl-1H-1,2,4-triazol-5(4H)-one;

3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-isopropyl-1H-1,2,4-triazol-5(4H)-one;

5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1,3,4-oxadiazol-2(3H)-one;

3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chloro-4-fluorophenyl)-4H-1,2,4-triazole;

2-(2-amino-5-(2-chlorophenyl)thiazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

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3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-ethyl-1H-1,2,4-triazol-5(4H)-one;

2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

4-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-5-(2-chlorophenyl)thiazol-2-amine;

3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-5-methyl-4H-1,2,4-triazole;

3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole;

2-(4-(2-chlorophenyl)-1H-pyrazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(4-(2-chlorophenyl)-1H-pyrazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile;

3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-pyrazole;

3-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one;

2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile;

3-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one;

5-(2-chlorophenyl)-4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)thiazol-2-amine;

2-(4-(2-chloro-4-fluorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide;

5-(2-chlorophenyl)-4-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)pyrimidin-2-amine;

4-(2-chlorophenyl)-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-pyrazole;

4-(2-chlorophenyl)-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-5(4H)-one;

2-(1-(2-chlorophenyl)-1H-tetrazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2-chlorophenyl)-1H-tetrazole;

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5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazol-3-amine;

N2-(2,4-dichlorophenyl)-N2,N9,N9-trimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide;

3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chloro-4-(trifluoromethyl)phenyl)-4H-1,2,4-triazole;

N-(2-chloro-4-fluorophenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

9-cyano-N-(2,4-difluorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

4-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2-chlorophenyl)-2H-1,2,3-triazole;

3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole;

5-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1,2,4-triazole;

2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

N-(2-aminoethyl)-2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

8-cyano-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene-2-carboxylic acid (2-chloro-(4-methylcarbamoyl)phenyl)-methyl-amide;

N-(2-chloro-4-(methylcarbamoyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

8-methylcarbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene-2-carboxylic acid (2-chloro-(4-methylcarbamoyl)phenyl)-methyl-amide;

N2-(2-chlorophenyl)-N9-ethyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide;

N-(2,4-dichlorophenyl)-N-methyl-9-(piperazine-1-carbonyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-acetamidoethyl)-2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-morpholinoethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

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2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-(dimethylamino)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(1,3-dihydroxypropan-2-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

N2-(2-chloro-4-(methylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide;

5-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazol-3-amine;

5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-2-acetaminopyridine;

N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N-methyl-(3-hydroxymethyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-(1H-pyrazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-((R)-2-hydroxypropyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

4-(2-chlorophenyl)-3-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4H-1,2,4-triazole;

8-bromo-2-[4-(2-chloro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

N-(2-chlorophenyl)-N-methyl-(8-amino-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide;

N-(2-chlorophenyl)-N-methyl-(8-acetamino-4,5-dihydropyrido-[4,3-b]thieno[2,3-d]oxepin-2)-carboxamide;

N-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chlorophenyl)-N-methyl-8-(3-methyl-1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-methylamine;

3-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole;

3-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-1H-1,2,4-triazol-5(4H)-one;

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N-(4-carbamoyl-2-chlorophenyl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N2-(2,4-dichlorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

4-(4,5-dihydropyrido[4,3-b]thieno[2,3-d]oxepin-2-yl)-5-(2-chlorophenyl)-2H-1,2,3-triazole;

2-(1-(2-chlorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile;

4,5-dihydro-6-oxa-1-thia-3-aza-benzo[e]azulene-2-carboxylic acid (2-chloro-phenyl)-methyl-amide;

N-(2-chlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[3,2-d]oxepine-2-carboxamide;

2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(4-(2-chloro-4-(methylcarbamoyl)phenyl)-4H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

N-(2-acetamidoethyl)-2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

N-(2-amino-2-methylpropyl)-2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

N8-(2-acetamidoethyl)-N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-(2-(dimethylamino)ethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

5-(6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)benzen-2-methylamine;

9-cyano-N-(2,4-dichlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

3-(8-(pyrazol-4-yl)-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole;

N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-(2-hydroxyethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

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N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-isopropyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N8-(2-amino-2-methylpropyl)-N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

2-(1-(2-chloro-4-(dimethylcarbamoyl)phenyl)-1H-1,2,4-triazol-5-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

4-(5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-1-yl)-3-chloro-N,N-dimethylbenzamide;

N-(2-chloro-4-(dimethylcarbamoyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

2-(9-cyano-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene)-N-(2-chloro-4-(methylcarbamoyl)phenyl)-N-methyl-carboxamide;

2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-isobutyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-ethyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N8-isobutyl-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

5-(3-methylcarbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)pyridin-2-amine;

4-(3-methylcarbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2-chlorophenyl)-2H-1,2,3-triazole;

N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N8-(2-aminoethyl)-N2-(2-chloro-4-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

3-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole;

2-(4-(2-chloro-4-fluorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carbonitrile;

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9-bromo-N-(2,4-dichlorophenyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-cyanophenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2-chloro-4-(trifluoromethyl)phenyl)-9-cyano-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2,4-dichlorophenyl)-N-methyl-9-(4-methylpiperazine-1-carbonyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N-(2,4-dichlorophenyl)-9-((3S,5R)-3,5-dimethylpiperazine-1-carbonyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2-carboxamide;

N2-(2,4-dichlorophenyl)-N9-(2-hydroxyethyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,9-dicarboxamide;

N-(4-(dimethylcarbamoyl)phenyl)-N-methyl-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide;

2-(4-(2-chlorophenyl)-1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide; and

2-(4-(2-chlorophenyl)-1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide.

16. A compound of claim 1 selected from:

2-(8-bromo-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene)-N-(2,4-difluoro)phenyl)-N-methyl-carboxamide;

3-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-2-(2,4-difluorophenyl)-2H-1,2,4-triazole;

4-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2,4-difluorophenyl)-2H-1,2,3-triazole;

3-(9-bromo-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole;

N2-(2-chloro-4-fluorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

2-(1-(2-chloro-4-(dimethylcarbamoyl)phenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

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N2-(2-chloro-4-(methylcarbamoyl)phenyl)-N2-(2-hydroxyethyl)-N8-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

3-(8-carbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-4-(2-fluorophenyl)-4H-1,2,4-triazole;

(2-(4-(2,4-difluorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(4-methylpiperazin-1-yl)methanone;

2-(4-(2,4-difluorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide;

2-(4-(2,4-difluorophenyl)-4H-1,2,4-triazol-3-yl)-N-(2-hydroxyethyl)-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide;

2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile;

N-(4-(dimethylcarbamoyl)phenyl)-N-methyl-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepine)-9-carboxamide;

4-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2,4-difluorophenyl)-2H-1,2,3-triazole;

3-(8-cyano-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole;

3-(8-methylcarbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-4-(2-fluorophenyl)-4H-1,2,4-triazole;

2-(1-(2-hydroxyethyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

3-(8-methylcarbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-2-(2,5-difluorophenyl)-2H-1,2,4-triazole;

5-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

5-(9-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-isopropyl-1H-1,2,4-triazole;

3-(8-methylcarbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-2-(2-fluorophenyl)-2H-pyrazole;

N2-(2-chloro-4-fluorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chloro-5-(dimethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chloro-5-(dimethylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

2-(4-isopropyl-1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

3-(8-carbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-2-(2,4-difluorophenyl)-2H-1,2,4-triazole;

3-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole;

3-(2-cyano-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2,4-difluorophenyl)-4H-1,2,4-triazole;

3-(8-carbamoyl-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-2-(2,5-difluorophenyl)-2H-1,2,4-triazole;

5-(8-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-isopropyl-1H-1,2,4-triazole;

3-(8-(1H-pyrazol-4-yl)-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulen-2-yl)-2-(2-fluorophenyl)-2H-pyrazole;

1-(2,4-difluorophenyl)-5-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazole;

2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide;

9-bromo-2-[2-(2,4-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

5-(9-(1H-pyrazol-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide;

(2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(piperazin-1-yl)methanone;

4-(3-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-(2,4-difluorophenyl)-2H-1,2,3-triazole;

8-(1H-pyrazol-4-yl)-4,5-dihydro-6-oxa-1-aza-3-thia-benzo[e]azulene-2-carboxylic acid-N-(2,4-difluorophenyl)-N-methyl-amide;

N2-(4-carbamoyl-2-chlorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

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2-(1-(2-chloro-5-(dimethylcarbamoyl)phenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-[4-(2,4-Difluoro-phenyl)-4H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-9-carboxylic acid amide;

3-(2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)pyridine;

8-(1H-pyrazol-4-yl)-2-[2-(2,5-difluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-pyrazol-4-yl)-2-[2-(2-fluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

5-(2-chloro-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2,4-difluorophenyl)-1H-imidazole;

2-(1-(1,1,1-trifluoropropan-2-yl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

N2-(2-chloro-4-(4-methylpiperazine-1-carbonyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

2-(5-cyclopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide;

2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-N-(2-hydroxyethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

N-(2-acetamidoethyl)-2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-N-(2-(pyrrolidin-1-yl)ethyl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

(2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)((R)-3-(dimethylamino)pyrrolidin-1-yl)methanone;

2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide;

(2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)((S)-3-(dimethylamino)pyrrolidin-1-yl)methanone;

5-(3-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

2-(1-(2,2,2-trifluoroethyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

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2-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-3-(2,4-difluorophenyl)-pyrazine;

5-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-4-(2,4-difluorophenyl)-1H-imidazole;

N2-(2-chloro-4-(piperazine-1-carbonyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(4-(4-acetylpiperazine-1-carbonyl)-2-chlorophenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

2-[5-(2,4-Difluoro-phenyl)-[1,2,3]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide;

2-(1-isobutyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

9-bromo-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

4-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-3-(2,4-difluorophenyl)-1,2,5-oxadiazole;

9-(1H-pyrazol-4-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

5-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

(9-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-2-yl)(4-methylpiperazin-1-yl)methanone;

2-(5-tert-Butyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

2-(5-tert-Butyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide;

2-(5-Isopropyl-[1,2,3]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide;

2-(1-(1,1,1-trifluoropropan-2-yl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(1-(1,1,1-trifluoropropan-2-yl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(1-(2-hydroxy-2-methylpropyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

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N2-(4-carbamoyl-2-chlorophenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chloro-4-(2-hydroxypropylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

2-(1-cyclobutyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-9-carboxamide;

2-(1-cyclobutyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

9-(1H-3,5-dimethylpyrazol-4-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

(3-chloro-4-(5-(4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1H-1,2,4-triazol-1-yl)phenyl)(4-methylpiperazin-1-yl)methanone;

2-(1-(2-(dimethylamino)ethyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

(2-(1-(2-hydroxy-2-methylpropyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(4-methylpiperazin-1-yl)methanone;

2-[5-(2,4-Difluoro-phenyl)-[1,2,4]triazol-1-yl]-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide;

N2-(2-chloro-4-(2-(dimethylamino)ethylcarbamoyl)phenyl)-N2,N8-dimethyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

N2-(2-chloro-4-(2-(dimethylamino)ethylcarbamoyl)phenyl)-N2-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-2,8-dicarboxamide;

5-(8-(4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-isopropyl-1H-1,2,4-triazole;

2-(2-aminopyridin-4-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile;

5-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-6-(2,4-difluorophenyl)pyridin-2-amine;

8-(1H-pyrazol-4-yl)-(4H-4-isobutyl-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

(2-(1-(2,4-difluorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(4-methylpiperazin-1-yl)methanone;

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(2-(1-(2-chlorophenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)(4-methylpiperazin-1-yl)methanone;

2-(1-(3-methylbutan-2-yl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(5-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-1H-1,2,4-triazol-1-yl)-N,N-dimethylethanamine;

2-(5-(2-(4-(2-chlorophenyl)-4H-1,2,4-triazol-3-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-8-yl)-1H-1,2,4-triazol-1-yl)ethanol;

2-(1-(4-((1H-1,2,4-triazol-1-yl)methyl)phenyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

(4-methylpiperazin-1-yl)(2-(1-(2,2,2-trifluoroethyl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-9-yl)methanone;

8-(1-methylimidazol-2-yl)-(4H-4-isopropyl-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-3,5-dimethylpyrazol-4-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-pyrazol-4-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-pyrazol-4-yl)-(4-(*R*-1-methylisobutyl-4H)-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-pyrazol-4-yl)-(4-(*S*-1-methylisobutyl-4H)-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-pyrazol-4-yl)-(4-(*R*-1-methylpropyl-4H)-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-pyrazol-4-yl)-(4-(*S*-1-methylpropyl-4H)-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-pyrazol-4-yl)-(2-trifluoroethyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

5-(2-(1H-3,5-dimethylpyrazol-4-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

5-(2-(1H-pyrazol-4-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

5-(2-(2-methylpyrid-3-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

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5-(2-(N-2-(pyrrolidin-1-yl)ethylcarbamoyl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

5-((2-N-benzylcarbamoyl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

2-(1-(1,1,1-trifluoro-3-methylbutan-2-yl)-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide;

2-(5-Isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid amide;

8-carbamoyl-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

2-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-3-(2,4-difluorophenyl)-5-aminopyrazine;

9-(imidazo-2-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-pyrazol-4-yl)-((1,1,1-trifluoropropan-2-yl)-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-5-methyl-pyrazol-4-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

2-(5-Isopropyl-[1,2,4]triazol-1-yl)-8-(1*H*-pyrazol-4-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(imidazo-2-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(2-amino-pyrid-5-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

9-(carbamoyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-pyrazol-4-yl)-(1-cyclopropylmethyl-1H-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

2-(5-Isopropyl-[1,2,4]triazol-1-yl)-9-(1*H*-pyrazol-4-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

2-(5-Isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-9-carboxylic acid amide;

8-(1H-pyrazol-4-yl)-(4-isopropyl-4H-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

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8-(methylcarbamate)-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

9-(2-amino-pyrid-5-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-pyrazol-5-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(carbamoyl)-(2-trifluoroethyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

9-(tetrazol-5-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(cyano)-(2-trifluoroethyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

2-(5-isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-8-carboxylic acid (2-hydroxy-ethyl)-amide;

2-(5-isopropyl-[1,2,4]triazol-1-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene-9-carboxylic acid (2-hydroxy-ethyl)-amide;

8-(carbamoyl)-((1,1,1-trifluoropropan-2-yl)-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(morpholinomethanimine)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(1H-pyrazol-4-yl)-(2-isopropyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

2-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-5-aminopyrazine;

8-(aminomethyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(6-methylpyrid-3-yl)-(2-trifluoroethyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-((2-methylsulfonylethyl)-amide)-(4-isopropyl-4H-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(methylcarbamoyl)-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(2-aminopyrid-5-yl)-(2-trifluoroethyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

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8-(acetamidomethyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(tetrazol-5-yl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(formamidinyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(methylformamidinyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(carbamoyl)-(2-isopropyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

5-(2-(morpholin-4-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

5-(2-(N-benzylamino)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

(2-isopropyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

(2-trifluoroethyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(hydroxymethyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(N-(pyrid-2-yl)formamidinyl)-2-isopropyl-2H-1,2,4-triazol-3-yl-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

8-(N-2-(*S*-3-hydroxypyrrolidin-1-yl)ethylcarbamoyl)-(2-trifluoroethyl-2H-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

5-(2-carbamoyl-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-2-amino-6-ethylpyridine;

8-(methylcarbamoyl)-(2-trifluoroethyl-2H-5-amino-1,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-1-aza-benzo[e]azulene;

5-(8-bromo-4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2-yl)-1-isopropyl-1H-1,2,4-triazole;

2-(1-isopropyl-1H-1,2,4-triazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carbonitrile;

5-(2-(*N*-piperazinyl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-1-(2,4-difluorophenyl)-1H-1,2,4-triazole;

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5-(2-(3R,5S-dimethylpiperazin-l-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yl)-l-(2,4-difluorophenyl)-lH-l,2,4-triazole;

5-((2-(4-dimethyiamino)piperidm»l-yl)-6,7-dihydropyrido[3,2-b]thieno[2,3-d]oxepin-9-yI)-1 -(2,4-dirluorophenyl)-1H-1,2,4-triazole;

8-(3-(2-oxopyrrolidin-l-yl)propanamidomethyl)-(2-trifluoroethyl»2H-l$_5$2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-l-aza-benzo[e]azulene;

8-(methylcarbamoyl)-(2-trifluoroetnyl-2H»l,2,4-triazol-3-yl)-4,5-dihydro-6--oxa-3-thia-1 -aza-benzo[e]azulene;

(2-(2-isopropyl-2H-I,2,4-triazol-3-yl)-4,5-dihydro-6-oxa-3-thia-l-aza-benzo[e]azulen-9-yl)(4-isopropylpiperazin-l~yl)methanone;

9-((2-methylsulfonylethyl)-amide)--(4-isopropyl-4H-L2,4-triazol-5-yl)~4,5-dihydro»6-oxa-3-thia-l -aza-benzo[e]azulene;

3-(9"bromo»4,5-dihydro-6-oxa-l-thia-benzo[e]azulen-2~yl)-4-(2,4-dichloro-phenyl)-4H-[1,2,4]triazole; and

N-(2-aminoethyl)-2-(4-(2-chlorophenyl)-5-oxo-4,5-dihydro-lH-l,2,4-triazol-3-yl)" 4,5~dihydrobenzo[b]thieno[2,3"d]oxepine-8-carboxamide.

17. A pharmaceutical composition comprised of a compound of claim 1 and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

18. The pharmaceutical composition according to claim 17, further comprising an additional therapeutic agent selected from a chemotherapeutic agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders.

19. Use of a compound of claim 1 for the manufacture of a medicament for treating cancer in a mammal comprised of administering to said mammal a therapeutically effective amount of the compound, wherein the cancer is breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, kerato acanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, pancreatic, myeloid disorders, lymphoma, hairy cells, buccal cavity, naso-pharyngeal, pharynx, lip,

tongue, mouth, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's or leukemia.

20. A process for making a pharmaceutical composition which comprises combining a compound of claim 1 with a pharmaceutically acceptable carrier.

21. The use of a compound according to claim 1 in the manufacture of a medicament for the prophylactic or therapeutic treatment of cancer.

22. An *in vitro* method for inhibiting or modulating lipid kinase activity, comprising contacting the lipid kinase with an effective inhibitory amount of a compound of claim 1.

23. The method of claim 22 wherein the lipid kinase is PI3K.

24. The method of claim 23 wherein the PI3K is the pi 10 alpha subunit.

25. Use of of a compound of claim 1for the manufacture of a medicament for inhibiting or modulating lipid kinase activity in a mammal, comprising administering to the mammal a therapeutically effective amount of the compound.

26. The use according to claim 25 wherein the lipid kinase is PI3K.

27. Use of a compound of claim 1 for the manufacture of a medicament for use in therapy.

28. A kit for treating a PI3K-mediated condition, comprising:

a) a first pharmaceutical composition comprising a compound of claim 1; and

b) instructions for use.

29. The compound (4,5-dihydrobenzo[b]thieno[2,3-d]oxepin-2~yl)(3,4-dihydroquinolin-l(2H)-yl)methanone or a stereoisomer, geometric isomer, tautomer, or pharmaceutically acceptable salt thereof.

30. The compound 2-(l-(2-(trifiuoromethyl)"lH-benzo[d]imidazol-5-yl)-lH-1,2,4-1xiazol-5-yl)-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide or a stereoisomer, geometric isomer, tautomer, or pharmaceutically acceptable salt thereof.