

MACROCYCLIC INHIBITORS OF ATP CITRATE LYASE**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of and priority to U.S. Patent Application No. 63/595,012, filed on November 1, 2023, the entire contents of which are incorporated by reference herein.

BACKGROUND

[0002] A combination of human genetic factors, overnutrition, and a sedentary lifestyle promote derangements in cholesterol and triglyceride metabolism. These derangements can manifest as one or more risk factors associated with increased probability of developing a number of life-threatening metabolic and/or cardiovascular diseases. The importance of maintaining cholesterol homeostasis in humans is strongly supported by both epidemiologic cohort studies and meta-analyses of multiple Mendelian and statin randomized trials that clearly demonstrate an association between elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) (hypercholesterolemia) and atherosclerotic cardiovascular disease (ASCVD) risk. (Ference et al. (2017) *Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel.*, Eur. Heart J., 38, 2459–2472; Silverman et al., (2016) *Association between lowering LDL- C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis.*, JAMA, 316, 1289–1297).

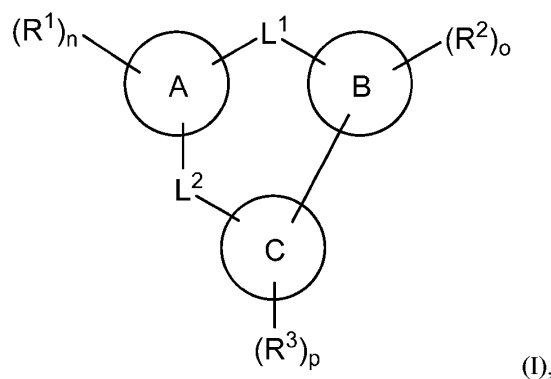
[0003] While an association between ASCVD and circulating triglyceride levels is less clear (Helgadottir et al., (2016), *Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease.*, Nat. Genet., 48, 634–639; Miller et al., (2011), *Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association.*, Circulation, 123, 2292–2333), aberrations in triglyceride metabolism also manifest as other metabolic ASCVD risk factors including insulin resistance, type 2 diabetes, and nonalcoholic fatty liver disease (NAFLD). (Cohen et al., (2011), *Human fatty liver disease: old questions and new insights.*, Science, 332, 1519–1523; Armstrong et al., (2014), *Extrahepatic complications of nonalcoholic fatty liver disease.*, Hepatology 59, 1174–1197). Moreover, NAFLD poses an independent health challenge as one of the most common causes of chronic liver disease and hepatocellular carcinoma, leading causes of liver-related morbidity and mortality in the Western world. (Loomba and Sanyal, (2013), *The global NAFLD epidemic.*, Nat. Rev. Gastroenterol. Hepatol., 10, 686–690).

[0004] Neither ASCVD nor NAFLD (also known as metabolic dysfunction-associated fatty liver disease (MAFLD)) is adequately addressed by currently available treatment options. Many patients are not effectively treated for lipid disorders with the current standard of care, ASCVD remains the leading cause of death and disability in the Western world. (Mendis, (2010), *The contribution of the Framingham Heart Study to the prevention of cardiovascular disease: a global perspective.*, Prog. Cardiovasc. Dis., 53, 10–14). As such, new therapeutic strategies that target cholesterol and triglyceride metabolism are required. ATP-citrate lyase (ACLY) is an enzyme uniquely positioned at the intersection of nutrient catabolism, and cholesterol and fatty acid biosynthesis, a metabolic nexus shown to be dysregulated in multiple disease states. Significant evidence supports that ACLY-derived acetyl-coenzyme A (CoA) serves not only as carbon precursor for cholesterol and fatty acid biosynthesis, but also as a key metabolic checkpoint used by multiple cell types to sense nutrient availability and coordinate metabolic adaptations with multiple effector functions. Thus, there is an unmet need to develop new therapeutic agents that modulate (e.g., inhibit) ACLY activity to treat metabolic and/or cardiovascular diseases.

SUMMARY

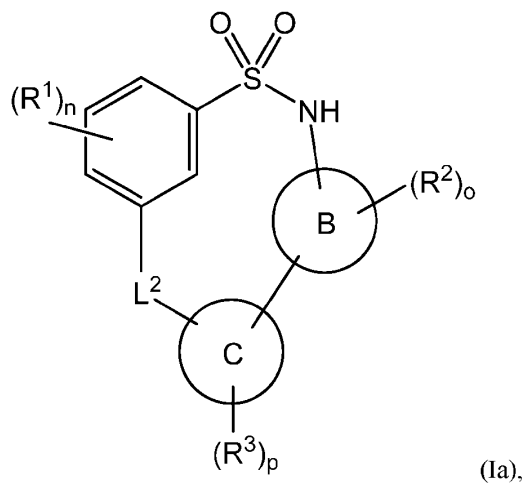
[0005] Provided herein are compounds designed to function as modulators (e.g., inhibitors) of ATP citrate lyase (ACLY). Such compounds can be useful as therapeutic agents for treating conditions, diseases, and disorders associated with aberrant metabolism, such as NAFLD or MAFLD, nonalcoholic steatohepatitis (NASH) or metabolic dysfunction-associated steatohepatitis (MASH), type-2 diabetes, chronic kidney disease, inflammation, autoimmunity, and cancer.

[0006] In one aspect, provided herein are compounds of formula (I)



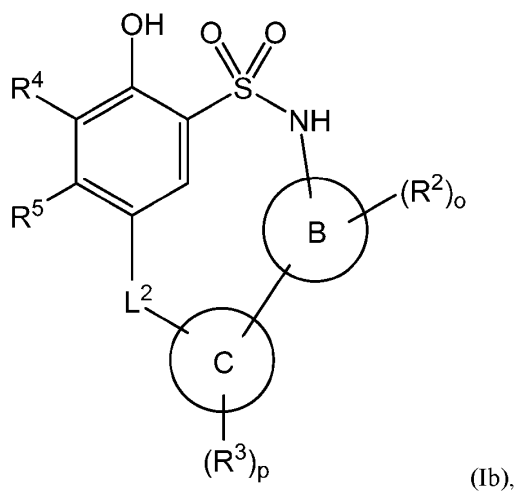
or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0007] In another aspect, provided herein are compounds of formula (Ia)



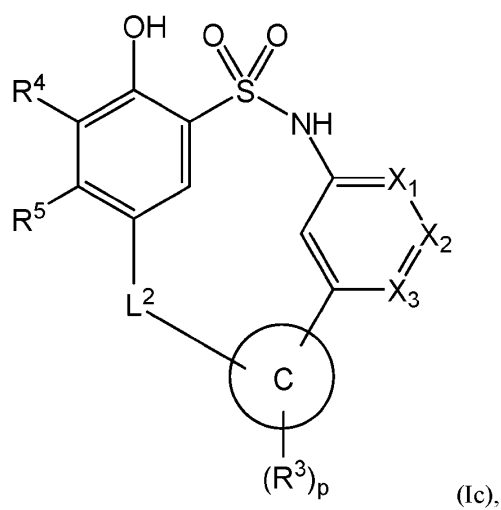
or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0008] In another aspect, provided herein are compounds of formula (Ib)



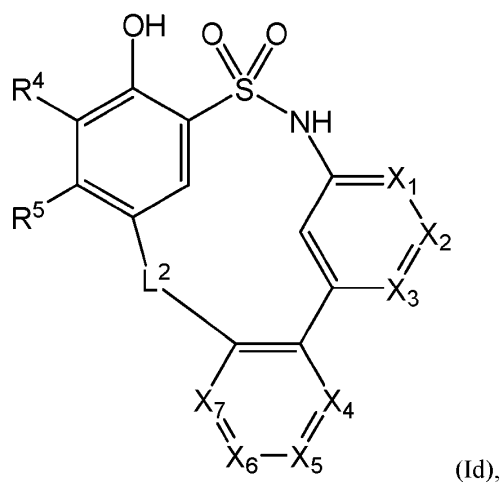
or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0009] In another aspect, provided herein are compounds of formula (Ic)



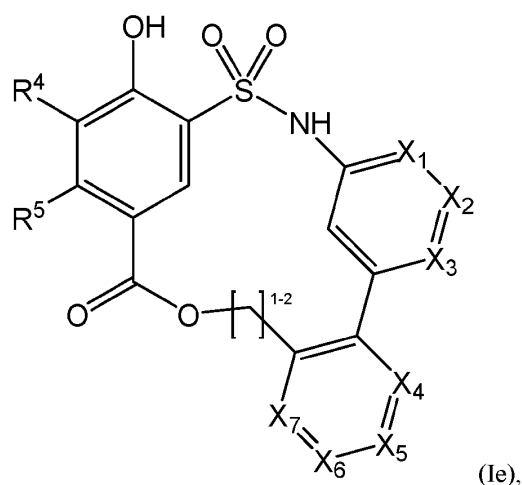
or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0010] In another aspect, provided herein are compounds of formula (Id)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0011] In another aspect, provided herein are compounds of formula (Ie)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein.

[0012] In certain embodiments, the compounds of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id), or formula (Ie) are selected from the compounds of Table 1 or a stereoisomer and/or a pharmaceutically acceptable salt thereof.

[0013] In another aspect, provided herein are pharmaceutical compositions comprising a compound disclosed herein or a stereoisomer and/or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

[0014] A compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id), or formula (Ie), or a stereoisomer and/or a pharmaceutically acceptable salt thereof; or a pharmaceutical composition of the invention can be used in treating the various conditions, diseases, and disorders described herein. For example, the methods of treatment can include inhibiting ACLY, inhibiting cholesterol synthesis, and/or suppressing fatty acid biosynthesis. In some embodiments, the condition, disease, or disorder can be a liver condition, disease, or disorder such as NAFLD/MAFLD or NASH/MASH and the methods include treating the liver condition, disease, or disorder such as NAFLD/MAFLD or NASH/MASH. In some embodiments, the condition, disease, or disorder can be type-2 diabetes and the methods include treating type-2 diabetes. In some embodiments, the condition, disease, or disorder can be inflammation and the methods include treating inflammation. In some embodiments, the condition, disease, or disorder is chronic kidney disease, and the methods include treating chronic kidney disease. In some embodiments, the condition, disease, or disorder is

autoimmunity, and the methods include treating autoimmunity. In some embodiments, the condition, disease, or disorder is cancer, and the methods include treating cancer.

DETAILED DESCRIPTION

[0015] As generally described herein, the disclosure provides compounds of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id), and formula (Ie), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, and pharmaceutical compositions containing the same. The compounds and compositions described herein function as modulators (e.g., inhibitors) of ACLY. The disclosure also provides methods of using the compounds and compositions disclosed herein to treat a variety of conditions, diseases, and disorders associated with aberrant metabolism. Such conditions, diseases, and disorders include, but are not limited to NAFLD/MAFLD, NASH/MASH, type-2 diabetes, chronic kidney disease, inflammation, autoimmunity, and cancer.

Definitions

[0016] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

[0017] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0018] Throughout the description, where compositions and kits are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions and kits of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0019] In the application, where an element or component is said to be included in and/or selected from a list of recited elements or components, it should be understood that the element or component can be any one of the recited elements or components, or the element or component can be selected from a group consisting of two or more of the recited elements or components.

[0020] Further, it should be understood that elements and/or features of a composition or a method described herein can be combined in a variety of ways without departing from the spirit and scope of the present invention, whether explicit or implicit herein. For example, where reference is made to a particular compound, that compound can be used in various embodiments of compositions of the present invention and/or in methods of the present invention, unless otherwise understood from the context. In other words, within this application, embodiments have been described and depicted in a way that enables a clear and concise application to be written and drawn, but it is intended and will be appreciated that embodiments may be variously combined or separated without parting from the present teachings and invention(s). For example, it will be appreciated that all features described and depicted herein can be applicable to all aspects of the invention(s) described and depicted herein.

[0021] The articles “a” and “an” are used in this disclosure to refer to one or more than one (i.e., to at least one) of the grammatical object of the article, unless the context is inappropriate. By way of example, “an element” means one element or more than one element. By way of further example “an analogue” means one analogue or more than one analogue.

[0022] The term “and/or” is used in this disclosure to mean either “and” or “or” unless indicated otherwise.

[0023] It should be understood that the expression “at least one of” includes individually each of the recited objects after the expression and the various combinations of two or more of the recited objects unless otherwise understood from the context and use. The expression “and/or” in connection with three or more recited objects should be understood to have the same meaning unless otherwise understood from the context.

[0024] The use of the term “include,” “includes,” “including,” “have,” “has,” “having,” “contain,” “contains,” or “containing,” including grammatical equivalents thereof, should be understood generally as open-ended and non-limiting, for example, not excluding additional unrecited elements or steps, unless otherwise specifically stated or understood from the context.

[0025] Where the use of the term “about” is before a quantitative value, the present invention also includes the specific quantitative value itself, unless specifically stated otherwise. As used herein, the term “about” refers to a $\pm 10\%$, $\pm 5\%$, $\pm 3\%$, $\pm 2\%$, or $\pm 1\%$ variation from the nominal value unless otherwise indicated or inferred from the context.

[0026] Where a molecular weight is provided and not an absolute value, for example, of a polymer, then the molecular weight should be understood to be an average molecule weight, unless otherwise stated or understood from the context.

[0027] It should be understood that the order of steps or order for performing certain actions is immaterial so long as the present invention remain operable. Moreover, two or more steps or actions may be conducted simultaneously.

[0028] At various places in the present specification, variable or parameters are disclosed in groups or in ranges. It is specifically intended that the description include each and every individual subcombination of the members of such groups and ranges. For example, “C₁₋₆ alkyl” is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl. By way of another example, an integer in the range of 0 to 40 is specifically intended to individually disclose 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, and 40, and an integer in the range of 1 to 20 is specifically intended to individually disclose 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20.

Additional examples include that the phrase “optionally substituted with 1-5 substituents” is specifically intended to individually disclose a chemical group that can include 0, 1, 2, 3, 4, 5, 0-5, 0-4, 0-3, 0-2, 0-1, 1-5, 1-4, 1-3, 1-2, 2-5, 2-4, 2-3, 3-5, 3-4, and 4-5 substituents.

[0029] The use of any and all examples, or exemplary language herein, for example, “such as” or “including,” is intended merely to illustrate better the present invention and does not pose a limitation on the scope of the invention unless claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the present invention.

Chemical Definitions

[0030] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers,

Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0031] The compounds of the disclosure can contain one or more chiral centers and/or double bonds and therefore, can exist as stereoisomers, such as geometric isomers, and enantiomers or diastereomers. The term “stereoisomers,” when used herein, consists of all geometric isomers, enantiomers and/or diastereomers of the compound. For example, when a compound is shown with specific chiral center(s), the compound depicted without such chirality at that and other chiral centers of the compound are within the scope of the present disclosure, i.e., the compound depicted in two-dimensions with “flat” or “straight” bonds rather than in three dimensions, for example, with solid or dashed wedge bonds.

[0032] More specifically, a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id), or formula (Ie)) can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, (Wiley-VCH: Weinheim, 2009); Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0033] As used herein a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (*i.e.*, in enantiomeric excess). In other words, an “*S*” form of the compound is substantially free from the “*R*” form of the compound and is, thus, in enantiomeric excess of the “*R*” form. The term “enantiomerically pure” or “pure enantiomer” denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than

95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

[0034] Geometric isomers, resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a cycloalkyl or heterocycloalkyl, can also exist in the compounds of the present disclosure. The symbol $\equiv$ denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the “Z” or “E” configuration, where the terms “Z” and “E” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the “E” and “Z” isomers.

[0035] Substituents around a carbon-carbon double bond alternatively can be referred to as “cis” or “trans,” where “cis” represents substituents on the same side of the double bond and “trans” represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as “cis” or “trans.” The term “cis” represents substituents on the same side of the plane of the ring and the term “trans” represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated “cis/trans.”

[0036] A compound described herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D or deuterium), and ^3H (T or tritium); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; and F may be in any isotopic form, including ^{18}F and ^{19}F . Other examples of isotopes that can be incorporated into compounds described herein include isotopes of nitrogen, phosphorus, and chlorine, such as ^{15}N , ^{31}P , ^{32}P , ^{35}S , and ^{36}Cl , respectively. As an example of an isotopic compound, a compound described herein can have one or more H atoms replaced with deuterium.

[0037] The terms described herein are intended to have the meanings presented and can be useful in understanding the description and intended scope of the present disclosure. When describing the disclosure, which may include a compound disclosed herein or a stereoisomer and/or a pharmaceutically acceptable salt thereof, pharmaceutical compositions containing

such compounds and methods of using such compounds and compositions, the defined terms, if present, have their ascribed meanings unless otherwise indicated.

[0038] Unless otherwise stated, the term “substituted” is to be defined as set out herein. It should be further understood that the terms “groups” and “radicals” can be considered interchangeable when used herein.

[0039] As used herein, “alkyl” refers to a radical (e.g., a monovalent or divalent radical) of a straight-chain or branched saturated hydrocarbon group, e.g., having 1 to 20 carbon atoms (“C₁₋₂₀ alkyl”) such as a straight-chain or branched group of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C₁-C₆ alkyl, C₁-C₄ alkyl, and C₁-C₃ alkyl, respectively. For example, “C₁-C₆ alkyl” refers to a straight-chain or branched saturated hydrocarbon containing 1-6 carbon atoms. Examples of a C₁-C₆ alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, *sec*-butyl, *tert*-butyl, isopentyl, and neopentyl. In another example, “C₁-C₄ alkyl” refers to a straight-chain or branched saturated hydrocarbon containing 1-4 carbon atoms. Examples of a C₁-C₄ alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, *sec*-butyl and *tert*-butyl. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 3-methyl-2-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, *t*-butyl, pentyl, isopentyl, neopentyl, and hexyl.

[0040] As used herein, “carbocyclyl” or “carbocyclic” refers to a radical (e.g., a monovalent or divalent radical) of a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”); 3 to 7 ring carbon atoms (“C₃₋₇ carbocyclyl”); 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”); or 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include, without limitation, the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀),

cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or contain a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic carbocyclyl”). In certain embodiments, the carbocyclyl group, as defined above, can be saturated or can be partially unsaturated.

[0041] As used herein, “cycloalkyl” refers to a monovalent saturated cyclic, bicyclic, or bridged cyclic (e.g., adamantyl) hydrocarbon group of 3-12, 3-8, 3-6, 4-8, or 4-6 carbons, referred to herein, e.g., as “C₃₋₆ cycloalkyl,” derived from a cycloalkane. Exemplary cycloalkyl groups include, but are not limited to, cyclohexanes such as cyclohexyl and cyclohexenyl, cyclopentanes such as cyclopentyl and cyclopentenyl, cyclobutanes such as cyclobutyl, and cyclopropanes such as cyclopropyl.

[0042] As used herein, “heteroatom” refers to an atom of any element other than carbon or hydrogen and includes, for example, nitrogen (N), oxygen (O), silicon (Si), sulfur (S), phosphorus (P), and selenium (Se).

[0043] As used herein, “heterocyclyl” or “heterocyclic” refer to a radical (e.g., a monovalent or divalent radical) of a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“3-10 membered heterocyclyl”). In some embodiments, a heterocyclyl is 5- to 10-membered (“5-10 membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic heterocyclyl”), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. The terms “heterocycle,” “heterocyclyl,” “heterocyclyl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” may be used interchangeably.

[0044] As used herein, “aryl” refers to a radical of a monocyclic or bicyclic $4n+2$ aromatic ring system (e.g., having 6 or 10 electrons shared in a cyclic array) having 6–10 ring carbon atoms and zero heteroatoms provided in the aromatic ring system. Non-limiting examples of aryl groups include phenyl and naphthyl.

[0045] As used herein, “heteroaryl” refers to a radical (e.g., a monovalent or divalent radical) of a 5–14 membered monocyclic or bicyclic $4n+2$ aromatic ring system (e.g., having 6 or 10 electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system (“5–10 membered heteroaryl”). In certain embodiments, each heteroatom is independently selected from nitrogen, oxygen and sulfur. In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, i.e., either the ring bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl). Other non-limiting examples of heteroaryl groups include pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, and isoquinolinyl.

[0046] As used herein, “hetero” can be used to describe a compound or a group present on a compound where one or more carbon atoms in the compound or group have been replaced by a heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, e.g., heteroalkyl; carbocyclyl, e.g., heterocyclyl; aryl, e.g., heteroaryl; and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[0047] As used herein, “carbonyl” refers to the radical $-C(O)-$ or $C=O$.

[0048] As used herein, “cyano” refers to $-CN$.

[0049] As used herein, “hydroxy” and “hydroxyl” refer to the radical $-OH$.

[0050] As used herein, “oxo” refers to the radical $=O$ (double bonded oxygen).

[0051] As used herein, “halo” and “halogen” refer to an atom selected from fluorine (fluoro, $-F$), chlorine (chloro, $-Cl$), bromine (bromo, $-Br$), and iodine (iodo, $-I$). In certain embodiments, the halo group is bromo, fluoro, or chloro.

[0052] As used herein, “alkoxy” refers to an alkyl group which is attached to another moiety via an oxygen atom (–O(alkyl)). Alkoxy groups can have 1-6 or 2-6 carbon atoms and are referred to herein as C₁-C₆ alkoxy and C₂-C₆ alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to, methoxy, ethoxy, propyloxy, isopropoxy, and *tert*-butoxy.

[0053] As used herein, “haloalkyl” refers to an alkyl group as defined herein substituted with one or more halogen atoms where the halogens are independently selected from fluorine, chlorine, bromine, and iodine. In some embodiments, a haloalkyl has 1 to 6 carbon atoms (“C₁₋₆haloalkyl”).

[0054] As used herein, “haloalkoxy” refers to a haloalkyl group which is attached to another moiety via an oxygen atom such as, e.g., but are not limited to –OCHCF₂ or –OCF₃. In some embodiments, a haloalkoxy has 1 to 6 carbon atoms (“C₁₋₆haloalkoxy”).

[0055] As generally used herein, “substituted,” whether preceded by the term “optionally” or not, means that at least one hydrogen present on a group (e.g., a carbon or nitrogen atom) is replaced with a permissible substituent, e.g., a substituent which upon substitution results in a stable compound, e.g., a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position.

[0056] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, –OH, –OR^{aa}, –N(R^{cc})₂, –CN, –C(=O)R^{aa}, –C(=O)N(R^{cc})₂, –CO₂R^{aa}, –SO₂R^{aa}, –C(=NR^{bb})R^{aa}, –C(=NR^{cc})OR^{aa}, –C(=NR^{cc})N(R^{cc})₂, –SO₂N(R^{cc})₂, –SO₂R^{cc}, –SO₂OR^{cc}, –SOR^{aa}, –C(=S)N(R^{cc})₂, –C(=O)SR^{cc}, –C(=S)SR^{cc}, –P(=O)₂R^{aa}, –P(=O)(R^{aa})₂, –P(=O)₂N(R^{cc})₂, –P(=O)(NR^{cc})₂, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3–14 membered heterocyclyl, C₆₋₁₄ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein.

[0057] Each instance of R^{aa} is, independently, selected from C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3–14 membered heterocyclyl, C₆₋₁₄ aryl, and 5–

14 membered heteroaryl, or two R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups.

[0058] Each instance of R^{bb} is, independently, selected from hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -P(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -P(=O)₂N(R^{cc})₂, -P(=O)(NR^{cc})₂, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, or two R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups.

[0059] Each instance of R^{cc} is, independently, selected from hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, or two R^{cc} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups.

[0060] Each instance of R^{dd} is, independently, selected from halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{cc}, -ON(R^{ff})₂, -N(R^{ff})₂, -N(R^{ff})₃⁺X⁻, -N(OR^{cc})R^{ff}, -SH, -SR^{cc}, -SSR^{cc}, -C(=O)R^{cc}, -CO₂H, -CO₂R^{cc}, -OC(=O)R^{cc}, -OCO₂R^{cc}, -C(=O)N(R^{ff})₂, -OC(=O)N(R^{ff})₂, -NR^{ff}C(=O)R^{cc}, -NR^{ff}CO₂R^{cc}, -NR^{ff}C(=O)N(R^{ff})₂, -C(=NR^{ff})OR^{cc}, -OC(=NR^{ff})R^{cc}, -OC(=NR^{ff})OR^{cc}, -C(=NR^{ff})N(R^{ff})₂, -OC(=NR^{ff})N(R^{ff})₂, -NR^{ff}C(=NR^{ff})N(R^{ff})₂, -NR^{ff}SO₂R^{cc}, -SO₂N(R^{ff})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -OSO₂R^{cc}, -S(=O)R^{cc}, -Si(R^{cc})₃, -OSi(R^{cc})₃, -C(=S)N(R^{ff})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -SC(=S)SR^{cc}, -P(=O)₂R^{cc}, -P(=O)(R^{cc})₂, -OP(=O)(R^{cc})₂, -OP(=O)(OR^{cc})₂, C₁₋₆ alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S.

[0061] Each instance of R^{cc} is, independently, selected from C₁₋₆ alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, C₆₋₁₀ aryl, 3-10 membered heterocyclyl, and 3-10

membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{sg} groups.

[0062] Each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl, or two R^{ff} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{sg} groups.

[0063] Each instance of R^{sg} is, independently, halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OC(C_{1-6} alkyl), -ON(C_{1-6} alkyl)₂, -N(C_{1-6} alkyl)₂, -N(C_{1-6} alkyl)₃⁺X⁻, -NH(C_{1-6} alkyl)₂⁺X⁻, -NH₂(C_{1-6} alkyl)⁺X⁻, -NH₃⁺X⁻, -N(OC(C_{1-6} alkyl))(C_{1-6} alkyl), -N(OH)(C_{1-6} alkyl), -NH(OH), -SH, -SC(C_{1-6} alkyl), -SS(C_{1-6} alkyl), -C(=O)(C_{1-6} alkyl), -CO₂H, -CO₂(C_{1-6} alkyl), -OC(=O)(C_{1-6} alkyl), -OCO₂(C_{1-6} alkyl), -C(=O)NH₂, -C(=O)N(C_{1-6} alkyl)₂, -OC(=O)NH(C_{1-6} alkyl), -NHC(=O)(C_{1-6} alkyl), -N(C_{1-6} alkyl)C(=O)(C_{1-6} alkyl), -NHCO₂(C_{1-6} alkyl), -NHC(=O)N(C_{1-6} alkyl)₂, -NHC(=O)NH(C_{1-6} alkyl), -NHC(=O)NH₂, -C(=NH)O(C_{1-6} alkyl), -OC(=NH)(C_{1-6} alkyl), -OC(=NH)OC(C_{1-6} alkyl), -C(=NH)N(C_{1-6} alkyl)₂, -C(=NH)NH(C_{1-6} alkyl), -C(=NH)NH₂, -OC(=NH)N(C_{1-6} alkyl)₂, -OC(NH)NH(C_{1-6} alkyl), -OC(NH)NH₂, -NHC(NH)N(C_{1-6} alkyl)₂, -NHC(=NH)NH₂, -NHCO₂(C_{1-6} alkyl), -SO₂N(C_{1-6} alkyl)₂, -SO₂NH(C_{1-6} alkyl), -SO₂NH₂, -SO₂C(C_{1-6} alkyl), -SO₂OC(C_{1-6} alkyl), -OSO₂C(C_{1-6} alkyl), -SOC(C_{1-6} alkyl), -Si(C_{1-6} alkyl)₃, -OSi(C_{1-6} alkyl)₃, -C(=S)N(C_{1-6} alkyl)₂, C(=S)NH(C_{1-6} alkyl), C(=S)NH₂, -C(=O)S(C_{1-6} alkyl), -C(=S)SC(C_{1-6} alkyl), -SC(=S)SC(C_{1-6} alkyl), -P(=O)₂(C_{1-6} alkyl), -P(=O)(C_{1-6} alkyl)₂, -OP(=O)(C_{1-6} alkyl)₂, -OP(=O)(OC(C_{1-6} alkyl))₂, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R^{sg} substituents can be joined to form =O or =S.

[0064] X⁻ is a counterion. A "counterion" or "anionic counterion" is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (e.g., F⁻, Cl⁻, Br⁻, I⁻), NO₃⁻, ClO₄⁻, OH⁻, H₂PO₄⁻, HSO₄⁻, sulfonate ions (e.g., methanesulfonate, trifluoromethanesulfonate, p-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), and carboxylate ions (e.g., acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

[0065] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and Claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

[0066] As used herein, “compound” refers to the compound itself and its pharmaceutically acceptable salts, hydrates, esters and N-oxides including its various stereoisomers and its isotopically-labelled forms, unless otherwise understood from the context of the description or expressly limited to one particular form of the compound, i.e., the compound itself, a specific stereoisomer and/or isotopically-labelled compound, or a pharmaceutically acceptable salt, a hydrate, an ester, or an N-oxide thereof. It should be understood that a compound can refer to a pharmaceutically acceptable salt, or a hydrate, an ester or an N-oxide of a stereoisomer of the compound and/or an isotopically-labelled compound.

[0067] Further, if a variable is not accompanied by a definition, then the variable is defined as found elsewhere in the disclosure unless understood to be different from the context. In addition, the definition of each variable and/or substituent, for example, C₁-C₆ alkyl, R², R^b, w and the like, when it occurs more than once in any structure or compound, can be independent of its definition elsewhere in the same structure or compound.

[0068] Definitions of the variables and/or substituents in formulae and/or compounds herein encompass multiple chemical groups. The present disclosure includes embodiments where, for example, i) the definition of a variable and/or substituent is a single chemical group selected from those chemical groups set forth herein, ii) the definition is a collection of two or more of the chemical groups selected from those set forth herein, and iii) the compound is defined by a combination of variables and/or substituents in which the variables and/or substituents are defined by (i) or (ii).

Other definitions

[0069] As used herein, “pharmaceutically acceptable” and “pharmacologically acceptable,” refer to compounds, molecular entities, compositions, materials, and/or dosage forms that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA Office of Biologics standards.

[0070] As used herein, “pharmaceutically acceptable carrier” and “pharmaceutically acceptable excipient,” refer to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical

administration. Pharmaceutical acceptable carriers can include phosphate buffered saline solution, water, emulsions (e.g., such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives.

[0071] As used herein, “pharmaceutically acceptable salt” refers to any salt of an acidic or a basic group that may be present in a compound of the present disclosure, which salt is compatible with pharmaceutical administration. As is known to those of skill in the art, “salts” of the compounds of the present disclosure may be derived from inorganic or organic acids and bases. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases.

Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like.

Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0072] As used herein, a “subject” to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or a non-human animal, e.g., a mammal such as primates (e.g., cynomolgus

monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal. The terms “human,” “patient,” and “subject” are used interchangeably herein.

[0073] As used herein, and unless otherwise specified, the terms “treat,” “treating” and “treatment” contemplate an action that occurs while a subject is suffering from the specified disease, disorder or condition, which reduces the severity of the disease, disorder or condition, or retards or slows the progression of the disease, disorder or condition (“therapeutic treatment”), and also contemplates an action that occurs before a subject begins to suffer from the specified disease, disorder or condition (“prophylactic treatment”).

[0074] As used herein, “effective amount” or “therapeutically-effective amount” refers to the amount of a compound (e.g., bempedoic acid), a combination of compounds (e.g., bempedoic acid and ezetimibe), a pharmaceutical composition (e.g., a pharmaceutical composition of the present disclosure), or a fixed-dose combination (e.g., a fixed-dose combination of the present disclosure) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route.

[0075] As used herein, “disease,” “disorder,” “condition,” or “illness,” can be used interchangeably unless otherwise underacted or understood from the context, refers to a state of being or health status of a patient or subject capable of being treated with a compound, pharmaceutical composition, or method provided herein. In some embodiments, the compounds and methods described herein comprise reduction or elimination of one or more symptoms of the disease, disorder, or condition, or illness e.g., through administration of the compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id), formula (Ie), or a stereoisomer and/or a pharmaceutically acceptable salt thereof.

[0076] As used herein, “administering” means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arterial, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, etc. By “co-administer” it is meant that a composition described herein is administered at the same time,

just prior to, or just after the administration of one or more additional therapies (e.g., anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). The compound of the invention can be administered alone or can be co-administered to the patient. Co-administration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g., to reduce metabolic degradation).

[0077] As used herein, “liver disorder” refers generally to a disease, a disorder, and/or a condition affecting the liver, and may have a wide range of severity encompassing, for example, simple accumulation of fat in the hepatocytes (steatosis), macrovesicular steatosis, periportal and lobular inflammation (steatohepatitis), cirrhosis, fibrosis, liver cancers, and liver failure.

[0078] As used herein, “fatty liver disease” (“FLD”), which is also called “fatty liver,” refers to a disease leading to liver injury caused by abnormal fat accumulation in liver cells. FLD may arise from a number of sources, including excessive alcohol consumption and metabolic disorders, such as those associated with insulin resistance, obesity, and hypertension.

[0079] As used herein, “non-alcoholic fatty liver disease” (“NAFLD”) and “metabolic dysfunction-associated fatty liver disease” (“MAFLD”) are used interchangeably and refer to the spectrum of disorders resulting from an accumulation of fat in liver cells in individuals with no history of excessive alcohol consumption. In the mildest form, NAFLD/MAFLD refers to hepatic steatosis.

[0080] As used herein, “drug-induced liver disease” or “toxic liver injury” refers to a disease or a condition in which an active agent has caused injury to the liver.

[0081] As used herein, “alcoholic liver disease,” also called “alcoholic liver injury,” refers to a disease caused by fat accumulation in liver cells, caused at least in part by alcohol ingestion. Examples include, but are not limited to, diseases such as alcoholic simple fatty liver, alcoholic steatohepatitis (“ASH”), alcoholic hepatic fibrosis, alcoholic cirrhosis, alcoholic fatty liver disease, and the like. It should be noted that alcoholic steatohepatitis is also called alcoholic fatty hepatitis and includes alcoholic hepatic fibrosis.

[0082] As used herein, “fatty liver of pregnancy” refers to acute fatty liver conditions that can arise during pregnancy and can be life-threatening.

[0083] As used herein, “altering lipid metabolism” refers to an observable (measurable) change in at least one aspect of lipid metabolism, including, but not limited to, total blood

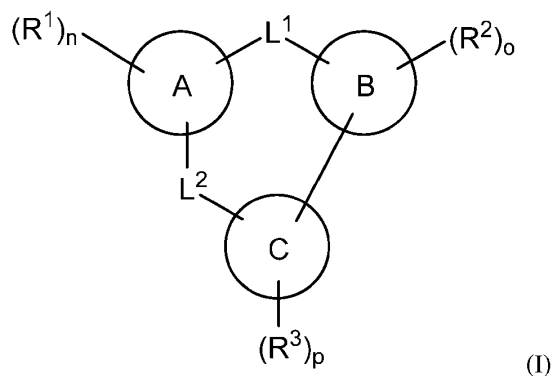
lipid content, blood HDL cholesterol, blood LDL cholesterol, blood VLDL cholesterol, blood triglyceride, blood Lp(a), blood apo A-I, blood apo E and blood non-esterified fatty acids.

[0084] As used herein, “altering glucose metabolism” refers to an observable (measurable) change in at least one aspect of glucose metabolism, including, but not limited to, total blood glucose content, blood insulin, the blood insulin to blood glucose ratio, insulin sensitivity, and oxygen consumption.

[0085] Various aspects of the disclosure are set forth herein under headings and/or in sections for clarity; however, it is understood that all aspects, embodiments, or features of the disclosure described in one particular section are not to be limited to that particular section but rather can apply to any aspect, embodiment, or feature of the present disclosure.

Compounds

[0086] Disclosed herein, in one aspect, are compounds of formula (I):



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl or 9-membered bicyclic heteroaryl;

Ring B is phenyl or 5-6 membered heteroaryl;

Ring C is selected from the group consisting of phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, and 5-6 membered heteroaryl;

R^1 is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^2 is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkoxy, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from R^{2A} , or

optionally two R^2 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl, a 9-membered bicyclic heterocyclyl, or a 9-membered bicyclic heteroaryl;

R^3 is independently, for each occurrence, selected from the group consisting of cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and $-C(O)N(R^A)(R^B)$, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkoxy;

L^1 is $^*-S(O)_2N(R^C)-^{**}$, wherein $*$ denotes the point of attachment to Ring A and ** denotes the point of attachment to Ring B;

L^2 is selected from the group consisting of $\#-C(O)O-##$, $\#-C(O)-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-O-##$, $\#-C(O)O-(C_{1-6}haloalkyl)-##$, and $C_{1-6}alkyl$, wherein $\#$ denotes the point of attachment to Ring A and $##$ denotes the point of attachment to Ring C;

R^{2A} is halogen or C_{1-6} alkoxy;

R^A is hydrogen or C_{1-6} alkyl;

R^B is hydrogen or C_{1-6} alkyl;

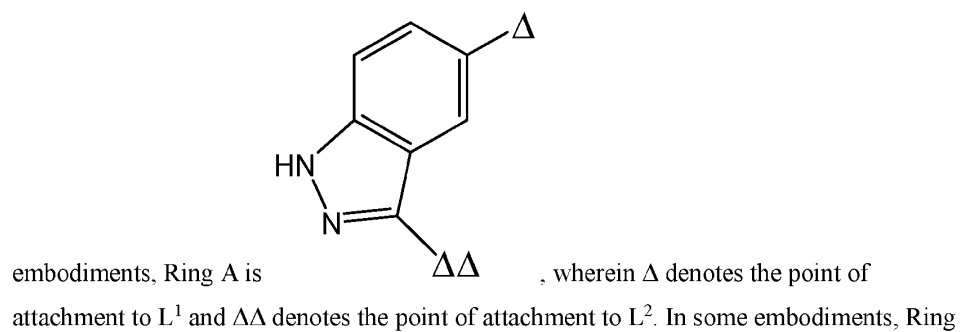
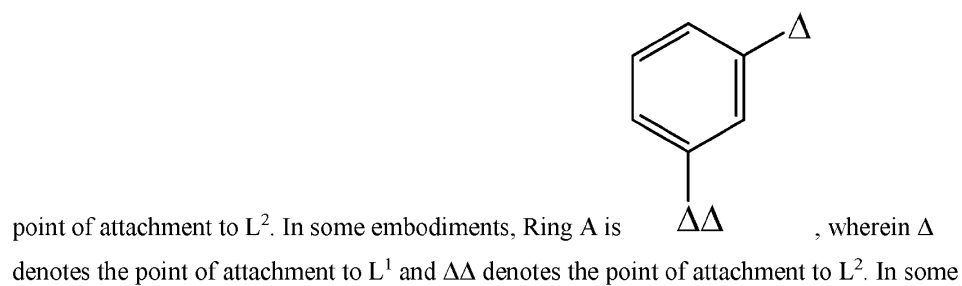
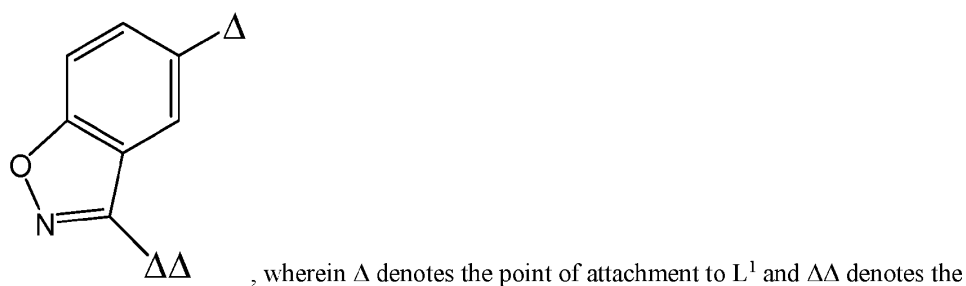
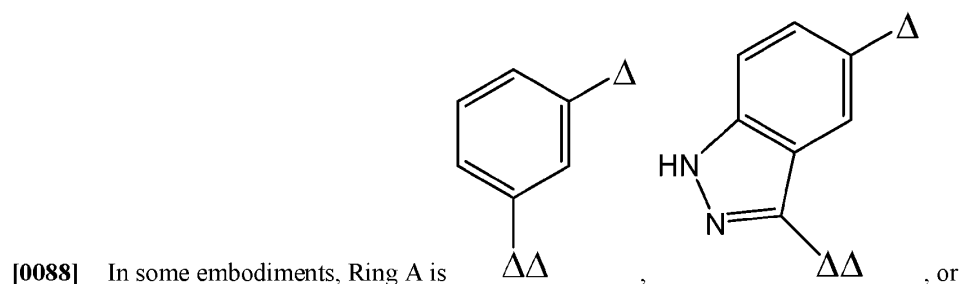
R^C is hydrogen or C_{1-3} alkyl;

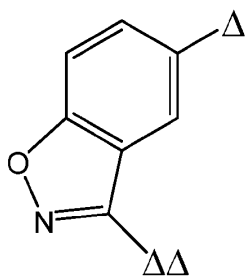
n is 2 or 3;

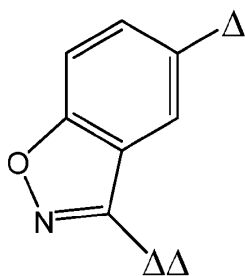
o is 0, 1, or 2; and

p is 0, 1, or 2.

[0087] In some embodiments, Ring A is phenyl, indazolyl, or benzo[d]isoxazolyl.

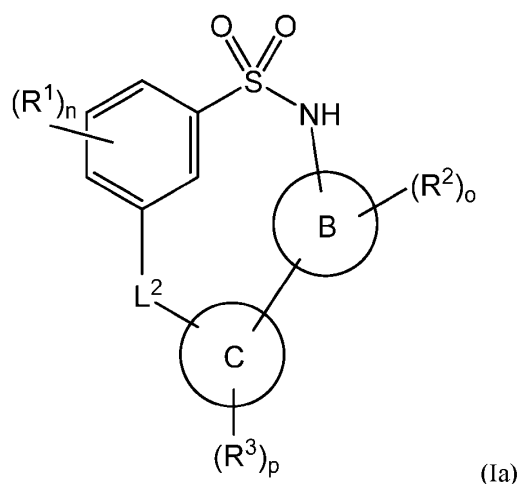




A is , wherein Δ denotes the point of attachment to L¹ and ΔΔ denotes the point of attachment to L².

[0089] In some embodiments, L¹ is *-S(O)₂N(H)-**, wherein * denotes the point of attachment to Ring A and ** denotes the point of attachment to Ring B.

[0090] In another aspect, provided herein are compounds of formula (Ia):



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring B is phenyl or 5-6 membered heteroaryl;

Ring C is selected from the group consisting of phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, and 5-6 membered heteroaryl;

R¹ is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, and 6-membered heterocyclyl;

R² is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₁₋₆haloalkoxy, -O-C₃₋₆cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from R^{2A}, or

optionally two R^2 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl, a 9-membered bicyclic heterocyclyl, or a 9-membered bicyclic heteroaryl;

R^3 is independently, for each occurrence, selected from the group consisting of cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and $-C(O)N(R^A)(R^B)$, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkoxy;

L^2 is selected from the group consisting of $\#-C(O)O-\#\#$, $\#-C(O)-(C_{1-6}alkyl)-\#\#$, $\#-C(O)O-(C_{1-6}alkyl)-\#\#$, $\#-C(O)O-(C_{1-6}alkyl)-O-\#\#$, $\#-C(O)O-(C_{1-6}haloalkyl)-\#\#$, and $C_{1-6}alkyl$, wherein $\#$ denotes the point of attachment to Ring A and $\#\#$ denotes the point of attachment to Ring C;

R^{2A} is halogen or C_{1-6} alkoxy;

R^A is hydrogen or C_{1-6} alkyl;

R^B is hydrogen or C_{1-6} alkyl;

n is 2 or 3;

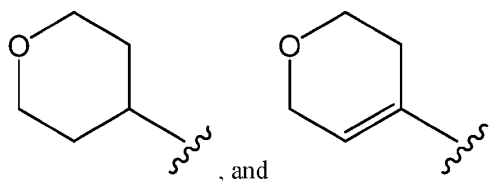
o is 1 or 2; and

p is 0, 1, or 2.

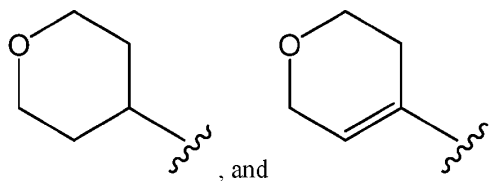
[0091] In some embodiments, n is 2.

[0092] In some embodiments, n is 3.

[0093] In some embodiments, R^1 is, independently, for each occurrence, selected from the group consisting of bromo, chloro, fluoro, hydroxyl, $-CH_3$, $-CF_3$, cyclopropyl,



[0094] In some embodiments, n is 2 and R^1 is, independently, for each occurrence, selected from the group consisting of bromo, chloro, hydroxyl, $-CF_3$, cyclopropyl,



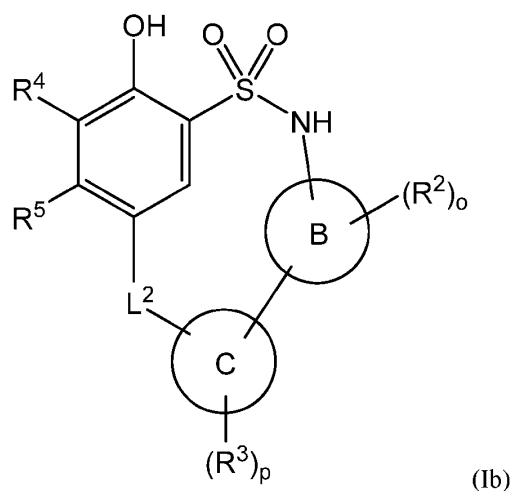
[0095] In some embodiments, n is 2 and R^1 is, independently, for each occurrence, bromo, chloro, or hydroxyl.

[0096] In some embodiments, n is 2 and R^1 is, independently, for each occurrence, bromo or hydroxyl.

[0097] In some embodiments, n is 2 and R^1 is, independently, for each occurrence, chloro or hydroxyl.

[0098] In some embodiments, n is 3 and R^1 is independently, for each occurrence, chloro, fluoro, hydroxyl, and CH_3 .

[0099] In another aspect, provided herein are compounds of formula (Ib):



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring B is phenyl or 5-6 membered heteroaryl;

Ring C is phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, C₃-6cycloalkyl, or 5-6 membered heteroaryl;

R^2 is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, cyano, C₁-6alkyl, C₁-6haloalkyl, C₁-6alkoxy, C₃-6cycloalkyl, C₁-6haloalkoxy, -O-C₃-6cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from R^{2A} ; or

optionally two R^2 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl, a 9-membered bicyclic heterocyclyl, or a 9-membered bicyclic heteroaryl;

R^3 is independently, for each occurrence, selected from the group consisting of cyano, halogen, C₁-6alkyl, C₁-6haloalkyl, C₁-6alkoxy, C₁-6haloalkoxy, and -C(O)N(R^A)(R^B), wherein

the C₁₋₆alkyl is optionally substituted with one or more substituents independently selected from C₁₋₆alkoxy;

R⁴ is selected from the group consisting of halogen, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, and 6-membered heterocyclyl;

R⁵ is hydrogen or halogen;

L² is selected from the group consisting of #-C(O)O-##, #-C(O)-(C₁₋₆alkyl)-##, #-C(O)O-(C₁₋₆alkyl)-##, #-C(O)O-(C₁₋₆alkyl)-O-##, #-C(O)O-(C₁₋₆haloalkyl)-##, and C₁₋₆alkyl, wherein # denotes the point of attachment to Ring A and ## denotes the point of attachment to Ring C;

R^{2A} is halogen or C₁₋₆alkoxy;

R^A is hydrogen or C₁₋₆alkyl;

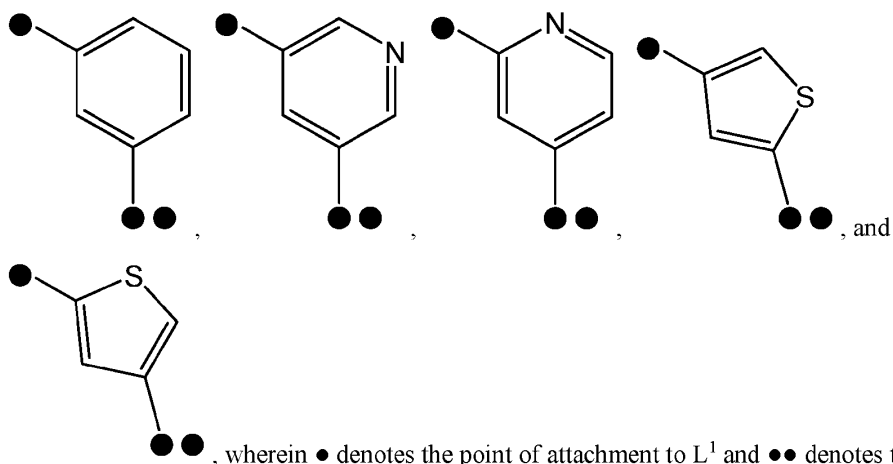
R^B is hydrogen or C₁₋₆alkyl;

o is 1 or 2; and

p is 0, 1, or 2.

[0100] In some embodiments, Ring B is phenyl, thiophenyl, or pyridinyl.

[0101] In some embodiments, Ring B is selected from the group consisting of

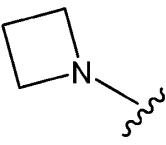


, wherein • denotes the point of attachment to L¹ and •• denotes the point of attachment to Ring C.

[0102] In some embodiments, o is 1.

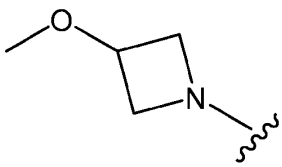
[0103] In some embodiments, o is 2.

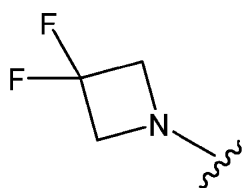
[0104] In some embodiments, R² is, independently, for each occurrence, selected from the group consisting of chloro, fluoro, cyano, hydroxyl, -CH₃, -CF₃, -O-CH₃, -O-CH₂CH₃, -O-

CHF₂, -O-CF₃, cyclopropyl, -O-cyclopropyl, morpholinyl, and , wherein

 is optionally substituted with one or more substituents independently selected from fluoro and -O-CH₃.

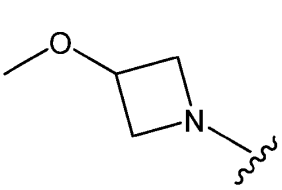
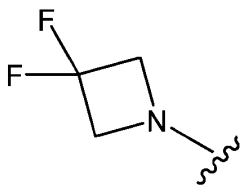
[0105] In some embodiments, R² is, independently, for each occurrence, selected from the group consisting of chloro, fluoro, cyano, hydroxyl, -CH₃, -CF₃, -O-CH₃, -O-CH₂CH₃, -O-

CHF₂, -O-CF₃, cyclopropyl, -O-cyclopropyl, morpholinyl, , and



[0106] In some embodiments, R² is selected from the group consisting of chloro, fluoro, CF₃, and -O-CH₃.

[0107] In some embodiments, o is 1 and R² is selected from the group cyano, chloro, fluoro, hydroxyl, -CF₃, -O-CF₃, -O-CHF₂, cyclopropyl, -O-cyclopropyl, -O-CH₃, -O-

CH₂CH₃, morpholinyl, , and .

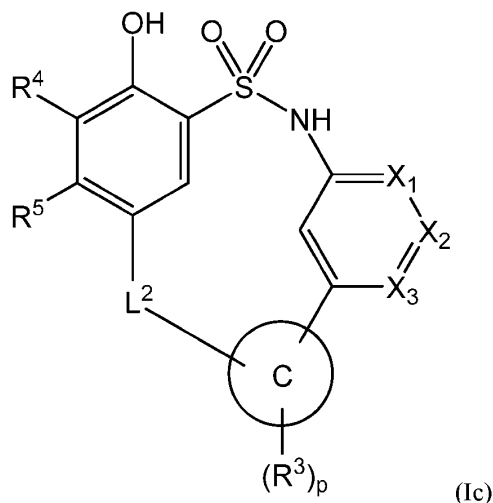
[0108] In some embodiments, o is 1 and R² is chloro.

[0109] In some embodiments, o is 1 and R² is -O-CH₃.

[0110] In some embodiments, two R² groups on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 5 membered carbocyclyl, a 5-membered heterocyclyl, or a 5-membered heteroaryl.

[0111] In some embodiments, o is 0.

[0112] In another aspect, provided herein are compounds of formula (Ic):



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring C is selected from the group consisting of phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, and 5-6 membered heteroaryl;

R^3 is independently, for each occurrence, selected from the group consisting of cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and $-C(O)N(R^A)(R^B)$, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkoxy;

R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^5 is hydrogen or halogen;

X_1 is CR^6 or N;

X_2 is CR^7 or N;

X_3 is CR^8 or N;

R^6 is selected from the group consisting of hydrogen, cyano, halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from halogen;

R^7 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with C_{1-6} alkoxy; or

R^6 and R^7 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic heteroaryl or a 9-membered bicyclic heterocyclyl;

R^8 is hydrogen or halogen; or

R^7 and R^8 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl;

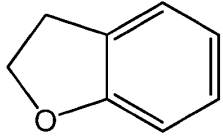
L^2 is selected from the group consisting of $\#-C(O)O-##$, $\#-C(O)-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-O-##$, $\#-C(O)O-(C_{1-6}haloalkyl)-##$, and $C_{1-6}alkyl$, wherein # denotes the point of attachment to Ring A and ## denotes the point of attachment to Ring C;

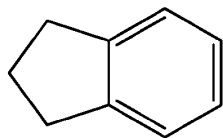
R^A is hydrogen or $C_{1-6}alkyl$;

R^B is hydrogen or $C_{1-6}alkyl$; and

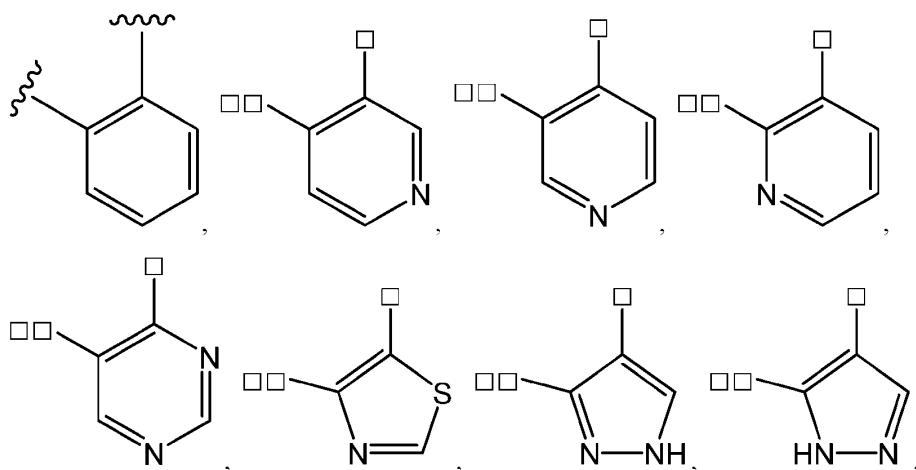
p is 0, 1, or 2.

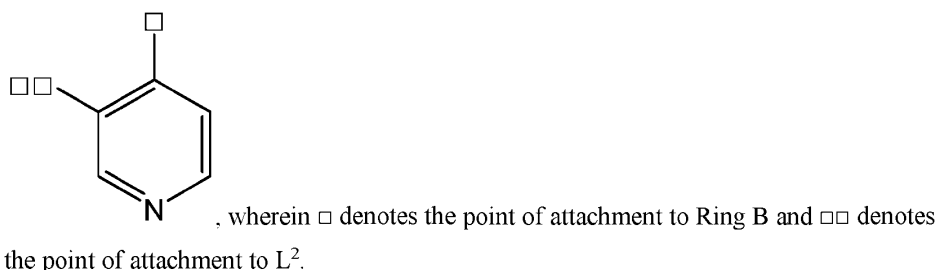
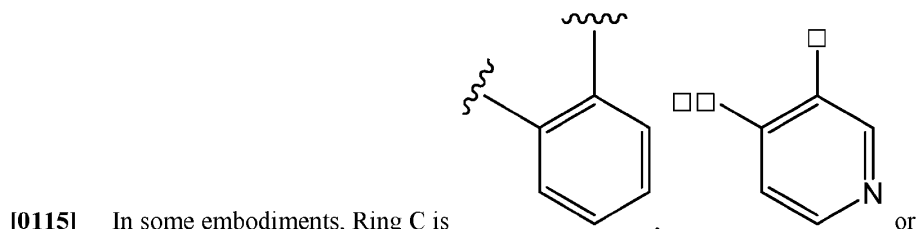
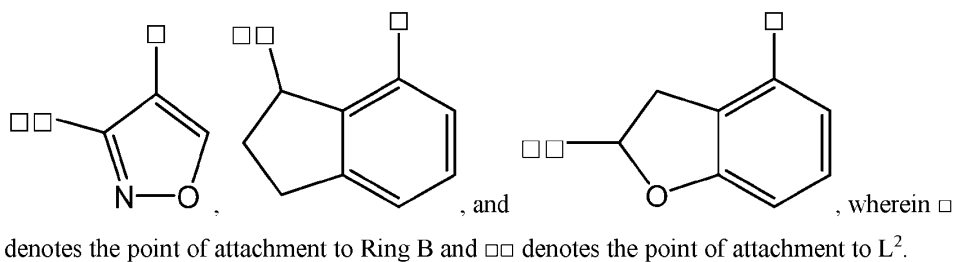
[0113] In some embodiments, Ring C is selected from the group consisting of cyclopropyl,

phenyl, pyridinyl, thiazolyl, pyrimidinyl, pyrazolyl, isoxazolyl, , and



[0114] In some embodiments, Ring C is selected from the group consisting of





[0116] In some embodiments, p is 1.

[0117] In some embodiments, p is 2.

[0118] In some embodiments, R³ is, independently, for each occurrence, selected from the group consisting of cyano, bromo, fluoro, -CH₃, -CHF₂, -CF₃, -O-CH₃, -O-CHF₂, -CH₂CH₂-O-CH₃, -C(O)NH₂, and -CH₂CHF₂.

[0119] In some embodiments, R³ is, independently, for each occurrence, selected from the group consisting of cyano, fluoro, CF₃, O-CH₃, and -O-CHF₂.

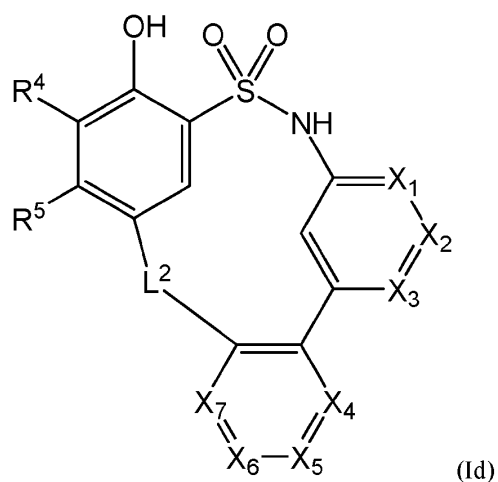
[0120] In some embodiments, p is 1 and R³ is selected from the group consisting of cyano, bromo, fluoro, -CH₃, -CHF₂, -CF₃, -O-CH₃, -O-CHF₂, -CH₂CH₂-O-CH₃, -C(O)NH₂, and -CH₂CHF₂.

[0121] In some embodiments, p is 1 and R³ is selected from the group consisting of cyano, fluoro, CF₃, -O-CH₃, and -O-CHF₂.

[0122] In certain embodiments, p is 2 and R³ is fluoro.

[0123] In some embodiments, p is 0.

[0124] In another aspect, provided herein are compounds of formula (Id):



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^5 is hydrogen or halogen;

X_1 is CR^6 or N;

X_2 is CR^7 or N;

X_3 is CR^8 or N;

X_4 is CH or N;

X_5 is CR^9 or N;

X_6 is CR^{10} or N;

X_7 is CR^{11} or N;

R^6 is selected from the group consisting of hydrogen, cyano, halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from halogen;

R^7 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with C_{1-6} alkoxy; or

R^6 and R^7 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic heteroaryl or a 9-membered bicyclic heterocyclyl;

R^8 is hydrogen or halogen; or

R^7 and R^8 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl;

R^9 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} haloalkyl, $-C(O)N(R^A)(R^B)$, and C_{1-6} alkoxy;

R^{10} is selected from the group consisting of hydrogen, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and C_{1-6} alkoxy;

R^{11} is hydrogen, halogen, or C_{1-6} alkyl; and

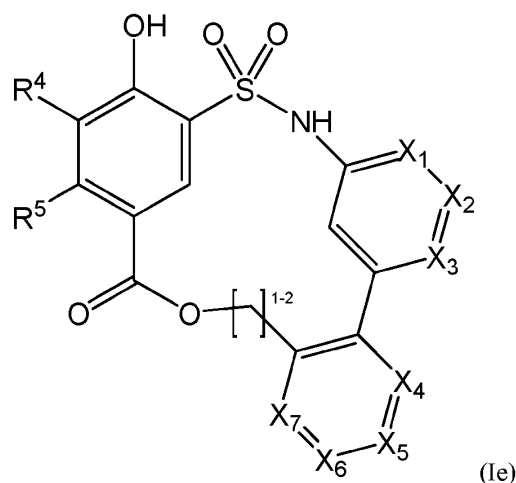
L^2 is selected from the group consisting of $\#-C(O)O-\#\#$, $\#-C(O)-(C_{1-6}alkyl)-\#\#$, $\#-C(O)O-(C_{1-6}alkyl)-\#\#$, $\#-C(O)O-(C_{1-6}alkyl)-O-\#\#$, $\#-C(O)O-(C_{1-6}haloalkyl)-\#\#$, and $C_{1-6}alkyl$, wherein $\#$ denotes the point of attachment to Ring A and $\#\#$ denotes the point of attachment to Ring C;

R^A is hydrogen or C_{1-6} alkyl; and

R^B is hydrogen or C_{1-6} alkyl.

[0125] In some embodiments, L^2 is selected from the group consisting of $\#-C(O)O-\#\#$, $\#-C(O)O-CH_2-\#\#$, $\#-C(O)O-C(CH_3)(H)-\#\#$, $\#-C(O)O-C(CH_2F)(H)-\#\#$, $\#-C(O)O-(CH_2)_2-\#\#$, $\#-C(O)O-(CH_2)_2-O-\#\#$, $-(CH_2)_2-$, $-(CH_2)_3-$, and $\#-C(O)-(CH_2)_3-\#\#$, wherein $\#$ denotes the point of attachment to Ring A and $\#\#$ denotes the point of attachment to Ring C. In some embodiments, L^2 is $\#-C(O)O-CH_2-\#\#$ or $\#-C(O)O-(CH_2)_2-\#\#$, wherein $\#$ denotes the point of attachment to Ring A and $\#\#$ denotes the point of attachment to Ring C. In some embodiments, L^2 is $\#-C(O)O-CH_2-\#\#$, wherein $\#$ denotes the point of attachment to Ring A and $\#\#$ denotes the point of attachment to Ring C.

[0126] In another aspect, provided herein are compounds of formula (Ie):



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^5 is hydrogen or halogen;

X_1 is CR^6 or N;

X_2 is CR^7 or N;

X_3 is CR^8 or N;

X_4 is CH or N;

X_5 is CR^9 or N;

X_6 is CR^{10} or N;

X_7 is CR^{11} or N;

R^6 is selected from the group consisting of hydrogen, cyano, halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from halogen;

R^7 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with C_{1-6} alkoxy; or

R^6 and R^7 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic heteroaryl or a 9-membered bicyclic heterocyclyl;

R^8 is hydrogen or halogen; or

R^7 and R^8 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl;

R^9 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} haloalkyl, $-C(O)N(R^A)(R^B)$, and C_{1-6} alkoxy;

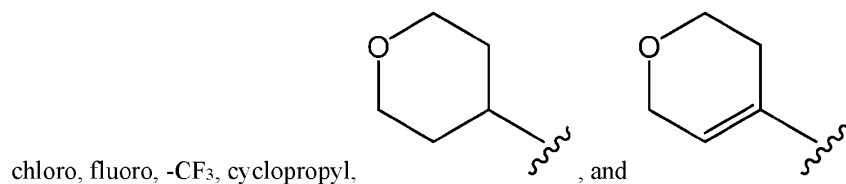
R^{10} is selected from the group consisting of hydrogen, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and C_{1-6} alkoxy;

R^{11} is hydrogen, halogen, or C_{1-6} alkyl;

R^A is hydrogen or C_{1-6} alkyl; and

R^B is hydrogen or C_{1-6} alkyl.

[0127] In some embodiments, R^4 is selected from the group consisting of bromo,



[0128] In some embodiments, R^4 is bromo or chloro.

[0129] In some embodiments, R^4 is bromo.

[0130] In some embodiments, R^4 is chloro.

[0131] In some embodiments, R^5 is hydrogen or fluoro.

[0132] In some embodiments, R^5 is hydrogen.

[0133] In some embodiments, R^5 is fluoro.

[0134] In some embodiments, R^4 is bromo or chloro and R^5 is hydrogen.

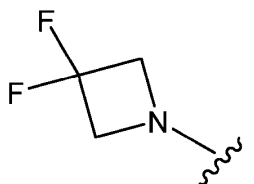
[0135] In some embodiments, R^4 is bromo and R^5 is hydrogen. R^4 is chloro and R^5 is hydrogen.

[0136] In some embodiments, X_1 is CR^6 , X_2 is CR^7 , and X_3 is CR^8 .

[0137] In some embodiments, X_1 is CR^6 , X_2 is N, and X_3 is CR^8 .

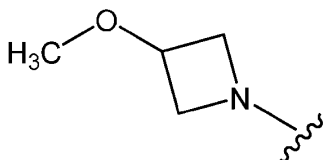
[0138] In some embodiments, X_1 is N, X_2 is CR^7 , and X_3 is CR^8 .

[0139] In some embodiments, R^6 is selected from the group consisting of hydrogen, cyano, chloro, fluoro, hydroxyl, $-CF_3$, $-O-CH_3$, $-O-CH_2-CH_3$, $-O-CHF_2$, $-O-CF_3$, cyclopropyl, and



[0140] In some embodiments, R^6 is selected from the group consisting of chloro, fluoro, CF_3 , and $-O-CH_3$.

[0141] In some embodiments, R^7 is selected from the group consisting of hydrogen, cyano, chloro, fluoro, $-CH_3$, $-CF_3$, cyclopropyl, $-O$ -cyclopropyl, morpholinyl, and



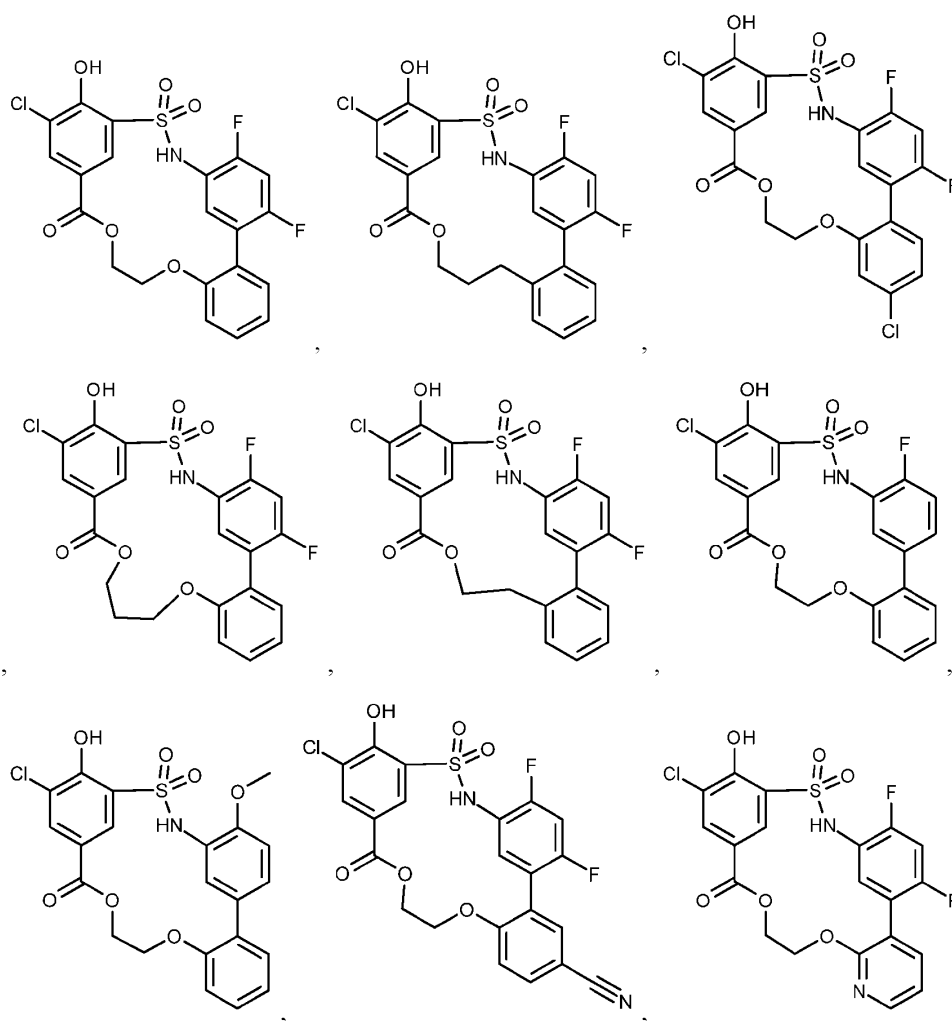
[0142] In some embodiments, R^7 is hydrogen or fluoro.

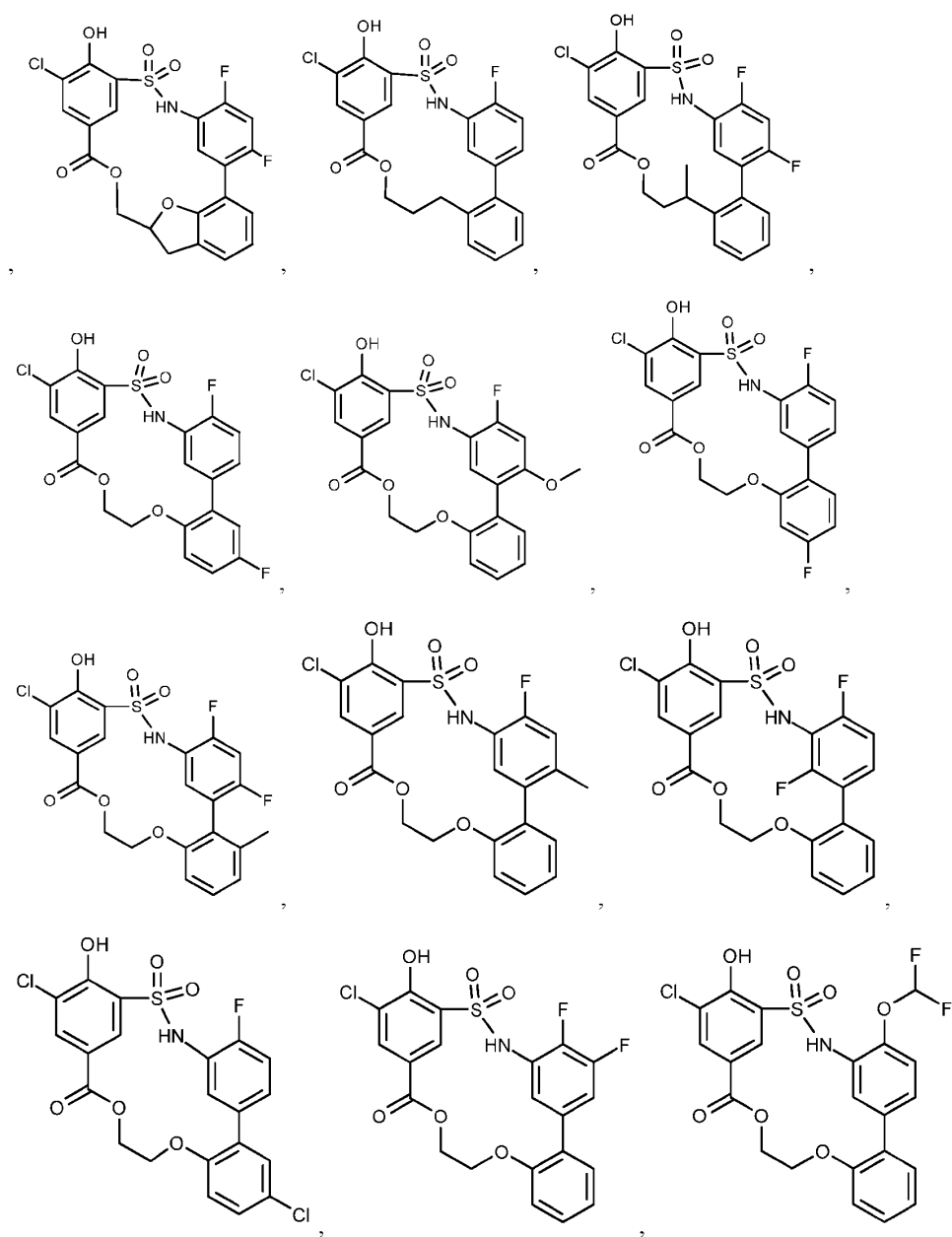
- [0143] In some embodiments, R⁷ is hydrogen.
- [0144] In some embodiments, R⁷ is fluoro.
- [0145] In some embodiments, R⁸ is hydrogen or fluoro.
- [0146] In some embodiments, R⁸ is hydrogen.
- [0147] In some embodiments, R⁸ is fluoro.
- [0148] In certain embodiments, R⁶ is selected from the group consisting of chloro, fluoro, CF₃, and -O-CH₃; R⁷ is hydrogen or fluoro; and R⁸ is hydrogen or fluoro.
- [0149] In some embodiments, R⁶ and R⁷ are taken together, along with the atoms to which they are attached, to form a 5 membered heteroaryl or a 5 membered heterocyclyl.
- [0150] In some embodiments, R⁷ and R⁸ may be taken together, along with the atoms to which they are attached, to form a 5-6 membered carbocyclyl.
- [0151] In some embodiments, X₁ is CR⁶, X₂ is CR⁷, and X₃ is CR⁸, wherein R⁶ is selected from the group consisting of chloro, fluoro, CF₃, and -O-CH₃; R⁷ is hydrogen or fluoro; and R⁸ is hydrogen or fluoro.
- [0152] In some embodiments, X₄ is CH, X₅ is CR⁹, X₆ is CR¹⁰, and X₇ is CR¹¹.
- [0153] In some embodiments, X₄ is CH, X₅ is CR⁹, X₆ is CR¹⁰, and X₇ is CH.
- [0154] In some embodiments, X₄ is CH, X₅ is N, X₆ is CR¹⁰, and X₇ is CR¹¹.
- [0155] In some embodiments, X₄ is CH, X₅ is CR⁹, X₆ is N, and X₇ is CR¹¹.
- [0156] In some embodiments, X₄ is CH, X₅ is CR⁹, X₆ is CR¹⁰, and X₇ is N.
- [0157] In some embodiments, X₄ is N, X₅ is CR⁹, X₆ is N, and X₇ is CR¹¹.
- [0158] In some embodiments, R⁹ is selected from the group consisting of hydrogen, cyano, bromo, fluoro, -CF₃, -O-CH₃, and -C(O)NH₂.
- [0159] In some embodiments, R⁹ is fluoro, cyano, or -O-CH₃.
- [0160] In some embodiments, R¹⁰ is selected from the group consisting of hydrogen, fluoro, -CHF₂, -CF₃, -O-CH₃, and -O-CHF₂.
- [0161] In some embodiments, R¹⁰ is selected from the group consisting of hydrogen, fluoro, CF₃, -O-CHF₂, and -O-CH₃.
- [0162] In some embodiments, R¹¹ is hydrogen, fluoro, or CH₃.
- [0163] In some embodiments, R¹¹ is hydrogen.
- [0164] In some embodiments, R⁹ is fluoro, cyano, or -O-CH₃; R¹⁰ is selected from the group consisting of hydrogen, fluoro, CF₃, -O-CHF₂, and -O-CH₃; and R¹¹ is hydrogen.
- [0165] In some embodiments, X₄ is CH, X₅ is CR⁹, X₆ is CH, and X₇ is CH, wherein R⁹ is cyano or fluoro.

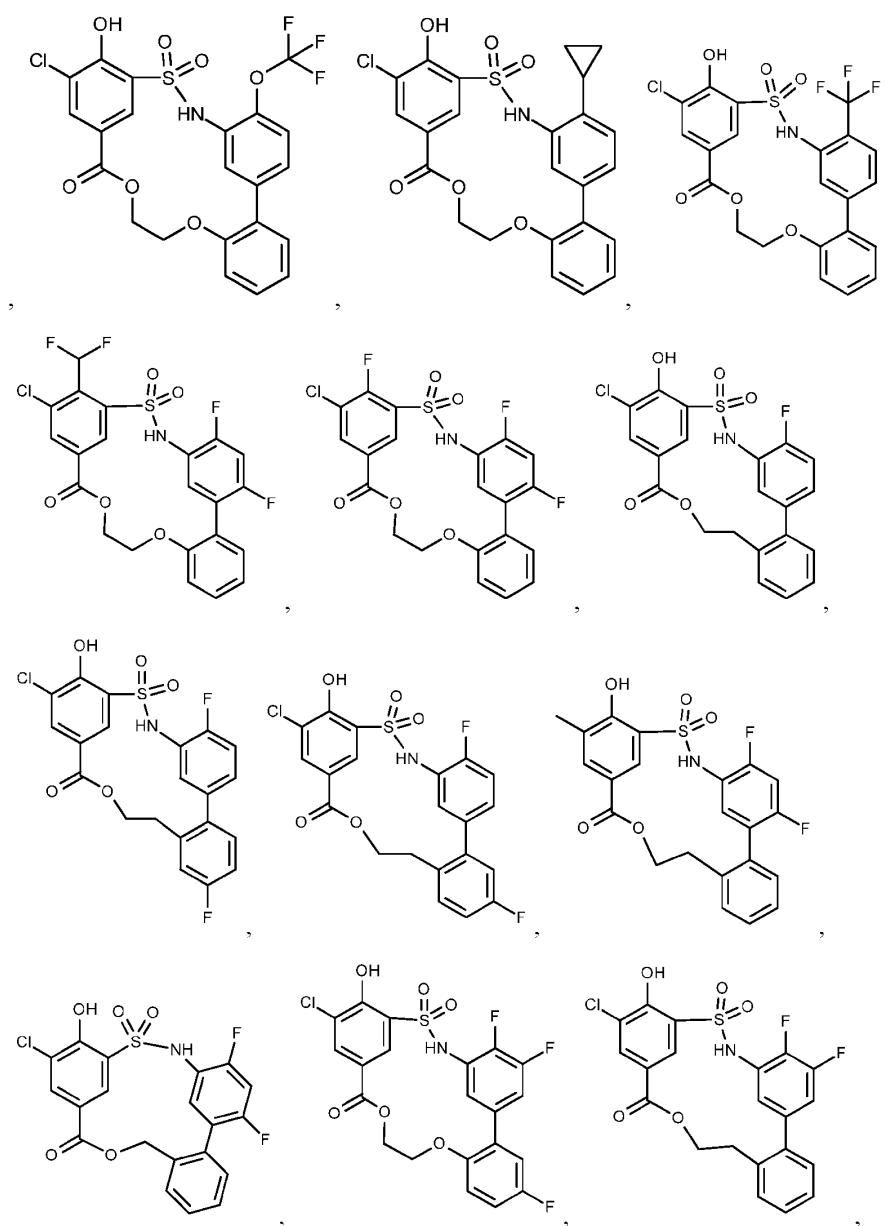
[0166] In some embodiments, X_4 is CH, X_5 is N, X_6 is CR^{10} , and X_7 is CH, wherein R^{10} is fluoro, CF_3 , $-O-CHF_2$, and $-O-CH_3$.

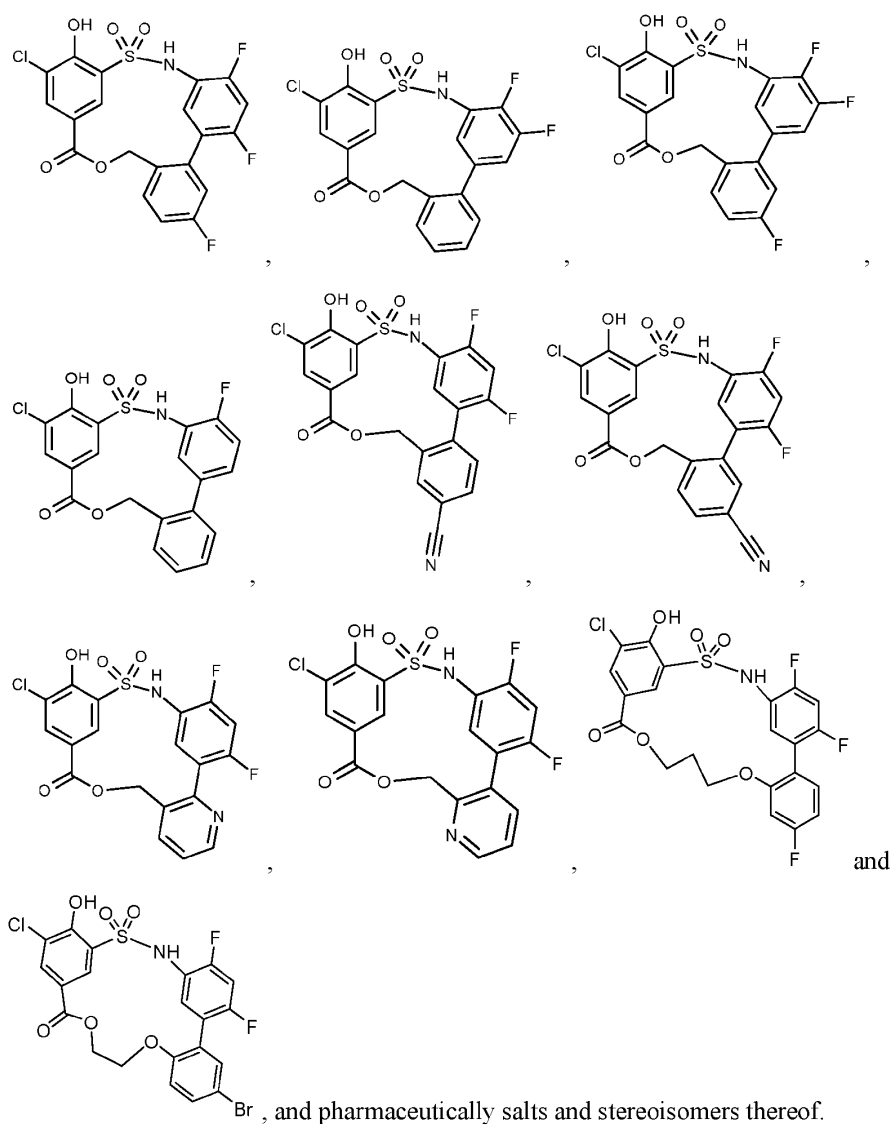
[0167] In some embodiments, X_4 is CH, X_5 is CR^9 , X_6 is N, and X_7 is CH, wherein R^9 is $-O-CH_3$.

[0168] In some embodiments, the compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id), or formula (Ie) is not a compound selected from the group consisting of:









[0169] In another aspect, provided herein is a compound selected from the group consisting of:

13-chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-chloro-4-fluoro-14-hydroxy-16,16-dioxo-20-(trifluoromethyl)-9-oxa-16λ6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one;

13-chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-4-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-4-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-19-cyclopropyl-4-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-6,19-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-4,20-difluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11,13,15(23),18,20-nonaen-10-one;

13-chloro-5,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-5,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-5-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-5-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-19,21-difluoro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-4-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

13,19-dichloro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-4-fluoro-14-hydroxy-19-methoxy-20-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one;

13,19-dichloro-5-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-19-(3,3-difluoroazetidin-1-yl)-5-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-5,19,20-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-4-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-20,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-chloro-21-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-4,5-difluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

13-chloro-5,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-chloro-4,19,21-trifluoro-14-hydroxy-6-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one;

13-chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-4-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one;
4-bromo-13-chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one;
13-chloro-20-cyclopropyl-5-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;
13-chloro-4-fluoro-14-hydroxy-16,16-dioxo-19-(trifluoromethoxy)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;
13-bromo-20-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;
13-bromo-4-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one;
13-bromo-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile;
13-bromo-14-hydroxy-19-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;
13-bromo-19,21-difluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;
13-bromo-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile;
13-bromo-19,21-difluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;
13-bromo-20-fluoro-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile;

13-bromo-14-hydroxy-19-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-21-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-19,21-difluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

13-bromo-21-fluoro-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile;

13-bromo-14-hydroxy-19-methoxy-20-methyl-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-20-chloro-14-hydroxy-19-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-bromo-14-hydroxy-19-methoxy-20-methyl-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile;

13-bromo-5-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-19,21-difluoro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-bromo-19,21-difluoro-14-hydroxy-4-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-bromo-14-hydroxy-5,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

13-bromo-20-fluoro-14-hydroxy-5,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

13-bromo-21-fluoro-14-hydroxy-4,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-20-fluoro-14-hydroxy-4,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-19,21-difluoro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

13-bromo-14-hydroxy-5,19-dimethoxy-20-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-14-hydroxy-5-methoxy-16,16-dioxo-19-(trifluoromethoxy)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-19-chloro-14-hydroxy-4-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

13-bromo-20-chloro-14-hydroxy-4,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

13-bromo-14-hydroxy-4,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17,20-triazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-21-fluoro-14-hydroxy-5,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one;

13-bromo-5-(difluoromethoxy)-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-5-(difluoromethoxy)-21-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

12-bromo-4-(difluoromethyl)-13-hydroxy-18-methoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16,19-tetrazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-4-(2,2-difluoroethyl)-18,20-difluoro-13-hydroxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-5-(2,2-difluoroethyl)-18,20-difluoro-13-hydroxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),3,10(22),11,13,17(21),18-octaen-9-one;

13-bromo-20-fluoro-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile;

13-bromo-20-fluoro-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carboxamide;

13-bromo-4,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-14-hydroxy-19-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-14-hydroxy-19-methoxy-16,16-dioxo-4-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-4-(trifluoromethyl)-9-oxa-16 λ 6-thia-3,5,17-triazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-14-hydroxy-5-methoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

12-chloro-18,20-difluoro-13-hydroxy-15,15-dioxo-8-oxa-5,15 λ 6-dithia-3,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),3,10,12,14(22),17(21),18-octaen-9-one;

12-chloro-18,20-difluoro-13-hydroxy-4-methyl-15,15-dioxo-8-oxa-3,15 λ 6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),4,10,12,14(22),17(21),18-octaen-9-one;

12-chloro-18,20-difluoro-13-hydroxy-15,15-dioxo-8-oxa-3,15 λ 6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),4,10,12,14(22),17(21),18-octaen-9-one;

12-chloro-18,20-difluoro-13-hydroxy-15,15-dioxo-4,8-dioxo-15 λ 6-thia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one;

12-chloro-19-fluoro-13-hydroxy-18-methoxy-15,15-dioxo-4-(trifluoromethyl)-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2(6),4,10(22),11,13,17,19-octaen-9-one;

13-chloro-5-(difluoromethoxy)-19,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-5,20-difluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-5,21-difluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-19-ethoxy-5-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11(23),12,14,18,20-nonaen-10-one;

13-chloro-5-fluoro-14-hydroxy-19-methoxy-20-methyl-16,16-dioxo-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

5,19-dichloro-11-fluoro-20-hydroxy-2,2-dioxo-15-oxa-2λ6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one;

5,19-dichloro-20-hydroxy-11-methoxy-2,2-dioxo-15-oxa-2λ6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one;

13-chloro-4-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16λ6-thia-17,19-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-chloro-5-fluoro-14-hydroxy-10,16,16-trioxo-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-19-carbonitrile;

13-chloro-4-fluoro-14-hydroxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16λ6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

12-chloro-18,20-difluoro-13-hydroxy-4-methyl-15,15-dioxo-8-oxa-15λ6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10,12,14(22),17(21),18-octaen-9-one;

12-chloro-18,20-difluoro-13-hydroxy-15,15-dioxo-4-(trifluoromethyl)-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2(6),4,10,12,14(22),17,19-octaen-9-one;

13-bromo-5,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-5-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-5-(difluoromethoxy)-20-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

12-bromo-18,20-difluoro-13-hydroxy-4-methyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-13-hydroxy-18-methoxy-4-methyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-4-(difluoromethyl)-18,20-difluoro-13-hydroxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-18,20-difluoro-13-hydroxy-4-(2-methoxyethyl)-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one;

19-bromo-5-chloro-20-hydroxy-10-methoxy-2,2-dioxo-15-oxa-2 λ 6,6-dithia-3,11-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one;

19-bromo-5-chloro-20-hydroxy-2,2-dioxo-11-(trifluoromethyl)-15-oxa-2 λ 6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one;

19-bromo-20-hydroxy-2,2-dioxo-11-(trifluoromethyl)-15-oxa-2 λ 6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one;

19-bromo-11-fluoro-20-hydroxy-2,2-dioxo-15-oxa-2 λ 6,5-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4(22),6,8,10,12,17,19-octaen-16-one;

12-bromo-18,20-difluoro-13-hydroxy-5-methyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),3,10,12,14(22),17(21),18-octaen-9-one;

13-cyclopropyl-4,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-(3,6-dihydro-2H-pyran-4-yl)-4,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

4,19,21-trifluoro-14-hydroxy-16,16-dioxo-13-tetrahydropyran-4-yl-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-bromo-19-chloro-21-fluoro-14-hydroxy-4-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

19-bromo-5-chloro-20-hydroxy-2,2,16-trioxo-15-oxa-2 λ 6,6-dithia-3-azatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaene-10-carbonitrile;

13-bromo-14-hydroxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile;

13-bromo-4-fluoro-14-hydroxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaene-19-carbonitrile;

12-bromo-18-chloro-13-hydroxy-15,15-dioxo-4-(trifluoromethyl)-8-oxa-3,15 λ 6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2(6),4,10,12,14(22),17,19-octaen-9-one;

13-bromo-19-chloro-14-hydroxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile;

13-bromo-14-hydroxy-4-methoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-bromo-19-(difluoromethoxy)-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

13-bromo-19-chloro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one;

13-bromo-19-chloro-21-fluoro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one;

13-bromo-19-cyclopropyl-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-bromo-14-hydroxy-4-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-19-carbonitrile;

13-bromo-14-hydroxy-10,16,16-trioxo-19-(trifluoromethoxy)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile;

13-bromo-20-fluoro-14-hydroxy-5-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-19-carbonitrile;

13-bromo-19-cyclopropyl-14-hydroxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaene-4-carbonitrile;

13-bromo-5-(difluoromethyl)-19,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one;

13-bromo-19-chloro-21-fluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one;

13-bromo-20-chloro-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaene-4-carbonitrile;

4,13-dibromo-14-hydroxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

12-bromo-4-(difluoromethyl)-19-fluoro-13-hydroxy-18-methoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

13-bromo-14-hydroxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile;

14-chloro-4,20,22-trifluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracosa-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one;

14-chloro-4,20,21-trifluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one;

14-chloro-4-fluoro-15-hydroxy-20-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12(24),13,15,19(23),20-nonaen-11-one;

14-chloro-4,22-difluoro-15-hydroxy-20-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2,4,6,12,14,16(24),19(23),20-nonaen-11-one;

14-chloro-4-fluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-18,22,23-triazapentacyclo[17.6.1.112,16.02,7.020,24]heptacos-1(26),2(7),3,5,12,14,16(27),19,21,24-decaen-11-one;

14-chloro-4-fluoro-15-hydroxy-11,17,17-trioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2,4,6,12,14,16(24),19(23),20-nonaene-21-carbonitrile;

14-chloro-5-fluoro-15-hydroxy-20-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one;

14-chloro-20-cyclopropyl-5-fluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one;

14-chloro-5,20,22-trifluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one;

14-chloro-5-fluoro-15-hydroxy-17,17-dioxo-20-(trifluoromethoxy)-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one;

14-bromo-4,20,22-trifluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one;

14-chloro-20,22-difluoro-15-hydroxy-4-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2,4,6,12,14,16(24),19(23),20-nonaen-11-one;

14-chloro-21-cyclopropyl-5-fluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2,4,6,12,14,16(24),19(23),20-nonaen-11-one;

11-chloro-3,5-difluoro-10-hydroxy-8,8-dioxo-15-oxa-8 λ 6-thia-7-azapentacyclo[14.6.1.12,6.19,13.019,23]pentacos-1(23),2,4,6(25),9(24),10,12,19,21-nonaen-14-one;

14-chloro-21-(cyclopropoxy)-4-fluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one;

14-chloro-4-fluoro-15-hydroxy-21-(3-methoxyazetidin-1-yl)-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one;

14-chloro-4-fluoro-15-hydroxy-21-morpholino-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one;

14-chloro-4-fluoro-15-hydroxy-17,17-dioxo-10,21-dioxo-17 λ 6-thia-18-azapentacyclo[17.6.1.112,16.02,7.020,24]heptacos-1(26),2(7),3,5,12,14,16(27),19,24-nonaen-11-one;

14-chloro-5-fluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azapentacyclo[17.6.1.112,16.02,7.021,25]heptacos-1(25),2,4,6,12,14,16(27),19(26),20-nonaen-11-one;

4-bromo-14-chloro-15-hydroxy-20-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one;

13-bromo-19,21-difluoro-14-hydroxy-4-methyl-16,16-dioxo-9-oxa-3,16 λ 6-dithia-5,17-diazatetracyclo[16.3.1.111,15.02,6]tricos-1(22),2(6),4,11,13,15(23),18,20-octaen-10-one;

14-chloro-4-fluoro-15-hydroxy-17,17-dioxo-20-(trifluoromethyl)-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one;

14-chloro-5-fluoro-15-hydroxy-17,17-dioxo-20-(trifluoromethyl)-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one;

5-fluoro-15-hydroxy-20-methoxy-17,17-dioxo-14-(trifluoromethyl)-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one;

5,14-difluoro-15-hydroxy-20-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracosa-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one;

15-chloro-4,21,23-trifluoro-16-hydroxy-18,18-dioxo-8,11-dioxa-18 λ 6-thia-19-azatetracyclo[18.3.1.113,17.02,7]pentacosa-1(23),2(7),3,5,13,15,17(25),20(24),21-nonaen-12-one;

15-chloro-22-fluoro-16-hydroxy-18,18-dioxo-8,11-dioxa-18 λ 6-thia-19-azatetracyclo[18.3.1.113,17.02,7]pentacosa-1(23),2(7),3,5,13,15,17(25),20(24),21-nonaen-12-one;

4-bromo-15-chloro-16-hydroxy-21-methoxy-18,18-dioxo-8,11-dioxa-18 λ 6-thia-19-azatetracyclo[18.3.1.113,17.02,7]pentacosa-1(23),2(7),3,5,13,15,17(25),20(24),21-nonaen-12-one;

15-chloro-5-fluoro-16-hydroxy-21-methoxy-18,18-dioxo-8,11-dioxa-18 λ 6-thia-4,19-diazatetracyclo[18.3.1.113,17.02,7]pentacosa-1(24),2(7),3,5,13,15,17(25),20,22-nonaen-12-one;

13-chloro-4,19,21-trifluoro-14-hydroxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

12-bromo-18,20-difluoro-13-hydroxy-4,7-dimethyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one;

15-chloro-21,23-difluoro-16-hydroxy-18,18-dioxo-11,26-dioxa-18 λ 6-thia-19-azapentacyclo[18.3.1.16,9.113,17.02,7]hexacosa-1(24),2(7),3,5,13(25),14,16,20,22-nonaen-12-one;

13-chloro-4-fluoro-8-(fluoromethyl)-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-chloro-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-bromo-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-chloro-5,20-difluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹.15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

22-chloro-5,7-difluoro-20-methyl-2,2-dioxo-2 λ 6-thia-3,19,20-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(24),4,6,8(26),9(14),10,12,18,21(25),22-decaen-23-ol;

22-chloro-5,7-difluoro-2,2-dioxo-20-oxa-2 λ 6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaen-23-ol;

22-chloro-5,7-difluoro-2,2-dioxo-2 λ 6-thia-3,19,20-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaen-23-ol;

14-chloro-13,20,22-trifluoro-15-hydroxy-17,17-dioxo-17 λ 6-thia-18-azatetracyclo[17.3.1.1¹².16.02,7]tetracosa-1(22),2(7),3,5,12(24),13,15,19(23),20-nonaen-11-one;

22-chloro-5-methoxy-2,2-dioxo-20-oxa-2 λ 6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(23),4(26),5,7,9(14),10,12,18,21,24-decaen-23-ol;

22-chloro-5,7,12-trifluoro-2,2-dioxo-20-oxa-2 λ 6-thia-3,11,19-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(23),4(26),5,7,9(14),10,12,18,21,24-decaen-23-ol;

22-chloro-7,12-difluoro-5-methoxy-2,2-dioxo-20-oxa-2 λ 6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(23),4(26),5,7,9(14),10,12,18,21,24-decaen-23-ol;

22-bromo-7,12-difluoro-5-methoxy-2,2-dioxo-20-oxa-2 λ 6-thia-3,11,19-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaen-23-ol;

22-chloro-5,7-difluoro-12-methoxy-2,2-dioxo-20-oxa-2 λ 6-thia-3,11,19-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaen-23-ol;

22-chloro-11-fluoro-5-methoxy-2,2-dioxo-20-oxa-2 λ 6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaen-23-ol;

21-chloro-7,12-difluoro-5-methoxy-2,2-dioxo-19-oxa-2 λ 6-thia-3,18-diazapentacyclo[15.5.2.14,8.0⁹,14.0²⁰,24]pentacosa-1(22),4(25),5,7,9(14),10,12,17,20,23-decaen-22-ol;

21-chloro-5,7,12-trifluoro-2,2-dioxo-19-oxa-2 λ 6-thia-3,11,18-triazapentacyclo[15.5.2.14,8.0⁹,14.0²⁰,24]pentacosa-1(22),4(25),5,7,9(14),10,12,17,20,23-decaen-22-ol;

11-chloro-3,5-difluoro-10-hydroxy-8,8-dioxo-15-oxa-8 λ 6-thia-7-azapentacyclo[14.6.1.12,6.19,13.0¹⁹,23]pentacosa-1(23),2,4,6(25),9(24),10,12,19,21-nonaen-14-one, Enantiomer 1;

11-chloro-3,5-difluoro-10-hydroxy-8,8-dioxo-15-oxa-8 λ 6-thia-7-azapentacyclo[14.6.1.12,6.19,13.0¹⁹,23]pentacosa-1(23),2,4,6(25),9(24),10,12,19,21-nonaen-14-one, Enantiomer 2;

13-chloro-4,19,21-trifluoro-14-hydroxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.0²,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one, Enantiomer 1;

13-Chloro-4,19,21-trifluoro-14-hydroxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.0²,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one, Enantiomer 2;

13-chloro-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.0²,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1;

13-chloro-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.0²,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 2;

13-bromo-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.0²,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1;

13-bromo-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.0²,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 2;

13-chloro-4-fluoro-8-(fluoromethyl)-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.0²,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1;

13-chloro-4-fluoro-8-(fluoromethyl)-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 2;

12-bromo-18,20-difluoro-13-hydroxy-4,7-dimethyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.1¹¹⁰.14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one, Enantiomer 1;

12-bromo-18,20-difluoro-13-hydroxy-4,7-dimethyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.1¹¹⁰.14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one, Enantiomer 2;

13-chloro-5,20-difluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1;

13-chloro-5,20-difluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 2;

13-bromo-21-fluoro-14-hydroxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaene-4-carbonitrile;

13-bromo-20-fluoro-14-hydroxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaene-4-carbonitrile;

13-bromo-14-hydroxy-4-methoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one;

13-bromo-19-chloro-14-hydroxy-5-methoxy-20-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

13-bromo-14-hydroxy-5-methoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

13-bromo-19-chloro-20-fluoro-14-hydroxy-4-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-bromo-14-hydroxy-10,16,16-trioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-19-carbonitrile;

13-bromo-21-fluoro-14-hydroxy-5-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-19-carbonitrile;

13-bromo-20-fluoro-14-hydroxy-4,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one;

12-bromo-18-chloro-4-(difluoromethyl)-20-fluoro-13-hydroxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

13-bromo-20-fluoro-14,19-dihydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one;

13-bromo-20-fluoro-14,19-dihydroxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile;

12-bromo-4-(difluoromethyl)-13-hydroxy-18-(trifluoromethyl)-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.1(10,14).0(2,6)]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-18-(difluoromethoxy)-4-(difluoromethyl)-13-hydroxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16,19-tetrazatetracyclo[15.3.1.1(10,14).0(2,6)]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-4-(difluoromethyl)-13-hydroxy-18-(trifluoromethyl)-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16,19-tetrazatetracyclo[15.3.1.1(10,14).0(2,6)]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-13-hydroxy-18-methoxy-4-(trifluoromethyl)-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16,19-tetrazatetracyclo[15.3.1.1(10,14).0(2,6)]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-13-hydroxy-18-methoxy-4-(trifluoromethyl)-15,15-dioxo-8-oxa-15 λ 6-dithia-5,16,19-triazatetracyclo[15.3.1.1(10,14).0(2,6)]docosa-1(20),2(6),4,10(22),11,13,17(21),18-octaen-9-one;

12-chloro-4-(difluoromethyl)-13-hydroxy-18-methoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16,19-tetrazatetracyclo[15.3.1.1(10,14).0(2,6)]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-4-(difluoromethyl)-13-hydroxy-18-(trifluoromethoxy)-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16,19-tetrazatetracyclo[15.3.1.1(10,14).0(2,6)]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-4-(difluoromethyl)-13-hydroxy-18-methoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.1(10,14).0(2,6)]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-18-chloro-4-(difluoromethyl)-13-hydroxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.1(10,14).0(2,6)]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-19-chloro-4-(difluoromethyl)-13-hydroxy-18-methoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.1(10,14).0(2,6)]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

12-bromo-18-chloro-4-(difluoromethyl)-19-fluoro-13-hydroxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.1(10,14).0(2,6)]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one;

13-bromo-19-chloro-5-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1(11,15).0(2,7)]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

13-bromo-5,20-difluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1(11,15).0(2,7)]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

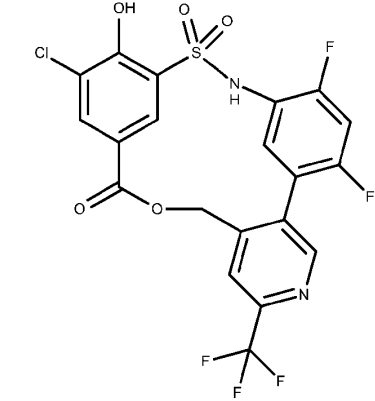
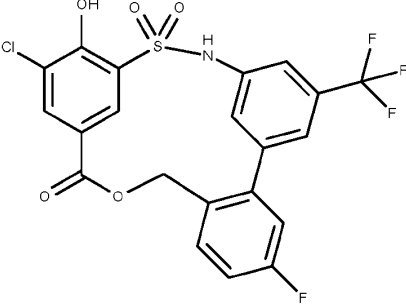
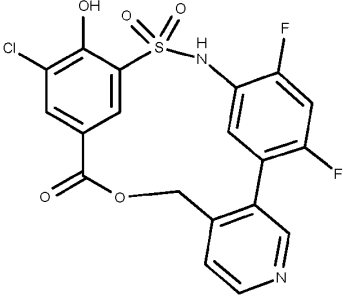
13-bromo-5-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.1(11,15).0(2,7)]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one;

or

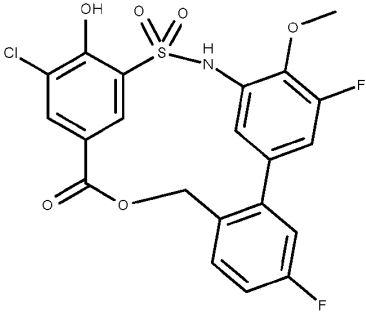
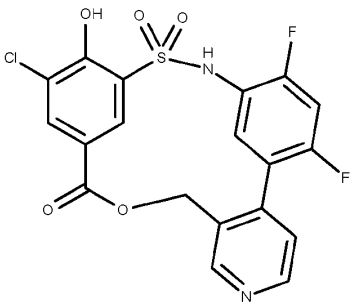
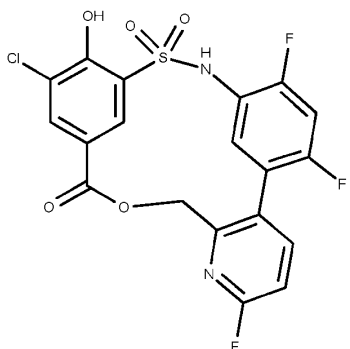
a pharmaceutically acceptable salt thereof.

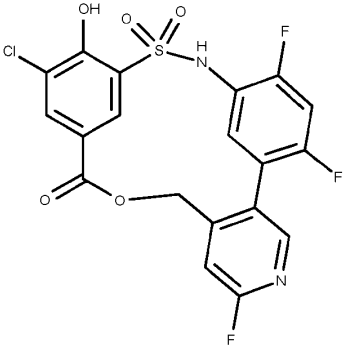
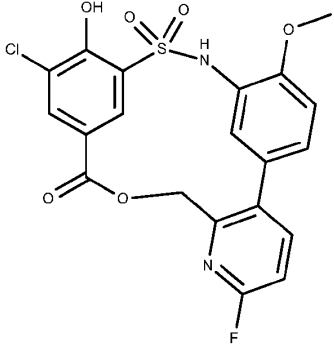
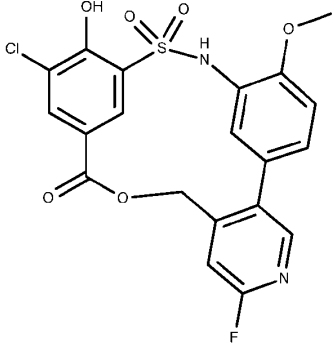
[0170] In some embodiments, the compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id), or formula (Ie), is one or more compounds selected from Table 1:

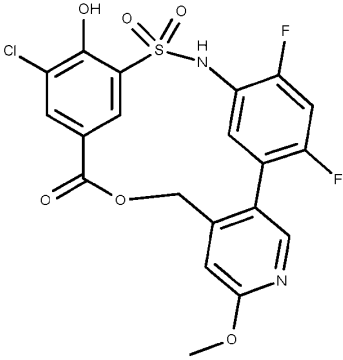
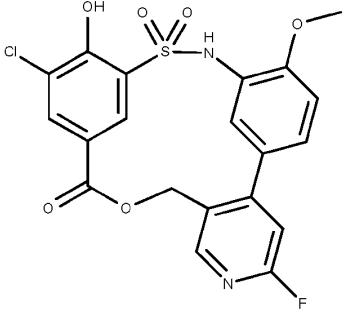
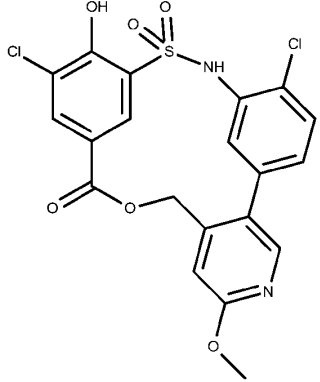
Table 1. List of compounds.

Compound No.	Structure
1	
2	
3	

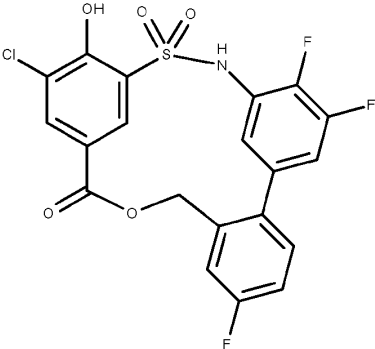
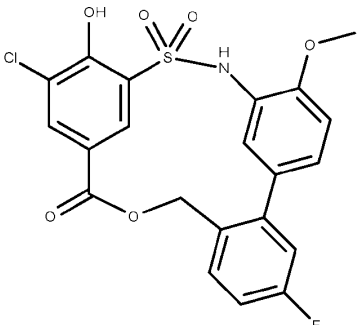
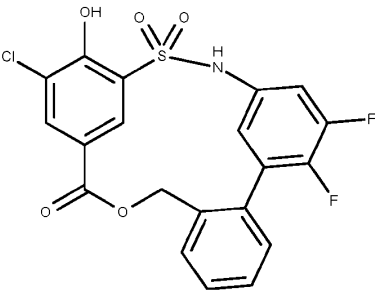
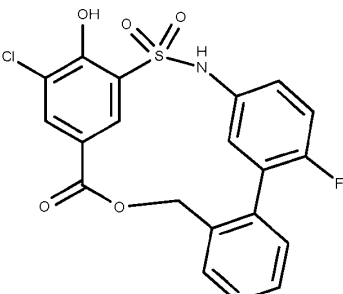
Compound No.	Structure
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5	 <chem>COc1ccncc1Cc2cc(F)ccc2C(=O)O)c3cc(O)c(Cl)cc3S(=O)(=O)N</chem>
6	 <chem>Clc1cc(O)cc(S(=O)(=O)Nc2cc(C3CC3)ccc2Cc4cc(F)ccc4C(=O)O)c1</chem>
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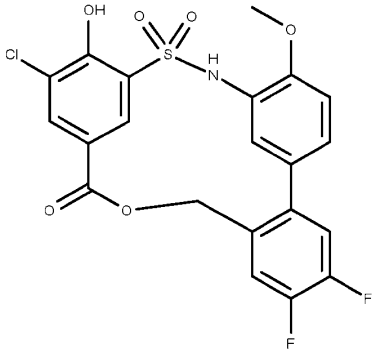
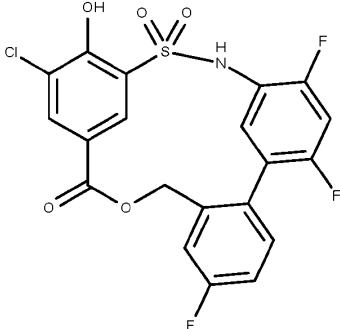
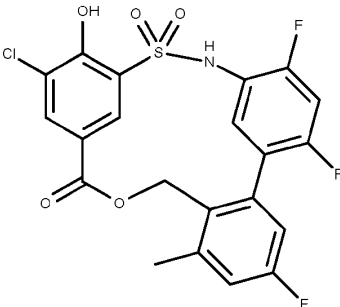
Compound No.	Structure
8	 Chemical structure of Compound 8: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 4-chloro-3-hydroxyphenyl group. The right ring is a 2-fluoro-4-methoxyphenyl group. This right ring is further substituted with a 2-fluorophenyl group at the 1-position and a 2-((4-chloro-3-hydroxyphenyl)sulfonylamino)ethyl ester group at the 4-position.
9	 Chemical structure of Compound 9: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 4-chloro-3-hydroxyphenyl group. The right ring is a 2,4-difluorophenyl group. This right ring is further substituted with a 3-pyridyl group at the 1-position and a 2-((4-chloro-3-hydroxyphenyl)sulfonylamino)ethyl ester group at the 4-position.
10	 Chemical structure of Compound 10: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 4-chloro-3-hydroxyphenyl group. The right ring is a 2,4-difluorophenyl group. This right ring is further substituted with a 4-fluoropyridin-2-yl group at the 1-position and a 2-((4-chloro-3-hydroxyphenyl)sulfonylamino)ethyl ester group at the 4-position.

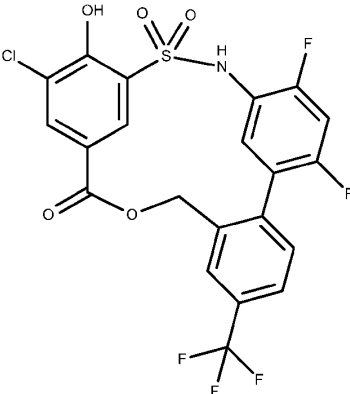
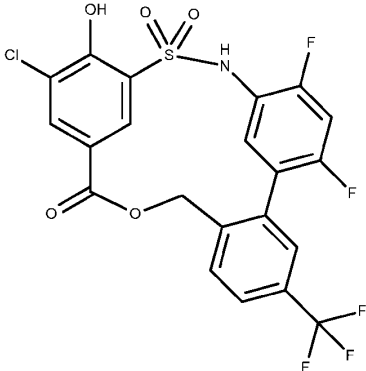
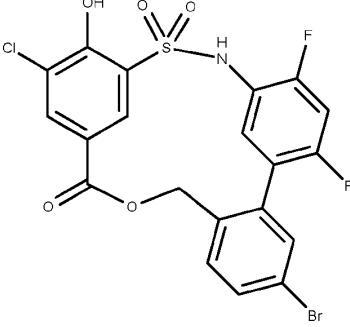
Compound No.	Structure
11	 Chemical structure of Compound 11: A pyridine ring substituted with a fluorine atom at the 3-position and a 2-(4-chloro-3-hydroxyphenyl)sulfonyl group at the 4-position. The pyridine ring is also substituted with a 2-(4-chloro-3-hydroxyphenyl)sulfonyl group at the 2-position. The pyridine ring is also substituted with a 2-(4-chloro-3-hydroxyphenyl)sulfonyl group at the 6-position.
12	 Chemical structure of Compound 12: A pyridine ring substituted with a fluorine atom at the 3-position and a 2-(4-chloro-3-hydroxyphenyl)sulfonyl group at the 4-position. The pyridine ring is also substituted with a 2-(4-chloro-3-hydroxyphenyl)sulfonyl group at the 2-position. The pyridine ring is also substituted with a 2-(4-chloro-3-hydroxyphenyl)sulfonyl group at the 6-position.
13	 Chemical structure of Compound 13: A pyridine ring substituted with a fluorine atom at the 3-position and a 2-(4-chloro-3-hydroxyphenyl)sulfonyl group at the 4-position. The pyridine ring is also substituted with a 2-(4-chloro-3-hydroxyphenyl)sulfonyl group at the 2-position. The pyridine ring is also substituted with a 2-(4-chloro-3-hydroxyphenyl)sulfonyl group at the 6-position.

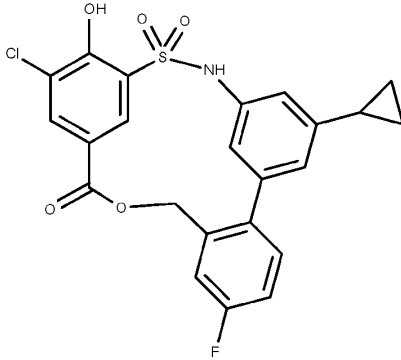
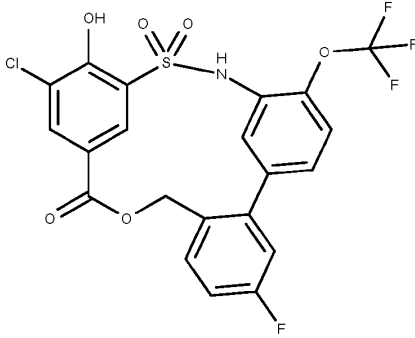
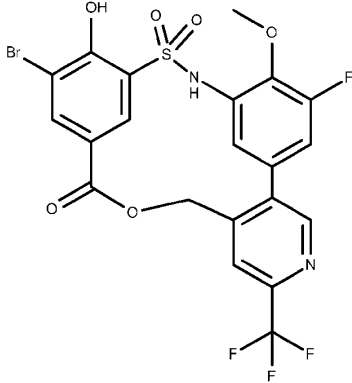
Compound No.	Structure
14	 Chemical structure of Compound 14: A molecule featuring a 3-chloro-4-hydroxyphenyl group connected via a sulfonamide linkage to a 2,4-difluorophenyl group. This 2,4-difluorophenyl group is further connected to a 4-methoxypyridine ring. The 4-methoxypyridine ring is also connected via an ester linkage to a 3-chloro-4-hydroxyphenyl group.
15	 Chemical structure of Compound 15: A molecule featuring a 3-chloro-4-hydroxyphenyl group connected via a sulfonamide linkage to a 4-methoxyphenyl group. This 4-methoxyphenyl group is further connected to a 3-fluoropyridine ring. The 3-fluoropyridine ring is also connected via an ester linkage to a 3-chloro-4-hydroxyphenyl group.
16	 Chemical structure of Compound 16: A molecule featuring a 3-chloro-4-hydroxyphenyl group connected via a sulfonamide linkage to a 3-chlorophenyl group. This 3-chlorophenyl group is further connected to a 4-methoxypyridine ring. The 4-methoxypyridine ring is also connected via an ester linkage to a 3-chloro-4-hydroxyphenyl group.

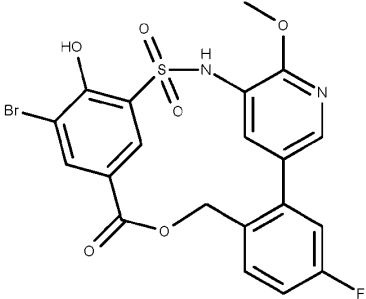
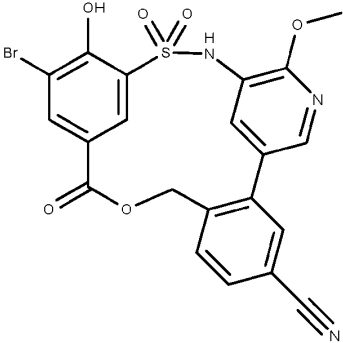
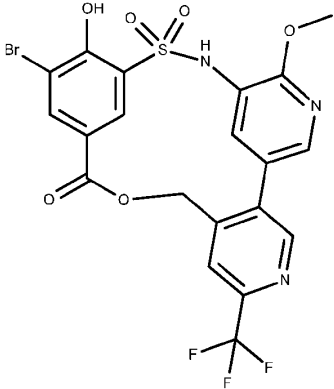
Compound No.	Structure
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18	<chem>Clc1ccc(NC(=O)c2cc(Cl)cc(O)c2)cc1CCc3ccc(F)cc3</chem>
19	<chem>FC1(F)CCN1c2ccc(NC(=O)c3cc(Cl)cc(O)c3)cc2CCc4ccc(F)cc4</chem>

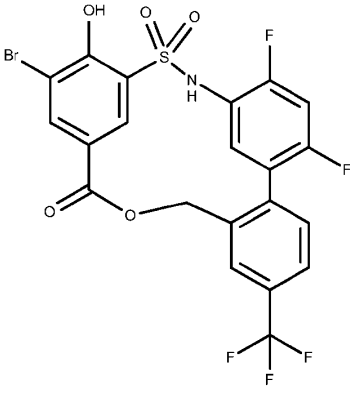
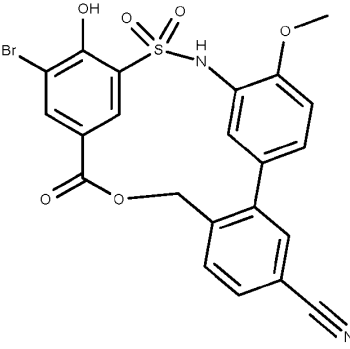
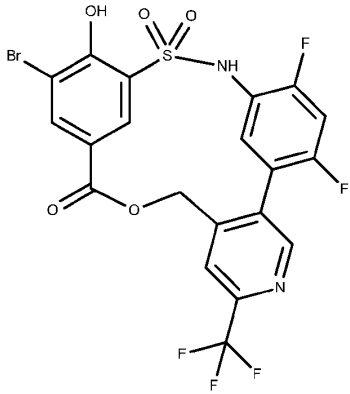
Compound No.	Structure
20	 Chemical structure of Compound 20: A central benzene ring is substituted at the 1-position with a 2-chloro-4-hydroxyphenyl group, at the 2-position with a 2,4-difluorophenyl group, and at the 3-position with a 2-fluorophenyl group. The central ring is also substituted at the 4-position with a 2-chloro-4-hydroxyphenyl group. The central ring is substituted at the 1-position with a 2-chloro-4-hydroxyphenyl group, at the 2-position with a 2,4-difluorophenyl group, and at the 3-position with a 2-fluorophenyl group. The central ring is substituted at the 4-position with a 2-chloro-4-hydroxyphenyl group.
21	 Chemical structure of Compound 21: A central benzene ring is substituted at the 1-position with a 2-chloro-4-hydroxyphenyl group, at the 2-position with a 2,4-difluorophenyl group, and at the 3-position with a 2-fluorophenyl group. The central ring is also substituted at the 4-position with a 2-chloro-4-hydroxyphenyl group. The central ring is substituted at the 1-position with a 2-chloro-4-hydroxyphenyl group, at the 2-position with a 2,4-difluorophenyl group, and at the 3-position with a 2-fluorophenyl group. The central ring is substituted at the 4-position with a 2-chloro-4-hydroxyphenyl group.
22	 Chemical structure of Compound 22: A central benzene ring is substituted at the 1-position with a 2-chloro-4-hydroxyphenyl group, at the 2-position with a 2,4-difluorophenyl group, and at the 3-position with a 2-fluorophenyl group. The central ring is also substituted at the 4-position with a 2-chloro-4-hydroxyphenyl group. The central ring is substituted at the 1-position with a 2-chloro-4-hydroxyphenyl group, at the 2-position with a 2,4-difluorophenyl group, and at the 3-position with a 2-fluorophenyl group. The central ring is substituted at the 4-position with a 2-chloro-4-hydroxyphenyl group.
23	 Chemical structure of Compound 23: A central benzene ring is substituted at the 1-position with a 2-chloro-4-hydroxyphenyl group, at the 2-position with a 2,4-difluorophenyl group, and at the 3-position with a 2-fluorophenyl group. The central ring is also substituted at the 4-position with a 2-chloro-4-hydroxyphenyl group. The central ring is substituted at the 1-position with a 2-chloro-4-hydroxyphenyl group, at the 2-position with a 2,4-difluorophenyl group, and at the 3-position with a 2-fluorophenyl group. The central ring is substituted at the 4-position with a 2-chloro-4-hydroxyphenyl group.

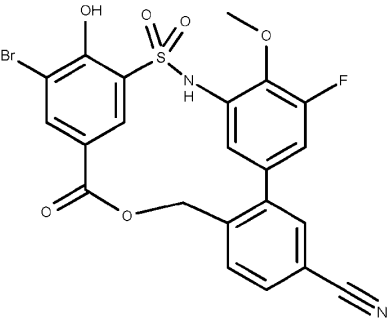
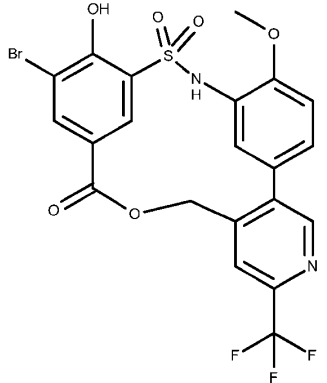
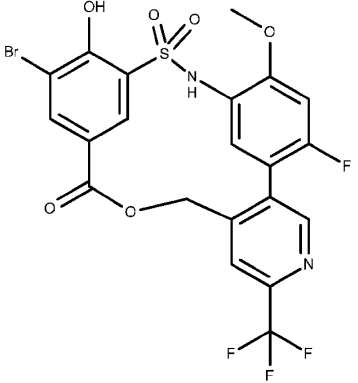
Compound No.	Structure
24	 Chemical structure of Compound 24: A central benzene ring is substituted at the 1-position with a 4-chloro-3-hydroxybenzoyl group, at the 2-position with a 4-methoxyphenyl group, and at the 4-position with a 2,6-difluorophenyl group. The central ring is also substituted at the 3-position with a 4-chloro-3-hydroxybenzoyl group.
25	 Chemical structure of Compound 25: A central benzene ring is substituted at the 1-position with a 4-chloro-3-hydroxybenzoyl group, at the 2-position with a 2,6-difluorophenyl group, and at the 4-position with a 2,6-difluorophenyl group. The central ring is also substituted at the 3-position with a 4-chloro-3-hydroxybenzoyl group.
26	 Chemical structure of Compound 26: A central benzene ring is substituted at the 1-position with a 4-chloro-3-hydroxybenzoyl group, at the 2-position with a 2,6-difluorophenyl group, and at the 4-position with a 2,6-difluorophenyl group. The central ring is also substituted at the 3-position with a 4-chloro-3-hydroxybenzoyl group.

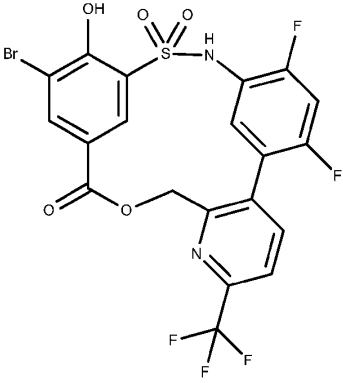
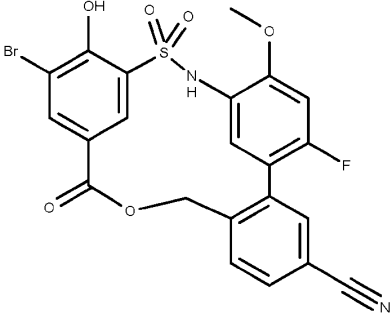
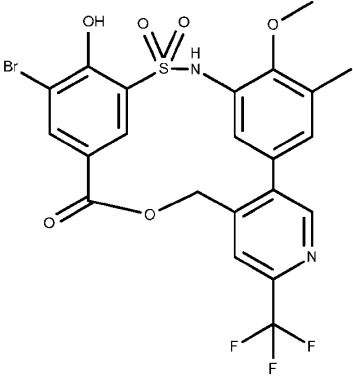
Compound No.	Structure
27	 Chemical structure of Compound 27: A central benzene ring is substituted at the 1-position with a trifluoromethyl group (-CF₃), at the 2-position with a (4-chloro-3-hydroxyphenyl)methyl ester group (-CH₂OC(=O)-C₆H₃(OH)(Cl)), and at the 4-position with a (2,6-difluorophenyl)amino group (-NH-C₆H₃(F)₂). The trifluoromethyl group is represented by a carbon atom bonded to three fluorine atoms.
28	 Chemical structure of Compound 28: A central benzene ring is substituted at the 1-position with a trifluoromethyl group (-CF₃), at the 2-position with a (4-chloro-3-hydroxyphenyl)methyl ester group (-CH₂OC(=O)-C₆H₃(OH)(Cl)), and at the 4-position with a (2,6-difluorophenyl)amino group (-NH-C₆H₃(F)₂). The trifluoromethyl group is represented by a carbon atom bonded to three fluorine atoms.
29	 Chemical structure of Compound 29: A central benzene ring is substituted at the 1-position with a bromine atom (-Br), at the 2-position with a (4-chloro-3-hydroxyphenyl)methyl ester group (-CH₂OC(=O)-C₆H₃(OH)(Cl)), and at the 4-position with a (2,6-difluorophenyl)amino group (-NH-C₆H₃(F)₂). The bromine atom is represented by the symbol 'Br'.

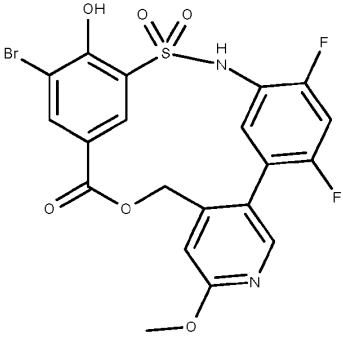
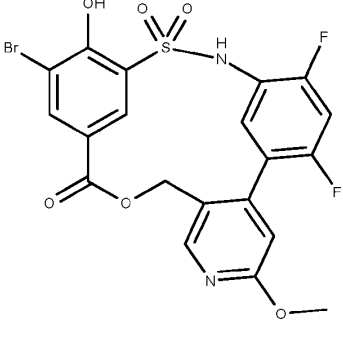
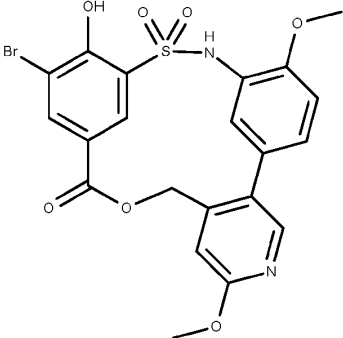
Compound No.	Structure
30	 Chemical structure of Compound 30: A central benzene ring is substituted at the 1-position with a 4-chloro-3-hydroxyphenyl group via a sulfonamide linkage (-SO₂NH-). At the 2-position, it is substituted with a 4-(cyclopropylmethyl)phenyl group. At the 3-position, it is substituted with a 4-fluorophenyl group. At the 4-position, it is substituted with a 4-(2-(4-chloro-3-hydroxyphenyl)-2-oxoethyl)phenyl group via an ester linkage (-COO-).
31	 Chemical structure of Compound 31: A central benzene ring is substituted at the 1-position with a 4-chloro-3-hydroxyphenyl group via a sulfonamide linkage (-SO₂NH-). At the 2-position, it is substituted with a 4-(2-(4-chloro-3-hydroxyphenyl)-2-oxoethyl)phenyl group via an ester linkage (-COO-). At the 3-position, it is substituted with a 4-fluorophenyl group. At the 4-position, it is substituted with a 4-(2-(4-chloro-3-hydroxyphenyl)-2-oxoethyl)phenyl group via an ester linkage (-COO-).
32	 Chemical structure of Compound 32: A central benzene ring is substituted at the 1-position with a 4-bromo-3-hydroxyphenyl group via a sulfonamide linkage (-SO₂NH-). At the 2-position, it is substituted with a 4-(2-(4-bromo-3-hydroxyphenyl)-2-oxoethyl)phenyl group via an ester linkage (-COO-). At the 3-position, it is substituted with a 4-fluorophenyl group. At the 4-position, it is substituted with a 4-(2-(4-bromo-3-hydroxyphenyl)-2-oxoethyl)phenyl group via an ester linkage (-COO-).

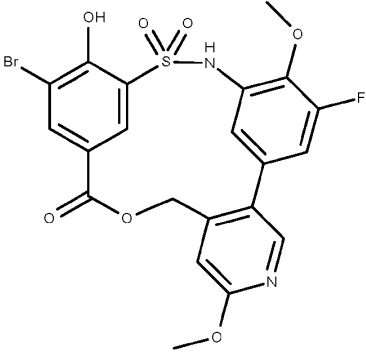
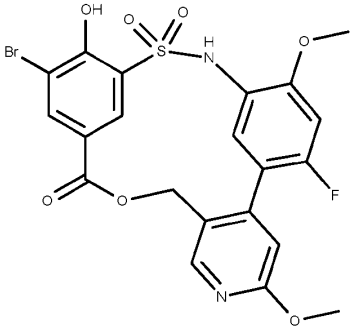
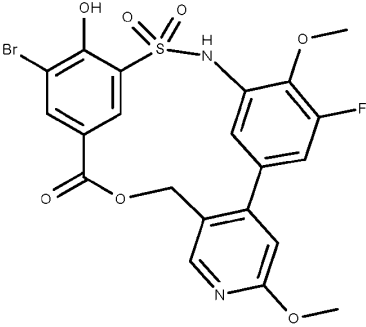
Compound No.	Structure
33	 Chemical structure of Compound 33: A molecule featuring a central benzene ring substituted with a fluorine atom (F) and a methoxy group (OCH₃). This central ring is connected via an ester linkage to a 4-bromo-2-hydroxyphenyl group and via a sulfonamide linkage to a 4-methoxyphenyl group.
34	 Chemical structure of Compound 34: A molecule featuring a central benzene ring substituted with a nitrile group (CN) and a methoxy group (OCH₃). This central ring is connected via an ester linkage to a 4-bromo-2-hydroxyphenyl group and via a sulfonamide linkage to a 4-methoxyphenyl group.
35	 Chemical structure of Compound 35: A molecule featuring a central benzene ring substituted with a trifluoromethyl group (CF₃) and a methoxy group (OCH₃). This central ring is connected via an ester linkage to a 4-bromo-2-hydroxyphenyl group and via a sulfonamide linkage to a 4-methoxyphenyl group.

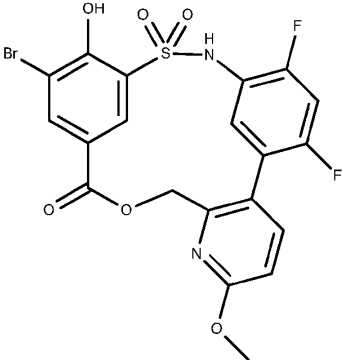
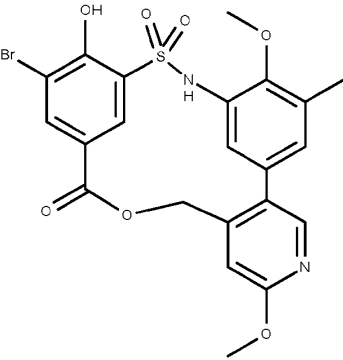
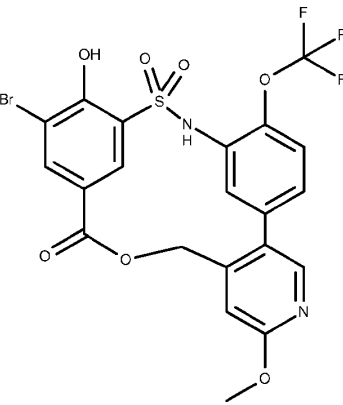
Compound No.	Structure
36	 Chemical structure of Compound 36: A central benzene ring is substituted at the 1-position with a trifluoromethyl group (CF₃), at the 2-position with a (4-bromo-3-hydroxyphenyl)sulfonamide group, and at the 4-position with a (4-cyano-3-methoxyphenyl)methyl ester group.
37	 Chemical structure of Compound 37: A central benzene ring is substituted at the 1-position with a trifluoromethyl group (CF₃), at the 2-position with a (4-bromo-3-hydroxyphenyl)sulfonamide group, and at the 4-position with a (4-cyano-3-methoxyphenyl)methyl ester group.
38	 Chemical structure of Compound 38: A central benzene ring is substituted at the 1-position with a trifluoromethyl group (CF₃), at the 2-position with a (4-bromo-3-hydroxyphenyl)sulfonamide group, and at the 4-position with a (4-cyano-3-methoxyphenyl)methyl ester group.

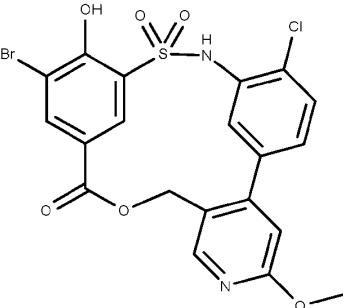
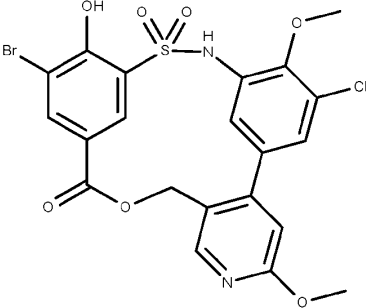
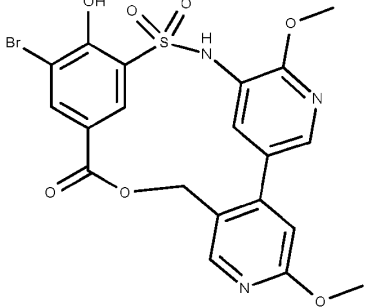
Compound No.	Structure
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40	
41	

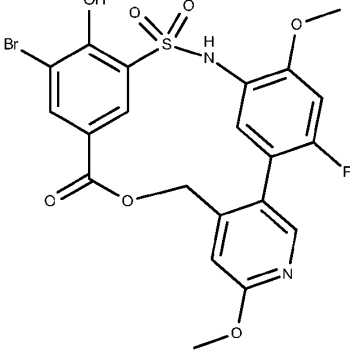
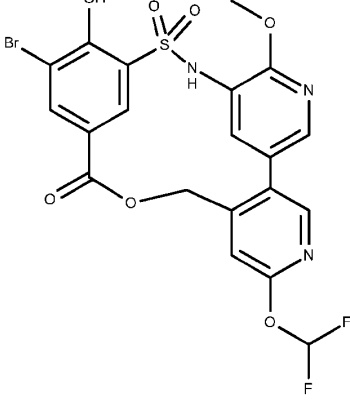
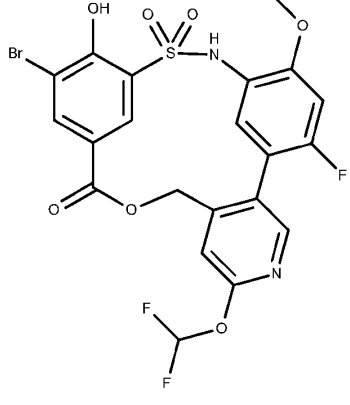
Compound No.	Structure
42	 Chemical structure of Compound 42: A sulfonamide derivative. The sulfonamide group is attached to a benzene ring substituted with a bromine atom and a hydroxyl group. The sulfonamide nitrogen is attached to a benzene ring substituted with two fluorine atoms. The sulfonamide sulfur is attached to a benzene ring substituted with a bromine atom and a hydroxyl group. The sulfonamide nitrogen is attached to a benzene ring substituted with two fluorine atoms. The sulfonamide sulfur is attached to a benzene ring substituted with a bromine atom and a hydroxyl group. The sulfonamide nitrogen is attached to a benzene ring substituted with two fluorine atoms. The sulfonamide sulfur is attached to a benzene ring substituted with a bromine atom and a hydroxyl group.
43	 Chemical structure of Compound 43: A sulfonamide derivative. The sulfonamide group is attached to a benzene ring substituted with a bromine atom and a hydroxyl group. The sulfonamide nitrogen is attached to a benzene ring substituted with a methoxy group and a fluorine atom. The sulfonamide sulfur is attached to a benzene ring substituted with a bromine atom and a hydroxyl group. The sulfonamide nitrogen is attached to a benzene ring substituted with a methoxy group and a fluorine atom. The sulfonamide sulfur is attached to a benzene ring substituted with a bromine atom and a hydroxyl group.
44	 Chemical structure of Compound 44: A sulfonamide derivative. The sulfonamide group is attached to a benzene ring substituted with a bromine atom and a hydroxyl group. The sulfonamide nitrogen is attached to a benzene ring substituted with a methoxy group and a methyl group. The sulfonamide sulfur is attached to a benzene ring substituted with a bromine atom and a hydroxyl group. The sulfonamide nitrogen is attached to a benzene ring substituted with a methoxy group and a methyl group. The sulfonamide sulfur is attached to a benzene ring substituted with a bromine atom and a hydroxyl group.

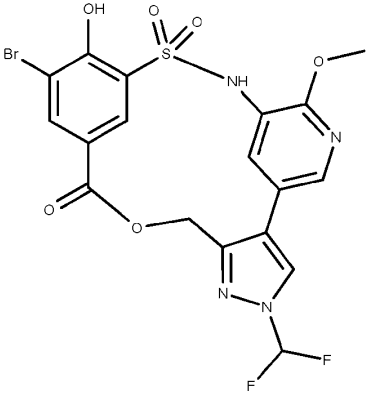
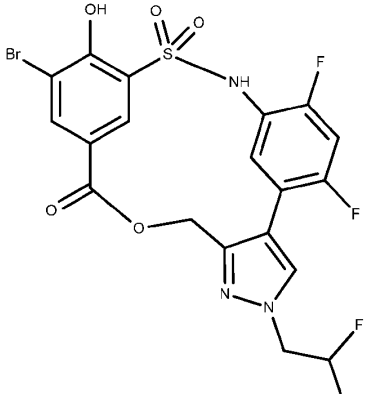
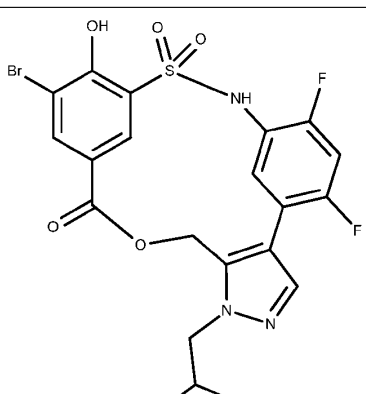
Compound No.	Structure
48	 Chemical structure of Compound 48: A complex molecule featuring a central pyridine ring substituted with a methoxy group at the 3-position. This pyridine ring is connected via a methylene group to a carboxylate group, which is further linked to a 4-bromo-3-hydroxyphenyl ring. The 4-bromo-3-hydroxyphenyl ring is also connected via a sulfonamide group to a 2,6-difluorophenyl ring.
49	 Chemical structure of Compound 49: A complex molecule featuring a central pyridine ring substituted with a methoxy group at the 3-position. This pyridine ring is connected via a methylene group to a carboxylate group, which is further linked to a 4-bromo-3-hydroxyphenyl ring. The 4-bromo-3-hydroxyphenyl ring is also connected via a sulfonamide group to a 2,6-difluorophenyl ring.
50	 Chemical structure of Compound 50: A complex molecule featuring a central pyridine ring substituted with a methoxy group at the 3-position. This pyridine ring is connected via a methylene group to a carboxylate group, which is further linked to a 4-bromo-3-hydroxyphenyl ring. The 4-bromo-3-hydroxyphenyl ring is also connected via a sulfonamide group to a 4-methoxyphenyl ring.

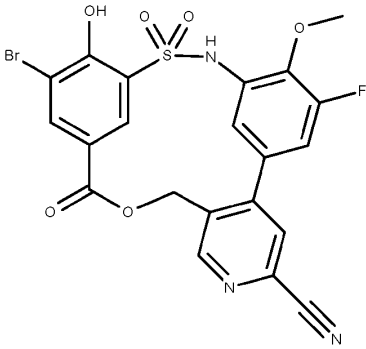
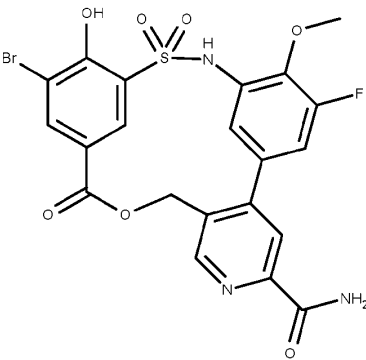
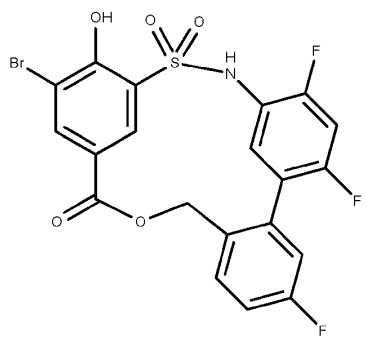
Compound No.	Structure
51	 Chemical structure of Compound 51: A molecule featuring a central pyridine ring substituted with a methoxy group at the 3-position. This pyridine ring is connected via a methylene group to an ester linkage, which is further connected to a 4-bromo-2-hydroxyphenyl group. The pyridine ring is also connected via a methylene group to a sulfonamide group, which is further connected to a 4-fluoro-2-methoxyphenyl group.
52	 Chemical structure of Compound 52: A molecule featuring a central pyridine ring substituted with a methoxy group at the 3-position. This pyridine ring is connected via a methylene group to an ester linkage, which is further connected to a 4-bromo-2-hydroxyphenyl group. The pyridine ring is also connected via a methylene group to a sulfonamide group, which is further connected to a 4-fluoro-2-methoxyphenyl group.
53	 Chemical structure of Compound 53: A molecule featuring a central pyridine ring substituted with a methoxy group at the 3-position. This pyridine ring is connected via a methylene group to an ester linkage, which is further connected to a 4-bromo-2-hydroxyphenyl group. The pyridine ring is also connected via a methylene group to a sulfonamide group, which is further connected to a 4-fluoro-2-methoxyphenyl group.

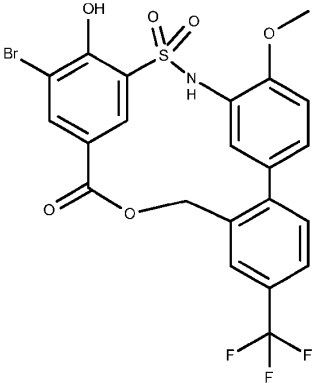
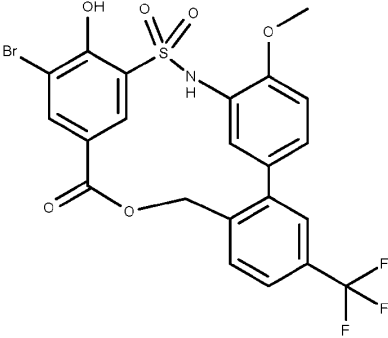
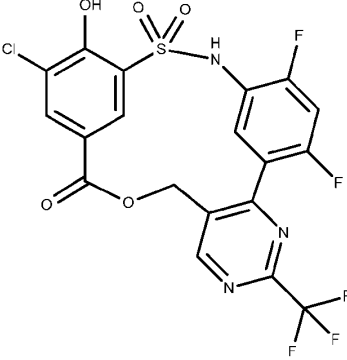
Compound No.	Structure
54	 Chemical structure of Compound 54: A pyridine ring substituted with a methoxy group at the 3-position and a (2-bromo-4-hydroxyphenyl)methyl ester at the 4-position. The pyridine ring is also substituted with a (2,6-difluorophenyl) group at the 2-position. The (2,6-difluorophenyl) group is further substituted with a sulfonamide group (-SO₂NH-) at the 1-position, which is connected to the 4-position of the pyridine ring.
55	 Chemical structure of Compound 55: A pyridine ring substituted with a methoxy group at the 3-position and a (2-bromo-4-hydroxyphenyl)methyl ester at the 4-position. The pyridine ring is also substituted with a (2,6-dimethoxyphenyl) group at the 2-position. The (2,6-dimethoxyphenyl) group is further substituted with a sulfonamide group (-SO₂NH-) at the 1-position, which is connected to the 4-position of the pyridine ring.
56	 Chemical structure of Compound 56: A pyridine ring substituted with a methoxy group at the 3-position and a (2-bromo-4-hydroxyphenyl)methyl ester at the 4-position. The pyridine ring is also substituted with a (2-(trifluoromethoxy)phenyl) group at the 2-position. The (2-(trifluoromethoxy)phenyl) group is further substituted with a sulfonamide group (-SO₂NH-) at the 1-position, which is connected to the 4-position of the pyridine ring.

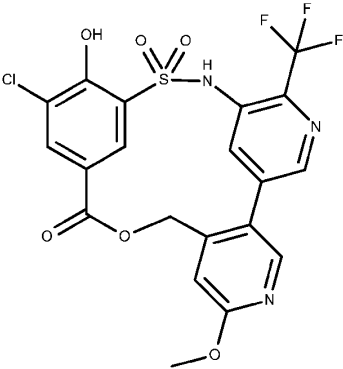
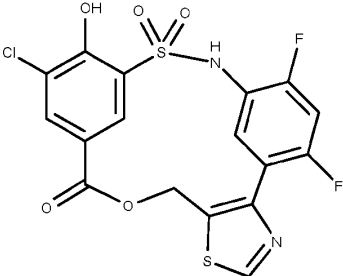
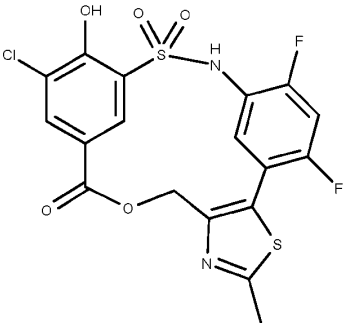
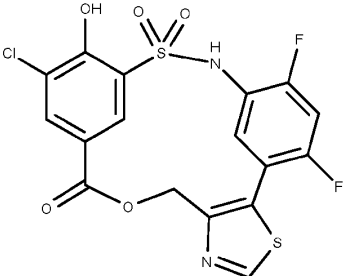
Compound No.	Structure
57	 Chemical structure of Compound 57: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 4-bromo-2-hydroxyphenyl group. The right ring is a 4-chloro-2-methoxyphenyl group. This sulfonamide is further substituted with a 4-methoxy-2-pyridyl group via an ester linkage (-COOCH₂-) and a 4-methoxy-2-pyridyl group via a direct bond.
58	 Chemical structure of Compound 58: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 4-bromo-2-hydroxyphenyl group. The right ring is a 4-chloro-2-methoxyphenyl group. This sulfonamide is further substituted with a 4-methoxy-2-pyridyl group via an ester linkage (-COOCH₂-) and a 4-methoxy-2-pyridyl group via a direct bond.
59	 Chemical structure of Compound 59: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 4-bromo-2-hydroxyphenyl group. The right ring is a 4-methoxy-2-pyridyl group. This sulfonamide is further substituted with a 4-methoxy-2-pyridyl group via an ester linkage (-COOCH₂-) and a 4-methoxy-2-pyridyl group via a direct bond.

Compound No.	Structure
60	 Chemical structure of Compound 60: A molecule featuring a central pyridine ring substituted with a methoxy group at the 3-position and a 4-(2-bromo-3-hydroxyphenyl)acetate group at the 5-position. The pyridine ring is also substituted with a 4-(2-bromo-3-hydroxyphenyl)acetate group at the 2-position. The pyridine ring is further substituted with a 4-(2-bromo-3-hydroxyphenyl)acetate group at the 6-position.
61	 Chemical structure of Compound 61: A molecule featuring a central pyridine ring substituted with a methoxy group at the 3-position and a 4-(2-bromo-3-hydroxyphenyl)acetate group at the 5-position. The pyridine ring is also substituted with a 4-(2-bromo-3-hydroxyphenyl)acetate group at the 2-position. The pyridine ring is further substituted with a 4-(2-bromo-3-hydroxyphenyl)acetate group at the 6-position.
62	 Chemical structure of Compound 62: A molecule featuring a central pyridine ring substituted with a methoxy group at the 3-position and a 4-(2-bromo-3-hydroxyphenyl)acetate group at the 5-position. The pyridine ring is also substituted with a 4-(2-bromo-3-hydroxyphenyl)acetate group at the 2-position. The pyridine ring is further substituted with a 4-(2-bromo-3-hydroxyphenyl)acetate group at the 6-position.

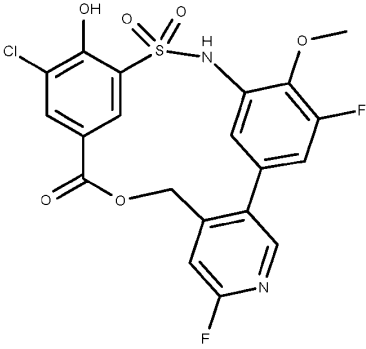
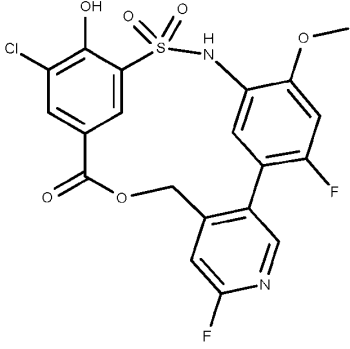
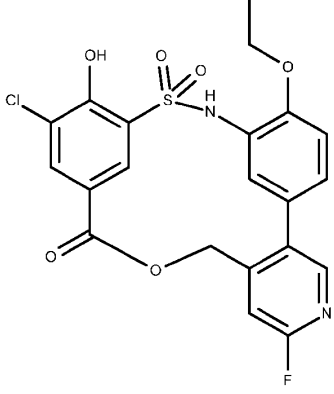
Compound No.	Structure
63	 Chemical structure of Compound 63: A molecule featuring a 4-bromo-3-hydroxyphenyl group connected via a sulfonamide linkage to a pyridine ring. The pyridine ring is substituted with a methoxy group at the 3-position and a 1,2,4-triazole ring at the 4-position. The triazole ring is further substituted with a 2-fluoroethyl group and a 2-((2-bromo-4-hydroxyphenyl)sulfonyl)ethyl ester group.
64	 Chemical structure of Compound 64: A molecule featuring a 4-bromo-3-hydroxyphenyl group connected via a sulfonamide linkage to a pyridine ring. The pyridine ring is substituted with a methoxy group at the 3-position and a 1,2,4-triazole ring at the 4-position. The triazole ring is further substituted with a 2-fluoroethyl group and a 2-((2-bromo-4-hydroxyphenyl)sulfonyl)ethyl ester group.
65	 Chemical structure of Compound 65: A molecule featuring a 4-bromo-3-hydroxyphenyl group connected via a sulfonamide linkage to a pyridine ring. The pyridine ring is substituted with a methoxy group at the 3-position and a 1,2,4-triazole ring at the 4-position. The triazole ring is further substituted with a 2-fluoroethyl group and a 2-((2-bromo-4-hydroxyphenyl)sulfonyl)ethyl ester group.

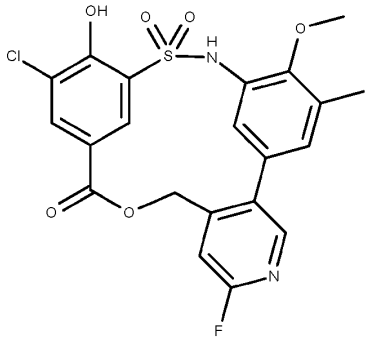
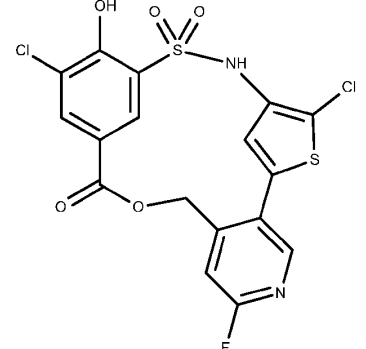
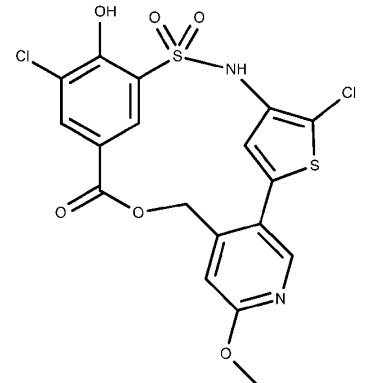
Compound No.	Structure
66	
67	
68	

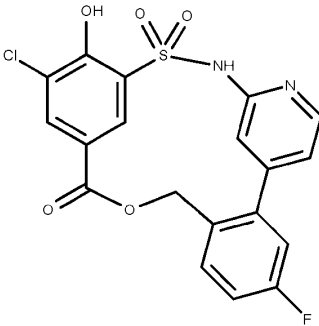
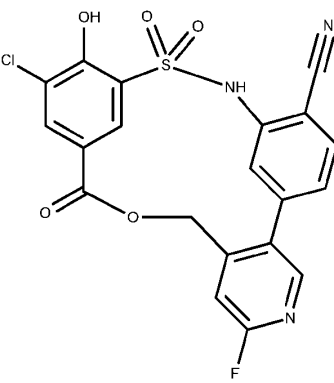
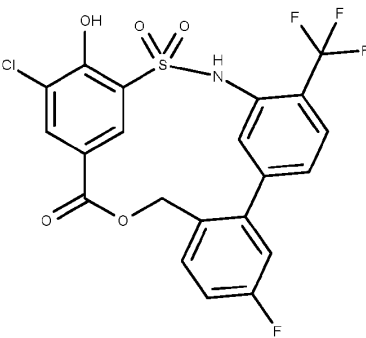
Compound No.	Structure
69	 Chemical structure of compound 69: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 4-bromo-2-hydroxyphenyl group. The right ring is a 4-methoxyphenyl group. This 4-methoxyphenyl group is further substituted at the para position with a 4-(trifluoromethyl)phenyl group. The 4-(trifluoromethyl)phenyl group is connected via a methylene group to an ester linkage (-COO-), which is attached to the 4-bromo-2-hydroxyphenyl ring.
70	 Chemical structure of compound 70: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 4-bromo-2-hydroxyphenyl group. The right ring is a 4-methoxyphenyl group. This 4-methoxyphenyl group is further substituted at the para position with a 4-(trifluoromethyl)phenyl group. The 4-(trifluoromethyl)phenyl group is connected via a methylene group to an ester linkage (-COO-), which is attached to the 4-bromo-2-hydroxyphenyl ring.
71	 Chemical structure of compound 71: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 4-chloro-2-hydroxyphenyl group. The right ring is a 2,6-difluorophenyl group. This 2,6-difluorophenyl group is further substituted at the para position with a 4-(trifluoromethyl)pyridine group. The 4-(trifluoromethyl)pyridine group is connected via a methylene group to an ester linkage (-COO-), which is attached to the 4-chloro-2-hydroxyphenyl ring.

Compound No.	Structure
72	
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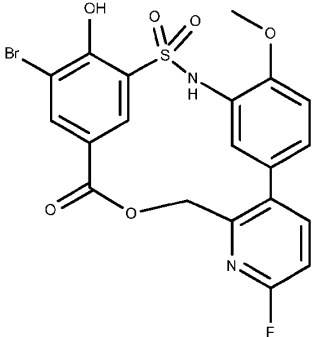
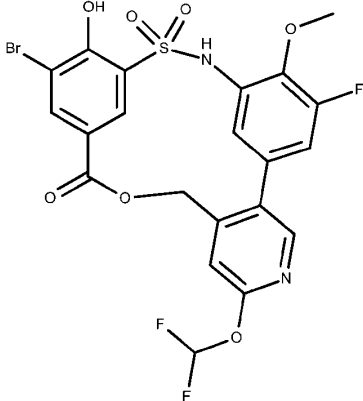
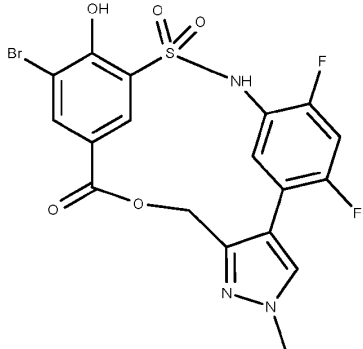
Compound No.	Structure
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77	<chem>COc1cc(F)cc(F)c1Nc2cc(Cl)cc(O)c2S(=O)(=O)Cc3cc(F)cc(F)c3Cc4cc(F)cc(F)c4</chem>
78	<chem>COc1cc(F)cc(F)c1Nc2cc(Cl)cc(O)c2S(=O)(=O)Cc3cc(F)cc(F)c3Cc4cc(F)cc(F)c4</chem>

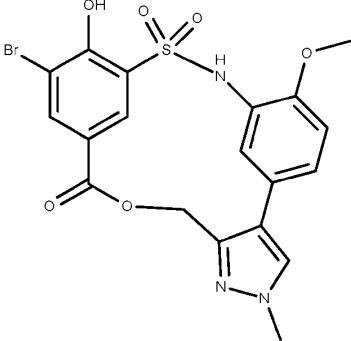
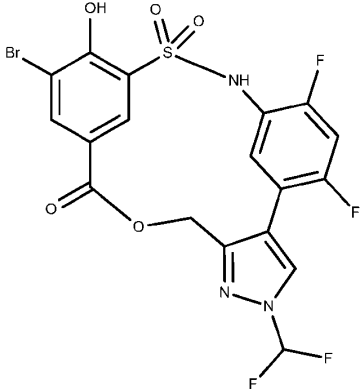
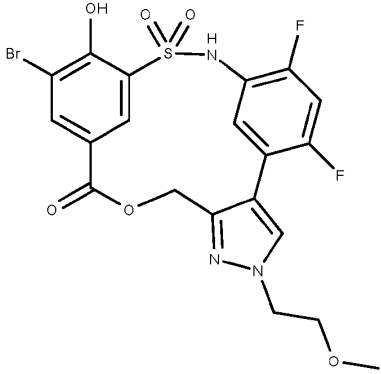
Compound No.	Structure
79	 Chemical structure of Compound 79: A molecule featuring a central pyridine ring substituted with a fluorine atom at the 3-position. This pyridine ring is connected via a methylene group to an ester linkage (-O-C(=O)-). The ester is further connected to a benzene ring substituted with a chlorine atom at the 4-position and a hydroxyl group at the 3-position. A sulfonamide group (-SO₂NH-) is attached to the benzene ring at the 1-position, which is in turn connected to another benzene ring. This second benzene ring is substituted with a methoxy group (-OCH₃) at the 4-position and a fluorine atom at the 3-position.
80	 Chemical structure of Compound 80: A molecule featuring a central pyridine ring substituted with a fluorine atom at the 3-position. This pyridine ring is connected via a methylene group to an ester linkage (-O-C(=O)-). The ester is further connected to a benzene ring substituted with a chlorine atom at the 4-position and a hydroxyl group at the 3-position. A sulfonamide group (-SO₂NH-) is attached to the benzene ring at the 1-position, which is in turn connected to another benzene ring. This second benzene ring is substituted with a methoxy group (-OCH₃) at the 4-position and a fluorine atom at the 3-position.
81	 Chemical structure of Compound 81: A molecule featuring a central pyridine ring substituted with a fluorine atom at the 3-position. This pyridine ring is connected via a methylene group to an ester linkage (-O-C(=O)-). The ester is further connected to a benzene ring substituted with a chlorine atom at the 4-position and a hydroxyl group at the 3-position. A sulfonamide group (-SO₂NH-) is attached to the benzene ring at the 1-position, which is in turn connected to another benzene ring. This second benzene ring is substituted with an ethoxy group (-OCH₂CH₃) at the 4-position.

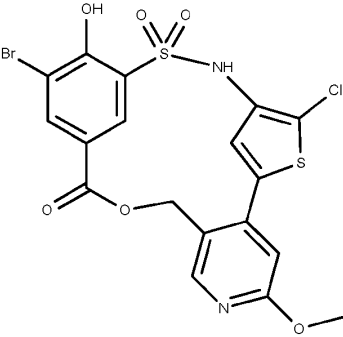
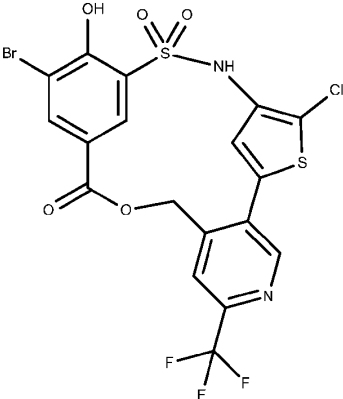
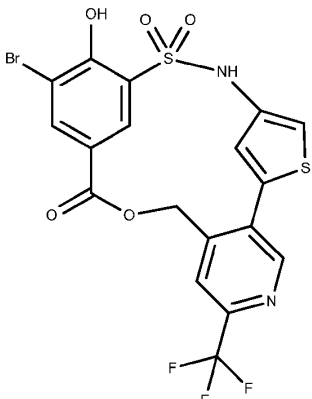
Compound No.	Structure
82	 Chemical structure of Compound 82: A molecule featuring a central pyridine ring substituted with a fluorine atom at the 4-position. The pyridine ring is connected via a methylene group to an ester group, which is further connected to a 3-chloro-4-hydroxyphenyl ring. The pyridine ring is also connected via a methylene group to a 2-methoxy-5-methylphenyl ring, which is further connected to a sulfonamide group (SO₂NH-).
83	 Chemical structure of Compound 83: A molecule featuring a central pyridine ring substituted with a fluorine atom at the 4-position. The pyridine ring is connected via a methylene group to an ester group, which is further connected to a 3-chloro-4-hydroxyphenyl ring. The pyridine ring is also connected via a methylene group to a 2-chloro-5-thienyl ring, which is further connected to a sulfonamide group (SO₂NH-).
84	 Chemical structure of Compound 84: A molecule featuring a central pyridine ring substituted with a methoxy group at the 4-position. The pyridine ring is connected via a methylene group to an ester group, which is further connected to a 3-chloro-4-hydroxyphenyl ring. The pyridine ring is also connected via a methylene group to a 2-chloro-5-thienyl ring, which is further connected to a sulfonamide group (SO₂NH-).

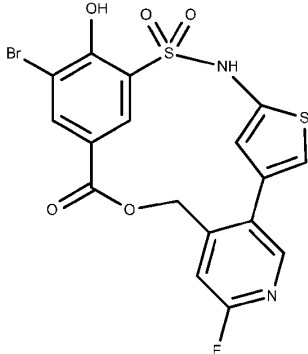
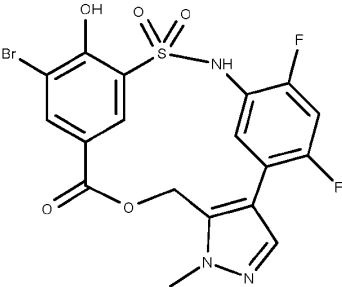
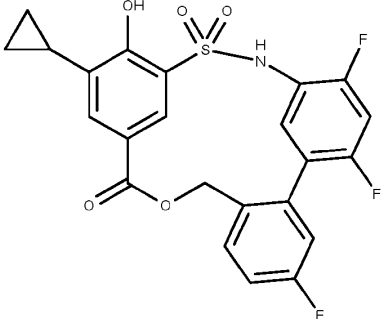
Compound No.	Structure
85	 Chemical structure of Compound 85: A central sulfonamide group (SO₂NH-) connects a 3-chloro-4-hydroxyphenyl ring to a 2-(4-fluorophenyl)-2-(4-oxo-4-(4-chloro-3-hydroxyphenyl)-4-oxobutoxy)ethyl group. The sulfonamide nitrogen is also connected to a 2-(4-cyano-2-(4-fluorophenyl)-2-(4-oxo-4-(4-chloro-3-hydroxyphenyl)-4-oxobutoxy)ethyl)pyridine ring.
86	 Chemical structure of Compound 86: A central sulfonamide group (SO₂NH-) connects a 3-chloro-4-hydroxyphenyl ring to a 2-(4-fluorophenyl)-2-(4-oxo-4-(4-chloro-3-hydroxyphenyl)-4-oxobutoxy)ethyl group. The sulfonamide nitrogen is also connected to a 2-(4-cyano-2-(4-fluorophenyl)-2-(4-oxo-4-(4-chloro-3-hydroxyphenyl)-4-oxobutoxy)ethyl)pyridine ring.
87	 Chemical structure of Compound 87: A central sulfonamide group (SO₂NH-) connects a 3-chloro-4-hydroxyphenyl ring to a 2-(4-fluorophenyl)-2-(4-oxo-4-(4-chloro-3-hydroxyphenyl)-4-oxobutoxy)ethyl group. The sulfonamide nitrogen is also connected to a 2-(4-(trifluoromethyl)-2-(4-fluorophenyl)-2-(4-oxo-4-(4-chloro-3-hydroxyphenyl)-4-oxobutoxy)ethyl)pyridine ring.

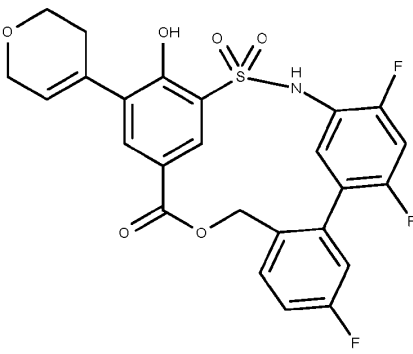
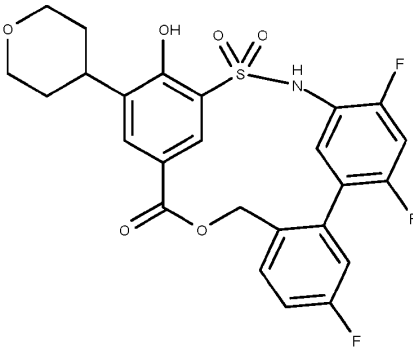
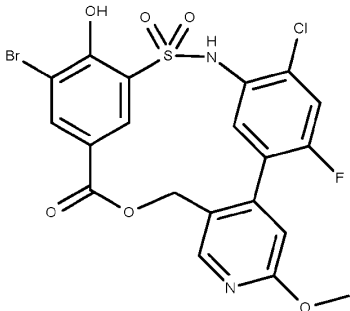
Compound No.	Structure
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89	 <chem>Clc1cc(O)cc(S(=O)(=O)Nc2cc(F)cc(F)c2C3=NC(S)=NC=C3COCC(=O)Oc4ccc(Br)cc4)c1</chem>
90	 <chem>BrC1=CC(O)=CC(S(=O)(=O)Nc2cc(F)cc(F)c2C3=CC=CC(=C3N)C(F)=C3COCC(=O)Oc4ccc(Br)cc4)=C1</chem>

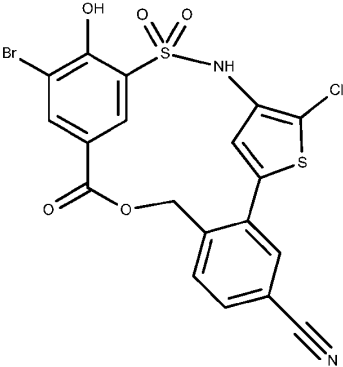
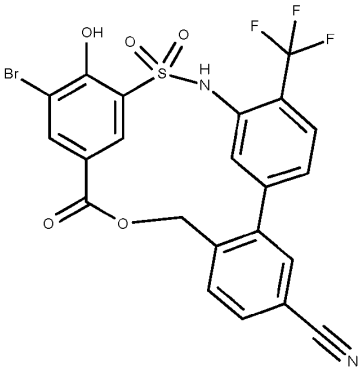
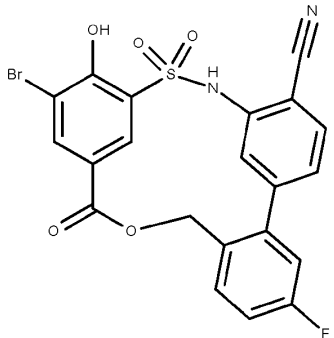
Compound No.	Structure
91	 Chemical structure of Compound 91: A molecule featuring a 4-bromo-2-hydroxyphenyl group connected via a sulfonamide linkage to a 4-methoxyphenyl group. The 4-methoxyphenyl group is further connected via a methylene bridge to a 2-fluoropyridine ring. The 4-bromo-2-hydroxyphenyl group is also connected via an ester linkage to a methylene bridge, which is connected to the 2-fluoropyridine ring.
92	 Chemical structure of Compound 92: A molecule featuring a 4-bromo-2-hydroxyphenyl group connected via a sulfonamide linkage to a 4-methoxy-2-fluorophenyl group. The 4-methoxy-2-fluorophenyl group is further connected via a methylene bridge to a 2-fluoropyridine ring. The 4-bromo-2-hydroxyphenyl group is also connected via an ester linkage to a methylene bridge, which is connected to the 2-fluoropyridine ring. The 2-fluoropyridine ring is substituted with a difluoromethoxy group.
93	 Chemical structure of Compound 93: A molecule featuring a 4-bromo-2-hydroxyphenyl group connected via a sulfonamide linkage to a 2,4-difluorophenyl group. The 2,4-difluorophenyl group is further connected via a methylene bridge to a 1-methyl-1H-imidazole ring. The 4-bromo-2-hydroxyphenyl group is also connected via an ester linkage to a methylene bridge, which is connected to the 1-methyl-1H-imidazole ring.

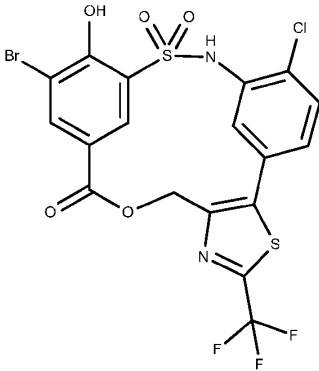
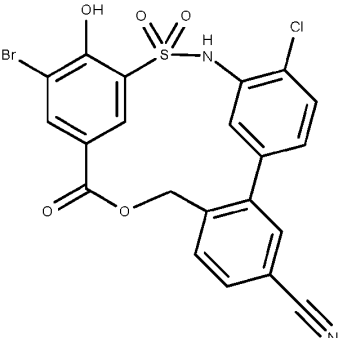
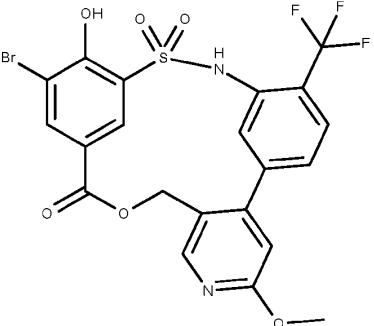
Compound No.	Structure
94	 Chemical structure of Compound 94: A 4-bromo-3-hydroxybenzoate derivative. The benzoate ring is substituted with a bromine atom at the 4-position and a hydroxyl group at the 3-position. The ester group is linked to a 1-methyl-1H-imidazole ring via a methylene bridge. The imidazole ring is further substituted with a 4-methoxyphenyl group at the 2-position and a sulfonamide group at the 4-position. The sulfonamide group is linked to a 4-bromo-3-hydroxyphenyl ring via a sulfonyl group.
95	 Chemical structure of Compound 95: A 4-bromo-3-hydroxybenzoate derivative. The benzoate ring is substituted with a bromine atom at the 4-position and a hydroxyl group at the 3-position. The ester group is linked to a 1,1-difluoroethyl-1H-imidazole ring via a methylene bridge. The imidazole ring is further substituted with a 2,4-difluorophenyl group at the 2-position and a sulfonamide group at the 4-position. The sulfonamide group is linked to a 4-bromo-3-hydroxyphenyl ring via a sulfonyl group.
96	 Chemical structure of Compound 96: A 4-bromo-3-hydroxybenzoate derivative. The benzoate ring is substituted with a bromine atom at the 4-position and a hydroxyl group at the 3-position. The ester group is linked to a 1-(3-methoxypropyl)-1H-imidazole ring via a methylene bridge. The imidazole ring is further substituted with a 2,4-difluorophenyl group at the 2-position and a sulfonamide group at the 4-position. The sulfonamide group is linked to a 4-bromo-3-hydroxyphenyl ring via a sulfonyl group.

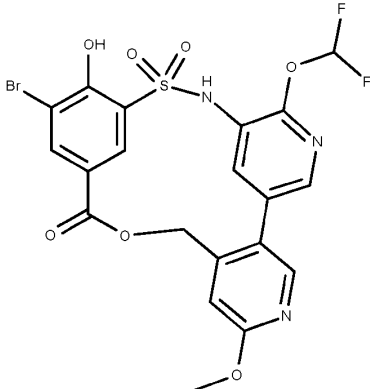
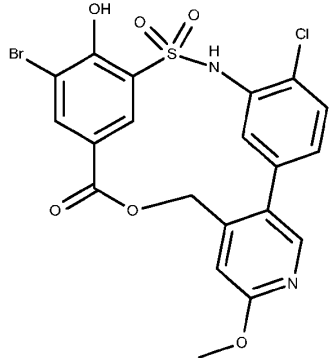
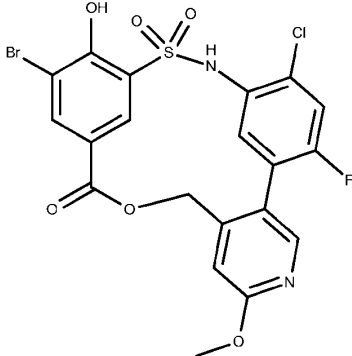
Compound No.	Structure
97	 Chemical structure of Compound 97: A molecule featuring a central pyridine ring substituted with a methoxy group (-OCH₃) at the 4-position and a (2-bromo-4-hydroxyphenyl)sulfonyl group (-SO₂-NH-C₆H₃(Br)(OH)) at the 2-position. The pyridine ring is also substituted with a (2-chloro-5-thienyl)methyl group (-CH₂-C₆H₄(Cl)-S) at the 3-position. The pyridine ring is further substituted with a (2-bromo-4-hydroxyphenyl)sulfonyl group (-SO₂-NH-C₆H₃(Br)(OH)) at the 2-position.
98	 Chemical structure of Compound 98: A molecule featuring a central pyridine ring substituted with a trifluoromethyl group (-CF₃) at the 4-position and a (2-bromo-4-hydroxyphenyl)sulfonyl group (-SO₂-NH-C₆H₃(Br)(OH)) at the 2-position. The pyridine ring is also substituted with a (2-chloro-5-thienyl)methyl group (-CH₂-C₆H₄(Cl)-S) at the 3-position. The pyridine ring is further substituted with a (2-bromo-4-hydroxyphenyl)sulfonyl group (-SO₂-NH-C₆H₃(Br)(OH)) at the 2-position.
99	 Chemical structure of Compound 99: A molecule featuring a central pyridine ring substituted with a trifluoromethyl group (-CF₃) at the 4-position and a (2-bromo-4-hydroxyphenyl)sulfonyl group (-SO₂-NH-C₆H₃(Br)(OH)) at the 2-position. The pyridine ring is also substituted with a (2-chloro-5-thienyl)methyl group (-CH₂-C₆H₄(Cl)-S) at the 3-position. The pyridine ring is further substituted with a (2-bromo-4-hydroxyphenyl)sulfonyl group (-SO₂-NH-C₆H₃(Br)(OH)) at the 2-position.

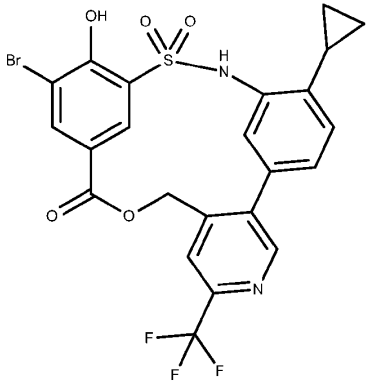
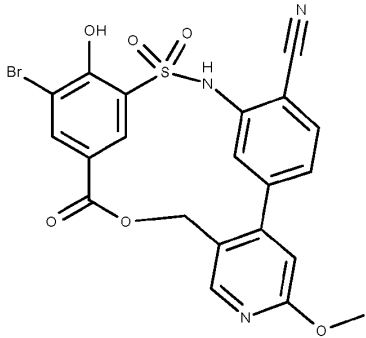
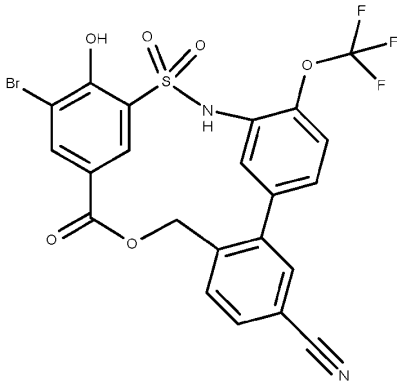
Compound No.	Structure
100	 Chemical structure of Compound 100: A central sulfonamide group (SO₂NH-) connects a 4-bromo-3-hydroxyphenyl ring to a thienopyridine system. The thienopyridine system consists of a thiophene ring fused to a pyridine ring, which has a fluorine substituent. A methylene group (-CH₂-) links the thiophene ring to an ester group (-COO-), which is further connected to the 4-bromo-3-hydroxyphenyl ring.
101	 Chemical structure of Compound 101: A central sulfonamide group (SO₂NH-) connects a 4-bromo-3-hydroxyphenyl ring to a 2,6-difluorophenyl ring. A methylene group (-CH₂-) links the 2,6-difluorophenyl ring to a 1-methyl-1H-imidazole ring, which is also connected to the sulfonamide group.
102	 Chemical structure of Compound 102: A central sulfonamide group (SO₂NH-) connects a 4-cyclopropyl-3-hydroxyphenyl ring to a 2,6-difluorophenyl ring. A methylene group (-CH₂-) links the 2,6-difluorophenyl ring to a 4-fluorophenyl ring, which is also connected to the sulfonamide group.

Compound No.	Structure
103	 Chemical structure of Compound 103: A central sulfonamide group (SO₂NH-) connects two aromatic systems. The left system is a benzene ring with a hydroxyl group (OH) at the 2-position, a morpholine ring at the 4-position, and a methyl ester group (-COOCH₂-) at the 6-position. The right system is a benzene ring with two fluorine atoms (F) at the 2 and 4 positions, and a 4-fluorophenyl group at the 6-position.
104	 Chemical structure of Compound 104: A central sulfonamide group (SO₂NH-) connects two aromatic systems. The left system is a benzene ring with a hydroxyl group (OH) at the 2-position, a morpholine ring at the 4-position, and a methyl ester group (-COOCH₂-) at the 6-position. The right system is a benzene ring with two fluorine atoms (F) at the 2 and 4 positions, and a 4-fluorophenyl group at the 6-position.
105	 Chemical structure of Compound 105: A central sulfonamide group (SO₂NH-) connects two aromatic systems. The left system is a benzene ring with a hydroxyl group (OH) at the 2-position, a bromine atom (Br) at the 4-position, and a methyl ester group (-COOCH₂-) at the 6-position. The right system is a benzene ring with a chlorine atom (Cl) at the 2-position, a fluorine atom (F) at the 4-position, and a 4-methoxypyridin-2-yl group at the 6-position.

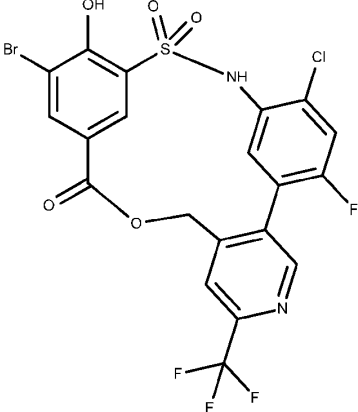
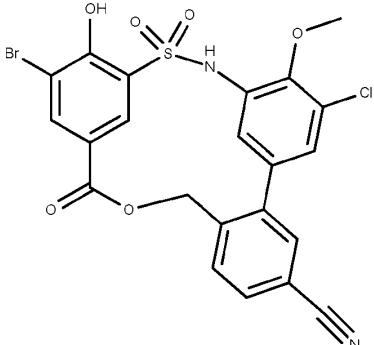
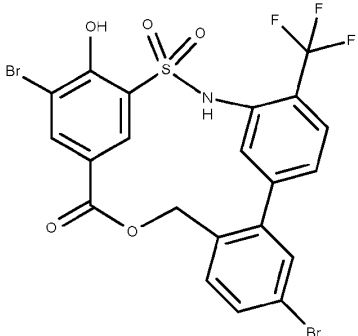
Compound No.	Structure
106	 Chemical structure of Compound 106: A central benzene ring is substituted with a nitrile group (-C≡N) at the para position and a (4-bromo-3-hydroxyphenyl)acetate group at the other para position. The acetate group is linked via an ester bond to a thienothiopyran derivative. The thienothiopyran ring is substituted with a chlorine atom at the 2-position and a sulfamoyl group (-SO₂NH-) at the 4-position. The sulfamoyl group is further linked to a 4-bromo-3-hydroxyphenyl ring.
107	 Chemical structure of Compound 107: A central benzene ring is substituted with a nitrile group (-C≡N) at the para position and a (4-bromo-3-hydroxyphenyl)acetate group at the other para position. The acetate group is linked via an ester bond to a biphenyl derivative. The biphenyl system is substituted with a trifluoromethyl group (-CF₃) at the 2-position of the upper ring and a sulfamoyl group (-SO₂NH-) at the 4-position of the lower ring. The sulfamoyl group is further linked to a 4-bromo-3-hydroxyphenyl ring.
108	 Chemical structure of Compound 108: A central benzene ring is substituted with a nitrile group (-C≡N) at the para position and a (4-bromo-3-hydroxyphenyl)acetate group at the other para position. The acetate group is linked via an ester bond to a biphenyl derivative. The biphenyl system is substituted with a nitrile group (-C≡N) at the 2-position of the upper ring and a fluorine atom at the 4-position of the lower ring. The sulfamoyl group (-SO₂NH-) is linked to a 4-bromo-3-hydroxyphenyl ring.

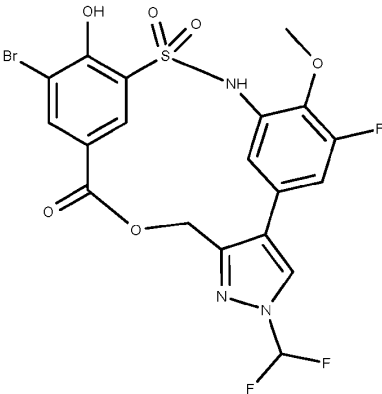
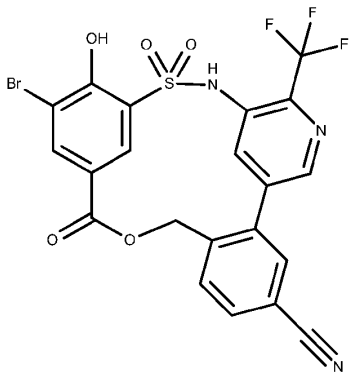
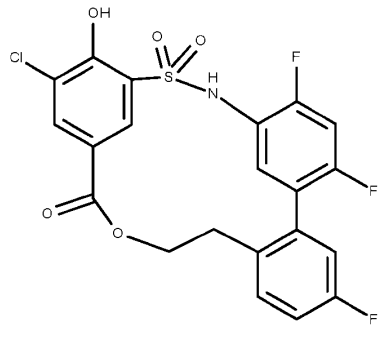
Compound No.	Structure
109	
110	
111	

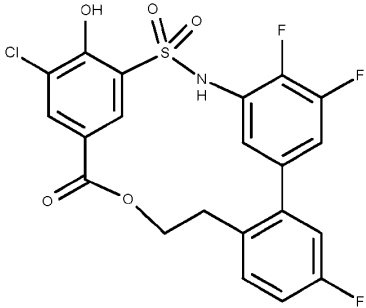
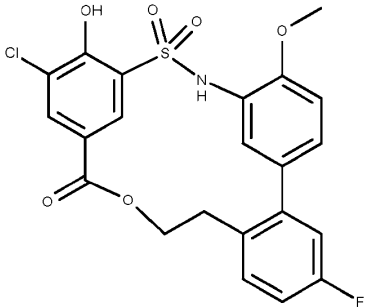
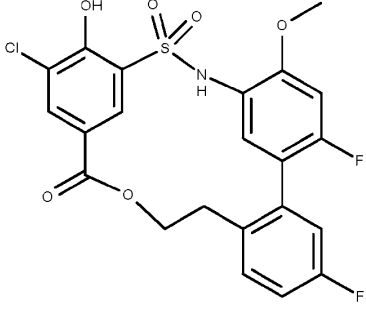
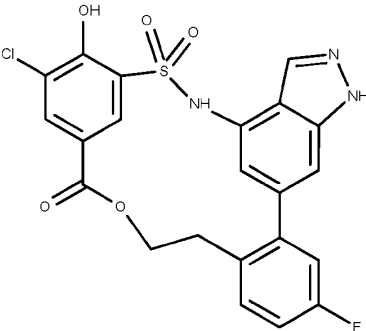
Compound No.	Structure
112	 Chemical structure of Compound 112: A pyridine ring substituted with a methoxy group at the 3-position and a (4-bromo-2-hydroxyphenyl)sulfonamido group at the 4-position. The pyridine ring is also substituted with a (4-chloro-2-fluorophenyl)methyl group at the 2-position. The pyridine ring is further substituted with a (4-bromo-2-hydroxyphenyl)sulfonamido group at the 4-position.
113	 Chemical structure of Compound 113: A pyridine ring substituted with a methoxy group at the 3-position and a (4-chloro-2-fluorophenyl)methyl group at the 2-position. The pyridine ring is further substituted with a (4-bromo-2-hydroxyphenyl)sulfonamido group at the 4-position.
114	 Chemical structure of Compound 114: A pyridine ring substituted with a methoxy group at the 3-position and a (4-chloro-2-fluorophenyl)methyl group at the 2-position. The pyridine ring is further substituted with a (4-bromo-2-hydroxyphenyl)sulfonamido group at the 4-position.

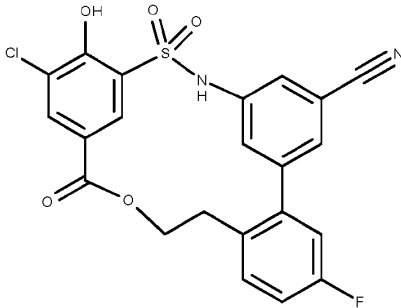
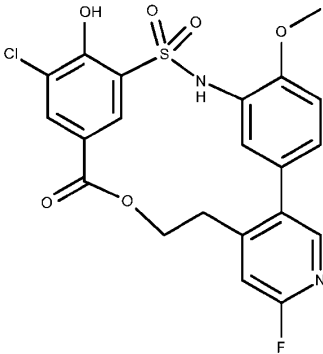
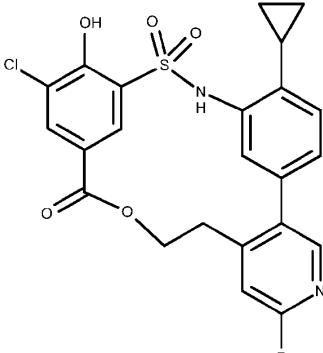
Compound No.	Structure
115	 Chemical structure of Compound 115: A sulfonamide derivative. It features a central benzene ring substituted with a bromine atom (Br), a hydroxyl group (OH), and a sulfonamide group (-SO₂NH-). The sulfonamide nitrogen is connected to a pyridine ring. The pyridine ring is further substituted with a cyclopropyl group and a side chain containing an ester linkage (-COOCH₂-) and a trifluoromethyl group (-CF₃).
116	 Chemical structure of Compound 116: A sulfonamide derivative. It features a central benzene ring substituted with a bromine atom (Br), a hydroxyl group (OH), and a sulfonamide group (-SO₂NH-). The sulfonamide nitrogen is connected to a pyridine ring. The pyridine ring is further substituted with a nitrile group (-C≡N) and a side chain containing an ester linkage (-COOCH₂-) and a methoxy group (-OCH₃).
117	 Chemical structure of Compound 117: A sulfonamide derivative. It features a central benzene ring substituted with a bromine atom (Br), a hydroxyl group (OH), and a sulfonamide group (-SO₂NH-). The sulfonamide nitrogen is connected to a pyridine ring. The pyridine ring is further substituted with a trifluoromethoxy group (-OCF₃) and a side chain containing an ester linkage (-COOCH₂-) and a nitrile group (-C≡N).

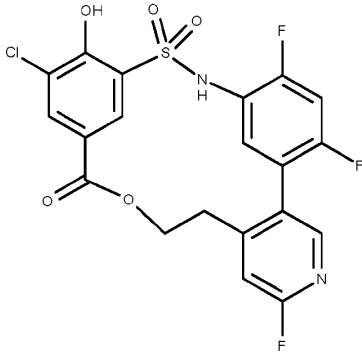
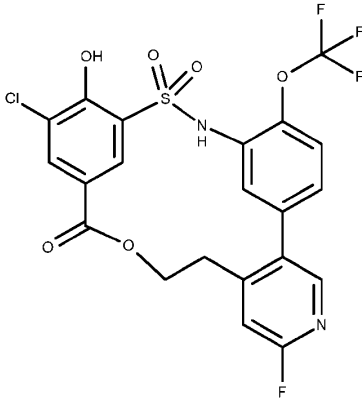
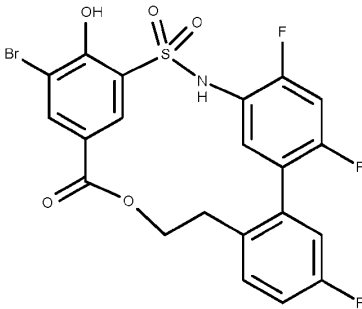
Compound No.	Structure
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119	 <chem>c1ccccc1CCOC(=O)c2cc(C(=O)NS(=O)(=O)c3cc(O)c(Br)cc3)ccc2C#N</chem>
120	 <chem>FC(F)Cc1ccncc1CCOC(=O)c2cc(C(=O)NS(=O)(=O)c3cc(O)c(Br)cc3)ccc2C#N</chem>

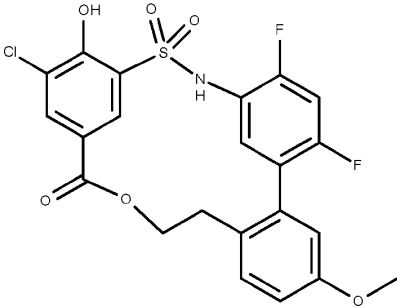
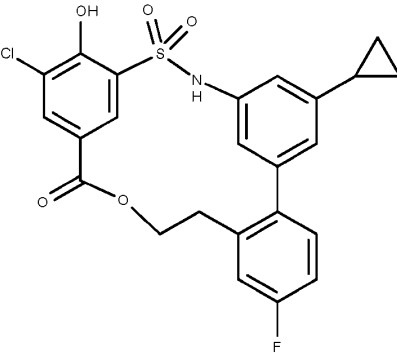
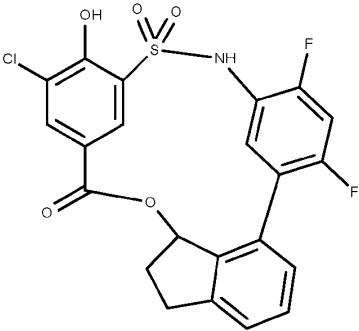
Compound No.	Structure
121	 Chemical structure of Compound 121: A central pyridine ring is substituted at the 2-position with a trifluoromethyl group (CF₃) and at the 4-position with a (4-bromo-3-hydroxyphenyl)methyl ester group. The pyridine ring is also substituted at the 3-position with a (2-chloro-4-fluorophenyl)methyl ester group.
122	 Chemical structure of Compound 122: A central pyridine ring is substituted at the 2-position with a trifluoromethyl group (CF₃) and at the 4-position with a (4-bromo-3-hydroxyphenyl)methyl ester group. The pyridine ring is also substituted at the 3-position with a (2-chloro-4-methoxyphenyl)methyl ester group.
123	 Chemical structure of Compound 123: A central pyridine ring is substituted at the 2-position with a trifluoromethyl group (CF₃) and at the 4-position with a (4-bromo-3-hydroxyphenyl)methyl ester group. The pyridine ring is also substituted at the 3-position with a (2-chloro-4-methoxyphenyl)methyl ester group.

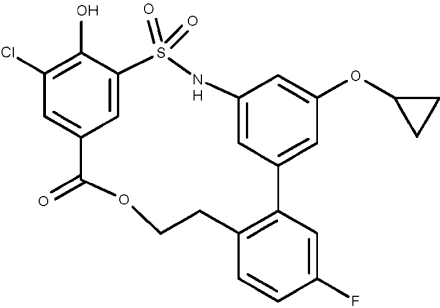
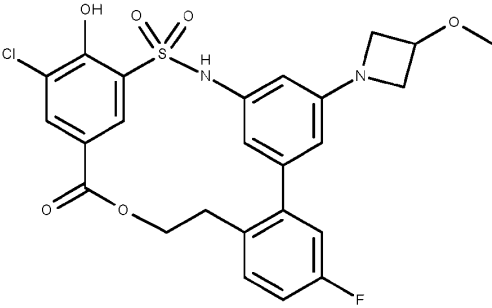
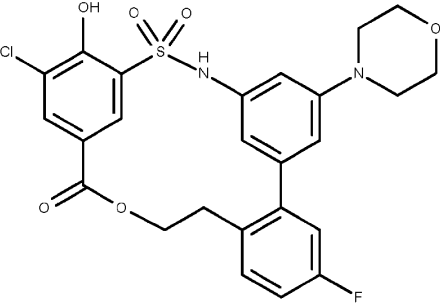
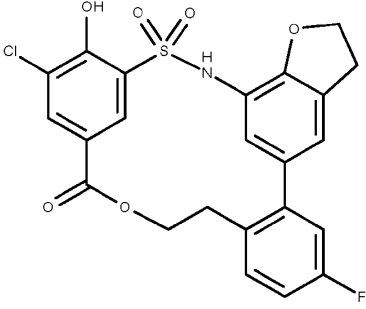
Compound No.	Structure
124	 Chemical structure of Compound 124: A sulfonamide derivative. The sulfonamide group (SO₂NH-) is attached to a 4-bromo-3-hydroxyphenyl ring. The sulfonamide nitrogen is also attached to a 4-methoxy-3-fluorophenyl ring. The sulfonamide group is further connected via a methylene chain to a 1,2,4-triazole ring, which is substituted with a 2-fluoroethyl group.
125	 Chemical structure of Compound 125: A sulfonamide derivative. The sulfonamide group (SO₂NH-) is attached to a 4-bromo-3-hydroxyphenyl ring. The sulfonamide nitrogen is also attached to a 4-(trifluoromethyl)pyridin-2-yl ring. The sulfonamide group is further connected via a methylene chain to a 4-cyano-2-phenyl ring.
126	 Chemical structure of Compound 126: A sulfonamide derivative. The sulfonamide group (SO₂NH-) is attached to a 4-chloro-3-hydroxyphenyl ring. The sulfonamide nitrogen is also attached to a 2,4-difluorophenyl ring. The sulfonamide group is further connected via a propyl chain to a 3,5-difluorophenyl ring.

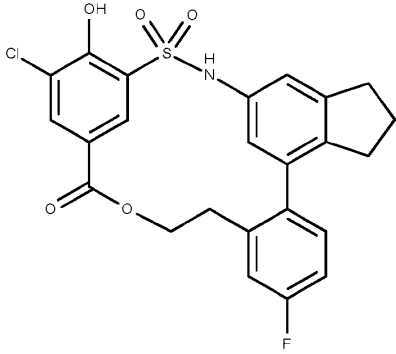
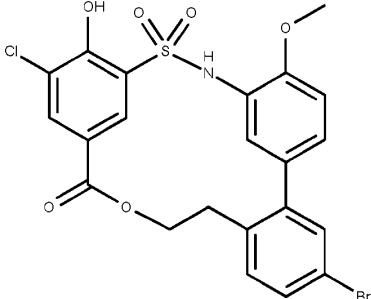
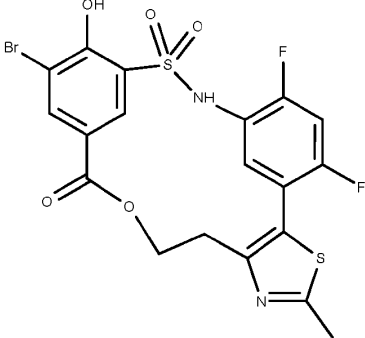
Compound No.	Structure
127	 Chemical structure of Compound 127: A 4-chloro-3-hydroxyphenyl ring is substituted at the 2-position with a sulfonamide group (-SO₂NH-) and at the 4-position with an ester group (-COO-). The sulfonamide nitrogen is connected to a 2,6-difluorophenyl ring. The ester oxygen is connected via a propyl chain to a 3-fluorophenyl ring.
128	 Chemical structure of Compound 128: A 4-chloro-3-hydroxyphenyl ring is substituted at the 2-position with a sulfonamide group (-SO₂NH-) and at the 4-position with an ester group (-COO-). The sulfonamide nitrogen is connected to a 3-methoxyphenyl ring. The ester oxygen is connected via a propyl chain to a 3-fluorophenyl ring.
129	 Chemical structure of Compound 129: A 4-chloro-3-hydroxyphenyl ring is substituted at the 2-position with a sulfonamide group (-SO₂NH-) and at the 4-position with an ester group (-COO-). The sulfonamide nitrogen is connected to a 2-methoxy-5-fluorophenyl ring. The ester oxygen is connected via a propyl chain to a 3-fluorophenyl ring.
130	 Chemical structure of Compound 130: A 4-chloro-3-hydroxyphenyl ring is substituted at the 2-position with a sulfonamide group (-SO₂NH-) and at the 4-position with an ester group (-COO-). The sulfonamide nitrogen is connected to a benzimidazole ring system. The ester oxygen is connected via a propyl chain to a 3-fluorophenyl ring.

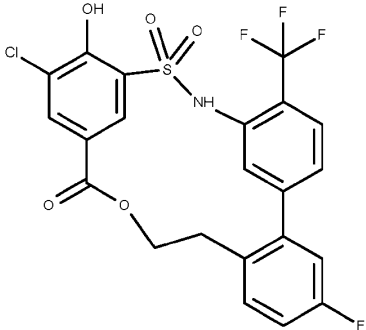
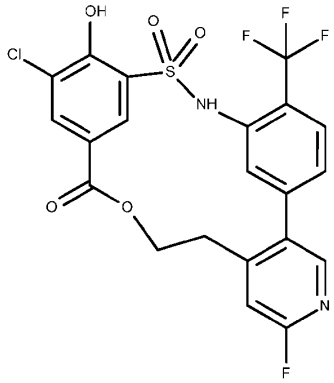
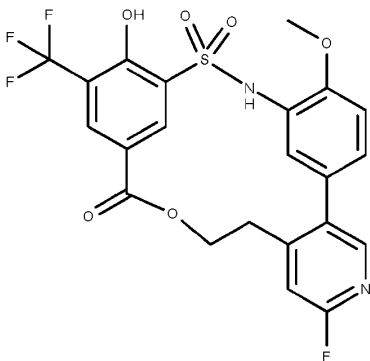
Compound No.	Structure
131	 Chemical structure of Compound 131: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 2-chloro-4-hydroxyphenyl group. The right ring is a 4-cyano-2-(3-(4-fluorophenyl)propyl)phenyl group. The two rings are linked via an ester group (-COO-) attached to the 3-position of the left ring and the 1-position of the right ring.
132	 Chemical structure of Compound 132: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 2-chloro-4-hydroxyphenyl group. The right ring is a 4-methoxy-2-(3-(4-fluoropyridin-2-yl)propyl)phenyl group. The two rings are linked via an ester group (-COO-) attached to the 3-position of the left ring and the 1-position of the right ring.
133	 Chemical structure of Compound 133: A molecule featuring a central sulfonamide group (-SO₂NH-) connecting two aromatic rings. The left ring is a 2-chloro-4-hydroxyphenyl group. The right ring is a 4-(cyclopropyl)-2-(3-(4-fluoropyridin-2-yl)propyl)phenyl group. The two rings are linked via an ester group (-COO-) attached to the 3-position of the left ring and the 1-position of the right ring.

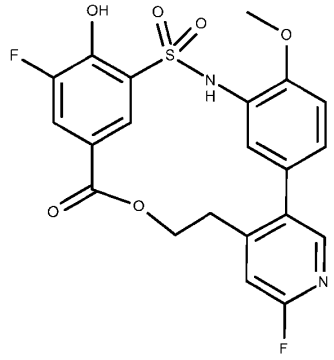
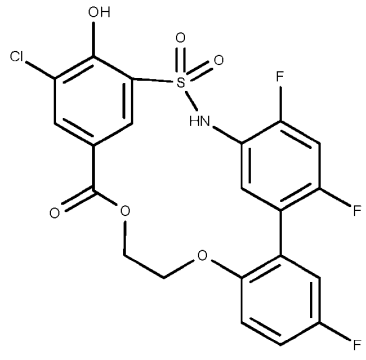
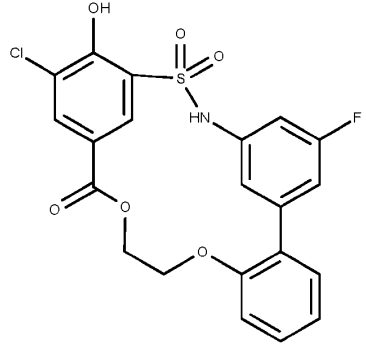
Compound No.	Structure
134	 Chemical structure of Compound 134: A 4-chloro-3-hydroxyphenyl ring is connected via a sulfonamide group (-SO₂NH-) to a 2,4-difluorophenyl ring. The 4-chloro-3-hydroxyphenyl ring is also connected via an ester group (-COO-) to a 4-(2-fluoropyridin-4-yl)butyl chain.
135	 Chemical structure of Compound 135: A 4-chloro-3-hydroxyphenyl ring is connected via a sulfonamide group (-SO₂NH-) to a 4-(trifluoromethoxy)phenyl ring. The 4-chloro-3-hydroxyphenyl ring is also connected via an ester group (-COO-) to a 4-(2-fluoropyridin-4-yl)butyl chain.
136	 Chemical structure of Compound 136: A 4-bromo-3-hydroxyphenyl ring is connected via a sulfonamide group (-SO₂NH-) to a 2,4-difluorophenyl ring. The 4-bromo-3-hydroxyphenyl ring is also connected via an ester group (-COO-) to a 4-(2-fluorophenyl)butyl chain.

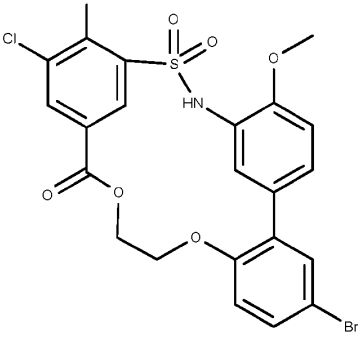
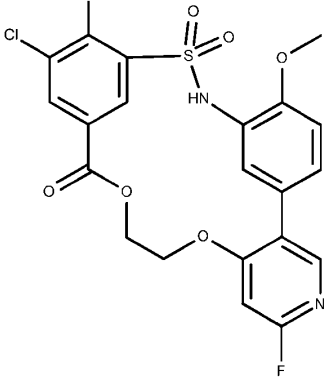
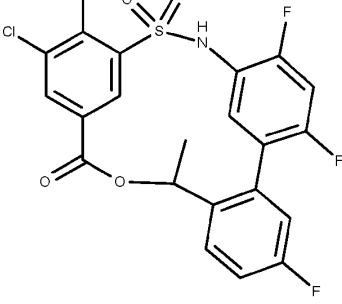
Compound No.	Structure
137	 Chemical structure of Compound 137: A sulfonamide derivative. The sulfonamide group is attached to a benzene ring substituted with a hydroxyl group and a chlorine atom. The sulfonamide nitrogen is attached to a benzene ring substituted with two fluorine atoms. The sulfonamide sulfur is also attached to a benzene ring substituted with a methoxy group and a propyl chain. The propyl chain is further substituted with a methoxy group.
138	 Chemical structure of Compound 138: A sulfonamide derivative. The sulfonamide group is attached to a benzene ring substituted with a hydroxyl group and a chlorine atom. The sulfonamide nitrogen is attached to a benzene ring substituted with a cyclopropyl group. The sulfonamide sulfur is also attached to a benzene ring substituted with a fluorine atom and a propyl chain. The propyl chain is further substituted with a methoxy group.
139	 Chemical structure of Compound 139: A sulfonamide derivative. The sulfonamide group is attached to a benzene ring substituted with a hydroxyl group and a chlorine atom. The sulfonamide nitrogen is attached to a benzene ring substituted with two fluorine atoms. The sulfonamide sulfur is also attached to a benzene ring substituted with a methoxy group and a propyl chain. The propyl chain is further substituted with a methoxy group.

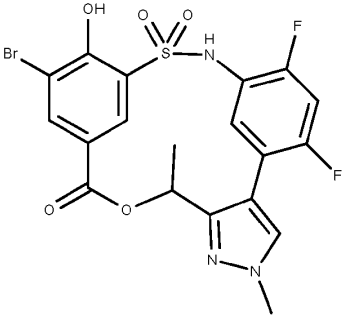
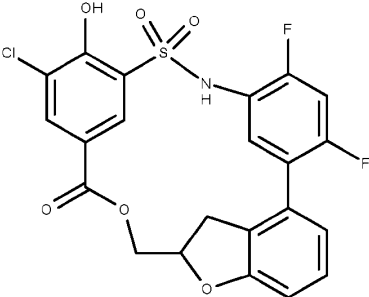
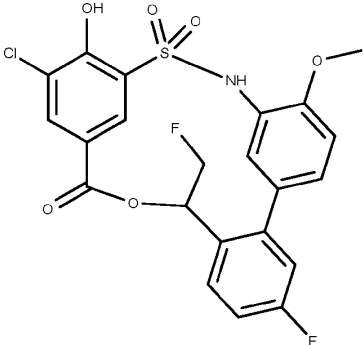
Compound No.	Structure
140	 Chemical structure of Compound 140: A 2-chloro-4-(4-(4-fluorophenyl)butyrate)-6-hydroxyphenyl sulfonamide. The sulfonamide group is linked to a 4-(4-fluorophenyl)butyrate chain, which is further linked to a 4-(4-fluorophenyl)butyrate chain. The sulfonamide group is also linked to a 4-(4-fluorophenyl)butyrate chain.
141	 Chemical structure of Compound 141: A 2-chloro-4-(4-(4-fluorophenyl)butyrate)-6-hydroxyphenyl sulfonamide. The sulfonamide group is linked to a 4-(4-fluorophenyl)butyrate chain, which is further linked to a 4-(4-fluorophenyl)butyrate chain. The sulfonamide group is also linked to a 4-(4-fluorophenyl)butyrate chain.
142	 Chemical structure of Compound 142: A 2-chloro-4-(4-(4-fluorophenyl)butyrate)-6-hydroxyphenyl sulfonamide. The sulfonamide group is linked to a 4-(4-fluorophenyl)butyrate chain, which is further linked to a 4-(4-fluorophenyl)butyrate chain. The sulfonamide group is also linked to a 4-(4-fluorophenyl)butyrate chain.
143	 Chemical structure of Compound 143: A 2-chloro-4-(4-(4-fluorophenyl)butyrate)-6-hydroxyphenyl sulfonamide. The sulfonamide group is linked to a 4-(4-fluorophenyl)butyrate chain, which is further linked to a 4-(4-fluorophenyl)butyrate chain. The sulfonamide group is also linked to a 4-(4-fluorophenyl)butyrate chain.

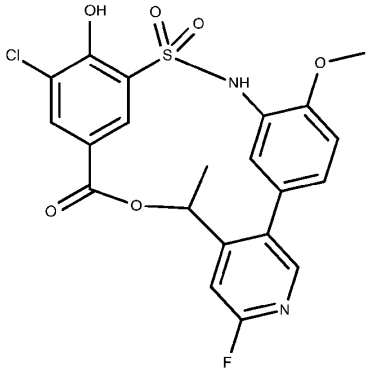
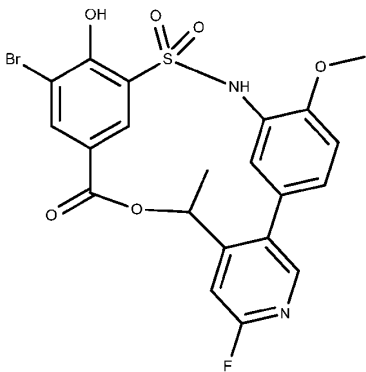
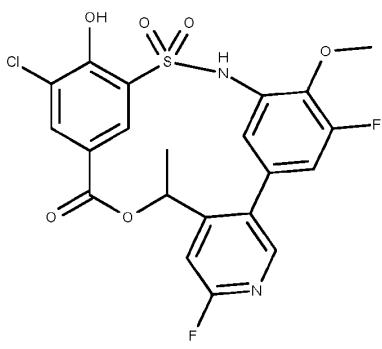
Compound No.	Structure
144	 Chemical structure of Compound 144: A sulfonamide derivative. The central sulfonamide group (SO₂NH-) connects a 3-chloro-4-hydroxyphenyl ring to a 1-(cyclopentyl)phenyl ring. The 1-(cyclopentyl)phenyl ring is further substituted with a 3-(4-fluorophenyl)propyl ester group.
145	 Chemical structure of Compound 145: A sulfonamide derivative. The central sulfonamide group (SO₂NH-) connects a 3-chloro-4-hydroxyphenyl ring to a 3-methoxyphenyl ring. The 3-methoxyphenyl ring is further substituted with a 3-(4-bromophenyl)propyl ester group.
146	 Chemical structure of Compound 146: A sulfonamide derivative. The central sulfonamide group (SO₂NH-) connects a 3-bromo-4-hydroxyphenyl ring to a 2,4-difluorophenyl ring. The 2,4-difluorophenyl ring is further substituted with a 3-(4-methyl-1,3,4-thiazol-5-yl)propyl ester group.

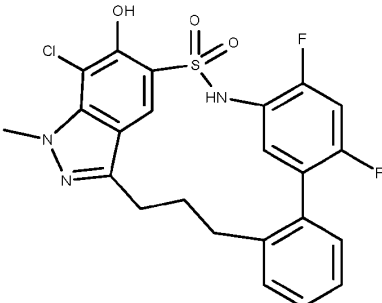
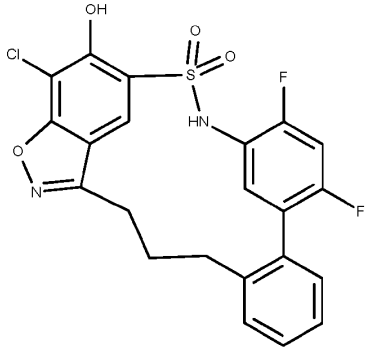
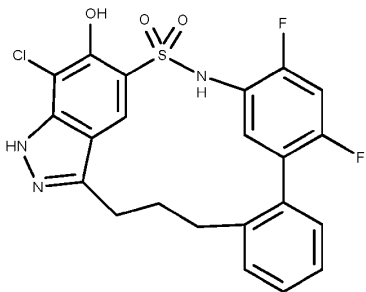
Compound No.	Structure
147	 Chemical structure of Compound 147: A 4-chloro-3-hydroxybenzoate derivative. The benzoate ring is substituted with a chlorine atom at the 4-position and a hydroxyl group at the 3-position. It is linked via an ester bond to a 3-(4-(4-(trifluoromethyl)phenyl)phenyl)propyl group. The sulfonamide group is attached to the benzoate ring at the 2-position and linked to a 4-(4-(trifluoromethyl)phenyl)phenyl group.
148	 Chemical structure of Compound 148: A 4-chloro-3-hydroxybenzoate derivative. The benzoate ring is substituted with a chlorine atom at the 4-position and a hydroxyl group at the 3-position. It is linked via an ester bond to a 3-(4-(4-(2-fluoropyridin-5-yl)phenyl)phenyl)propyl group. The sulfonamide group is attached to the benzoate ring at the 2-position and linked to a 4-(4-(trifluoromethyl)phenyl)phenyl group.
149	 Chemical structure of Compound 149: A 4-(trifluoromethyl)-3-hydroxybenzoate derivative. The benzoate ring is substituted with a trifluoromethyl group at the 4-position and a hydroxyl group at the 3-position. It is linked via an ester bond to a 3-(4-(4-(2-fluoropyridin-5-yl)phenyl)phenyl)propyl group. The sulfonamide group is attached to the benzoate ring at the 2-position and linked to a 4-(4-(methoxy)phenyl)phenyl group.

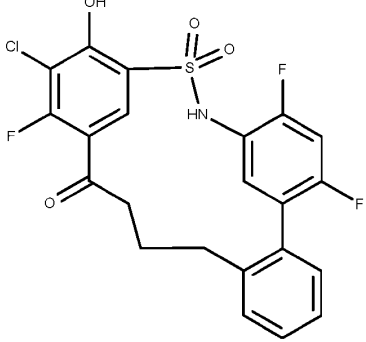
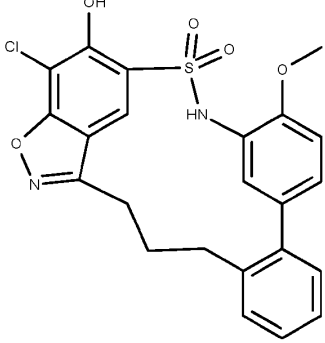
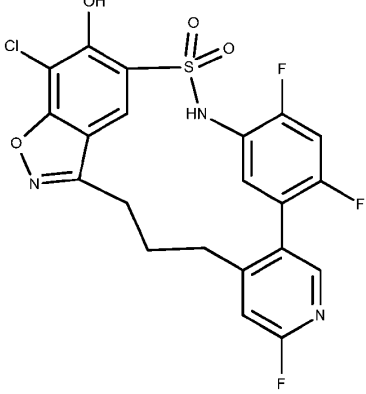
Compound No.	Structure
150	 Chemical structure of Compound 150: A central sulfonamide group (SO₂NH-) connects two aromatic systems. On the left, a benzene ring is substituted with a hydroxyl group (OH) at the 3-position, a fluorine atom (F) at the 4-position, and a carboxylate group (-COO-) at the 1-position. The carboxylate group is linked via an ester bond to a 2-(4-fluoropyridin-2-yl)ethyl chain. On the right, the sulfonamide group is attached to a benzene ring substituted with a methoxy group (-OCH₃) at the 3-position and a 2-(4-fluorophenyl)ethyl chain at the 1-position.
151	 Chemical structure of Compound 151: A central sulfonamide group (SO₂NH-) connects two aromatic systems. On the left, a benzene ring is substituted with a hydroxyl group (OH) at the 3-position, a chlorine atom (Cl) at the 4-position, and a carboxylate group (-COO-) at the 1-position. The carboxylate group is linked via an ester bond to a 2-(2,4-difluorophenoxy)ethyl chain. On the right, the sulfonamide group is attached to a benzene ring substituted with fluorine atoms (F) at the 3 and 4 positions and a 2-(2,4-difluorophenoxy)ethyl chain at the 1-position.
152	 Chemical structure of Compound 152: A central sulfonamide group (SO₂NH-) connects two aromatic systems. On the left, a benzene ring is substituted with a hydroxyl group (OH) at the 3-position, a chlorine atom (Cl) at the 4-position, and a carboxylate group (-COO-) at the 1-position. The carboxylate group is linked via an ester bond to a 2-(phenoxy)ethyl chain. On the right, the sulfonamide group is attached to a benzene ring substituted with fluorine atoms (F) at the 3 and 4 positions and a 2-(phenoxy)ethyl chain at the 1-position.

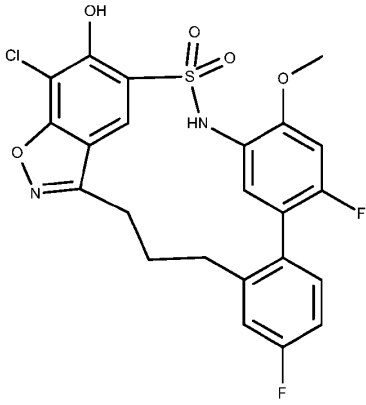
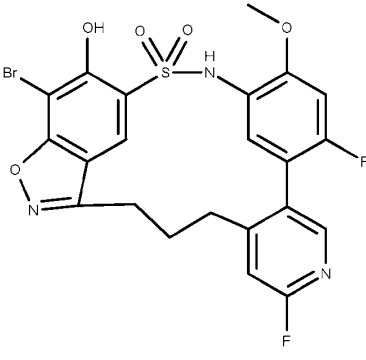
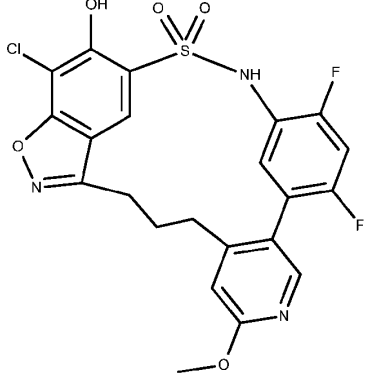
Compound No.	Structure
153	 Chemical structure of Compound 153: A central sulfonamide group (SO₂NH-) connects two aromatic rings. The left ring is a 3-chloro-4-hydroxyphenyl group. The right ring is a 4-methoxyphenyl group. The sulfonamide nitrogen is further connected via a 2-ethoxyethyl ester linkage to a 3-bromophenyl group.
154	 Chemical structure of Compound 154: A central sulfonamide group (SO₂NH-) connects two aromatic rings. The left ring is a 3-chloro-4-hydroxyphenyl group. The right ring is a 4-methoxyphenyl group. The sulfonamide nitrogen is further connected via a 2-ethoxyethyl ester linkage to a 3-fluoropyridin-2-yl group.
155	 Chemical structure of Compound 155: A central sulfonamide group (SO₂NH-) connects two aromatic rings. The left ring is a 3-chloro-4-hydroxyphenyl group. The right ring is a 2,4-difluorophenyl group. The sulfonamide nitrogen is further connected via a 1-(4-fluorophenyl)ethyl ester linkage to a 4-fluorophenyl group.

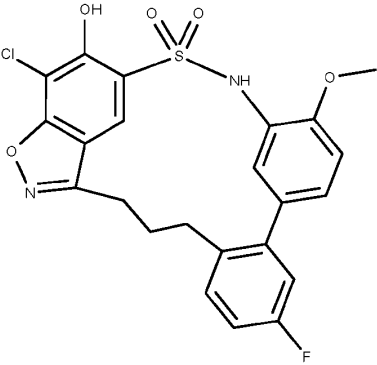
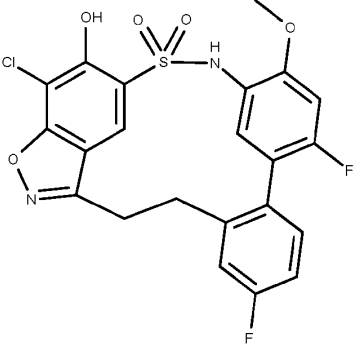
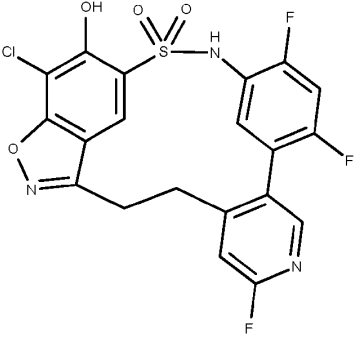
Compound No.	Structure
156	
157	
158	

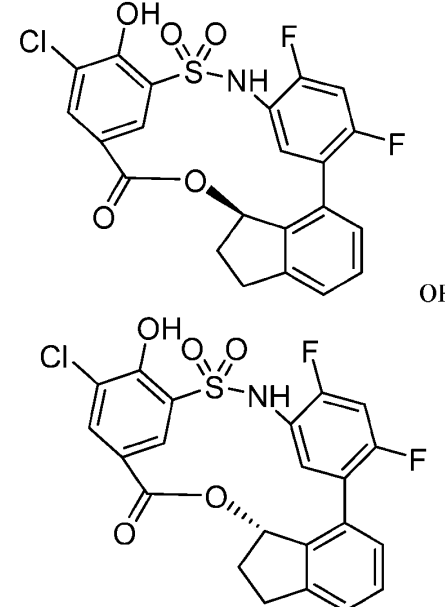
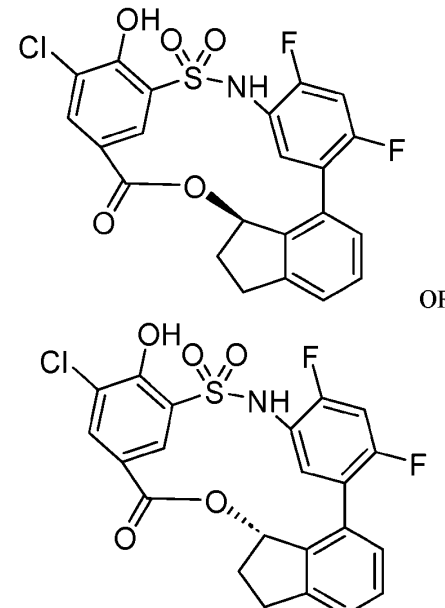
Compound No.	Structure
159	
160	
161	

Compound No.	Structure
162	
163	
164	

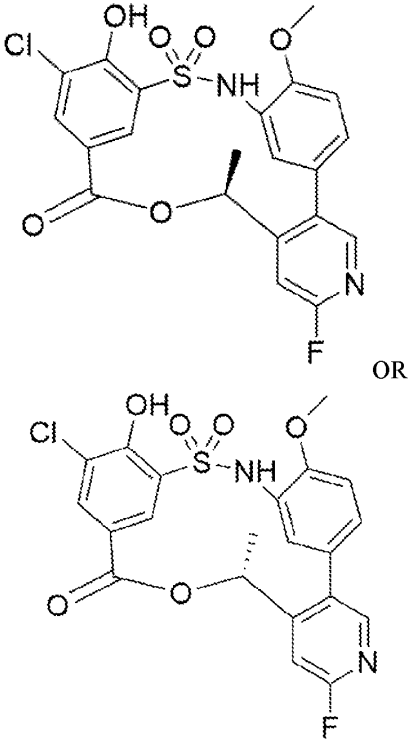
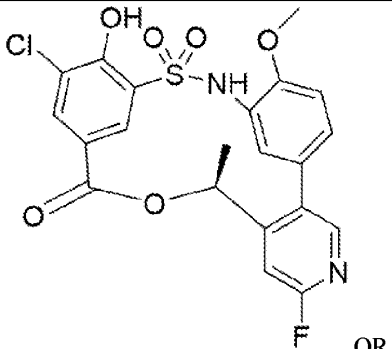
Compound No.	Structure
165	 Chemical structure of Compound 165: A benzimidazole ring system substituted with a hydroxyl group (OH), a chlorine atom (Cl), and a fluorine atom (F). The benzimidazole ring is connected via a three-carbon chain to a phenyl ring. The phenyl ring is further substituted with a sulfonamide group (-SO₂NH-) and a 2,4-difluorophenyl group.
166	 Chemical structure of Compound 166: A benzimidazole ring system substituted with a hydroxyl group (OH), a chlorine atom (Cl), and a fluorine atom (F). The benzimidazole ring is connected via a three-carbon chain to a phenyl ring. The phenyl ring is further substituted with a sulfonamide group (-SO₂NH-) and a 3-methoxyphenyl group.
167	 Chemical structure of Compound 167: A benzimidazole ring system substituted with a hydroxyl group (OH), a chlorine atom (Cl), and a fluorine atom (F). The benzimidazole ring is connected via a three-carbon chain to a phenyl ring. The phenyl ring is further substituted with a sulfonamide group (-SO₂NH-) and a 2,4-difluorophenyl group.

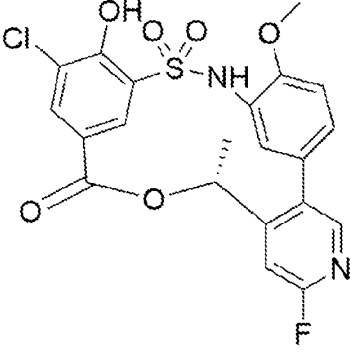
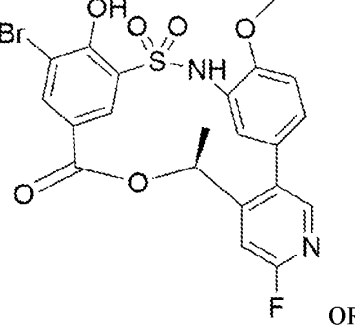
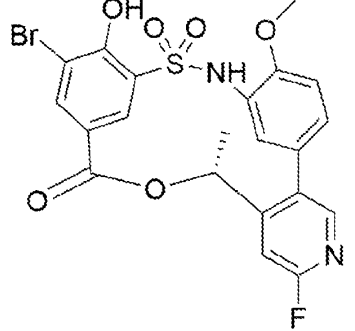
Compound No.	Structure
168	 Chemical structure of Compound 168: A 5-chloro-2-hydroxy-1,2,3,4-tetrahydroisoxazole ring is connected via a 3-phenylpropyl chain to a 4-fluorophenyl ring. This 4-fluorophenyl ring is further connected via a sulfonamide group (-SO₂NH-) to a 3-fluoro-4-methoxyphenyl ring.
169	 Chemical structure of Compound 169: A 5-bromo-2-hydroxy-1,2,3,4-tetrahydroisoxazole ring is connected via a 3-(4-fluoropyridin-2-yl)propyl chain to a 4-fluorophenyl ring. This 4-fluorophenyl ring is further connected via a sulfonamide group (-SO₂NH-) to a 3-fluoro-4-methoxyphenyl ring.
170	 Chemical structure of Compound 170: A 5-chloro-2-hydroxy-1,2,3,4-tetrahydroisoxazole ring is connected via a 3-(4-methoxy-3-pyridyl)propyl chain to a 4-fluorophenyl ring. This 4-fluorophenyl ring is further connected via a sulfonamide group (-SO₂NH-) to a 3,5-difluorophenyl ring.

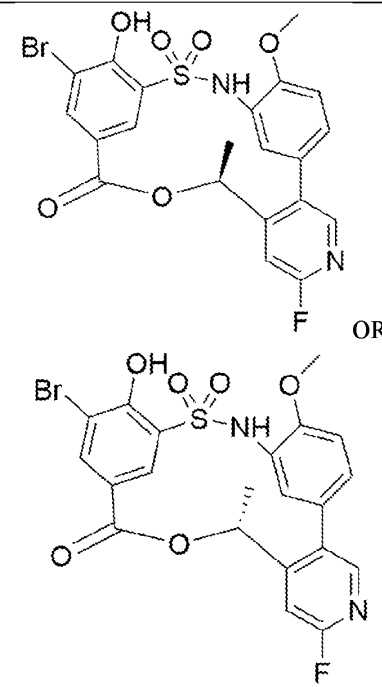
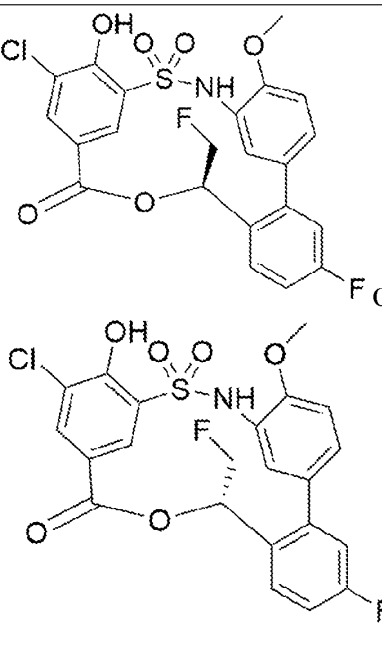
Compound No.	Structure
171	 Chemical structure of Compound 171: A molecule featuring a 5-chloro-2-hydroxy-1,2,3,4-tetrahydroisoxazole ring system. This is connected via a propyl chain to a 4-fluorophenyl ring. The 4-fluorophenyl ring is further connected via a propyl chain to a 3-methoxyphenyl ring. The 3-methoxyphenyl ring is connected via a sulfonamide group (-SO₂NH-) to the 5-chloro-2-hydroxy-1,2,3,4-tetrahydroisoxazole ring system.
172	 Chemical structure of Compound 172: A molecule featuring a 5-chloro-2-hydroxy-1,2,3,4-tetrahydroisoxazole ring system. This is connected via a propyl chain to a 4-fluorophenyl ring. The 4-fluorophenyl ring is further connected via a propyl chain to a 3-fluoro-4-methoxyphenyl ring. The 3-fluoro-4-methoxyphenyl ring is connected via a sulfonamide group (-SO₂NH-) to the 5-chloro-2-hydroxy-1,2,3,4-tetrahydroisoxazole ring system.
173	 Chemical structure of Compound 173: A molecule featuring a 5-chloro-2-hydroxy-1,2,3,4-tetrahydroisoxazole ring system. This is connected via a propyl chain to a 4-fluoropyridine ring. The 4-fluoropyridine ring is further connected via a propyl chain to a 3,5-difluorophenyl ring. The 3,5-difluorophenyl ring is connected via a sulfonamide group (-SO₂NH-) to the 5-chloro-2-hydroxy-1,2,3,4-tetrahydroisoxazole ring system.

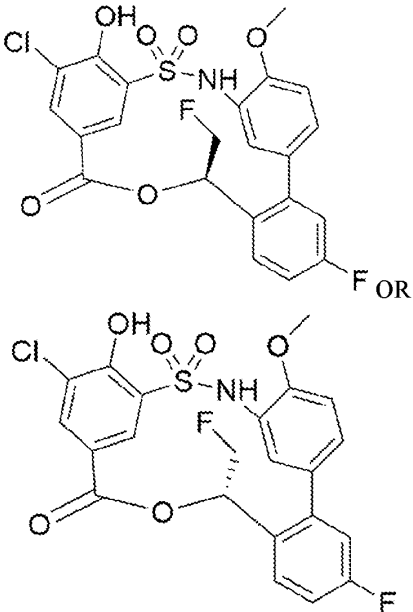
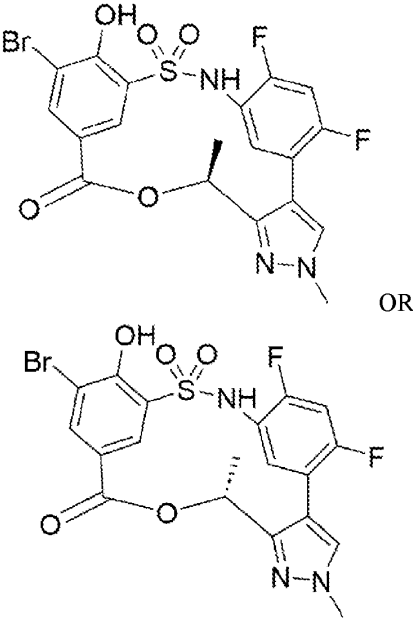
Compound No.	Structure
174	 Chemical structure of Compound 174, showing two enantiomers separated by "OR". The structure consists of a 2-chloro-4-hydroxybenzoate moiety linked via an ester bond to a fluorene moiety. The fluorene moiety is further substituted with a 2,6-difluorophenyl group. The stereochemistry at the chiral center is indicated by a wedge bond in the top structure and a dashed bond in the bottom structure.
175	 Chemical structure of Compound 175, showing two enantiomers separated by "OR". The structure is identical to Compound 174, consisting of a 2-chloro-4-hydroxybenzoate moiety linked via an ester bond to a fluorene moiety, which is further substituted with a 2,6-difluorophenyl group. The stereochemistry at the chiral center is indicated by a wedge bond in the top structure and a dashed bond in the bottom structure.

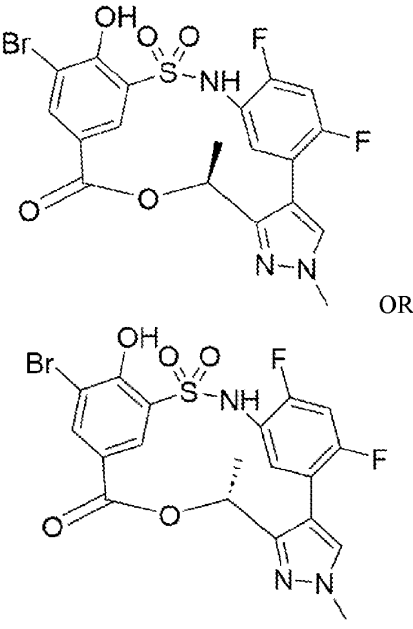
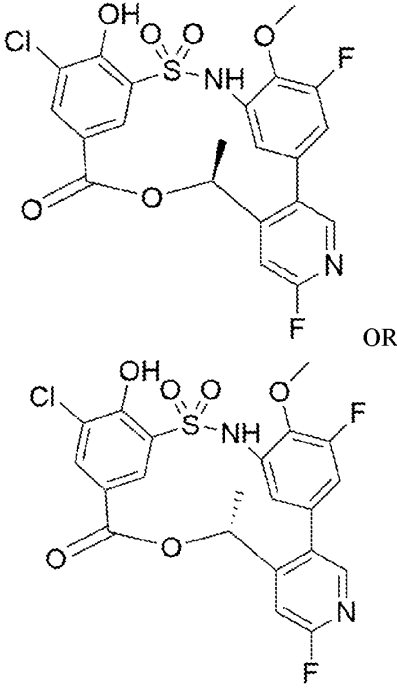
Compound No.	Structure
176	Chemical structures of Compound 176 enantiomers. The structures show a central chiral center (C*) bonded to a 4-chloro-3-hydroxyphenyl group, a 2,4-difluorophenyl group, a 3,5-difluorophenyl group, and a 4-fluorophenyl group. The chiral center is also bonded to a 4-chloro-3-hydroxyphenyl group via a sulfonamide linkage (SO₂NH) and a 4-fluorophenyl group via an ester linkage (O-C(=O)-). The structures are shown as a pair of enantiomers, with the top structure having a wedge bond to the 4-fluorophenyl group and the bottom structure having a dashed bond to the 4-fluorophenyl group.
177	Chemical structures of Compound 177 enantiomers. The structures show a central chiral center (C*) bonded to a 4-chloro-3-hydroxyphenyl group, a 2,4-difluorophenyl group, a 3,5-difluorophenyl group, and a 4-fluorophenyl group. The chiral center is also bonded to a 4-chloro-3-hydroxyphenyl group via a sulfonamide linkage (SO₂NH) and a 4-fluorophenyl group via an ester linkage (O-C(=O)-). The structures are shown as a pair of enantiomers, with the top structure having a wedge bond to the 4-fluorophenyl group and the bottom structure having a dashed bond to the 4-fluorophenyl group.

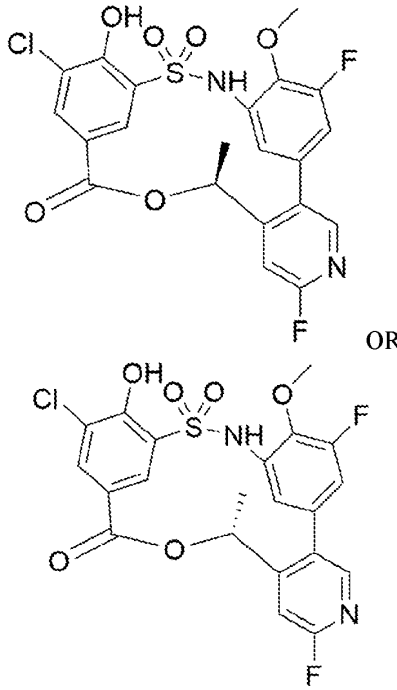
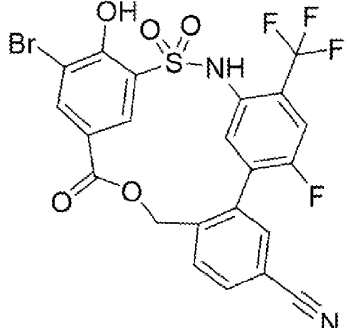
Compound No.	Structure
178	 Chemical structure of Compound 178, showing two enantiomers separated by "OR". The structure consists of a 3-chloro-4-hydroxyphenyl group connected via a sulfonamide bridge to a 4-methoxyphenyl group. This 4-methoxyphenyl group is further connected to a 2-fluoropyridine ring. The pyridine ring is also connected to a chiral center (marked with a wedge bond) which is part of an ester linkage to a 3-chloro-4-hydroxyphenyl group.
179	 Chemical structure of Compound 179, showing two enantiomers separated by "OR". The structure is identical to Compound 178, but the chiral center is marked with a dashed bond instead of a wedge bond.

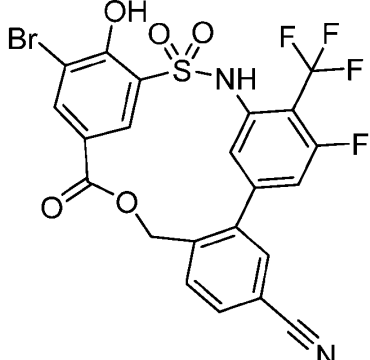
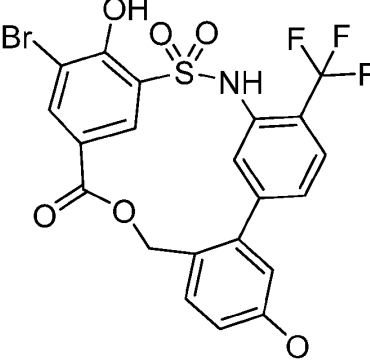
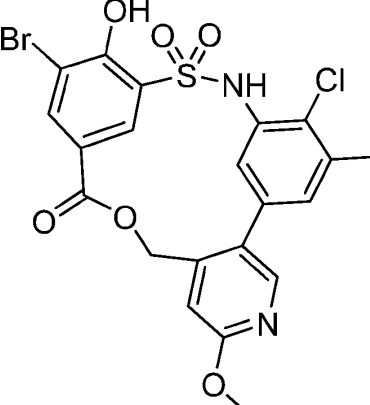
Compound No.	Structure
	
180	 OR 

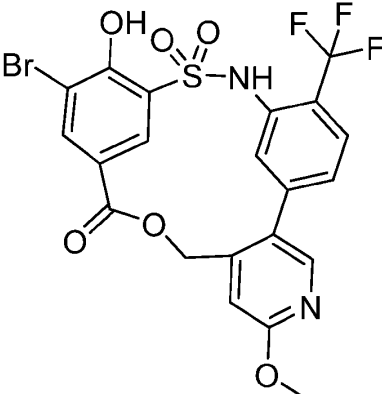
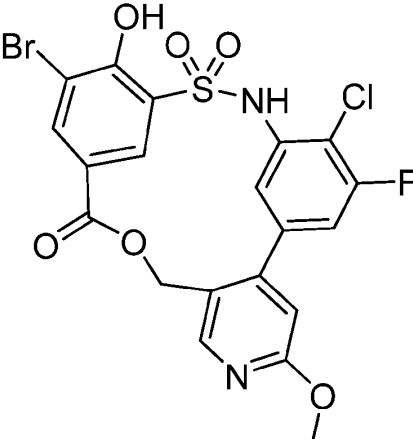
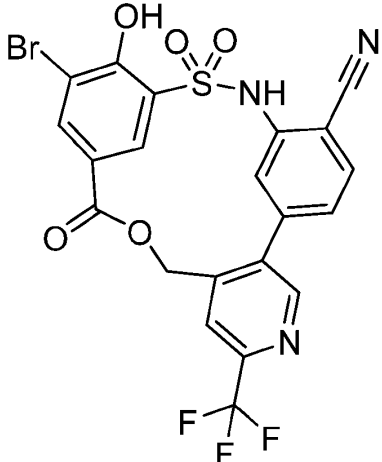
Compound No.	Structure
181	 Chemical structures for Compound 181. The top structure shows a sulfonamide derivative with a bromophenyl group, a hydroxyl group, and a pyridine ring substituted with a methoxy group and a fluorine atom. The bottom structure is identical to the top one, but the stereochemistry of the chiral center is inverted. The two structures are separated by the text "OR".
182	 Chemical structures for Compound 182. The top structure shows a sulfonamide derivative with a chlorophenyl group, a hydroxyl group, and a pyridine ring substituted with a methoxy group and a fluorine atom. The bottom structure is identical to the top one, but the stereochemistry of the chiral center is inverted. The two structures are separated by the text "OR".

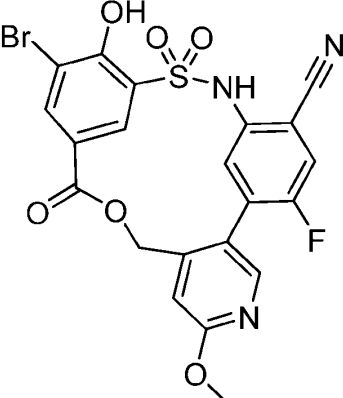
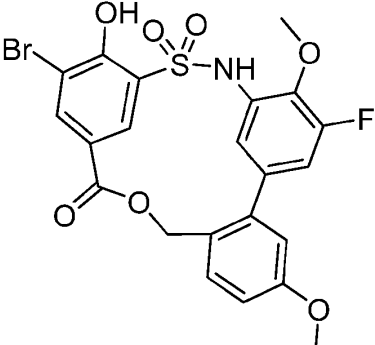
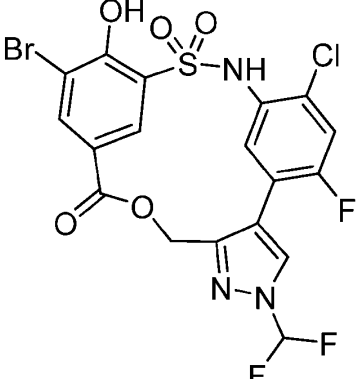
Compound No.	Structure
183	 Chemical structures for Compound 183. The top structure shows a sulfonamide derivative with a 4-chloro-3-hydroxyphenyl group, a 4-methoxyphenyl group, and a 4-fluorophenyl group, connected via a chiral center (F and OR). The bottom structure is identical but with a fluorine atom (F) instead of an OR group.
184	 Chemical structures for Compound 184. The top structure shows a sulfonamide derivative with a 4-bromo-3-hydroxyphenyl group, a 2,6-difluorophenyl group, and a 1,2,3-triazole ring, connected via a chiral center (F and OR). The bottom structure is identical but with a fluorine atom (F) instead of an OR group.

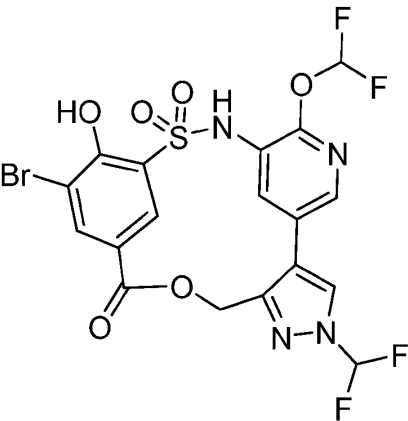
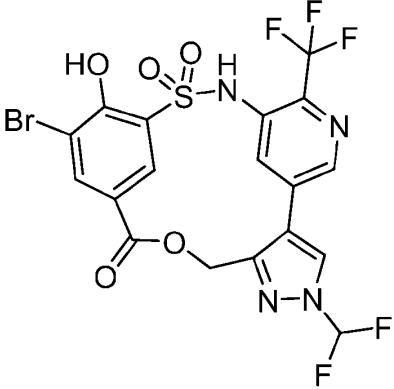
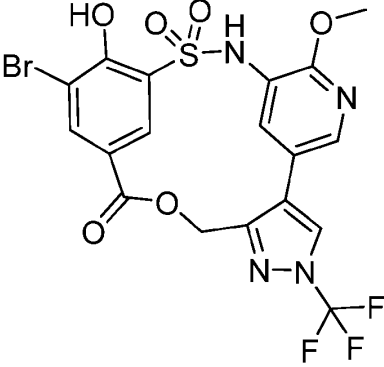
Compound No.	Structure
185	 OR
186	 OR

Compound No.	Structure
187	 Chemical structure of Compound 187, showing two enantiomers separated by "OR". The structure features a 2-chloro-3-hydroxybenzoyl group linked via an ester to a chiral center. This chiral center is also bonded to a 2-methoxy-3-fluorophenyl group and a 4-fluoropyridin-2-yl group. The two enantiomers differ in the stereochemistry of the chiral center, indicated by a wedge bond in the top structure and a dashed bond in the bottom structure.
188	 Chemical structure of Compound 188, featuring a 2-bromo-3-hydroxybenzoyl group linked via an ester to a methylene group. This methylene group is bonded to a 4-cyanophenyl ring, which is in turn linked to a 2,3,4-trifluorophenyl group. A sulfonamide group (-SO₂NH₂) is attached to the 2-position of the 2,3,4-trifluorophenyl ring.

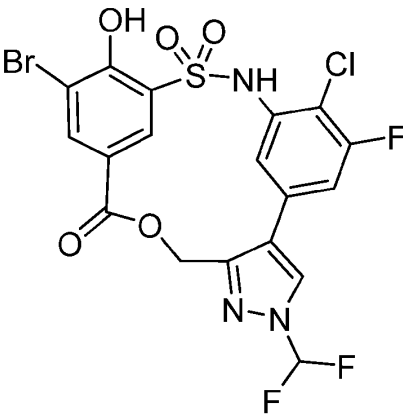
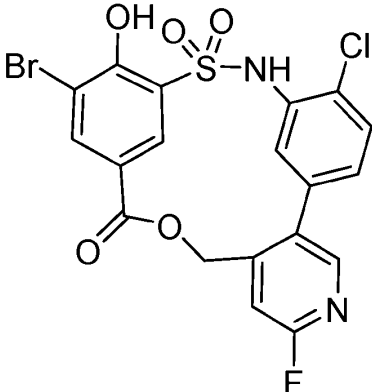
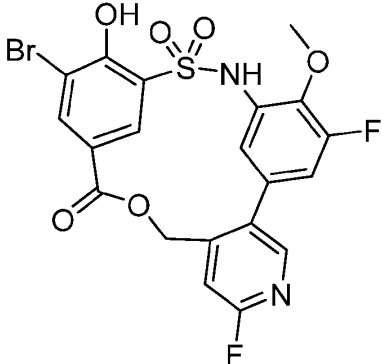
Compound No.	Structure
189	 Chemical structure of Compound 189: A molecule featuring a central benzene ring substituted with a cyano group (-C≡N) at the para position and a (4-bromo-3-hydroxyphenyl)sulfonyl group (-SO₂-NH-C₆H₃(Br)(OH)) at the other para position. This central ring is also connected via a methylene group to a 4-(4-(trifluoromethyl)phenyl)phenyl group. The 4-(4-(trifluoromethyl)phenyl)phenyl group is further linked via an ester group (-COO-) to a 4-bromo-3-hydroxyphenyl group.
190	 Chemical structure of Compound 190: A molecule featuring a central benzene ring substituted with a methoxy group (-OCH₃) at the para position and a (4-bromo-3-hydroxyphenyl)sulfonyl group (-SO₂-NH-C₆H₃(Br)(OH)) at the other para position. This central ring is also connected via a methylene group to a 4-(4-(trifluoromethyl)phenyl)phenyl group. The 4-(4-(trifluoromethyl)phenyl)phenyl group is further linked via an ester group (-COO-) to a 4-bromo-3-hydroxyphenyl group.
191	 Chemical structure of Compound 191: A molecule featuring a central benzene ring substituted with a methoxy group (-OCH₃) at the para position and a (4-bromo-3-hydroxyphenyl)sulfonyl group (-SO₂-NH-C₆H₃(Br)(OH)) at the other para position. This central ring is also connected via a methylene group to a 4-(4-(chloromethyl)phenyl)pyridine group. The 4-(4-(chloromethyl)phenyl)pyridine group is further linked via an ester group (-COO-) to a 4-bromo-3-hydroxyphenyl group.

Compound No.	Structure
192	 Chemical structure of Compound 192: A pyridine ring substituted with a methoxy group at the 3-position and a (4-bromo-2-hydroxyphenyl)acetate group at the 4-position. The pyridine ring is also substituted with a (4-(trifluoromethyl)phenyl) group at the 2-position. The trifluoromethyl group is represented as a carbon atom bonded to three fluorine atoms.
193	 Chemical structure of Compound 193: A pyridine ring substituted with a methoxy group at the 3-position and a (4-bromo-2-hydroxyphenyl)acetate group at the 4-position. The pyridine ring is also substituted with a (2-chloro-4-fluorophenyl) group at the 2-position. The chlorine atom is represented as 'Cl' and the fluorine atom as 'F'.
194	 Chemical structure of Compound 194: A pyridine ring substituted with a trifluoromethyl group at the 3-position and a (4-(trifluoromethyl)phenyl)acetate group at the 4-position. The pyridine ring is also substituted with a (4-cyanophenyl) group at the 2-position. The trifluoromethyl group is represented as a carbon atom bonded to three fluorine atoms, and the cyano group is represented as a carbon atom bonded to a nitrogen atom with a triple bond.

Compound No.	Structure
195	 Chemical structure of Compound 195: A macrocyclic molecule featuring a central pyrazole ring. The pyrazole ring is substituted with a methoxy group (-OCH₃) at the 4-position and a (2-bromo-4-hydroxyphenyl)acetate group at the 5-position. The pyrazole ring is also substituted with a (2-cyano-4-fluorophenyl)methyl group at the 3-position. The pyrazole ring is further substituted with a (2-bromo-4-hydroxyphenyl)acetate group at the 5-position.
196	 Chemical structure of Compound 196: A macrocyclic molecule featuring a central pyrazole ring. The pyrazole ring is substituted with a methoxy group (-OCH₃) at the 4-position and a (2-bromo-4-hydroxyphenyl)acetate group at the 5-position. The pyrazole ring is also substituted with a (2-methoxy-4-fluorophenyl)methyl group at the 3-position. The pyrazole ring is further substituted with a (2-bromo-4-hydroxyphenyl)acetate group at the 5-position.
197	 Chemical structure of Compound 197: A macrocyclic molecule featuring a central pyrazole ring. The pyrazole ring is substituted with a (2-bromo-4-hydroxyphenyl)acetate group at the 5-position and a (2-chloro-4-fluorophenyl)methyl group at the 3-position. The pyrazole ring is also substituted with a (2-fluoro-4-fluorophenyl)methyl group at the 3-position. The pyrazole ring is further substituted with a (2-bromo-4-hydroxyphenyl)acetate group at the 5-position.

Compound No.	Structure
201	
202	
203	

Compound No.	Structure
207	
208	
209	

Compound No.	Structure
210	
211	
212	

Compound No.	Structure
213	

Pharmaceutical Compositions and Routes of Administration

[0171] Compounds provided in accordance with the present disclosure are usually administered in the form of pharmaceutical compositions. This invention therefore provides pharmaceutical compositions that contain, as the active ingredient, one or more of the compounds described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id), or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. The pharmaceutical compositions described herein may be administered alone or in combination with other therapeutic agents. Such compositions are prepared in a manner well known in the pharmaceutical art (see, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G. S. Banker & C. T. Rhodes, Eds.))

[0172] The pharmaceutical compositions described herein may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, for example as described in those patents and patent applications incorporated by reference, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

[0173] One mode for administration is parenteral, particularly by injection. The forms in which the novel compositions of the present disclosure may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles. Aqueous solutions in saline are also conventionally used for injection, but less preferred in the context of the present disclosure. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[0174] Sterile injectable solutions are prepared by incorporating a compound according to the present disclosure in the required amount in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0175] Oral administration is another route for administration of compounds in accordance with the disclosure. Administration may be via capsule or enteric coated tablets, or the like. In making the pharmaceutical compositions that include at least one compound described herein, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0176] Some examples of suitable excipients include, but are not limited to, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxybenzoates; sweetening agents; and flavoring agents.

[0177] The compositions of the disclosure can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Pat. Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345. Another formulation for use in the methods of the present disclosure employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present disclosure in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Pat. Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0178] The compositions are preferably formulated in a unit dosage form. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient (e.g., a tablet, capsule, ampoule). The compounds are generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered usually will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0179] For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present disclosure. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is

dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills, and capsules.

[0180] The tablets or pills of the present disclosure may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0181] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device, or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

[0182] In some embodiments, a pharmaceutical composition comprises a disclosed compound (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

Methods of Treatment

[0183] In various embodiments, a compound disclosed herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, including a pharmaceutical composition, may be used for the treatment or prevention of a variety of conditions, diseases, and disorders. The methods of treating a condition, disease, or disorder described herein generally comprise administering to a patient in need thereof, a therapeutically effective

amount of a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)) or a stereoisomer and/or a pharmaceutically acceptable salt thereof, to treat the condition, disease, or disorder.

[0184] In typical embodiments, the present disclosure is intended to encompass a compound disclosed herein, or a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure includes an enantiomer, a mixture of enantiomers, a stereoisomer, or mixture of stereoisomers (pure or as a racemic or non-racemic mixture) of a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)).

[0185] Examples of conditions, diseases, and disorders include, but are not limited to, cardiovascular disease, atrial fibrillation, blood clotting, coronary heart disease, hypercoagulable states, ischemia, myocardial infarction, myopathy, myositis, pulmonary embolism, stroke, peripheral vascular disease, pulmonary hypertension, pulmonary arterial hypertension, dyslipidemia, dyslipoproteinemia, a disorder of glucose metabolism, Alzheimer's disease, Parkinson's disease, diabetic nephropathy, diabetic retinopathy, insulin resistance, metabolic syndrome disorders (e.g., Syndrome X), galactosemia, HIV infection, a peroxisome proliferator activated receptor-associated disorder, septicemia, a thrombotic disorder, obesity, pancreatitis, hypertension, renal disease, cancer, inflammation (e.g., liver inflammation), inflammatory muscle diseases (e.g., polymyalgia rheumatica, polymyositis, and fibrositis), impotence, gastrointestinal disease, irritable bowel syndrome, inflammatory bowel disease, inflammatory disorders (e.g., asthma, vasculitis, ulcerative colitis, Crohn's disease, Kawasaki disease, Wegener's granulomatosis, (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and autoimmune chronic hepatitis), arthritis (e.g., rheumatoid arthritis, juvenile rheumatoid arthritis, and osteoarthritis), osteoporosis, soft tissue rheumatism (e.g., tendonitis), bursitis, autoimmune disease (e.g., systemic lupus and erythematosus), scleroderma, ankylosing spondylitis, gout, pseudogout, non-insulin dependent diabetes mellitus, diabetes (e.g., type 2), polycystic ovarian disease, hyperlipidemias (e.g., primary hyperlipidemia, familial hypercholesterolemia (FH), Hypercholesterolemia Frederickson Type IIa, Hypercholesterolemia Frederickson Type IIb, familial combined hyperlipidemia (FCH)), lipoprotein lipase deficiencies (e.g., hypertriglyceridemia, hypoalphalipoproteinemia, and hypercholesterolemia), lipoprotein abnormalities associated with diabetes, lipoprotein abnormalities associated with obesity, and lipoprotein abnormalities associated with Alzheimer's disease. In particular embodiments, the

methods include treating and/or preventing hyperlipidemia such as primary hyperlipidemia. In some embodiments, the methods include treating and/or preventing cardiovascular disease.

[0186] In certain embodiments, a compound disclosed herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, including a pharmaceutical composition, may be used for the treatment or prevention of one or more of high levels of low density lipoprotein cholesterol (LDL-C), high levels of apolipoprotein B (apoB), high levels of lipoprotein(a) (Lp(a)), high levels of very low density lipoprotein (VLDL), high levels of non-high density lipid cholesterol (non-HDL-C), high levels of total serum cholesterol (TC), high levels of high sensitivity c-reactive protein (hsCRP), high levels of fibrinogen, high levels of insulin, high levels of glucose, and low levels of high density lipoprotein cholesterol (HDL-C). In other words, methods of the disclosure can include lowering LDL-C, lowering apoB, lowering Lp(a), lowering VLDL, lowering non-HDL-C, lowering TC, and/or lowering hsCRP. Methods of the disclosure can include inhibiting ACLY, inhibiting cholesterol synthesis, and/or suppressing fatty acid biosynthesis. In some embodiments, an effective amount of a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure may be used as an adjunct to diet and maximally tolerated statin therapy to lower LDL-C in adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease. In some embodiments, an effective amount of a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure may be used for the treatment of non-insulin dependent diabetes mellitus without increasing weight gain.

[0187] In certain embodiments, a compound disclosed herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, including a pharmaceutical composition, may be used for the treatment or prevention of a variety of diseases and conditions, which include, but are not limited to aging, Alzheimer's disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, enhancing bile production, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, modulating C reactive protein, obesity, oxysterol

elimination in bile, pancreatitis, pancreatitius, Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, rhabdomyolysis, septicemia, sleep apnea, Syndrome X, and a thrombotic disorder.

[0188] In certain embodiments, provided herein is a method of treating a liver disorder selected from the group consisting of steatohepatitis, alcoholic liver disease, fatty liver, liver steatosis, liver cirrhosis, liver fibrosis, and acute fatty liver of pregnancy. In some embodiments, the disorder is steatohepatitis. In some embodiments, the steatohepatitis is NASH/MASH. In some embodiments, the disorder is alcoholic liver disease. In some embodiments, the disorder is fatty liver. In some embodiments, the disorder is liver steatosis, liver cirrhosis, or liver fibrosis. In some embodiments, the disorder is acute fatty liver of pregnancy. In some embodiments, the patient is an adult human.

[0189] In certain embodiments, the present disclosure provides a method for treating or preventing aging, Alzheimer's disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, enhancing bile production, enhancing reverse lipid transport, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, modulating C reactive protein, obesity, oxysterol elimination in bile, pancreatitis, pancreatitius, Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, septicemia, metabolic syndrome disorders (e.g., Syndrome X), or a thrombotic disorder.

[0190] In certain embodiments, the disorder is selected from the group consisting of lipodystrophy, lysosomal acid lipase deficiency, and a glycogen storage disease. In some embodiments, the patient is an adult human.

[0191] In certain embodiments, the disorder is selected from the group consisting of hepatitis C, an infection by human immunodeficiency virus, an alpha 1-antitrypsin deficiency, Bassen-Kornzweig syndrome, hypobetalipoproteinemia, Celiac disease, Wilson's disease, and Weber-Christian syndrome. In some embodiments, the disorder is hepatitis B. In some embodiments, the disorder is hepatitis C. In some embodiments, the disorder is an infection by human immunodeficiency virus. In some embodiments, the disorder is an alpha 1-antitrypsin deficiency. In some embodiments, the disorder is Bassen-Kornzweig syndrome. In some embodiments, the disorder is hypobetalipoproteinemia. In some embodiments, the disorder is Celiac disease or Wilson's disease. In some embodiments, the disorder is Weber-Christian syndrome. In some embodiments, the patient is an adult human.

[0192] In certain embodiments, the condition is selected from the group consisting of toxic liver injury, total parenteral nutrition, severe surgical weight loss, environmental toxicity, malnutrition, and starvation. In some embodiments, the condition is toxic liver injury. In some embodiments, the condition is total parenteral nutrition or severe surgical weight loss. In some embodiments, the condition is environmental toxicity. In some embodiments, the condition is malnutrition or starvation. In some embodiments, the patient is an adult human.

[0193] In various embodiments, provided herein are methods of treating NAFLD/MAFLD in a subject in need thereof, the methods generally comprise administering to the subject a therapeutically effect amount of a compound disclosed herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein.

[0194] In various embodiments, provided herein are methods of treating NASH/MASH in a subject in need thereof, the methods generally comprise administering to the subject a therapeutically effect amount of a compound disclosed herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein.

[0195] In various embodiments, provided herein are methods of treating type-2 diabetes in a subject in need thereof, the methods generally comprise administering to the subject a therapeutically effect amount of a compound disclosed herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein.

[0196] In various embodiments, provided herein are methods of treating inflammation in a subject in need thereof, the methods generally comprise administering to the subject a therapeutically effect amount of a compound disclosed herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein.

[0197] In various embodiments, provided herein are methods of treating chronic kidney disease in a subject in need thereof, the methods generally comprise administering to the subject a therapeutically effect amount of a compound disclosed herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a

stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein.

[0198] In various embodiments, provided herein are methods of treating autoimmunity in a subject in need thereof, the methods generally comprise administering to the subject a therapeutically effect amount of a compound disclosed herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein.

[0199] In various embodiments, provided herein are methods of treating cancer (e.g., a liver cancer) in a subject in need thereof, the methods generally comprise administering to the subject a therapeutically effect amount of a compound disclosed herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein.

[0200] In certain embodiments, in order to prolong the effect of a drug, a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, is administered by subcutaneous or intramuscular injection, or by dissolving or suspending the drug in an oil vehicle.

[0201] In certain embodiments, the actual dosage level of a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, in the pharmaceutical compositions of the present disclosure may be varied so as to obtain an amount of the compound (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0202] In certain embodiments, the selected dosage level is dependent upon a variety of factors including the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and

prior medical history of the patient being treated, and like factors well known in the medical arts.

[0203] In certain embodiments, a physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition as required.

[0204] In certain embodiments, a suitable daily dose of a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, will be an amount that corresponds to the lowest dose effective to produce a therapeutic effect. In certain embodiments, when a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, is co-administered with another therapeutic agent, the effective amount may be less than when the compound (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, is used in isolation.

[0205] In certain embodiments, the effective daily dose of a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, may be administered as two, three, four, five, six or more sub-doses. In certain embodiments, the two, three, four, five, six or more sub-doses are administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In some embodiments, dosing is one administration per day. In some embodiments, a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, is administered to a patient for 1 day, 5 days, 10 days, 20 days, 30 days, 1 week, 2 weeks, 3 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 1 year, 2 years, 3 years, 4 years, or 5 years. In some embodiments, a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, is administered to a patient for the duration of the patient's life span.

Combination Therapy

[0206] In various embodiments, a compound disclosed herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, including pharmaceutical compositions of the present disclosure, can be part of a combination therapy. In certain embodiments, the combination therapy comprises a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof; and a second therapeutic agent. In certain embodiments, the combination therapy comprises a pharmaceutical composition comprising an effective amount of a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof; and a second therapeutic agent.

[0207] In some embodiments, the second therapeutic agent is selected from the group comprising a lovastatin, a thiazolidinedione or fibrate, a bile-acid-binding-resin, a niacin, an anti-obesity drug, a hormone, an antiviral agent (e.g., to treat an underlying hepatitis C infection causing liver disease in the patient), an anticancer agent (e.g., to treat hepatocellular carcinoma or other cancer causing liver disease or fatty liver), an antioxidant, a medication that decreases insulin resistance, or a medication that improves lipid metabolism (e.g., treatments for hyperlipidemia), a tyroprostone, a sulfonylurea-based drug, a biguanide, an α -glucosidase inhibitor, an apolipoprotein A-I agonist, apolipoprotein E, a cardiovascular drug, an HDL-raising drug, an HDL enhancer, or a regulator of the apolipoprotein A-I, apolipoprotein A-IV and/or apolipoprotein genes.

[0208] In various embodiments, the second therapeutic agent can be bempedoic acid, a statin and/or ezetimibe.

[0209] In certain embodiments, the second therapeutic agent is bempedoic acid. In certain embodiments, the second therapeutic agent is ezetimibe. In certain embodiments, the second therapeutic agent is a statin. Examples of statins include, but are not limited to, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

[0210] In certain embodiments, administering a pharmaceutical composition of the present disclosure comprising a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, and a second therapeutic agent is intended to provide a beneficial effect from the co-action of the compound (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a

stereoisomer and/or a pharmaceutically acceptable salt thereof, and the second therapeutic agent. In some embodiments, the beneficial effect of the combination therapy may include pharmacokinetic or pharmacodynamic co-action resulting from the combination of the compound (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, and the second therapeutic agent.

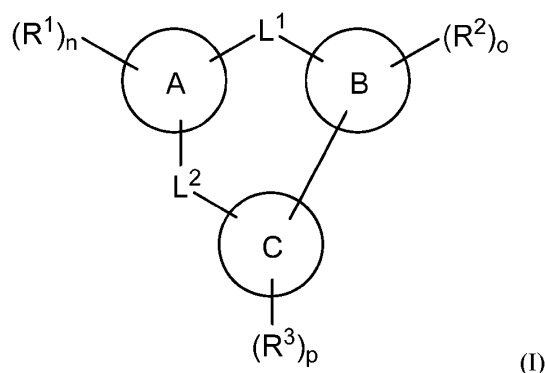
Kits

[0211] In various embodiments, the disclosure provides kits for treating a condition, disease or disorder described herein. In some embodiments, a kit comprises: i) instructions for treating a condition, disease or disorder, for example, as described herein, and ii) a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof (e.g., a pharmaceutical composition comprising an effective amount of a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof). In some embodiments, the kit may comprise one or more unit dosage forms containing an amount of a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof, that is effective for treating the condition, disease, or disorder.

[0212] The description herein includes multiple aspects and embodiments of the present disclosure, including methods of making a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof; methods of using a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof; compositions comprising an effective amount of a compound described herein (e.g., a compound of formula (I), formula (Ia), formula (Ib), formula (Ic), formula (Id) or formula (Ie)), or a stereoisomer and/or a pharmaceutically acceptable salt thereof; and kits. The disclosure specifically includes all combinations and permutations of the aspects and embodiments as described herein.

Enumerated Embodiments

1. A compound of formula (I)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl or 9-membered bicyclic heteroaryl;

Ring B is phenyl or 5-6 membered heteroaryl;

Ring C is selected from the group consisting of phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, and 5-6 membered heteroaryl;

R^1 is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^2 is independently, for each occurrence, selected from the group consisting of halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkoxy, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from R^{2A} , or

optionally two R^2 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl, a 9-membered bicyclic heterocyclyl, or a 9-membered bicyclic heteroaryl;

R^3 is independently, for each occurrence, selected from the group consisting of cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and $-C(O)N(R^A)(R^B)$, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkoxy;

L^1 is $^*-S(O)_2N(R^C)-^{**}$, wherein * denotes the point of attachment to Ring A and ** denotes the point of attachment to Ring B;

L^2 is selected from the group consisting of $\#-C(O)O-\#\#$, $\#-C(O)-(C_{1-6}alkyl)-\#\#$, $\#-C(O)O-(C_{1-6}alkyl)-\#\#$, $\#-C(O)O-(C_{1-6}alkyl)-O-\#\#$, $\#-C(O)O-(C_{1-6}haloalkyl)-\#\#$, and $C_{1-6}alkyl$,

wherein # denotes the point of attachment to Ring A and ## denotes the point of attachment to Ring C;

R^{2A} is halogen or C_{1-6} alkoxy;

R^A is hydrogen or C_{1-6} alkyl;

R^B is hydrogen or C_{1-6} alkyl;

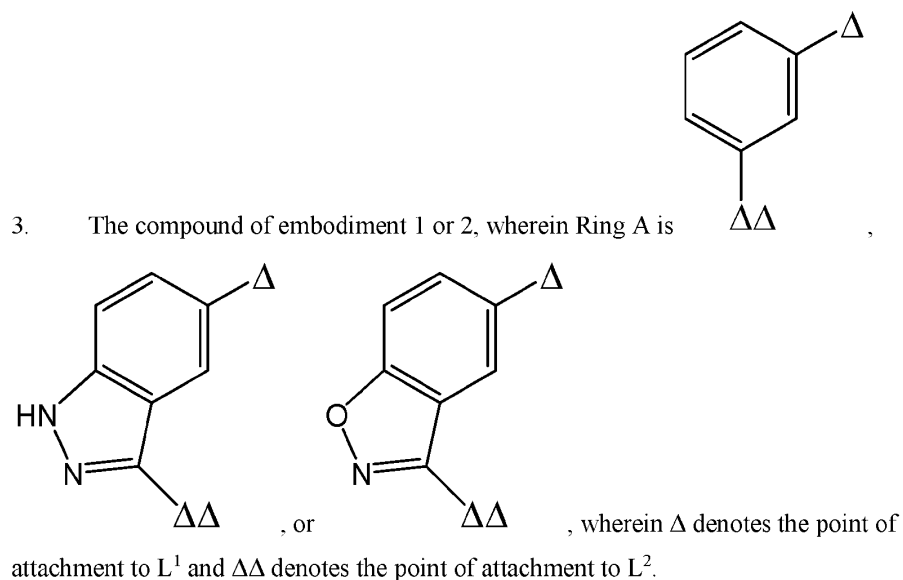
R^C is hydrogen or C_{1-3} alkyl;

n is 2 or 3;

o is 0, 1, or 2; and

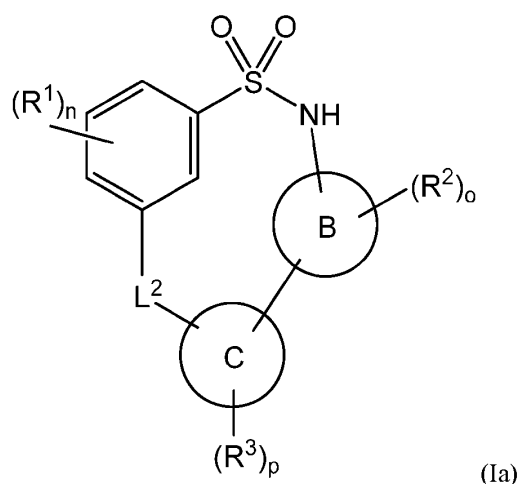
p is 0, 1, or 2.

2. The compound of embodiment 1, wherein Ring A is phenyl, indazolyl, or benzo[d]isoxazolyl.



4. The compound of any one of embodiments 1-3, wherein L^1 is $^*-S(O)_2N(H)-^{**}$, wherein * denotes the point of attachment to Ring A and ** denotes the point of attachment to Ring B.

5. A compound of formula (Ia)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring B is phenyl or 5-6 membered heteroaryl;

Ring C is selected from the group consisting of phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, and 5-6 membered heteroaryl;

R^1 is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^2 is independently, for each occurrence, selected from the group consisting of halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkoxy, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from R^{2A} ; or

optionally two R^2 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl, a 9-membered bicyclic heterocyclyl, or a 9-membered bicyclic heteroaryl;

R^3 is independently, for each occurrence, selected from the group consisting of cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and $-C(O)N(R^A)(R^B)$, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkoxy;

L^2 is selected from the group consisting of $\#-C(O)O-##$, $\#-C(O)-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-O-##$, $\#-C(O)O-(C_{1-6}haloalkyl)-##$, and $C_{1-6}alkyl$, wherein # denotes the point of attachment to Ring A and ## denotes the point of attachment to Ring C;

R^{2A} is halogen or C_{1-6} alkoxy;

R^A is hydrogen or C_{1-6} alkyl;

R^B is hydrogen or C_{1-6} alkyl;

n is 2 or 3;

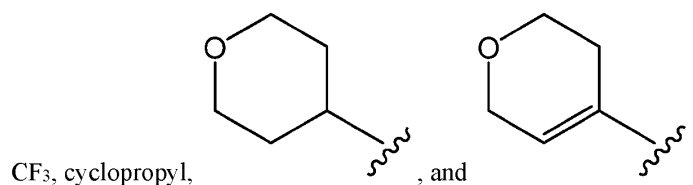
o is 1 or 2; and

p is 0, 1, or 2.

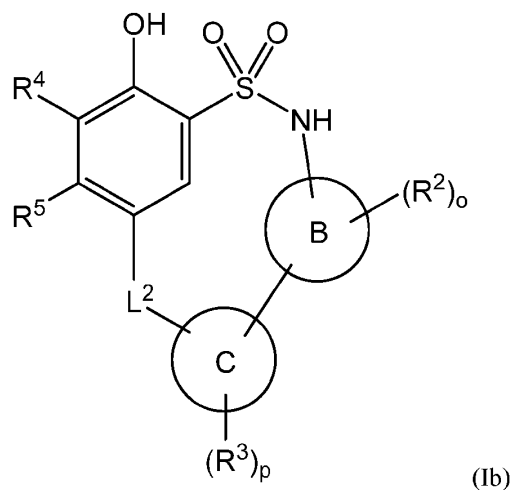
6. The compound of any one of embodiments 1-5, wherein n is 2.

7. The compound of any one of embodiments 1-5, wherein n is 3.

8. The compound of any one of embodiments 1-7, wherein R^1 is, independently, for each occurrence, selected from the group consisting of bromo, chloro, fluoro, hydroxyl, $-CH_3$, -



9. A compound of formula (Ib)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring B is phenyl or 5-6 membered heteroaryl;

Ring C is phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, C_{3-6} cycloalkyl, or 5-6 membered heteroaryl;

R^2 is independently, for each occurrence, selected from the group consisting of halogen, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkoxy, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from R^{2A} ; or

optionally two R^2 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl, a 9-membered bicyclic heterocyclyl, or a 9-membered bicyclic heteroaryl;

R^3 is independently, for each occurrence, selected from the group consisting of cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and $-C(O)N(R^A)(R^B)$, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkoxy;

R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^5 is hydrogen or halogen;

L^2 is selected from the group consisting of $\#-C(O)O-\##$, $\#-C(O)-(C_{1-6}alkyl)-\##$, $\#-C(O)O-(C_{1-6}alkyl)-\##$, $\#-C(O)O-(C_{1-6}alkyl)-O-\##$, $\#-C(O)O-(C_{1-6}haloalkyl)-\##$, and $C_{1-6}alkyl$, wherein $\#$ denotes the point of attachment to Ring A and $\##$ denotes the point of attachment to Ring C;

R^{2A} is halogen or C_{1-6} alkoxy;

R^A is hydrogen or $C_{1-6}alkyl$;

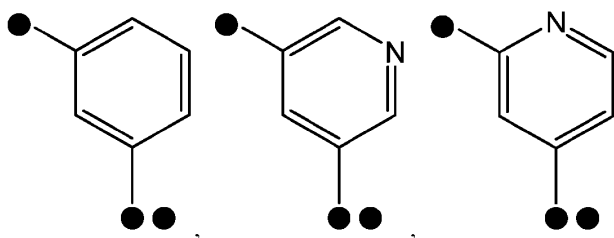
R^B is hydrogen or $C_{1-6}alkyl$;

o is 1 or 2; and

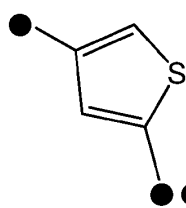
p is 0, 1, or 2.

10. The compound of any one of embodiments 1-9, wherein Ring B is phenyl, thiophenyl, or pyridinyl.

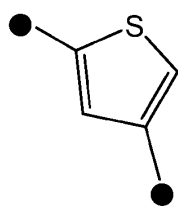
11. The compound of any one of embodiments 1-10, wherein Ring B is selected from



the group consisting of



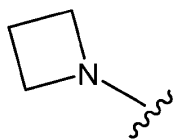
, and



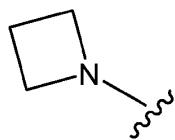
,

wherein • denotes the point of attachment to L^1 and •• denotes the point of attachment to Ring C.

12. The compound of any one of embodiments 1-11, wherein o is 1.
13. The compound of any one of embodiments 1-11, wherein o is 2.
14. The compound of any one of embodiments 1-13, wherein R^2 is, independently, for each occurrence, selected from the group consisting of chloro, fluoro, cyano, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CH}_2\text{CH}_3$, $-\text{O}-\text{CHF}_2$, $-\text{O}-\text{CF}_3$, cyclopropyl, $-\text{O}-\text{cyclopropyl}$, morpholinyl, and

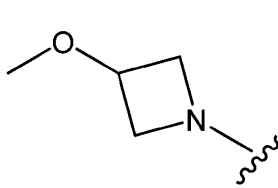


, wherein

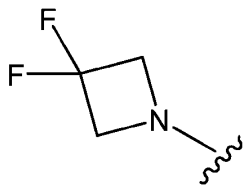


is optionally substituted with one or more substituents independently selected from fluoro and $-\text{O}-\text{CH}_3$.

15. The compound of any one of embodiments 1-14, wherein R^2 is, independently, for each occurrence, selected from the group consisting of chloro, fluoro, cyano, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CH}_2\text{CH}_3$, $-\text{O}-\text{CHF}_2$, $-\text{O}-\text{CF}_3$, cyclopropyl, $-\text{O}-\text{cyclopropyl}$, morpholinyl,



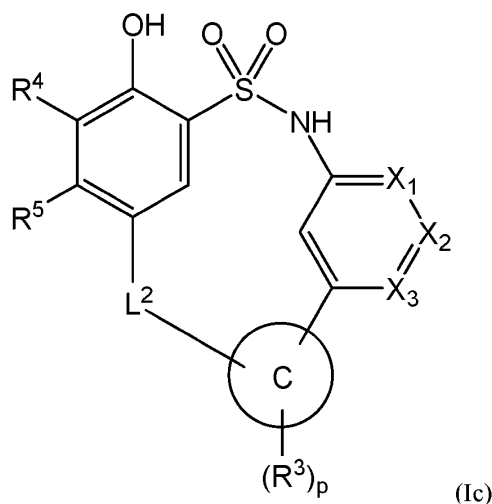
, and



16. The compound of any one of embodiments 1-11 and 13, wherein two R^2 groups on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 5 membered carbocyclyl, a 5-membered heterocyclyl, or a 5-membered heteroaryl.

17. The compound of any one of embodiments 1-11, wherein o is 0.

18. A compound of formula (Ic)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring C is selected from the group consisting of phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, and 5-6 membered heteroaryl;

R^3 is independently, for each occurrence, selected from the group consisting of cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and $-C(O)N(R^A)(R^B)$, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkoxy;

R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^5 is hydrogen or halogen;

X_1 is CR^6 or N;

X_2 is CR^7 or N;

X_3 is CR^8 or N;

R^6 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from halogen;

R^7 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with C_{1-6} alkoxy; or

R^6 and R^7 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic heteroaryl or a 9-membered bicyclic heterocyclyl;

R^8 is hydrogen or halogen; or

R^7 and R^8 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl;

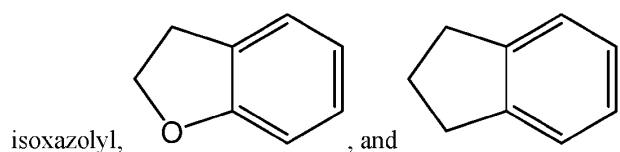
L^2 is selected from the group consisting of $\#-C(O)O-##$, $\#-C(O)-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-O-##$, $\#-C(O)O-(C_{1-6}haloalkyl)-##$, and $C_{1-6}alkyl$, wherein # denotes the point of attachment to Ring A and ## denotes the point of attachment to Ring C;

R^A is hydrogen or $C_{1-6}alkyl$;

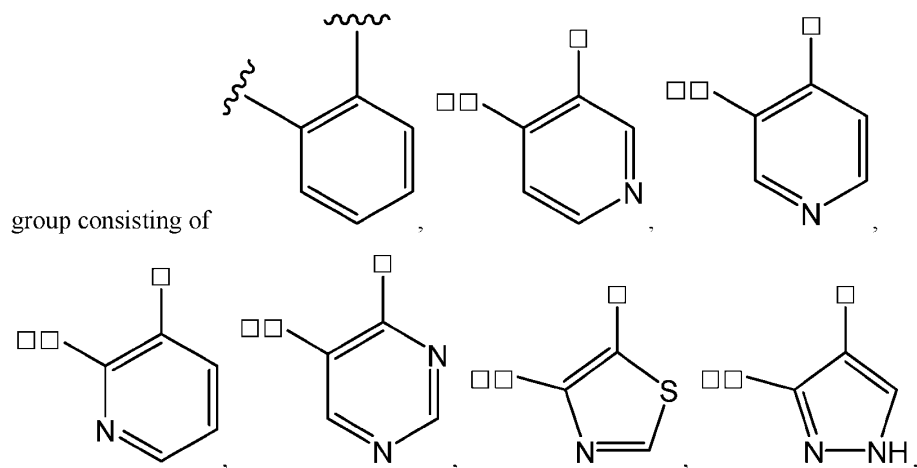
R^B is hydrogen or $C_{1-6}alkyl$; and

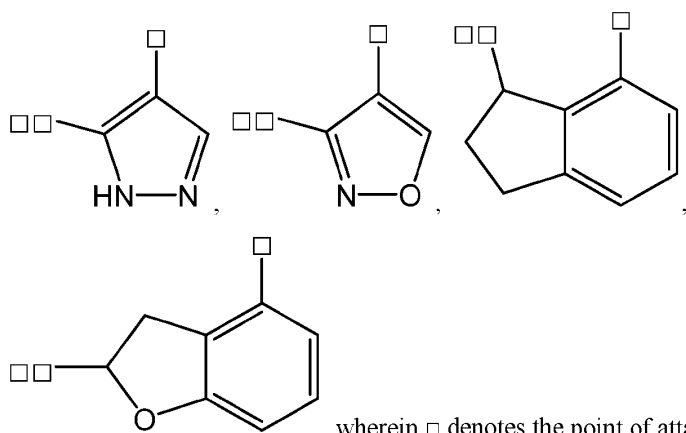
p is 0, 1, or 2.

19. The compound of any one of embodiments 1-18, wherein Ring C is selected from the group consisting of cyclopropyl, phenyl, pyridinyl, thiazolyl, pyrimidinyl, pyrazolyl,



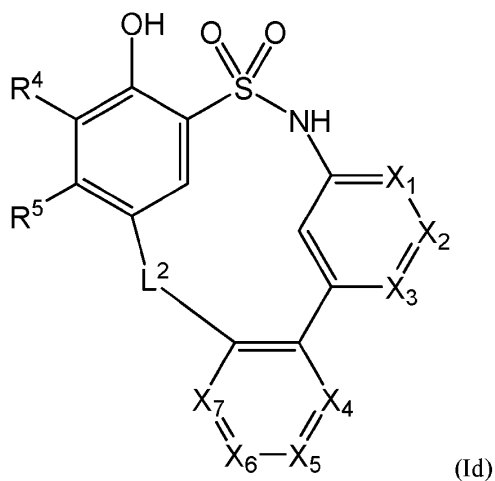
20. The compound of any one of embodiments 1-19, wherein Ring C is selected from the





, wherein □ denotes the point of attachment to Ring B and □□ denotes the point of attachment to L².

21. The compound of any one of embodiments 1-20, wherein p is 1.
22. The compound of any one of embodiments 1-20, wherein p is 2.
23. The compound of any one of embodiments 1-22, wherein R³ is, independently, for each occurrence, selected from the group consisting of cyano, bromo, fluoro, -CH₃, -CHF₂, -CF₃, -O-CH₃, -O-CHF₂, -CH₂CH₂-O-CH₃, -C(O)NH₂, and -CH₂CHF₂.
24. The compound of any one of embodiments 1-20, wherein p is 0.
25. A compound of formula (Id)



(Id)

or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^5 is hydrogen or halogen;

X_1 is CR^6 or N;

X_2 is CR^7 or N;

X_3 is CR^8 or N;

X_4 is CH or N;

X_5 is CR^9 or N;

X_6 is CR^{10} or N;

X_7 is CR^{11} or N;

R^6 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from halogen;

R^7 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with C_{1-6} alkoxy; or

R^6 and R^7 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic heteroaryl or a 9-membered bicyclic heterocyclyl;

R^8 is hydrogen or halogen; or

R^7 and R^8 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl;

R^9 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} haloalkyl, $-C(O)N(R^A)(R^B)$, and C_{1-6} alkoxy;

R^{10} is selected from the group consisting of hydrogen, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and C_{1-6} alkoxy;

R^{11} is hydrogen, halogen, or C_{1-6} alkyl; and

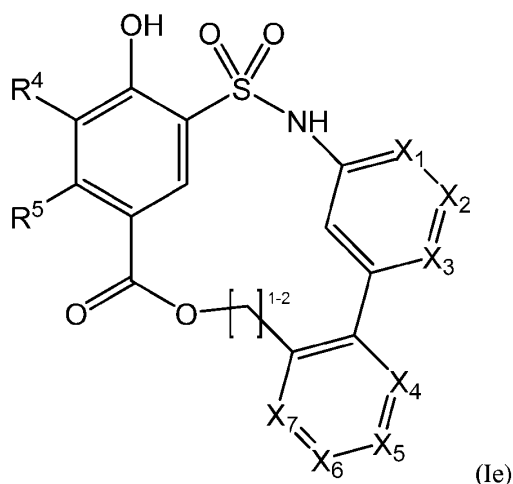
L^2 is selected from the group consisting of $\#-C(O)O-##$, $\#-C(O)-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-O-##$, $\#-C(O)O-(C_{1-6}haloalkyl)-##$, and $C_{1-6}alkyl$, wherein # denotes the point of attachment to Ring A and ## denotes the point of attachment to Ring C;

R^A is hydrogen or $C_{1-6}alkyl$; and

R^B is hydrogen or $C_{1-6}alkyl$.

26. The compound of any one of embodiments 1-25, wherein L^2 is selected from the group consisting of $\#-C(O)O-\#$, $\#-C(O)O-CH_2-\#$, $\#-C(O)O-C(CH_3)(H)-\#$, $\#-C(O)O-C(CH_2F)(H)-\#$, $\#-C(O)O-(CH_2)_2-\#$, $\#-C(O)O-(CH_2)_2-O-\#$, $-(CH_2)_2-$, $-(CH_2)_3-$, and $\#-C(O)-(CH_2)_3-\#$, wherein # denotes the point of attachment to Ring A and ## denotes the point of attachment to Ring C.

27. A compound of formula (Ie)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^5 is hydrogen or halogen;

X_1 is CR^6 or N;

X_2 is CR^7 or N;

X_3 is CR^8 or N;

X_4 is CH or N;

X_5 is CR^9 or N;

X_6 is CR^{10} or N;

X_7 is CR^{11} or N;

R^6 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6

membered heterocyclyl is optionally substituted with one or more substituents independently selected from halogen;

R^7 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with C_{1-6} alkoxy; or

R^6 and R^7 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic heteroaryl or a 9-membered bicyclic heterocyclyl;

R^8 is hydrogen or halogen; or

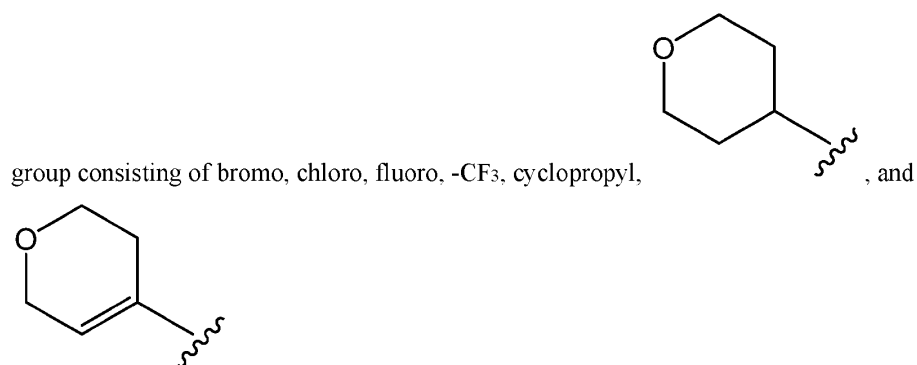
R^7 and R^8 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl;

R^9 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} haloalkyl, $-C(O)N(R^A)(R^B)$, and C_{1-6} alkoxy;

R^{10} is selected from the group consisting of hydrogen, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and C_{1-6} alkoxy; and

R^{11} is hydrogen, halogen, or C_{1-6} alkyl.

28. The compound of any one of embodiments 9-27, wherein R^4 is selected from the



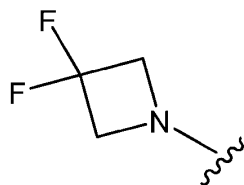
29. The compound of any one of embodiments 9-28, wherein R^5 is hydrogen or fluoro.

30. The compound of any one of embodiments 18-29, wherein X_1 is CR^6 , X_2 is CR^7 , and X_3 is CR^8 .

31. The compound of any one of embodiments 18-29, wherein X_1 is CR^6 , X_2 is N, and X_3 is CR^8 .

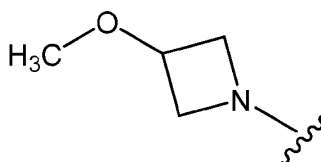
32. The compound of any one of embodiments 18-29, wherein X_1 is N, X_2 is CR^7 , and X_3 is CR^8 .

33. The compound of any one of embodiments 18-31, wherein R^6 is selected from the group consisting of hydrogen, cyano, chloro, fluoro, $-CF_3$, $-O-CH_3$, $-O-CH_2-CH_3$, $-O-CHF_2$, -



$-O-CF_3$, cyclopropyl, and

34. The compound of any one of embodiments 18-30 and 32, wherein R^7 is selected from the group consisting of hydrogen, cyano, chloro, fluoro, $-CH_3$, $-CF_3$, cyclopropyl, $-O-$



cyclopropyl, morpholinyl, and

35. The compound of any one of embodiments 18-34, wherein R^8 is hydrogen or fluoro.

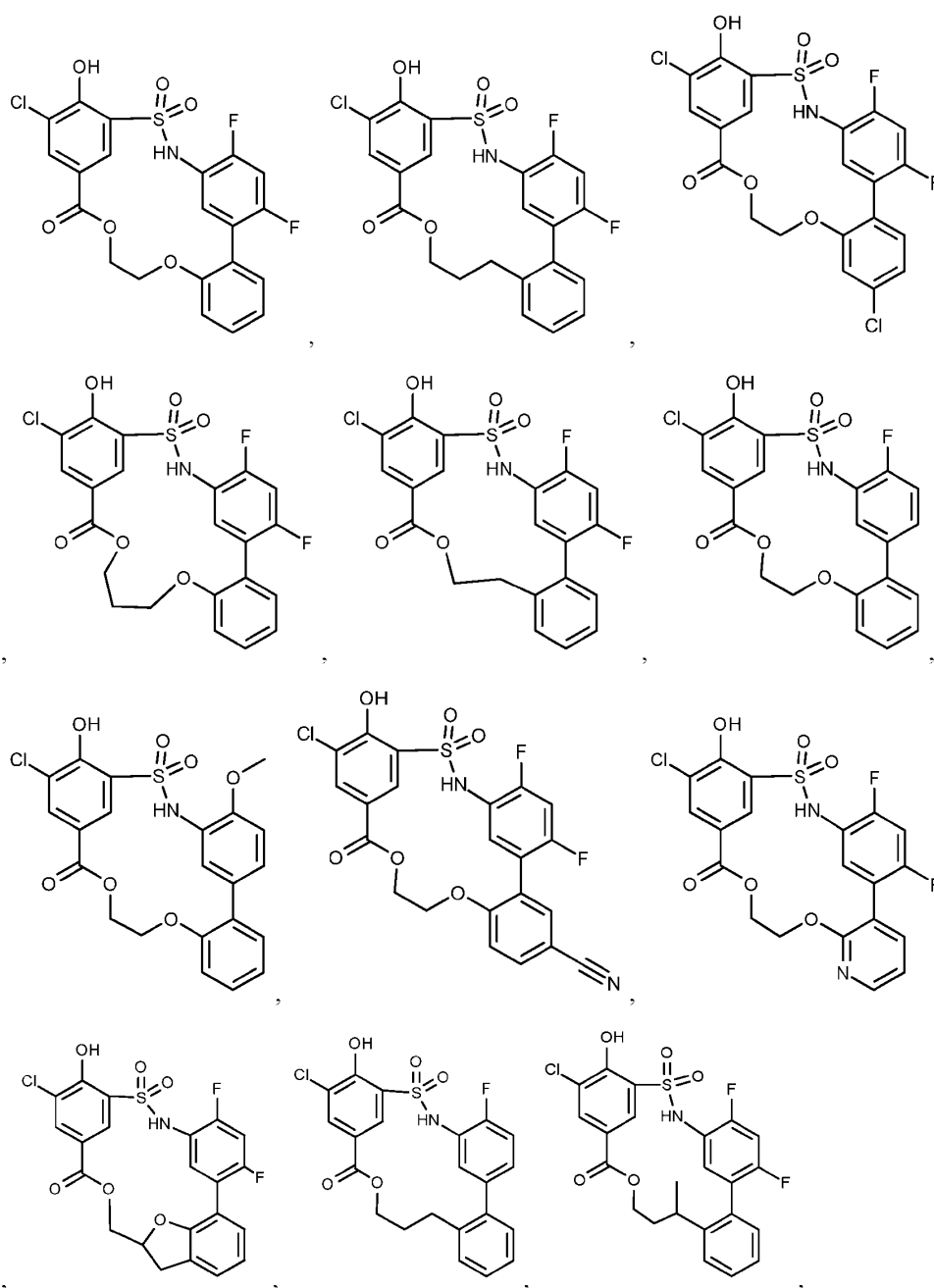
36. The compound of any one of embodiments 18-30, wherein R^6 and R^7 are taken together, along with the atoms to which they are attached, to form a 5 membered heteroaryl or a 5 membered heterocyclyl.

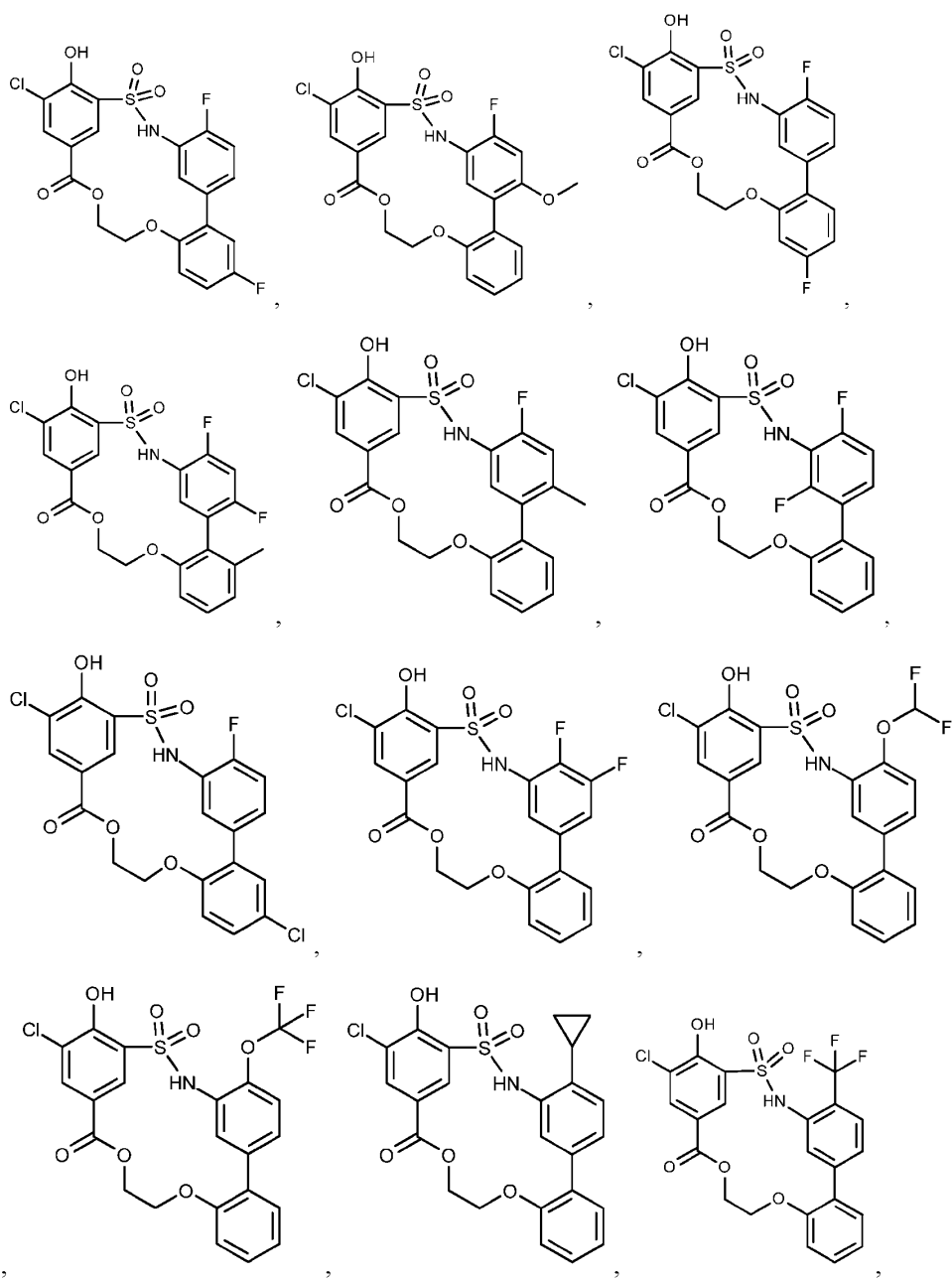
37. The compound of any one of embodiments 18-30, wherein R^7 and R^8 may be taken together, along with the atoms to which they are attached, to form a 5-6 membered carbocyclyl.

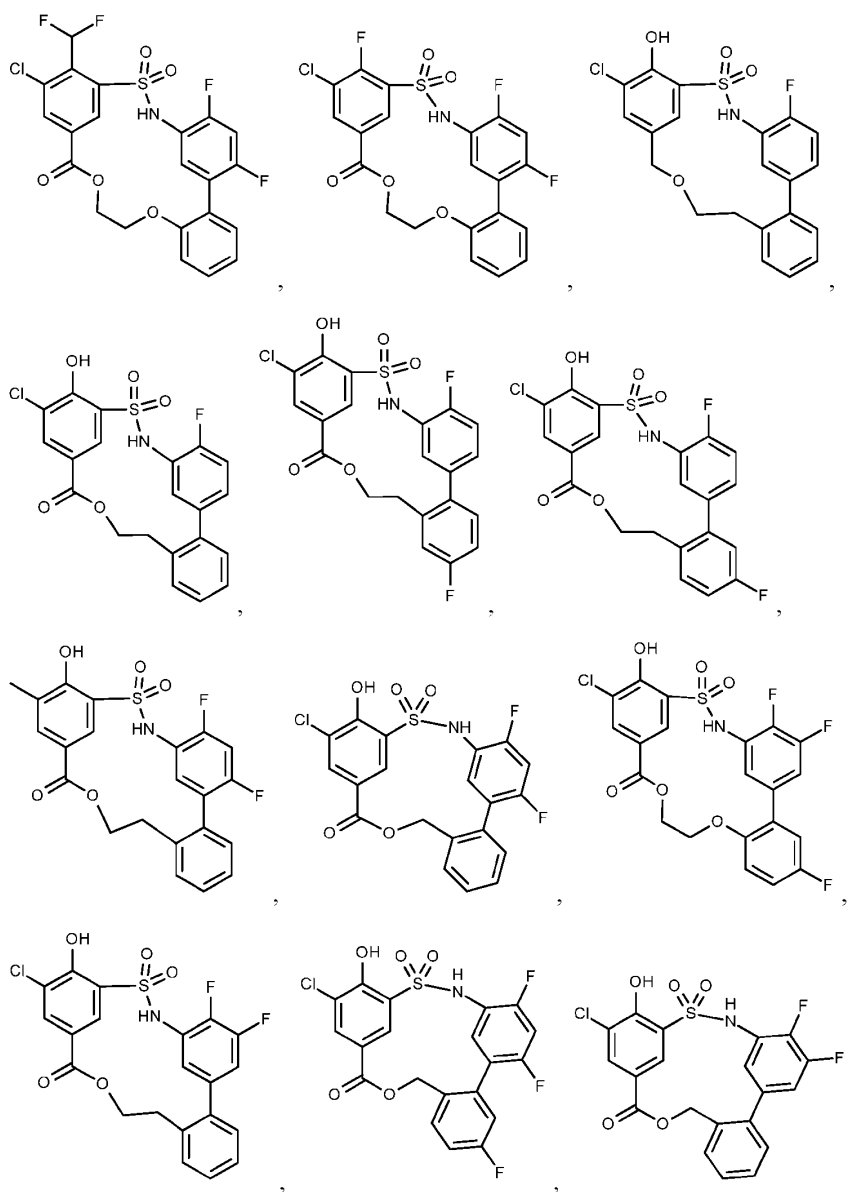
38. The compound of any one of embodiments 25-37, wherein X_4 is CH, X_5 is CR^9 , X_6 is CR^{10} , and X_7 is CR^{11} .

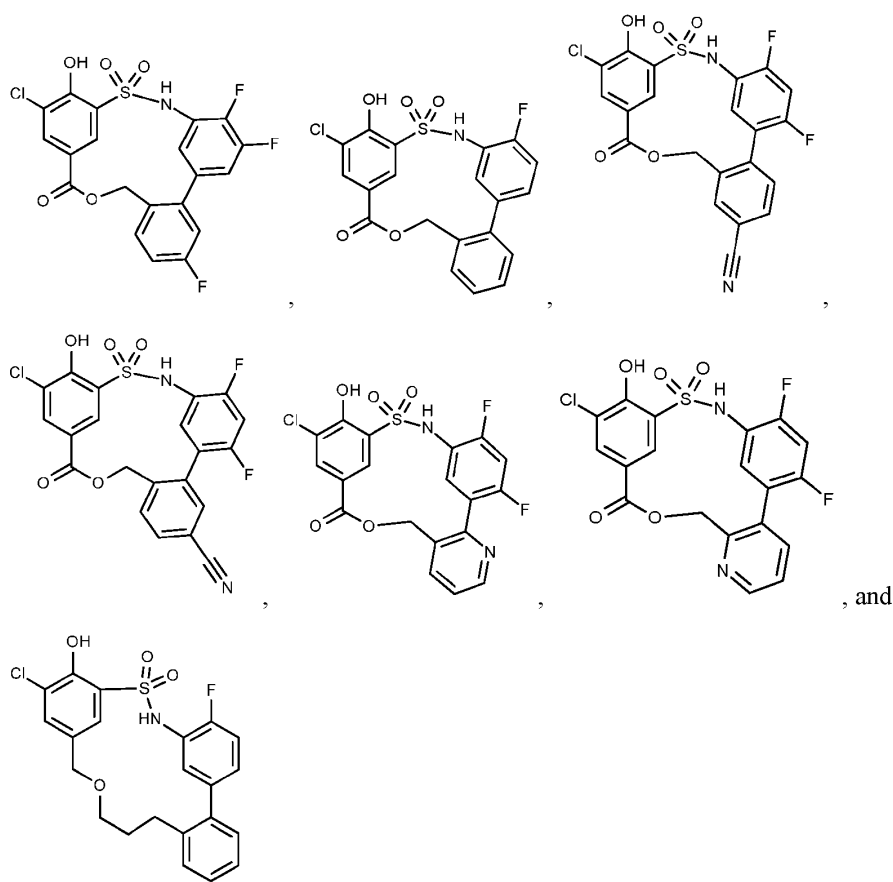
39. The compound of any one of embodiments 25-37, wherein X_4 is CH, X_5 is N, X_6 is CR^{10} , and X_7 is CR^{11} .

40. The compound of any one of embodiments 25-37, wherein X_4 is CH, X_5 is CR^9 , X_6 is N, and X_7 is CR^{11} .
41. The compound of any one of embodiments 25-37, wherein X_4 is CH, X_5 is CR^9 , X_6 is CR^{10} , and X_7 is N.
42. The compound of any one of embodiments 25-37, wherein X_4 is N, X_5 is CR^9 , X_6 is N, and X_7 is CR^{11} .
43. The compound of any one of embodiments 25-38 and 40-42, wherein R^9 is selected from the group consisting of hydrogen, cyano, bromo, fluoro, $-CF_3$, $-O-CH_3$, and $-C(O)NH_2$.
44. The compound of any one of embodiments 25-39 and 41, wherein R^{10} is selected from the group consisting of hydrogen, fluoro, $-CHF_2$, $-CF_3$, $-O-CH_3$, and $-O-CHF_2$.
45. The compound of any one of embodiments 25-40 and 42, wherein R^{11} is hydrogen, fluoro, or CH_3 .
46. The compound of any one of embodiments 1-42, wherein the compound of formula (I) is not a compound selected from the group consisting of:









47. A compound selected from any compound set forth in Table 1, or a pharmaceutically acceptable salt thereof.
48. A pharmaceutical composition comprising a compound of any one of embodiments 1-47; and a pharmaceutically acceptable carrier.
49. A method of inhibiting ACLY in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-47 or a pharmaceutical composition of embodiment 48.
50. The method of embodiment 49, wherein the subject has a liver condition, disease, or disorder.

51. The method of embodiment 49, wherein the liver condition, disease, or disorder is NAFLD or NASH.
52. The method of embodiment 49, wherein the subject has type-2 diabetes.
53. The method of embodiment 49, wherein the subject has inflammation.
54. The method of embodiment 49, wherein the subject has chronic kidney disease.
55. The method of embodiment 49, wherein the subject has autoimmunity.
56. The method of embodiment 49, wherein the subject has cancer.
57. A method of treating NAFLD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-47 or a pharmaceutical composition of embodiment 48.
58. A method of treating NASH in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-47 or a pharmaceutical composition of embodiment 48.
59. A method of treating type-2 diabetes in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-47 or a pharmaceutical composition of embodiment 48.
60. A method of treating inflammation in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-47 or a pharmaceutical composition of embodiment 48.
61. A method of treating chronic kidney disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-47 or a pharmaceutical composition of embodiment 48.

62. A method of treating autoimmunity in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-47 or a pharmaceutical composition of embodiment 48.

63. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-47 or a pharmaceutical composition of embodiment 48.

64. A method of treating a condition, disease, or disorder as described herein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of embodiments 1-47 or of the pharmaceutical composition of embodiment 48.

EXAMPLES

[0213] The representative examples that follow are intended to help illustrate the disclosure, and are not intended to, nor should they be construed to, limit the scope of the disclosure.

[0214] The compounds provided herein can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimal reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization.

[0215] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

[0216] The compounds provided herein may be isolated and purified by known standard procedures. Such procedures include recrystallization, filtration, flash chromatography, trituration, high pressure liquid chromatography (HPLC), or supercritical fluid chromatography (SFC). Note that flash chromatography may either be performed manually or

via an automated system. The compounds provided herein may be characterized by known standard procedures, such as nuclear magnetic resonance spectroscopy (NMR) or liquid chromatography mass spectrometry (LCMS). NMR chemical shifts are reported in part per million (ppm) and are generated using methods well known to those of skill in the art.

Analytical Methods

[0217] Method A: UHPLC-MS were performed in reverse phase using a Phenomenex Kinetex-XB C18 column (2.1 mm × 100 mm, 1.7 μm; temperature: 40 °C), with an injection volume of 1 μL at a flow rate of 0.6 mL/min and a gradient of 5 – 100% B over 5.30 min, then 100% B for 0.50 min, where A = 0.1% formic acid in water, and B = 0.1% formic acid in acetonitrile. A second gradient of 100 – 5% B was then applied over 0.02 min and held for 1.18 min. UV spectra were recorded at 215 nm; spectrum range: 200 – 400 nm. ELS data was collected on a Waters ELS detector when reported. Mass spectra were obtained using a Waters SQD, SQD2 or a QDA detector; ionization mode: electrospray positive or negative. Data were integrated and reported using Waters MassLynx and OpenLynx software.

[0218] Method B: UHPLC-MS were performed in reverse phase using a Waters UPLC BEH C18 column (2.1 mm × 100 mm, 1.7 μm; temperature: 55 °C), with an injection volume of 1 μL and at a flow rate of 0.6 mL/min and a gradient of 5 – 100% B over 5.30 min, then 100% B for 0.50 min, where A = 2 mM ammonium bicarbonate in water, buffered to pH 10, and B = acetonitrile. A second gradient of 100 – 5% B was then applied over 0.02 min and held for 1.18 min. UV spectra were recorded at 215 nm; spectrum range: 200 – 400 nm. Mass spectra were obtained using a Waters Quattro Premier XE, QDa or aSQD2; ionization mode: electrospray positive or negative. Data were integrated and reported using Waters MassLynx and OpenLynx software.

[0219] Method C: UHPLC-MS were performed in reverse phase using a Waters UPLC CORTECS C8 column (2.1 mm × 100 mm, 1.6 μm; temperature: 40 °C), with an injection volume of 1 μL at a flow rate of 0.6 mL/min and a gradient of 5 – 100% B over 5.30 min, then 100% B for 0.50 min, where A = 0.1% formic acid in water, and B = 0.1% formic acid in acetonitrile. A second gradient of 100 – 5% B was then applied over 0.02 min and held for 1.18 min. UV spectra were recorded at 215 nm; spectrum range: 200 – 400 nm. ELS data was collected using a Waters ELS detector when reported. Mass spectra were obtained using a Waters SQD, SQD2 or a QDa; ionization mode: electrospray positive or negative. Data were integrated and reported using Waters MassLynx and OpenLynx software.

[0220] Method D: UHPLC-MS were performed in reverse phase system using a Waters UPLC BEH C18 column (2.1 mm × 50 mm, 1.7 μm; temperature: 40 °C), with an injection volume of 1 μL at a flow rate of 0.9 mL/min and a gradient of 5 – 100% B over 1.10 min, then 100% B for 0.25 min, where A = 0.1% formic acid in water, and B = 0.1% formic acid in acetonitrile. A second gradient of 100 – 5% B was then applied over 0.05 min and held for 0.10 min. UV spectra were recorded at 215 nm; spectrum range: 200 – 400 nm. Mass spectra were obtained using a Waters SQD, SQD2 or a QDA detector; ionization mode: electrospray positive or negative. Data were integrated and reported using Waters MassLynx and OpenLynx software.

[0221] Method E: UHPLC-MS were performed in reverse phase using a Phenomenex Kinetex Evo C18 column (2.1 mm × 50 mm, 1.7 μm; temperature 40 °C), with an injection volume of 1 μL at a flow rate of 1.0 mL/min and a gradient of 1 – 100% B over 1.10 min, then 100% B for 0.25 min, where A = water + 0.2% ammonium hydroxide and B = acetonitrile. A second gradient of 100 – 1% B was then applied over 0.05 min and held for 0.40 min. UV spectra were recorded at 215 nm; spectrum range: 200 – 400 nm. Mass spectra were obtained using a Waters QDa or a SQD2; ionization mode: electrospray positive or negative. Data were integrated and reported using Waters MassLynx and OpenLynx software.

[0222] Method F: Analytical (MET/UPLC/1906) (M12) UHPLC-MS were performed in reverse phase using a Waters UPLC CORTECS C8 column (2.1 mm × 50 mm, 1.6 μm; temperature: 40 °C), with an injection volume of 1 μL at a flow rate of 0.9 mL/min and a gradient of 5 – 100% B over 1.10 min, then 100% B for 0.30 min, where A = 0.1% formic acid in water, and B = 0.1% formic acid in acetonitrile. A second gradient of 100 – 5% B was then applied over 0.02 min and held for 0.28 min. UV spectra were recorded at 215 nm; spectrum range: 200 – 400 nm. ELS data was collected using a Waters ELS detector when reported. Mass spectra were obtained using a Waters SQD2 or a QDa; ionization mode: electrospray positive or negative. Data were integrated and reported using Waters MassLynx and OpenLynx software.

Preparative HPLC Methods

[0223] Method P1: LC were performed in reverse phase using a Waters Sunfire™ C18 column (30 mm × 100 mm, 5 μm; temperature: room temperature), with an injection volume of 1500 μL at a flow rate of 40 mL/min at 30% B for 1.90 min then a gradient of 30 – 95% B over 9.60 min and held for 1.97 min, where A = 0.1% formic acid in water and B = 0.1%

formic acid in acetonitrile. A second gradient of 95 – 30% B was then applied over 0.33 min and held for 1.65 min. UV spectra were recorded at 215 nm.

[0224] Method P2: LC were performed in reverse phase using a Waters Sunfire™ C18 column (30 mm × 100 mm, 5 µm; temperature: room temperature), with an injection volume of 1500 µL at a flow rate of 40 mL/min at 10% B for 1.90 min then a gradient of 10 – 95% B over 14.10 min and held for 2.0 min, where A = 0.1% formic acid in water and B = 0.1% formic acid in acetonitrile. A second gradient of 95 – 10% B was then applied over 0.20 min and held for a further 1.25 min. UV spectra were recorded at 215 nm.

[0225] Method P3: LC were performed in reverse phase using a Waters XBridge™ C18 column (30 mm × 100 mm, 5 µm; temperature: room temperature), with an injection volume of 1500 µL at a flow rate of 40 mL/min at 10% B for 2.00 min then a gradient of 10 – 95% B over 14.00 min and held for 2.00 min, where A = 0.2% ammonium hydroxide in water and B = 0.2% ammonium hydroxide in acetonitrile. A second gradient of 95 – 10% B was then applied over 0.20 min and held for 1.25 min. UV spectra were recorded at 215 nm.

Abbreviations

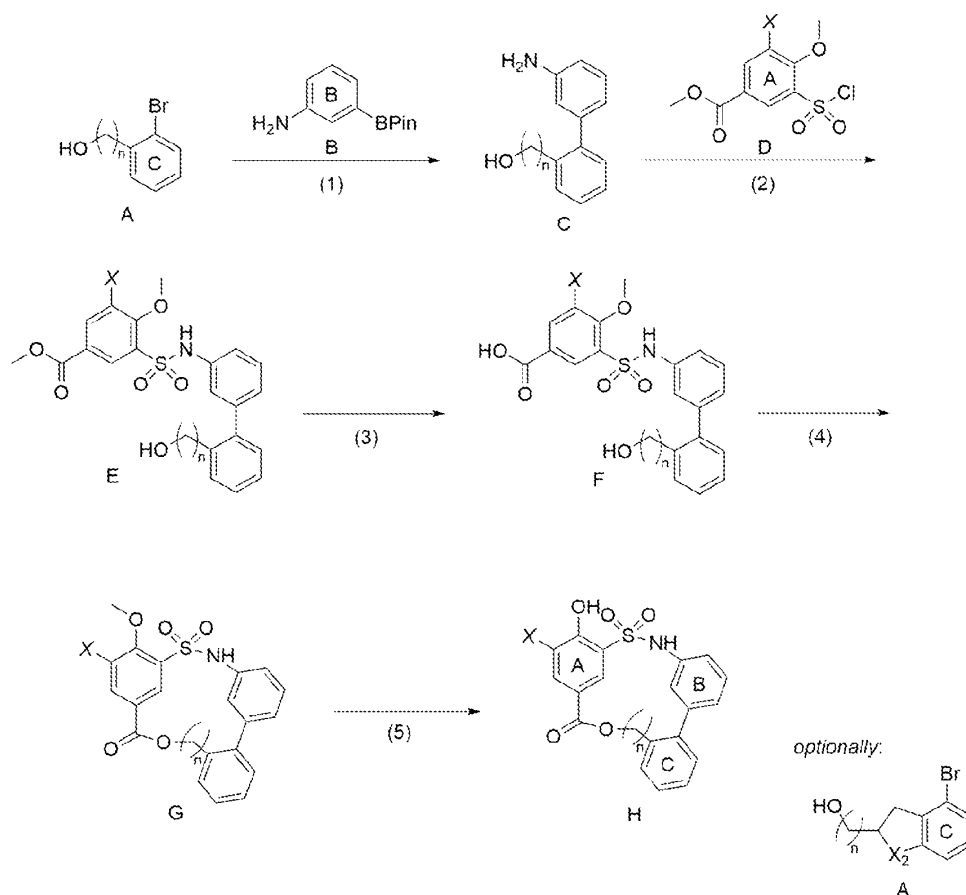
aq.	aqueous
BF ₃ etherate	boron trifluoride diethyl etherate
BSA	bovine serum albumin
CDCl ₃	deuterated chloroform
CHCl ₃	chloroform
CO ₂	carbon dioxide
conc.	concentrated
CV	column volumes
DAST	diethylaminosulfur trifluoride
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DCDMH	1,3-dichloro-5,5-dimethyl dantoin
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide

DPPA	diphenylphosphoryl azide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTT	dithiothreitol
ESI	electrospray ionization
Et ₂ O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
FBS	fetal bovine serum
FCC	flash column chromatography
HCl	hydrogen chloride
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HG2	Hoveyda-Grubbs Catalyst®, 2 nd generation
H ₂ O	water
HPLC	high-performance liquid chromatography
IPA	isopropanol
K ₂ CO ₃	potassium carbonate
LCMS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar
mCPBA	metachloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
MeMgBr	methylmagnesium bromide
MgSO ₄	magnesium sulfate
N ₂	nitrogen
NaBH ₄	sodium borohydride
NaHCO ₃	sodium bicarbonate
Na ₂ CO ₃	sodium carbonate
Na ₂ SO ₄	sodium sulfate
Na ₂ S ₂ O ₃	sodium thiosulfate
NBS	<i>N</i> -bromosuccinimide
NH ₄ Cl	ammonium hydrochloride
NMI	1-methyl-1 <i>H</i> -imidazole

NMR	nuclear magnetic resonance
org	organic
PBS	phosphate-buffered saline
Pd	palladium
Pd/C	palladium on carbon
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
Pd(dppf)Cl ₂	1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Pt	platinum
rpm	revolutions per minute
RM	reaction mixture
RT	retention time
r.t.	room temperature
sat.	saturated
SCX	strong cation exchange cartridge (benzenesulfonic acid-functionalized silica)
SFC	supercritical fluid chromatography
SiO ₂	silicon dioxide (silica gel for FCC)
TBDMSCl	<i>tert</i> -butyldimethylsilyl chloride
TBME	<i>tert</i> -butyl methyl ether
TCFH	<i>N</i> -[chloro(dimethylamino)methylidene]- <i>N</i> -methylmethanaminium hexafluorophosphate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
wt%	weight percent

[0226] In some embodiments, compounds of the disclosure may be synthesized using the procedure outlined in General Scheme 1:

General Scheme 1



[0227] In General Scheme 1, starting material **A** is reacted with pinacol boronic ester intermediate **B** using palladium-catalyzed cross coupling conditions (e.g., Pd(dppf)Cl₂, K₂CO₃, dioxane, 100 °C, 18 hours) to yield intermediate **C**. Rings B and C may be optionally substituted or be 6-membered or 5-membered heteroaromatics. Ring C may optionally be a 9-membered bicycle where X₂ is O or C.

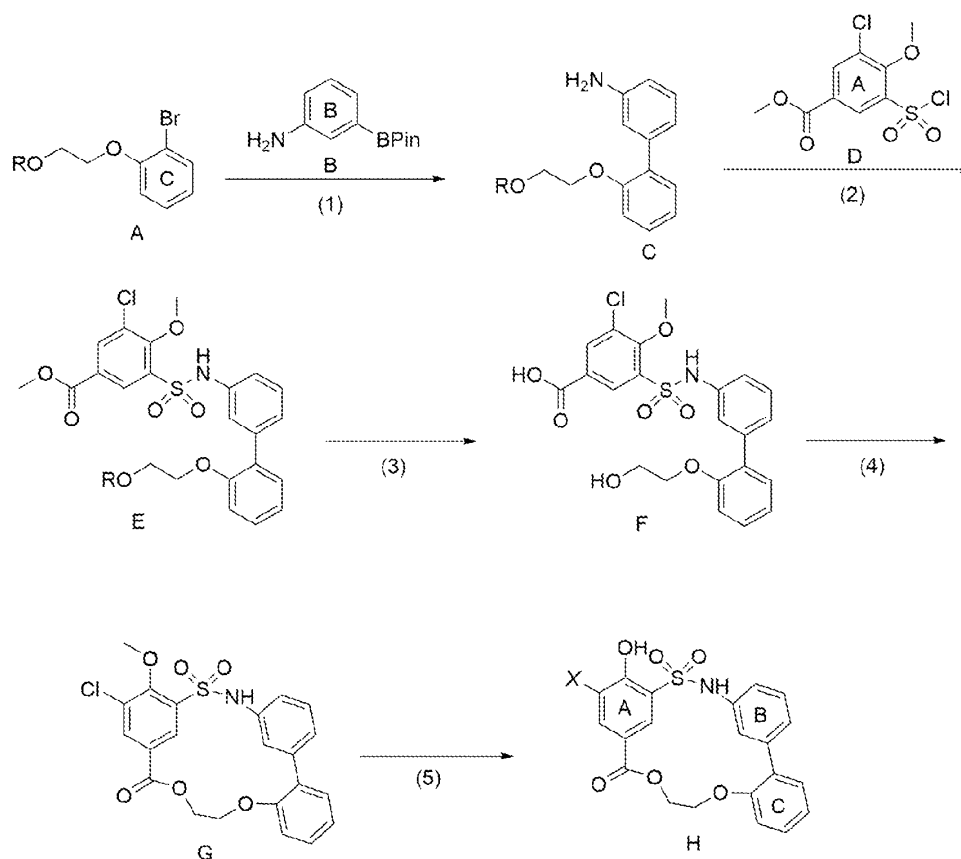
[0228] Intermediate **C** is reacted with sulfonyl chloride intermediate **D** under basic conditions (e.g., pyridine, 50 °C, 1 hour) to yield intermediate **E**. Substituent X represents Cl, Br, F or trifluoromethyl. modify length of alcohol to be modular)

[0229] Intermediate **E** undergoes ester hydrolysis under basic conditions (e.g., NaOH (aq.), THF, r.t., 3 hours) to yield intermediate **F**. Intermediate **F** undergoes cyclization using ester coupling conditions (e.g., DCC, DMAP, DCM, r.t., 24 hours; or TCFH, NMI, MeCN, r.t., 2-18 hours) to yield intermediate **G**. Finally, intermediate **G** undergoes ether cleavage (using

e.g., iodocyclohexane, anhydrous DMF, 120 °C, 1-3 hours; or lithium iodide, anhydrous pyridine, 80 °C, 6-18 hours) to yield final product **H**.

[0230] In some embodiments, compounds of the disclosure may be synthesized using the procedure outlined in General Scheme 2:

General Scheme 2



[0231] In General Scheme 2, starting material **A** is reacted with pinacol boronic ester intermediate **B** using palladium-catalyzed cross coupling conditions (e.g., $Pd(dppf)Cl_2$, K_2CO_3 , dioxane, 100 °C, 18 hours) to yield intermediate **C**. Rings **B** and **C** may be optionally substituted. **R** is a silyl protecting group.

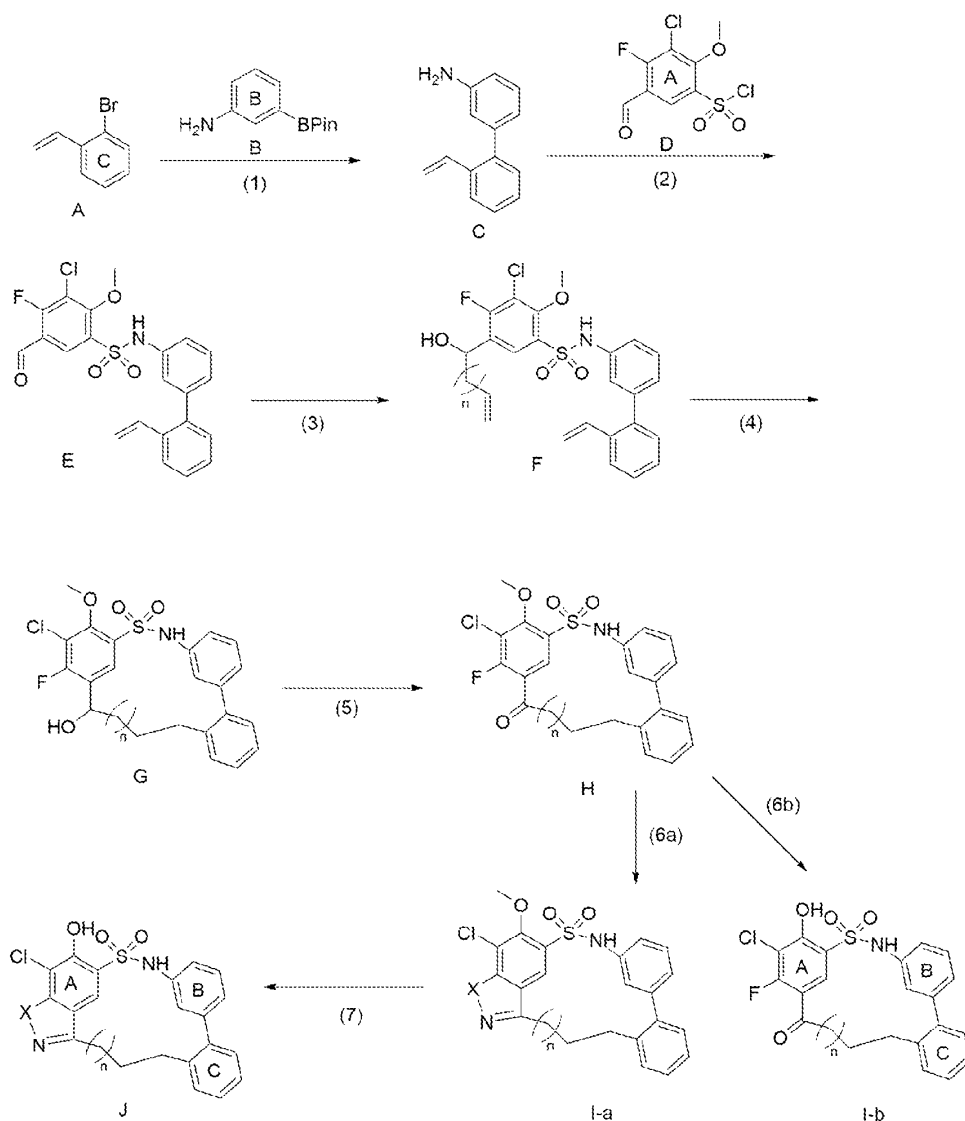
[0232] Intermediate **C** is reacted with sulfonyl chloride intermediate **D** under basic conditions (e.g., pyridine, 50 °C, 1 hour) to yield intermediate **E**.

[0233] Intermediate **E** undergoes ester hydrolysis under basic conditions (e.g., $NaOH$ (aq.), THF, r.t., 3 hours) and acidic deprotection of the silyl group to yield intermediate **F**. Intermediate **F** undergoes cyclization using ester coupling conditions (e.g., DCC, DMAP,

DCM, r.t., 24 hours; or TCFH, NMI, MeCN, r.t., 2-18 hours) to yield intermediate **G**. Finally, intermediate **G** undergoes ether cleavage (using e.g., iodocyclohexane, anhydrous DMF, 120 °C, 1-3 hours; or lithium iodide, anhydrous pyridine, 80 °C, 6-18 hours) to yield final product **H**.

[0234] In some embodiments, compounds of the disclosure may be synthesized using the procedure outlined in General Scheme 3:

General Scheme 3



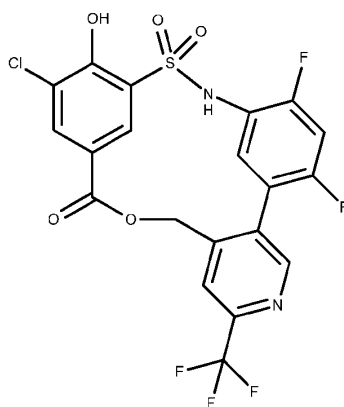
[0235] In General Scheme 3, starting material **A** is reacted with pinacol boronic ester intermediate **B** using palladium-catalyzed cross coupling conditions (e.g., Pd(dppf)Cl₂, K₂CO₃, dioxane, 100 °C, 18 hours) to yield intermediate **C**. Rings B and C may be optionally substituted.

[0236] Intermediate **C** is reacted with sulfonyl chloride intermediate **D** under basic conditions (e.g., pyridine, 50 °C, 1 hour) to yield intermediate **E**. Substituent X represents Cl, Br, F or trifluoromethyl. modify length of alcohol to be modular)

[0237] Intermediate **E** is reacted with a Grignard reagent to yield intermediate **F** wherein n can be 0 or 1. Intermediate **F** undergoes cyclization via ring closing metathesis and the resulting alkene is reduced with Pd/C to yield intermediate **G**. Intermediate **G** is oxidized with DMP to yield Intermediate **H**. Intermediate **H** undergoes ether cleavage (using e.g., iodocyclohexane, anhydrous DMF, 120 °C, 1-3 hours; or lithium iodide, anhydrous pyridine, 80 °C, 6-18 hours) to yield final product **I-b**.

[0238] Alternatively, Intermediate **H** is reacted with acetoneoxime or *N*-methylhydrazine to form Intermediate **I-a**. Intermediate **I-a** undergoes ether cleavage (using e.g., iodocyclohexane, anhydrous DMF, 120 °C, 1-3 hours; or lithium iodide, anhydrous pyridine, 80 °C, 6-18 hours) to yield final product **J**. X can be O or N.

Example 1 - Synthesis of 13-Chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosan-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 1)



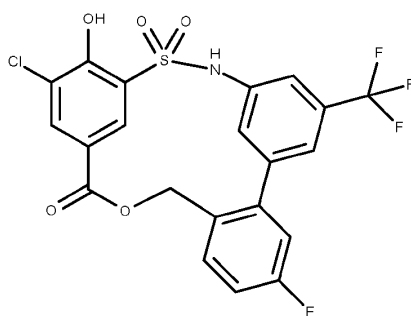
[0239] A mixture of *Intermediate 6* (100 mg, 0.16 mmol), lithium iodide (215 mg, 1.61 mmol) and anhydrous pyridine (2 mL) was heated at 90 °C for 3 h 45 min. The reaction

mixture was diluted with EtOAc (40 mL), washed with sat. aq. Na₂S₂O₃ (30 mL), 1 M aq. HCl (30 mL) and brine (30 mL), then passed through a phase separator and then concentrated. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (44 mg, 51% Yield, 97% purity).

¹H NMR (400 MHz, DMSO) δ 10.21 (br. s, 1H), 8.69 (s, 1H), 8.21 (s, 1H), 7.94 (d, J = 2.2 Hz, 1H), 7.61 – 7.46 (m, 1H), 7.22 (d, J = 2.2 Hz, 1H), 7.18 – 7.05 (m, 1H), 5.61 (d, J = 13.7 Hz, 1H), 5.24 (d, J = 13.6 Hz, 1H).

LCMS: m/z = 519.0/520.9 [M-H]⁻, (ESI⁻), RT = 4.03, Method A

Example 2 – Synthesis of 13-Chloro-4-fluoro-14-hydroxy-16,16-dioxo-20-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1.11,15.02,7]tricos-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one (Compound 2)

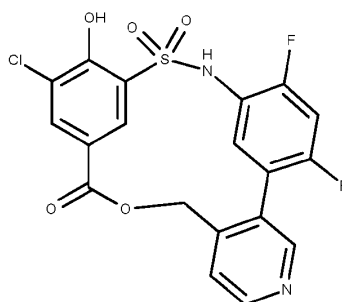


[0240] *Intermediate 7* (93% purity, 240 mg, 0.433 mmol), pyridine (5.4 mL) and lithium iodide (580 mg, 4.33 mmol) were added to a pressure vial. The mixture was heated at 80 °C for 1.5 h and was then allowed to cool to r.t. and concentrated under a stream of nitrogen. The organics were diluted with EtOAc (50 mL), washed with HCl (2 x 50 mL of a 1 M aqueous solution), Na₂SO₃ (30 mL of a saturated aqueous solution) and brine (30 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as pale brown solid (71 mg, 32% Yield, 98% purity).

¹H NMR (500 MHz, DMSO) δ 10.44 (s, 1H), 7.89 (d, J = 2.2 Hz, 1H), 7.81 (s, 1H), 7.63 (dd, J = 8.5, 5.8 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.24 – 7.20 (m, 1H), 7.13 (d, J = 2.2 Hz, 1H), 5.35 (s, 2H).

LCMS: m/z = 500.0/502.0 [M-H]⁻, (ESI⁻), RT = 4.26, Method A

Example 3 – Synthesis of 13-Chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.1.11,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 3)

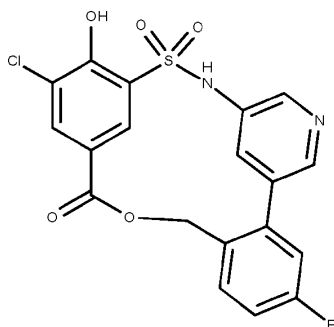


[0241] To a solution of 13-chloro-19,21-difluoro-14-methoxy-16,16-dioxo-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.1.11,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 76% purity, 200 mg, 0.326 mmol) in anhydrous pyridine (28 mL) was added lithium iodide (460 mg, 3.44 mmol). The reaction mixture was heated at 80 °C. After 4.5 h, the reaction was stopped then cooled to r.t. and the pyridine was removed under reduced pressure to give an orange gum. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as white solid (43 mg, 28% Yield, 95% purity).

¹H NMR (400 MHz, DMSO) δ 10.17 (s, 1H), 8.69 (d, J = 4.9 Hz, 1H), 8.48 (s, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.62 (d, J = 5.0 Hz, 1H), 7.58 – 7.46 (m, 1H), 7.23 (d, J = 2.2 Hz, 1H), 7.04 – 6.86 (m, 1H), 5.46 (d, J = 13.3 Hz, 1H), 5.18 (d, J = 13.3 Hz, 1H).

LCMS: m/z = 451.0 & 453.0 [M-H]⁻, (ESI⁻), RT = 3.12, Method A

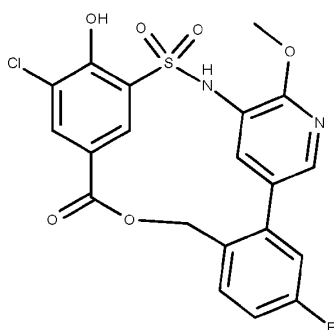
Example 4 – Synthesis of 13-Chloro-4-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.1¹¹¹.15.0²,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 4)



[0242] To a solution of 13-chloro-4-fluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.1¹¹¹.15.0²,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 75% purity, 69.0 mg, 0.115 mmol) in anhydrous pyridine (2.0 mL) in a pressure tube was added lithium iodide (109 mg, 0.807 mmol). The reaction mixture was heated at 80 °C for 3 h. The volatiles were removed under reduced pressure. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as white solid (15 mg, 30% Yield, 100% purity). ¹H NMR (500 MHz, DMSO) δ 10.34 (s, 1H), 8.62 (d, J = 1.9 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.64 (dd, J = 8.5, 5.8 Hz, 1H), 7.30 (ddd, J = 8.6, 8.5, 2.8 Hz, 1H), 7.23 (dd, J = 9.3, 2.8 Hz, 1H), 7.20 (s, 1H), 7.00 (d, J = 2.2 Hz, 1H), 5.46 – 5.27 (m, 2H).

LCMS: m/z = 435/437 [M+H]⁺, (ESI⁺), RT = 3.47, Method A

Example 5 – Synthesis of 13-Chloro-4-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 5)

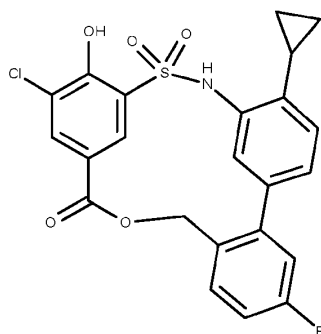


[0243] To a solution of 13-chloro-4-fluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 95% purity, 110 mg, 0.218 mmol) in anhydrous pyridine (2.0 mL) in a pressure tube was added lithium iodide (109 mg, 0.807 mmol) (108 mg). The reaction mixture was heated at 80 °C for 4 h. After cooling, the volatiles were removed under reduced pressure. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as white solid (55.0 mg, 54% Yield, 99% purity).

¹H NMR (500 MHz, DMSO) δ 9.73 (s, 1H), 8.13 (d, J = 2.2 Hz, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.65 – 7.57 (m, 1H), 7.50 (d, J = 2.2 Hz, 1H), 7.32 – 7.24 (m, 3H), 5.68 – 5.55 (m, 1H), 5.27 – 5.09 (m, 1H), 3.55 (s, 3H).

LCMS: m/z = 465, 467 [M+H]⁺, (ESI⁺), RT = 3.89, Method A

Example 6 – Synthesis of 13-Chloro-19-cyclopropyl-4-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricosal-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 6)

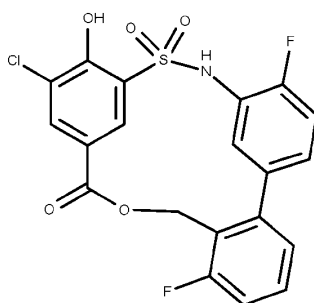


[0244] To a solution of 13-chloro-19-cyclopropyl-4-fluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricosal-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 95% purity, 220 mg, 0.428 mmol) in anhydrous pyridine (8 mL) was added lithium iodide (500 mg, 3.74 mmol). The reaction mixture was heated at 80 °C for 3.5 h and was then allowed to cool to r.t.. The organics were diluted with EtOAc (80 mL), then washed with HCl (2 x 100 mL of a 1 M aqueous solution), Na₂SO₃ (40 mL of a saturated aqueous solution), brine (40 mL), dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by FCC (10 g SiO₂ cartridge, 0 – 100% EtOAc in DCM) to afford the title compound as off-white solid (55 mg, 26% Yield, 96% purity).

¹H NMR (500 MHz, DMSO) δ 9.90 (s, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = 8.5, 5.9 Hz, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 7.8, 2.0 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.11 (dd, J = 9.4, 2.8 Hz, 1H), 6.90 (d, J = 1.9 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 5.42 – 5.33 (m, 1H), 5.28 – 5.18 (m, 1H), 2.20 – 2.14 (m, 1H), 0.92 – 0.83 (m, 2H), 0.67 – 0.59 (m, 1H), 0.18 – 0.06 (m, 1H).

LCMS: m/z = 472.1 / 474.2 [M-H]⁻, (ESI⁻), RT = 2.71, Method B

Example 7 – Synthesis of 13-Chloro-6,19-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 7)

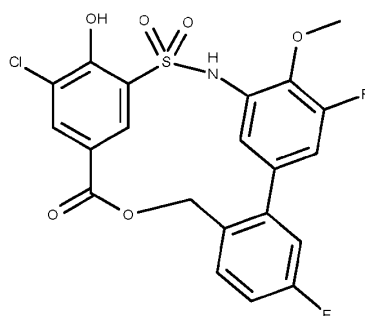


[0245] To a solution of 13-chloro-6,19-difluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹.15.0^{2,7}]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 6*, 91% purity, 80 mg, 0.156 mmol) in anhydrous pyridine (3.4 mL) was added lithium iodide (23 mg, 0.172 mmol). The reaction mixture was heated at 80 °C for 19 h. The reaction mixture was dissolved in EtOAc (50 mL) and washed with 1 M aq. HCl (50 mL). The aqueous phase was extracted further with EtOAc (2 x 50 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (50 mL) and brine (50 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude material as a white solid. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as light pink solid (61 mg, 85% Yield, 98% purity).

¹H NMR (500 MHz, DMSO) δ 10.06 (br. s, 1H), 7.92 (d, J = 2.2 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.46 – 7.41 (m, 1H), 7.33 – 7.25 (m, 2H), 7.15 (d, J = 2.2 Hz, 1H), 7.07 – 7.03 (m, 1H), 6.73 (dd, J = 7.4, 2.3 Hz, 1H), 5.65 (d, J = 13.0 Hz, 1H), 5.20 (d, J = 13.0 Hz, 1H).

LCMS: $m/z = 450.0 / 452.0$ [M-H]⁻, (ESI⁻), RT = 4.05, Method A

Example 8 – Synthesis of 13-Chloro-4,20-difluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 8)

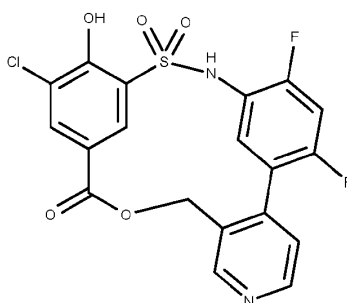


[0246] Lithium iodide (137 mg, 1.02 mmol) was added to a stirring solution of 13-chloro-4,20-difluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 89% purity, 274 mg, 0.492 mmol) in anhydrous pyridine (7 mL) in a 20 mL pressure vial at r.t.. The vial was sealed and the mixture stirred at 90 °C for 7 h, allowed to cool to r.t., and left to stand for 3 days. The reaction mixture was diluted with sat. aq. sodium thiosulphate (~30 mL) and 1 M aq. HCl (~30 mL). The mixture became monophasic following addition of HCl and a white precipitate formed. To this suspension was added brine (~30 mL), and the suspension was then extracted with EtOAc (~30 mL). The aqueous phase was passed through a phase separator. The precipitate that had collected on the phase separator was washed with EtOAc (~30 mL), the organic phases were combined and concentrated to dryness in vacuo. The residue was purified by reverse phase FCC (12 g C18 cartridge, 0.1% formic acid as modifier, eluting MeCN in H₂O: 10%, 2 CV; 10-50%, 2 CV; 50%, 2 CV; 50-65%, 2 CV; 65%, 2 CV; 65-85%, 10 CV; 85-100%, 2 CV; 100%, 4 CV), followed by trituration with water and finally by preparative HPLC (Method P1) to afford the title compound as white solid (22 mg, 0.0452 mmol, 9.2% Yield, 99% purity).

¹H NMR (500 MHz, DMSO) δ 9.81 (s, 1H), 7.93 (dd, J = 2.2, 1.0 Hz, 1H), 7.61 (dd, J = 8.5, 5.9 Hz, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.39 (ddd, J = 12.0, 1.4, 1.4 Hz, 1H), 7.27 (ddd, J = 8.5, 8.5, 2.8 Hz, 1H), 7.22 (dd, J = 9.4, 2.8 Hz, 1H), 7.04 (dd, J = 1.6, 1.6 Hz, 1H), 5.50 (d, J = 12.5 Hz, 1H), 5.19 (d, J = 12.6 Hz, 1H), 3.55 (d, J = 1.9 Hz, 3H).

LCMS: m/z = 480.3, 482.3 [M-H]⁻, (ESI⁻), RT = 4.07, Method A

Example 9 – Synthesis of 13-Chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.1¹¹.15.0²,7]tricoso-1(22),2,4,6,11,13,15(23),18,20-nonaen-10-one (Compound 9)

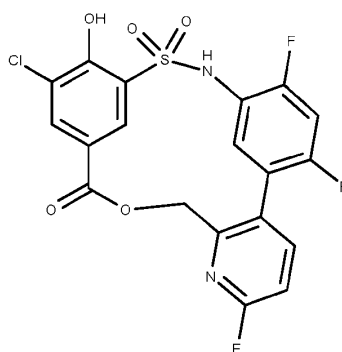


[0247] To a solution of 13-chloro-19,21-difluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.1¹¹.15.0²,7]tricoso-1(22),2,4,6,11,13,15(23),18,20-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 65% purity, 20 mg, 0.0278 mmol) in anhydrous pyridine (1 mL) was added lithium iodide (50 mg, 0.374 mmol). The reaction mixture was heated at 80 °C for 2 h then cooled to r.t and stirred for 1 h, then concentrated. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as white solid (8.0 mg, 62% Yield, 98% purity).

¹H NMR (500 MHz, DMSO) δ 8.74 (s, 1H), 8.66 (d, J = 4.9 Hz, 1H), 7.84 (s, 1H), 7.49 (dd, J = 9.8, 9.8 Hz, 1H), 7.37 (d, J = 5.0 Hz, 1H), 7.20 (d, J = 2.3 Hz, 1H), 6.93 (dd, J = 7.9, 7.9 Hz, 1H), 5.45 (d, J = 13.0 Hz, 1H), 5.13 (d, J = 12.9 Hz, 1H).

LCMS: m/z = 453.0/454.8 [M+H]⁺, (ESI⁺), RT = 3.29, Method A

Example 10 – Synthesis of 13-Chloro-5,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 10)

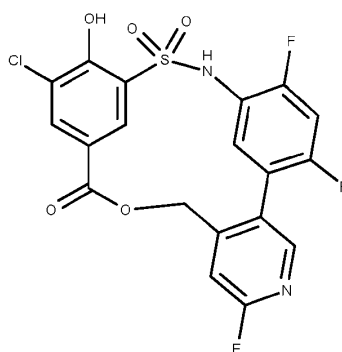


[0248] To a solution of 13-chloro-5,19,21-trifluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 9, using a similar method to intermediate 7*, 99% purity, 120 mg, 0.245 mmol) in anhydrous pyridine (10 mL) was added lithium iodide (300 mg, 2.24 mmol). The reaction mixture was heated at 80 °C for 5.5 h, then stirred at r.t. for 11 h. The organics were diluted with EtOAc (30 mL), washed with HCl (100 mL of a 1 M aqueous solution), then Na₂SO₃ (30 mL of a saturated aqueous solution) then brine (30 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as off-white solid (89 mg, 74% Yield, 96% purity).

¹H NMR (500 MHz, DMSO) δ 10.19 (br. s, 1H), 8.01 – 7.96 (m, 1H), 7.96 (d, J = 2.2 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.33 (dd, J = 8.3, 2.9 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 7.07 – 7.02 (m, 1H), 5.36 – 5.27 (m, 2H).

LCMS: m/z = 469.0 / 470.9 [M-H]⁻, (ESI⁻), RT = 3.68, Method A

Example 11 – Synthesis of 13-Chloro-5,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 11)

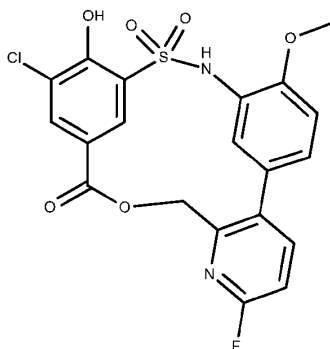


[0249] To a solution of 13-chloro-5,19,21-trifluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 11, using a similar method to intermediate 7*, 90% purity, 60 mg, 0.124 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (166 mg, 1.24 mmol). The reaction mixture was heated at 80 °C for 3 h, then at r.t. overnight. The RM was diluted with EtOAc (50 mL) and washed with 1 M aq. HCl (30 mL), sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL), then passed through a phase separator and then concentrated. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as off-white solid (26 mg, 44% Yield, 99% purity).

¹H NMR (500 MHz, DMSO) δ 10.14 (br s, 1H), 8.18 (s, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.22 (d, J = 2.2 Hz, 1H), 7.07 – 6.98 (m, 1H), 5.48 (d, J = 13.5 Hz, 1H), 5.16 (d, J = 13.4 Hz, 1H).

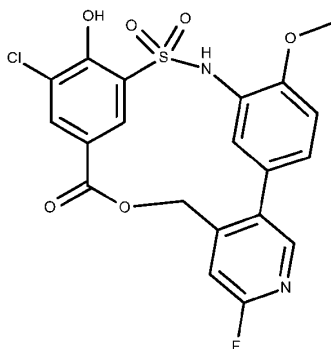
LCMS: m/z = 469.3/471.3 [M-H]⁻, (ESI⁻), RT = 3.69, Method A

Example 12 – Synthesis of 13-Chloro-5-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 12)



[0250] To a solution of 13-chloro-5-fluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 9, using a similar method to intermediate 6*, 95% purity, 89 mg, 0.186 mmol) in anhydrous pyridine (7.4 mL) was added lithium iodide (30 mg, 0.224 mmol). The reaction mixture was heated at 80 °C for 15 h. The pyridine was removed under reduced pressure and the residue was dissolved in EtOAc (5 mL) and washed with NH₄Cl (aq.) (5 mL) and then passed through a phase separator cartridge and concentrated under reduced pressure. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as white solid (70 mg, 81% Yield, 99% purity). ¹H NMR (400 MHz, DMSO) δ 9.29 (s, 1H), 8.04 – 7.94 (m, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.34 – 7.23 (m, 3H), 6.70 (d, J = 8.3 Hz, 1H), 5.89 (d, J = 13.7 Hz, 1H), 4.88 (d, J = 13.5 Hz, 1H), 3.43 (s, 3H). LCMS: m/z = 463.1 & 465.1 [M-H]⁻, (ESI⁻), RT = 3.53, Method A

Example 13 – Synthesis of 13-Chloro-5-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 13)

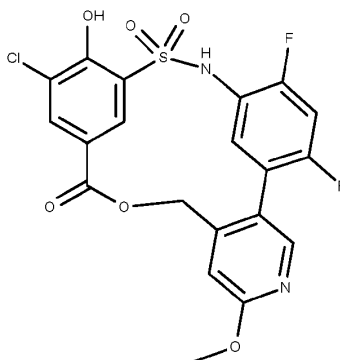


[0251] To a solution of 13-chloro-5,19,21-trifluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 11, using a similar method to intermediate 7*, 52% purity, 150 mg, 0.163 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (43 mg, 0.33 mmol). The reaction mixture was heated at 80 °C for 15 h. The cooled reaction mixture was diluted with EtOAc (50 mL) and washed with 1 M aq. HCl (30 mL), sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL), then passed through a phase separator and then concentrated. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as off-white solid (57 mg, 73% Yield, 97% purity).

¹H NMR (500 MHz, DMSO) δ 9.31 (s, 1H), 8.20 (s, 1H), 7.90 – 7.80 (m, 1H), 7.44 (d, J = 1.9 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.31 – 7.18 (m, 2H), 6.74 (d, J = 8.4 Hz, 1H), 5.68 (d, J = 13.4 Hz, 1H), 5.15 (d, J = 13.4 Hz, 1H), 3.44 (s, 3H).

LCMS: m/z = 463.1/465.1 [M-H]⁻, (ESI⁻), RT = 3.38, Method A

Example 14 - Synthesis of 13-Chloro-19,21-difluoro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹.15.0²,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 14)

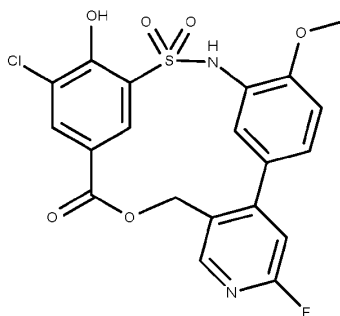


[0252] To a solution of *intermediate 13*, 97% purity, 1653 mg, 3.179 mmol) in anhydrous pyridine (20 mL) was added lithium iodide (1.50 g, 11.2 mmol). The reaction mixture was heated at 90 °C for 6 h. The reaction mixture was cooled to r.t., diluted with EtOAc (20 mL), washed with sat. aq. Na₂S₂O₃ (2 x 20 mL), 1 M aq. HCl (4 x 20 mL) and brine (20 mL), then dried over Na₂SO₄, filtered, and concentrated. The residue was taken into ethanol (~70 mL), sonicated to give a milky white solution, and concentrated to dryness. This was repeated three times, then the solids were dried in a vacuum oven overnight at 60 °C to afford the title product as an off-white solid (1276 mg, 79% Yield, 95% purity).

¹H NMR (500 MHz, DMSO) δ 10.15 (s, 1H), 8.05 (s, 1H), 7.96 (d, J = 2.2 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.21 (d, J = 2.2 Hz, 1H), 7.08 (s, 1H), 6.93 – 6.85 (m, 1H), 5.41 (d, J = 13.2 Hz, 1H), 5.08 (d, J = 13.1 Hz, 1H), 3.90 (s, 3H).

LCMS: m/z = 481.0/483.0 [M-H]⁻, (ESI⁻), RT = 3.91, Method A

Example 15 – Synthesis of 13-Chloro-4-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 15)

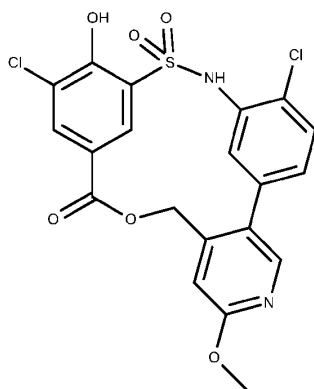


[0253] A mixture of 13-chloro-4-fluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised from intermediate 17, using a similar method to intermediate 13*, 69% purity, 26 mg, 0.0375 mmol), lithium iodide (25 mg, 0.19 mmol) and anhydrous pyridine (2 mL) was heated at 90 °C for 2 h. The RM was cooled to r.t., diluted with EtOAc (25 mL), washed with sat. aq. Na₂S₂O₃ (25 mL), 1 M aq. HCl (25 mL) and brine (25 mL), then passed through a phase separator and concentrated. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (9.0 mg, 51% Yield, 99% purity).

¹H NMR (500 MHz, DMSO) δ 9.32 (s, 1H), 8.39 (s, 1H), 7.85 (d, J = 2.2 Hz, 1H), 7.36 (dd, J = 8.4, 2.3 Hz, 1H), 7.31 – 7.26 (m, 3H), 6.77 (d, J = 8.5 Hz, 1H), 5.81 – 4.97 (m, 2H), 3.45 (s, 3H).

LCMS: m/z = 465.0/466.9 [M+H]⁺, (ESI⁺), RT = 3.49, Method A

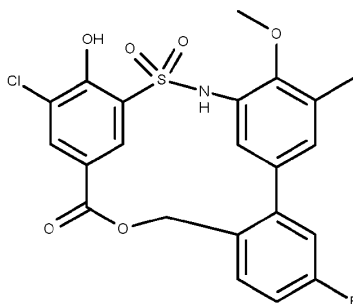
Example 16 – Synthesis of 13,19-Dichloro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (Compound 16)



[0254] Lithium iodide (105 mg, 0.784 mmol) was added to a stirring solution of 13,19-dichloro-5,14-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 13*, 148 mg, 0.299 mmol) in anhydrous pyridine (4.0 mL) in a pressure vial. The reaction vessel was sealed, and the mixture stirred at 90 °C for 2 h 30 m. The reaction mixture was allowed to cool to r.t., diluted with EtOAc (~15 mL), and washed sequentially with sat. aq. sodium thiosulphate (~15 mL), 1 M HCl (aq.) (~20 mL), and brine (~15 mL). The organic phase was passed through a phase separator and concentrated to dryness in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (49 mg, 100% purity, 34% yield).
¹H NMR (500 MHz, DMSO) δ 10.03 (s, 1H), 8.09 (s, 1H), 7.91 (d, J = 2.3 Hz, 1H), 7.34 (d, J = 1.2 Hz, 2H), 7.31 (d, J = 2.2 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.08 (s, 1H), 5.63 – 4.98 (m, 2H), 3.91 (s, 3H).

LCMS: m/z = 481.0, 483.0 [M+H]⁺, (ESI⁺), RT = 1.52, Method B

Example 17 – Synthesis of 13-Chloro-4-fluoro-14-hydroxy-19-methoxy-20-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricos-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (Compound 17)

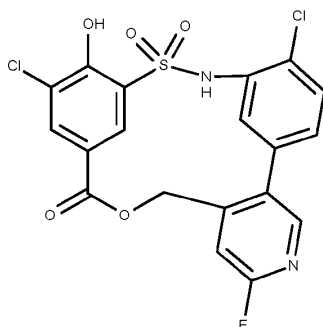


[0255] To a solution of 13-chloro-4-fluoro-14,19-dimethoxy-20-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 98%, 138 mg, 0.275 mmol) in anhydrous pyridine (5 mL) was added lithium iodide (74 mg, 0.553 mmol). The reaction mixture was heated at 80 °C for 1 h. The organics were diluted with EtOAc (30 mL), washed with HCl (2 x 30 mL of a 1 M aqueous solution), Na₂SO₃ (10 mL of a saturated aqueous solution), brine (2 x 20 mL) and then dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a light pink solid (59 mg, 99% purity, 44% Yield).

¹H NMR (500 MHz, DMSO) δ 9.48 (s, 1H), 7.89 – 7.83 (m, 1H), 7.59 (dd, J = 8.5, 5.9 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.19 – 7.16 (m, 1H), 7.14 (dd, J = 9.4, 2.8 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 5.47 – 5.38 (m, 1H), 5.24 – 5.15 (m, 1H), 3.42 (s, 3H), 2.10 – 2.05 (m, 3H).

LCMS: m/z = 476.0/478.0 [M-H]⁻, (ESI⁻), RT = 4.24, Method A

Example 18 – Synthesis of 13,19-Dichloro-5-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹.15.0^{2,7}]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 18)

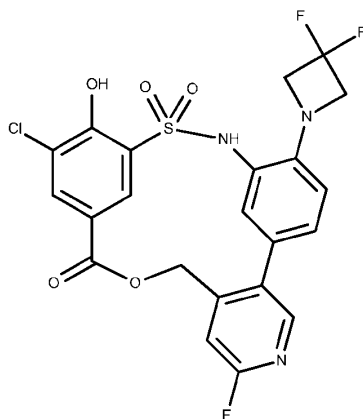


[0256] To a solution of 13,19-dichloro-5-fluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹.15.0^{2,7}]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 11, using a similar method to intermediate 6*, 97%, 60 mg, 0.120 mmol) in anhydrous pyridine (2.1 mL) was added lithium iodide (80 mg, 0.598 mmol). The reaction mixture was heated at 80 °C for 1 h. The organics were diluted with EtOAc (30 mL), washed with HCl (2 x 30 mL of a 1 M aqueous solution), Na₂SO₃ (10 mL of a saturated aqueous solution), brine (2 x 20 mL) and then dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a light pink solid (21 mg, 95% purity, 35% Yield).

¹H NMR (500 MHz, DMSO) δ 10.00 (br.s, 1H), 8.19 (s, 1H), 7.90 – 7.85 (m, 1H), 7.49 (d, J = 1.9 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.31 (d, J = 2.3 Hz, 1H), 7.26 – 7.23 (m, 1H), 5.59 – 5.49 (m, 1H), 5.31 – 5.21 (m, 1H).

LCMS: m/z = 467.0 / 469.0 [M-H]⁻, (ESI⁻), RT = 3.62, Method A

Example 19 – Synthesis of 13-Chloro-19-(3,3-difluoroazetidin-1-yl)-5-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 19)

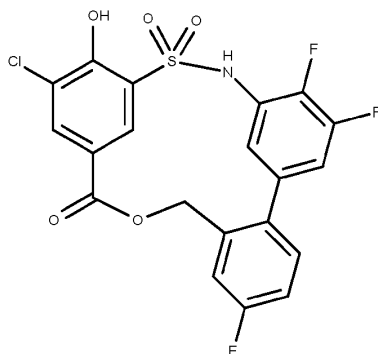


[0257] To a solution of 13-chloro-19-(3,3-difluoroazetidin-1-yl)-5-fluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediates 11 and 19, using a similar method to intermediate 7*, 67% purity, 150 mg, 0.28 mmol) in anhydrous pyridine (3.7 mL) was added lithium iodide (186 mg, 1.39 mmol). The reaction mixture was heated at 80 °C for 16 h. The reaction mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 20 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (8.3 mg, 99% purity, 5.6% Yield).

¹H NMR (500 MHz, DMSO) δ 9.64 (s, 1H), 7.94 (s, 1H), 7.86 (s, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 8.3, 2.0 Hz, 1H), 7.21 (d, J = 2.2 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.24 (d, J = 2.0 Hz, 1H), 5.68 – 4.99 (m, 2H), 4.67 – 4.30 (m, 4H).

LCMS: m/z = 526.0/527.9 [M+H]⁺, (ESI⁺), RT = 3.94, Method A

Example 20 – Synthesis of 13-Chloro-5,19,20-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.1¹¹,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (Compound 20)

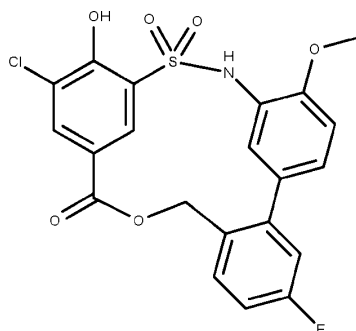


[0258] 13-chloro-5,19,20-trifluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.1¹¹,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 80% purity, 220 mg, 0.36 mmol) and iodocyclohexane (0.23 mL, 1.79 mmol) were weighed in a pressure vial and anhydrous DMF (5.5 mL) was added. The reaction mixture was placed at 120 °C and stirred at that temp for 45 min. The mixture was cooled to r.t. The organics were diluted with EtOAc (40 mL), washed with 1 M HCl (100 mL), Na₂SO₃ (40 mL of a saturated aqueous solution), then brine (40 mL). The EtOAc layer was passed through phase separator paper and concentrated in vacuo. The residue was purified by FCC (10 g SiO₂ cartridge, 0-80% EtOAc in heptane) followed by lyophilisation to afford the title compound as a white solid (111 mg, 96% purity, 62% Yield).

¹H NMR (400 MHz, DMSO) δ 7.66 (s, 1H), 7.51 – 7.43 (m, 2H), 7.33 – 7.23 (m, 2H), 7.21 (d, J = 2.4 Hz, 1H), 6.83 (d, J = 6.0 Hz, 1H), 5.49 – 5.33 (m, 1H), 5.25 – 5.04 (m, 1H).

LCMS: m/z = 468.0 & 470.0 [M-H]⁻, (ESI⁻), RT = 4.19, Method A

Example 21 – Synthesis of 13-Chloro-4-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (Compound 21)

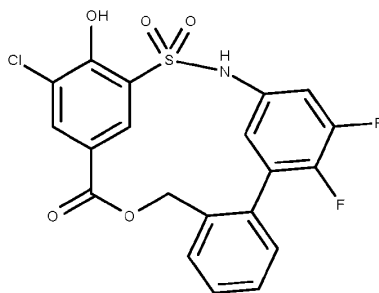


[0259] 13-Chloro-4-fluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 100% purity, 120 mg, 0.25 mmol) and iodocyclohexane (0.042 mL, 0.325 mmol) were weighed in a pressure vial and anhydrous DMF (3.6 mL) was added. The reaction mixture was placed at 120 °C and stirred for 2 h. The mixture was then purified by preparative HPLC (Method P1) to afford the title compound as a white solid (67 mg, 100% purity, 58% Yield).

¹H NMR (400 MHz, DMSO) δ 9.30 (s, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = 8.3, 5.9 Hz, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.32 – 7.16 (m, 4H), 6.73 (d, J = 8.5 Hz, 1H), 5.59 (d, J = 12.7 Hz, 1H), 5.11 (d, J = 12.7 Hz, 1H), 3.44 (s, 3H).

LCMS: m/z = 462.1 & 464.1 [M-H]⁻, (ESI⁻), RT = 4.04, Method A

Example 22 – Synthesis of 13-Chloro-20,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 22)

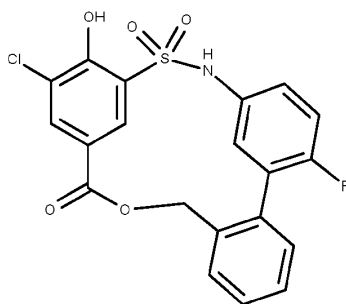


[0260] *Intermediate 20* (95% purity, 130 mg, 0.265 mmol) and iodocyclohexane (285 mg, 1.36 mmol) were combined and the mixture dissolved in anhydrous DMF (3.5 mL). The mixture was heated to 120 °C and stirred for 2 h. The mixture was allowed to cool to r.t., added to sat. aq. Na₂S₂O₃ (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a pale yellow solid (73 mg, 98% purity, 60% Yield).

¹H NMR (500 MHz, DMSO) δ 10.30 (s, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.51 – 7.46 (m, 2H), 7.35 – 7.30 (m, 1H), 7.29 – 7.22 (m, 1H), 7.16 (d, J = 2.1 Hz, 1H), 6.63 – 6.59 (m, 1H), 5.51 (d, J = 12.8 Hz, 1H), 5.06 (d, J = 12.8 Hz, 1H).

LCMS: m/z = 450.0/452.0 [M-H]⁻, (ESI⁻), RT = 4.20, Method A

Example 23 – Synthesis of 13-Chloro-21-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16λ6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 23)

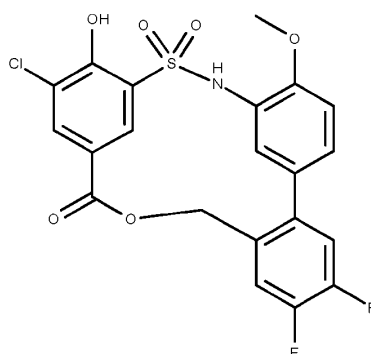


[0261] To a solution of 13-chloro-21-fluoro-14-methoxy-16,16-dioxo-9-oxa-16λ6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (synthesised using a similar method to intermediate 7, 67% purity, 150 mg, 0.224 mmol) in anhydrous DMF (20 mL) was added iodocyclohexane (0.30 mL, 2.32 mmol). The reaction mixture was heated at 120 °C for 3 h. The mixture was allowed to cool to r.t. and added to sat. aq. Na₂S₂O₃ (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (72 mg, 97% purity, 72% Yield).

^1H NMR (500 MHz, DMSO) δ 10.12 (s, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.50 – 7.46 (m, 1H), 7.46 – 7.43 (m, 1H), 7.34 – 7.27 (m, 2H), 7.22 – 7.16 (m, 1H), 7.12 (d, J = 2.1 Hz, 1H), 6.79 (dd, J = 6.6, 2.7 Hz, 1H), 5.45 (d, J = 12.6 Hz, 1H), 5.07 (d, J = 12.6 Hz, 1H).

LCMS: m/z = 432.3 / 434.3 $[\text{M-H}]^-$, (ESI-), RT = 4.08, Method A

Example 24 – Synthesis of 13-Chloro-4,5-difluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 24)

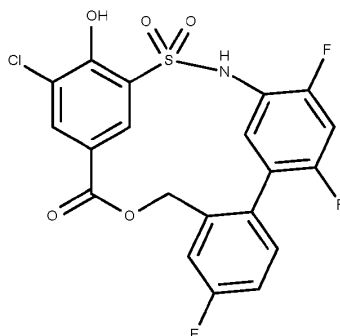


[0262] To a solution of 13-chloro-4,5-difluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 93% purity, 135 mg, 0.25 mmol) in anhydrous DMF (3 mL) in a pressure vial was added iodocyclohexane (0.04 mL, 0.33 mmol). The reaction mixture was heated to 100 °C for 24 h. After cooling, the reaction was quenched by pouring onto sat aq. $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL). The mixture was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with 1 M aq. HCl (10 mL), then brine (10 mL) and were dried over MgSO_4 , filtered and concentrated. The residue was purified by preparative HPLC (Method P1) followed by trituration with MeCN to afford the title compound as a beige solid (44 mg, 99% purity, 36% Yield).

^1H NMR (500 MHz, DMSO) δ 9.31 (s, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.70 (dd, J = 11.6, 8.2 Hz, 1H), 7.48 (dd, J = 11.2, 8.1 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.27 (dd, J = 8.5, 2.2 Hz, 1H), 7.21 (d, J = 2.2 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 5.57 (d, J = 12.8 Hz, 1H), 5.09 (d, J = 12.9 Hz, 1H), 3.43 (s, 3H).

LCMS: m/z = 480, 482 $[\text{M-H}]^-$, (ESI-), RT = 4.11, Method A

Example 25 – Synthesis of 13-Chloro-5,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.1¹¹.15.0²,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 25)

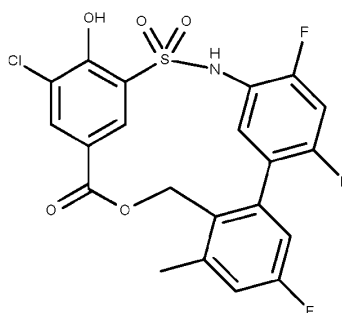


[0263] A solution of 13-chloro-5,19,21-trifluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.1¹¹.15.0²,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 80% purity, 250 mg, 0.413 mmol) and iodocyclohexane (270 μ L, 2.09 mmol) in anhydrous DMF (5 mL) was heated to 120 °C for 1.5 h. The reaction mixture was diluted with EtOAc (20 ml) and washed with sat. Na₂SO₃ (20 ml), HCl 1 M (20 ml) and brine (20 ml). The combined organic phases were dried over MgSO₄ and evaporated under vacuum. The residue was dissolved in DMSO/MeCN/water and filtered. The filtrate was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (36 mg, 96% purity, 18% Yield).

¹H NMR (400 MHz, DMSO) δ 7.84 (s, 1H), 7.47 – 7.32 (m, 2H), 7.30 – 7.19 (m, 2H), 7.15 (s, 1H), 6.77 (dd, J = 8.1, 8.1 Hz, 1H), 5.33 (d, J = 12.8 Hz, 1H), 5.03 (d, J = 12.8 Hz, 1H).

LCMS: m/z = 468.0/470.0 [M-H]⁻, (ESI⁻), RT = 4.10, Method A

Example 26 – Synthesis of 13-Chloro-4,19,21-trifluoro-14-hydroxy-6-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one (Compound 26)

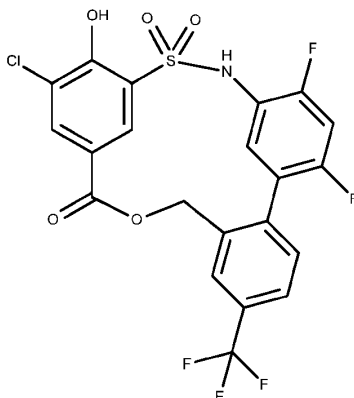


[0264] 13-chloro-4,19,21-trifluoro-14-methoxy-6-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 94% purity, 269 mg, 0.508 mmol), anhydrous DMF (20 mL) and iodocyclohexane (0.65 mL, 5.03 mmol) were added to a pressure vial. The vial was sealed and heated at 120 °C for 1 h then allowed to cool to r.t.. The reaction mixture was added to sat aq. Na₂S₂O₃ (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (72 mg, 97% purity, 28% Yield).

¹H NMR (500 MHz, DMSO) δ 10.02 (s, 1H), 8.00 – 7.92 (m, 1H), 7.62 – 7.53 (m, 1H), 7.20 (dd, J = 9.7, 2.8 Hz, 1H), 7.15 (d, J = 2.2 Hz, 1H), 6.93 (dd, J = 8.9, 2.8 Hz, 1H), 6.63 – 6.54 (m, 1H), 5.68 (d, J = 13.1 Hz, 1H), 4.84 (d, J = 13.1 Hz, 1H), 2.58 (s, 3H).

LCMS: m/z = 482.0 / 484.0 [M-H]⁻, (ESI⁻), RT = 4.33, Method A

Example 27 – Synthesis of 13-Chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (Compound 27)

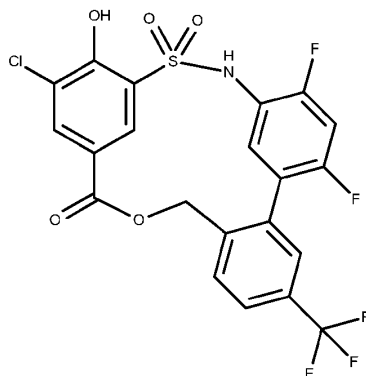


[0265] 13-chloro-19,21-difluoro-14-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 85% purity, 156 mg, 0.29 mmol) and iodocyclohexane (0.19 mL, 1.43 mmol) were weighed in a pressure vial and anhydrous DMF (4.9 mL) was added. The reaction mixture was stirred at 120 °C for 1.5 h. The mixture was diluted with EtOAc (40 mL), washed with 1 M HCl (50 mL), Na₂S₂O₃ (40 mL of a sat. aq. solution), then brine (40 mL). The EtOAc layer was passed through a phase separator and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a brown solid (33 mg, 97% purity, 21% Yield).

¹H NMR (400 MHz, DMSO) δ 10.15 (br. s, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.84 (dd, J = 8.2, 2.0 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.23 (d, J = 2.2 Hz, 1H), 6.93 – 6.84 (m, 1H), 5.59 (d, J = 13.0 Hz, 1H), 5.16 (d, J = 13.0 Hz, 1H).

LCMS: m/z = 518.0/519.9 [M-H]⁻, (ESI⁻), RT = 4.23, Method A

Example 28 – Synthesis of 13-Chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-4-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹.15.0^{2,7}]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (Compound 28)

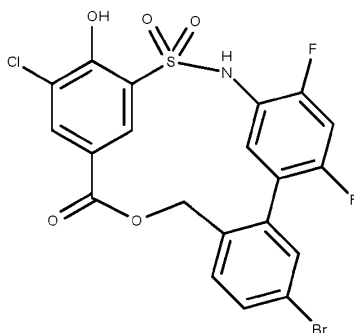


[0266] 13-chloro-19,21-difluoro-14-methoxy-16,16-dioxo-4-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹.15.0^{2,7}]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 100% purity, 28 mg, 0.0524 mmol) and iodocyclohexane (0.033 mL, 0.257 mmol) were weighed in a pressure vial and anhydrous DMF (0.9 mL) was added. The reaction mixture was stirred at 120 °C for 1.5 h. The mixture was diluted with EtOAc (40 mL), washed with 1 M HCl (50 mL), Na₂S₂O₃ (40 mL of a sat. aq. solution), then brine (40 mL). The organic layer was passed through a phase separator and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white powder (12 mg, 97% purity, 43% Yield).

¹H NMR (500 MHz, DMSO) δ 7.89 – 7.84 (m, 2H), 7.82 (d, J = 8.1 Hz, 1H), 7.66 (s, 1H), 7.51 – 7.46 (m, 1H), 7.23 (d, J = 2.2 Hz, 1H), 6.96 – 6.92 (m, 1H), 5.51 (d, J = 13.3 Hz, 1H), 5.17 (d, J = 13.1 Hz, 1H).

LCMS: m/z = 518.0/520.0 [M-H]⁻, (ESI⁻), RT = 4.22, Method A

Example 29 – Synthesis of 4-Bromo-13-chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.0^{2,7}]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (Compound 29)

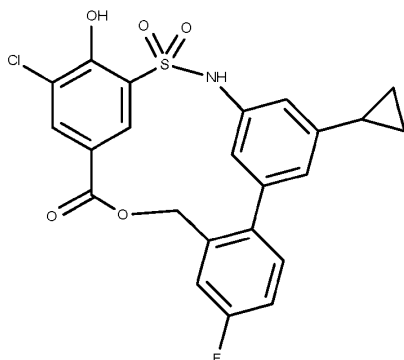


[0267] 4-bromo-13-chloro-19,21-difluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.0^{2,7}]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 93% purity, 113 mg, 0.19 mmol) and iodocyclohexane (0.12 mL, 0.946 mmol) were weighed in a pressure vial and anhydrous DMF (3.2 mL) was added. The reaction mixture was stirred at 120 °C for 1.5 h. The mixture was diluted with EtOAc (40 mL), washed with 1 M HCl (50 mL), Na₂S₂O₃ (40 mL of a sat. aq. solution), then brine (40 mL). The EtOAc layer was passed through a phase separator and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a brown solid (57 mg, 95% purity, 53% Yield).

¹H NMR (500 MHz, DMSO) δ 10.10 (s, 1H), 7.94 (d, J = 2.2 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.56 – 7.47 (m, 3H), 7.21 (d, J = 2.2 Hz, 1H), 6.87 – 6.80 (m, 1H), 5.44 (d, J = 12.9 Hz, 1H), 5.05 (d, J = 12.8 Hz, 1H).

LCMS: m/z = 529.9/531.9 [M-H]⁻, (ESI⁻), RT = 4.22, Method A

Example 30 – Synthesis of 13-Chloro-20-cyclopropyl-5-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 30)

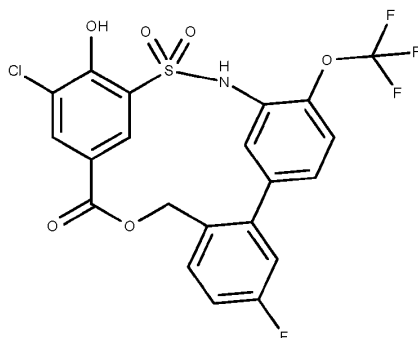


[0268] To a solution of 13-chloro-20-cyclopropyl-5-fluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 91% purity, 295 mg, 0.6 mmol) in anhydrous DMF (8.9 mL) was added iodocyclohexane (150 μ L, 1.16 mmol). The reaction mixture was stirred at 120 °C for 1.75 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (171 mg, 99% purity, 59% Yield).

^1H NMR (500 MHz, DMSO) δ 10.81 (br s, 1H), 10.00 (s, 1H), 7.90 (d, J = 2.1 Hz, 1H), 7.45 (dd, J = 9.5, 2.3 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.13 (d, J = 2.1 Hz, 1H), 7.06 – 7.02 (m, 1H), 6.71 (d, J = 1.9 Hz, 1H), 6.62 – 6.57 (m, 1H), 5.39 (d, J = 12.6 Hz, 1H), 5.30 (d, J = 12.6 Hz, 1H), 1.85 (tt, J = 8.4, 5.0 Hz, 1H), 0.97 – 0.87 (m, 2H), 0.64 – 0.58 (m, 1H), 0.58 – 0.49 (m, 1H).

LCMS: m/z = 472.1/474.1 $[\text{M}-\text{H}]^-$, (ESI-), RT = 4.41, Method A

Example 31 – Synthesis of 13-Chloro-4-fluoro-14-hydroxy-16,16-dioxo-19-(trifluoromethoxy)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 31)

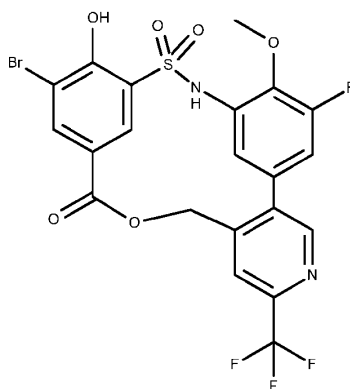


[0269] 13-chloro-4-fluoro-14-methoxy-16,16-dioxo-19-(trifluoromethoxy)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 7*, 98% purity, 170 mg, 0.313 mmol) and iodocyclohexane (330 mg, 1.57 mmol) were combined and the mixture dissolved into anhydrous DMF (5 mL). The mixture was heated to 80 °C and stirred for 24 h. Sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (74 mg, 97% purity, 44% Yield).

¹H NMR (500 MHz, DMSO) δ 10.22 (s, 1H), 7.89 (d, J = 2.2 Hz, 1H), 7.62 (dd, J = 8.5, 5.8 Hz, 1H), 7.49 (dd, J = 8.5, 2.2 Hz, 1H), 7.33 (dd, J = 8.5, 1.8 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.20 (dd, J = 9.3, 2.8 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 5.37 – 5.28 (m, 2H).

LCMS: m/z = 516.2/518.3 [M-H]⁻, (ESI⁻), RT = 4.30, Method A

Example 32 – Synthesis of 13-Bromo-20-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 32)

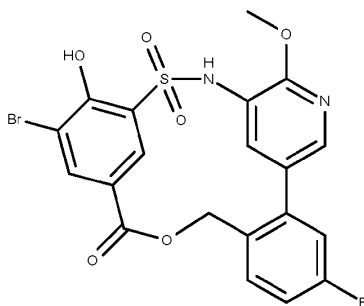


[0270] *Intermediate 24* (95 mg, 99% purity, 0.153 mmol) and lithium iodide (25 mg, 0.187 mmol) were dissolved into anhydrous pyridine (3 mL). The mixture was heated to 80 °C and stirred for 18 h. The mixture was cooled to r.t. Sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (56 mg, 98% purity, 62% Yield).

¹H NMR (500 MHz, DMSO) δ 9.78 (s, 1H), 8.70 (s, 1H), 8.21 (s, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.12 (d, J = 2.0 Hz, 1H), 5.64 (d, J = 13.2 Hz, 1H), 5.38 (d, J = 13.2 Hz, 1H), 3.60 (d, J = 2.1 Hz, 3H).

LCMS: m/z = 577.0/579.0 [M+H]⁺, (ESI⁺), RT = 4.16, Method A

Example 33 – Synthesis of 13-Bromo-4-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one (Compound 33)

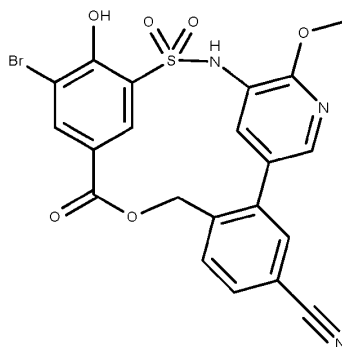


[0271] Lithium iodide (83 mg, 0.620 mmol) was added to a stirred solution of 13-bromo-4-fluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 24*, 88% purity, 145 mg, 0.244 mmol) in anhydrous pyridine (4 mL) in a pressure tube (10 mL) and the mixture stirred at 90 °C for 3 h 30 m. The reaction vessel was allowed to cool to r.t., and the reaction mixture was diluted with EtOAc (25 mL) and washed with sat. aq. sodium thiosulphate (25 mL), 1 M aq. HCl (25 mL), and brine (25 mL). The organic phase was passed through a phase separator and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a light pink solid (57 mg, 99% purity, 46 % Yield).

¹H NMR (500 MHz, DMSO) δ 9.78 (s, 1H), 8.15 (d, J = 2.2 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.66 – 7.57 (m, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.31 – 7.25 (m, 2H), 5.61 (d, J = 13.0 Hz, 1H), 5.22 (d, J = 13.0 Hz, 1H), 3.58 (s, 3H).

LCMS: m/z = 508.9, 510.9 [M+H]⁺, (ESI⁺), RT = 3.97, Method A

Example 34 – Synthesis of 13-Bromo-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile (Compound 34)

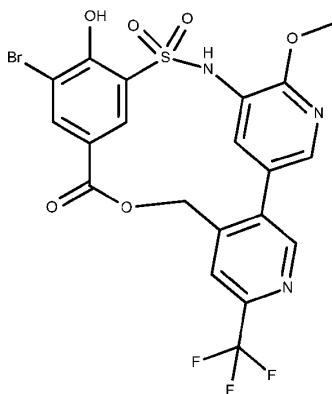


[0272] A mixture of *intermediate 26* (86% purity, 150 mg, 0.283 mmol), lithium iodide (191 mg, 1.41 mmol) and anhydrous pyridine (3 mL) was stirred at 90 °C for 2 h 30. The reaction mixture was diluted with EtOAc (40 mL), washed with sat. aq. Na₂S₂O₃ (30 mL), 1 M aq. HCl (30 mL) and brine (30 mL), then passed through a phase separator and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (26.5 mg, 99% purity, 18% yield).

¹H NMR (500 MHz, DMSO) δ 9.73 (s, 1H), 8.15 (d, J = 2.2 Hz, 1H), 8.02 (d, J = 2.2 Hz, 1H), 7.93 (dd, J = 7.9, 1.8 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 2.2 Hz, 1H), 7.31 (d, J = 2.2 Hz, 1H), 5.73 (d, J = 13.3 Hz, 1H), 5.28 (d, J = 13.3 Hz, 1H), 3.58 (s, 3H).

LCMS: m/z = 516.0/518.0 [M+H]⁺, (ESI⁺), RT = 3.76, Method A

Example 35 – Synthesis of 13-Bromo-14-hydroxy-19-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 35)

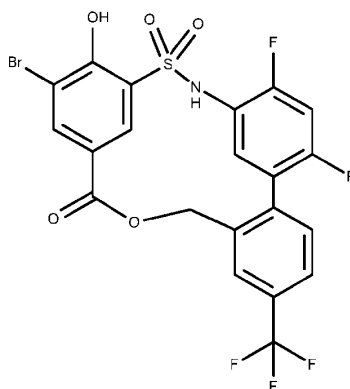


[0273] In a pressure vial, 13-bromo-14,19-dimethoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 26*, 90% purity, 151 mg, 0.250 mmol) was dissolved in anhydrous pyridine (6.4 mL) and lithium iodide (293 mg, 2.19 mmol) was added. The reaction mixture was heated at 70 °C for 16 h. The reaction mixture was concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (88.0 mg, 98% purity, 62% yield).

¹H NMR (500 MHz, DMSO) δ 9.82 (s, 1H), 8.75 (s, 1H), 8.20 (s, 1H), 8.18 (d, J = 2.2 Hz, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 5.90 – 5.68 (m, 1H), 5.44 – 5.32 (m, 1H), 3.59 (s, 3H).

LCMS: m/z = 558.0/560.0 [M-H]⁻, (ESI⁻), RT = 3.98, Method A

Example 36 – Synthesis of 13-Bromo-19,21-difluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 36)

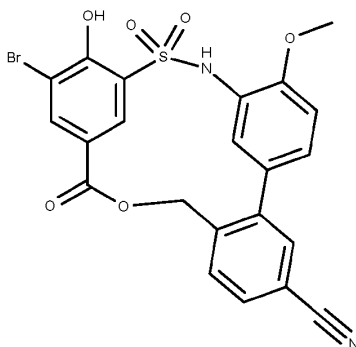


[0274] 13-bromo-19,21-difluoro-14-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 24*, 95% purity, 140 mg, 0.230 mmol) and lithium iodide (155 mg, 1.16 mmol) were combined and the mixture dissolved into anhydrous pyridine (7 mL). The mixture was heated to 80 °C and stirred for 18 h. The mixture was cooled to r.t. Sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (70 mg, 95% purity, 51% Yield).

¹H NMR (500 MHz, DMSO) δ 10.15 (s, 1H), 8.09 (d, J = 2.2 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 8.0, 2.0 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 2.2 Hz, 1H), 6.85 – 6.74 (m, 1H), 5.63 (d, J = 13.0 Hz, 1H), 5.13 (d, J = 13.0 Hz, 1H).

LCMS: m/z = 561.9/563.9 [M-H]⁻, (ESI⁻), RT = 4.42, Method A

Example 37 – Synthesis of 13-Bromo-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile (Compound 37)

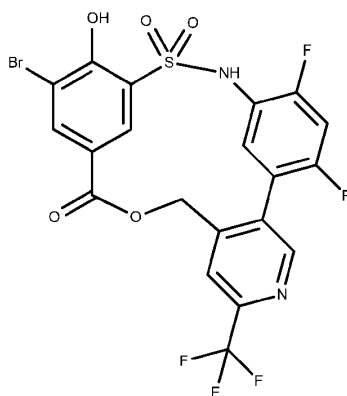


[0275] To a solution of 13-bromo-14,19-dimethoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile (*synthesised using a similar method to intermediate 24*, 79% purity, 100 mg, 0.179 mmol) in anhydrous pyridine (3 mL) was added lithium iodide (84 mg, 0.628 mmol). The reaction mixture was heated at 100 °C for 3 h. The reaction mixture was cooled to r.t. The organics were diluted with EtOAc (5 mL), washed with 2 M Na₂S₂O₃ (5 mL), 1 M HCl (5 mL), then brine (5 mL). The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (20 mg, 98% purity, 21% Yield).

¹H NMR (500 MHz, DMSO) δ 9.32 (s, 1H), 7.99 (d, J=2.2 Hz, 1H), 7.89 (dd, J=7.8, 1.8 Hz, 1H), 7.82 (d, J=1.8 Hz, 1H), 7.75 (d, J=7.9 Hz, 1H), 7.36 (d, J=2.3 Hz, 1H), 7.31 (dd, J=8.4, 2.2 Hz, 1H), 7.22 (d, J=2.2 Hz, 1H), 6.76 (d, J=8.5 Hz, 1H), 5.70 (d, J=13.0 Hz, 1H), 5.18 (d, J=13.2 Hz, 1H), 3.46 (s, 3H).

LCMS: m/z = 513.0/515.0 [M-H]⁻, (ESI⁻), RT = 3.89, Method A

Example 38 – Synthesis of 13-Bromo-19,21-difluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosan-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 38)

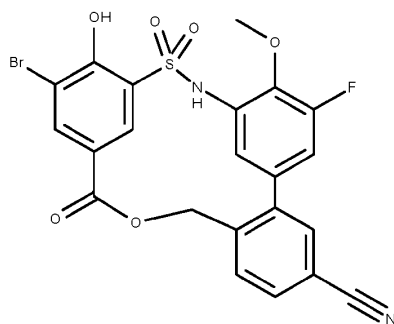


[0276] To a solution of 13-bromo-19,21-difluoro-14-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosan-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 24*, 97% purity, 174 mg, 0.3 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (201 mg, 1.5 mmol). The reaction mixture was heated at 80 °C for 5 h. The reaction mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (100 mg, 95% purity, 56% Yield).

¹H NMR (500 MHz, DMSO) δ 10.24 (br.s, 1H), 8.67 (s, 1H), 8.21 (s, 1H), 8.09 (d, J = 2.2 Hz, 1H), 7.63 – 7.55 (m, 1H), 7.21 (d, J = 2.2 Hz, 1H), 7.06 – 6.96 (m, 1H), 5.66 (d, J = 13.6 Hz, 1H), 5.20 (d, J = 13.5 Hz, 1H).

LCMS: m/z = 565.1/567.1 [M+H]⁺, (ESI⁺), RT = 4.09, Method A

Example 39 – Synthesis of 13-Bromo-20-fluoro-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile (Compound 39)

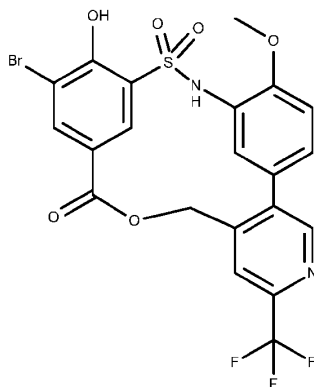


[0277] 13-bromo-20-fluoro-14,19-dimethoxy-10,16,16-trioxo-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile (*synthesised using a similar method to intermediate 26*, 140 mg, 0.238 mmol) and lithium iodide (445 mg, 3.30 mmol) were combined and dissolved into anhydrous pyridine (12 mL). The mixture was then heated to 100 °C and stirred for 3 h. The mixture was cooled to r.t. Sat. aq. Na₂S₂O₃ (30 mL) was added, and the mixture was extracted with DCM (3 x 30 mL). The combined organic extracts were washed with 1 M aq. HCl (30 mL), then brine (30 mL) and were dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a pale brown solid (115 mg, 96% purity, 62% Yield).

¹H NMR (500 MHz, DMSO) δ 9.78 (s, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.92 (dd, J = 7.9, 1.8 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.42 (dd, J = 12.1, 2.1 Hz, 1H), 7.06 – 7.01 (m, 1H), 5.60 (d, J = 12.9 Hz, 1H), 5.27 (d, J = 13.0 Hz, 1H), 3.57 (d, J = 2.0 Hz, 3H).

LCMS: m/z = 531.0 / 532.9 [M-H]⁻, (ESI⁻), RT = 4.04, Method A

Example 40 – Synthesis of 13-Bromo-14-hydroxy-19-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 40)

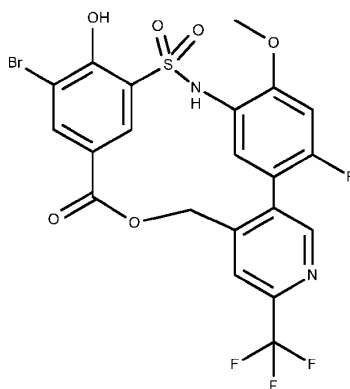


[0278] 13-Bromo-14,19-dimethoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (synthesised using a similar method to intermediate 26, 375 mg, 0.634 mmol) and lithium iodide (100 mg, 0.747 mmol) were combined and the mixture dissolved into anhydrous pyridine (12 mL). The mixture was heated to 80 °C and stirred for 18 h. The mixture was cooled to r.t. Sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (2 x 50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated. The crude material was taken into EtOH (200 mL) with heat (80 °C) and stirring until observed dissolution and evaporated to dryness. This process was repeated and the resultant solid was transferred to a vial and dried in a vacuum oven to give the title compound (235 mg, 98% purity, 65% Yield) as an off-white solid.

¹H NMR (500 MHz, DMSO) δ 9.42 (s, 1H), 8.73 (s, 1H), 8.16 (s, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.30 (d, J = 2.2 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 5.77 (d, J = 13.5 Hz, 1H), 5.29 (d, J = 13.6 Hz, 1H), 3.48 (s, 3H).

LCMS: m/z = 559.0/560.9 [M+H]⁺, (ESI⁺), RT = 4.09, Method A

Example 41 – Synthesis of 13-Bromo-21-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ ,6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 41)

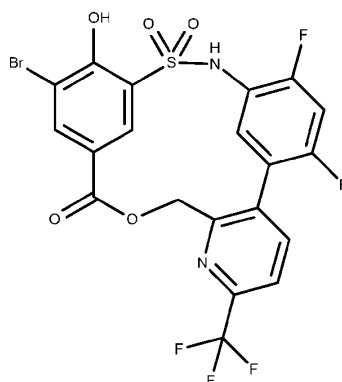


[0279] 13-Bromo-21-fluoro-14,19-dimethoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ ,6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 26*, 210 mg, 0.355 mmol) and lithium iodide (55 mg, 0.411 mmol) were combined and the mixture dissolved into anhydrous pyridine (7 mL). The mixture was heated to 80 °C and stirred for 18 h. The mixture was cooled to r.t. Sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (142 mg, 97% purity, 67% Yield).

¹H NMR (500 MHz, DMSO) δ 9.50 (s, 1H), 8.77 (s, 1H), 8.18 (s, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.38 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 11.8 Hz, 1H), 5.47 (d, J = 13.9 Hz, 1H), 5.40 (d, J = 14.0 Hz, 1H), 3.52 (s, 3H).

LCMS: m/z = 577.0/578.9 [M+H]⁺, (ESI⁺), RT = 4.15, Method A

Example 42 – Synthesis of 13-Bromo-19,21-difluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricosan-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 42)

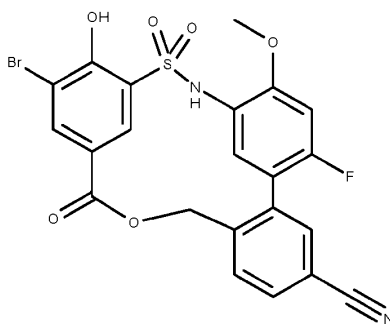


[0280] To a solution of 13-bromo-19,21-difluoro-14-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricosan-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised using a similar method to intermediate 26*, 98% purity, 250 mg, 0.423 mmol) in anhydrous pyridine (3 mL) was added lithium iodide (566 mg, 4.23 mmol). The reaction mixture was heated at 90 °C for 3 h. Organics were diluted with EtOAc (10 mL), washed with sat. aq. Na₂S₂O₃ (10 mL), 1 M HCl (3 x 10 mL), then brine (10 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (107 mg, 96% purity, 43% Yield).

¹H NMR (500 MHz, DMSO) δ 10.21 (s, 1H), 8.11 – 8.06 (m, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.09 – 7.02 (m, 1H), 5.55 (d, J = 13.6 Hz, 1H), 5.39 (d, J = 13.5 Hz, 1H).

LCMS: m/z = 562.9/565.0 [M-H]⁻, (ESI⁻), RT = 4.28, Method A

Example 43 – Synthesis of 13-Bromo-21-fluoro-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile (Compound 43)

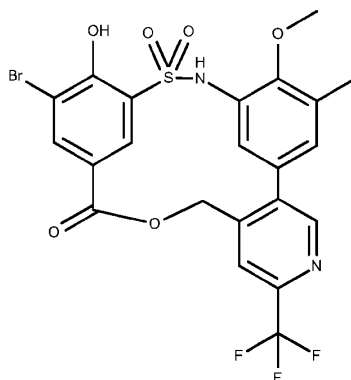


[0281] 13-Bromo-21-fluoro-14,19-dimethoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile (*synthesised using a similar method to intermediate 26*, 100% purity, 215 mg, 0.393 mmol) and lithium iodide (524 mg, 3.89 mmol) were dissolved into anhydrous pyridine (14 mL). The mixture was then heated to 80 °C and stirred for 5.5 h. The reaction mixture was concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (130 mg, 100% purity, 62% Yield).

¹H NMR (500 MHz, DMSO) δ 9.49 – 9.36 (m, 1H), 8.05 – 8.01 (m, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.88 (d, J = 1.7 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 2.2 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 11.8 Hz, 1H), 5.39 (d, J = 13.3 Hz, 1H), 5.31 (d, J = 13.4 Hz, 1H), 3.52 (s, 3H).

LCMS: m/z = 531.4/533.5 [M-H]⁻, (ESI⁻), RT = 3.84, Method A

Example 44 – Synthesis of 13-Bromo-14-hydroxy-19-methoxy-20-methyl-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 44)

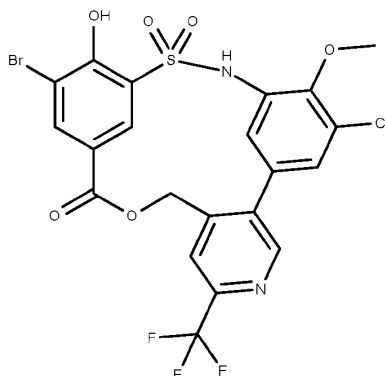


[0282] 13-Bromo-14,19-dimethoxy-20-methyl-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 26*, 193 mg, 0.325 mmol) and lithium iodide (50 mg, 0.374 mmol) were dissolved in anhydrous pyridine (6 mL) and the reaction mixture was stirred at 80 °C for 20 h. The reaction mixture was cooled to r.t. then diluted with EtOAc (30 mL) and washed with sat. aq. Na₂S₂O₃ solution (30 mL), 1 M aq. HCl (30 mL), and brine (30 mL). The organic component was dried over MgSO₄, filtered, and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (126 mg, 99% purity, 67% yield).

¹H NMR (400 MHz, DMSO) δ 9.65 (br. s, 1H), 8.64 (s, 1H), 8.18 (s, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.44 (d, J = 2.2 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.02 (d, J = 2.2 Hz, 1H), 5.59 (d, J = 13.2 Hz, 1H), 5.42 (d, J = 13.3 Hz, 1H), 3.50 (s, 3H), 2.11 (s, 3H)

LCMS: m/z = 573.0/575.0 [M+H]⁺, (ESI⁺), RT = 3.98, Method C

Example 45 – Synthesis of 13-Bromo-20-chloro-14-hydroxy-19-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 45)

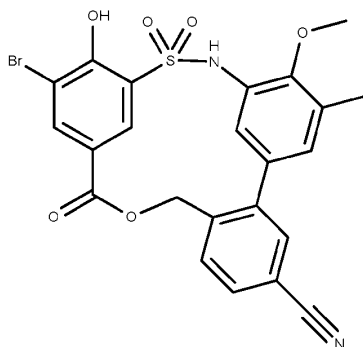


[0283] To a solution of 13-bromo-20-chloro-14,19-dimethoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 26*, 250 mg, 0.41 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (137.637 mg, 1.03 mmol). The mixture was heated at 80 °C for 5 h. The mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (136 mg, 98% purity, 55% Yield).

¹H NMR (500 MHz, DMSO) δ 9.98 (br s, 1H), 8.68 (s, 1H), 8.21 (s, 1H), 8.07 (d, J = 2.1 Hz, 1H), 7.64 (d, J = 2.1 Hz, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.21 (d, J = 2.1 Hz, 1H), 5.61 (d, J = 13.2 Hz, 1H), 5.43 (d, J = 13.3 Hz, 1H), 3.58 (s, 3H).

LCMS: m/z = 593.0/595.0 [M+H]⁺, (ESI⁺), RT = 4.34, Method A

Example 46 – Synthesis of 13-Bromo-14-hydroxy-19-methoxy-20-methyl-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile (Compound 46)

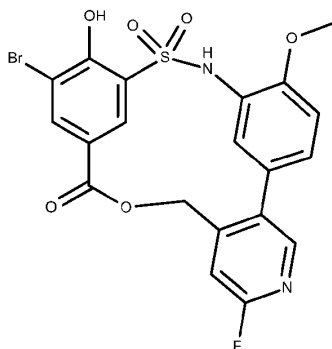


[0284] A mixture of 13-bromo-14,19-dimethoxy-20-methyl-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile (*synthesised using a similar method to intermediate 26*, 518 mg, 0.925 mmol) and lithium iodide (300 mg, 2.22 mmol) in anhydrous pyridine (10 mL) was stirred at 90 °C under N₂ for 3 h. The mixture was diluted with EtOAc (50 mL) and washed successively with sat aq. Na₂S₂O₃ solution (50 mL), water (50 mL), 1 M aq. HCl solution (50 mL), and brine (50 mL). The organic component was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as a beige solid (178 mg, 99% purity, 36% yield).

¹H NMR (500 MHz, DMSO) δ 9.60 (br. s, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.89 (dd, J = 7.9, 1.7 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 1.7 Hz, 1H), 7.46 (d, J = 2.1 Hz, 1H), 7.22 (d, J = 2.1 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 5.53 (d, J = 12.8 Hz, 1H), 5.30 (d, J = 12.8 Hz, 1H), 3.45 (s, 3H), 2.10 (s, 3H).

LCMS: m/z = 527.0/529.0 [M-H]⁻, (ESI⁻), RT = 3.80, Method C

Example 47 – Synthesis of 13-Bromo-5-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 47)

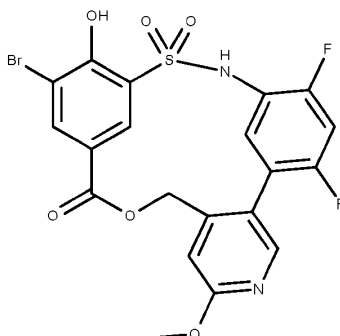


[0285] To a solution of 13-bromo-5-fluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 11, using a similar method to intermediate 24*, 95% purity, 84 mg, 0.152 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (166 mg, 1.24 mmol) and the mixture was heated at 80 °C for 15 h. Further lithium iodide (35 mg, 0.261 mmol) was added and the mixture was heated to 100 °C for 3 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (51 mg, 95% purity, 62% Yield).

¹H NMR (500 MHz, DMSO) δ 9.39 (s, 1H), 8.20 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.45 (d, J = 1.9 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.30 (dd, J = 8.5, 2.2 Hz, 1H), 7.22 (d, J = 2.2 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 5.67 (d, J = 13.3 Hz, 1H), 5.18 (d, J = 13.4 Hz, 1H), 3.47 (s, 3H).

LCMS: m/z = 506.9/508.9 [M-H]⁻, (ESI⁻), RT = 3.65, Method A

Example 48 – Synthesis of 13-Bromo-19,21-difluoro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 48)

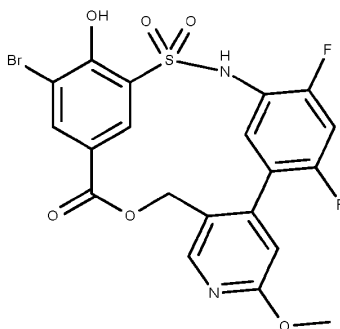


[0286] To a solution of 13-bromo-19,21-difluoro-5,14-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (*synthesised from intermediate 12, using a similar method to intermediate 24*, 95% purity, 44 mg, 0.0772 mmol) in anhydrous pyridine (2 mL) was added lithium iodide (36 mg, 0.273 mmol) and the mixture was heated at 100 °C for 3 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (20 mg, 98% purity, 48% Yield).

¹H NMR (500 MHz, DMSO) δ 10.09 (br s, 1H), 8.05 (d, J=18.3 Hz, 2H), 7.56 - 7.44 (m, 1H), 7.20 (d, J=2.2 Hz, 1H), 7.07 (s, 1H), 6.86 - 6.79 (m, 1H), 5.42 (d, J=13.1 Hz, 1H), 5.05 (d, J=13.0 Hz, 1H), 3.90 (s, 3H).

LCMS: m/z = 524.9/526.9 [M-H]⁻, (ESI⁻), RT = 3.99, Method A

Example 49 – Synthesis of 13-Bromo-19,21-difluoro-14-hydroxy-4-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 49)

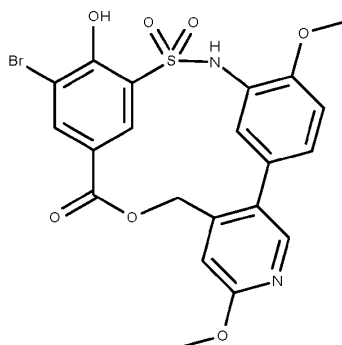


[0287] To a solution of 13-bromo-19,21-difluoro-4,14-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised from intermediate 28, using a similar method to intermediate 26*, 97% purity, 60 mg, 0.108 mmol) in anhydrous pyridine (2 mL) was added lithium iodide (72 mg, 0.538 mmol) and the mixture was heated at 90 °C for 3 h. The mixture was diluted with EtOAc (10 mL), washed with 2 M Na₂S₂O₃ (10 mL), 1 M HCl (3 x 10 mL), then brine (10 mL). The organic layer was dried over Na₂SO₄, filtered, then concentrated and lyophilised to afford the title compound as a white solid (40 mg, 98% purity, 68% Yield).

¹H NMR (500 MHz, DMSO) δ 10.15 (s, 1H), 8.32 (s, 1H), 8.08 (d, J = 2.1 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.18 (d, J = 2.1 Hz, 1H), 6.79 – 6.72 (m, 2H), 5.49 (d, J = 12.8 Hz, 1H), 4.96 (d, J = 12.7 Hz, 1H), 3.88 (s, 3H).

LCMS: m/z = 524.9/526.9 [M-H]⁻, (ESI⁻), RT = 3.99, Method A

Example 50 – Synthesis of 13-Bromo-14-hydroxy-5,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 50)

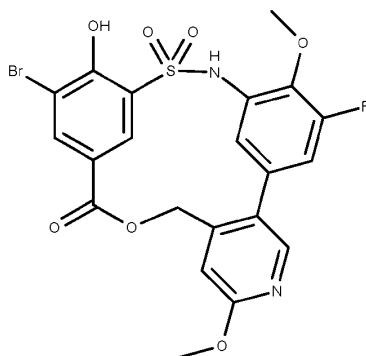


[0288] A mixture of 13-bromo-5,14,19-trimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised from intermediate 12, using a similar method to intermediate 26*, 81% purity, 215 mg, 0.325 mmol), lithium iodide (109 mg, 0.813 mmol) and anhydrous pyridine (2 mL) was heated at 90 °C for 3 h. The mixture was cooled to r.t., diluted with EtOAc (50 mL), washed with sat. aq. Na₂S₂O₃ (50 mL), 1 M aq. HCl (50 mL) and brine (30 mL), then dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (76 mg, 98% purity, 44% Yield) as a white solid.

¹H NMR (500 MHz, DMSO) δ 9.29 (s, 1H), 8.09 (s, 1H), 7.99 (s, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 8.4, 2.3 Hz, 1H), 7.16 (d, J = 2.2 Hz, 1H), 7.04 (s, 1H), 6.75 (d, J = 8.5 Hz, 1H), 5.58 (d, J = 13.0 Hz, 1H), 5.07 (d, J = 13.1 Hz, 1H), 3.90 (s, 3H), 3.46 (s, 3H).

LCMS: m/z = 518.9/520.9 [M-H]⁻, (ESI⁻), RT = 3.85, Method A

Example 51 – Synthesis of 13-Bromo-20-fluoro-14-hydroxy-5,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1.11,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 51)

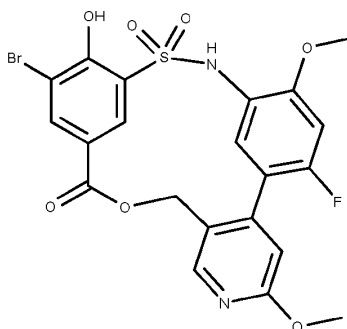


[0289] A mixture of 13-bromo-20-fluoro-5,14,19-trimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1.11,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised from intermediate 12, using a similar method to intermediate 26*, 260 mg, 0.446 mmol), lithium iodide (150 mg, 1.12 mmol) and anhydrous pyridine (2 mL) was heated at 90 °C for 3 h. The mixture was cooled to r.t., diluted with EtOAc (5 mL), washed with sat. aq. Na₂S₂O₃ (5 mL), 1 M aq. HCl (3 x 5 mL) and brine (5 mL), then dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a yellow solid (73 mg, 99% purity, 30% Yield).

¹H NMR (500 MHz, DMSO) δ 9.74 (s, 1H), 8.07 (s, 1H), 8.05 (d, J = 2.1 Hz, 1H), 7.45 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 12.1, 2.1 Hz, 1H), 7.07 (s, 1H), 6.99 (s, 1H), 5.48 (s, 1H), 5.17 (s, 1H), 3.90 (s, 3H), 3.57 (d, J = 2.0 Hz, 3H).

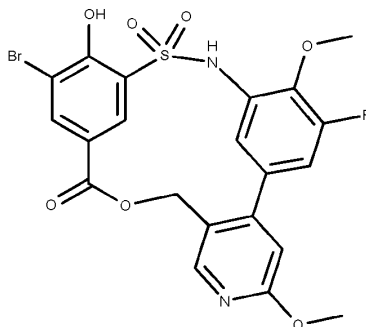
LCMS: m/z = 537.0/539.0 [M-H]⁻, (ESI⁻), RT = 4.04, Method A

Example 52 – Synthesis of 13-Bromo-21-fluoro-14-hydroxy-4,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 52)



[0290] To a solution of 13-bromo-21-fluoro-4,14,19-trimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 28, using a similar method to intermediate 26*, 95% purity, 162 mg, 0.293 mmol) in anhydrous pyridine (8.0 mL) was added lithium iodide (345 mg, 2.58 mmol) and the mixture was heated at 80 °C for 6 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (89 mg, 99% purity, 56% Yield). ¹H NMR (500 MHz, DMSO) δ 9.53 (s, 1H), 8.31 (s, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.05 (d, J = 7.9 Hz, 1H), 6.92 (d, J = 11.8 Hz, 1H), 6.86 (s, 1H), 5.28 (dd, J = 12.7, 2.0 Hz, 1H), 5.20 (d, J = 12.7 Hz, 1H), 3.91 (s, 3H), 3.54 (s, 3H). LCMS: m/z = 539.0/540.9 [M+H]⁺, (ESI⁺), RT = 3.96, Method A

Example 53 – Synthesis of 13-Bromo-20-fluoro-14-hydroxy-4,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 53)

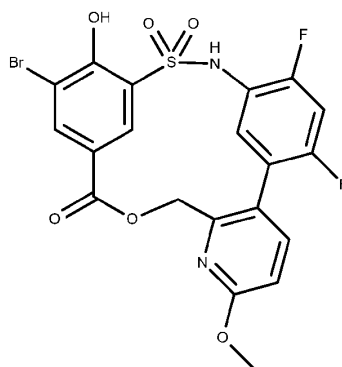


[0291] To a solution of 13-bromo-20-fluoro-4,14,19-trimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 28, using a similar method to intermediate 26*, 90% purity, 191 mg, 0.345 mmol) in anhydrous pyridine (9.5 mL) was added lithium iodide (407 mg, 3.04 mmol) and the mixture was heated at 80 °C for 16 h. The mixture was concentrated and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (51 mg, 96% purity, 26% Yield).

¹H NMR (500 MHz, DMSO) δ 9.85 (s, 1H), 8.31 (s, 1H), 8.07 (d, J = 2.2 Hz, 1H), 7.50 – 7.36 (m, 2H), 6.97 – 6.91 (m, 1H), 6.79 (s, 1H), 5.38 (br. s, 1H), 5.25 (br. s, 1H), 3.90 (s, 3H), 3.59 (d, J = 2.0 Hz, 3H).

LCMS: m/z = 539.0/541.0 [M+H]⁺, (ESI⁺), RT = 4.04, Method A

Example 54- Synthesis of 13-Bromo-19,21-difluoro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.1¹¹¹.15.0^{2,7}]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 54)

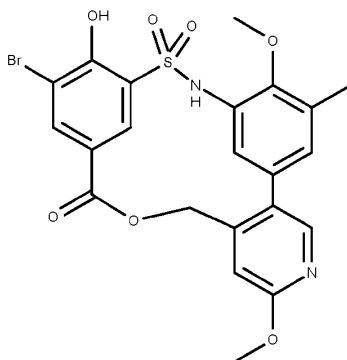


[0292] To a solution of 13-bromo-19,21-difluoro-5,14-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.1¹¹¹.15.0^{2,7}]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised from intermediate 29, using a similar method to intermediate 26*, 98% purity, 250 mg, 0.453 mmol) in anhydrous pyridine (3 mL) was added lithium iodide (303 mg, 2.26 mmol) and the mixture was heated at 90 °C for 3 h. The mixture was diluted with EtOAc (10 mL), washed with sat. aq. Na₂S₂O₃ (10 mL), 1 M HCl (3 x 10 mL), then brine (10 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo to afford the title compound as an off-white solid (115 mg, 97% purity, 47% yield).

¹H NMR (500 MHz, DMSO) δ 10.15 (s, 1H), 8.10 (d, J = 2.2 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.27 (d, J = 2.1 Hz, 1H), 6.95 – 6.88 (m, 2H), 5.35 (d, J = 13.2 Hz, 1H), 5.27 (d, J = 13.1 Hz, 1H), 3.92 (s, 3H).

LCMS: m/z = 525.0/527.0 [M-H]⁻, (ESI⁻), RT = 4.22, Method A

Example 55 – Synthesis of 13-Bromo-14-hydroxy-5,19-dimethoxy-20-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 55)

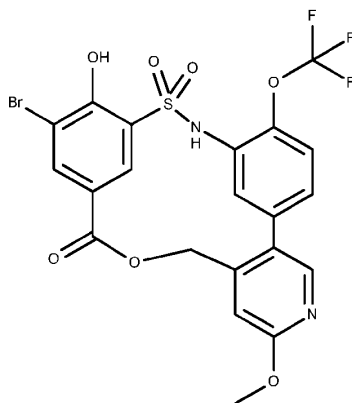


[0293] 13-Bromo-5,14,19-trimethoxy-20-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 12, using a similar method to intermediate 26*, 95% purity, 110 mg, 0.201 mmol) and lithium iodide (268 mg, 1.99 mmol) were dissolved into anhydrous pyridine (7.2 mL). The mixture was then heated to 80 °C and stirred for 20 h. The mixture was concentrated and the residue was purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as an off-white solid (75.6 mg, 99% purity, 70% yield) as an off-white solid.

¹H NMR (500 MHz, DMSO) δ 9.63 – 9.53 (m, 1H), 8.04 – 8.02 (m, 1H), 8.00 (s, 1H), 7.45 (d, J = 2.2 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.05 (s, 1H), 6.89 (s, 1H), 5.42 (d, J = 12.8 Hz, 1H), 5.20 (d, J = 12.7 Hz, 1H), 3.89 (s, 3H), 3.47 (s, 3H), 2.09 (s, 3H).

LCMS: m/z = 535.0/537.0 [M+H]⁺, (ESI⁺), RT = 4.11, Method A

Example 56 – Synthesis of 13-Bromo-14-hydroxy-5-methoxy-16,16-dioxo-19-(trifluoromethoxy)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 56)

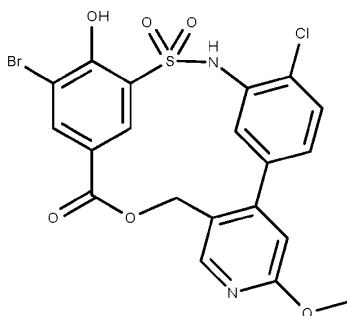


[0294] 13-Bromo-5,14-dimethoxy-16,16-dioxo-19-(trifluoromethoxy)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 12, using a similar method to intermediate 26*, 98% purity, 40 mg, 0.0679 mmol) and lithium iodide (91 mg, 0.671 mmol) were dissolved into anhydrous pyridine (2.4 mL). The mixture was then heated to 80 °C and stirred for 4 h. The mixture was concentrated and the residue was purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as an off-white solid (17.4 mg, 97% purity, 43% yield).

¹H NMR (500 MHz, DMSO) δ 10.36 – 10.08 (m, 1H), 8.05 (s, 1H), 8.03 (s, 1H), 7.49 (dd, J = 8.6, 2.1 Hz, 1H), 7.37 (dd, J = 8.3, 1.8 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.07 (s, 1H), 6.97 (d, J = 2.2 Hz, 1H), 5.32 (s, 2H), 3.89 (s, 3H).

LCMS: m/z = 575.2/577.2 [M+H]⁺, (ESI⁺), RT = 4.17, Method A

Example 57- Synthesis of 13-Bromo-19-chloro-14-hydroxy-4-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 57)

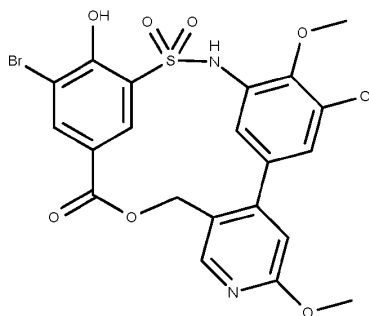


[0295] To a solution of 13-bromo-19-chloro-4,14-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised from intermediate 28, using a similar method to intermediate 26*, 88 mg, 0.163 mmol) in anhydrous pyridine (3 mL) was added lithium iodide (111 mg, 0.829 mmol). The reaction mixture was heated at 80 °C overnight. The mixture was cooled to r.t., diluted with EtOAc (20 mL), washed with sat. aq. Na₂S₂O₃ (20 mL), 2 M aq. HCl (20 mL) and brine (20 mL), then dried over Na₂SO₄, filtered, and concentrated. The resulting solid was dried in the vacuum oven overnight to afford the title compound as a light pink solid (68.8 mg, 98% purity, 79% yield).

¹H NMR (500 MHz, DMSO) δ 10.07 (br. s, 1H), 8.30 (s, 1H), 8.00 (s, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.41 (dd, J = 8.2, 2.0 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.03 (s, 1H), 6.76 (s, 1H), 5.29 (s, 2H), 3.89 (s, 3H)

LCMS: m/z = 522.9/524.9 [M-H]⁻, (ESI⁻), RT = 4.01, Method A

Example 58 – Synthesis of 13-Bromo-20-chloro-14-hydroxy-4,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.1.11,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 58)

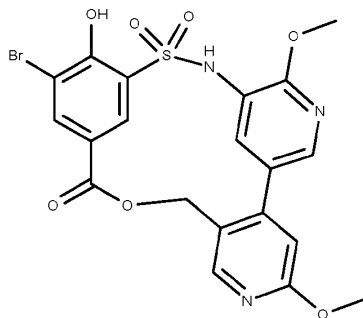


[0296] To a solution of 13-bromo-20-chloro-4,14,19-trimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.1.11,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised from intermediate 28, using a similar method to intermediate 26*, 70 mg, 0.113 mmol) in anhydrous pyridine (2 mL) was added lithium iodide (77 mg, 0.575 mmol). The reaction mixture was heated at 80 °C overnight. The mixture was cooled to r.t., diluted with EtOAc (20 mL), washed with sat. aq. Na₂S₂O₃ (20 mL), 2 M aq. HCl (20 mL) and brine (20 mL), then dried over Na₂SO₄, filtered, and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (16.6 mg, 99% purity, 26% yield).

¹H NMR (500 MHz, DMSO) δ 9.92 (br s, 1H), 8.31 (s, 1H), 8.05 (d, J = 2.1 Hz, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.44 (d, J = 2.2 Hz, 1H), 7.07 (s, 1H), 6.78 (s, 1H), 5.33 (s, 1H), 5.26 (s, 1H), 3.89 (s, 3H), 3.55 (s, 3H).

LCMS: m/z = 553.0/555.0 [M-H]⁻, (ESI⁻), RT = 4.22, Method A

Example 59 – Synthesis of 13-Bromo-14-hydroxy-4,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17,20-triazatetracyclo[16.3.1.1¹¹¹.15.0^{2,7}]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 59)

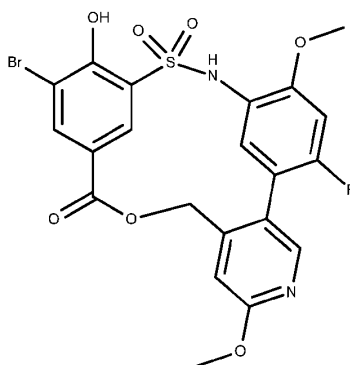


[0297] In a pressure vial, 13-bromo-4,14,19-trimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17,20-triazatetracyclo[16.3.1.1¹¹¹.15.0^{2,7}]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 28, using a similar method to intermediate 26*, 210 mg, 0.380 mmol) was dissolved in anhydrous pyridine (7.0 mL) and lithium iodide (450 mg, 3.36 mmol) was added. The reaction mixture was heated at 80 °C for 1 h 45 min. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (104 mg, 99% purity, 52% yield).

¹H NMR (500 MHz, DMSO) δ 9.79 (s, 1H), 8.32 (s, 1H), 8.18 (d, J = 2.3 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H), 7.44 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 2.2 Hz, 1H), 6.87 (s, 1H), 5.48 (s, 1H), 5.26 (s, 1H), 3.90 (s, 3H), 3.60 (s, 3H).

LCMS: m/z = 520.0/522.0 [M-H]⁻, (ESI⁻), RT = 3.74, Method A

Example 60 -Synthesis of 13-Bromo-21-fluoro-14-hydroxy-5,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one (Compound 60)

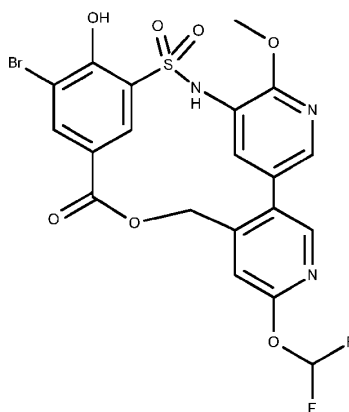


[0298] Lithium iodide (128 mg, 0.956 mmol) was added to a stirring solution of 13-bromo-21-fluoro-5,14,19-trimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one (*synthesised from intermediate 12, using a similar method to intermediate 26*, 180 mg, 0.322 mmol) in anhydrous pyridine (4.0 mL) and the mixture was stirred at 90 °C for 1 hour 45 minutes. The reaction mixture was allowed to cool to r.t., diluted with EtOAc (~15 mL), and washed sequentially with sat. aq. sodium thiosulphate (~15 mL), 1 M HCl (aq.) (~15 mL), and brine (~15 mL). The organic phase was passed through a phase separator and concentrated to dryness in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a beige solid (59.0 mg, 100% purity, 34% yield).

¹H NMR (500 MHz, DMSO) δ 9.48 (s, 1H), 8.12 (s, 1H), 8.05 (d, J = 2.1 Hz, 1H), 7.38 (d, J = 2.1 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.06 (s, 1H), 6.85 (d, J = 11.5 Hz, 1H), 5.29 (d, J = 13.2 Hz, 1H), 5.20 (d, J = 13.4 Hz, 1H), 3.91 (s, 3H), 3.52 (s, 3H).

LCMS: m/z = 539.0, 541.0 [M+H]⁺, (ESI⁺), RT = 4.00, Method A

Example 61 – Synthesis of 13-Bromo-5-(difluoromethoxy)-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 61)

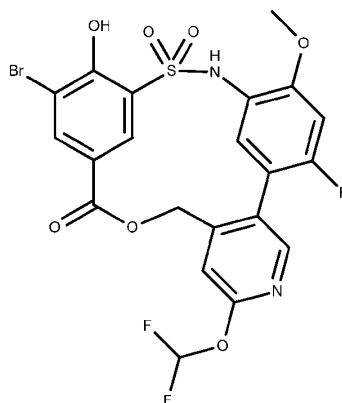


[0299] 13-Bromo-5-(difluoromethoxy)-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 31, using a similar method to intermediate 26*, 100 mg, 0.168 mmol) and lithium iodide (25 mg, 0.187 mmol) were combined and the mixture dissolved into anhydrous pyridine (3 mL). The mixture was heated to 80 °C and stirred for 18 h. The mixture was cooled to r.t., diluted with EtOAc (50 mL), washed with sat. aq. Na₂S₂O₃ (50 mL), 2 M aq. HCl (2 x 50 mL) and brine (50 mL), then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (59 mg, 99% purity, 62% Yield).

¹H NMR (500 MHz, DMSO) δ 9.73 (s, 1H), 8.25 (s, 1H), 8.12 (d, J = 2.2 Hz, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.76 (t, J = 72.6 Hz, 1H), 7.52 (d, J = 2.2 Hz, 1H), 7.37 (s, 1H), 7.31 (d, J = 2.2 Hz, 1H), 5.68 (d, J = 13.5 Hz, 1H), 5.24 (d, J = 13.5 Hz, 1H), 3.59 (s, 3H).

LCMS: m/z = 558.0/560.0 [M+H]⁺, (ESI⁺), RT = 4.02, Method A

Example 62 – Synthesis of 13-Bromo-5-(difluoromethoxy)-21-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹.15.02,7]tricosal(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 62)

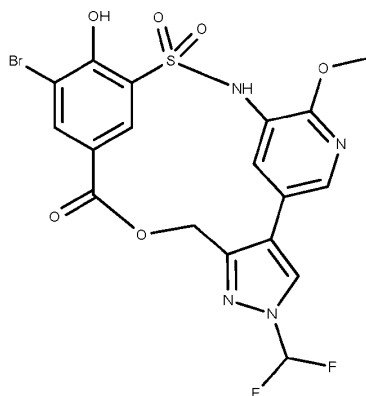


[0300] To a solution of 13-bromo-5-(difluoromethoxy)-21-fluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹.15.02,7]tricosal(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (synthesised from intermediate 31, using a similar method to intermediate 26, 250 mg, 0.390 mmol) in anhydrous pyridine (3 mL) was added lithium iodide (157 mg, 1.17 mmol). The reaction mixture was heated at 70 °C for 3 h. The mixture was cooled to r.t., diluted with EtOAc (20 mL), washed with sat. aq. Na₂S₂O₃ (20 mL), 2 M aq. HCl (20 mL) and brine (20 mL), then dried over Na₂SO₄, filtered, and concentrated. The residue was purified by preparative HPLC (Method P1) to afford a crude product. This dissolved in anhydrous pyridine (3.0 mL), lithium iodide (80.0 mg, 0.598 mmol) was added, and the reaction stirred again for 3 h at 70 °C. The mixture was cooled to r.t., diluted with EtOAc (20 mL), washed with sat. aq. Na₂S₂O₃ (20 mL), 2 M aq. HCl (20 mL) and brine (20 mL), then dried over Na₂SO₄, filtered, and concentrated to afford the title compound as an off-white solid (74.4 mg, 97% purity, 32% yield).

¹H NMR (400 MHz, DMSO) δ 9.48 (s, 1H), 8.26 (s, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.76 (t, J = 72.5 Hz, 1H), 7.38 (d, J = 2.2 Hz, 1H), 7.36 (s, 1H), 7.17 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 11.7 Hz, 1H), 5.35 (d, J = 13.5 Hz, 1H), 5.30 – 5.26 (m, 1H), 3.52 (s, 3H).

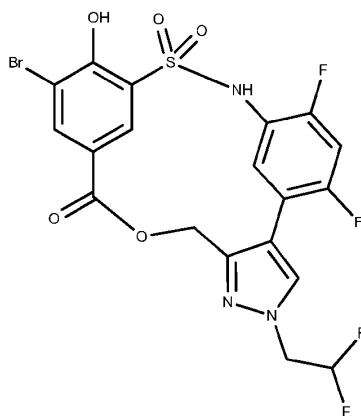
LCMS: m/z = 573.0/575.0 [M-H]⁻, (ESI⁻), RT = 4.21, Method A

Example 63 – Synthesis of 12-Bromo-4-(difluoromethyl)-13-hydroxy-18-methoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16,19-tetrazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (Compound 63)



[0301] A mixture of 12-bromo-4-(difluoromethyl)-13,18-dimethoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16,19-tetrazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (*synthesised from intermediate 33, using a similar method to intermediate 26*, 195 mg, 0.350 mmol), lithium iodide (50.0 mg, 0.37 mmol) and anhydrous pyridine (5 mL) was heated at 80 °C for 16 h. The mixture was cooled to r.t., sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 2 M aq. HCl (2 x 50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound as a white solid (175 mg, 98% purity, 92% yield).
¹H NMR (500 MHz, DMSO) δ 9.75 (s, 1H), 8.42 (s, 1H), 8.08 (d, J = 2.2 Hz, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.86 (t, J = 59.0 Hz, 1H), 7.47 (d, J = 2.2 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H), 5.42 (s, 2H), 3.62 (s, 3H).
 LCMS: m/z = 531.0/533.0 [M-H]⁻, (ESI⁻), RT = 3.60, Method A

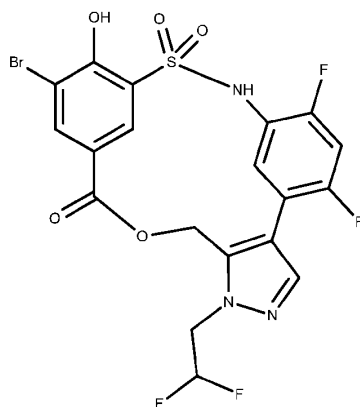
Example 64 – Synthesis of 12-Bromo-4-(2,2-difluoroethyl)-18,20-difluoro-13-hydroxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (Compound 64)



[0302] A mixture of 12-bromo-4-(2,2-difluoroethyl)-18,20-difluoro-13-methoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (*synthesised from intermediate 36, using a similar method to intermediate 26*, 250 mg, 0.430 mmol), lithium iodide (290 mg, 2.17 mmol) and anhydrous pyridine (4 mL) was heated at 80 °C for 16 h. The mixture was cooled to r.t., diluted with EtOAc (50 mL), washed with sat. aq. Na₂S₂O₃ (50 mL), 2 M aq. HCl (2 x 50 mL) and brine (50 mL), then dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound as a white solid (217 mg, 99% purity, 91% yield).
¹H NMR (500 MHz, DMSO) δ 10.18 (br. s, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.94 (s, 1H), 7.49 – 7.42 (m, 2H), 6.97 – 6.90 (m, 1H), 6.41 (tt, J = 54.7, 3.7 Hz, 1H), 5.30 (s, 2H), 4.65 (td, J = 15.2, 3.7 Hz, 2H).

LCMS: m/z = 550.0/552.0 [M+H]⁺, (ESI⁺), RT = 3.69, Method A

Example 65 – Synthesis of 12-Bromo-5-(2,2-difluoroethyl)-18,20-difluoro-13-hydroxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),3,10(22),11,13,17(21),18-octaen-9-one (Compound 65)

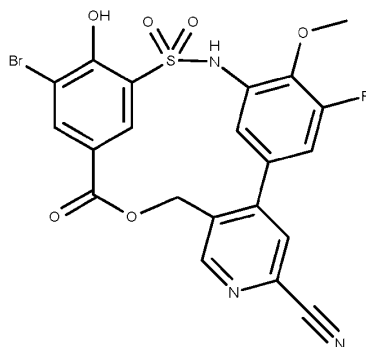


[0303] A mixture of 12-bromo-5-(2,2-difluoroethyl)-18,20-difluoro-13-methoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),3,10(22),11,13,17(21),18-octaen-9-one (*synthesised from intermediate 37, using a similar method to intermediate 26*, 400 mg, 0.709 mmol), lithium iodide (480 mg, 3.59 mmol) and anhydrous pyridine (7 mL) was heated at 80 °C for 16 h. The mixture was cooled to r.t., diluted with EtOAc (50 mL), washed with sat. aq. Na₂S₂O₃ (50 mL), 2 M aq. HCl (2 x 50 mL) and brine (50 mL), then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (220 mg, 98% purity, 55% yield).

¹H NMR (500 MHz, DMSO) δ 10.13 (br. s, 1H), 8.15 (d, J = 2.2 Hz, 1H), 7.61 (s, 1H), 7.51 – 7.43 (m, 1H), 7.39 (d, J = 2.1 Hz, 1H), 6.86 – 6.77 (m, 1H), 6.45 (tt, J = 54.7, 3.4 Hz, 1H), 5.41 (s, 2H), 4.84 (td, J = 15.4, 3.4 Hz, 2H).

LCMS: m/z = 548.0/549.9 [M-H]⁻, (ESI⁻), RT = 3.69, Method A

Example 66 – Synthesis of 13-Bromo-20-fluoro-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.1¹¹.15.0²,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile (Compound 66)

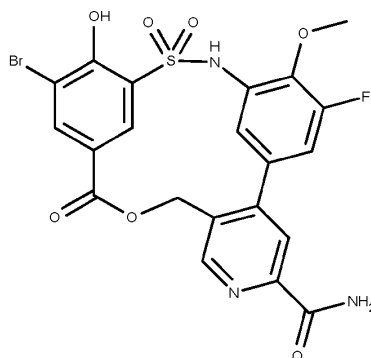


[0304] *Intermediate 41* (60 mg), lithium iodide (70.0 mg, 0.52 mmol) and anhydrous pyridine (3 mL) was stirred at 80 °C for 1.5 h. The mixture was diluted with EtOAc (40 mL), washed with sat. aq. Na₂S₂O₃ (30 mL), 1 M aq. HCl (30 mL) and brine (30 mL), then passed through a phase separator and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (1.8 mg, 90% purity, 5.3 % Yield).

¹H NMR (500 MHz, DMSO) δ 9.53 (br. s, 1H), 8.92 (s, 1H), 8.08 (s, 1H), 7.97 (s, 1H), 7.45 (dd, J = 11.9, 2.2 Hz, 1H), 7.40 (d, J = 2.3 Hz, 1H), 7.14 (s, 1H), 5.94 – 5.06 (m, 2H), 3.57 (d, J = 2.2 Hz, 3H).

LCMS: m/z = 534.0/536.0 [M-H]⁻, (ESI⁻), RT = 3.78, Method A

Example 67 – Synthesis of 13-Bromo-20-fluoro-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carboxamide (Compound 67)

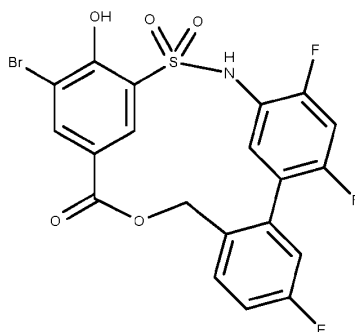


[0305] The title compound was isolated during the purification of *Example 66* to afford an off-white solid (5.0 mg, 99% purity, 15.8 % Yield).

¹H NMR (500 MHz, DMSO) δ 9.96 – 9.47 (m, 1H), 8.79 (s, 1H), 8.28 – 8.21 (m, 1H), 8.06 – 7.94 (m, 1H), 7.86 (s, 1H), 7.77 – 7.72 (m, 1H), 7.51 – 7.43 (m, 1H), 7.42 – 7.38 (m, 1H), 7.03 – 6.94 (m, 1H), 5.62 – 5.26 (m, 2H), 3.74 – 3.55 (m, 3H).

LCMS: m/z = 552.0/554.0 [M+H]⁺, (ESI⁺), RT = 3.23, Method A

Example 68 – Synthesis of 13-Bromo-4,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11,13,15(23),18(22),19-nonaen-10-one (Compound 68)



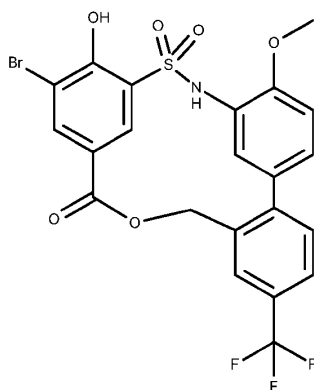
[0306] 13-Bromo-4,19,21-trifluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 24*, 98% purity, 146 mg, 0.27 mmol)

and iodocyclohexane (0.18 mL, 1.35 mmol) were dissolved in anhydrous DMF (5 mL) and the mixture was stirred at 120 °C for 1 h. After cooling to r.t., organics were diluted with EtOAc (25 mL), washed with 1 M HCl (25 mL), 2 M Na₂S₂O₃ (25 mL), then brine (25 mL). The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a brown solid (78 mg, 98% purity, 55% Yield).

¹H NMR (500 MHz, DMSO) δ 10.13 (br. s, 1H), 8.07 (d, J = 2.2 Hz, 1H), 7.63 (dd, J = 8.6, 5.8 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.35 – 7.27 (m, 1H), 7.24 – 7.16 (m, 2H), 6.80 – 6.73 (m, 1H), 5.48 (d, J = 12.7 Hz, 1H), 5.04 (d, J = 12.7 Hz, 1H).

LCMS: m/z = 511.9/514.0 [M-H]⁻, (ESI⁻), RT = 4.19, Method A

Example 69 – Synthesis of 13-Bromo-14,19-dimethoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16λ6-thia-17-azatetracyclo[16.3.1.1.11,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 69)

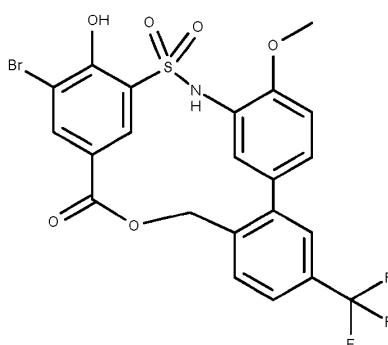


[0307] 13-Bromo-14,19-dimethoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16λ6-thia-17-azatetracyclo[16.3.1.1.11,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 24*, 95% purity, 100 mg, 0.166 mmol) and iodocyclohexane (42 mg, 0.200 mmol) were combined and the mixture dissolved into DMF (3 mL). The mixture was heated to 100 °C and stirred for 18 h. The mixture was cooled to r.t. Sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (61 mg, 96% purity, 63% Yield).

¹H NMR (500 MHz, DMSO) δ 9.35 (s, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.97 (d, J = 2.0 Hz, 1H), 7.82 (dd, J = 8.0, 2.0 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.34 (dd, J = 8.4, 2.3 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 5.69 (d, J = 12.9 Hz, 1H), 5.26 (d, J = 12.8 Hz, 1H), 3.47 (s, 3H).

LCMS: m/z = 556.0/558.0 [M-H]⁻, (ESI⁻), RT = 4.50, Method A

Example 70 – Synthesis of 13-Bromo-14-hydroxy-19-methoxy-16,16-dioxo-4-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹.15.0²,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 70)

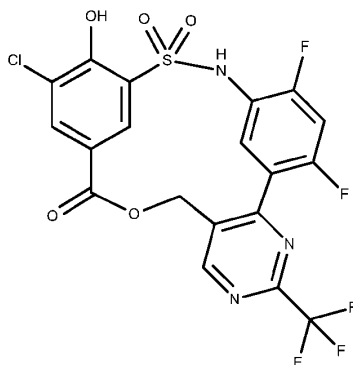


[0308] 13-Bromo-14,19-dimethoxy-16,16-dioxo-4-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹.15.0²,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 24*, 95% purity, 100 mg, 0.166 mmol) and iodocyclohexane (42 mg, 0.200 mmol) were combined and the mixture dissolved into DMF (3 mL). The mixture was heated to 100 °C and stirred for 18 h. The mixture was cooled to r.t. Sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a pale brown solid (77 mg, 95% purity, 79% Yield).

¹H NMR (500 MHz, DMSO) δ 9.37 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.65 (s, 1H), 7.38 (d, J = 2.2 Hz, 1H), 7.33 (dd, J = 8.4, 2.2 Hz, 1H), 7.20 (d, J = 2.2 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 5.70 (d, J = 13.0 Hz, 1H), 5.22 (d, J = 13.0 Hz, 1H), 3.48 (s, 3H).

LCMS: m/z = 556.0/558.0 [M-H]⁻, (ESI⁻), RT = 4.45, Method A

Example 71 – Synthesis of 13-Chloro-19,21-difluoro-14-hydroxy-16,16-dioxo-4-(trifluoromethyl)-9-oxa-16 λ ,6-thia-3,5,17-triazatetracyclo[16.3.1.111,15.02,7]tricosan-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 71)

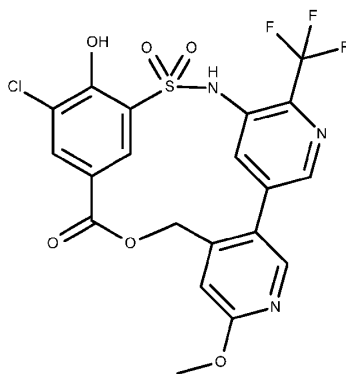


[0309] A pressure vial was charged with 13-chloro-19,21-difluoro-14-methoxy-16,16-dioxo-4-(trifluoromethyl)-9-oxa-16 λ ,6-thia-3,5,17-triazatetracyclo[16.3.1.111,15.02,7]tricosan-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 47, using a similar method to intermediate 7*, 90% purity, 25 mg, 0.04 mmol), lithium iodide (56.0 mg, 0.42 mmol), and anhydrous pyridine (2.5 mL) and the reaction mixture was heated at 80 °C overnight. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (12 mg, 99% purity, 54% Yield).

¹H NMR (500 MHz, DMSO) δ 10.16 (br s, 1H), 9.26 (s, 1H), 7.92 (d, J = 2.2 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.17 (d, J = 2.2 Hz, 1H), 7.14 – 7.07 (m, 1H), 5.66 (d, J = 13.7 Hz, 1H), 5.21 (d, J = 13.6 Hz, 1H).

LCMS: m/z = 520.0/521.9 [M-H]⁻, (ESI⁻), RT = 3.98, Method A

Example 72- Synthesis of 13-Chloro-14-hydroxy-5-methoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.1¹¹.15.0^{2,7}]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 72)

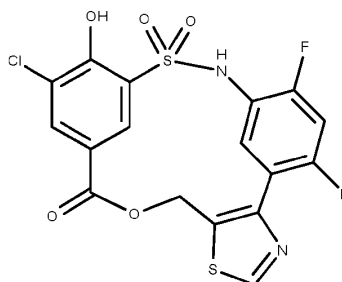


[0310] A mixture of 13-chloro-5,14-dimethoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.1¹¹.15.0^{2,7}]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised from intermediates 49 and 50, using a similar method to intermediate 13*, 235 mg, 0.435 mmol) and lithium iodide (140.0 mg, 1.04 mmol) in anhydrous pyridine (5 mL) was stirred at 90 °C for 1 h and then at 80 °C for 17 h. The reaction mixture was concentrated in vacuo then suspended in EtOAc (60 mL) and washed successively with sat. aq. Na₂S₂O₃ solution (40 mL), 1 M aq. HCl solution (40 mL) and brine (40 mL). The organic component was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (111 mg, 96% purity, 48% yield).

¹H NMR (500 MHz, DMSO) δ 10.61 (br. s, 1H), 8.82 (s, 1H), 8.04 (s, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.27 (s, 1H), 7.13 (s, 1H), 6.94 (d, J = 2.2 Hz, 1H), 5.43 (s, 2H), 3.90 (s, 3H).

LCMS: m/z = 516.0 [M+H]⁺, (ESI⁺), RT = 3.48, Method C

Example 73 – Synthesis of 12-Chloro-18,20-difluoro-13-hydroxy-15,15-dioxo-8-oxa-5,15λ6-dithia-3,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),3,10,12,14(22),17(21),18-octaen-9-one (Compound 73)

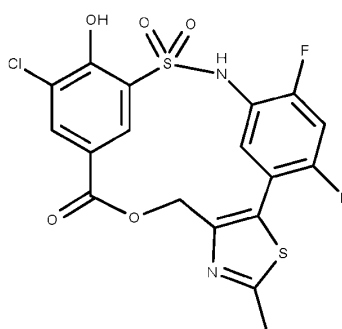


[0311] To a solution of 12-chloro-18,20-difluoro-13-methoxy-15,15-dioxo-8-oxa-5,15λ6-dithia-3,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),3,10,12,14(22),17(21),18-octaen-9-one (*synthesised from intermediate 52, using a similar method to intermediate 7*, 84% purity, 43 mg, 0.0764 mmol) in anhydrous pyridine (4.5 mL) was added lithium iodide (108 mg, 0.807 mmol). The reaction mixture was heated at 100 °C for 4 h and then 80 °C overnight. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (29 mg, 95% purity, 78% Yield).

¹H NMR (500 MHz, DMSO) δ 10.13 (s, 1H), 9.13 (s, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.30 (d, J = 2.2 Hz, 1H), 6.88 – 6.82 (m, 1H), 5.49 (s, 2H).

LCMS: m/z = 457.0/459.0 [M-H]⁻, (ESI⁻), RT = 3.38, Method A

Example 74 – Synthesis of 12-Chloro-18,20-difluoro-13-hydroxy-4-methyl-15,15-dioxo-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),4,10,12,14(22),17(21),18-octaen-9-one (Compound 74)

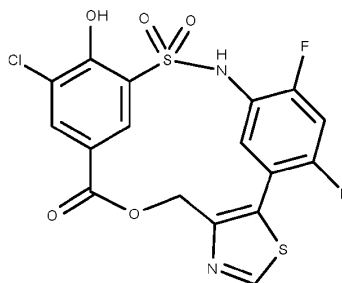


[0312] To a solution of 12-chloro-18,20-difluoro-13-methoxy-4-methyl-15,15-dioxo-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),4,10,12,14(22),17(21),18-octaen-9-one (*synthesised from methyl 5-bromo-2-methyl-thiazole-4-carboxylate, using a similar method to intermediate 7*, 78% purity, 165 mg, 0.26 mmol) in anhydrous pyridine (8 mL) was added lithium iodide (354 mg, 2.64 mmol). The reaction mixture was heated at 90 °C for 1 h 45 min. The cooled RM was diluted with EtOAc (50 mL) and washed with 1 M aq. HCl (30 mL), sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL), then passed through a phase separator and then concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (52 mg, 99% purity, 41% Yield).

¹H NMR (500 MHz, DMSO) δ 8.02 – 7.92 (m, 1H), 7.54 – 7.40 (m, 2H), 7.20 – 7.05 (m, 1H), 5.39 (s, 2H), 2.68 (s, 3H).

LCMS: m/z = 473.1/475.1 [M+H]⁺, (ESI⁺), RT = 3.55, Method A

Example 75 – Synthesis of 12-Chloro-18,20-difluoro-13-hydroxy-15,15-dioxo-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),4,10,12,14(22),17(21),18-octaen-9-one (Compound 75)



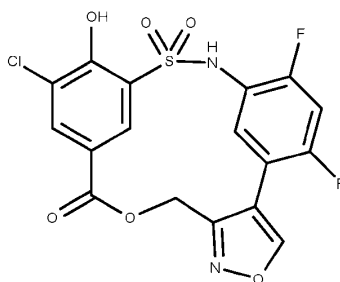
[0313] To a solution of 12-chloro-18,20-difluoro-13-methoxy-15,15-dioxo-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),4,10,12,14(22),17(21),18-octaen-9-one (*synthesised from methyl 5-bromo-1,3-thiazole-4-carboxylate, using a similar method to intermediate 6*, 95% purity, 80 mg, 0.16 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (215 mg, 1.61 mmol). The reaction mixture was heated at 90 °C for 1 h 45 min. The cooled RM was diluted with EtOAc (50 mL) and washed with 1 M aq. HCl (30 mL), sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL), then passed through a phase separator and then concentrated. The residue was purified by preparative HPLC (Method P1) to afford the

title compound as an off-white solid (40 mg, 99% purity, 54% Yield).

^1H NMR (400 MHz, DMSO) δ 9.20 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.64 – 7.48 (m, 1H), 7.45 (d, J = 2.2 Hz, 1H), 7.20 – 7.01 (m, 1H), 5.49 (s, 2H).

LCMS: m/z = 457.0/459.0 $[\text{M-H}]^-$, (ESI-), RT = 3.48, Method A

Example 76 – Synthesis of 12-Chloro-18,20-difluoro-13-hydroxy-15,15-dioxo-4,8-dioxo-15 λ 6-thia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one (Compound 76)

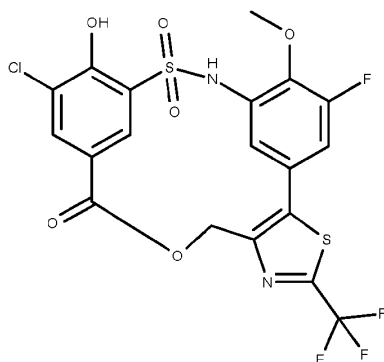


[0314] A mixture of 12-chloro-18,20-difluoro-13-methoxy-15,15-dioxo-4,8-dioxo-15 λ 6-thia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one (*synthesised from intermediate 53, using a similar method to intermediate 13*, 280 mg, 0.613 mmol), lithium iodide (410.208 mg, 3.06 mmol) and anhydrous pyridine (5 mL) was heated at 90 °C for 3 h. The mixture was cooled to r.t., diluted with EtOAc (50 mL), washed with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL), 1 M aq. HCl (50 mL) and brine (30 mL), then dried over Na_2SO_4 , filtered, concentrated and dried in the vacuum oven for 3 h at 50 °C to afford the title compound as a white solid (241 mg, 98% purity, 87% Yield).

^1H NMR (500 MHz, DMSO) δ 10.23 (s, 1H), 9.15 (s, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.68 – 7.48 (m, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.16 – 7.01 (m, 1H), 5.45 (s, 2H).

LCMS: m/z = 441.0/443.0 $[\text{M-H}]^-$, (ESI-), RT = 3.52, Method A

Example 77 – Synthesis of 12-Chloro-19-fluoro-13-hydroxy-18-methoxy-15,15-dioxo-4-(trifluoromethyl)-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2(6),4,10(22),11,13,17,19-octaen-9-one (Compound 77)

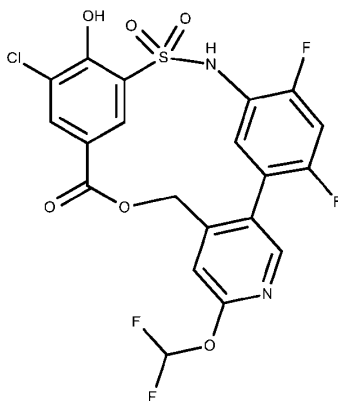


[0315] Lithium iodide (63.0 mg, 0.471 mmol) was added to a stirring solution of 12-chloro-19-fluoro-13,18-dimethoxy-15,15-dioxo-4-(trifluoromethyl)-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2(6),4,10(22),11,13,17,19-octaen-9-one (synthesised from intermediate 54, using a similar method to intermediate 13, 93% purity, 121 mg, 0.204 mmol) in anhydrous pyridine (4.0 mL) at r.t. The reaction vessel was sealed and the mixture stirred at 90 °C for 1 h 30 m. The reaction mixture was allowed to cool to r.t., diluted with EtOAc (~15 mL), and washed sequentially with sat. aq. sodium thiosulphate (~15 mL), 1 M HCl (aq.) (~15 mL), and brine (~15 mL). The organic phase was passed through a phase separator and concentrated to dryness in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (19.8 mg, 98% purity, 18% yield).

¹H NMR (500 MHz, DMSO) δ 9.89 (s, 1H), 7.96 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.48 (dd, J = 11.9, 2.1 Hz, 1H), 7.30 – 7.25 (m, 1H), 5.56 (s, 2H), 3.63 (d, J = 2.4 Hz, 3H).

LCMS: m/z = 539.0 [M+H]⁺, (ESI⁺), RT = 4.42, Method A

Example 78 – Synthesis of 13-Chloro-5-(difluoromethoxy)-19,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 78)

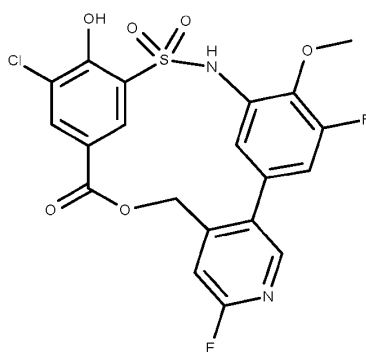


[0316] To a solution of 13-chloro-5-(difluoromethoxy)-19,21-difluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 31, using a similar method to intermediate 13*, 394 mg, 0.643 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (753 mg, 5.63 mmol) and the reaction mixture was heated at 80 °C for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound (203 mg, 95% purity, 58% Yield) as a pale-yellow solid.

¹H NMR (500 MHz, DMSO) δ 10.20 (s, 1H), 8.19 (s, 1H), 7.97 (d, J = 2.2 Hz, 1H), 7.75 (t, J = 72.4 Hz, 1H), 7.55 – 7.46 (m, 1H), 7.39 (s, 1H), 7.22 (d, J = 2.3 Hz, 1H), 7.03 – 6.88 (m, 1H), 5.49 (d, J = 13.9 Hz, 1H), 5.13 (d, J = 13.3 Hz, 1H).

LCMS: m/z = 517.0/519.0 [M-H]⁻, (ESI⁻), RT = 4.05, Method A

Example 79 – Synthesis of 13-Chloro-5,20-difluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 79)

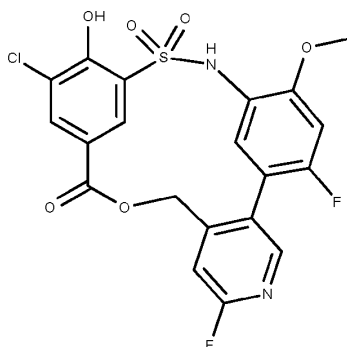


[0317] To a solution of 13-chloro-5,20-difluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 11, using a similar method to intermediate 13*, 101 mg, 0.161 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (188 mg, 1.40 mmol) and the mixture was heated at 80 °C for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (29 mg, 100% purity, 38% Yield).

¹H NMR (500 MHz, DMSO) δ 9.46 (s, 1H), 8.26 (s, 1H), 7.92 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 1.8 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 11.8 Hz, 1H), 5.40 (d, J = 13.6 Hz, 1H), 5.28 (dd, J = 13.7, 2.0 Hz, 1H), 3.49 (s, 3H).

LCMS: m/z = 481.0/483.0 [M-H]⁻, (ESI⁻), RT = 3.69, Method A

Example 80 – Synthesis of 13-Chloro-5,21-difluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 80)

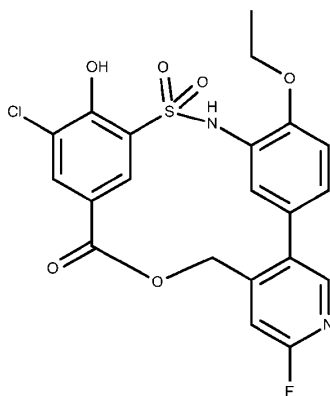


[0318] To a solution of 13-chloro-5,21-difluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 11, using a similar method to intermediate 13*, 83 mg, 0.149 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (175 mg, 1.31 mmol) and the reaction mixture was heated at 80 °C for 16 h. The mixture was concentrated under reduced pressure and purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (38 mg, 95% purity, 50% Yield).

¹H NMR (500 MHz, DMSO) δ 9.46 (s, 1H), 8.26 (s, 1H), 7.92 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 1.8 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 11.8 Hz, 1H), 5.40 (d, J = 13.6 Hz, 1H), 5.28 (dd, J = 13.7, 2.0 Hz, 1H), 3.49 (s, 3H).

LCMS: m/z = 481.0/483.0 [M-H]⁻, (ESI⁻), RT = 3.61, Method A

Example 81- Synthesis of 13-Chloro-19-ethoxy-5-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹,15.02,7]tricoso-1(22),2(7),3,5,11(23),12,14,18,20-nonaen-10-one (Compound 81)

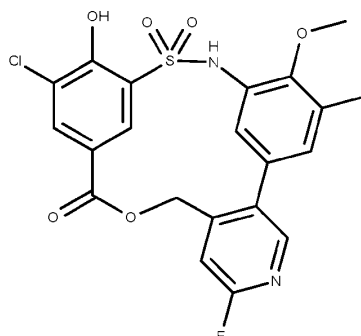


[0319] Lithium iodide (53 mg, 0.396 mmol) was added to a stirring solution of 13-chloro-19-ethoxy-5-fluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹,15.02,7]tricoso-1(22),2(7),3,5,11(23),12,14,18,20-nonaen-10-one (synthesised from intermediate 11, using a similar method to intermediate 13, 146 mg, 0.195 mmol) in anhydrous pyridine (4 mL) in a pressure vial (10 mL) and the mixture was stirred at 90 °C for 3 hours. The mixture was allowed to cool to r.t., diluted with EtOAc (~15 mL), and washed sequentially with sat. aq. sodium thiosulphate (~15 mL), 1 M HCl (aq.) (~15 mL), and brine (~15 mL). The organic phase was passed through a phase separator and concentrated to dryness. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (40.3 mg, 94% purity, 40.5 % Yield).

¹H NMR (500 MHz, DMSO) δ 9.18 (s, 1H), 8.22 (s, 1H), 7.85 (d, J = 2.2 Hz, 1H), 7.45 (d, J = 1.9 Hz, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.4, 2.3 Hz, 1H), 6.69 (d, J = 8.5 Hz, 1H), 5.70 (d, J = 13.4 Hz, 1H), 5.13 (d, J = 13.4 Hz, 1H), 3.92 – 3.83 (m, 1H), 1.21 (t, J = 6.9 Hz, 3H).

LCMS: m/z = 477.3, 479.3 [M-H]⁻, (ESI⁻), RT = 3.74, Method A

Example 82 – Synthesis of 13-Chloro-5-fluoro-14-hydroxy-19-methoxy-20-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 82)

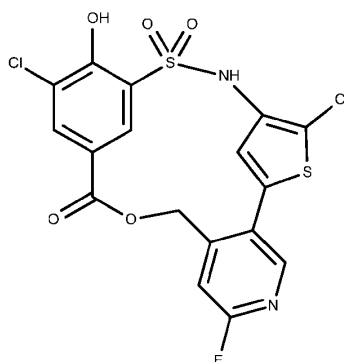


[0320] A mixture of 13-chloro-5-fluoro-14,19-dimethoxy-20-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised from intermediate 11, using a similar method to intermediate 13*, 92% purity, 119 mg, 0.241 mmol), lithium iodide (163 mg, 1.21 mmol) and anhydrous pyridine (2.4 mL) was stirred at 90 °C for 3 h and then at r.t. overnight. The mixture was diluted with EtOAc (40 mL), washed with sat. aq. Na₂S₂O₃ (30 mL), 1 M aq. HCl (30 mL) and brine (30 mL), then passed through a phase separator and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (48 mg, 41 % yield).

¹H NMR (400 MHz, DMSO) δ 8.12 (s, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 2.5 Hz, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.14 (Br. s, 2H), 6.97 (d, J = 2.1 Hz, 1H), 5.29 (d, J = 12.6 Hz, 1H), 4.96 (d, J = 12.7 Hz, 1H), 3.33 (s, 3H), 2.04 (s, 3H).

LCMS: m/z = 479.3 / 481.2 [M+H]⁺, (ESI⁺), RT = 3.80, Method A

Example 83 - Synthesis of 5,19-Dichloro-11-fluoro-20-hydroxy-2,2-dioxo-15-oxa-2 λ 6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one (Compound 83)

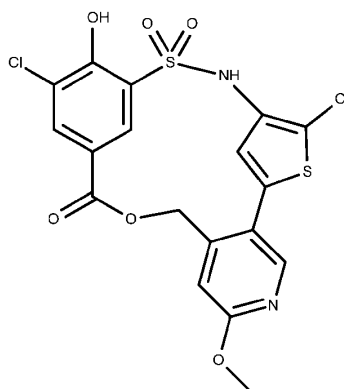


[0321] A crude mixture containing 5,19-dichloro-11,20-dimethoxy-2,2-dioxo-15-oxa-2 λ 6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one and 5,19-dichloro-11-fluoro-20-methoxy-2,2-dioxo-15-oxa-2 λ 6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one (*synthesised from intermediate 60, using a similar method to intermediate 13*, total of 200 mg, 0.12 mmol) was dissolved in anhydrous pyridine (2.0 mL) and lithium iodide (130 mg, 0.971 mmol) and the reaction mixture was heated at 90 °C for 4.5 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound (24.4 mg, 98% purity, 43% yield) as a light brown solid.

¹H NMR (500 MHz, DMSO) δ 10.28 (br. s, 1H), 8.27 (s, 1H), 8.03 (d, J = 2.3 Hz, 1H), 7.48 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 6.77 (s, 1H), 5.50 (s, 2H).

LCMS: m/z = 474.9/476.9/479.1 [M+H]⁺, (ESI⁺), RT = 3.83, Method A

Example 84 – Synthesis of 5,19-Dichloro-20-hydroxy-11-methoxy-2,2-dioxo-15-oxa-2 λ 6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one (Compound 84)

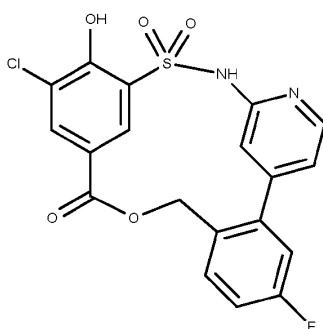


[0322] The title compound was isolated as a second component from the purification of *Example 83*, as an off-white solid (18.7 mg, 95% purity, 31% yield).

¹H NMR (500 MHz, DMSO) δ 10.89 (br. s, 1H), 10.23 (br. s, 1H), 8.18 (s, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.06 (s, 1H), 6.66 (s, 1H), 5.41 (s, 2H), 3.90 (s, 3H).

LCMS: m/z = 486.9/488.9/491.0 [M+H]⁺, (ESI⁺), RT = 4.08, Method A

Example 85 – Synthesis of 13-Chloro-4-fluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17,19-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 85)



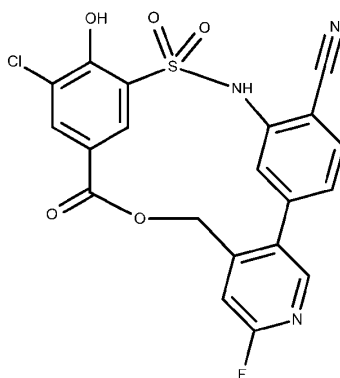
[0323] To a solution of 13-chloro-4-fluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17,19-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 62, using a similar method to intermediate 7*, 152 mg, 0.34 mmol) in anhydrous pyridine (4.5 mL) was added lithium iodide (227 mg, 1.69

mmol). The reaction mixture was heated at 80 °C for 5 h. The reaction mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (34 mg, 99% purity, 23% Yield).

¹H NMR (500 MHz, DMSO) δ 8.07 (d, J = 5.3 Hz, 1H), 7.88 (d, J = 2.2 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.62 – 7.53 (m, 1H), 7.45 – 7.42 (m, 1H), 7.38 – 7.33 (m, 2H), 7.31 (dd, J = 5.2, 1.5 Hz, 1H), 5.43 – 5.32 (m, 1H), 5.27 – 5.18 (m, 1H).

LCMS: m/z = 435.0/437.0 [M+H]⁺, (ESI⁺), RT = 3.50, Method A

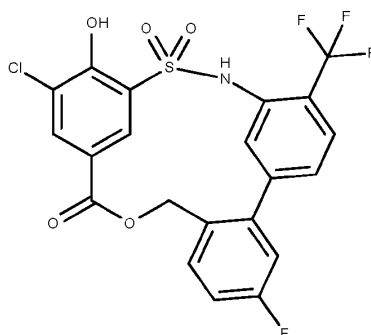
Example 86 – Synthesis of 13-Chloro-5-fluoro-14-hydroxy-10,16,16-trioxo-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.1¹¹.15.0²,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-19-carbonitrile (Compound 86)



[0324] To a solution of 13-chloro-5-fluoro-14-methoxy-10,16,16-trioxo-9-oxa-16λ6-thia-4,17-diazatetracyclo[16.3.1.1¹¹.15.0²,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-19-carbonitrile (*synthesised from intermediate 11, using similar methods to intermediates 62 and 7*, 240 mg, 0.31 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (210 mg, 1.57 mmol). The reaction mixture was heated at 80 °C for 5 h. The reaction mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (20 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (49 mg, 99% purity, 34% Yield).

¹H NMR (500 MHz, DMSO) δ 8.08 (s, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.70 (dd, J = 7.9, 1.6 Hz, 1H), 7.52 (d, J = 1.9 Hz, 1H), 6.85 (d, J = 2.1 Hz, 1H), 6.77 (d, J = 1.6 Hz, 1H), 5.58 – 5.46 (m, 1H), 5.41 – 5.25 (m, 1H), OH, NH peaks not observed
LCMS: m/z = 460.0/461.9 [M+H]⁺, (ESI⁺), RT = 3.38, Method A

Example 87 – Synthesis of 13-Chloro-4-fluoro-14-hydroxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16λ6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 87)

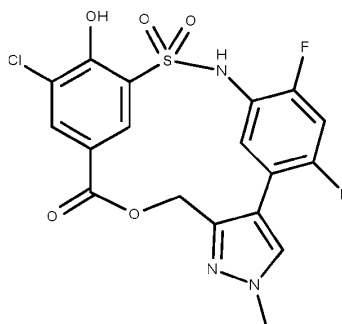


[0325] 13-Chloro-4-fluoro-14-methoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16λ6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (*synthesised from (2-bromo-4-fluoro-phenyl)methanol, using similar methods to intermediates 62 and 7*, 95% purity, 300 mg, 0.552 mmol) and iodocyclohexane (600 mg, 2.86 mmol) were combined and the mixture dissolved into anhydrous DMF (7.5 mL). The mixture was heated to 120 °C and stirred for 2 h. The reaction mixture was allowed to cool to r.t., sat aq. Na₂S₂O₃ (50 mL) was added, and the mixture extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated. The residue was purified by FCC (25 g SiO₂ cartridge, 0-40% MeOH in DCM) followed by preparative HPLC (Method P1) to afford the title compound as an off-white solid (102 mg, 99% purity, 36% Yield).

¹H NMR (500 MHz, DMSO) δ 10.33 (br. s, 1H), 7.90 (d, J = 2.1 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.33 – 7.26 (m, 1H), 7.22 (d, J = 2.2 Hz, 1H), 7.18 (dd, J = 9.3, 2.7 Hz, 1H), 7.04 (s, 1H), 5.35 (s, 2H).

LCMS: m/z = 500.2/502.2 [M-H]⁻, (ESI⁻), RT = 4.18, Method A

Example 88 – Synthesis of 12-Chloro-18,20-difluoro-13-hydroxy-4-methyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10,12,14(22),17(21),18-octaen-9-one (Compound 88)

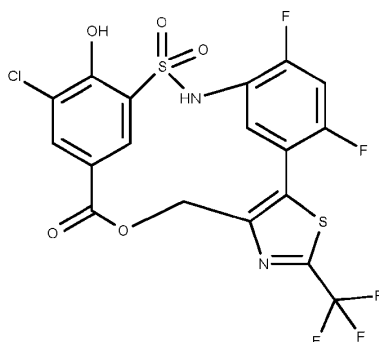


[0326] 12-Chloro-18,20-difluoro-13-methoxy-4-methyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10,12,14(22),17(21),18-octaen-9-one (*synthesised from methyl 4-bromo-1-methyl-pyrazole-3-carboxylate, using similar methods to intermediates 52 and 6*, 38.0 mg, 0.08 mmol) and iodocyclohexane (0.05 mL, 0.4 mmol) were dissolved in anhydrous DMF (2 mL) and the mixture was stirred at 120 °C for 30 mins. The mixture was diluted with EtOAc (25 mL), washed with 1 M HCl (25 mL), 2 M Na₂S₂O₃ (25 mL), then brine (25 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (8.0 mg, 97% yield, 21% Yield).

¹H NMR (500 MHz, DMSO) δ 10.10 (br s, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.43 (d, J = 2.2 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.00 – 6.93 (m, 1H), 5.24 (s, 2H), 3.85 (s, 3H).

LCMS: m/z = 454.0/456.0 [M-H]⁻, (ESI⁻), RT = 3.32, Method A

Example 89 – Synthesis of 12-Chloro-18,20-difluoro-13-hydroxy-15,15-dioxo-4-(trifluoromethyl)-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2(6),4,10,12,14(22),17,19-octaen-9-one (Compound 89)

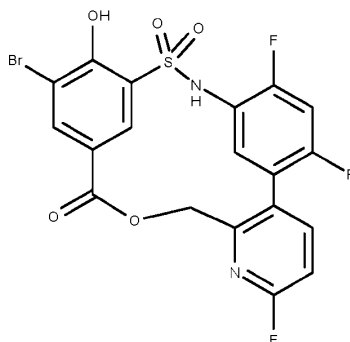


[0327] To a stirred solution of 12-chloro-18,20-difluoro-13-methoxy-15,15-dioxo-4-(trifluoromethyl)-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2(6),4,10,12,14(22),17,19-octaen-9-one (*synthesised from methyl 5-bromo-2-(trifluoromethyl)thiazole-4-carboxylate, using similar methods to intermediates 52 and 7*, 92% purity, 125 mg, 0.213 mmol) in anhydrous DMF (2 mL) was added iodocyclohexane (0.14 mL, 1.06 mmol) and the reaction mixture was heated to 100 °C for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (74 mg, 99%, 65% Yield).

¹H NMR (400 MHz, DMSO) δ 10.32 (s, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.67 – 7.54 (m, 1H), 7.43 (d, J = 2.2 Hz, 1H), 7.34 – 7.25 (m, 1H), 5.54 (s, 2H).

LCMS: m/z = 524.9/526.8 [M-H]⁻, (ESI⁻), RT = 4.15, Method A

Example 90 – Synthesis of 13-Bromo-5,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 90)

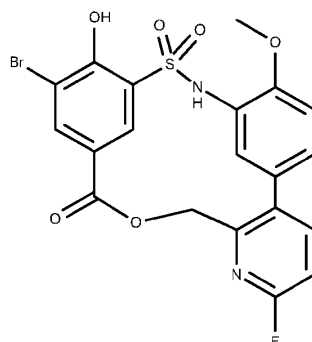


[0328] 13-Bromo-5,19,21-trifluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 9, using similar methods to intermediates 47 and 24*, 120 mg, 0.215 mmol) and lithium iodide (145 mg, 1.08 mmol) were combined and the mixture dissolved into anhydrous pyridine (4 mL). The mixture was heated to 80 °C and stirred for 18 h. The mixture was cooled to r.t., sat aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (94 mg, 95% purity, 80% Yield).

¹H NMR (500 MHz, DMSO) δ 10.15 (br s, 1H), 8.08 (s, 1H), 7.99 – 7.93 (m, 1H), 7.56 – 7.48 (m, 1H), 7.32 (dd, J = 8.3, 2.9 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.01 – 6.94 (m, 1H), 5.37 – 5.25 (m, 2H).

LCMS: m/z = 513.0/515.0 [M-H]⁻, (ESI⁻), RT = 3.88, Method A

Example 91 – Synthesis of 13-Bromo-5-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 91)

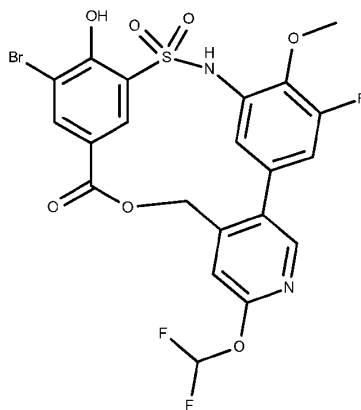


[0329] 13-Bromo-5-fluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-6,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 9, using similar methods to intermediates 47 and 24*, 120 mg, 0.115 mmol) and lithium iodide (30 mg, 0.224 mmol) were combined and the mixture dissolved into anhydrous pyridine (2 mL). The mixture was heated to 80 °C and stirred for 18 h. The mixture was cooled to r.t., sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (20 mg, 96% purity, 33% Yield).

¹H NMR (500 MHz, DMSO) δ 9.26 (s, 1H), 8.03 – 7.96 (m, 2H), 7.38 (d, J = 2.2 Hz, 1H), 7.31 – 7.28 (m, 2H), 7.25 (d, J = 2.2 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 5.88 (d, J = 13.5 Hz, 1H), 4.89 (d, J = 13.5 Hz, 1H), 3.45 (s, 3H).

LCMS: m/z = 507.0/509.0 [M-H]⁻, (ESI⁻), RT = 3.84, Method A

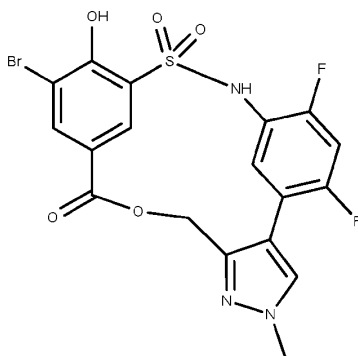
Example 92 – Synthesis of 13-Bromo-5-(difluoromethoxy)-20-fluoro-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 92)



[0330] In a pressure vial, 13-bromo-5-(difluoromethoxy)-20-fluoro-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 30, using similar methods to intermediates 52 and 26*, 207 mg, 0.351 mmol) was dissolved in anhydrous pyridine (9.5 mL) and lithium iodide (415 mg, 3.10 mmol) was added. The reaction mixture was heated at 70 °C for 3 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (143 mg, 99% purity, 70% yield).

¹H NMR (500 MHz, DMSO) δ 9.82 (s, 1H), 8.19 (s, 1H), 8.07 (d, J = 2.2 Hz, 1H), 7.75 (t, J = 72.6 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.41 (dd, J = 12.0, 2.1 Hz, 1H), 7.37 (s, 1H), 7.05 – 7.01 (m, 1H), 5.55 (d, J = 13.0 Hz, 1H), 5.25 (d, J = 13.2 Hz, 1H), 3.58 (d, J = 2.0 Hz, 3H). LCMS: m/z = 573.0/575.0 [M-H]⁻, (ESI⁻), RT = 4.25, Method A

Example 93- Synthesis of 12-Bromo-18,20-difluoro-13-hydroxy-4-methyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (Compound 93)

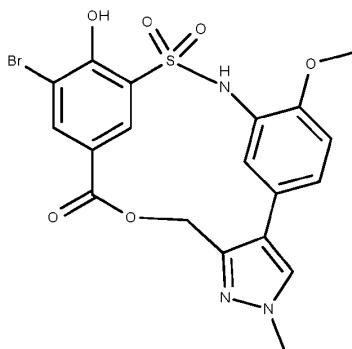


[0331] A mixture of 12-bromo-18,20-difluoro-13-methoxy-4-methyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (*synthesised from methyl 4-bromo-1-methyl-pyrazole-3-carboxylate, using similar methods to intermediates 52 and 24*, 321 mg, 0.437 mmol), lithium iodide (292 mg, 2.18 mmol) and anhydrous pyridine (4 mL) was heated at 90 °C for 4 h. The mixture was diluted with EtOAc (50 mL), washed with sat. aq. Na₂S₂O₃ (540 ml), 2 M aq. HCl (40 mL) then brine (40 mL). The organic was passed through a phase separator and then concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (90 mg, 99% purity, 41 % yield).

¹H NMR (500 MHz, DMSO) δ 10.13 (br. s, 1H), 8.13 (s, 1H), 7.82 (s, 1H), 7.55 – 7.19 (m, 2H), 7.01 – 6.81 (m, 1H), 5.25 (s, 2H), 3.84 (s, 3H).

LCMS: m/z = 498.0/499.9 [M-H]⁻, (ESI⁻), RT = 3.44, Method A

Example 94 – Synthesis of 12-Bromo-13-hydroxy-18-methoxy-4-methyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (Compound 94)

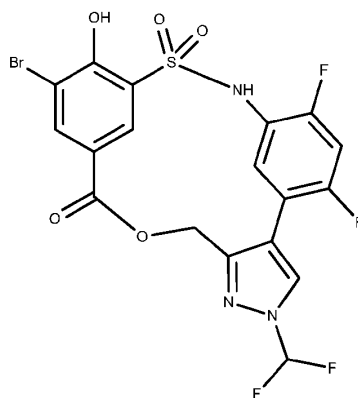


[0332] Lithium iodide (111 mg, 0.829 mmol) was added to a stirring solution of 12-bromo-13,18-dimethoxy-4-methyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10(22),11,13,17,19-octaen-9-one (*synthesised from methyl 4-bromo-1-methyl-pyrazole-3-carboxylate, using similar methods to intermediates 52 and 24*, 68% purity, 274 mg, 0.350 mmol) in anhydrous pyridine (5 mL) in a 10 mL pressure vial. The vessel was sealed and the mixture stirred at 90 °C for 3 h 30 m. The mixture was allowed to cool to r.t and diluted with sat. aq. sodium thiosulphate (~25 mL), 1 M aq. HCl (~25 mL), forming a white precipitate. The mixture was filtered, then extracted with CHCl₃/IPA (3:1) (3 x ~15 mL then 3 x ~20 mL). The organic phase was combined with the collected precipitate and concentrated to dryness in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (49 mg, 100% purity, 28% Yield).

¹H NMR (400 MHz, DMSO) δ 9.32 (s, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.78 (s, 1H), 7.41 (d, J = 2.2 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H), 7.06 (dd, J = 8.3, 2.2 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 5.27 (s, 2H), 3.85 (s, 3H), 3.48 (s, 3H).

LCMS: m/z = 492.3, 494.3 [M-H]⁻, (ESI⁻), RT = 3.20, Method A

Example 95 – Synthesis of 12-Bromo-4-(difluoromethyl)-18,20-difluoro-13-hydroxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (Compound 95)

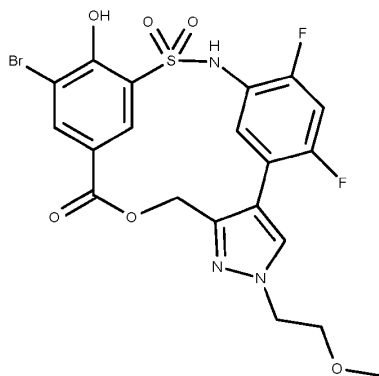


[0333] A mixture of 12-bromo-4-(difluoromethyl)-18,20-difluoro-13-methoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (*synthesised from intermediate 32, using similar methods to intermediates 52 and 24*, 91% purity, 340 mg, 0.433 mmol), lithium iodide (289.445 mg, 2.16 mmol) and anhydrous pyridine (4 mL) was heated at 90 °C for 3 h. The mixture was cooled to r.t., diluted with EtOAc (40 mL), washed with sat. aq. Na₂S₂O₃ (30 mL), 1 M aq. HCl (30 mL) and brine (30 mL), then passed through a phase separator and then concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (139 mg, 0.257 mmol, 59% Yield).

¹H NMR (500 MHz, DMSO) δ 10.20 (s, 1H), 8.44 (s, 1H), 8.24 – 8.12 (m, 1H), 7.85 (t, J = 58.9 Hz, 1H), 7.56 – 7.48 (m, 1H), 7.44 (d, J = 2.2 Hz, 1H), 7.05 – 6.85 (m, 1H), 5.35 (s, 2H).

LCMS: m/z = 534.0/536.0 [M-H]⁻, (ESI⁻), RT = 3.81, Method A

Example 96 – Synthesis of 12-Bromo-18,20-difluoro-13-hydroxy-4-(2-methoxyethyl)-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one (Compound 96)

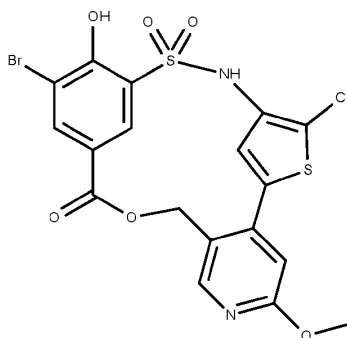


[0334] A mixture of 12-bromo-18,20-difluoro-13-methoxy-4-(2-methoxyethyl)-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one (*synthesised from intermediate 63, using similar methods to intermediates 52 and 24*, 250 mg, 0.448 mmol), lithium iodide (300 mg, 2.24 mmol) and anhydrous pyridine (10 mL) was heated at 90 °C for 3 h. The mixture was cooled to r.t., diluted with EtOAc (50 mL), washed with sat. aq. Na₂S₂O₃ (50 mL), 1 M aq. HCl (50 mL) and brine (30 mL), then dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (92 mg, 100% purity, 38% Yield).

¹H NMR (500 MHz, DMSO) δ 10.04 (br. s, 1H), 8.04 (s, 1H), 7.86 (s, 1H), 7.45 (d, J = 2.3 Hz, 1H), 7.41 – 7.33 (m, 1H), 7.02 – 6.94 (m, 1H), 5.23 (s, 2H), 4.26 (t, J = 5.3 Hz, 2H), 3.72 (t, J = 5.3 Hz, 2H), 3.25 (s, 3H).

LCMS: m/z = 543.9/545.0 [M-H]⁻, (ESI⁻), RT = 3.50, Method A

Example 97 – Synthesis of 19-Bromo-5-chloro-20-hydroxy-10-methoxy-2,2-dioxo-15-oxa-2 λ 6,6-dithia-3,11-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one (Compound 97)

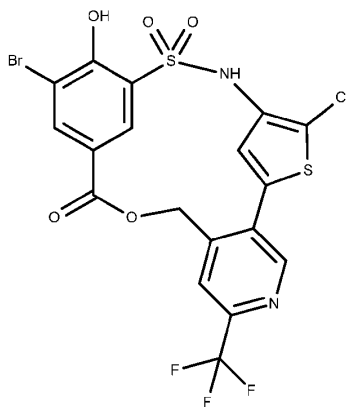


[0335] In a pressure vial, 19-bromo-5-chloro-10,20-dimethoxy-2,2-dioxo-15-oxa-2 λ 6,6-dithia-3,11-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one (*synthesised from intermediate 66, using a similar method to intermediate 26*, 150 mg, 0.253 mmol) was dissolved in anhydrous pyridine (6.5 mL) and lithium iodide (298 mg, 2.23 mmol) was added. The reaction mixture was heated at 80 °C for 3 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (73.6 mg, 98% purity, 54% yield).

^1H NMR (500 MHz, DMSO) δ 10.32 (s, 1H), 8.30 (s, 1H), 8.15 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H), 6.90 (s, 1H), 6.69 (s, 1H), 5.39 (s, 2H), 3.89 (s, 3H).

LCMS: m/z = 528.9/530.9/532.9 $[\text{M}-\text{H}]^-$, (ESI $^-$), RT = 4.18, Method A

Example 98 – Synthesis of 19-Bromo-5-chloro-20-hydroxy-2,2-dioxo-11-(trifluoromethyl)-15-oxa-2,6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one (Compound 98)

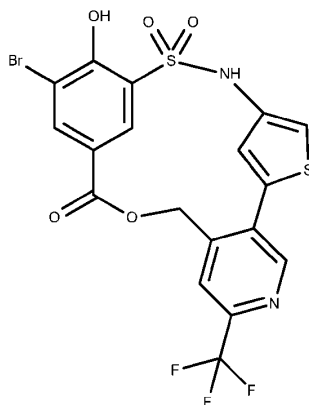


[0336] In a pressure vial, *intermediate 69* (62 mg, 0.104 mmol) was dissolved in anhydrous pyridine (3.0 mL) and lithium iodide (123 mg, 0.919 mmol) was added. The reaction mixture was heated at 80 °C for 4 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (20.8 mg, 100% purity, 35% yield).

¹H NMR (500 MHz, DMSO) δ 10.31 (s, 1H), 8.74 (s, 1H), 8.19 (s, 1H), 8.16 (d, J = 2.2 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 6.81 (s, 1H), 5.60 (s, 2H).

LCMS: m/z = 566.9/568.9/570.9 [M-H]⁻, (ESI⁻), RT = 4.27, Method A

Example 99 – Synthesis of 19-Bromo-20-hydroxy-2,2-dioxo-11-(trifluoromethyl)-15-oxa-2 λ 6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one (Compound 99)

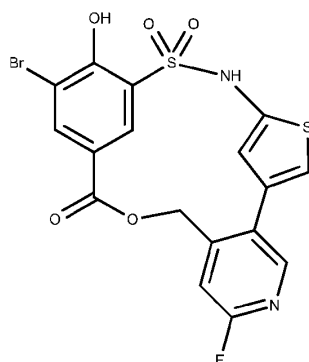


[0337] In a pressure vial, *intermediate 70* (56 mg, 0.0652 mmol) was dissolved in anhydrous pyridine (1.8 mL) and lithium iodide (80 mg, 0.598 mmol) was added. The reaction mixture was heated at 70 °C for 6 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (31.7 mg, 98% purity, 89% yield).

¹H NMR (500 MHz, DMSO) δ 10.18 (s, 1H), 8.72 (s, 1H), 8.18 (s, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.36 (s, 1H), 7.07 (d, J = 2.1 Hz, 1H), 6.68 (s, 1H), 5.61 (s, 2H).

LCMS: m/z = 532.9/534.9 [M-H]⁻, (ESI⁻), RT = 4.15, Method A

Example 100 – Synthesis of 19-Bromo-11-fluoro-20-hydroxy-2,2-dioxo-15-oxa-2 λ 6,5-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4(22),6,8,10,12,17,19-octaen-16-one (Compound 100)

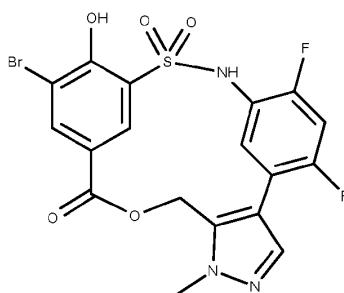


[0338] To a solution of 19-bromo-11-fluoro-20-methoxy-2,2-dioxo-15-oxa-2 λ 6,5-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4(22),6,8,10,12,17,19-octaen-16-one (synthesised from intermediate 11 and *tert*-butyl (4-bromothiophen-2-yl)carbamate, using a similar method to intermediate 26, 33% purity, 44 mg, 0.0291 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (166 mg, 1.24 mmol). The reaction mixture was heated at 80 °C for 4 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a yellow solid (7.2 mg, 97% purity, 49% Yield) as a yellow solid.

¹H NMR (500 MHz, DMSO) δ 10.57 (br. s, 1H), 8.16 (s, 1H), 8.12 (d, J = 2.1 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.26 – 7.22 (m, 1H), 6.67 (s, 1H), 5.72 – 5.29 (m, 2H).

LCMS: m/z = 482.9/484.9 [M-H]⁻, (ESI⁻), RT = 3.66, Method A

Example 101 – Synthesis of 12-Bromo-18,20-difluoro-13-hydroxy-5-methyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),3,10,12,14(22),17(21),18-octaen-9-one (Compound 101)

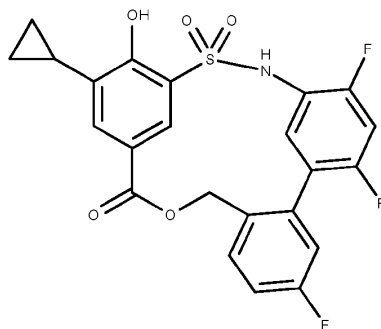


[0339] 12-Bromo-18,20-difluoro-13-methoxy-5-methyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2(6),3,10,12,14(22),17(21),18-octaen-9-one (synthesised from methyl 4-bromo-1-methyl-1H-pyrazole-5-carboxylate, using similar methods to intermediates 52 and 26, 73 mg, 0.13 mmol) and iodocyclohexane (0.08 mL, 0.65 mmol) were dissolved in anhydrous DMF (3 mL) and the mixture was stirred at 120 °C for 30 mins. The mixture was diluted with EtOAc (25 mL), washed with 2 M Na₂S₂O₃ (25 mL), 1 M HCl (25 mL), then brine (25 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (5.0 mg, 7.5% Yield).

¹H NMR (500 MHz, DMSO) δ 8.12 (s, 1H), 7.51 – 7.44 (m, 1H), 7.43 (s, 1H), 7.38 (d, J=2.2 Hz, 1H), 6.74 – 6.67 (m, 1H), 5.37 (s, 2H), 3.96 (s, 3H).

LCMS: $m/z = 498.0/500.0$ [M-H]⁻, (ESI⁻), RT = 3.48, Method A

Example 102 – Synthesis of 13-Cyclopropyl-4,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricosan-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 102)

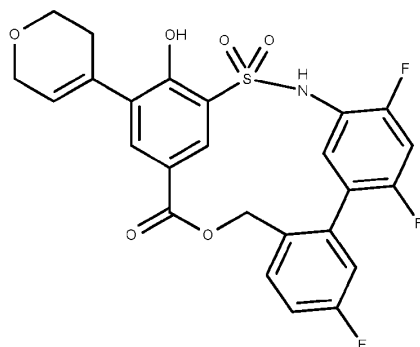


[0340] To a solution of *intermediate 73* (88 mg, 0.180 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (192 mg, 1.43 mmol) and the reaction mixture was heated at 100 °C for 16 h. The mixture was allowed to cool to r.t. and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (47.9 mg, 97% purity, 54.4 % Yield).

¹H NMR (500 MHz, DMSO) δ 10.08 (br. s, 1H), 9.91 (br. s, 1H), 7.61 (dd, J = 8.5, 5.8 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.41 (d, J = 2.1 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.17 (dd, J = 9.2, 2.8 Hz, 1H), 7.06 (d, J = 2.1 Hz, 1H), 6.68 – 6.60 (m, 1H), 5.48 (d, J = 12.8 Hz, 1H), 5.00 (d, J = 12.7 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.00 – 0.91 (m, 2H), 0.71 – 0.60 (m, 2H).

LCMS: $m/z = 474.1$ [M-H]⁻, (ESI⁻), RT = 4.22, Method A

Example 103 – Synthesis of 13-(3,6-Dihydro-2H-pyran-4-yl)-4,19,21-trifluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹.15.0^{2,7}]tricosan-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 103)

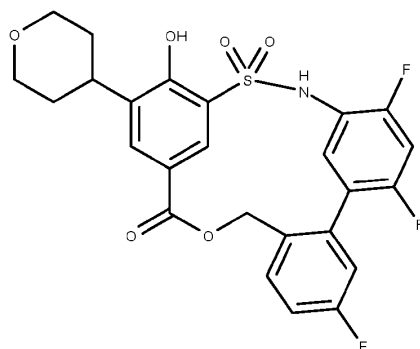


[0341] To a solution of *intermediate* 75 (80% purity, 174 mg, 0.262 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (307 mg, 2.29 mmol). The reaction mixture was heated at 90 °C for 5 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (77 mg, 99% purity, 56% Yield).

¹H NMR (500 MHz, DMSO) δ 10.03 (s, 2H), 7.69 (d, J = 2.3 Hz, 1H), 7.63 (dd, J = 8.6, 5.8 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.35 – 7.27 (m, 1H), 7.18 (dd, J = 9.3, 2.8 Hz, 1H), 7.16 (d, J = 2.2 Hz, 1H), 6.71 – 6.65 (m, 1H), 5.98 (t, J = 2.1 Hz, 1H), 5.51 (d, J = 12.7 Hz, 1H), 5.02 (d, J = 12.7 Hz, 1H), 4.21 – 4.16 (m, 2H), 3.78 (t, J = 5.4 Hz, 2H), 2.40 – 2.34 (m, 2H).

LCMS: m/z = 516.1 [M-H]⁻, (ESI⁻), RT = 4.04, Method A

Example 104 – Synthesis of 4,19,21-Trifluoro-14-hydroxy-16,16-dioxo-13-tetrahydropyran-4-yl-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 104)



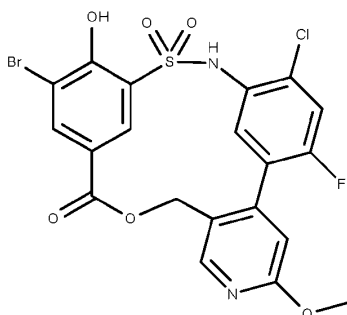
[0342] A solution of Example 103 (60.0 mg, 0.12 mmol) in EtOAc (5 mL) was degassed using vacuum/nitrogen (x3) and then dioxoplatinum (3.0 mg, 0.01 mmol) was added and the reaction mixture degassed using vacuum/nitrogen (x3). Then the reaction mixture was placed under a hydrogen environment by degassing using vacuum/hydrogen (x1). The reaction mixture was stirred at r.t. under a hydrogen atmosphere for 5 days. The RM was filtered through celite, with more celite added on top of the Pt, the celite was washed with EtOAc (40 mL). The filtrate was then concentrated under reduced pressure. The residue was then dissolved in EtOAc (5 mL) was degassed using vacuum/nitrogen (x3) and 10% Pd/C (50% wet) (25 mg, 0.0117 mmol) was added and the reaction mixture degassed using vacuum/nitrogen (x3). Then the reaction mixture was placed under a hydrogen environment by degassing using vacuum/hydrogen (x1). The reaction mixture was stirred at r.t. under a hydrogen atmosphere for 5 days. The RM was filtered through celite, with more celite added on top of the Pd, the celite was washed with EtOAc (40 mL). The filtrate was then concentrated under reduced pressure. The residue was dissolved in EtOH (15 mL) and cycled through an H-Cube at 30 °C and 30 bar for 6 h, followed by cycles at 60 °C and 60 bar for a total of 9 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (12.6 mg, 88% purity, 18% yield)

¹H NMR (500 MHz, DMSO) δ 10.15 (br. s, 1H), 9.82 (br. s, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.62 (dd, J = 8.6, 5.8 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.33 – 7.28 (m, 1H), 7.18 – 7.15 (m, 1H), 7.11 (d, J = 2.1 Hz, 1H), 6.66 – 6.59 (m, 1H), 5.52 (d, J = 12.8 Hz, 1H), 5.01 (d, J = 12.7 Hz,

1H), 3.98 – 3.88 (m, 2H), 3.51 – 3.39 (m, 2H), 3.19 – 3.09 (m, 1H), 1.72 – 1.63 (m, 3H), 1.64 – 1.52 (m, 1H).

LCMS: m/z = 518.1 [M-H]⁻, (ESI⁻), RT = 4.03, Method A

Example 105 – Synthesis of 13-Bromo-19-chloro-21-fluoro-14-hydroxy-4-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 105)

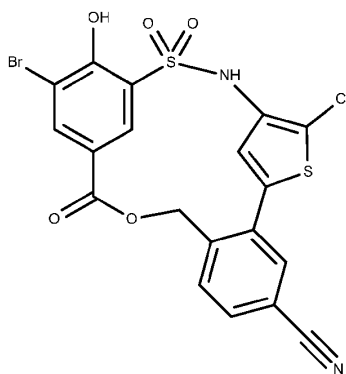


[0343] A mixture of 13-bromo-19-chloro-21-fluoro-4,14-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesised from intermediate 28, using a similar method to intermediate 26*, 95% purity, 180 mg, 0.323 mmol), lithium iodide (218 mg, 1.61 mmol) and anhydrous pyridine (3 mL) was stirred at 90 °C for 2 h. The mixture was diluted with EtOAc (40 mL), washed with sat. aq. Na₂S₂O₃ (30 mL), 1 M aq. HCl (30 mL) and brine (30 mL), then passed through a phase separator and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (109 mg, 99% purity, 61% yield).

¹H NMR (400 MHz, DMSO) δ 10.18 (br. s, 1H), 8.33 (s, 1H), 8.08 (d, J = 2.2 Hz, 1H), 7.70 (d, J = 9.3 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 6.90 (d, J = 7.2 Hz, 1H), 6.82 (s, 1H), 5.44 (d, J = 12.8 Hz, 1H), 5.02 (d, J = 12.7 Hz, 1H), 3.89 (s, 3H).

LCMS: m/z = 543.2/545.1 [M+H]⁺, (ESI⁺), RT = 4.10, Method A

Example 106 – Synthesis of 19-Bromo-5-chloro-20-hydroxy-2,2,16-trioxo-15-oxa-2λ6,6-dithia-3-azatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaene-10-carbonitrile (Compound 106)

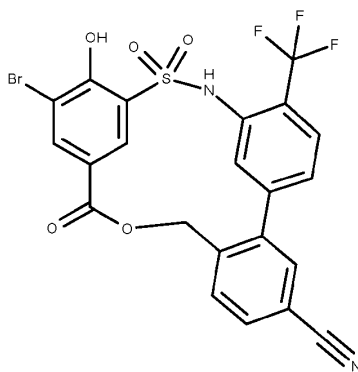


[0344] In a pressure vial, 19-bromo-5-chloro-20-methoxy-2,2,16-trioxo-15-oxa-2λ6,6-dithia-3-azatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaene-10-carbonitrile (*synthesised using a similar method to intermediate 69*, 80 mg, 0.138 mmol) was dissolved in anhydrous pyridine (2.5 mL) and lithium iodide (158 mg, 1.18 mmol) was added. The reaction mixture was heated at 80 °C for 4 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (29 mg, 98% purity, 39% yield).

¹H NMR (400 MHz, DMSO) δ 10.29 (s, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.95 (dd, J = 7.9, 1.8 Hz, 1H), 7.90 (d, J = 1.7 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 2.2 Hz, 1H), 6.66 (s, 1H), 5.52 (s, 2H).

LCMS: m/z = 522.9/524.9/526.8 [M-H]⁻, (ESI⁻), RT = 4.59, Method A

Example 107 – Synthesis of 13-Bromo-14-hydroxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile (Compound 107)

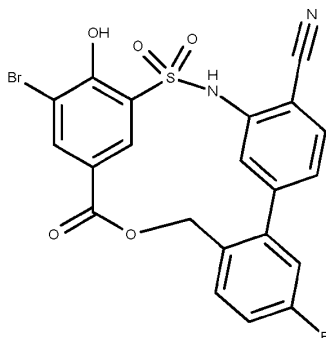


[0345] 13-Bromo-14-methoxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile (*synthesised using similar methods to intermediates 62 and 26*, 92% purity, 594 mg, 0.963 mmol) was dissolved in anhydrous pyridine (9.2 mL) and lithium iodide (902 mg, 6.74 mmol) was added. The reaction mixture was heated at 70 °C for 4 h. The mixture was concentrated under reduced pressure and The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (175 mg, 99% purity, 33% yield).

^1H NMR (400 MHz, DMSO) δ 10.29 (s, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.94 (dd, J = 7.9, 1.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.68 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 6.99 (d, J = 1.6 Hz, 1H), 5.45 (s, 2H).

LCMS: m/z = 551.0/553.0 $[\text{M}-\text{H}]^-$, (ESI $^-$), R_T = 4.58, Method A

Example 108 – Synthesis of 13-Bromo-4-fluoro-14-hydroxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaene-19-carbonitrile (Compound 108)

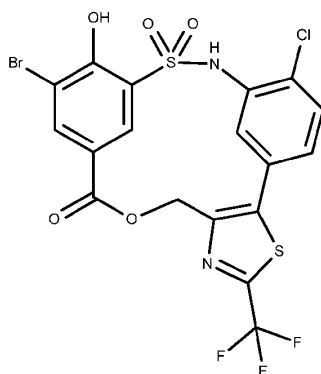


[0346] Lithium iodide (181 mg, 1.35 mmol) was added to a stirring solution of 13-bromo-4-fluoro-14-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaene-19-carbonitrile (*synthesised using similar methods to intermediates 62 and 26*, 400 mg, 0.541 mmol) in anhydrous pyridine (6.0 mL) in a pressure vial. The reaction vessel was sealed and the mixture stirred at 90 °C for 1.5 h. The mixture was allowed to cool to r.t., diluted with EtOAc (~20 mL), washed with saturated Na₂S₂O₃ solution (aq.) (~20 mL), 1 M HCl solution (aq.) (~20 mL) and brine (~20 mL), and the organic phase concentrated to dryness in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a yellow solid (54.9 mg, 97% purity, 20% yield).

¹H NMR (400 MHz, DMSO) δ 8.07 (d, J = 2.1 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.71 (dd, J = 7.9, 1.6 Hz, 1H), 7.61 (dd, J = 8.5, 5.8 Hz, 1H), 7.26 (td, J = 8.5, 2.8 Hz, 1H), 7.07 (dd, J = 9.2, 2.8 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.58 (d, J = 1.6 Hz, 1H), 5.48 (d, J = 10.7 Hz, 1H), 5.24 (d, J = 12.2 Hz, 1H).

LCMS: m/z = 500.9, 502.9 [M-H]⁻, (ESI⁻), RT = 1.37, Method A

Example 109 – Synthesis of 12-Bromo-18-chloro-13-hydroxy-15,15-dioxo-4-(trifluoromethyl)-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2(6),4,10,12,14(22),17,19-octaen-9-one (Compound 109)

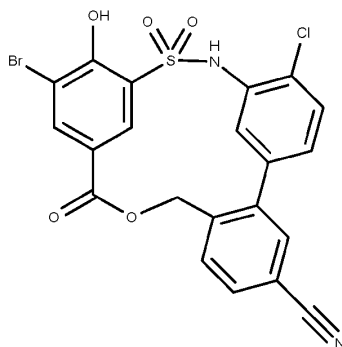


[0347] To a solution of 12-bromo-18-chloro-13-methoxy-15,15-dioxo-4-(trifluoromethyl)-8-oxa-3,15λ6-dithia-5,16-diazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2(6),4,10,12,14(22),17,19-octaen-9-one (*synthesised from intermediate 54, using a similar methods to intermediates 52 and 26*, 272 mg, 0.424 mmol) in anhydrous pyridine (4.0 mL) in a pressure tube was added lithium iodide (170 mg, 1.27 mmol) and the mixture was heated to 80 °C and stirred for 6 h. After cooling, the reaction was quenched by pouring onto sat. aq. Na₂S₂O₃ (25 mL). After extraction with DCM (3 x 20 mL), the combined organic extracts were washed with 1 M aq. HCl (20 mL), then brine (50 mL) and were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (164 mg, 97% purity, 66% yield).

¹H NMR (400 MHz, DMSO) δ 10.25 (br. s, 1H), 8.10 (d, J = 2.2 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.50 (dd, J = 8.3, 2.1 Hz, 1H), 7.45 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 5.56 (s, 2H).

LCMS: m/z = 569, 571 [M+H]⁺, (ESI⁺), RT = 4.52, Method A

Example 110 – Synthesis of 13-Bromo-19-chloro-14-hydroxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile (Compound 110)

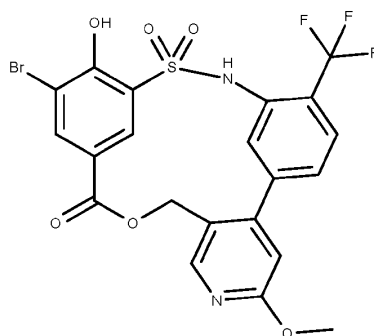


[0348] To a solution of 13-bromo-19-chloro-14-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile (*synthesised using a similar method to intermediate 26*, 450 mg, 0.767 mmol) in anhydrous pyridine (10 mL) was added lithium iodide (515 mg, 3.85 mmol). The reaction mixture was heated at 70 °C overnight. The mixture was cooled to r.t., diluted with EtOAc (20 mL), washed with sat. aq. Na₂S₂O₃ (20 mL), 2 M aq. HCl (20 mL) and brine (20 mL), then dried over Na₂SO₄, filtered, and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (107 mg, 99% purity, 27% yield).

¹H NMR (400 MHz, DMSO) δ 10.11 (br. s, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.92 (dd, J = 7.9, 1.8 Hz, 1H), 7.80 (d, J = 1.7 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.46 – 7.37 (m, 2H), 7.30 (d, J = 2.2 Hz, 1H), 7.14 – 7.09 (m, 1H), 5.54 (d, J = 12.9 Hz, 1H), 5.32 (d, J = 13.0 Hz, 1H).

LCMS: m/z = 518.9 [M-H]⁻, (ESI⁻), RT = 1.53, Method A

Example 111 – Synthesis of 13-Bromo-14-hydroxy-4-methoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 111)

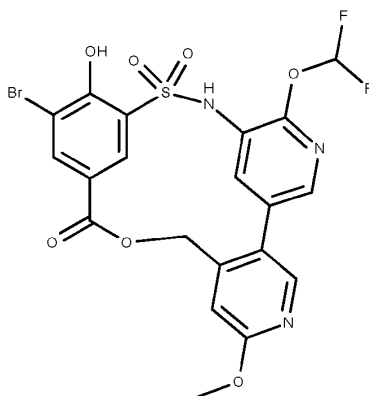


[0349] To a solution of 13-bromo-4,14-dimethoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (synthesised from intermediate 28, using a similar methods to intermediates 62 and 26, 370 mg, 0.65 mmol) in anhydrous pyridine (6 mL) was added lithium iodide (216 mg, 1.61 mmol). The reaction mixture was heated at 80 °C for 5 h. The reaction mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (123 mg, 97% purity, 33% Yield).

¹H NMR (400 MHz, DMSO) δ 10.35 (br.s, 1H), 8.33 (s, 1H), 8.06 (d, J = 2.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.14 (d, J = 2.1 Hz, 1H), 6.88 (d, J = 1.7 Hz, 1H), 6.73 (s, 1H), 5.50 – 5.19 (m, 2H), 3.88 (s, 3H).

LCMS: m/z = 559.0/561.0 [M+H]⁺, (ESI⁺), RT = 4.36, Method A

Example 112 – Synthesis of 13-Bromo-19-(difluoromethoxy)-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 112)

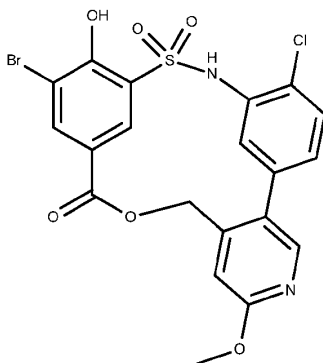


[0350] 13-Bromo-19-(difluoromethoxy)-5,14-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17,20-triazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from intermediate 76, using a similar methods to intermediates 49 and 26*, 151 mg, 0.264 mmol) was dissolved in anhydrous pyridine (2.5 mL) and lithium iodide (247 mg, 1.85 mmol) was added. The reaction mixture was heated at 80 °C for 1 h and then at 70 °C for 5 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (99 mg, 98% purity, 66% yield).

¹H NMR (400 MHz, DMSO) δ 10.28 (br. s, 1H), 8.26 (d, J = 2.2 Hz, 1H), 8.08 (s, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.52 (t, J = 72.1 Hz, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.24 (d, J = 2.2 Hz, 1H), 7.09 (s, 1H), 5.43 (s, 1H), 5.33 (s, 1H), 3.90 (s, 3H).

LCMS: m/z = 556.0/558.0 [M-H]⁻, (ESI⁻), RT = 3.93, Method A

Example 113 – Synthesis of 13-Bromo-19-chloro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one (Compound 113)

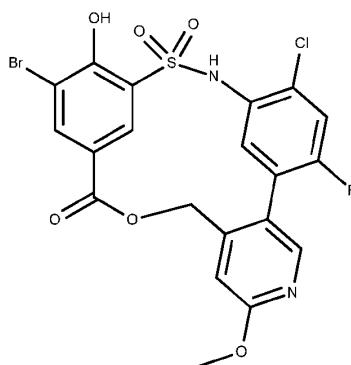


[0351] Lithium iodide (82 mg, 0.613 mmol) was added to a stirring solution of 13-bromo-19-chloro-5,14-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one (*synthesised from intermediate 12, using a similar method to intermediate 26*, 153 mg, 0.281 mmol) in anhydrous pyridine (3.0 mL) in a pressure vial. The reaction vessel was sealed and the mixture stirred at 90 °C until reaction completion was confirmed by LCMS. The reaction mixture was allowed to cool to r.t., diluted with EtOAc (~10 mL), and washed sequentially with saturated Na₂S₂O₃ solution (aq.) (~10 mL), 1 M HCl solution (aq.) (~10 mL), and brine (~10 mL). The organic phase was passed through a phase separator and concentrated to dryness in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (42 mg, 100% purity, 29% yield).

¹H NMR (400 MHz, DMSO) δ 10.06 (s, 1H), 8.21 – 7.92 (m, 2H), 7.45 – 7.34 (m, 2H), 7.30 (d, J = 2.2 Hz, 1H), 7.08 (d, J = 1.6 Hz, 2H), 5.58 – 5.10 (m, 2H), 3.91 (s, 3H).

LCMS: m/z = 525, 527 & 529 [M+H]⁺, (ESI⁺), RT = 4.01, Method A

Example 114 – Synthesis of 13-Bromo-19-chloro-21-fluoro-14-hydroxy-5-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one (Compound 114)

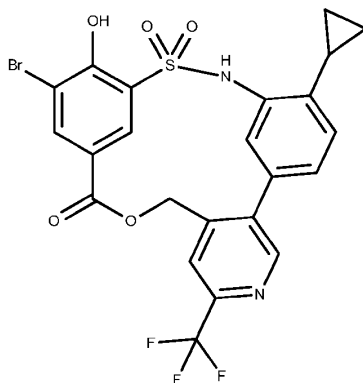


[0352] Lithium iodide (146 mg, 1.09 mmol) was added to a stirring solution of 13-bromo-19-chloro-21-fluoro-5,14-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one (*synthesised from intermediate 12, using a similar method to intermediate 26*, 259 mg, 0.460 mmol) in anhydrous pyridine (6.0 mL) in a pressure vial (20 mL). The vessel was sealed and the mixture stirred at 90 °C until reaction completion was confirmed by LCMS. The reaction mixture was allowed to cool to r.t., diluted with EtOAc (~20 mL), and washed sequentially with saturated Na₂S₂O₃ solution (aq.) (~20 mL), 1 M HCl solution (aq.) (~20 mL), and brine (~20 mL). The organic phase was passed through a phase separator and concentrated to dryness in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (91.5 mg, 100% purity, 37% yield).

¹H NMR (400 MHz, DMSO) δ 10.14 (s, 1H), 8.18 – 8.02 (m, 2H), 7.61 (d, J = 9.2 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.09 (s, 1H), 7.00 (d, J = 7.5 Hz, 1H), 5.37 (d, J = 13.3 Hz, 1H), 5.12 (d, J = 13.0 Hz, 1H), 3.91 (s, 3H).

LCMS: m/z = 543, 545 & 547 [M+H]⁺, (ESI⁺), RT = 4.16, Method A

Example 115 – Synthesis of 13-Bromo-19-cyclopropyl-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 115)

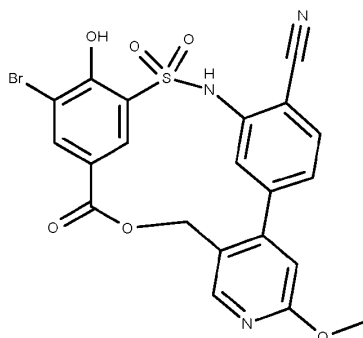


[0353] To a solution of 13-bromo-19-cyclopropyl-14-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 24*, 490 mg, 0.84 mmol) in anhydrous pyridine (7 mL) was added lithium iodide (281 mg, 2.1 mmol). The reaction mixture was heated at 80 °C for 5 h. The reaction mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (328 mg, 98% purity, 67% Yield) as a white solid.

¹H NMR (400 MHz, DMSO) δ 10.02 (s, 1H), 8.61 (s, 1H), 8.17 (s, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.34 (dd, J = 8.1, 1.9 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 5.57 – 5.40 (m, 2H), 2.28 – 2.16 (m, 1H), 0.99 – 0.87 (m, 2H), 0.73 – 0.54 (m, 1H), 0.32 – 0.15 (m, 1H).

LCMS: m/z = 569.0/571.0 [M+H]⁺, (ESI⁺), RT = 4.40, Method A

Example 116 – Synthesis of 13-Bromo-14-hydroxy-4-methoxy-10,16,16-trioxo-9-oxa-16 λ ,6-thia-5,17-diazatetracyclo[16.3.1.1¹¹¹,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-19-carbonitrile (Compound 116)

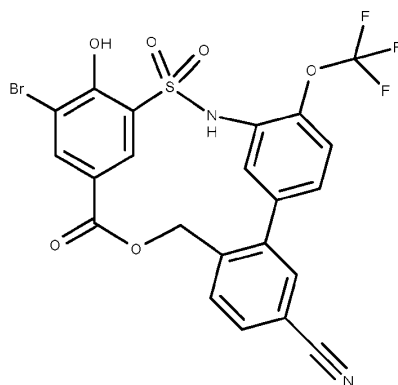


[0354] 13-Bromo-4,14-dimethoxy-10,16,16-trioxo-9-oxa-16 λ ,6-thia-5,17-diazatetracyclo[16.3.1.1¹¹¹,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-19-carbonitrile (*synthesised from intermediate 28, using a similar methods to intermediates 62 and 26*, 72 mg, 0.129 mmol) was dissolved in anhydrous pyridine (1.5 mL) and lithium iodide (121 mg, 0.904 mmol) was added. The reaction mixture was heated at 80 °C for 1 h and then at 70 °C for 1 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) followed by trituration with water (3 x 5 mL) and finally preparative HPLC (Method P3) to afford the title compound as a white solid (21.1 mg, 95% purity, 30% yield).

¹H NMR (400 MHz, DMSO) δ 10.64 (s, 1H), 8.30 (s, 1H), 8.11 – 7.90 (m, 2H), 7.70 (dd, J = 7.9, 1.7 Hz, 1H), 6.83 (d, J = 2.1 Hz, 1H), 6.66 (s, 1H), 6.58 (d, J = 1.6 Hz, 1H), 5.48 (s, 1H), 5.16 (s, 1H), 3.86 (s, 3H).

LCMS: m/z = 514.0/516.0 [M-H]⁻, (ESI⁻), RT = 3.65, Method A

Example 117 – Synthesis of 13-Bromo-14-hydroxy-10,16,16-trioxo-19-(trifluoromethoxy)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.0^{2,7}]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile (Compound 117)

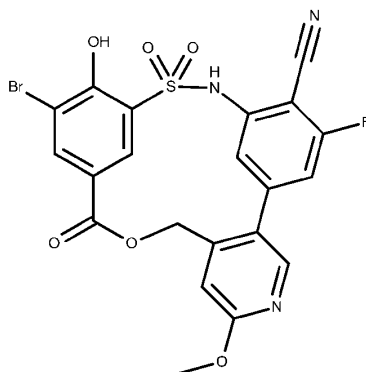


[0355] 13-Bromo-14-methoxy-10,16,16-trioxo-19-(trifluoromethoxy)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹¹.15.0^{2,7}]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-4-carbonitrile (*synthesised using a similar method to intermediate 26*, 94 mg, 0.161 mmol) and lithium iodide (215 mg, 1.59 mmol) were dissolved in anhydrous pyridine (5.7 mL). The mixture was then heated to 80 °C and stirred for a total of 6 h. The mixture was concentrated in vacuo and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (43 mg, 97% purity, 46% yield) as a white solid.

¹H NMR (400 MHz, DMSO) δ 10.47 – 10.06 (m, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.92 (dd, J = 7.9, 1.7 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.54 (dd, J = 8.5, 2.2 Hz, 1H), 7.43 – 7.35 (m, 1H), 7.26 (d, J = 2.1 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 5.46 – 5.39 (m, 2H).

LCMS: m/z = 566.9/568.9 [M-H]⁻, (ESI⁻), RT = 4.16, Method A

Example 118 – Synthesis of 13-Bromo-20-fluoro-14-hydroxy-5-methoxy-10,16,16-trioxo-9-oxa-16 λ ,6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹,15.0²,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-19-carbonitrile (Compound 118)

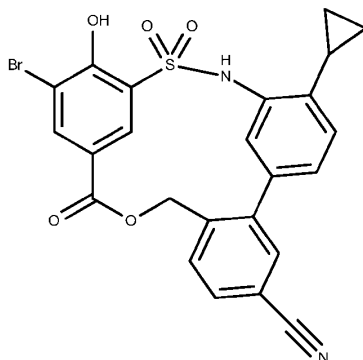


[0356] A mixture of 13-bromo-20-fluoro-5,14-dimethoxy-10,16,16-trioxo-9-oxa-16 λ ,6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹,15.0²,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-19-carbonitrile (*synthesised from intermediate 12, using similar methods to intermediates 62 and 26*, 100 mg, 0.173 mmol), lithium iodide (117 mg, 0.87 mmol) and anhydrous pyridine (2 mL) was stirred at 90 °C for 4 h and then at 80 °C for a further 1 h. The mixture was cooled to r.t., diluted with EtOAc (50 mL), washed with sat. aq. Na₂S₂O₃ (30 mL), water (40 mL) and brine (30 mL), then passed through a phase separator and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (47.0 mg, 100% purity, 51% yield).

¹H NMR (400 MHz, DMSO) δ 8.10 (d, J = 2.1 Hz, 1H), 7.96 (s, 1H), 7.78 (d, J = 9.6 Hz, 1H), 7.08 (s, 1H), 6.88 (d, J = 2.1 Hz, 1H), 6.52 (d, J = 1.3 Hz, 1H), 5.60 – 5.15 (m, 2H), 3.88 (s, 3H).

LCMS: m/z = 534.0/536.0 [M+H]⁺, (ESI⁺), RT = 3.86, Method A

Example 119 – Synthesis of 13-Bromo-19-cyclopropyl-14-hydroxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaene-4-carbonitrile (Compound 119)

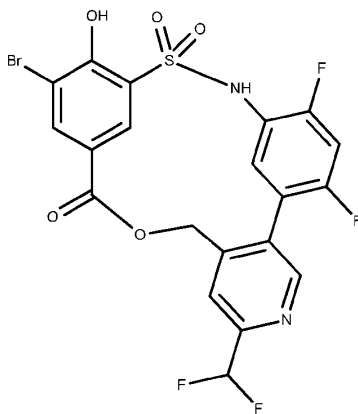


[0357] To a solution of 13-bromo-19-cyclopropyl-14-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaene-4-carbonitrile (*synthesised using a similar method to intermediate 26*, 400 mg, 0.74 mmol) in anhydrous pyridine (6 mL) was added lithium iodide (248 mg, 1.85 mmol). The reaction mixture was heated at 80 °C for 5 h. The reaction mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (20 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (20 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (274 mg, 99% purity, 70% Yield).

¹H NMR (400 MHz, DMSO) δ 9.98 (s, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.88 (dd, J = 7.9, 1.8 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 7.33 – 7.26 (m, 2H), 6.84 (d, J = 1.9 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 5.48 (d, J = 12.8 Hz, 1H), 5.34 (d, J = 12.8 Hz, 1H), 2.26 – 2.13 (m, 1H), 0.99 – 0.85 (m, 2H), 0.70 – 0.52 (m, 1H), 0.35 – 0.15 (m, 1H).

LCMS: m/z = 523.0/525.0 [M-H]⁻, (ESI⁻), RT = 4.27, Method A

Example 120 – Synthesis of 13-Bromo-5-(difluoromethyl)-19,21-difluoro-14-hydroxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosan-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one (Compound 120)

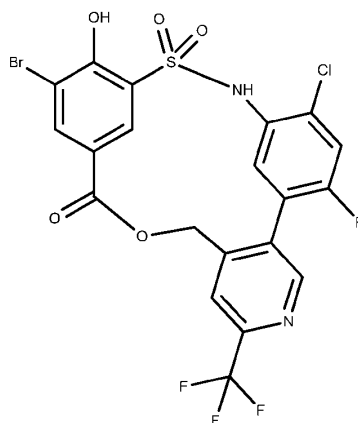


[0358] A mixture of 13-bromo-5-(difluoromethyl)-19,21-difluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosan-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one (*synthesised from intermediate 79, using a similar method to intermediate 26*, 27 mg, 0.0409 mmol), lithium iodide (11.0 mg, 0.08 mmol) and anhydrous pyridine (0.5 mL) was heated at 80 °C for 16 h. The mixture was cooled to r.t., sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (13.0 mg, 98% purity, 57% yield).

¹H NMR (400 MHz, DMSO) δ 8.58 (s, 1H), 8.08 – 8.01 (m, 1H), 7.95 (s, 1H), 7.62 – 7.50 (m, 1H), 7.21 (d, J = 2.2 Hz, 1H), 7.20 – 6.91 (m, 2H), 5.58 (d, J = 13.5 Hz, 1H), 5.18 (d, J = 13.4 Hz, 1H).

LCMS: m/z = 546.9/548.9 [M+H]⁺, (ESI⁺), RT = 4.02, Method A

Example 121 – Synthesis of 13-Bromo-19-chloro-21-fluoro-14-hydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one (Compound 121)

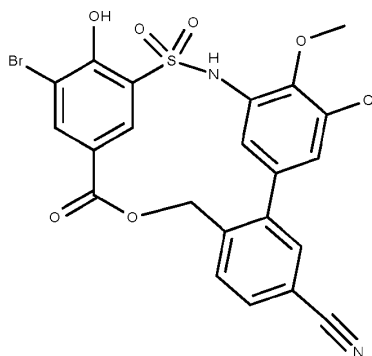


[0359] A mixture of 13-bromo-19-chloro-21-fluoro-14-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11(23),12,14,18(22),19-nonaen-10-one (*synthesised using a similar method to intermediate 26*, 150 mg, 0.247 mmol), lithium iodide (165.0 mg, 1.23 mmol) and anhydrous pyridine (3 mL) was heated at 100 °C for 3 h. The mixture was cooled to r.t., sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (91.0 mg, 98% pure, 62% yield).

¹H NMR (400 MHz, DMSO) δ 10.21 (br. s, 1H), 8.72 (s, 1H), 8.22 (s, 1H), 8.08 (d, J = 2.2 Hz, 1H), 7.69 (d, J = 9.3 Hz, 1H), 7.31 (d, J = 2.2 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 5.58 (d, J = 13.7 Hz, 1H), 5.28 (d, J = 13.6 Hz, 1H).

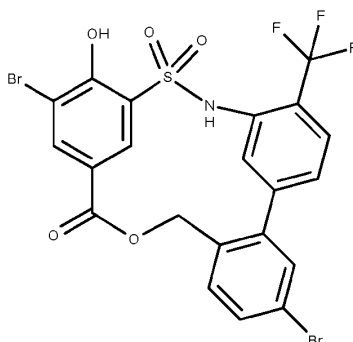
LCMS: m/z = 580.9/582.8/584.8 [M+H]⁺, (ESI⁺), RT = 4.28, Method A

Example 122 – Synthesis of 13-Bromo-20-chloro-14-hydroxy-19-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹.15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaene-4-carbonitrile (Compound 122)



[0360] Lithium iodide (71.0 mg, 0.530 mmol) was added to a stirring solution of 13-bromo-20-chloro-14,19-dimethoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹.15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaene-4-carbonitrile (*synthesised using a similar method to intermediate 26*, 127 mg, 0.221 mmol) in anhydrous pyridine (3.0 mL) in a pressure vial. The reaction vessel was sealed and the mixture stirred at 90 °C for until LCMS analysis indicated the reaction had reached completion. The reaction mixture was allowed to cool to r.t., diluted with EtOAc (~10 mL), and washed sequentially with Na₂S₂O₃ solution (aq.) (~10 mL), 1 M HCl solution (aq.) (~10 mL), and brine (~10 mL). The organic phase was dried by passing through a hydrophobic frit and concentrated to dryness in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a beige solid (25.3 mg, 96% pure, 20% yield). ¹H NMR (400 MHz, DMSO) δ 9.93 (s, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.92 (dd, J = 7.8, 1.8 Hz, 1H), 7.82 – 7.74 (m, 2H), 7.58 (d, J = 2.1 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.14 (d, J = 2.1 Hz, 1H), 5.55 (d, J = 12.9 Hz, 1H), 5.30 (d, J = 12.9 Hz, 1H), 3.53 (s, 3H). LCMS: m/z = 546.9, 548.9 [M-H]⁻, (ESI⁻), RT = 4.15, Method A

Example 123 – Synthesis of 4,13-Dibromo-14-hydroxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 123)

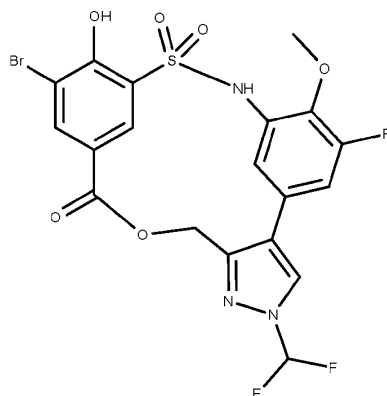


[0361] 4,13-Dibromo-14-methoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ ,6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised using similar methods to intermediate 62 and 26*, 73 mg, 0.109 mmol) and lithium iodide (144 mg, 1.07 mmol) were dissolved in anhydrous pyridine (3.9 mL). The mixture was then heated to 80 °C and stirred for 6 h. The reaction mixture was concentrated in vacuo and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (18.5 mg, 96% purity, 27% yield) as a white solid.

^1H NMR (400 MHz, DMSO) δ 8.06 – 8.00 (m, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.54 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 2.1 Hz, 1H), 7.19 – 7.16 (m, 1H), 6.93 (s, 1H), 5.40 – 5.28 (m, 2H).

LCMS: m/z = 603.8/605.8/607.8 $[\text{M-H}]^-$, (ESI-), RT = 4.55, Method A

Example 124 – Synthesis of 12-Bromo-4-(difluoromethyl)-19-fluoro-13-hydroxy-18-methoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (Compound 124)

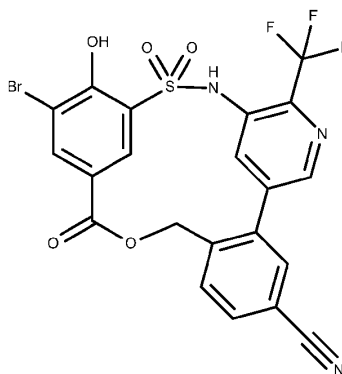


[0362] A mixture of 12-bromo-4-(difluoromethyl)-19-fluoro-13,18-dimethoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one (*synthesised from intermediate 32, using similar methods to intermediates 52 and 26*, 565 mg, 0.955 mmol), lithium iodide (250.0 mg, 1.87 mmol) and anhydrous pyridine (12 mL) was heated at 100 °C for 3 h. The mixture was cooled to r.t., sat aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (415 mg, 96% purity, 76% yield).

¹H NMR (400 MHz, DMSO) δ 9.82 (s, 1H), 8.39 (s, 1H), 8.11 (d, J = 2.2 Hz, 1H), 7.84 (t, J = 59.0 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.27 (dd, J = 12.1, 2.0 Hz, 1H), 7.07 – 7.01 (m, 1H), 5.36 (s, 2H), 3.60 (d, J = 2.2 Hz, 3H).

LCMS: m/z = 548.0/549.9 [M+H]⁺, (ESI⁺), RT = 3.89, Method A

Example 125 – Synthesis of 13-Bromo-14-hydroxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ ,6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile (Compound 125)

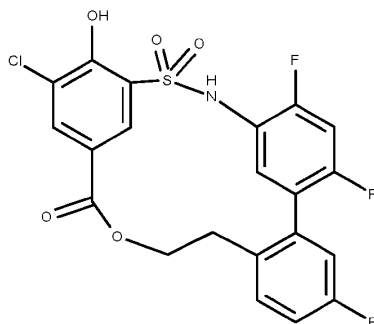


[0363] A mixture of 13-bromo-14-methoxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ ,6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile (*synthesised from intermediate 49, using similar methods to intermediates 62 and 26*, 344 mg, 0.575 mmol) and lithium iodide (200.0 mg, 1.49 mmol) in anhydrous pyridine (6 mL) was stirred at 80 °C under N₂ for 18 h. The reaction mixture was cooled to r.t. then diluted with sat. aq. Na₂S₂O₃ solution (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed successively with 1 M aq. HCl (50 mL) and brine (50 mL) then dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) followed by trituration with water to afford the title compound as an off-white solid (82.0 mg, 95% purity, 24% yield) as an off-white solid.

¹H NMR (400 MHz, DMSO) δ 8.91 – 8.86 (m, 1H), 8.07 (d, J = 2.2 Hz, 1H), 7.98 (dd, J = 7.9, 1.7 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 1.7 Hz, 1H), 7.28 – 7.23 (m, 1H), 6.97 – 6.92 (m, 1H), 5.63 – 5.43 (m, 2H).

LCMS: m/z = 554.0/555.9 [M+H]⁺, (ESI⁺), RT = 3.88, Method A

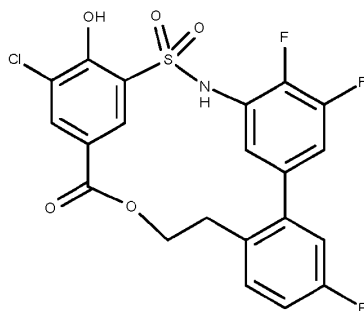
Example 126 – Synthesis of 14-Chloro-4,20,22-trifluoro-15-hydroxy-17,17-dioxo-10-oxa-17λ6-thia-18-azatetracyclo[17.3.1.1.12,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (Compound 126)



[0364] *Intermediate 84* (216.0 mg, 0.43 mmol), iodocyclohexane (0.28 mL, 2.15 mmol) and anhydrous DMF (10 mL) were added to a pressure vial. The mixture was stirred at 120 °C for 30 minutes. The mixture was diluted with EtOAc (25 mL), washed with 1 M HCl (25 mL), 2 M Na₂S₂O₃ (25 mL), then brine (25 mL). The EtOAc layer was passed through a phase separator and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (181 mg, 96% purity, 84% Yield). ¹H NMR (500 MHz, DMSO) δ 10.30 (br. s, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.67 – 7.60 (m, 1H), 7.57 (dd, J = 8.7, 5.9 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.31 – 7.23 (m, 1H), 6.90 (dd, J = 9.5, 2.8 Hz, 1H), 6.70 – 6.64 (m, 1H), 4.55 (t, J = 11.4 Hz, 1H), 4.22 (dt, J = 10.8, 3.2 Hz, 1H), 3.02 (d, J = 14.8 Hz, 1H), 2.85 – 2.75 (m, 1H).

LCMS: m/z = 482.0/484.0 [M-H]⁻, (ESI⁻), RT = 4.08, Method A

Example 127 – Synthesis of 14-Chloro-4,20,21-trifluoro-15-hydroxy-17,17-dioxo-10-oxa-17λ6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (Compound 127)

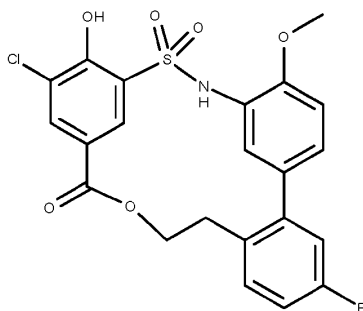


[0365] To a solution of 14-chloro-4,20,21-trifluoro-15-methoxy-17,17-dioxo-10-oxa-17λ6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (*synthesised using a similar method to Intermediate 84*, 93% purity, 100 mg, 0.187 mmol) in anhydrous pyridine (7 mL) was added lithium iodide (250 mg, 1.87 mmol). The reaction mixture was heated at 80 °C for 2 h. The organics were diluted with EtOAc (30 mL), washed with HCl (30 mL of a 1 M aqueous solution), Na₂SO₃ (10 mL of a saturated aqueous solution), brine (2 x 20 mL) and then dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as an off-white solid (28 mg, 95% purity, 29% Yield).

¹H NMR (400 MHz, DMSO) δ 7.95 – 7.90 (m, 1H), 7.56 (dd, J = 8.7, 5.9 Hz, 2H), 7.39 (d, J = 2.1 Hz, 1H), 7.29 – 7.19 (m, 1H), 6.89 (dd, J = 9.6, 2.8 Hz, 1H), 6.55 – 6.49 (m, 1H), 4.48 – 4.23 (m, 2H), 3.14 – 2.92 (m, 2H).

LCMS: m/z = 482.0 / 484.0 [M-H]⁻, (ESI⁻), RT = 4.15, Method A

Example 128 – Synthesis of 14-Chloro-4-fluoro-15-hydroxy-20-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracosa-1(22),2(7),3,5,12(24),13,15,19(23),20-nonaen-11-one (Compound 128)

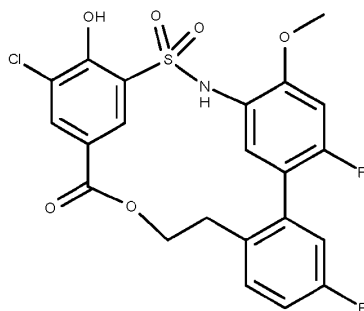


[0366] To a solution of 14-chloro-4-fluoro-15,20-dimethoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracosa-1(22),2(7),3,5,12(24),13,15,19(23),20-nonaen-11-one (*synthesised using a similar method to Intermediate 84*, 144.0 mg, 0.28 mmol) in anhydrous DMF (3 mL) was added iodocyclohexane (43 μ L, 0.33 mmol). The reaction mixture was stirred at 100 °C in a sealed tube overnight for 23 hours. The mixture was cooled to r.t., retreated with iodocyclohexane (10 μ L, 0.08 mmol) and then stirred at 100 °C in a sealed vial overnight for a further 24 hours. The mixture was cooled to r.t. and purified by preparative HPLC (Method P2) to afford the title compound as a white solid (87 mg, 100% purity, 65% Yield).

^1H NMR (500 MHz, DMSO) δ 10.54 (s, 1H), 9.67 (s, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.26 (dd, J = 8.4, 2.3 Hz, 1H), 7.22 – 7.15 (m, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.88 (dd, J = 9.8, 2.8 Hz, 1H), 4.58 – 4.26 (m, 2H), 3.78 (s, 3H), 3.24 – 2.83 (m, 2H).

LCMS: m/z = 476.4/478.3 $[\text{M-H}]^-$, (ESI-), RT = 4.06, Method A

Example 129 – Synthesis of 14-Chloro-4,22-difluoro-15-hydroxy-20-methoxy-17,17-dioxo-10-oxa-17 λ ,6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2,4,6,12,14,16(24),19(23),20-nonaen-11-one (Compound 129)

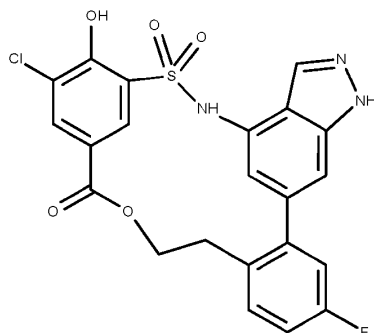


[0367] To a solution of 14-chloro-4,22-difluoro-15,20-dimethoxy-17,17-dioxo-10-oxa-17 λ ,6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one (*synthesised using a similar method to Intermediate 84*, 117.0 mg, 0.22 mmol) in anhydrous DMF (4 mL) was added iodocyclohexane (36 μ L, 0.28 mmol). The reaction mixture was stirred at 100 °C for 22 h. The solvent was removed under reduced pressure and the residue purified by preparative HPLC (Method P1) to afford the title compound as a white solid (59 mg, 95% purity, 53% Yield).

¹H NMR (500 MHz, DMSO) δ 10.46 (br s, 1H), 9.76 (br s, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.54 (dd, J = 8.7, 5.9 Hz, 1H), 7.49 (d, J = 2.1 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.18 (d, J = 11.7 Hz, 1H), 6.86 (dd, J = 9.6, 2.8 Hz, 1H), 6.60 (d, J = 7.9 Hz, 1H), 4.55 – 4.47 (m, 1H), 4.37 – 4.30 (m, 1H), 3.85 (s, 3H), 3.03 – 2.96 (m, 1H), 2.85 – 2.75 (m, 1H).

LCMS: m/z = 494.0/496.0 [M-H]⁻, (ESI⁻), RT = 4.12, Method A

Example 130 – Synthesis of 14-Chloro-4-fluoro-15-hydroxy-17,17-dioxo-10-oxa-17λ6-thia-18,22,23-triazapentacyclo[17.6.1.112,16.02,7.020,24]heptacosal(26),2(7),3,5,12,14,16(27),19,21,24-decaen-11-one (Compound 130)

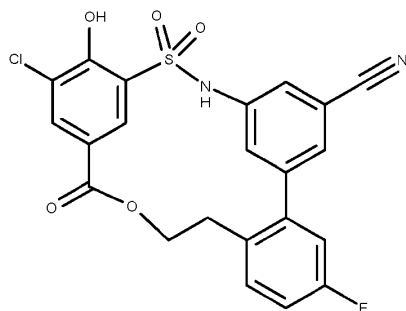


[0368] To a solution of 14-chloro-4-fluoro-15-methoxy-17,17-dioxo-10-oxa-17λ6-thia-18,22,23-triazapentacyclo[17.6.1.112,16.02,7.020,24]heptacosal(26),2(7),3,5,12,14,16(27),19,21,24-decaen-11-one (*synthesised using a similar method to Intermediate 84*, 149.0 mg, 0.18 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (119.202 mg, 0.89 mmol). The reaction mixture was heated at 90 °C for 5 h. The mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL), then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (27 mg, 97% purity, 31% Yield).

¹H NMR (500 MHz, DMSO) δ 13.24 (s, 1H), 10.68 (br.s, 2H), 8.20 (s, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.38 (s, 1H), 7.28 – 7.20 (m, 1H), 7.00 (dd, J = 9.6, 2.8 Hz, 1H), 6.62 (s, 1H), 4.38 – 4.20 (m, 2H), 3.23 – 2.82 (m, 2H).

LCMS: m/z = 488.0/490.0 [M+H]⁺, (ESI⁺), RT = 3.48, Method A

Example 131 – Synthesis of 14-Chloro-4-fluoro-15-hydroxy-11,17,17-trioxo-10-oxa-17λ6-thia-18-azatetracyclo[17.3.1.1.12,16.02,7]tetracosa-1(22),2,4,6,12,14,16(24),19(23),20-nonaene-21-carbonitrile (Compound 131)

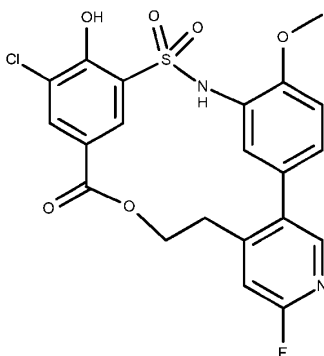


[0369] To a solution of 14-chloro-4-fluoro-15-methoxy-11,17,17-trioxo-10-oxa-17λ6-thia-18-azatetracyclo[17.3.1.1.12,16.02,7]tetracosa-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaene-21-carbonitrile (*synthesised using a similar method to Intermediate 84*, 94% purity, 68 mg, 0.131 mmol) in anhydrous pyridine (5 mL) was added lithium iodide (218 mg, 1.63 mmol). The reaction mixture was heated at 80 °C for 1 h. The mixture was diluted with EtOAc (30 mL), washed with HCl (2 x 30 mL of a 1 M aqueous solution), Na₂SO₃ (10 mL of a saturated aqueous solution), brine (2 x 20 mL), then dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound (38 mg, 98% purity, 60% Yield) as a light pink solid.

¹H NMR (400 MHz, DMSO) δ 7.88 – 7.85 (m, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 7.57 (dd, J = 8.7, 5.9 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.32 – 7.25 (m, 2H), 7.07 (dd, J = 9.5, 2.8 Hz, 1H), 4.28 (s, 2H), 2.98 (t, 2H)

LCMS: m/z = 471.0 / 473.0 [M-H]⁻, (ESI⁻), RT = 3.98, Method A

Example 132 – Synthesis of 14-Chloro-5-fluoro-15-hydroxy-20-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one (Compound 132)

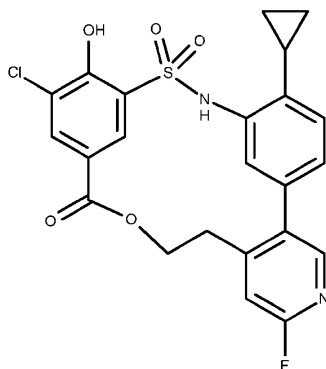


[0370] A mixture of 14-chloro-5-fluoro-15,20-dimethoxy-17,17-dioxo-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one (synthesised from Intermediate 85 using a similar method to Intermediate 84, 355.0 mg, 0.6 mmol), lithium iodide (162 mg, 1.21 mmol) and anhydrous pyridine (8 mL) was heated at 80 °C for 1.5 h. Further lithium iodide (243 mg, 1.81 mmol) was added and the mixture was stirred at r.t. for 4 h. The mixture was diluted with EtOAc (60 mL), washed with sat. aq. Na₂S₂O₃ (40 mL), 1 M aq. HCl (2 x 40 mL) and brine (40 mL), then dried with Na₂SO₄, filtered and concentrated. To the resulting residue was added EtOAc (30 mL), the mixture warmed to 40 °C for 2 mins and then sonicated for 5 min at r.t. The resulting suspension was filtered and the collected solid dried in the vacuum oven to afford the title compound as a white solid (226 mg, 97% purity, 76% Yield).

¹H NMR (500 MHz, DMSO) δ 10.57 (br. s, 1H), 9.71 (s, 1H), 7.95 (s, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.44 – 7.36 (m, 1H), 7.32 (dd, J = 8.5, 2.2 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 6.80 (s, 1H), 4.58 – 4.42 (m, 2H), 3.79 (s, 3H), 3.25 – 2.89 (m, 2H).

LCMS: m/z = 477.0/479.0 [M-H]⁻, (ESI⁻), RT = 3.58, Method A

Example 133 – Synthesis of 14-Chloro-20-cyclopropyl-5-fluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one (Compound 133)

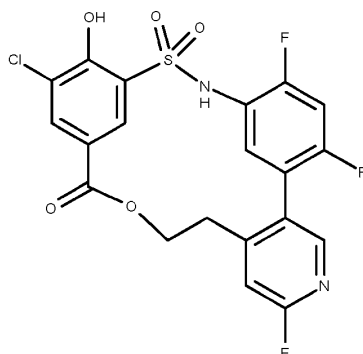


[0371] A mixture of 14-chloro-20-cyclopropyl-5-fluoro-15-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one (synthesised from Intermediate 85 using a similar method to Intermediate 84, 295.0 mg, 0.56 mmol), lithium iodide (746 mg, 5.57 mmol) and anhydrous pyridine (8 mL) was heated at 80 °C for 1 h, followed by heating at 90 °C for 1.5 h. The mixture was diluted with EtOAc (50 mL), washed with sat. aq. Na₂S₂O₃ (40 mL), 1 M aq. HCl (40 mL) and brine (40 mL), then passed through a phase separator and then concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (134 mg, 99% purity, 49% Yield).

¹H NMR (400 MHz, DMSO) δ 10.78 – 9.65 (m, 2H), 7.92 (d, J = 2.1 Hz, 1H), 7.87 (s, 1H), 7.44 – 7.41 (m, 1H), 7.37 (d, J = 2.1 Hz, 1H), 7.29 (dd, J = 8.0, 1.9 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.55 – 6.49 (m, 1H), 4.78 – 4.19 (m, 2H), 3.25 – 2.92 (m, 2H), 2.49 – 2.43 (m, 1H), 1.13 – 0.99 (m, 2H), 0.87 – 0.51 (m, 2H).

LCMS: m/z = 487.0/489.0 [M-H]⁻, (ESI⁻), RT = 3.97, Method A

Example 134 – Synthesis of 14-Chloro-5,20,22-trifluoro-15-hydroxy-17,17-dioxo-10-oxa-17λ6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one (Compound 134)

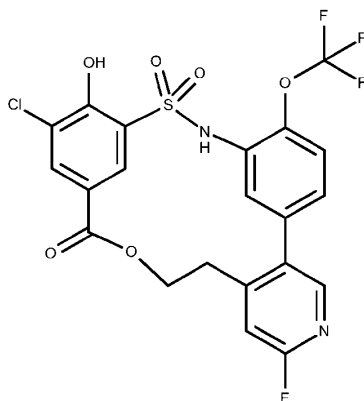


[0372] To a solution of 14-chloro-5,20,22-trifluoro-15-methoxy-17,17-dioxo-10-oxa-17λ6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one (*synthesised from Intermediate 85 using a similar method to Intermediate 84*, 185.0 mg, 0.21 mmol) in anhydrous pyridine (4.75 mL) was added lithium iodide (278 mg, 2.08 mmol) and the mixture was heated at 90 °C for 5.5 h and then cooled to r.t. The mixture was diluted with EtOAc (50 mL) and washed with 1 M aq. HCl (30 mL), sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL), then passed through a phase separator and concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (56 mg, 99% purity, 55% Yield).

¹H NMR (400 MHz, DMSO) δ 7.96 – 7.88 (m, 2H), 7.75 – 7.63 (m, 1H), 7.50 – 7.40 (m, 1H), 7.36 (d, J = 2.1 Hz, 1H), 6.78 – 6.68 (m, 1H), 4.68 – 4.54 (m, 1H), 4.33 – 4.17 (m, 1H), 3.17 – 3.08 (m, 1H), 2.95 – 2.76 (m, 1H).

LCMS: m/z = 483.0/485.0 [M-H]⁻, (ESI⁻), RT = 3.70, Method A

Example 135 – Synthesis of 14-Chloro-5-fluoro-15-hydroxy-17,17-dioxo-20-(trifluoromethoxy)-10-oxa-17λ6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one (Compound 135)

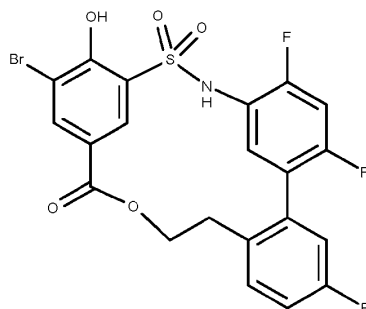


[0373] A mixture of 14-chloro-5-fluoro-15-methoxy-17,17-dioxo-20-(trifluoromethoxy)-10-oxa-17λ6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one (synthesised from Intermediate 85 using a similar method to Intermediate 84, 170 mg, 0.187 mmol), lithium iodide (250 mg, 1.87 mmol) and anhydrous pyridine (2.8 mL) was heated at 90 °C for 1.5 h. The mixture was diluted with EtOAc (50 mL), washed with sat. aq. Na₂S₂O₃ (40 mL), 1 M aq. HCl (40 mL) and brine (40 mL), then passed through a phase separator and then concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (44 mg, 98% purity, 43% Yield).

¹H NMR (500 MHz, DMSO) δ 11.39 – 9.50 (m, 2H), 7.98 (s, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.52 (dd, J = 8.5, 2.2 Hz, 1H), 7.45 (s, 1H), 7.35 (d, J = 2.2 Hz, 1H), 6.95 – 6.83 (m, 1H), 4.70 – 4.24 (m, 2H), 3.19 – 2.98 (m, 2H).

LCMS: m/z = 531.0/533.0 [M-H]⁻, (ESI⁻), RT = 3.94, Method A

Example 136 – Synthesis of 14-Bromo-4,20,22-trifluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.1¹².16.0^{2,7}]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (Compound 136)

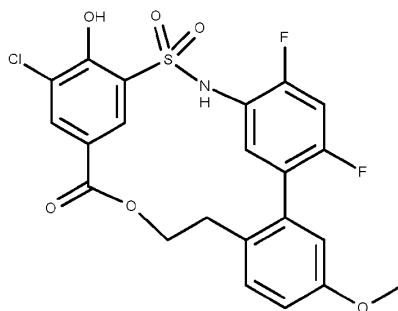


[0374] 14-Bromo-4,20,22-trifluoro-15-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.1¹².16.0^{2,7}]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (*synthesised from Intermediate 21 using a similar method to Intermediate 84*, 50.0 mg, 0.09 mmol) and iodocyclohexane (0.055 mL, 0.429 mmol) were weighed in a pressure vial and anhydrous DMF (2 mL) was added. The reaction mixture was heated to 120 °C for 45 minutes. The mixture was diluted with EtOAc (25 mL), washed with 1 M HCl (25 mL), 2 M Na₂S₂O₃ (25 mL), then brine (25 mL). The EtOAc layer was passed through a phase separator and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white powder (27 mg, 96% purity, 57% Yield).

¹H NMR (500 MHz, DMSO) δ 10.29 (s, 1H), 8.07 (d, J = 2.2 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.57 (dd, J = 8.7, 5.9 Hz, 1H), 7.41 (d, J = 2.1 Hz, 1H), 7.31 – 7.24 (m, 1H), 6.90 (dd, J = 9.4, 2.8 Hz, 1H), 6.71 – 6.64 (m, 1H), 4.55 (t, J = 11.5 Hz, 1H), 4.21 (dt, J = 10.7, 3.2 Hz, 1H), 3.02 (d, J = 14.6 Hz, 1H), 2.85 – 2.76 (m, 1H).

LCMS: m/z = 526.0/528.0 [M-H]⁻, (ESI⁻), RT = 4.10, Method A

Example 137 – Synthesis of 14-Chloro-20,22-difluoro-15-hydroxy-4-methoxy-17,17-dioxo-10-oxa-17 λ ,6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2,4,6,12,14,16(24),19(23),20-nonaen-11-one (Compound 137)

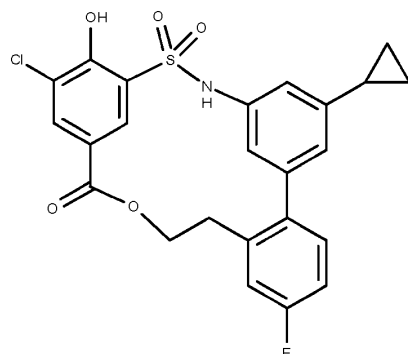


[0375] To a solution of 14-chloro-20,22-difluoro-4,15-dimethoxy-17,17-dioxo-10-oxa-17 λ ,6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (*synthesised using a similar method to Intermediate 84*, 92% purity, 253 mg, 0.456 mmol) in anhydrous pyridine (8 mL) was added lithium iodide (122 mg, 0.912 mmol). The reaction mixture was heated at 80 °C for 1 h. The organics were diluted with EtOAc (30 mL), washed with HCl (30 mL of a 1 M aqueous solution), Na₂S₂O₃ (10 mL of a saturated aqueous solution), brine (20 mL) and then dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (124 mg, 96% purity, 53% Yield) as an off-white solid.

¹H NMR (500 MHz, DMSO) δ 10.27 (br. s, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.44 – 7.39 (m, 1H), 7.39 – 7.37 (m, 1H), 6.98 (dd, J = 8.6, 2.8 Hz, 1H), 6.69 – 6.62 (m, 1H), 6.54 (d, J = 2.7 Hz, 1H), 4.52 (t, J = 11.4 Hz, 1H), 4.23 – 4.15 (m, 1H), 3.69 (s, 3H), 2.98 – 2.91 (m, 1H), 2.81 – 2.69 (m, 1H).

LCMS: m/z = 494.0 / 496.0 [M-H]⁻, (ESI⁻), RT = 4.07, Method A

Example 138 – Synthesis of 14-Chloro-21-cyclopropyl-5-fluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.1¹².16.02,7]tetracos-1(22),2,4,6,12,14,16(24),19(23),20-nonaen-11-one (Compound 138)

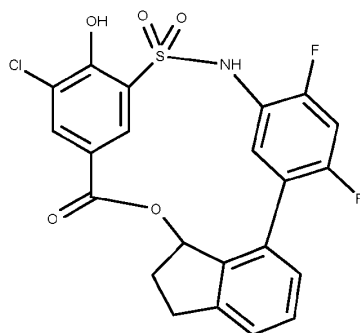


[0376] To a solution of 14-chloro-21-cyclopropyl-5-fluoro-15-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.1¹².16.02,7]tetracos-1(22),2,4,6,12,14,16(24),19(23),20-nonaen-11-one (*synthesised using a similar method to Intermediate 84*, 148.0 mg, 0.29 mmol) in anhydrous DMF (5.9 mL) was added iodocyclohexane (50 μ L, 0.39 mmol). The reaction mixture was stirred at 120 °C for 8 h. Further iodocyclohexane (25 μ L, 0.19 mmol) was added and the mixture was heated to 120 °C for 1 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (73 mg, 98% purity, 50% Yield).

¹H NMR (500 MHz, DMSO) δ 10.68 (br s, 1H), 10.36 (s, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.37 (dd, J = 10.2, 2.7 Hz, 1H), 7.17 – 7.04 (m, 3H), 6.99 – 6.94 (m, 1H), 6.59 (s, 1H), 4.32 (t, J = 4.9 Hz, 2H), 3.04 (s, 2H), 2.01 (tt, J = 8.3, 5.0 Hz, 1H), 1.04 – 0.97 (m, 2H), 0.75 – 0.68 (m, 2H).

LCMS: m/z = 486.3/488.4 [M-H]⁻, (ESI⁻), RT = 4.47, Method A

Example 139 – Synthesis of 11-Chloro-3,5-difluoro-10-hydroxy-8,8-dioxo-15-oxa-8λ6-thia-7-azapentacyclo[14.6.1.12,6.19,13.019,23]pentacosal-1(23),2,4,6(25),9(24),10,12,19,21-nonaen-14-one (Compound 139)

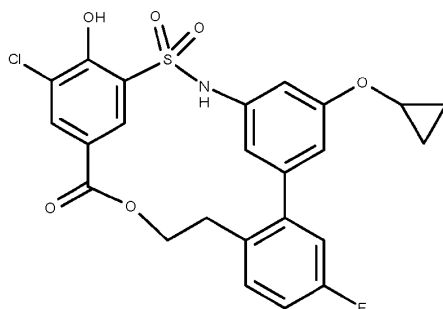


[0377] To a solution of 11-chloro-3,5-difluoro-10-methoxy-8,8-dioxo-15-oxa-8λ6-thia-7-azapentacyclo[14.6.1.12,6.19,13.019,23]pentacosal-1(23),2,4,6(25),9(24),10,12,19,21-nonaen-14-one (*synthesised using a similar method to Intermediate 84*, 88% purity, 343 mg, 0.614 mmol) in anhydrous pyridine (22 mL) was added lithium iodide (805 mg, 6.01 mmol). The reaction mixture was heated at 80 °C for 3 h, then allowed to cool to r.t. over 30 minutes followed by stirring at r.t. for 15 h. The organics were diluted with EtOAc (30 mL), washed with HCl (2 x 30 mL of a 1 M aqueous solution), then Na₂S₂O₃ (10 mL of a saturated aqueous solution), then brine (2 x 20 mL), dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (215 mg, 99% yield, 73% Yield).

¹H NMR (500 MHz, DMSO) δ 10.34 (s, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.51 – 7.44 (m, 3H), 7.43 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 1.3 Hz, 1H), 7.18 – 7.12 (m, 1H), 6.09 (t, J = 7.4 Hz, 1H), 3.14 – 2.99 (m, 2H), 2.83 – 2.72 (m, 1H), 2.05 – 1.93 (m, 1H).

LCMS: m/z = 476.1 / 478.1 [M-H]⁻, (ESI⁻), RT = 4.18, Method A

Example 140 – Synthesis of 14-Chloro-21-(cyclopropoxy)-4-fluoro-15-hydroxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one (Compound 140)

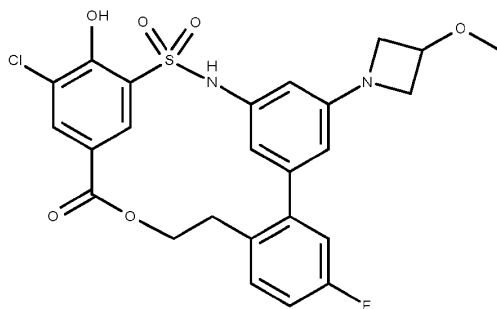


[0378] To a solution of 14-chloro-21-(cyclopropoxy)-4-fluoro-15-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one (*synthesised from Intermediate 86 using a similar method to Intermediate 84*, 112.0 mg, 0.22 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (57.9 mg, 0.43 mmol) and reaction mixture was heated at 80 °C for 18 h. The mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude material as a white solid. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (58 mg, 98% purity, 52% Yield).

¹H NMR (500 MHz, DMSO) δ 10.78 (br,s, 1H), 10.46 (s, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.53 (dd, J = 8.6, 5.9 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.05 – 7.01 (m, 1H), 7.00 – 6.96 (m, 2H), 6.58 – 6.52 (m, 1H), 4.41 – 4.13 (m, 2H), 3.92 – 3.80 (m, 1H), 3.19 – 2.92 (m, 2H), 0.83 – 0.73 (m, 2H), 0.73 – 0.61 (m, 2H).

LCMS: m/z = 502.0/504.0 [M-H]⁻, (ESI⁻), RT = 4.38, Method A

Example 141 – Synthesis of 14-Chloro-4-fluoro-15-hydroxy-21-(3-methoxyazetidin-1-yl)-17,17-dioxo-10-oxa-17λ6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one (Compound 141)

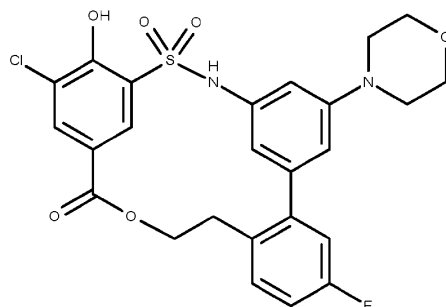


[0379] A pressure vial was charged with 14-chloro-4-fluoro-15-methoxy-21-(3-methoxyazetidin-1-yl)-17,17-dioxo-10-oxa-17λ6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one (synthesised from Intermediate 87 using a similar method to Intermediate 84, 160.0 mg, 0.29 mmol), lithium iodide (392.0 mg, 2.93 mmol), and anhydrous pyridine (10 mL), and the mixture was heated at 100 °C overnight. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as a white solid (99 mg, 99% purity, 63% Yield).

¹H NMR (500 MHz, DMSO) δ 10.74 (br. s, 1H), 10.32 (s, 1H), 7.92 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.50 (dd, J = 8.7, 5.9 Hz, 1H), 7.23 – 7.16 (m, 1H), 6.92 (dd, J = 9.6, 2.8 Hz, 1H), 6.44 – 6.40 (m, 1H), 6.32 – 6.28 (m, 1H), 6.22 (s, 1H), 4.32 (t, J = 6.2, 4.2 Hz, 1H), 4.29 (br. s, 2H), 4.07 (dd, J = 8.3, 6.2 Hz, 2H), 3.64 (dd, J = 8.4, 4.1 Hz, 2H), 3.24 (s, 3H), 3.10 (br. s, 2H).

LCMS: m/z = 531./533.0 [M-H]⁻, (ESI⁻), RT = 4.23, Method A

Example 142 – Synthesis of 14-Chloro-4-fluoro-15-hydroxy-21-morpholino-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one (Compound 142)

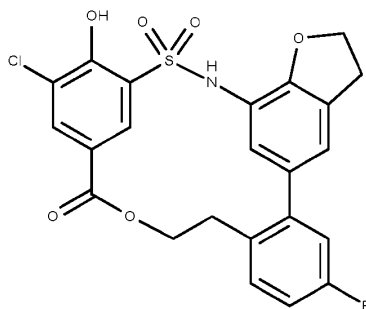


[0380] A pressure vial was charged with 14-chloro-4-fluoro-15-methoxy-21-morpholino-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one (*synthesised from Intermediate 88 using a similar method to Intermediate 84*, 100.0 mg, 0.18 mmol), lithium iodide (245.0 mg, 1.83 mmol), and anhydrous pyridine (6.5 mL), and the mixture was heated at 100 °C overnight. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as a pale brown solid (54 mg, 99% purity, 54% Yield).

¹H NMR (500 MHz, DMSO) δ 10.70 (br. s, 1H), 10.34 (s, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.52 (dd, J = 8.7, 6.0 Hz, 1H), 7.25 – 7.17 (m, 1H), 6.93 (dd, J = 9.7, 2.7 Hz, 2H), 6.87 – 6.83 (m, 1H), 6.33 (s, 1H), 4.29 (br. s, 2H), 3.77 – 3.71 (m, 4H), 3.19 – 3.14 (m, 4H), 3.08 (br. s, 2H).

LCMS: m/z = 531.1/533.1 [M-H]⁻, (ESI⁻), RT = 4.07, Method A

Example 143 – Synthesis of 14-Chloro-4-fluoro-15-hydroxy-17,17-dioxo-10,21-dioxo-17λ6-thia-18-azapentacyclo[17.6.1.112,16.02,7.020,24]heptacos-1(26),2(7),3,5,12,14,16(27),19,24-nonaen-11-one (Compound 143)

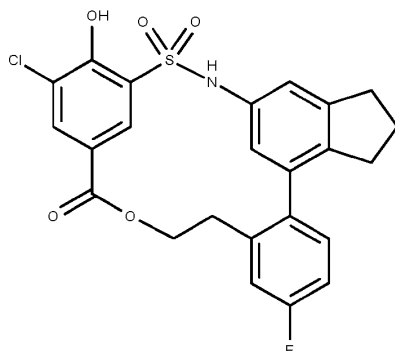


[0381] A pressure vial was charged with 14-chloro-4-fluoro-15-methoxy-17,17-dioxo-10,21-dioxo-17λ6-thia-18-azapentacyclo[17.6.1.112,16.02,7.020,24]heptacos-1(26),2(7),3,5,12,14,16(27),19,24-nonaen-11-one (*synthesised from Intermediate 89 using a similar method to Intermediate 84*, 109.0 mg, 0.22 mmol), lithium iodide (291.0 mg, 2.17 mmol), and anhydrous pyridine (8 mL) and the mixture was heated at 100 °C for 4 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as an off-white solid (74 mg, 95% purity, 67% Yield).

¹H NMR (500 MHz, DMSO) δ 10.35 (br. s, 1H), 9.91 (br. s, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.20 – 7.12 (m, 2H), 6.77 (dd, J = 9.7, 2.8 Hz, 1H), 6.29 (d, J = 1.8 Hz, 1H), 4.62 (t, J = 8.8 Hz, 2H), 4.49 (br. s, 1H), 4.25 (br. s, 1H), 3.30 – 3.15 (m, 3H), 2.89 (br. s, 1H).

LCMS: m/z = 488.0/490.0 [M-H]⁻, (ESI⁻), RT = 4.00, Method A

Example 144 – Synthesis of 14-Chloro-5-fluoro-15-hydroxy-17,17-dioxo-10-oxa-17λ6-thia-18-azapentacyclo[17.6.1.112,16.02,7.021,25]heptacosal(25),2,4,6,12,14,16(27),19(26),20-nonaen-11-one (Compound 144)

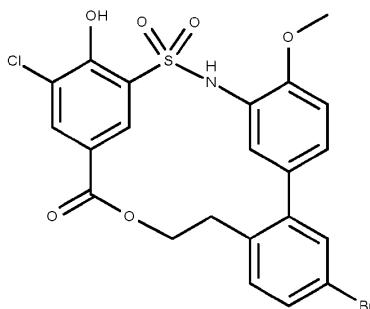


[0382] To a solution of 14-chloro-5-fluoro-15-methoxy-17,17-dioxo-10-oxa-17λ6-thia-18-azapentacyclo[17.6.1.112,16.02,7.021,25]heptacosal(25),2,4,6,12,14,16(27),19(26),20-nonaen-11-one (*synthesised from Intermediate 90 using a similar method to Intermediate 84*, 240.0 mg, 0.48 mmol) in anhydrous DMF (9.6 mL) was added iodocyclohexane (80 μL, 0.62 mmol). The reaction mixture was stirred at 120 °C for 8 h. Further iodocyclohexane (40 μL, 0.31 mmol) was added and the mixture heated to 120 °C for 1 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (83 mg, 99% purity, 35% Yield).

¹H NMR (500 MHz, DMSO) δ 10.71 (br s, 1H), 10.34 (s, 1H), 7.93 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 2.1 Hz, 1H), 7.38 (dd, J = 10.2, 2.3 Hz, 1H), 7.29 (s, 1H), 7.14 – 7.05 (m, 2H), 6.57 (s, 1H), 4.37 – 4.29 (m, 2H), 3.07 – 2.88 (m, 3H), 2.75 – 2.63 (m, 2H), 2.48 – 2.38 (m, 1H), 2.13 – 1.91 (m, 2H).

LCMS: m/z = 486.3/488.4 [M-H]⁻, (ESI⁻), RT = 4.54, Method A

Example 145 – Synthesis of 4-Bromo-14-chloro-15-hydroxy-20-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (Compound 145)

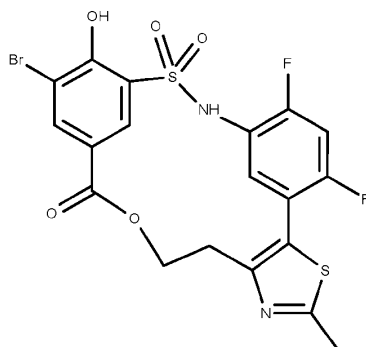


[0383] 4-bromo-14-chloro-15,20-dimethoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (*synthesised from Intermediate 91 using a similar method to Intermediate 84*, 97%, 120 mg, 0.211 mmol) and iodocyclohexane (50 mg, 0.238 mmol) were combined and the mixture dissolved in DMF (4.8 mL). The mixture was heated to 100 °C and stirred for 18 h. Further iodocyclohexane (10.0 mg, 0.05 mmol) was added and the mixture was stirred at 100 °C for a further 3 h. The mixture was cooled to r.t. Sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (95 mg, 98% purity, 82% Yield).

¹H NMR (500 MHz, DMSO) δ 10.54 (br. s, 1H), 9.63 (s, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.53 (dd, J = 8.3, 2.2 Hz, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 8.5, 2.3 Hz, 1H), 7.22 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H), 6.77 (s, 1H), 4.51 – 4.41 (m, 1H), 4.39 – 4.31 (m, 1H), 3.78 (s, 3H), 3.23 – 3.13 (m, 1H), 2.94 – 2.82 (m, 1H).

LCMS: m/z = 536.0/537.9/539.9 [M-H]⁻, (ESI⁻), RT = 4.38, Method A

Example 146 – Synthesis of 13-bromo-19,21-difluoro-14-hydroxy-4-methyl-16,16-dioxo-9-oxa-3,16λ6-dithia-5,17-diazatetracyclo[16.3.1.111,15.02,6]tricos-1(22),2(6),4,11,13,15(23),18,20-octaen-10-one (Compound 146)

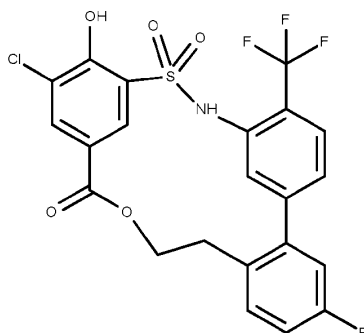


[0384] To a solution of 13-bromo-19,21-difluoro-14-methoxy-4-methyl-16,16-dioxo-9-oxa-3,16λ6-dithia-5,17-diazatetracyclo[16.3.1.111,15.02,6]tricos-1(22),2(6),4,11,13,15(23),18,20-octaen-10-one (*synthesised from Intermediate 92 using a similar method to Intermediate 84*, 223.0 mg, 0.41 mmol) in anhydrous pyridine (6 mL) was added lithium iodide (273.644 mg, 2.04 mmol). The reaction mixture was heated at 80 °C for 5 h. The mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (90 mg, 99% purity, 41% Yield).

¹H NMR (500 MHz, DMSO) δ 10.31 (br.s, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.41 (d, J = 2.1 Hz, 1H), 6.85 – 6.77 (m, 1H), 4.45 – 4.34 (m, 2H), 2.96 – 2.85 (m, 2H), 2.64 (s, 3H). Phenol OH not observed.

LCMS: m/z = 531.0/532.9 [M+H]⁺, (ESI⁺), RT = 3.66, Method A

Example 147 – Synthesis of 14-Chloro-4-fluoro-15-hydroxy-17,17-dioxo-20-(trifluoromethyl)-10-oxa-17,6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one (Compound 147)

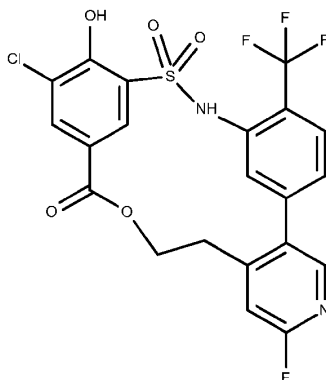


[0385] To a solution of *Intermediate 98* (400.0 mg, 0.75 mmol) in anhydrous pyridine (12 mL) was added lithium iodide (1.01 g, 7.55 mmol). The reaction mixture was heated at 90 °C for 18 h. The reaction mixture was dissolved in EtOAc (50 mL) and washed with 1 M aq. HCl (50 mL). The aqueous phase was extracted further with EtOAc (2 x 50 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (50 mL) and brine (50 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was taken into DMSO (~15 mL) then water (~5 mL) was added, resulting white solid was filtered off and washed with MeCN:water (1:1, ~15 mL) and dried in a vacuum oven to afford the title compound as a white solid (327 mg, 97% purity, 81% Yield).

¹H NMR (500 MHz, DMSO) δ 10.45 (br s, 2H), 7.92 (d, J = 2.1 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.41 – 7.35 (m, 1H), 7.29 – 7.21 (m, 1H), 6.85 (dd, J = 9.6, 2.8 Hz, 1H), 6.65 (s, 1H), 4.71 – 4.55 (m, 1H), 4.27 – 4.11 (m, 1H), 3.19 – 3.08 (m, 1H), 3.03 – 2.89 (m, 1H).

LCMS: m/z = 514.0/516.0 [M-H]⁻, (ESI⁻), RT = 4.35, Method A

Example 148 – Synthesis of 14-Chloro-5-fluoro-15-hydroxy-17,17-dioxo-20-(trifluoromethyl)-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.1.12,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one (Compound 148)

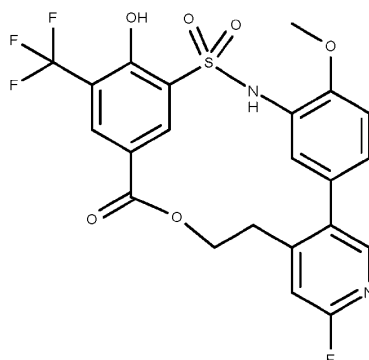


[0386] To a solution of 14-chloro-5-fluoro-15-methoxy-17,17-dioxo-20-(trifluoromethyl)-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.1.12,16.02,7]tetracos-1(23),2(7),3,5,12,14,16(24),19,21-nonaen-11-one (*synthesised using a similar method to Intermediate 98*, 262.0 mg, 0.49 mmol) in anhydrous pyridine (6 mL) was added lithium iodide (330 mg, 2.47 mmol). The reaction mixture was heated at 80 °C for 5 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (46 mg, 99% purity, 18% Yield).

¹H NMR (500 MHz, DMSO) δ 10.49 (br.s, 1H), 7.96 – 7.91 (m, 2H), 7.91 (s, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 1.4 Hz, 1H), 7.40 – 7.32 (m, 1H), 6.70 (s, 1H), 4.79 – 4.63 (m, 1H), 4.35 – 4.20 (m, 1H), 3.20 – 3.03 (m, 2H). OH peak not observed.

LCMS: m/z = 517.0/518.9 [M+H]⁺, (ESI⁺), RT = 3.83, Method A

Example 149 – Synthesis of 5-fluoro-15-hydroxy-20-methoxy-17,17-dioxo-14-(trifluoromethyl)-10-oxa-17 λ ,6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (Compound 149)

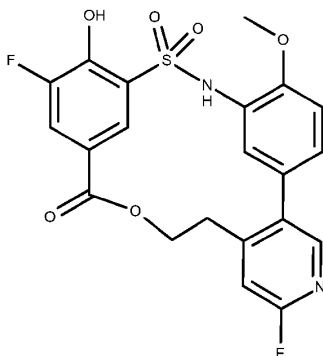


[0387] To a solution of 5-fluoro-15,20-dimethoxy-17,17-dioxo-14-(trifluoromethyl)-10-oxa-17 λ ,6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (*synthesised from Intermediate 99* using a similar method to *Intermediate 84*, 53 mg, 0.0523 mmol) in anhydrous pyridine (6.2 mL) was added lithium iodide (14 mg, 0.105 mmol) and the mixture heated to 90 °C and stirred for 18 h. The mixture was allowed to cool to r.t then concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (25 mg, 98% purity, 91% Yield) as a white solid.

¹H NMR (500 MHz, DMSO) δ 9.71 (br s, 1H), 7.99 (s, 1H), 7.94 (s, 1H), 7.68 (d, J = 2.2 Hz, 1H), 7.39 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 6.85 (s, 1H), 4.48 (s, 2H), 3.80 (s, 3H), 3.03 (s, 2H).

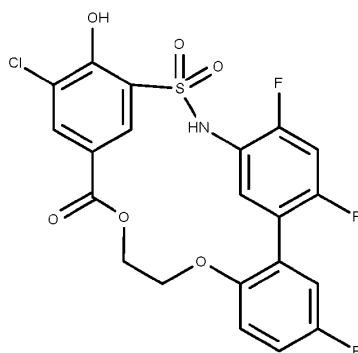
LCMS: m/z = 511.0 [M-H]⁻, (ESI⁻), RT = 3.86, Method D

Example 150 – Synthesis of 5,14-Difluoro-15-hydroxy-20-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one (Compound 150)



[0388] 5,14-Difluoro-15,20-dimethoxy-17,17-dioxo-10-oxa-17 λ 6-thia-4,18-diazatetracyclo[17.3.1.112,16.02,7]tetracos-1(23),2(7),3,5,12(24),13,15,19,21-nonaen-11-one (synthesised from Intermediate 100 using a similar method to Intermediate 84, 45.0 mg, 0.09 mmol) and iodocyclohexane (0.02 mL, 0.18 mmol) were dissolved in anhydrous DMF (3 mL) and the mixture was stirred at 80 °C for 2 h. Further iodocyclohexane (0.036 mL, 0.275 mmol) was added and the mixture stirred at 100 °C until complete conversion was observed by LCMS. The mixture was diluted with EtOAc (25 mL), washed with 1 M HCl (25 mL), 2 M Na₂S₂O₃ (25 mL), then brine (25 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (15 mg, 93% purity, 33% Yield).
¹H NMR (500 MHz, DMSO) δ 11.30 (br s, 1H), 9.48 (s, 1H), 7.98 (s, 1H), 7.69 (dd, J = 10.8, 2.2 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.27 (dd, J = 8.5, 2.3 Hz, 1H), 7.07 (d, J = 8.5 Hz, 1H), 6.87 (s, 1H), 4.71 – 4.27 (m, 2H), 3.73 (s, 3H), 3.19 – 2.97 (m, 2H).
 LCMS: m/z = 461.0 [M-H]⁻, (ESI⁻), RT = 3.22, Method A

Example 151 – Synthesis of 15-Chloro-4,21,23-trifluoro-16-hydroxy-18,18-dioxo-8,11-dioxo-18,6-thia-19-azatetracyclo[18.3.1.113,17.02,7]pentacos-1(23),2(7),3,5,13,15,17(25),20(24),21-nonaen-12-one (Compound 151)

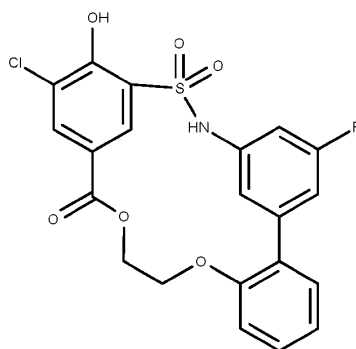


[0389] *Intermediate 106* (99% purity, 530 mg, 1.02 mmol) and iodocyclohexane (0.67 mL, 5.18 mmol) were combined and in anhydrous DMF (16.3 mL). The mixture was heated to 120 °C and stirred for 2 h. The mixture was allowed to cool to r.t., added to sat. aq. Na₂S₂O₃ (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by FCC (50 g SiO₂ cartridge, 20-100% DCM in heptane) to afford the title compound as a white solid (66 mg, 98% purity, 13% Yield).

¹H NMR (500 MHz, DMSO) δ 10.46 (br s, 1H), 8.06 (d, J = 2.1 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.33 – 7.27 (m, 1H), 7.27 – 7.18 (m, 3H), 4.36 – 4.31 (m, 2H), 4.31 – 4.25 (m, 2H).

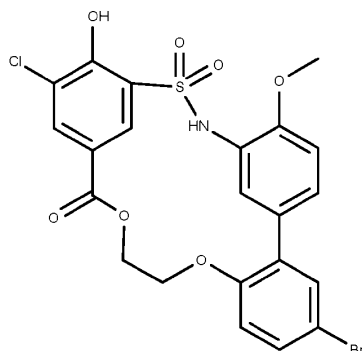
LCMS: m/z = 498.3/500.3 [M-H]⁻, (ESI⁻), RT = 3.98, Method A

Example 152 – Synthesis of 15-chloro-22-fluoro-16-methoxy-18,18-dioxo-8,11-dioxo-18λ6-thia-19-azatetracyclo[18.3.1.113,17.02,7]pentacos-1(23),2(7),3,5,13,15,17(25),20(24),21-nonaen-12-one (Compound 152)



[0390] 15-Chloro-22-fluoro-16-methoxy-18,18-dioxo-8,11-dioxo-18λ6-thia-19-azatetracyclo[18.3.1.113,17.02,7]pentacos-1(23),2(7),3,5,13,15,17(25),20(24),21-nonaen-12-one (*synthesised using a similar method to Intermediate 106*, 66%, 150 mg, 0.207 mmol), anhydrous DMF (5 mL) and iodocyclohexane (134 uL, 1.04 mmol) were added to pressure vial. The vial was heated at 120 °C for 1.5 h. The mixture was cooled to r.t., diluted with EtOAc (40 mL) and washed with sat. aq. Na₂S₂O₃ (30 mL), water (30 mL), 1 M aq. HCl (30 mL) and brine (30 mL). The combined organic was passed through a phase separator and then concentrated. The residue was purified by FCC (10 g SiO₂ cartridge, 0-20% MeOH in DCM). The resultant product was sonicated in EtOH (3 mL). Water was added (5 mL) and the solid filtered washing with further water (2 x 10 mL). The solid was dried in a Genevac and vacuum oven to afford the title compound as an off-white solid (121 mg, 95% purity). ¹H NMR (500 MHz, DMSO) δ 10.95 (s, 1H), 8.25 (d, J = 2.0 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.41 (ddd, J = 8.3, 7.3, 1.8 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.28 – 7.22 (m, 3H), 7.11 – 7.05 (m, 1H), 6.98 – 6.93 (m, 1H), 4.43 – 4.39 (m, 2H), 4.36 – 4.26 (m, 2H). LCMS: m/z = 462.0/464.0 [M-H]⁻, (ESI⁻), RT = 3.94, Method D

Example 153 – Synthesis of 4-Bromo-15-chloro-16-hydroxy-21-methoxy-18,18-dioxo-8,11-dioxa-18λ6-thia-19-azatetracyclo[18.3.1.113,17.02,7]pentacosa-1(23),2(7),3,5,13,15,17(25),20(24),21-nonaen-12-one (Compound 153)

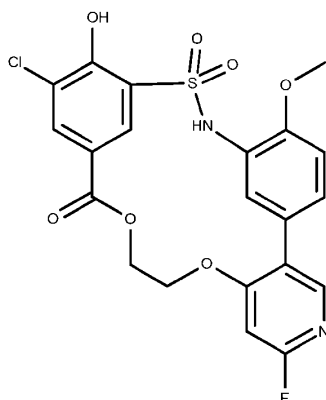


[0391] 4-Bromo-15-chloro-16,21-dimethoxy-18,18-dioxo-8,11-dioxa-18λ6-thia-19-azatetracyclo[18.3.1.113,17.02,7]pentacosa-1(23),2(7),3,5,13,15,17(25),20(24),21-nonaen-12-one (*synthesised using a similar method to Intermediate 106*, 98%, 100 mg, 0.172 mmol) and iodocyclohexane (45 mg, 0.214 mmol) were combined in DMF (4 mL). The mixture was heated to 100 °C and stirred for 24 h. Sat. aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with 1 M aq. HCl (50 mL), then brine (50 mL) and were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (56 mg, 99% purity, 58% Yield).

¹H NMR (500 MHz, DMSO) δ 10.94 (br. s, 1H), 9.50 (s, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.54 (dd, J = 8.7, 2.6 Hz, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.41 (d, J = 2.1 Hz, 1H), 7.28 (d, J = 2.2 Hz, 1H), 7.18 – 7.13 (m, 2H), 6.80 (d, J = 8.6 Hz, 1H), 4.34 – 4.30 (m, 2H), 4.29 – 4.24 (m, 2H), 3.41 (s, 3H).

LCMS: m/z = 552.0/553.9/555.9 [M-H]⁻, (ESI⁻), RT = 4.44, Method A

Example 154 – Synthesis of 15-Chloro-5-fluoro-16-hydroxy-21-methoxy-18,18-dioxo-8,11-dioxa-18λ6-thia-4,19-diazatetracyclo[18.3.1.113,17.02,7]pentacosa-1(24),2(7),3,5,13,15,17(25),20,22-nonaen-12-one (Compound 154)

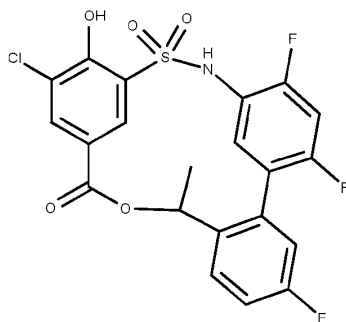


[0392] To a solution of 15-chloro-5-fluoro-16,21-dimethoxy-18,18-dioxo-8,11-dioxa-18λ6-thia-4,19-diazatetracyclo[18.3.1.113,17.02,7]pentacosa-1(24),2(7),3,5,13,15,17(25),20,22-nonaen-12-one (*synthesised using a similar method to Intermediate 106*, 210.0 mg, 0.41 mmol) in anhydrous pyridine (6 mL) was added lithium iodide (110.5 mg, 0.83 mmol). The reaction mixture was heated at 80 °C for 5 h. The mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) followed by trituration with 1:1 MeCN/water (20 mL) to afford the title compound as a white solid (102 mg, 99% purity, 49% Yield).

¹H NMR (500 MHz, DMSO) δ 11.11 (br.s, 1H), 9.52 (br.s, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.99 (s, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.12 (dd, J = 8.4, 2.1 Hz, 1H), 7.02 (s, 1H), 6.91 (d, J = 8.5 Hz, 1H), 4.46 – 4.33 (m, 4H), 3.53 (s, 3H).

LCMS: m/z = 495.0/497.0 [M+H]⁺, (ESI⁺), RT = 3.48, Method A

Example 155 – Synthesis of 13-Chloro-4,19,21-trifluoro-14-hydroxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 155)

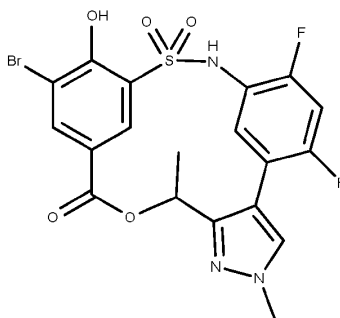


[0393] To a solution of 13-chloro-4,19,21-trifluoro-14-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesised from Intermediate 107* using a similar method to *Intermediate 106*, 60% purity, 160 mg, 0.193 mmol) in anhydrous pyridine (5 mL) was added lithium iodide (366 mg, 2.73 mmol). The reaction mixture was heated at 80 °C for 18 h. The organics were diluted with EtOAc (30 mL), washed with HCl (2 x 30 mL of a 1 M aqueous solution), Na₂S₂O₃ (10 mL of a saturated aqueous solution), brine (2 x 20 mL) and then dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (39 mg, 83% purity, 35% Yield)) as an off-white solid.

¹H NMR (500 MHz, DMSO) δ 8.02 (d, J = 2.2 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.58 (dd, J = 8.7, 5.9 Hz, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.33 – 7.25 (m, 1H), 7.05 (dd, J = 9.3, 2.8 Hz, 1H), 6.58 – 6.53 (m, 1H), 6.20 (q, J = 6.8 Hz, 1H), 1.45 (d, J = 7.0 Hz, 3H). 2 exchangeable protons not observed.

LCMS: m/z = 482.1 / 484.1 [M-H]⁻, (ESI⁻), RT = 4.18, Method A

Example 156 – Synthesis of 12-Bromo-18,20-difluoro-13-hydroxy-4,7-dimethyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.1¹⁰.14.0^{2,6}]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one (Compound 156)

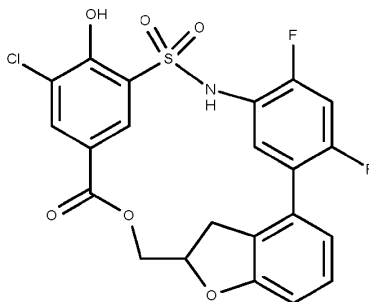


[0394] To a solution of 12-bromo-18,20-difluoro-13-methoxy-4,7-dimethyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.1¹⁰.14.0^{2,6}]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one (*synthesised from Intermediate 108 using a similar method to Intermediate 84*, 140 mg, 0.233 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (266 mg, 1.99 mmol) and the mixture was heated at 90 °C for 4 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (73 mg, 95% purity, 58% Yield).

¹H NMR (500 MHz, DMSO) δ 10.16 (s, 1H), 8.18 (d, J = 2.1 Hz, 1H), 7.79 (s, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.51 – 7.44 (m, 1H), 6.84 (s, 1H), 6.06 (q, J = 6.6 Hz, 1H), 3.84 (s, 3H), 1.50 (d, J = 6.7 Hz, 3H).

LCMS: m/z = 512.0/514.0 [M-H]⁻, (ESI⁻), RT = 3.65, Method A

Example 157 – Synthesis of 15-Chloro-21,23-difluoro-16-hydroxy-18,18-dioxo-11,26-dioxa-18 λ 6-thia-19-azapentacyclo[18.3.1.16,9.113,17.02,7]hexacosa-1(24),2(7),3,5,13(25),14,16,20,22-nonaen-12-one (Compound 157)

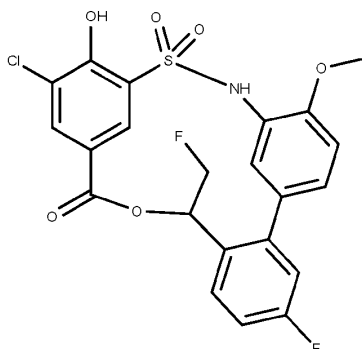


[0395] 15-Chloro-21,23-difluoro-16-methoxy-18,18-dioxo-11,26-dioxa-18 λ 6-thia-19-azapentacyclo[18.3.1.16,9.113,17.02,7]hexacosa-1(24),2(7),3,5,13(25),14,16,20,22-nonaen-12-one (*synthesised from Intermediate 109 using a similar method to Intermediate 84*, 30% purity, 200 mg, 0.118 mmol), anhydrous DMF (3 mL) and iodocyclohexane (153 μ L, 1.18 mmol) were added to pressure vial. The vial was sealed and heated at 120 °C for 1.5 h. The mixture was allowed to cool to r.t, diluted with EtOAc (50 mL), washed with sat. aq. Na₂S₂O₃ (40 mL), water (40 mL), 1 M aq. HCl (40 mL), then brine (40 mL) passed through a phase separator and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (30% yield, 200 mg, 0.118 mmol).

¹H NMR (500 MHz, DMSO) δ 7.59 – 7.48 (m, 2H), 7.40 (d, J = 2.1 Hz, 1H), 7.12 – 7.05 (m, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.54 – 6.35 (m, 1H), 5.72 – 5.60 (m, 1H), 5.20 – 5.12 (m, 1H), 4.69 (dd, J = 12.8, 2.7 Hz, 1H), 4.50 (d, J = 12.7 Hz, 1H), 2.44 – 2.37 (m, 1H).

LCMS: m/z = 492.1/494.0.1 [M-H]⁻, (ESI⁻), RT = 3.77, Method A

Example 158 – Synthesis of 13-Chloro-4-fluoro-8-(fluoromethyl)-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 158)

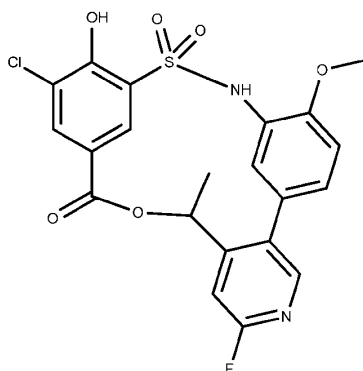


[0396] A mixture of 13-chloro-4-fluoro-8-(fluoromethyl)-14,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (*synthesised from Intermediate 110 using a similar method to Intermediate 84*, 130 mg, 0.24 mmol), lithium iodide (157 mg, 1.18 mmol) and anhydrous pyridine (3.7 mL) was heated at 90 °C for 3 h. The cooled mixture was diluted with EtOAc (40 mL), washed with sat. aq. Na₂S₂O₃ (40 mL), 1 M aq. HCl (50 mL) and brine (40 mL), then passed through a phase separator and then concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (86 mg, 99% purity, 73% Yield).

¹H NMR (500 MHz, CDCl₃) δ 9.25 (s, 1H), 8.04 – 7.95 (m, 1H), 7.66 – 7.58 (m, 1H), 7.57 – 7.52 (m, 2H), 7.19 – 7.12 (m, 1H), 7.08 – 7.02 (m, 2H), 6.98 (s, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.19 – 6.00 (m, 1H), 5.37 – 5.00 (m, 2H), 3.52 (s, 3H).

LCMS: m/z = 494.4/496.3 [M-H]⁻, (ESI⁻), RT = 3.95, Method A

Example 159 – Synthesis of 13-Chloro-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 159)

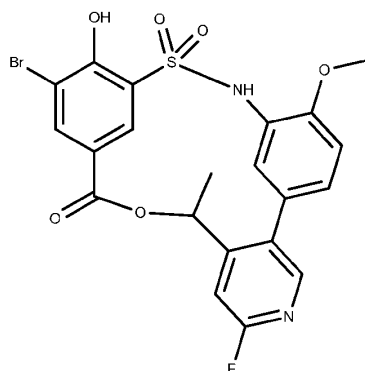


[0397] A mixture of 13-chloro-5-fluoro-14,19-dimethoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (*synthesised from Intermediate 111 using a similar method to Intermediate 84*, 205 mg, 0.362 mmol), lithium iodide (96.86 mg, 0.72 mmol) and anhydrous pyridine (6 mL) was heated at 90 °C for 4 h and then allowed to cool to r.t. The mixture was diluted with EtOAc (40 mL), washed with sat. aq. Na₂S₂O₃ (30 mL), 1 M aq. HCl (30 mL) and brine (30 mL), then passed through a phase separator and then concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (92 mg, 99% purity, 53% Yield).

¹H NMR (500 MHz, CDCl₃) δ 9.22 (br. s, 1H), 8.13 (s, 1H), 8.00 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 2.2 Hz, 1H), 7.49 (d, J = 2.1 Hz, 1H), 7.08 (s, 1H), 7.01 (dd, J = 8.4, 2.2 Hz, 1H), 6.99 (s, 1H), 6.51 (d, J = 8.4 Hz, 1H), 6.09 – 6.02 (m, 1H), 3.52 (s, 3H), 1.87 (d, J = 6.3 Hz, 3H).

LCMS: m/z = 477.0/479.0 [M-H]⁻, (ESI⁻), RT = 3.78, Method A

Example 160 – Synthesis of 13-Bromo-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 160)

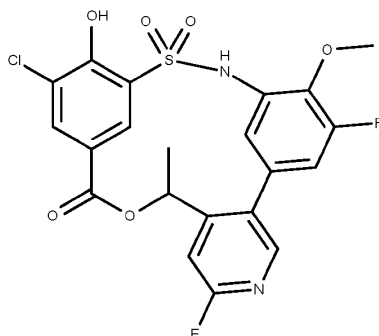


[0398] A mixture of 13-bromo-5-fluoro-14,19-dimethoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (*synthesised from Intermediate 111 using a similar method to Intermediate 84*, 260.0 mg, 0.37 mmol), lithium iodide (99.7 mg, 0.75 mmol) and anhydrous pyridine (6.2 mL) was heated at 90 °C for 3 h. The cooled mixture was diluted with EtOAc (40 mL), washed with sat. aq. Na₂S₂O₃ (30 mL), 1 M aq. HCl (30 mL) and brine (30 mL), then passed through a phase separator and then concentrated. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (118 mg, 99% purity, 60% Yield).

¹H NMR (500 MHz, CDCl₃) δ 9.31 (s, 1H), 8.17 (d, J = 2.0 Hz, 1H), 8.13 (s, 1H), 7.53 (d, J = 2.2 Hz, 1H), 7.52 (d, J = 2.1 Hz, 1H), 7.08 (s, 1H), 7.01 (dd, J = 8.4, 2.2 Hz, 1H), 6.99 (s, 1H), 6.50 (d, J = 8.4 Hz, 1H), 6.13 – 5.98 (m, 1H), 3.52 (s, 3H), 1.87 (d, J = 6.3 Hz, 3H).

LCMS: m/z = 521.0/523.0 [M-H]⁻, (ESI⁻), RT = 3.92, Method A

Example 161 – Synthesis of 13-Chloro-5,20-difluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 161)

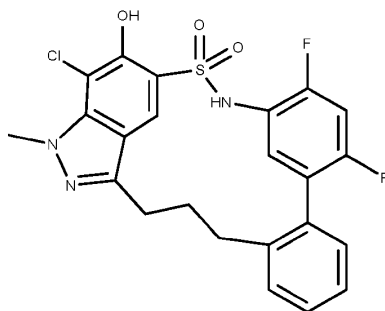


[0399] To a solution of 13-chloro-5,20-difluoro-14,19-dimethoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (*synthesised from Intermediate 111 using a similar method to Intermediate 84*, 500.0 mg, 0.98 mmol) in anhydrous pyridine (10 mL) was added lithium iodide (327.5 mg, 2.45 mmol) and the reaction mixture was heated at 80 °C for 5 h. The mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (30 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with sat. aq. Na₂S₂O₃ (30 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (170 mg, 99% purity, 35% Yield) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 9.20 (s, 1H), 8.12 (s, 1H), 8.09 (d, J = 2.1 Hz, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.40 (t, J = 1.7 Hz, 1H), 7.12 – 7.06 (m, 2H), 6.81 (dd, J = 11.9, 2.1 Hz, 1H), 6.03 – 5.95 (m, 1H), 3.65 (s, 3H), 1.90 (d, J = 6.3 Hz, 3H).

LCMS: m/z = 497.0/498.9 [M+H]⁺, (ESI⁺), RT = 3.93, Method A

Example 162 – Synthesis of 22-Chloro-5,7-difluoro-20-methyl-2,2-dioxo-2λ6-thia-3,19,20-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacos-1(24),4,6,8(26),9(14),10,12,18,21(25),22-decaen-23-ol (Compound 162)

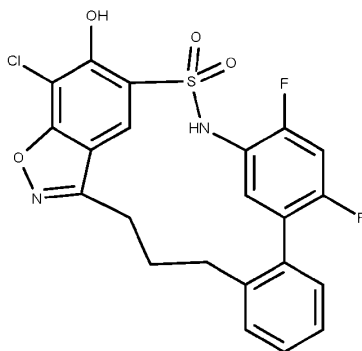


[0400] To a solution of *Intermediate 117* (204 mg, 0.411 mmol) in dry pyridine (1.50 mL) was introduced *N*-methylhydrazine (0.5 mL of a 194 mg/mL solution in dry pyridine, 2.057 mmol) and DMAP (51 mg, 0.411 mmol). The reaction mixture was warmed to 80 °C for 60 minutes then 100 °C for 120 minutes under an atmosphere of nitrogen. After cooling, hydrogen chloride (0.64 mL of a 4 M solution in 1,4-dioxane, 2.56 mmol) was introduced and the reaction mixture warmed to 100 °C for 24 hours. Further hydrogen chloride (0.32 mL of a 4 M solution in 1,4-dioxane, 1.28 mmol) was introduced and the reaction mixture warmed to 100 °C for 18 hours then 110 °C for 24 hours. The reaction mixture was concentrated in vacuo and the residue suspended in deionised water to which was introduced saturated aqueous tartaric acid to adjust the pH to 2. After stirring for 5 minutes at r.t., the aqueous suspension was filtered and the filter cake washed with deionised water (1 mL). The solid was dried in a vacuum oven and the resulting solid purified by preparative HPLC (Method P3) to afford the title compound as a tan amorphous solid (53.2 mg, 99% purity, 26% yield).

¹H NMR (400 MHz, DMSO, 353K) δ 7.82 (s, 1H), 7.45 – 7.34 (m, 2H), 7.25 (t, J = 7.3 Hz, 1H), 7.20 – 7.04 (m, 3H), 4.17 (s, 3H), 3.00 (br, t, J = 6.0 Hz, 2H), 2.30 - 2.21 (br, m, 2H), 2.00 (br, s, 2H)

LCMS: m/z = 490.1, 492.1 [M+H]⁺, (ESI⁺), RT = 3.98, Method A

Example 163 – Synthesis of 22-Chloro-5,7-difluoro-2,2-dioxo-20-oxa-2λ6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacos-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaen-23-ol (Compound 163)

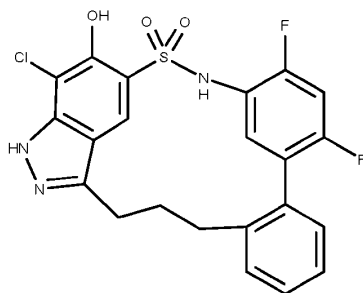


[0401] To a solution of *Intermediate 118* (188 mg, 0.383 mmol) in pyridine (5.0 mL) was introduced hydrogen chloride (0.5 mL of a 4 M solution in 1,4-dioxane, 2.00 mmol). The reaction mixture was warmed to 105 °C for 8 h with stirring. After cooling, the reaction mixture was concentrated in vacuo and the residual solid suspended in water/acetonitrile (9:1, 5.0 mL) and subjected to sonication for 30 seconds, followed by vigorous stirring at r.t. for 30 minutes. The resulting suspension was filtered and the filter cake washed with water/acetonitrile (9:1, 1.0 mL) and dried in a vacuum oven. The dried solid was dissolved in ethyl acetate (6.0 mL), extracted with 1 M aqueous hydrochloric acid (2 x 3 mL extractions ~ 5 minutes each) and the organic phase dried over magnesium sulfate and filtered. The filtrate was concentrated in-vacuo to furnish a colourless oil which was dissolved in acetonitrile/water (1:1, 3.0 mL) and lyophilised to afford the title compound (65.2 mg, 36% yield) as an off-white solid:

¹H NMR (500 MHz, CDCl₃) δ 8.48 (br. s, 1H), 7.80 (s, 1H), 7.43 - 7.39 (m, 2H), 7.38 - 7.35 (m, 1H), 7.30 - 7.26 (m, 1H), 7.11 (dd, J = 7.6, 1.1 Hz, 1H), 7.02 (s, 1H), 6.71 - 6.66 (m, 1H), 3.21 - 3.14 (m, 1H), 3.10 - 3.05 (m, 1H), 2.56 - 2.49 (m, 1H), 2.23 - 2.03 (m, 3H).

LCMS: m/z = 475.3, 477.3 [M-H]⁻, (ESI⁻), RT = 2.33, Method A

Example 164 – Synthesis of 22-Chloro-5,7-difluoro-2,2-dioxo-2λ6-thia-3,19,20-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaen-23-ol (Compound 164)

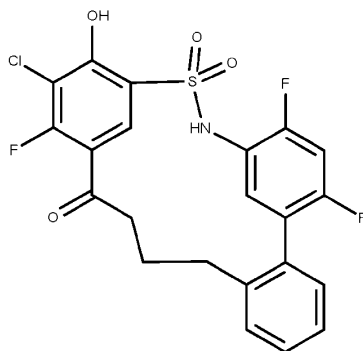


[0402] To a solution of *Intermediate 117* (140 mg at 95% purity, 0.282 mmol) in dry pyridine (2.0 mL) was introduced hydrazine hydrate (71 mg, 1.41 mmol) and DMAP (35 mg, 1.05 mmol). The stirred reaction mixture was warmed to 80 °C for one hour, then 100 °C for two hours. After cooling to r.t., the reaction mixture was concentrated in vacuo, re-dissolved in pyridine (3.0 mL) to which was introduced 4 M hydrogen chloride in 1,4-dioxane (~ 0.3 mL) dropwise. The reaction mixture was warmed to 110 °C (pressure tube) for 24 hours, an additional 0.05 mL 4 M hydrogen chloride in 1,4-dioxane introduced, and warming continued for another 9 hours. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the residue suspended in water and subjected to sonication until a fine tan precipitate resulted, which was collected by filtration. The tan precipitate was suspended in water 4 mL containing acetonitrile (0.3 mL), sonicated, and the suspension treated with 1 M aqueous hydrochloric acid to adjust the pH to 2. After sonication the acidic suspension was isolated by filtration, and the filter cake washed with deionised water (1 mL) and dried at the filter. The solid was further purified by preparative HPLC (Method P2) followed by lyophilisation to afford the title compound (46.5 mg, 36% yield) as an off-white solid:

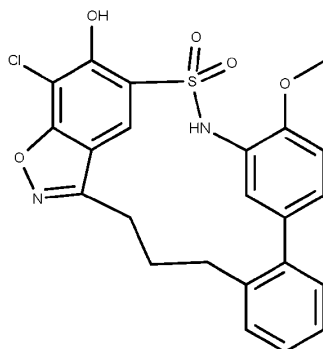
¹H NMR (500 MHz, DMSO) δ 13.06 (br. s, 1H), 7.83 (s, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.40 - 7.37 (m, 1H), 7.26 - 7.23 (m, 1H), 7.20 - 7.17 (m, 1H), 7.10 (d, J = 7.4 Hz, 1H), 7.08 - 7.04 (m, 1H), 3.12 - 2.89 (m, 2H), 2.39 - 2.25 (m, 1H), 2.15 - 1.83 (m, 3H).

LCMS: m/z = 476.1, 478.1 [M+H]⁺, (ESI⁺), RT = 3.11, Method C

Example 165 – Synthesis of 14-Chloro-13,20,22-trifluoro-15-hydroxy-17,17-dioxo-17λ6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2(7),3,5,12(24),13,15,19(23),20-nonaen-11-one (Compound 165)



Example 166 – Synthesis of 22-Chloro-5-methoxy-2,2-dioxo-20-oxa-2λ6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(23),4(26),5,7,9(14),10,12,18,21,24-decaen-23-ol (Compound 166)

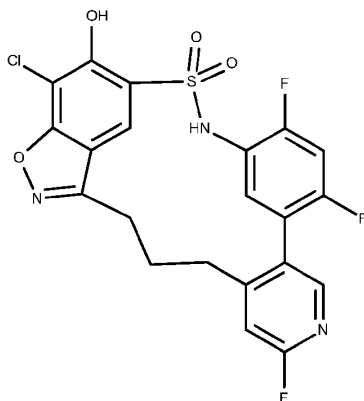


[0404] 22-Chloro-5,23-dimethoxy-20-oxa-2λ6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(23),4(26),5,7,9(14),10,12,18,21,24-decaene 2,2-dioxide (*synthesised using a similar method to Intermediate 118*, 104.0 mg, 0.21 mmol) and iodocyclohexane (0.036 mL, 0.278 mmol) were weighed in a pressure vial and anhydrous DMF (3 mL) was added. The mixture was stirred at 100 °C for 17 h. The mixture was then purified by preparative HPLC (Method P1) to afford the title compound as a white solid (55 mg, 100% purity, 54% Yield).

¹H NMR (400 MHz, DMSO) δ 11.68 (s, 1H), 8.83 (s, 1H), 7.97 (s, 1H), 7.43 – 7.36 (m, 1H), 7.36 – 7.29 (m, 1H), 7.24 – 7.16 (m, 1H), 7.16 – 7.12 (m, 1H), 7.06 (d, J = 1.4 Hz, 1H), 6.80 – 6.73 (m, 1H), 6.73 – 6.67 (m, 1H), 3.68 (s, 3H), 3.09 (t, J = 6.1 Hz, 2H), 2.37 – 2.21 (m, 2H), 2.04 – 1.82 (m, 2H).

LCMS: m/z = 469.1 & 471.1 [M-H]⁻, (ESI⁻), RT = 4.28, Method A

Example 167 – Synthesis of 22-Chloro-5,7,12-trifluoro-2,2-dioxo-20-oxa-2λ6-thia-3,11,19-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosal(23),4(26),5,7,9(14),10,12,18,21,24-decaen-23-ol (Compound 167)

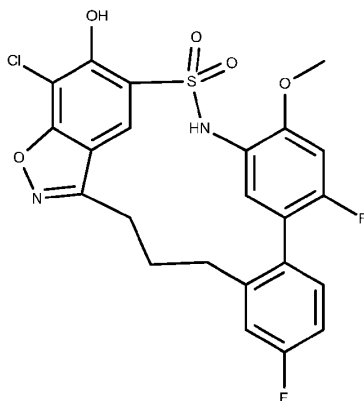


[0405] 22-Chloro-5,7,12-trifluoro-23-methoxy-20-oxa-2λ6-thia-3,11,19-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosal(23),4(26),5,7,9(14),10,12,18,21,24-decaene 2,2-dioxide (*synthesised using a similar method to Intermediate 118*, 25.0 mg, 0.05 mmol) and lithium iodide (33.0 mg, 0.25 mmol) were weighed in a pressure vial and pyridine (2 mL) was added. The reaction mixture was placed at 80 °C and stirred for 6.5 h. The pyridine was removed under reduced pressure and the residue was dissolved in EtOAc (2 mL) and washed with NH₄Cl (aq.) (2 mL) and then passed through a phase separator cartridge and concentrated under reduced pressure. The residue was purified by FCC (10 g SiO₂ cartridge, 0-60% EtOAc in heptane) followed by preparative HPLC (Method P1) to afford the title compound (7.9 mg, 100% purity, 32% Yield) as a white solid.

¹H NMR (400 MHz, DMSO) δ 8.03 (s, 1H), 7.91 (s, 1H), 7.41 – 7.15 (m, 3H), 3.22 – 2.90 (m, 4H), 2.13 – 1.95 (m, 2H).

LCMS: m/z = 496 & 498 [M+H]⁺, (ESI⁺), RT = 3.53, Method A

Example 168 – Synthesis of 22-Chloro-7,12-difluoro-5-methoxy-2,2-dioxo-20-oxa-2λ6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(23),4(26),5,7,9(14),10,12,18,21,24-decaen-23-ol (Compound 168)

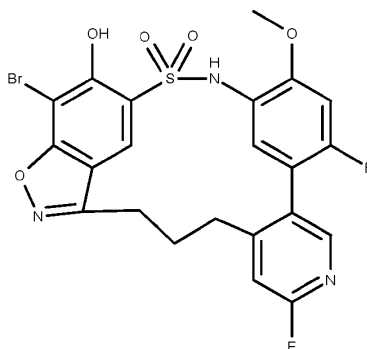


[0406] 22-Chloro-7,12-difluoro-5,23-dimethoxy-20-oxa-2λ6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(23),4(26),5,7,9(14),10,12,18,21,24-decaene 2,2-dioxide (*synthesised using a similar method to Intermediate 118*, 117.0 mg, 0.22 mmol) and iodocyclohexane (0.038 mL, 0.294 mmol) were weighed in a pressure vial and anhydrous DMF (3.1 mL) was added. The reaction mixture was placed at 100 °C and stirred for 18 h. The mixture was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (74 mg, 100% purity, 65% Yield).

¹H NMR (400 MHz, DMSO) δ 11.65 (s, 1H), 9.07 (s, 1H), 7.83 (s, 1H), 7.28 (dd, J = 10.2, 2.7 Hz, 1H), 7.19 – 7.13 (m, 1H), 7.13 – 7.05 (m, 2H), 6.73 (d, J = 11.1 Hz, 1H), 3.65 (s, 3H), 3.22 – 3.07 (m, 1H), 3.07 – 2.88 (m, 1H), 2.43 – 2.29 (m, 1H), 2.05 – 1.78 (m, 3H).

LCMS: m/z = 507 & 505 [M-H]⁻, (ESI⁻), RT = 4.05, Method A

Example 169 – Synthesis of 22-Bromo-7,12-difluoro-5-methoxy-2,2-dioxo-20-oxa-2 λ 6-thia-3,11,19-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacos-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaen-23-ol (Compound 169)

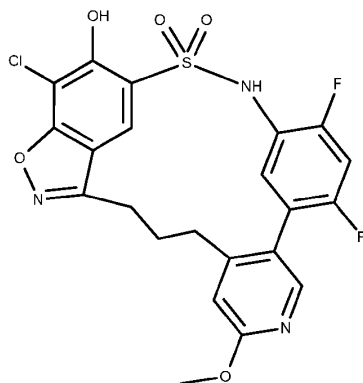


[0407] To a solution of 22-bromo-7,12-difluoro-5,23-dimethoxy-20-oxa-2 λ 6-thia-3,11,19-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacos-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaene 2,2-dioxide (*synthesised using a similar method to Intermediate 118*, 30 mg, 0.0530 mmol) in anhydrous pyridine (1.5 mL) was added lithium iodide (26 mg, 0.194 mmol). The reaction mixture was heated at 80 °C for 15 h. The mixture was allowed to cool to r.t. and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (19.3 mg, 97% purity, 64 % Yield).

¹H NMR (500 MHz, DMSO) δ 11.19 (s, 1H), 9.18 (s, 1H), 8.02 (s, 1H), 7.89 (s, 1H), 7.28 (d, J = 1.4 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 11.2 Hz, 1H), 3.70 (s, 3H), 3.23 – 2.95 (m, 4H), 2.01 (s, 2H).

LCMS: m/z = 550.0/552.0 [M-H]⁻, (ESI⁻), RT = 3.62, Method A

Example 170 – Synthesis of 22-Chloro-5,7-difluoro-12-methoxy-2,2-dioxo-20-oxa-2λ6-thia-3,11,19-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaen-23-ol (Compound 170)

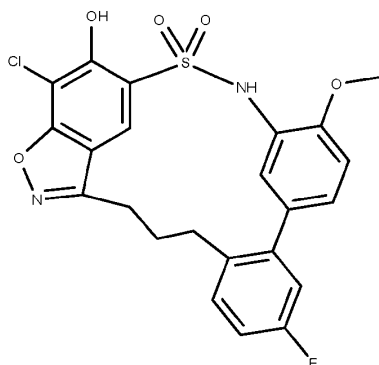


[0408] To a solution of 22-chloro-5,7-difluoro-12,23-dimethoxy-20-oxa-2λ6-thia-3,11,19-triazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaene 2,2-dioxide (*synthesised using a similar method to Intermediate 118*, 75 mg, 0.144 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (170 mg, 1.27 mmol). The reaction mixture was heated at 90 °C for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (29 mg, 100% purity, 40% Yield).

¹H NMR (500 MHz, DMSO) δ 11.64 (br. s, 1H), 10.30 (br. s, 1H), 7.99 – 7.86 (m, 2H), 7.31 – 7.10 (m, 2H), 6.85 (s, 1H), 3.86 (s, 3H), 3.12 (s, 2H), 2.28 (br. s, 2H), 1.99 (s, 2H).

LCMS: m/z = 506.0/508.0 [M-H]⁻, (ESI⁻), RT = 3.70, Method A

Example 171 – Synthesis of 22-Chloro-11-fluoro-5-methoxy-2,2-dioxo-20-oxa-2λ6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaen-23-ol (Compound 171)

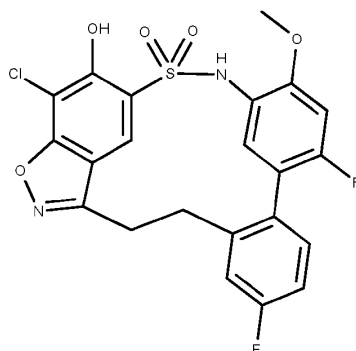


[0409] To a solution of 22-chloro-11-fluoro-5,23-dimethoxy-20-oxa-2λ6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacosa-1(24),4(26),5,7,9(14),10,12,18,21(25),22-decaene 2,2-dioxide (*synthesised using a similar method to Intermediate 118*, 110 mg, 0.219 mmol) in anhydrous pyridine (4 mL) was added lithium iodide (259 mg, 1.94 mmol). The reaction mixture was heated at 80 °C for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (54 mg, 99% purity, 50% Yield).

¹H NMR (500 MHz, DMSO) δ 11.66 (s, 1H), 8.88 (s, 1H), 7.96 (s, 1H), 7.43 (dd, J = 8.7, 6.0 Hz, 1H), 7.22 – 7.12 (m, 2H), 6.91 (dd, J = 9.6, 2.8 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 6.73 (dd, J = 8.3, 2.1 Hz, 1H), 3.68 (s, 3H), 3.09 (t, J = 6.1 Hz, 2H), 2.28 – 2.23 (m, 2H), 2.00 – 1.90 (m, 2H).

LCMS: m/z = 487.0/489.1 [M-H]⁻, (ESI⁻), RT = 4.15, Method A

Example 172 – Synthesis of 21-Chloro-7,12-difluoro-5-methoxy-2,2-dioxo-19-oxa-2λ6-thia-3,18-diazapentacyclo[15.5.2.14,8.09,14.020,24]pentacos-1(22),4(25),5,7,9(14),10,12,17,20,23-decaen-22-ol (Compound 172)

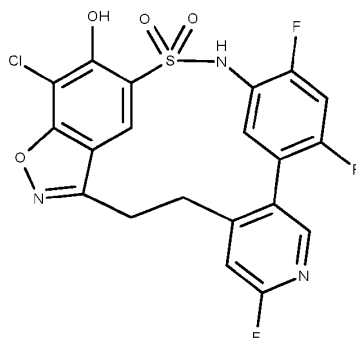


[0410] 21-Chloro-7,12-difluoro-5,22-dimethoxy-19-oxa-2λ6-thia-3,18-diazapentacyclo[15.5.2.14,8.09,14.020,24]pentacos-1(22),4(25),5,7,9(14),10,12,17,20,23-decaene 2,2-dioxide (synthesised from Intermediate 119 using a similar method to Intermediate 118, 85.0 mg, 0.17 mmol) and iodocyclohexane (0.028 mL, 0.216 mmol) were weighed in a pressure vial and anhydrous DMF (2.3 mL) was added. The reaction mixture was placed at 100 °C and stirred for 22 h. The mixture was cooled to r.t. and purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (16.0 mg, 100% purity, 19% yield).

¹H NMR (500 MHz, DMSO) δ 10.47 (s, 1H), 9.45 (s, 1H), 7.43 – 7.30 (m, 2H), 7.19 (d, J = 11.3 Hz, 1H), 7.03 – 6.90 (m, 2H), 5.30 (d, J = 8.1 Hz, 1H), 3.89 (s, 3H), 3.56 – 3.44 (m, 2H), 3.03 – 2.90 (m, 1H), 2.80 – 2.66 (m, 1H)

LCMS: m/z = 493 & 495 [M+H]⁺, (ESI⁺), RT = 3.90, Method D

Example 173 – Synthesis of 21-Chloro-5,7,12-trifluoro-2,2-dioxo-19-oxa-22,6-thia-3,11,18-triazapentacyclo[15.5.2.14,8.09,14.020,24]pentacosal(22),4(25),5,7,9(14),10,12,17,20,23-decaen-22-ol (Compound 173)



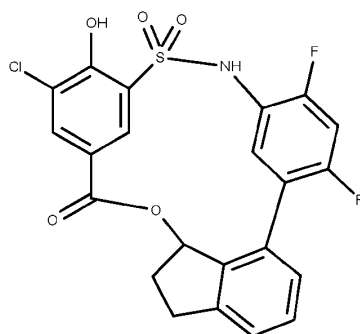
[0411] 21-Chloro-5,7,12-trifluoro-22-methoxy-19-oxa-22,6-thia-3,11,18-triazapentacyclo[15.5.2.14,8.09,14.020,24]pentacosal(22),4(25),5,7,9(14),10,12,17,20,23-decaene 2,2-dioxide (*synthesised from Intermediate 119 using a similar method to Intermediate 118*, 52.0 mg, 0.1 mmol) and lithium iodide (70.0 mg, 0.523 mmol) were weighed in a pressure vial and pyridine (4 mL) was added. The reaction mixture was placed at 100 °C and stirred for 1.5 h. The mixture was cooled to r.t. and purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (10.0 mg, 100% purity, 20% yield) as an off-white solid.

¹H NMR (500 MHz, DMSO) δ 7.92 (s, 1H), 7.67 (t, J = 9.6 Hz, 1H), 7.49 – 7.34 (m, 2H), 5.62 (t, J = 8.0 Hz, 1H), 3.65 – 3.53 (m, 1H), 3.46 – 3.42 (m, 1H), 3.11 – 3.01 (m, 1H), 2.82 – 2.65 (m, 1H)

LCMS: m/z = 482.0 & 483.9 [M+H]⁺, (ESI⁺), RT = 3.55, Method A

Example 174 – Synthesis of 11-Chloro-3,5-difluoro-10-hydroxy-8,8-dioxo-15-oxa-8λ6-thia-7-azapentacyclo[14.6.1.12,6.19,13.019,23]pentacosa-1(23),2,4,6(25),9(24),10,12,19,21-nonaen-14-one, Enantiomer 1 (Compound 174)

Example 175 – Synthesis of 11-Chloro-3,5-difluoro-10-hydroxy-8,8-dioxo-15-oxa-8λ6-thia-7-azapentacyclo[14.6.1.12,6.19,13.019,23]pentacosa-1(23),2,4,6(25),9(24),10,12,19,21-nonaen-14-one, Enantiomer 2 (Compound 175)



[0412] *Example 139* (161 mg) was purified by chiral SFC (Chiralcel OJ-H column, 250 x 10 mm, 5 μM; flow rate 15 mL/min; 15% methanol, 85% CO₂) to afford two components: 11-chloro-3,5-difluoro-10-hydroxy-8,8-dioxo-15-oxa-8λ6-thia-7-azapentacyclo[14.6.1.12,6.19,13.019,23]pentacosa-1(23),2,4,6(25),9(24),10,12,19,21-nonaen-14-one, Enantiomer 1 (54 mg, pink solid):

¹H NMR (400 MHz, DMSO) δ 10.33 (br. s, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.45 – 7.41 (m, 1H), 7.29 (d, J = 6.9 Hz, 1H), 7.19 – 7.10 (m, 1H), 6.09 (t, J = 7.4 Hz, 1H), 3.17 (s, 2H), 3.12 – 2.97 (m, 2H), 2.86 – 2.73 (m, 1H), 2.06 – 1.93 (m, 1H).

Chiral analytical SFC: RT = 2.29 min (Chiralcel OJ-H column, 250 x 4.6 mm, 5 μM; flow rate 4 mL/min; 25% methanol, 75% CO₂)

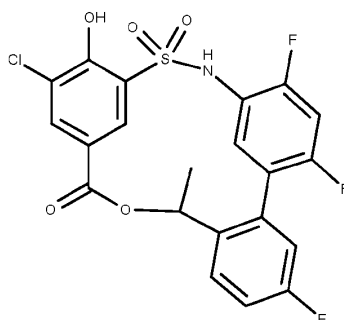
11-chloro-3,5-difluoro-10-hydroxy-8,8-dioxo-15-oxa-8λ6-thia-7-azapentacyclo[14.6.1.12,6.19,13.019,23]pentacosa-1(23),2,4,6(25),9(24),10,12,19,21-nonaen-14-one, Enantiomer 2 (52 mg, pink solid):

¹H NMR (400 MHz, DMSO) δ 7.88 (s, 1H), 7.53 – 7.42 (m, 3H), 7.41 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 6.8 Hz, 1H), 7.18 – 7.09 (m, 1H), 6.09 (t, J = 7.4 Hz, 1H), 3.17 (s, 1H), 3.11 – 2.97 (m, 2H), 2.83 – 2.73 (m, 1H), 2.05 – 1.91 (m, 1H).

Chiral analytical SFC: RT = 2.84 min (Chiralcel OJ-H column, 250 x 4.6 mm, 5 μM; flow rate 4 mL/min; 25% methanol, 75% CO₂)

Example 176 – Synthesis of 13-Chloro-4,19,21-trifluoro-14-hydroxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one, Enantiomer 1 (Compound 176)

Example 177 – Synthesis of 13-Chloro-4,19,21-trifluoro-14-hydroxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one, Enantiomer 2 (Compound 177)



[0413] *Example 155* (31 mg) was purified by chiral SFC (Chiralpak AD-H column, 250 x 10 mm, 5 μ M; flow rate 15 mL/min; 25% IPA, 75% CO₂) to afford two components: 13-chloro-4,19,21-trifluoro-14-hydroxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one, Enantiomer 1 (11 mg, off-white solid)

¹H NMR (500 MHz, DMSO) δ 9.96 (s, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.69 – 7.62 (m, 1H), 7.58 (dd, J = 8.7, 5.9 Hz, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.34 – 7.24 (m, 1H), 7.04 (dd, J = 9.3, 2.8 Hz, 1H), 6.60 – 6.48 (m, 1H), 6.20 (q, J = 6.8 Hz, 1H), 1.44 (dd, J = 7.0, 1.3 Hz, 3H)

Chiral analytical SFC: RT = 1.31 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μ M; flow rate 4 mL/min; 30% IPA, 70% CO₂)

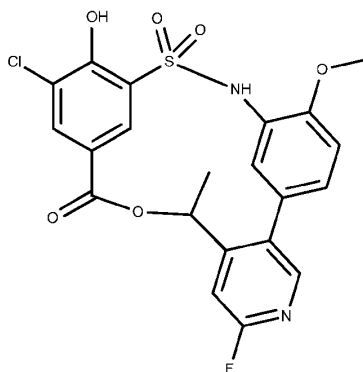
13-chloro-4,19,21-trifluoro-14-hydroxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one, Enantiomer 2 (11 mg, off-white solid)

¹H NMR (500 MHz, DMSO) δ 8.00 (s, 1H), 7.68 – 7.61 (m, 1H), 7.58 (dd, J = 8.7, 5.9 Hz, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.04 (dd, J = 9.4, 2.8 Hz, 1H), 6.58 – 6.52 (m, 1H), 6.19 (q, J = 6.9 Hz, 1H), 1.45 (d, J = 6.9 Hz, 3H)

Chiral analytical SFC: RT = 2.98 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μ M; flow rate 4 mL/min; 30% IPA, 70% CO₂)

Example 178 – Synthesis of 13-Chloro-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1 (Compound 178)

Example 179 – Synthesis of 13-Chloro-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 2 (Compound 179)



[0414] *Example 159* was purified by chiral SFC (Chiralpak AD-H column, 250 x 20 mm, 5 μ M; flow rate 60 mL/min; 20% ethanol, 80% CO₂) to afford two components:

13-chloro-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1 (24 mg, off-white solid)

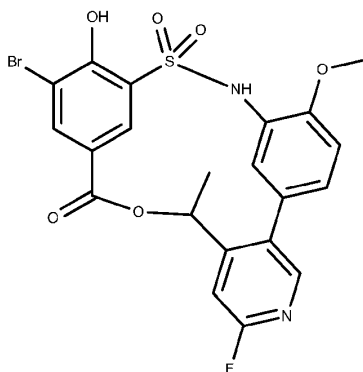
Chiral analytical SFC: RT = 3.25 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μ M; flow rate 4 mL/min; 25% ethanol, 75% CO₂)

13-chloro-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 2 (26.8 mg, off-white solid)

Chiral analytical SFC: RT = 4.49 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μ M; flow rate 4 mL/min; 25% ethanol, 75% CO₂)

Example 180- Synthesis of 13-Bromo-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1 (Compound 180)

Example 181 – Synthesis of 13-Bromo-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 2 (Compound 181)



[0415] *Example 160* (80 mg) was purified by chiral SFC (Chiralpak AD-H column, 250 x 21 mm, 5 μ M; flow rate 60 mL/min; 20% ethanol, 80% CO₂) to afford two components:

13-bromo-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1 (22.7 mg, pale brown solid)

¹H NMR (500 MHz, CDCl₃) δ 9.33 (s, 1H), 8.26 – 8.08 (m, 2H), 7.62 – 7.47 (m, 2H), 7.10 (s, 1H), 7.05 – 6.99 (m, 2H), 6.52 (d, J = 8.4 Hz, 1H), 6.16 – 6.03 (m, 1H), 3.54 (s, 3H), 1.89 (d, J = 6.4 Hz, 3H).

Chiral analytical SFC: RT = 6.36 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μ M; flow rate 4 mL/min; 20% ethanol, 80% CO₂)

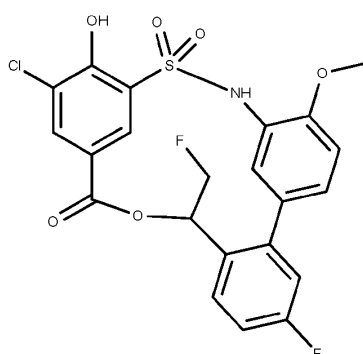
13-bromo-5-fluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosal-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 2 (20.5 mg, pale brown solid)

¹H NMR (500 MHz, CDCl₃) δ 9.33 (s, 1H), 8.19 (d, J = 2.1 Hz, 1H), 8.16 (s, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.55 (d, J = 2.1 Hz, 1H), 7.10 (s, 1H), 7.03 (dd, J = 8.4, 2.2 Hz, 1H), 7.00 (s, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.13 – 6.04 (m, 1H), 3.54 (s, 3H), 1.89 (d, J = 6.4 Hz, 3H)

Chiral analytical SFC: RT = 9.09 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μ M; flow rate 4 mL/min; 20% ethanol, 80% CO₂)

Example 182 – Synthesis of 13-Chloro-4-fluoro-8-(fluoromethyl)-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1 (Compound 182)

Example 182 – Synthesis of 13-Chloro-4-fluoro-8-(fluoromethyl)-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1 (Compound 183)



[0416] *Example 158* (70 mg) was purified by was purified by chiral SFC (Chiralpak AD-H column, 250 x 10 mm, 5 μ M; flow rate 15 mL/min; 25% ethanol, 75% CO₂) to afford two components:

13-chloro-4-fluoro-8-(fluoromethyl)-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1 (29 mg, off-white solid)

¹H NMR (500 MHz, CDCl₃) δ 9.25 (s, 1H), 8.09 – 7.94 (m, 1H), 7.67 – 7.58 (m, 1H), 7.58 – 7.52 (m, 2H), 7.19 – 7.12 (m, 1H), 7.07 – 7.01 (m, 2H), 6.97 (s, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.15 – 5.98 (m, 1H), 5.39 – 4.98 (m, 2H), 3.52 (s, 3H).

Chiral analytical SFC: RT = 2.99 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μ M; flow rate 4 mL/min; 25% ethanol, 75% CO₂)

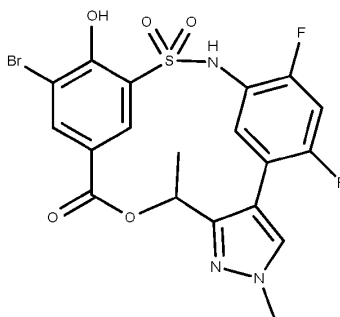
13-chloro-4-fluoro-8-(fluoromethyl)-14-hydroxy-19-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 2 (29 mg, off-white solid)

^1H NMR (500 MHz, CDCl_3) δ 9.25 (s, 1H), 8.05 – 7.94 (m, 1H), 7.65 – 7.58 (m, 1H), 7.57 – 7.53 (m, 2H), 7.19 – 7.13 (m, 1H), 7.08 – 7.03 (m, 2H), 6.98 (s, 1H), 6.49 (d, J = 8.3 Hz, 1H), 6.18 – 6.02 (m, 1H), 5.35 – 4.99 (m, 2H), 3.52 (s, 3H).

Chiral analytical SFC: RT = 5.11 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μM ; flow rate 4 mL/min; 25% ethanol, 75% CO_2)

Example 184 – Synthesis of 12-Bromo-18,20-difluoro-13-hydroxy-4,7-dimethyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one, Enantiomer 1 (Compound 184)

Example 185 – Synthesis of 12-Bromo-18,20-difluoro-13-hydroxy-4,7-dimethyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one, Enantiomer 2 (Compound 185)



[0417] *Example 156* (60 mg) was purified by chiral SFC (Chiralpak AD-H column, 250 x 10 mm, 5 μM ; flow rate 15 mL/min; 25% ethanol, 75% CO_2) to afford two components: 12-bromo-18,20-difluoro-13-hydroxy-4,7-dimethyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one, Enantiomer 1 (22 mg, off-white solid).

^1H NMR (500 MHz, DMSO) δ 10.07 (br. s, 1H), 8.12 (s, 1H), 7.78 (s, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.47 – 7.39 (m, 1H), 6.87 – 6.84 (m, 1H), 6.03 (q, J = 6.7 Hz, 1H), 3.83 (s, 3H), 1.50 (d, J = 6.7 Hz, 3H).

Chiral analytical SFC: RT = 2.11 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μM ; flow rate 4 mL/min; 25% ethanol, 75% CO_2)

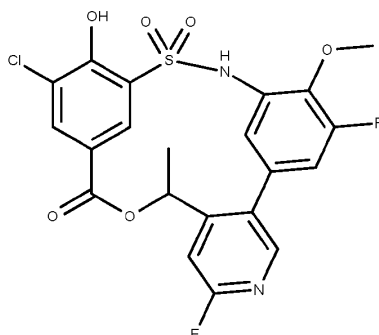
12-bromo-18,20-difluoro-13-hydroxy-4,7-dimethyl-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(21),2,5,10,12,14(22),17,19-octaen-9-one, Enantiomer 2 (17 mg, off-white solid).

¹H NMR (500 MHz, DMSO) δ 10.06 (br. s, 1H), 8.12 (s, 1H), 7.78 (s, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.46 – 7.38 (m, 1H), 6.88 – 6.84 (m, 1H), 6.05 – 6.00 (m, 1H), 3.83 (s, 3H), 1.50 (d, J = 6.6 Hz, 3H).

Chiral analytical SFC: RT = 3.06 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μ M; flow rate 4 mL/min; 25% ethanol, 75% CO₂)

Example 186 – Synthesis of 13-chloro-5,20-difluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1 (Compound 186)

Example 187 – Synthesis of 13-chloro-5,20-difluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 2 (Compound 187)



[0418] *Example 161* (150 mg) was purified by chiral SFC (Chiralpak AD-H column, 250 x 21 mm, 5 μ M; flow rate 60 mL/min; 25% methanol, 75% CO₂) to afford two components: 13-chloro-5,20-difluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1 (30 mg, pale brown solid).

¹H NMR (500 MHz, CDCl₃) δ 9.20 (s, 1H), 8.12 (s, 1H), 8.09 (d, J = 2.1 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.41 – 7.38 (m, 1H), 7.12 – 7.04 (m, 2H), 6.81 (dd, J = 11.8, 2.1 Hz, 1H), 6.06 – 5.93 (m, 1H), 3.65 (d, J = 3.5 Hz, 3H), 1.90 (d, J = 6.3 Hz, 3H).

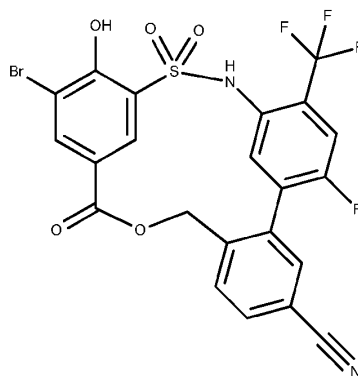
Chiral analytical SFC: RT = 2.60 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μ M; flow rate 4 mL/min; 25% ethanol, 75% CO₂)

13-chloro-5,20-difluoro-14-hydroxy-19-methoxy-8-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1.11,15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one, Enantiomer 1 (30 mg, pale brown solid).

¹H NMR (500 MHz, CDCl₃) δ 9.22 (s, 1H), 8.14 (s, 1H), 8.13 – 8.09 (m, 1H), 7.68 – 7.61 (m, 1H), 7.47 – 7.39 (m, 1H), 7.15 – 7.06 (m, 2H), 6.85 – 6.80 (m, 1H), 6.08 – 5.96 (m, 1H), 3.67 (d, J = 3.5 Hz, 3H), 1.92 (d, J = 6.3 Hz, 3H).

Chiral analytical SFC: RT = 4.22 min (Chiralpak AD-H column, 250 x 4.6 mm, 5 μ M; flow rate 4 mL/min; 25% ethanol, 75% CO₂)

Example 188 – Synthesis of 13-bromo-21-fluoro-14-hydroxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.11,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaene-4-carbonitrile (Compound 188)

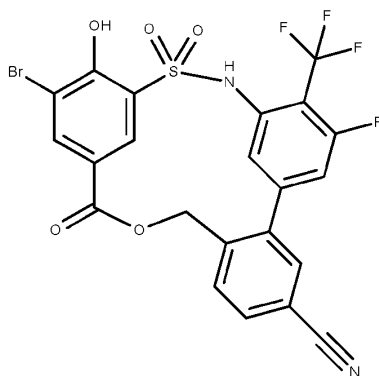


[0419] Lithium iodide (24 mg, 0.179 mmol) was added to a solution of 13-bromo-21-fluoro-14-methoxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.11,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaene-4-carbonitrile (*synthesized using similar methods to intermediates 62 and 26*, 75 mg, 0.126 mmol) in anhydrous pyridine (3 mL) in a pressure vial. The reaction vessel was sealed and the mixture stirred at 90 °C for 2 hours 30 minutes. The mixture was allowed to cool to r.t., diluted with EtOAc (~10 mL), and washed sequentially with saturated aqueous Na₂S₂O₃ solution (~10 mL), 1 M HCl (aq.) (~10 mL), and brine (~10 mL), and the organic phase dried through a hydrophobic frit, and concentrated to dryness in vacuo. The residue was purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as a white solid (10.7 mg, 15% yield, 98% purity).

¹H NMR (500 MHz, DMSO) δ 8.04 – 7.96 (m, 2H), 7.86 – 7.78 (m, 3H), 7.24 (s, 1H), 7.01 (d, J = 6.4 Hz, 1H), 5.55 (d, J = 13.0 Hz, 1H), 5.12 (d, J = 13.0 Hz, 1H).

LCMS: $m/z = 568.9/570.9$ [M-H]⁻, (ESI⁻), RT = 4.18, Method A

Example 189 – Synthesis of 13-bromo-20-fluoro-14-hydroxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹.15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaene-4-carbonitrile (Compound 189)

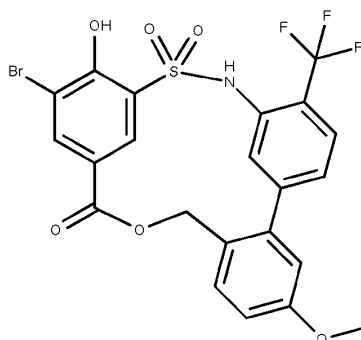


[0420] To a solution of 13-bromo-20-fluoro-14-methoxy-10,16,16-trioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1¹¹.15.02,7]tricoso-1(21),2,4,6,11(23),12,14,18(22),19-nonaene-4-carbonitrile (*synthesized using similar methods to intermediates 62 and 26*, 150 mg, 0.26 mmol) in anhydrous pyridine (3 mL) was added lithium iodide (68.6 mg, 0.51 mmol). The reaction mixture was heated at 80 °C for 5 h. The reaction mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (20 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with saturated aqueous Na₂S₂O₃ (20 mL) and brine (30 mL), then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (95 mg, 62% Yield, 95% purity).

¹H NMR (400 MHz, DMSO) δ 10.50 (br. s, 2H), 8.08 (d, J = 2.1 Hz, 1H), 7.93 (dd, J = 7.9, 1.7 Hz, 1H), 7.86 (d, J = 11.4 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 1.7 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 6.44 (s, 1H), 5.65 – 5.54 (m, 1H), 5.51 – 5.42 (m, 1H).

LCMS: $m/z = 568.9/570.9$ [M-H]⁻, (ESI⁻), RT = 4.13, Method A

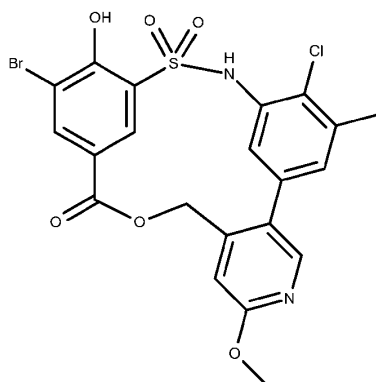
Example 190 – Synthesis of 13-bromo-14-hydroxy-4-methoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one (Compound 190)



[0421] Lithium iodide (65 mg, 0.486 mmol) was added to a solution of 13-bromo-4,14-dimethoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2,4,6,11(23),12,14,18,20-nonaen-10-one (*synthesized using similar methods to intermediates 62 and 26*, 166 mg, 0.261 mmol) in anhydrous pyridine (6 mL) in a pressure vial under N₂ atmosphere. The reaction vessel was sealed and the mixture stirred at 90 °C for 2 hours 20 minutes. The mixture was allowed to cool to r.t., diluted with EtOAc (~20 mL), and washed sequentially with saturated aqueous Na₂S₂O₃ (~20 mL), 1 M HCl (aq.) (~20 mL), and brine (~20 mL), and the organic phase dried through a hydrophobic frit, and concentrated to dryness in vacuo. The residue was purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as a white solid (28.1 mg, 19% yield, 96% purity).

¹H NMR (500 MHz, DMSO) δ 10.29 (s, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 2.1 Hz, 1H), 6.97 (dd, J = 8.5, 2.7 Hz, 1H), 6.88 (s, 1H), 6.77 (d, J = 2.7 Hz, 1H), 5.30 (d, J = 8.7 Hz, 2H), 3.75 (s, 3H).
LCMS: m/z = 556.0/558.0 [M-H]⁻, (ESI⁻), RT = 4.29, Method A

Example 191 – Synthesis of 13-bromo-19-chloro-14-hydroxy-5-methoxy-20-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 191)

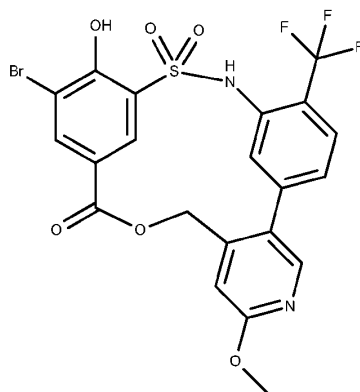


[0422] A mixture of 13-bromo-19-chloro-5,14-dimethoxy-20-methyl-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesized from intermediate 12 using a similar method to intermediate 26*, 112 mg, 0.194 mmol) and lithium iodide (60 mg, 0.45 mmol) in anhydrous pyridine (2 mL) was stirred at 90 °C under N₂ for 3 h. The reaction mixture was cooled to r.t. then diluted with saturated aqueous Na₂S₂O₃ solution (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic components were washed successively with 1 M aq. HCl (30 mL) and brine (30 mL) then dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was triturated with water (10 mL) and then purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as an off-white solid (43.7 mg, 41% yield, 99% purity).

¹H NMR (400 MHz, DMSO) δ 9.97 (br. s, 1H), 8.04 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.40 – 7.35 (m, 1H), 7.27 (d, J = 2.1 Hz, 1H), 7.06 (s, 1H), 6.88 (d, J = 2.1 Hz, 1H), 5.51 (d, J = 13.0 Hz, 1H), 5.21 (d, J = 12.5 Hz, 1H), 3.90 (s, 3H), 2.20 (s, 3H).

LCMS: m/z = 538.9/540.9/542.8 [M+H]⁺, (ESI⁺), RT = 4.19, Method A

Example 192 – Synthesis of 13-bromo-14-hydroxy-5-methoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 192)

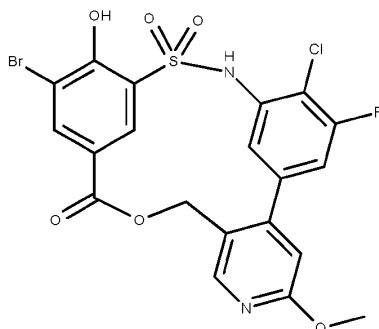


[0423] A mixture of 13-bromo-5,14-dimethoxy-16,16-dioxo-19-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (*synthesized from intermediate 50 using similar methods to intermediates 62 and 26*, 225 mg, 0.353 mmol), lithium iodide (238 mg, 1.77 mmol) and anhydrous pyridine (4 mL) was stirred at 90 °C for 2 h. The mixture was cooled to r.t., diluted with EtOAc (50 mL), washed with saturated aqueous Na₂S₂O₃ (30 mL), water (40 mL) and brine (30 mL), then passed through a phase separator and concentrated. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (116 mg, 59% yield).

¹H NMR (500 MHz, DMSO) δ 10.30 (br. , 2H), 8.05 (s, 1H), 8.01 (s, 1H), 7.76 – 7.70 (m, 1H), 7.68 – 7.56 (m, 1H), 7.17 (s, 1H), 7.09 (s, 1H), 6.95 (s, 1H), 5.34 (s, 2H), 3.90 (s, 3H).

LCMS: m/z = 559.0/561.0 [M+H]⁺, (ESI⁺), RT = 4.12, Method A

Example 193 – Synthesis of 13-bromo-19-chloro-20-fluoro-14-hydroxy-4-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Compound 193)

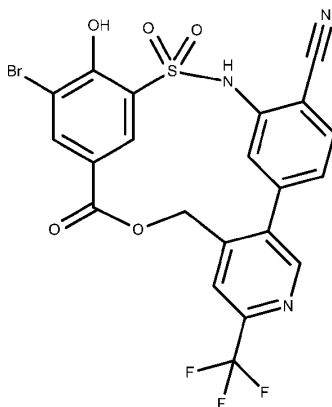


[0424] To a solution of 13-bromo-19-chloro-20-fluoro-4,14-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (*synthesized from intermediate 28 using a similar method to intermediate 26*, 55.0 mg, 0.1 mmol) in anhydrous pyridine (1.5 mL) was added lithium iodide (33 mg, 0.25 mmol). The reaction mixture was heated at 80 °C for 5 h. The reaction mixture was dissolved in EtOAc (30 mL) and washed with 1 M aq. HCl (20 mL). The aqueous phase was extracted further with EtOAc (2 x 30 mL) and the organics were combined, washed with saturated aqueous Na₂S₂O₃ (20 mL) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (20 mg, 35% Yield, 95% purity).

¹H NMR (400 MHz, DMSO) δ 8.32 (s, 1H), 8.06 (d, J = 2.2 Hz, 1H), 7.65 (dd, J = 9.4, 1.9 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 6.87 – 6.83 (m, 1H), 6.78 (s, 1H), 5.43 – 5.26 (m, 2H), 3.89 (s, 3H).

LCMS: m/z = 543.0/544.9 [M+H]⁺, (ESI⁺), RT = 4.02, Method A

Example 194 – Synthesis of 13-bromo-14-hydroxy-10,16,16-trioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-19-carbonitrile (Compound 194)

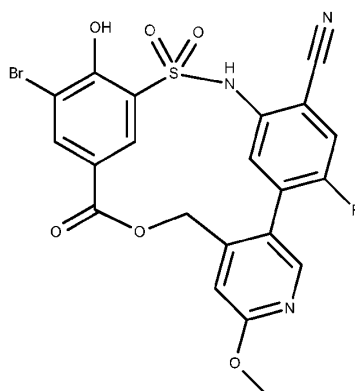


[0425] 13-bromo-14-methoxy-10,16,16-trioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaene-19-carbonitrile (*synthesized using a similar method to intermediate 26*, 132 mg, 0.232 mmol) and lithium iodide (62 mg, 0.463 mmol) were dissolved in anhydrous pyridine (8 mL). The mixture was heated to 80 °C and stirred for a total of 7 h. The reaction mixture was concentrated in vacuo and the residue was purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as an off-white solid (72.3 mg, 54% yield, 96% purity).

¹H NMR (500 MHz, DMSO) δ 10.77 – 10.60 (m, 1H), 8.57 (s, 1H), 8.24 (s, 1H), 8.09 (d, J = 7.6 Hz, 2H), 7.77 (dd, J = 7.9, 1.6 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.80 (d, J = 1.6 Hz, 1H), 5.74 – 5.63 (m, 1H), 5.44 – 5.28 (m, 1H).

LCMS: m/z = 551.9/553.9 [M-H]⁻, (ESI⁻), RT = 3.85, Method A

Example 195 – Synthesis of 13-bromo-21-fluoro-14-hydroxy-5-methoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-19-carbonitrile (Compound 195)

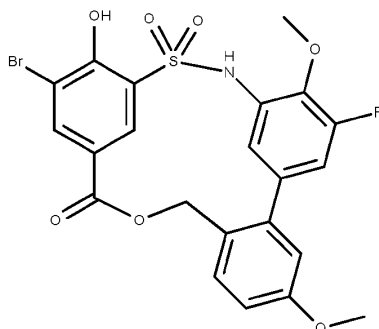


[0426] A mixture of 13-bromo-21-fluoro-5,14-dimethoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹¹.15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-19-carbonitrile (*synthesized from intermediate 12 using a similar method to intermediate 26*, 60.0 mg, 0.103 mmol), lithium iodide (69 mg, 0.51 mmol) and anhydrous pyridine (3 mL) was stirred at 90 °C for 7 h. The mixture was cooled to r.t., diluted with EtOAc (50 mL), washed with saturated aqueous Na₂S₂O₃ (30 mL), water (40 mL) and brine (30 mL), then passed through a phase separator and concentrated. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (116 mg, 59% yield).

¹H NMR (500 MHz, DMSO) δ 10.54 (br. s, 1H), 8.18 (d, J = 8.9 Hz, 1H), 8.10 (d, J = 2.1 Hz, 1H), 8.00 (s, 1H), 7.10 (s, 1H), 6.87 (d, J = 2.1 Hz, 1H), 6.67 (d, J = 6.6 Hz, 1H), 5.57 (d, J = 13.1 Hz, 1H), 4.96 (d, J = 13.0 Hz, 1H), 3.89 (s, 3H).

LCMS: m/z = 534.0/535.9 [M+H]⁺, (ESI⁺), RT = 3.81, Method A

Example 196 – Synthesis of 13-bromo-20-fluoro-14-hydroxy-4,19-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Compound 196)

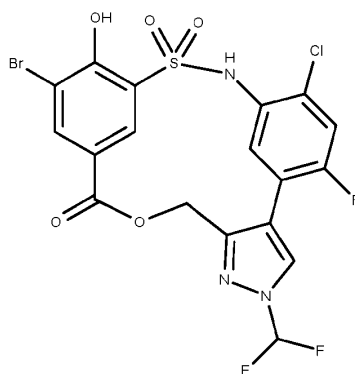


[0427] 13-bromo-20-fluoro-4,14,19-trimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (*synthesized using a similar method to intermediate 26*, 306 mg, 0.554 mmol) and lithium iodide (90 mg, 0.672 mmol) were dissolved into anhydrous pyridine (19.5 mL). The mixture was then heated to 80 °C and stirred overnight. The mixture was concentrated in vacuo and the residue was purified by preparative HPLC (Method P1) followed by lyophilisation to afford the title compound as an off-white solid (160 mg, 51% yield, 96% purity).

¹H NMR (400 MHz, DMSO) δ 9.80 (s, 1H), 8.06 (d, J = 2.2 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.36 (dd, J = 12.1, 2.1 Hz, 1H), 6.99 – 6.93 (m, 2H), 6.84 (d, J = 2.7 Hz, 1H), 5.43 (d, J = 12.3 Hz, 1H), 5.14 (d, J = 12.4 Hz, 1H), 3.79 (s, 3H), 3.57 (d, J = 2.0 Hz, 3H).

LCMS: m/z = 535.9/537.9 [M-H]⁻, (ESI⁻), RT = 4.27, Method A

Example 197 – Synthesis of 12-bromo-18-chloro-4-(difluoromethyl)-20-fluoro-13-hydroxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (Compound 197)

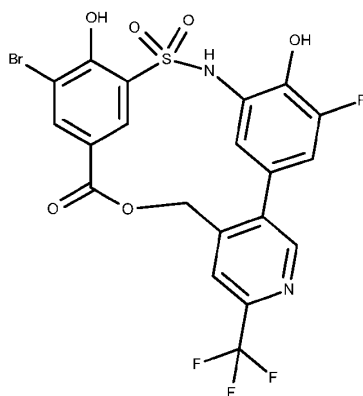


[0428] To a solution of 12-bromo-18-chloro-4-(difluoromethyl)-20-fluoro-13-methoxy-15,15-dioxo-8-oxa-15 λ 6-thia-4,5,16-triazatetracyclo[15.3.1.110,14.02,6]docosa-1(20),2,5,10(22),11,13,17(21),18-octaen-9-one (*synthesized from intermediate 33 using a similar method to intermediate 26*, 300 mg, 0.49 mmol) in anhydrous pyridine (5 mL) was added lithium iodide (130.4 mg, 0.97 mmol). The reaction mixture was heated at 80 °C for 6 h. The reaction mixture was dissolved in EtOAc (30 mL) and washed with saturated aqueous Na₂S₂O₃ (20 mL) then washed with 1 M aq. HCl (30 mL) (until aqueous layer is acidic) and brine (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by preparative HPLC to afford the title compound as a white solid (255 mg, 94% Yield, 99% purity).

¹H NMR (500 MHz, DMSO) δ 10.20 (br.s, 1H), 8.47 (s, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.86 (t, J = 58.9 Hz, 1H), 7.63 (d, J = 9.0 Hz, 1H), 7.47 (d, J = 2.2 Hz, 1H), 7.10 (d, J = 7.4 Hz, 1H), 5.35 (s, 2H).

LCMS: m/z = 549.9/551.8 [M-H]⁻, (ESI⁻), RT = 4.05, Method A

Example 198 – 13-bromo-20-fluoro-14,19-dihydroxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Compound 198)

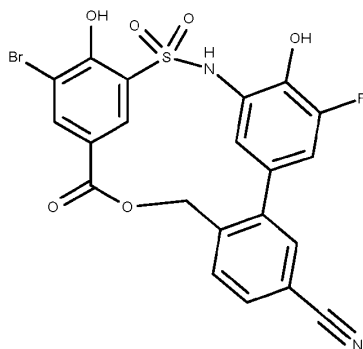


[0429] To a solution of *Intermediate 24* (100 mg, 0.17 mmol) in anhydrous pyridine (1.5 mL) was added lithium iodide (112.5 mg, 0.84 mmol) and the reaction mixture was heated at 90 °C for 16 h. The reaction mixture was dissolved in EtOAc (20 mL) and washed with 1 M aq. HCl (20 mL). The aqueous phase was extracted further with EtOAc (2 x 20 mL) and the organics were combined, washed with sat. aqueous Na₂S₂O₃ (20 mL) and brine (20 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by preparative HPLC (Method P1) to afford the title compound as a white solid (6.7 mg, 93% purity, 6.6% yield).

¹H NMR (500 MHz, DMSO) δ 10.23 (br.s, 1H), 9.47 (br.s, 1H), 8.68 (s, 1H), 8.18 (s, 1H), 8.03 (s, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.37 (dd, J = 11.1, 2.1 Hz, 1H), 6.98 (s, 1H), 5.72 – 5.60 (m, 1H), 5.44 – 5.29 (m, 1H).

LCMS: m/z = 563.0/565.0 [M+H]⁺, (ESI⁺), RT = 3.74, Method A

Example 199 – 13-bromo-20-fluoro-14,19-dihydroxy-10,16,16-trioxo-9-oxa-16λ6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile (Compound 199)

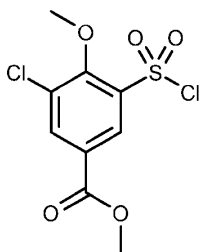


[0430] *Intermediate 26* (100 mg, 0.180 mmol) was dissolved in pyridine (1.0 mL) and lithium iodide (120 mg, 0.897 mmol) was added. The resulting mixture was heated to 80 °C for 5 h. The mixture was cooled to r.t. Sat aq. Na₂S₂O₃ (50 mL) was added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 2M aq. HCl (2 x 50 mL) and were passed through a hydrophobic frit and concentrated under reduced pressure. The residue was purified by preparative HPLC (Method P1) to afford the title compound as an off-white solid (6.2 mg, 90% purity, 6% yield).

¹H NMR (500 MHz, DMSO) δ 10.10 (br. s, 1H), 9.40 (br. s, 1H), 7.99 (s, 1H), 7.88 (dd, J = 7.8, 1.8 Hz, 1H), 7.77 (d, J = 1.7 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.31 (dd, J = 11.2, 2.1 Hz, 1H), 6.89 (s, 1H), 5.61 (d, J = 12.8 Hz, 1H), 5.23 (d, J = 12.9 Hz, 1H).

LCMS: m/z = 516.9/518.9 [M-H]⁻, (ESI⁻), RT = 3.56, Method A

Example 200 - Synthesis of Methyl 3-chloro-5-chlorosulfonyl-4-methoxy-benzoate (Intermediate 1)



Step 1

[0431] To a stirred solution of methyl 3-chloro-4-hydroxybenzoate (97% purity, 100 g, 0.520 mol) in a mixture of ethanol (900 mL) and acetic acid (100 mL) at ambient temperature was added bromine (40 mL, 0.776 mol) dropwise over 10 minutes. The reaction mixture was then stirred at ambient temperature for 2 hours. The reaction mixture was diluted with ethyl acetate (2 L) and washed with a mixture of saturated aqueous sodium thiosulfate (0.6 L) and water (0.4 L). The aqueous phase was back extracted with EtOAc (0.5 L). The organic layers were combined and washed with saturated aqueous sodium hydrogen carbonate (1 L). The carbonate wash was back extracted with EtOAc (0.5 L) and the extract added to the combined organic layers. The combined layers were washed with brine (1 L), dried over anhydrous sodium sulfate, filtered and the solvent concentrated in vacuo. The wet solid was triturated with cyclohexane (400 mL) for 10 minutes then the solid collected by vacuum filtration, rinsing the flask and cake with cyclohexane (2 x 100 mL). The solid was dried under a flow of nitrogen for 1 hour and then in the vacuum oven (40 °C) for a further 16 hours to afford the sodium 2-bromo-6-chloro-4-methoxycarbonyl-phenolate as a beige solid (147.90 g, 98% Yield, 99% purity).

^1H NMR (400 MHz, DMSO) δ 7.93 (d, J = 2.1 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), 3.78 (s, 3H).

LCMS: m/z = 263/265 [M-H] $^-$, (ESI $^-$), RT = 0.84, Method D

Step 2

[0432] To a stirred suspension of sodium 2-bromo-6-chloro-4-methoxycarbonyl-phenolate (99% purity, 147.90 g, 0.509 mol) and dipotassium carbonate (71.00 g, 0.514 mol) in DMF (1 L) at ambient temperature was added iodomethane (48 mL, 0.771 mol) portion-wise over 2 minutes. The reaction mixture was then stirred at ambient temperature for 16 hours. The

reaction mixture was poured into water (3 L) and the reaction mixture stirred at ambient temperature for a further 30 minutes, leading to the precipitation of a solid. The solid was collected by filtration, rinsing the flask and cake with water (2 x 500 mL) and then dried under a flow of air for 20 minutes. The solid was diluted with EtOAc (2.5 L) and brine (0.5 L) was added. The mixture was stirred at ambient temperature for a further 10 minutes then the layers were separated keeping the organic one. The organic layer was dried over anhydrous sodium sulfate and filtered using vacuum filtration rinsing the filter cake with EtOAc (0.5 L). The filtrates were combined, and decolorizing charcoal (106 g, 0.75 wt%) was added. The mixture was stirred at ambient temperature for 1 hour then filtered over a pad of silica (400 g, ~ 3 wt%) rinsing the pad with ethyl acetate (5 x 500 mL). The organic filtrates were combined, and the solvent evaporated in vacuo to afford methyl 3-bromo-5-chloro-4-methoxy-benzoate as white solid (128.60 g, 90% Yield, 99% purity).
¹H NMR (400 MHz, DMSO) δ 8.08 (d, J = 2.1 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H).

Step 3

[0433] To a stirred solution of methyl 3-bromo-5-chloro-4-methoxy-benzoate (58.50 g, 0.209 mol) in anhydrous 1,4-dioxane (0.85 L) was added DIPEA (47 mL, 0.272 mol). The solution was placed under vacuum for 5 minutes and then refilled with nitrogen gas. The flushing sequence was repeated 3 times. Pd₂(dba)₃ (5.85 g, 6.39 mmol), Xantphos (7.46 g, 12.9 mmol) and (4-tert-butylphenyl)methanethiol (44 mL, 0.237 mol) were added. The reaction mixture was flushed with N₂ (vacuum / N₂ cycles) another two times (5 min vacuum each time) and then heated at 100 °C for 5 hours. The reaction mixture was allowed to cool to ambient temperature overnight. The reaction mixture was filtered over a double layer of filter paper to remove spent catalyst and DIPEA salts and the filter cake rinsed with EtOAc (2 x 1 L). The combined filtrates were washed with 1 M hydrochloric acid (1 L), 50% brine (1 L) and brine (1 L), dried over Na₂SO₄, filtered and concentrated in vacuo to give the crude material as an orange oil. The oil was diluted with TBME (100 mL) and heptane (900 mL) and the solvent removed in vacuo. The crude material was diluted with TBME (300 mL) and adsorbed onto silica (200 g) and then purified by dry flash chromatography (1400 g of SiO₂) eluting with a gradient of TBME in heptane (1 - 5%, 18 L) and the product-containing fractions were combined and concentrated in vacuo to afford methyl 3-[(4-tert-butylphenyl)methylsulfanyl]-5-chloro-4-methoxy-benzoate as dark orange oil (83.40 g, 0.191 mol, 91% Yield, 87% purity).

^1H NMR (400 MHz, DMSO) δ 7.81 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 1.7 Hz, 4H), 4.26 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 1.25 (s, 9H).

LCMS: m/z = 377/379 [M-H] $^-$, (ESI $^-$), RT = 5.27, Method D

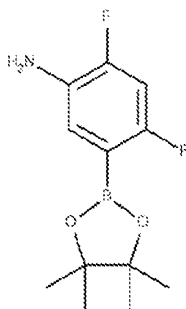
Step 4

[0434] To a stirred suspension of methyl 3-[(4-*tert*-butylphenyl)methylsulfanyl]-5-chloro-4-methoxy-benzoate (79% purity, 87.10 g, 0.182 mol) in a mixture of acetonitrile (1.2 L), acetic acid (74 mL) and water (74 mL) previously cooled at 0-5 °C (ice water bath) was added DCDMH (78.00 g, 0.396 mol) portion-wise over 5 minutes (temperature increased from 2.2 °C up to 17.4 °C). The reaction mixture was then stirred at 0-5 °C for a further 2 hours. The reaction mixture was diluted with EtOAc (2 L) and washed with 5% aqueous sodium carbonate solution (3 x 1 L) and brine (1.5 L). The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent concentrated in vacuo. The residue was diluted with TBME (50 mL) and heptane (500 mL) and the solvent concentrated in vacuo a second time. The residue was diluted with TBME (300 mL) and heptane (500 mL), triturated for 5 minutes with a spatula leading to the precipitation of a pale orange solid. The solid was removed by filtration and discarded. The filtrate was concentrated in vacuo to give a yellow oil (98.2 g) which was purified by dry flash column chromatography (1 kg silica) using a gradient of TBME in heptane (5% to 10%, 1 L fractions, 12 L) to afford the title compound as white solid (42.60 g, 0.140 mol, 77% Yield, 98% purity).

^1H NMR (400 MHz, DMSO) δ 8.27 (d, J = 2.2 Hz, 1H), 7.94 (d, J = 2.2 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H).

LCMS: m/z = 279/281 [M-H] $^-$, (ESI $^-$), RT = 0.96, Method D

Example 201 – Synthesis of 2,4-Difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (Intermediate 2)

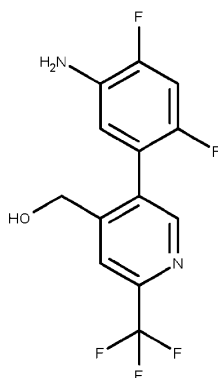


[0435] A mixture of 5-bromo-2,4-difluoroaniline (97% purity, 10 g, 46.6 mmol), bis(pinacolato)diboron (14 g, 55.1 mmol) and potassium acetate (14 g, 0.143 mol) in anhydrous 1,4-dioxane (300 mL) was degassed with N₂ for 10 mins before Pd(dppf)Cl₂ (3.50 g, 4.77 mmol) was added and the solution degassed for a further 2 mins. The reaction mixture was heated at 100 °C for 18 h. The reaction mixture was allowed to cool to r.t. before it was filtered through a pad of celite (washed with EtOAc until washings were colorless). The filtrate was concentrated in vacuo and was purified by FCC (350 g SiO₂ cartridge, 0-20% acetone in heptane) to give the title compound as viscous orange oil (10.20 g, 81% Yield, 95% purity).

¹H NMR (500 MHz, DMSO) δ 7.08 (dd, J = 10.9, 6.0 Hz, 1H), 6.93 (dd, J = 11.6, 9.0 Hz, 1H), 5.00 (s, 2H), 1.27 (s, 12H).

LCMS: m/z = 297.2 [M+MeCN+H]⁺, (ESI⁺), RT = 0.88, Method A

Example 202 – Synthesis of [5-(5-Amino-2,4-difluoro-phenyl)-2-(trifluoromethyl)-4-pyridyl]methanol (Intermediate 3)

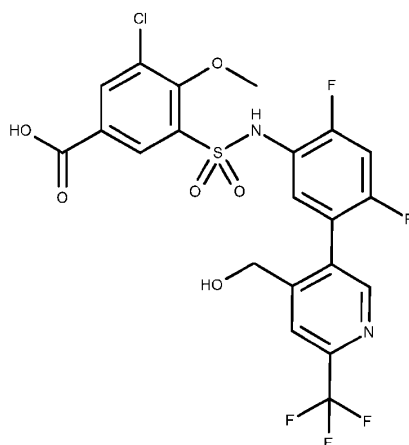


[0436] [5-Bromo-2-(trifluoromethyl)pyridine-4-yl]methanol (500 mg, 1.95 mmol), Intermediate 2 (577 mg, 2.15 mmol) and potassium carbonate (540 mg, 3.91 mmol) were dissolved into a mixture of 1,4-dioxane (12 mL) and water (1.2 mL) and the solution was degassed with nitrogen for 10 minutes. To the mixture was added Pd(dppf)Cl₂ (142.899 mg, 0.2 mmol), before a further 5 mins degassing. The reaction mixture was heated at 100 °C for 3.5 h. The mixture was filtered through celite washing with EtOAc and the filtrate concentrated. The residue was purified by FCC (25 g, SiO₂ column, 0-100% EtOAc in heptane) to give the title compound as yellow oil (526 mg, 84% Yield).

^1H NMR (400 MHz, DMSO) δ 8.56 (s, 1H), 8.02 (s, 1H), 7.24 (dd, J = 11.3, 9.8 Hz, 1H), 6.72 (dd, J = 9.8, 7.6 Hz, 1H), 5.72 – 5.58 (m, 1H), 5.22 (s, 2H), 4.48 – 4.26 (m, 2H).

LCMS: m/z : 305.0 $[\text{M}+\text{H}]^+$, (ESI+), RT = 0.78, Method D

Example 203 – Synthesis of Methyl 3-chloro-5-[[2,4-difluoro-5-[4-(hydroxymethyl)-6-(trifluoromethyl)-3-pyridyl]phenyl]sulfamoyl]-4-methoxy-benzoate (Intermediate 4)

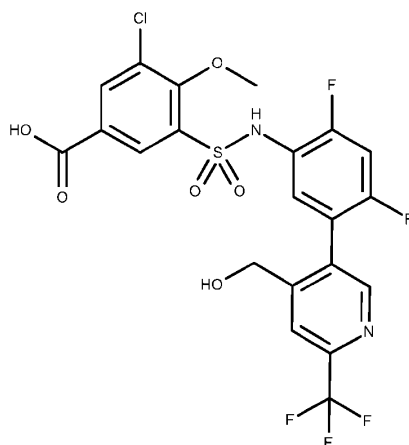


[0437] To a solution of *Intermediate 3* (520 mg, 1.62 mmol) in pyridine (6 mL) was added *Intermediate 1* (551 mg, 1.79 mmol) and the reaction mixture stirred at 50 °C for 1 h. The cooled reaction mixture was diluted with 1 M aq. HCl (50 mL) and extracted with EtOAc (2 x 50 ml). The combined organic extracts were washed with brine (50 ml) then passed through a phase separator and then concentrated. The material was purified by FCC (50 g SiO₂ cartridge, 0-80% EtOAc in heptane) to give the title compound as off-white solid (718 mg, 67% Yield).

^1H NMR (500 MHz, DMSO) δ 10.51 (s, 1H), 8.54 (s, 1H), 8.25 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.52 (t, J = 9.9 Hz, 1H), 7.35 (t, J = 8.1 Hz, 1H), 5.66 (t, J = 5.8 Hz, 1H), 4.34 (d, J = 5.6 Hz, 2H), 3.95 (s, 3H), 3.87 (s, 3H).

LCMS: m/z : 565.1/567.0 $[\text{M}-\text{H}]^-$, (ESI-), RT = 1.01, Method D

Example 204 – Synthesis of Methyl 3-chloro-5-[[2,4-difluoro-5-[4-(hydroxymethyl)-6-(trifluoromethyl)-3-pyridyl]phenyl]sulfamoyl]-4-methoxy-benzoate (Intermediate 5)

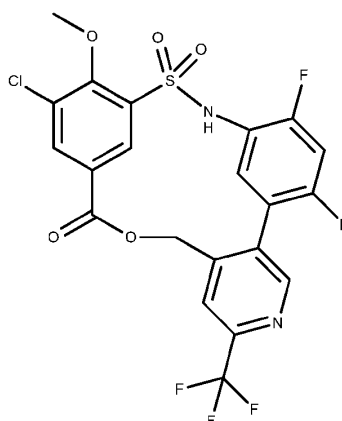


[0438] Intermediate 4 (715 mg, 1.08 mmol) was dissolved in THF (9 mL) and 2 M sodium hydroxide (3.0 mL, 6.0 mmol) added. The reaction mixture was stirred at r.t. for 2.5 h. The reaction mixture was concentrated under vacuum to remove the THF. The residue was diluted with water (30 mL), acidified with 2 M aq. HCl and extracted with DCM (3 x 30 mL). The combined organic was passed through a phase separator and then concentrated to give the title compound as pale orange oil (677 mg, 100% Yield, 90% purity).

¹H NMR (500 MHz, DMSO) δ 13.65 (s, 1H), 10.47 (s, 1H), 8.54 (s, 1H), 8.21 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 8.03 (s, 1H), 7.52 (t, J = 9.9 Hz, 1H), 7.36 (t, J = 8.1 Hz, 1H), 5.69 – 5.54 (m, 1H), 4.43 – 4.19 (m, 2H), 3.93 (s, 3H).

LCMS: m/z: 565.1/567.0 [M-H]⁻, (ESI⁻), RT = 1.01, Method D

Example 205 - Synthesis of 13-Chloro-19,21-difluoro-14-methoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosan-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Intermediate 6)

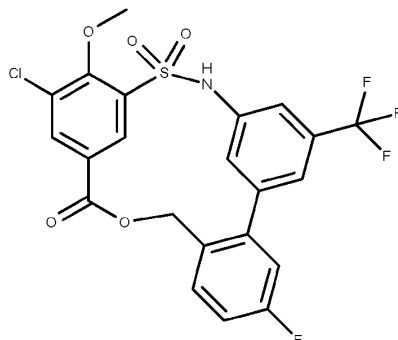


[0439] To a solution of Intermediate 5 (250 mg, 0.41 mmol) in DCM (25 mL) was added DMAP (25 mg, 0.2 mmol) followed by N,N'-diisopropylcarbodiimide (127 μ L, 0.81 mmol). The reaction mixture was stirred at r.t. for 16 h. Further DMAP (25 mg, 0.2 mmol) added and the reaction mixture stirred at r.t. for 5 h. The reaction mixture was diluted with 1 M aq. HCl (30 mL), passed through a phase separator and then concentrated. To the residue was added DCM (10 mL) and the mixture was sonicated for 5 mins. The mixture was filtered, washing with minimal DCM and the collected solid dried under vacuum to give the title compound as off-white solid (103 mg, 34% Yield, 86% purity).

¹H NMR (500 MHz, DMSO) δ 10.43 (s, 1H), 8.73 (s, 1H), 8.23 (s, 1H), 8.11 (d, J = 2.1 Hz, 1H), 7.59 – 7.46 (m, 1H), 7.39 – 7.35 (m, 1H), 7.26 (t, J = 8.0 Hz, 1H), 5.65 (d, J = 13.7 Hz, 1H), 5.30 (d, J = 13.7 Hz, 1H), 4.00 (s, 3H).

LCMS: m/z: 533.0/535.0 [M-H]⁻, (ESI⁻), RT = 1.05, Method D

Example 206 – Synthesis of 13-Chloro-4-fluoro-14-methoxy-16,16-dioxo-20-(trifluoromethyl)-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Intermediate 7)

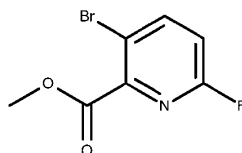


[0440] To a solution of 3-chloro-5-[[3-[5-fluoro-2-(hydroxymethyl)phenyl]-5-(trifluoromethyl)phenyl]sulfamoyl]-4-methoxy-benzoic acid (*synthesised using a similar method to intermediate 5*, 85% purity, 400 mg, 0.637 mmol) in DCM (35 mL) was added DMAP (20 mg, 0.164 mmol) and DCC (350 mg, 1.70 mmol). The reaction mixture was stirred at r.t. for 1.5 h and was then concentrated in vacuo. The organics were dissolved in DCM (10 mL) and to the organics was added HCl (15 mL of a 1 M aqueous solution). The biphasic mixture was stirred for 2 minutes before being passed through a phase separator. The organics were extracted further with DCM (2 x 5 mL) and passed through the phase separator. The combined organics were concentrated in vacuo. The residue was purified by FCC (10 g SiO₂ cartridge, 20-100% DCM in heptane) to afford the title compound as white solid (246 mg, 70% Yield, 93% purity).

¹H NMR (500 MHz, DMSO) δ 10.56 (s, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.82 – 7.77 (m, 1H), 7.65 (dd, J = 8.3, 5.8 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.18 – 7.13 (m, 1H), 5.44 – 5.32 (m, 2H), 4.00 (s, 3H).

LCMS: m/z = 514.1 / 516.0 [M-H]⁻, (ESI⁻), RT = 1.08, Method D

Example 207 – Synthesis of Methyl 3-bromo-6-fluoro-pyridine-2-carboxylate (Intermediate 8)

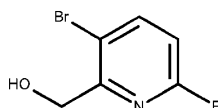


[0441] To a solution of nitrilooxonium tetrafluoroborate (1.70 g, 14.6 mmol) in DCM (50 mL) at 0 °C was slowly added methyl 6-amino-3-bromopyridine-2-carboxylate (2.6 g, 11.25 mmol). The reaction mixture was allowed to warm to r.t. and then stirred at r.t. for 4 h. To the reaction mixture was slowly added water (50 mL) and DCM (20 mL) and the resulting layers were separated. The aqueous was extracted with DCM (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by FCC (100 g SiO₂ cartridge, 0 - 40% EtOAc in heptane) to give the title compound as colourless oil (2.10 g, 80% Yield, 100% purity).

¹H NMR (500 MHz, DMSO) δ 8.43 (dd, J = 8.7, 6.9 Hz, 1H), 7.42 (dd, J = 8.8, 3.1 Hz, 1H), 3.91 (s, 3H).

LCMS: m/z = 233.9/235.9 [M+H]⁺, (ESI⁺), RT = 0.73, Method D

Example 208 – Synthesis of (3-Bromo-6-fluoro-2-pyridyl)methanol (Intermediate 9)

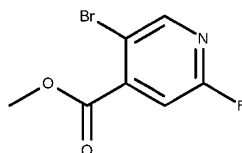


[0442] To a solution of *Intermediate 8* (2.1 g, 8.97 mmol) in THF (30 mL) and methanol (4 mL) was added lithium borohydride (1.25 g, 57.38 mmol). The reaction mixture was stirred at r.t. for 3 hours. The reaction was quenched by slow addition of water (20 mL) and was then concentrated to remove the THF/MeOH. The aqueous residue was extracted into EtOAc (3 x 50 mL) and the combined organic phases were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound as colourless oil that solidified on standing (1.79 g, 82% Yield, 85% purity).

¹H NMR (500 MHz, DMSO) δ 8.19 (dd, J = 8.5, 7.2 Hz, 1H), 7.10 (dd, J = 8.5, 3.3 Hz, 1H), 5.39 (t, J = 6.1 Hz, 1H), 4.55 (d, J = 6.1 Hz, 2H).

LCMS: m/z = 206.9/208.9 [M+H]⁺, (ESI⁺), RT = 0.54, Method D

Example 209 – Synthesis of Methyl 5-bromo-2-fluoro-pyridine-4-carboxylate (Intermediate 10)

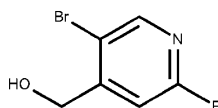


[0443] Nitrilooxonium tetrafluoroborate (10.20 g, 87.3 mmol) was added portion-wise to a solution of methyl 2-amino-5-bromopyridine-4-carboxylate (15.0 g, 64.92 mmol) in DCM (200 mL). The reaction mixture was allowed to warm to r.t. and then stirred for 16 h. Water (100 mL) was added to the reaction mixture then the layers separated. The aqueous was further extracted with DCM (2 x 50 mL). The combined organics were washed with brine (100 mL), passed through phase separator paper, and concentrated under reduced pressure. The crude was purified by FCC (100 g SiO₂ cartridge, 0 - 40% EtOAc in heptane) to give the title compound as pale-yellow oil (11.45 g, 67% Yield, 89% purity).

¹H NMR (400 MHz, DMSO) δ 8.65 – 8.59 (m, 1H), 7.63 (dd, J = 2.7, 0.5 Hz, 1H), 3.92 (s, 3H).

LCMS: m/z = 233.9/235.9 [M+H]⁺, (ESI⁺), RT = 0.80, Method D

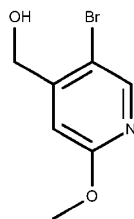
Example 210 – Synthesis of (5-bromo-2-fluoro-4-pyridyl)methanol (Intermediate 11)



[0444] To a solution of *Intermediate 10* (1.131 g, 4.45 mmol) in THF (15 mL) and MeOH (2.5 mL) was added lithium borohydride (582 mg, 26.72 mmol). The reaction mixture was stirred at r.t. for 15 min. The reaction was quenched by slow addition of water (20 mL) and then concentrated to remove the THF/MeOH. The aqueous residue was extracted into EtOAc (3 x 30 mL), the combined organic phases were washed with brine (20 mL), passed through phase separator paper, and the solvent removed under reduced pressure to afford the title compound as white solid (960 mg, 94% Yield, 90% purity).

¹H NMR (DMSO): 8.34 (d, J = 1.0 Hz, 1H), 7.23 (dt, J = 2.2, 1.2 Hz, 1H), 5.84 (t, J = 5.5 Hz, 1H), 4.53 (dd, J = 5.6, 1.2 Hz, 2H).

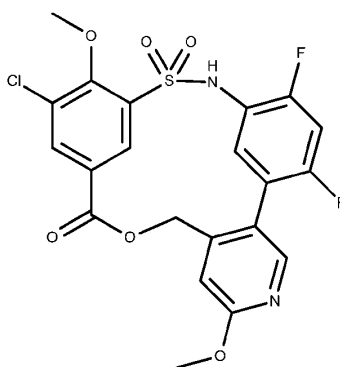
LCMS: m/z = 205.9/207.9 [M+H]⁺, (ESI⁺), RT = 0.58, Method D

Example 211 – Synthesis of (5-bromo-2-methoxy-4-pyridyl)methanol (Intermediate 12)

[0445] Sodium borohydride (438 mg, 11.6 mmol) was added to a stirring solution of 5-bromo-2-methoxypyridine-4-carbaldehyde (1.00 g, 4.63 mmol) in THF (15.0 mL) and methanol (5.0 mL) at r.t.. The reaction mixture was stirred for 30 minutes. The reaction was quenched by slow addition of water (20 mL), and the mixture concentrated in vacuo to remove THF/MeOH. The aqueous residue was extracted into DCM (3 x 20 mL), and the organic phases were combined, washed with brine (30 mL), passed through a phase separator, and concentrated to dryness in vacuo to afford the title product as white solid (1.41 g, 100% Yield, 100% purity).

¹H NMR (400 MHz, DMSO) δ 8.22 (s, 1H), 7.05 – 6.84 (m, 1H), 5.65 (t, J = 5.5 Hz, 1H), 4.45 (d, J = 4.4 Hz, 2H), 3.84 (s, 3H).

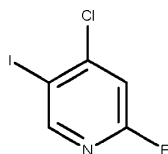
LCMS: m/z = 217.9/219.9 [M+H]⁺, (ESI⁺), RT = 0.66, Method D

Example 212 – Synthesis of 13-chloro-19,21-difluoro-5,14-dimethoxy-16,16-dioxo-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.1¹¹.15.0²,7]tricosan-1(22),2(7),3,5,11,13,15(23),18,20-nonaen-10-one (Intermediate 13)

[0446] A solution of 3-chloro-5-[[2,4-difluoro-5-[4-(hydroxymethyl)-6-methoxy-3-pyridyl]phenyl]sulfamoyl]-4-methoxy-benzoic acid (*synthesised from intermediate 12, using a similar method to intermediate 5*, 97% purity 2.50 g, 4.71 mmol) and NMI (0.56 mL, 7.06

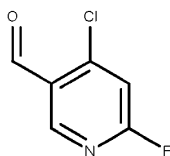
mmol) in MeCN (185 mL) was prepared. A second solution of TCFH (1.72 g, 6.13 mmol) and NMI (0.56 mL, 7.06 mmol) in MeCN (60 mL) was also prepared. The substrate solution was placed in a dropping funnel and added dropwise (over approx. 20 mins) to the stirred TCFH solution and the mixture left to stir at r.t. overnight. The reaction mixture was filtered. The filtrate was concentrated in vacuo then purified by FCC (100 g, SiO₂ cartridge, 0 - 100% DCM in heptane then 0-100% EtOAc in DCM) to give the title compound as white solid (727 mg, 1.39 mmol, 30% Yield, 95% purity). The solid from the filtration was purified by FCC (100 g SiO₂ column, 0 - 100% DCM in heptane then 0-100% EtOAc in DCM) to give additional title compound as white solid (906 mg, 1.79 mmol, 38% Yield, 98% purity). ¹H NMR (500 MHz, DMSO) δ 10.35 (s, 1H), 8.11 – 8.09 (m, 2H), 7.44 – 7.39 (m, 1H), 7.37 (d, J = 2.1 Hz, 1H), 7.10 (s, 1H), 7.08 – 7.04 (m, 1H), 5.41 (d, J = 13.2 Hz, 1H), 5.14 (d, J = 13.1 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H). LCMS: m/z = 495.0/497.0 [M-H]⁻, (ESI⁻), RT = 1.03, Method D

Example 213 – Synthesis of 4-Chloro-2-fluoro-5-iodo-pyridine (Intermediate 14)



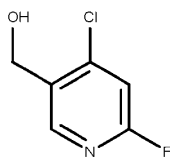
[0447] To a solution of nitrilooxonium tetrafluoroborate (1.23 g, 10.5 mmol) in DCM (35 mL) at 0 °C was slowly added a solution of 4-chloro-5-iodo-pyridin-2-amine (2.0 g, 7.86 mmol) in DCM (10 mL). The reaction mixture was allowed to warm to r.t. and then stirred at r.t. for 4.5 h. To the reaction mixture was slowly added water (10 mL) and sat. aq. NaHCO₃ (50 mL), then the layers separated. The aqueous was extracted with DCM (2 x 50 mL). The combined organics were passed through a phase separator and then concentrated. The material was purified by FCC (50 g SiO₂ cartridge, 0-100% EtOAc in heptane) to give the title product as a pale-yellow oil (1.47 g, 72% yield, 76% purity).

¹H NMR (500 MHz, DMSO) δ 8.68 (s, 1H), 7.69 (d, J = 2.2 Hz, 1H).

Example 214 – Synthesis of 4-Chloro-6-fluoro-pyridine-3-carbaldehyde (Intermediate 15)

[0448] To a solution of *Intermediate 14* (1.35 g, 3.99 mmol) in anhydrous THF (25 mL) was added 2.5 M *n*-BuLi in hexanes (3.1 mL, 7.75 mmol) at -78 °C. The mixture was stirred at -78 °C for 20 mins, followed by addition of ethyl formate (0.83 mL, 10.3 mmol). The reaction was stirred at -78 °C for 1 h. The reaction mixture was diluted with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were passed through a phase separator and concentrated. The residual material was purified by FCC (50 g SiO₂ cartridge, 0-100% EtOAc in heptane) to give the title compound (611 mg, 68% yield, 70% purity).

¹H NMR (500 MHz, DMSO) δ 10.24 (s, 1H), 8.74 (s, 1H), 7.73 (d, J = 1.9 Hz, 1H).

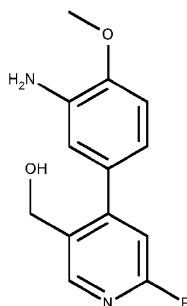
Example 215 – Synthesis of (4-Chloro-6-fluoro-3-pyridyl)methanol (Intermediate 16)

[0449] To a solution of *Intermediate 15* (70% purity, 370 mg, 1.62 mmol) in methanol (6 mL) at 0 °C was added NaBH₄ (154 mg, 4.06 mmol). The resulting mixture was then stirred at r.t. for 1 h. The reaction was quenched by addition of saturated aq. NH₄Cl (50 mL) and the MeOH removed under vacuum. The reaction mixture was extracted with DCM (4 x 50 mL), the combined organic passed through a phase separator and concentrated to give the title compound as an off-white solid (335 mg, 89% Yield, 70% purity).

¹H NMR (500 MHz, DMSO) δ 8.29 (d, J = 0.9 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 5.53 (t, J = 5.5 Hz, 1H), 4.63 – 4.54 (m, 2H).

LCMS: m/z = 161.9/163.9 [M+H]⁺, (ESI⁺), RT = 0.51, Method D

Example 216 – Synthesis of [4-(3-Amino-4-methoxy-phenyl)-6-fluoro-3-pyridyl]methanol (Intermediate 17)

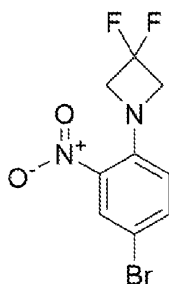


[0450] *Intermediate 16* (70% purity, 320 mg, 1.39 mmol), 2-methoxy-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (*synthesised using a similar method to intermediate 2*, 484 mg, 1.94 mmol) and potassium carbonate (479 mg, 3.47 mmol) were dissolved into a mixture of 1,4-dioxane (15 mL) and water (1.5 mL) and the solution was degassed with nitrogen for 5 min. To the mixture was added XPhos Pd G3 (117 mg, 0.139 mmol), before a further 5 mins degassing. The reaction mixture was heated at 100 °C overnight. The reaction mixture was filtered through celite washing with EtOAc and the filtrate concentrated. The material was purified by FCC (50 g SiO₂ cartridge, 0-100% EtOAc in heptane) to give the title product as pale brown solid (87 mg, 0.329 mmol, 24% Yield, 94% purity).

¹H NMR (400 MHz, DMSO) δ 8.28 (s, 1H), 6.95 (d, *J* = 1.7 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 2.2 Hz, 1H), 6.68 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.32 (t, *J* = 5.3 Hz, 1H), 4.87 (s, 2H), 4.47 (d, *J* = 5.3 Hz, 2H), 3.82 (s, 3H).

LCMS: *m/z* = 231.0/249.0 [M+H]⁺, (ESI⁺), RT = 0.53, Method D

Example 217 – Synthesis of 1-(4-Bromo-2-nitro-phenyl)-3,3-difluoro-azetidine (Intermediate 18)

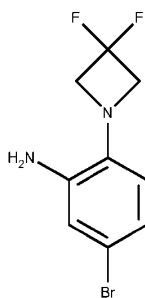


[0451] To a solution of 4-bromo-1-fluoro-2-nitrobenzene (1.00 g, 4.55 mmol) in anhydrous DMF (15 mL) at r.t. were added dicaesium carbonate (3.703 g, 11.36 mmol) and 3,3-difluoroazetidine hydrochloride (1:1) (707 mg, 5.45 mmol). The mixture was stirred at 50 °C for 16 h in a sealed tube. The mixture was taken up in EtOAc (50 mL) and the organics washed with 2 x 40 mL water then 1 x 40 mL saturated brine solution. The organic layer was dried (MgSO₄) before concentration to dryness. The residue was purified by FCC (25 g SiO₂ cartridge, 0-20% EtOAc in heptane) to afford the title compound as a yellow solid (1.18 g, 84% Yield, 95% purity).

¹H NMR (500 MHz, DMSO) δ 8.04 (d, J = 2.3 Hz, 1H), 7.73 (dd, J = 9.0, 2.4 Hz, 1H), 6.85 (d, J = 9.0 Hz, 1H), 4.43 – 4.35 (m, 4H).

LCMS: m/z = 292.9/294.9 [M+H]⁺, (ESI⁺), RT = 1.01, Method D

Example 218 – Synthesis of 5-Bromo-2-(3,3-difluoroazetidin-1-yl)aniline (Intermediate 19)

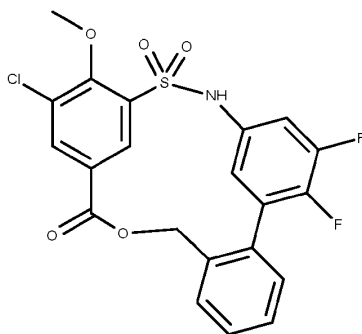


[0452] *Intermediate 18* (1.10 g, 3.75 mmol) was added to a solution of iron (2.72 g, 48.8 mmol) and ammonium chloride (3.21 g, 60.1 mmol) in ethanol (25 mL) and water (8 mL). The mixture was heated to 80 °C for 1.5 h. The mixture was allowed to cool to r.t. and then filtered through a pad of celite, washing with EtOAc (20 mL). The filtrate was concentrated under reduced pressure. The crude material was taken up in EtOAc (50 mL) and the organics washed with 2 x 40 mL water then 1 x 40 mL saturated brine solution. The organic layer was dried (MgSO₄) before concentration to dryness. The residue was purified by FCC (25 g SiO₂ cartridge, 0-30% EtOAc in heptane) to afford the title compound as a brown solid (845 mg, 80% Yield, 94% purity).

¹H NMR (500 MHz, DMSO) δ 6.80 (d, J = 2.3 Hz, 1H), 6.66 (dd, J = 8.3, 2.3 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 4.87 (s, 2H), 4.21 – 4.11 (m, 4H).

LCMS: m/z = 262.9/264.9 [M+H]⁺, (ESI⁺), RT = 0.92, Method D

Example 219 – Synthesis of 13-Chloro-20,21-difluoro-14-methoxy-16,16-dioxo-9-oxa-16λ6-thia-17-azatetracyclo[16.3.1.1.11,15.02,7]tricos-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Intermediate 20)

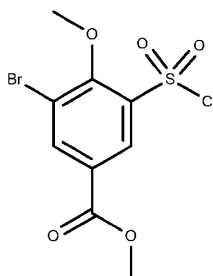


[0453] To a solution of 3-chloro-5-[[3,4-difluoro-5-[2-(hydroxymethyl)phenyl]phenyl]sulfamoyl]-4-methoxy-benzoic acid (*synthesised using a similar method to intermediate 5*, 90% purity, 600 mg, 1.12 mmol), DMAP (15 mg, 0.123 mmol) and triethylamine (351 μ L, 2.52 mmol) in dimethyl carbonate (45 mL) was added 2-chloro-1-methylpyridinium iodide (450 mg, 1.76 mmol). The reaction mixture was stirred at r.t. for 18 h. The mixture was diluted with DCM (50 mL) and 2 M aq. HCl (50 mL) was added. The mixture was separated and the aqueous phase extracted with DCM (2 x 50 mL). The combined organic fractions were washed with brine (100 mL), dried over Na_2SO_4 , filtered and dry-loaded onto silica. The crude material was purified by FCC (25 g SiO_2 cartridge, 20-100% DCM in heptane) to afford the title compound as a yellow solid (140 mg, 95% purity, 26% Yield).

^1H NMR (500 MHz, DMSO) δ 10.42 (s, 1H), 8.04 (s, 1H), 7.62 – 7.58 (m, 1H), 7.53 – 7.47 (m, 2H), 7.41 (s, 1H), 7.38 – 7.34 (m, 1H), 7.09 (s, 1H), 6.72 (s, 1H), 5.51 (d, J = 12.8 Hz, 1H), 5.09 (d, J = 12.7 Hz, 1H), 3.97 (s, 3H).

LCMS: m/z = 464.0 & 466.1 $[\text{M-H}]^-$, (ESI-), RT = 1.05, Method D

Example 220 – Synthesis of Methyl 3-bromo-5-chlorosulfonyl-4-methoxy-benzoate
methyl 3-bromo-5-chlorosulfonyl-4-methoxy-benzoate (Intermediate 21)



Step 1

[0454] In a 2 L, 3-neck round bottomed flask, fitted with a condenser, to a solution of methyl 3-bromo-4-methoxybenzoate (76.50 g, 0.312 mol) and silver triflate (96.25 g, 0.375 mol) in DCM (900 mL) was added iodine (95.07 g, 0.375 mol) slowly. The reaction was stirred at 35 °C, in darkness. The solution was then placed in a cold-water bath, and water (150 mL) was added slowly, while monitoring internal temperature. The solution was filtered, and the layers separated. The organic layer was transferred into a round bottom flask with overhead stirring, and then the solution was then quenched with 10% sodium thiosulphate solution (900 mL) and left to stir for 30 min, until the strong pink colour had dissipated to a beige solution. The layers were then separated, and the organic layer washed with brine (300 mL) then dried over magnesium sulphate (52 g) and concentrated in vacuo. The crude material was dissolved in DCM (40 mL) and heptane (70 mL), then purified using a dry flash column (1 kg silica pad, 0-10% TBME in heptane over 18 L) to afford methyl 3-bromo-5-iodo-4-methoxy-benzoate (79.7 g, 100% purity, 69% yield) as a white solid. ¹H NMR (400 MHz, DMSO) δ 8.29 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 2.0 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H).

Step 2

[0455] A stirred solution of methyl 3-bromo-5-iodo-4-methoxy-benzoate (118 g, 0.317 mol) and DIPEA (100 mL, 0.574 mol) in 1,4-dioxane (1.20 L) at r.t. was degassed under vacuum for 10 mins, then refilled with nitrogen and repeated 3 times. (4-tert-butylphenyl)methanethiol (62.0 mL, 0.332 mol), Pd₂dba₃ (6.00 g, 6.55 mmol) and Xantphos (11.0 g, 19.0 mmol) were added and then degassed under vacuum for 10 mins, then refilled with nitrogen. The solution was then heated to 56 °C for 2 h. The solution was cooled to r.t. and filtered, the precipitate was washed with ethyl acetate (2 x 500 mL). The filtrate was

slightly cooled with a water/ice bath, before being stirred for 10 mins with 1 M HCl (500 mL). The layers were separated and the organic layer was washed with brine (500 mL). The organic layer was then dried over magnesium sulphate (36 g) filtered and concentrated in vacuo. The residue was azeotroped with heptane (500 mL) and TBME (100 mL) and concentrated in vacuo. The crude material was then dissolved in DCM (100 mL) purified using a dry flash column (1.5 kg silica pad, 0-4% TBME in heptane over 18 L) to afford methyl 3-bromo-5-[(4-tert-butylphenyl)methylsulfanyl]-4-methoxy-benzoate (136 g, 95% purity, 96% yield) as an orange solid.

^1H NMR (400 MHz, DMSO) δ 7.89 (d, J = 1.9 Hz, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.33 (d, J = 1.1 Hz, 4H), 4.25 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 1.24 (s, 9H).

LCMS: m/z = 421.1/423.1 [M-H] $^-$, (ESI $^-$), RT = 1.15, Method D

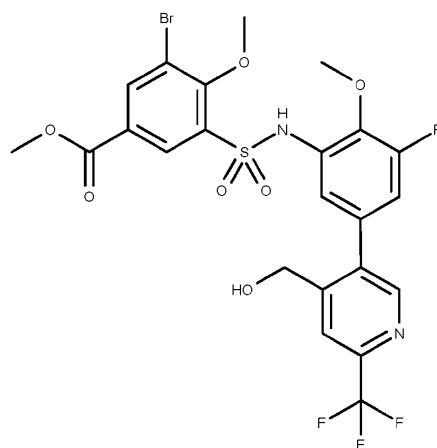
Step 3

[0456] In the 3 L jacketed vessel, temperature of cooling fluid (internal temp) was set to -5 °C. A solution of methyl 3-bromo-5-[(4-tert-butylphenyl)methylsulfanyl]-4-methoxy-benzoate (66.0 g, 0.148 mol) in MeCN (858 mL) was added, stirring was set to 150 rpm. Acetic acid (66.0 mL) and water (33.0 mL) were added, and the solution was stirred until the process temp reached ~2 °C. DCDMH (60.9 g, 0.309 mol) was then added portion wise over 50 min. After the addition had been completed the process temperature was raised to 5 °C, and the mixture was stirred for 1 h. The solution was then diluted with ethyl acetate (600 mL) and quenched with 5% NaHCO₃ solution (300 mL), keeping the process temperature below 6 °C (internal temperature was set to 2 °C). The solution was stirred for 5 mins, then the aqueous layer was decanted off. The organic layer was washed further with brine (2 x 300 mL), keeping the process temperature at < 6 °C. The organic layer was then dried over magnesium sulphate, filtered and concentrated in vacuo. The residue was azeotroped with TBME (120 mL) and heptane (600 mL). The crude material was then dissolved in DCM (150 mL) and purified using dry flash column (1 kg silica pad, 0-5% EtOAc in heptane over 20 L). The resultant crude product was stirred in TBME (210 mL) at 55 °C for 20 min, then allowed to cool to r.t. heptane (210 mL) was added and the mixture was stirred for a further 30 min. The precipitate was collected under vacuum filtration to afford the title compound (41.0 g, 95% purity, 77% yield) as a white powder.

^1H NMR (400 MHz, CDCl₃) δ 8.58 (t, J = 1.6 Hz, 2H), 4.19 (s, 3H), 3.97 (s, 3H).

LCMS: m/z = 324.9 [M-H] $^-$, (ESI $^-$), RT = 0.97, Method D

Example 221 – Synthesis of Methyl 3-bromo-5-[[3-fluoro-5-[4-(hydroxymethyl)-6-(trifluoromethyl)-3-pyridyl]-2-methoxy-phenyl]sulfamoyl]-4-methoxy-benzoate (Intermediate 22)

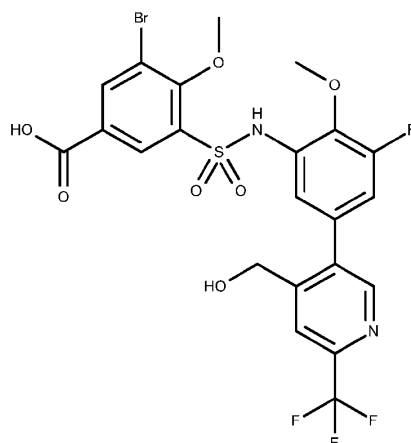


[0457] *Intermediate 21* (95%, 1.00 g, 2.77 mmol) and [5-(3-amino-5-fluoro-4-methoxy-phenyl)-2-(trifluoromethyl)-4-pyridyl]methanol (*synthesised using a similar method to intermediate 3*, 70%, 1.24 g, 2.74 mmol) were dissolved in pyridine (13 mL) and the mixture was heated to 50 °C and stirred for 1 h. The reaction mixture was allowed to cool to r.t. and was diluted with 1 M aq. HCl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The material was purified by FCC (50 g SiO₂ cartridge, 0 - 60% EtOAc in heptane) to give the title compound (1.16 g, 54% Yield, 80% purity) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 10.30 (s, 1H), 8.52 (s, 1H), 8.37 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 2.1 Hz, 1H), 8.00 (d, J = 0.8 Hz, 1H), 7.33 (dd, J = 12.1, 2.1 Hz, 1H), 7.15 – 7.11 (m, 1H), 5.65 (t, J = 5.6 Hz, 1H), 4.47 (d, J = 5.5 Hz, 2H), 3.98 (s, 3H), 3.87 (s, 3H), 3.64 (d, J = 1.9 Hz, 3H).

LCMS: m/z = 623.0/625.0 [M+H]⁺, (ESI⁺), RT = 1.07, Method D

Example 222 – Synthesis of 3-Bromo-5-[[3-fluoro-5-[4-(hydroxymethyl)-6-(trifluoromethyl)-3-pyridyl]-2-methoxy-phenyl]sulfamoyl]-4-methoxy-benzoic acid (Intermediate 23)

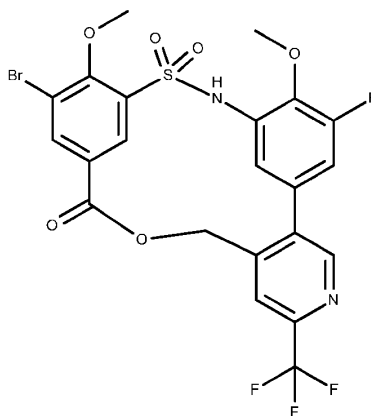


[0458] *Intermediate 22* (80% purity, 1.15 g, 1.48 mmol) was dissolved in THF (27 mL) and 2 M sodium hydroxide (7.5 mL, 15.0 mmol) was added. The resulting solution was stirred at r.t. for 16 h. The THF was removed under reduced pressure and the remaining aqueous solution was added to DCM (50 mL) and acidified with 2 M HCl (50 mL). The layers were separated and the aqueous phase was extracted with additional DCM (2 x 50 mL), before the combined organic phases were washed with brine (50 mL), dried over Na₂SO₄, filtered. The solids were taken into stirring 1 M HCl (~150 mL) and the solid that remained was collected by vacuum filtration (washed with 2 x 20 mL water) and dried in a vacuum oven to give the title compound (390 mg, 99% purity, 43% Yield) as a white solid.

¹H NMR (400 MHz, DMSO) δ 13.61 (s, 1H), 10.25 (s, 1H), 8.53 (s, 1H), 8.34 (d, J = 2.1 Hz, 1H), 8.25 (d, J = 2.1 Hz, 1H), 8.00 (s, 1H), 7.33 (dd, J = 12.1, 2.1 Hz, 1H), 7.14 – 7.10 (m, 1H), 5.65 (s, 1H), 4.48 (s, 2H), 3.96 (s, 3H), 3.63 (d, J = 1.9 Hz, 3H).

LCMS: m/z = 609.0/611.0 [M-H]⁻, (ESI⁻), RT = 0.95, Method D

Example 223 – Synthesis of 13-Bromo-20-fluoro-14,19-dimethoxy-16,16-dioxo-5-(trifluoromethyl)-9-oxa-16 λ 6-thia-4,17-diazatetracyclo[16.3.1.111,15.02,7]tricosan-1(21),2(7),3,5,11,13,15(23),18(22),19-nonaen-10-one (Intermediate 24)

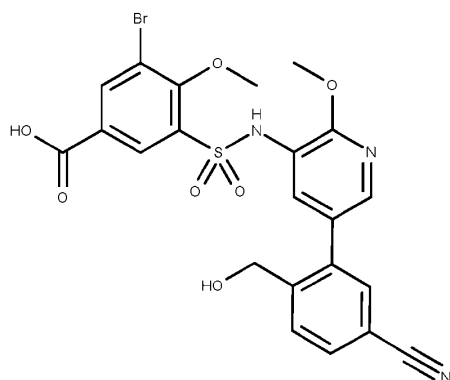


[0459] To a solution of *N,N'*-dicyclohexylcarbodiimide (350 mg, 1.7 mmol) and *Intermediate 23* (99%, 385 mg, 0.626 mmol) in DCM (30 mL) was added 4-dimethylaminopyridine (23 mg, 0.19 mmol). The reaction mixture was stirred for 18 h at r.t. NaHCO_3 (sat. aq., 50 mL) was added, the mixture was separated and the aqueous phase extracted with DCM (2 x 50 mL). The combined organic fractions were washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated. The material was purified by FCC (25 g SiO_2 cartridge, 20 - 100% DCM in heptane) to give the title compound as white solid (95 mg, 99% purity, 25% Yield).

^1H NMR (500 MHz, DMSO) δ 10.15 (s, 1H), 8.75 (s, 1H), 8.25 – 8.17 (m, 2H), 7.66 – 7.59 (m, 1H), 7.44 (s, 1H), 7.30 – 7.23 (m, 1H), 5.78 – 5.69 (m, 1H), 5.48 – 5.34 (m, 1H), 4.01 (s, 3H), 3.58 – 3.52 (m, 3H).

LCMS: m/z = 591.0/593.0 $[\text{M}+\text{H}]^+$, (ESI+), RT = 1.10, Method D

Example 224 – Synthesis of 3-Bromo-5-[[5-[5-cyano-2-(hydroxymethyl)phenyl]-2-methoxy-3-pyridyl]sulfamoyl]-4-methoxy-benzoic acid (Intermediate 25)

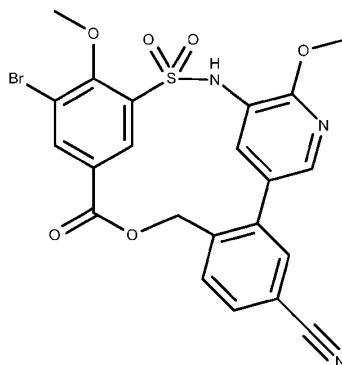


[0460] Methyl 3-bromo-5-[[5-[5-cyano-2-(hydroxymethyl)phenyl]-2-methoxy-3-pyridyl]sulfamoyl]-4-methoxy-benzoate (*synthesised using a similar method to intermediate 22*, 95% purity, 525 mg, 0.887 mmol) was dissolved in THF (10 mL) and potassium trimethylsilanolate (148 mg, 1.15 mmol) added. The reaction mixture was stirred at r.t. for 2 h. Further potassium trimethylsilanolate (34 mg, 0.266 mmol) added and the reaction mixture stirred at r.t. for 1.5 h. The reaction mixture was diluted with water (50 mL) and washed with DCM (2 x 30 mL). The aqueous was acidified with 1 M aq. HCl and then extracted with IPA:CHCl₃ 1:3 (2 x 40 mL). The combined organic extracts were passed through a phase separator and concentrated to give the title compound as pale yellow solid (458 mg, 90% purity, 85% yield).

¹H NMR (400 MHz, DMSO) δ 13.65 (br. s, 1H), 10.14 (s, 1H), 8.33 (d, J = 2.1 Hz, 1H), 8.22 (d, J = 2.1 Hz, 1H), 8.04 (d, J = 2.3 Hz, 1H), 7.88 (dd, J = 8.0, 1.7 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H), 7.66 (d, J = 2.2 Hz, 1H), 5.52 – 5.36 (m, 1H), 4.46 – 4.38 (m, 2H), 3.89 (s, 3H), 3.65 (s, 3H).

LCMS: m/z = 548.0/550.0 [M+H]⁺, (ESI⁺), RT = 0.84, Method D

Example 225 – Synthesis of 13-Bromo-14,19-dimethoxy-10,16,16-trioxo-9-oxa-16λ6-thia-17,20-diazatetracyclo[16.3.1.111,15.02,7]tricoso-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile (Intermediate 26)

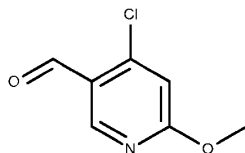


[0461] To a stirred solution of TCFH (144 mg, 0.512 mmol) and NMI (63 μ L, 0.80 mmol) in acetonitrile (20 mL) was added a solution of *intermediate 25* (99% purity, 240 mg, 0.394 mmol) and NMI (63 μ L, 0.80 mmol) in acetonitrile (20 mL) over 20 mins. The reaction mixture was stirred at r.t. overnight. The reaction mixture was concentrated. The residue was taken up in IPA:CHCl₃ 1:3 (60 mL) and washed with 1 M aq. HCl (40 mL) then brine (40 mL). The organic was passed through a phase separator and concentrated. The resulting solid was triturated in MeCN, and then dried under vacuum to give the title compound (151 mg, 86% purity, 62 % Yield) as an off-white solid.

¹H NMR (500 MHz, DMSO) δ 10.09 (s, 1H), 8.19 – 8.14 (m, 2H), 7.97 – 7.92 (m, 2H), 7.80 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 2.2 Hz, 1H), 7.44 (d, J = 2.2 Hz, 1H), 5.82 (d, J = 13.5 Hz, 1H), 5.30 (d, J = 13.5 Hz, 1H), 4.03 (s, 3H), 3.50 (s, 3H).

LCMS: m/z = 530.1/532.0 [M+H]⁺, (ESI⁺), RT = 0.98, Method D

Example 226 – Synthesis of 4-Chloro-6-methoxy-pyridine-3-carbaldehyde (Intermediate 27)



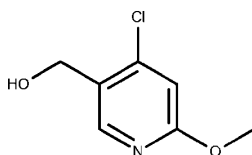
[0462] To a mixture of 5-bromo-4-chloro-2-methoxy-pyridine (2.50 g, 11.2 mmol) and lithium chloride (953 mg, 22.5 mmol) in anhydrous THF (26 mL) was added a solution of 2

M chloro(propan-2-yl)magnesium in THF (8.43 mL, 16.9 mmol) at -78° C. The stirred solution was allowed to warm to 0 °C over 1 h. DMF (2.2 mL, 28.53 mmol) was added slowly and the solution was left to stir for a further 1 h at 0 °C. Sat. NH₄Cl (30 mL) and 1 M HCl (10 mL) were added and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), passed through phase separator paper, and concentrated under reduced pressure to afford the title compound as an off-white solid (1.77 g, 100% purity, 92% yield).

¹H NMR (400 MHz, DMSO) δ 10.16 (s, 1H), 8.68 (s, 1H), 7.17 (s, 1H), 3.97 (s, 3H).

LCMS: m/z = 171.9/173.9 [M+H]⁺, (ESI⁺), RT = 0.75, Method D

Example 227 – Synthesis of (4-Chloro-6-methoxy-3-pyridyl)methanol (Intermediate 28)

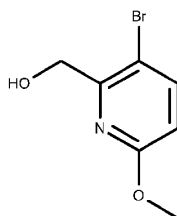


[0463] To a solution of *intermediate 27* (1.20 g, 6.99 mmol) in THF (14.0 mL) and MeOH (2.0 mL) was added sodium borohydride (1.32 g, 35.0 mmol) portion-wise and the mixture stirred at r.t. for 30 mins. The reaction was quenched by slow addition of water (20 mL) before being concentrated in vacuo to remove the THF/MeOH. The aqueous residue was extracted with DCM (3 x 20 mL) then the combined organics were washed with brine (20 mL), passed through a phase separator and concentrated in vacuo to afford the title compound as a white solid (1.19 g, 100% purity, 98% yield) as a white solid.

¹H NMR (400 MHz, DMSO) δ 8.20 (s, 1H), 6.97 (s, 1H), 5.30 (t, J = 5.5 Hz, 1H), 4.51 (d, J = 5.5 Hz, 2H), 3.85 (s, 3H).

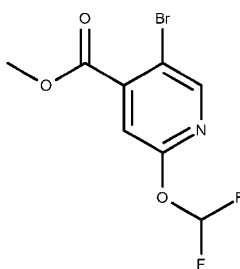
LCMS: m/z = 174.0/175.9 [M+H]⁺, (ESI⁺), RT = 0.57, Method D

Example 228 – Synthesis of (3-Bromo-6-methoxy-2-pyridyl)methanol (Intermediate 29)



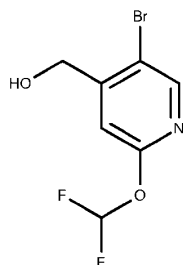
[0464] To a solution of ethyl 3-bromo-6-methoxy-pyridine-2-carboxylate (831 mg, 3.20 mmol) in THF (12.5 mL) and MeOH (1.75 mL) was added lithium borohydride (420 mg, 19.3 mmol) and the mixture was stirred at r.t. for 30 min. The reaction was quenched by slow addition of water (20 mL) and then concentrated to remove the THF/MeOH. The aqueous residue was extracted into DCM (3 x 30 mL), the combined organic phases were washed with brine (20 mL), passed through a phase separator, and the solvent removed under reduced pressure to afford the title compound as a green oil (653 mg, 95% purity, 89% Yield).
¹H NMR (500 MHz, DMSO) δ 7.87 (d, J = 8.6 Hz, 1H), 6.72 (d, J = 8.6 Hz, 1H), 5.10 (t, J = 5.6 Hz, 1H), 4.53 (d, J = 5.5 Hz, 2H), 3.88 (s, 3H).
LCMS: m/z = 217.9/219.9 [M+H]⁺, (ESI⁺), RT = 0.71, Method D

Example 229 – Synthesis of Methyl 5-bromo-2-(difluoromethoxy)pyridine-4-carboxylate (Intermediate 30)



[0465] A mixture of sodium chloro(difluoro)acetate (1.97 g, 12.9 mmol) and methyl 5-bromo-2-oxo-1,2-dihydropyridine-4-carboxylate (1.00 g, 4.31 mmol) was dissolved in anhydrous MeCN (50 mL) and heated to 90 °C for 20 h. The mixture was cooled to r.t. and vacuum filtered (washing with EtOAc). The filtrate was concentrated and the resultant residue purified by FCC (100 g SiO₂ cartridge, 0-60% EtOAc in heptane) to afford the title compound as a white solid (3.87 g, 100% purity, 63.7 % Yield).
¹H NMR (500 MHz, DMSO) δ 8.62 (s, 1H), 7.68 (t, J = 72.1 Hz, 1H), 7.48 (s, 1H), 3.91 (s, 3H).
LCMS: m/z = 281.9/283.9 [M+H]⁺, (ESI⁺), RT = 0.94, Method D

Example 230 – Synthesis of [5-Bromo-2-(difluoromethoxy)-4-pyridyl]methanol (Intermediate 31)

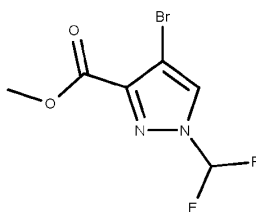


[0466] To a solution of *intermediate 30* (3.87 g, 13.7 mmol) in THF (90 mL) and MeOH (9 mL) was added lithium borohydride (1.75 g, 80.3 mmol) and the reaction mixture was stirred at r.t. for 30 min. The reaction was quenched by slow addition of water (20 mL) and then concentrated to remove the THF/MeOH. The aqueous residue was extracted into DCM (3 x 30 mL), the combined organic phases were washed with brine (20 mL), passed through a phase separator, and the solvent removed under reduced pressure to afford the title compound (3.32 g, 95% purity, 90% Yield) as a white solid.

¹H NMR (500 MHz, DMSO) δ 8.36 (s, 1H), 7.67 (t, J = 72.6 Hz, 1H), 7.13 (d, J = 1.3 Hz, 1H), 5.82 – 5.74 (m, 1H), 4.51 (d, J = 4.1 Hz, 2H).

LCMS: m/z = 254.0/255.9 [M+H]⁺, (ESI⁺), RT = 0.78, Method D

Example 231 – Synthesis of Methyl 4-bromo-1-(difluoromethyl)pyrazole-3-carboxylate (Intermediate 32)

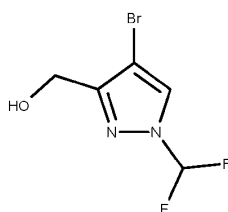


[0467] A mixture of methyl 4-bromo-1H-pyrazole-3-carboxylate (1.50 g, 7.32 mmol), K₂CO₃ (2.02 g, 14.6 mmol), 18-Crown-6 (96.7 mg, 0.37 mmol) and sodium chloro(difluoro)acetate (2.23 g, 14.6 mmol) in anhydrous MeCN (30 mL) was heated at 80 °C for 1 h, and then at 90 °C for 6 h. The mixture was quenched with water (50 mL), the MeCN removed under vacuum and the aqueous extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried (Na₂SO₄), filtered and

concentrated. The residue was purified by FCC (50 g SiO₂ cartridge, 0-20% EtOAc in heptane) to afford two components (regioisomeric products). The second eluting species afforded the title compound as a white solid (1.34 g, 100% purity, 72% Yield).

¹H NMR (500 MHz, DMSO) δ 8.15 (s, 1H), 8.08 (t, J = 58.0 Hz, 1H), 3.92 (s, 3H).

Example 232 – Synthesis of [4-Bromo-1-(difluoromethyl)pyrazol-3-yl]methanol (Intermediate 33)

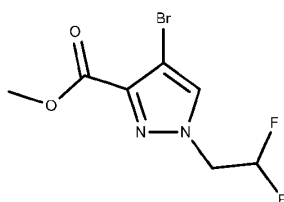


[0468] To a solution of *intermediate 32* (750 mg, 2.94 mmol) in THF (20 mL) and MeOH (2 mL) was added lithium borohydride (400 mg, 18.4 mmol) and the mixture was stirred at r.t. for 30 min. The reaction was quenched by slow addition of water (20 mL) and then concentrated to remove the THF/MeOH. The aqueous residue was extracted into DCM (3 x 30 mL), the combined organic phases were washed with brine (20 mL), passed through a phase separator, and the solvent removed under reduced pressure to afford the title compound as a pale yellow oil (419 mg, 97% purity, 61% Yield).

¹H NMR (500 MHz, DMSO) δ 8.49 (s, 1H), 7.75 (t, J = 58.9 Hz, 1H), 5.29 (t, J = 5.6 Hz, 1H), 4.43 (d, J = 5.3 Hz, 2H).

LCMS: m/z = 226.8/228.8 [M+H]⁺, (ESI⁺), RT = 0.54, Method D

Example 233 – Synthesis of Methyl 4-bromo-1-(2,2-difluoroethyl)pyrazole-3-carboxylate (Intermediate 34)



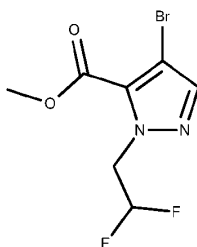
[0469] Dicaesium carbonate (3.20 g, 9.82 mmol) was added to a solution of methyl 4-bromo-1H-pyrazole-3-carboxylate (1.00 g, 4.88 mmol) and 1,1-difluoro-2-iodoethane (1.40 g, 7.29 mmol) in DMF (10 mL) and the mixture was stirred at 50 °C for 1 h. After cooling to

r.t. and concentrating in vacuo, the mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by FCC (50 g SiO₂ cartridge, 0-100% EtOAc in heptane) to afford two regioisomeric products. The first eluting component afforded the title compound as a colourless oil that solidified to a white solid upon standing (639 mg, 97% purity, 47% yield).

¹H NMR (500 MHz, DMSO) δ 7.89 (s, 1H), 6.39 (tt, J = 54.9, 3.7 Hz, 1H), 4.97 (td, J = 14.6, 3.7 Hz, 2H), 3.89 (s, 3H).

LCMS: m/z = 269.0/270.9 [M+H]⁺, (ESI⁺), RT = 0.84, Method D

Example 234 – Synthesis of Methyl 4-bromo-1-(2,2-difluoroethyl)pyrazole-5-carboxylate (Intermediate 35)

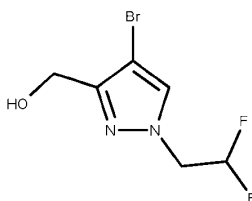


[0470] The title compound was isolated as the second eluting compound from the procedure described in Intermediate 34 to afford a colourless oil that solidified upon standing (632 mg, 97% purity, 47% yield).

¹H NMR (500 MHz, DMSO) δ 8.20 (s, 1H), 6.42 (tt, J = 54.4, 3.6 Hz, 1H), 4.73 (td, J = 15.2, 3.5 Hz, 2H), 3.82 (s, 3H).

LCMS: m/z = 269.0/270.9 [M+H]⁺, (ESI⁺), RT = 0.70, Method D

Example 235 – Synthesis of [4-Bromo-1-(2,2-difluoroethyl)pyrazol-3-yl]methanol (Intermediate 36)

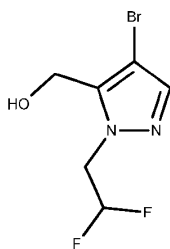


[0471] To a solution of *intermediate 34* (625 mg, 2.21 mmol) in THF (15 mL) and MeOH (1.5 mL) was added lithium borohydride (300 mg, 13.8 mmol). The reaction mixture was stirred at r.t. for 30 min. The reaction was quenched by slow addition of water (20 mL) and then concentrated to remove the THF/MeOH. The aqueous residue was extracted into DCM (3 x 30 mL), the combined organic phases were washed with brine (20 mL), passed through a phase separator, and the solvent removed under reduced pressure to afford the title compound as a pale yellow oil (500 mg, 99% purity, 93% Yield).

¹H NMR (500 MHz, DMSO) δ 7.95 (s, 1H), 6.34 (tt, J = 54.8, 3.7 Hz, 1H), 5.09 (t, J = 5.5 Hz, 1H), 4.58 (td, J = 15.1, 3.7 Hz, 2H), 4.36 (d, J = 5.5 Hz, 2H).

LCMS: m/z = 223.0/224.9 (ESI+), RT = 0.53, Method D

Example 236 – Synthesis of [4-Bromo-1-(2,2-difluoroethyl)pyrazol-5-yl]methanol (Intermediate 37)

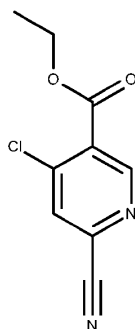


[0472] To a solution of *intermediate 35* (625 mg, 2.25 mmol) in THF (15 mL) and MeOH (1.5 mL) was added lithium borohydride (300 mg, 13.8 mmol). The reaction mixture was stirred at r.t. for 30 min. The reaction was quenched by slow addition of water (20 mL) and then concentrated to remove the THF/MeOH. The aqueous residue was extracted into DCM (3 x 30 mL), the combined organic phases were washed with brine (20 mL), passed through a phase separator, and the solvent removed under reduced pressure to afford the title compound (506 mg, 100% purity, 93% Yield) as a colourless oil.

¹H NMR (500 MHz, DMSO) δ 7.61 (s, 1H), 6.36 (tt, J = 55.1, 4.0 Hz, 1H), 5.59 – 5.52 (m, 1H), 4.68 (td, J = 14.6, 4.0 Hz, 2H), 4.53 (d, J = 4.4 Hz, 2H).

LCMS: m/z = 241.0/242.9 [M+H]⁺, (ESI+), RT = 0.58, Method D

Example 237 – Synthesis of Ethyl 4-chloro-6-cyano-pyridine-3-carboxylate (Intermediate 38)

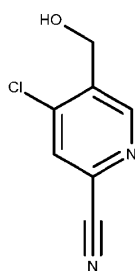


[0473] To a mixture of zinc cyanide (0.65 g, 5.57 mmol), ethyl 4,6-dichloropyridine-3-carboxylate (2.45 g, 11.1 mmol), Pd₂(dba)₃ (0.576 g, 0.56 mmol) and Xantphos (0.64 g, 1.11 mmol) was added anhydrous DMF (50 mL) under nitrogen. The reaction mixture was heated at 120 °C for 4 h, before it was allowed to cool to r.t. The reaction was taken up in EtOAc (50 ml) and the organics washed with 2 x 40 ml water then 1 x 40 ml saturated brine solution. The organic layer was dried (MgSO₄) before concentration to dryness. The crude was then purified by FCC (0-25% EtOAc in heptane) to afford the title compound ethyl 4-chloro-6-cyano-pyridine-3-carboxylate (1.57 g, 67% Yield) as a pale-yellow solid.

¹H NMR (500 MHz, DMSO) δ 9.07 (s, 1H), 8.51 (s, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H).

LCMS: m/z = 210.9/212.9 [M+H]⁺, (ESI⁺), RT = 0.83, Method D

Example 238 – Synthesis of 4-Chloro-5-(hydroxymethyl)pyridine-2-carbonitrile (Intermediate 39)



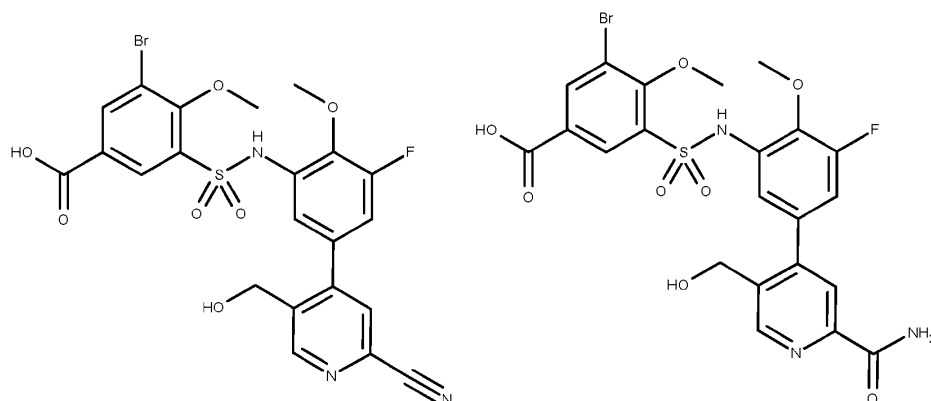
[0474] To a solution of *intermediate 38* (2.7 g, 10.9 mmol) in THF (60 mL) and MeOH (12 mL) was added lithium borohydride (712.102 mg, 32.69 mmol) portion wise at 0 °C. The

reaction mixture was stirred at 0 °C for 1 hr. The reaction was quenched by slow addition of cold water (10 mL) at 0 °C. The aqueous residue was extracted into EtOAc (3 x 10 mL), the combined organic phases were washed with brine (10 mL), passed through phase separator paper, and the solvent removed under reduced pressure. The residue was purified by FCC (50 g SiO₂ cartridge, 0-80% EtOAc in heptane) to afford the title compound as an off-white solid (1.51 g, 100% purity, 82% Yield).

¹H NMR (500 MHz, DMSO) δ 8.78 (s, 1H), 8.30 (s, 1H), 5.78 (t, J = 5.6 Hz, 1H), 4.68 (d, J = 4.3 Hz, 2H).

LCMS: m/z = 168.9/170.9 [M+H]⁺, (ESI⁺), RT = 0.51, Method D

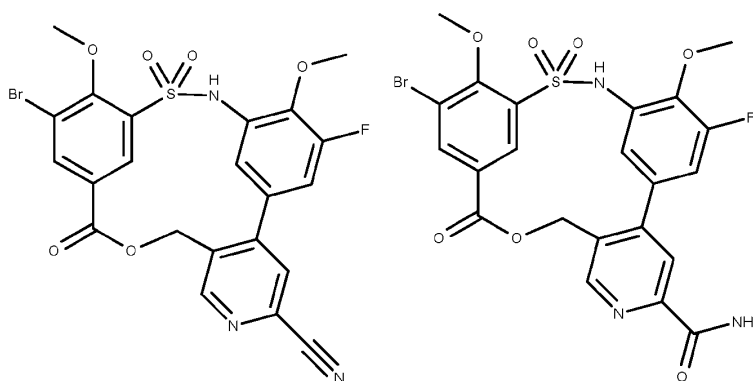
Example 239 – Synthesis of 3-Bromo-5-[[5-[2-cyano-5-(hydroxymethyl)-4-pyridyl]-3-fluoro-2-methoxy-phenyl]sulfamoyl]-4-methoxy-benzoic acid; 3-bromo-5-[[5-[2-carbamoyl-5-(hydroxymethyl)-4-pyridyl]-3-fluoro-2-methoxy-phenyl]sulfamoyl]-4-methoxy-benzoic acid (1:2) (Intermediate 40)



[0475] Methyl 3-bromo-5-[[5-[2-cyano-5-(hydroxymethyl)-4-pyridyl]-3-fluoro-2-methoxy-phenyl]sulfamoyl]-4-methoxy-benzoate (*synthesised from intermediate 39, using a similar method to intermediate 22*, 92% purity, 230 mg, 0.365 mmol) was dissolved in THF (3 mL) and 2 M sodium hydroxide (1.0 mL, 2.0 mmol) was added. The mixture was stirred at r.t. overnight. The mixture was diluted with water (20 mL) and DCM (30 mL) and the layers separated. The aqueous was acidified with 1 M aq. HCl (10 mL) and extracted with IPA:CHCl₃; 1:3 (2 x 40 ml). The combined organic was passed through a phase separator and then concentrated to give the title compound mixture (213 mg) as a pale-yellow solid. LCMS and NMR showed a mixture of nitrile and primary amide (1:2). NMR not fully characterised. Taken on to the next step as a mixture.

LCMS: $m/z = 584.0/586.0$ $[M+H]^+$, (ESI+), RT = 0.75; and $566.0/568.0$ $[M+H]^+$, (ESI+), RT = 0.86; Method D

Example 240 – Synthesis of 13-Bromo-20-fluoro-14,19-dimethoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carboxamide; 13-bromo-20-fluoro-14,19-dimethoxy-10,16,16-trioxo-9-oxa-16 λ 6-thia-5,17-diazatetracyclo[16.3.1.111,15.02,7]tricos-1(22),2(7),3,5,11,13,15(23),18,20-nonaene-4-carbonitrile (5:3) (Intermediate 41)

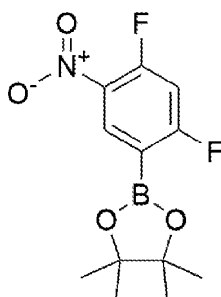


[0476] To a stirred solution of *Intermediate 40* (213 mg, 0.109 mmol) in MeCN (6 mL) was added NMI (104 μ L, 1.31 mmol) and TCFH (122 mg, 0.436 mmol) and the reaction was stirred at r.t. overnight. The mixture was concentrated. The residue was taken up in IPA:CHCl₃, 1:3 (30 mL) and washed with 1 M aq. HCl (30 mL). The organic was passed through a phase separator and concentrated, then triturated with MeCN to afford the title compound mixture as a white solid (60 mg).

This was carried on to the next step without further purification. NMR taken but not fully characterised.

LCMS: $m/z = 566.0/568.0$ $[M+H]^+$, (ESI+), RT = 0.89; and $547.9/550.0$ $[M+H]^+$, (ESI+), RT = 1.00; Method D

Example 241 – Synthesis of 2-(2,4-Difluoro-5-nitro-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 42)

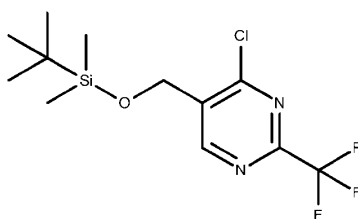


[0477] A mixture of Bis(pinacolato)diboron (2.00 g, 7.88 mmol) and 1-bromo-2,4-difluoro-5-nitrobenzene (1.50 g, 6.30 mmol) were combined in anhydrous 1,4-dioxane (32 mL) and nitrogen was bubbled through the solution for 10 mins then added potassium acetate (1.90 g, 19.4 mmol) and Pd(dppf)Cl₂ (481 mg, 0.656 mmol) were added. The reaction mixture was heated to 100 °C under nitrogen for 2 h. The mixture was allowed to cool to r.t. and then filtered through celite and washed with EtOAc (15 mL) with the solvent then removed under reduced pressure. The residue was purified by FCC (50 g SiO₂ cartridge, 0-100% EtOAc in heptane) to afford the title compound as a brown oil (518 mg, 94% Yield).

¹H NMR (500 MHz, CDCl₃) δ 8.53 (dd, J = 9.1, 5.8 Hz, 1H), 6.98 (dd, J = 10.8, 8.3 Hz, 1H), 1.37 (s, 13H).

LCMS: m/z = 248.1 [M+formic acid-H]⁻, (ESI⁻), RT = 0.59, Method D

Example 242 – Synthesis of Tert-butyl-[[4-chloro-2-(trifluoromethyl)pyrimidin-5-yl]methoxy]-dimethyl-silane (Intermediate 43)



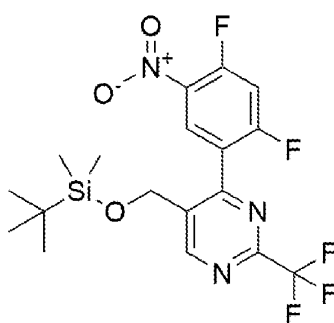
[0478] To a solution of [4-chloro-2-(trifluoromethyl)pyrimidin-5-yl]methanol (517 mg, 2.19 mmol) in anhydrous DMF (9 mL) was added imidazole (292 mg, 4.29 mmol) and the resulting solution was stirred at r. t. for 5 min. To the reaction mixture was then added TBDMSCl (450 mg, 2.99 mmol) and the reaction was stirred at 40 °C for 2 h. DCM (20 mL) and water (20 mL) were added and the aqueous layer was further extracted with DCM (2 x 20

mL). The organic layer was washed with brine (20 mL), passed through phase separator paper, and the solvent removed under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-100% DCM in heptane) to afford the title compound (589 mg, 94% purity, 77% Yield) as a colourless liquid.

¹H NMR (500 MHz, CDCl₃) δ 9.00 (s, 1H), 4.84 (s, 2H), 0.97 (s, 9H), 0.17 (s, 6H).

LCMS: m/z = - [M-H]⁻, (ESI⁻), RT = 1.29, Method D

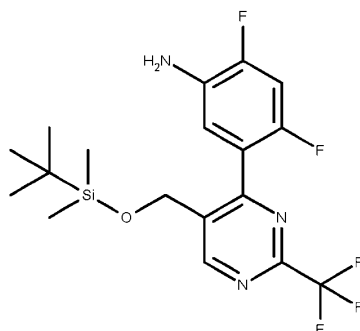
Example 243 – Synthesis of Tert-butyl-[[4-(2,4-difluoro-5-nitro-phenyl)-2-(trifluoromethyl)pyrimidin-5-yl]methoxy]-dimethyl-silane (Intermediate 44)



[0479] *Intermediate 42* (712 mg, 1.87 mmol), *intermediate 43* (539 mg, 1.55 mmol), and potassium carbonate (431.0 mg, 3.12 mmol) were dissolved in THF (16 mL) and water (2.5 mL) and the solution was degassed with nitrogen for 10 minutes. To the mixture was added palladium - tri-tert-butylphosphine (1:2) (87.0 mg, 0.17 mmol) before a further 5 mins' degassing. The reaction mixture was heated at 65 °C for 2 h. The solvent was removed under reduced pressure and the residue was purified by FCC (25 g SiO₂ cartridge, 0-100% DCM in heptane) to afford the title compound as a pale-yellow oil (570 mg, 94% purity, 77% Yield) as a pale-yellow oil.

¹H NMR (500 MHz, CDCl₃) δ 9.16 (s, 1H), 8.39 (dd, J = 8.1, 7.1 Hz, 1H), 7.22 (dd, J = 10.0, 9.1 Hz, 1H), 4.72 (s, 2H), 0.88 (s, 9H), 0.06 (s, 6H).

Example 244 – Synthesis of 5-[5-[[Tert-butyl(dimethyl)silyl]oxymethyl]-2-(trifluoromethyl)pyrimidin-4-yl]-2,4-difluoro-aniline (Intermediate 45)

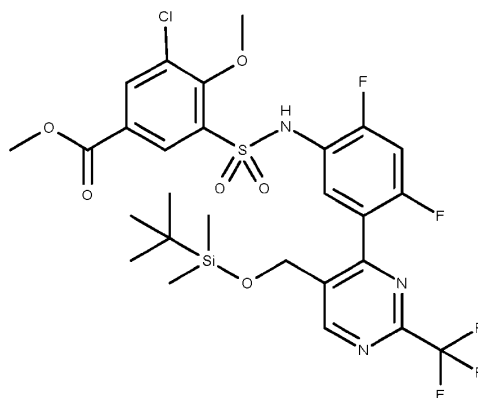


[0480] *Intermediate 44* (94%, 570 mg, 1.19 mmol) was added to a solution of iron (920 mg, 16.47 mmol) and ammonium chloride (1.05 g, 19.6 mmol) in ethanol (7.2 mL) and water (2.3 mL). The mixture was heated to 80 °C for 1.5 h. The mixture was allowed to cool to r.t. and then filtered through a pad of celite, washing with EtOAc (20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-50% EtOAc in heptane) to afford the title compound as a pale yellow solid (391 mg, 97% purity, 76% Yield).

¹H NMR (500 MHz, CDCl₃) δ 9.13 (s, 1H), 6.95 – 6.87 (m, 2H), 4.72 (s, 2H), 3.73 (br s, 2H), 0.90 (s, 9H), 0.06 (s, 6H).

LCMS: m/z = 420.3 [M+H]⁺, (ESI⁺), RT = 1.24, Method D

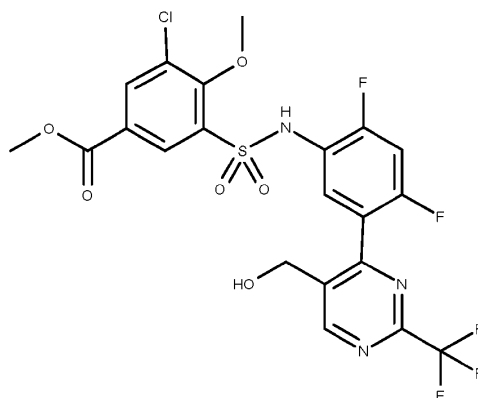
Example 245 – Synthesis of Methyl 3-[[5-[5-[[tert-butyl(dimethyl)silyl]oxymethyl]-2-(trifluoromethyl)pyrimidin-4-yl]-2,4-difluoro-phenyl]sulfamoyl]-5-chloro-4-methoxybenzoate (Intermediate 46)



[0481] *Intermediate 1* (300 mg, 1.0 mmol) was added to *intermediate 45* (381 mg, 0.88 mmol) in anhydrous pyridine (9 mL) and the mixture was stirred overnight at r.t. The solvent was removed under reduced pressure, the residue was redissolved in DCM (50 mL) and washed with sat. NH₄Cl solution (20 mL) and the aqueous layer was further extracted with DCM (2 x 30 mL). The combined organic layer was washed with brine (30 mL), passed through phase separator paper, and the solvent removed under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-100% DCM in heptane) to afford the title compound as a yellow oil (480 mg, 71% purity, 57% Yield) as a yellow oil.

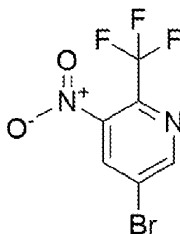
¹H NMR (400 MHz, CDCl₃) δ 9.15 (s, 1H), 8.36 – 8.27 (m, 2H), 7.65 (dd, J = 8.5, 7.2 Hz, 1H), 6.96 – 6.87 (m, 1H), 4.68 (s, 2H), 4.20 (s, 3H), 3.91 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H).
LCMS: m/z = 680.2/682.2 [M-H]⁻, (ESI⁻), RT = 1.22, Method D

Example 246 – Synthesis of Methyl 3-chloro-5-[[2,4-difluoro-5-[5-(hydroxymethyl)-2-(trifluoromethyl)pyrimidin-4-yl]phenyl]sulfamoyl]-4-methoxy-benzoate (Intermediate 47)



[0482] To a solution of *intermediate 46* (71% purity, 480 mg, 0.500 mmol) in methanol (7 mL) was added *p*-toluenesulfonic acid monohydrate (80 mg, 0.421 mmol). The reaction mixture was stirred for 3 h at r.t. The solvent was removed under reduced pressure and the residue was purified by FCC (10 g SiO₂ cartridge, 0-75% EtOAc in heptane) to afford the title compound as a yellow solid (331 mg, 75% purity, 87% Yield).

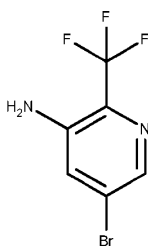
¹H NMR (400 MHz, CDCl₃) δ 9.19 (s, 1H), 8.33 (d, J = 2.1 Hz, 1H), 8.27 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 8.6, 7.2 Hz, 1H), 6.95 – 6.86 (m, 1H), 4.68 (s, 2H), 4.20 (s, 3H), 3.92 (s, 3H).
LCMS: m/z = 566.0/568.0 [M-H]⁻, (ESI⁻), RT = 0.97, Method D

Example 247 – Synthesis of 5-Bromo-3-nitro-2-(trifluoromethyl)pyridine (Intermediate 48)

[0483] To a solution of 2,5-dibromo-3-nitropyridine (2.00 g, 7.09 mmol) in anhydrous DMF (20.0 mL) were added copper (I) iodide (1.62 g, 8.51 mmol) and methyl difluoro(fluorosulfonyl)acetate (1.30 mL, 10.2 mmol). The reaction mixture was stirred at 100 °C under N₂ for 2 h. The reaction mixture was cooled to r.t. then poured into water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic components were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by FCC (50 g SiO₂ cartridge, 0-30% EtOAc in heptane) to afford the title compound as a yellow oil (1.70 g, 80% purity, 71% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.96 (d, J = 2.0 Hz, 1H), 8.37 (d, J = 2.0 Hz, 1H).

LCMS: m/z = 268.9/270.9 [M-H]⁻, (ESI⁻), RT = 0.82, Method E

Example 248 – Synthesis of 5-Bromo-2-(trifluoromethyl)pyridin-3-amine (Intermediate 49)

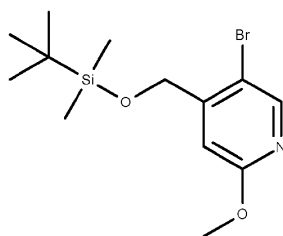
[0484] To a solution of *intermediate 48* (1.70 g, 5.01 mmol) in ethanol (20.0 mL) and water (2.0 mL) were added iron (1.40 g, 25.1 mmol) and ammonium chloride (1.60 g, 29.9 mmol) and the reaction mixture was stirred at 85 °C under N₂ for 20 h. The reaction mixture was cooled to r.t. and concentrated in vacuo to remove the EtOH. The residue was diluted with EtOAc (70 mL), filtered through celite, and washed with sat. aq. NaHCO₃ solution (70 mL). The aqueous component was extracted with EtOAc (70 mL) and the combined organic

components were washed with brine (100 mL), dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was loaded onto a 25 g SCX cartridge equilibrated with EtOAc. The column was eluted with 0 - 50 % 7 M methanolic ammonia/EtOAc and the product-containing fractions were combined and concentrated in vacuo. The residue was further purified by FCC (100 g SiO_2 cartridge, 100% DCM) to afford the title compound as a yellow solid (813 mg, 82% purity, 55% yield).

^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, J = 1.8 Hz, 1H), 7.29 – 7.27 (m, 1H), 4.28 (br. s, 2H).

LCMS: m/z = 240.8/242.8 $[\text{M}+\text{H}]^+$, (ESI+), RT = 0.80, Method D

Example 249 – Synthesis of (5-Bromo-2-methoxy-4-pyridyl)methoxy-tert-butyl-dimethyl-silane (Intermediate 50)

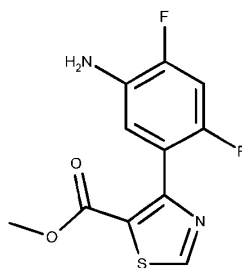


[0485] TBDMSCl (760 mg, 5.04 mmol) was added to a solution of (5-bromo-2-methoxy-4-pyridyl)methanol (95%, 947 mg, 4.13 mmol) and imidazole (350 mg, 5.14 mmol) in anhydrous DMF (13 mL). The reaction mixture was stirred at r.t. for 20 h. Further TBDMSCl (190 mg) and imidazole (90 mg) were added and the reaction mixture was stirred at r.t. for a further 20 h. The reaction mixture was concentrated in vacuo then suspended in water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic components were washed brine (70 mL), dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was purified by FCC (50 g SiO_2 cartridge, 0-50% TBME in heptane) to afford the title compound as a colourless oil (900 mg, 95% purity, 62% yield).

^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H), 6.99 – 6.94 (m, 1H), 4.67 – 4.61 (m, 2H), 3.92 (s, 3H), 0.97 (s, 9H), 0.14 (s, 6H).

LCMS: m/z = 332.0/334.0 $[\text{M}+\text{H}]^+$, (ESI+), RT = 1.24, Method D

Example 250 - Synthesis of Methyl 4-(5-amino-2,4-difluoro-phenyl)thiazole-5-carboxylate (Intermediate 51)

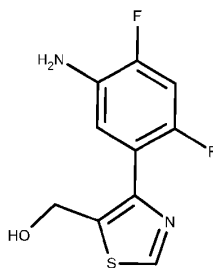


[0486] *Intermediate 2* (316 mg, 1.24 mmol), methyl 4-bromothiazole-5-carboxylate (250 mg, 1.13 mmol) and potassium carbonate (320 mg, 2.32 mmol) were dissolved into a mixture of 1,4-dioxane (5.4 mL) and water (0.67 mL) and the solution was degassed with nitrogen for 10 minutes. To the mixture was added Pd(dppf)Cl₂ (82 mg, 0.112 mmol), before a further 5 mins' degassing. The reaction mixture was heated at 100 °C for 2 h. The mixture was filtered through celite and concentrated under reduced pressure and the residue was purified by FCC (25 g SiO₂ cartridge, 0-100% EtOAc in heptane) to afford the title compound as a light orange oil (398 mg, 75% purity, 98% Yield).

¹H NMR (500 MHz, DMSO) δ 9.35 (s, 1H), 7.12 (dd, J = 11.3, 9.9 Hz, 1H), 6.92 (dd, J = 9.9, 7.4 Hz, 1H), 5.13 (s, 2H), 3.75 (s, 3H).

LCMS: m/z = 271.1 [M+H]⁺, (ESI⁺), RT = 0.69, Method D

Example 251 – Synthesis of [4-(5-Amino-2,4-difluoro-phenyl)thiazol-5-yl]methanol (Intermediate 52)



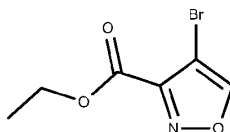
[0487] To a solution of *intermediate 51* (398 mg, 1.13 mmol) in THF (3.85 mL) and MeOH (0.621 mL) was added lithium borohydride (125.0 mg, 5.74 mmol) and the reaction mixture was stirred at r.t. for 1 h. The reaction was quenched by slow addition of water (20 mL) and then concentrated to remove the THF/MeOH. The aqueous residue was extracted

into EtOAc (3 x 50 mL), the combined organic phases were washed with brine, passed through phase separator paper, and the solvent removed under reduced pressure to afford the title compound as a colourless oil (281 mg, 74% purity, 76% Yield).

^1H NMR (500 MHz, DMSO) δ 9.05 (s, 1H), 7.14 (dd, J = 11.4, 10.0 Hz, 1H), 6.89 (dd, J = 10.0, 7.5 Hz, 1H), 5.70 (t, J = 5.5 Hz, 1H), 5.12 (s, 2H), 4.56 (dd, J = 5.5, 1.4 Hz, 2H).

LCMS: m/z = 243.1 $[\text{M}+\text{H}]^+$, (ESI+), RT = 0.50, Method D

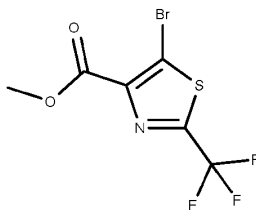
Example 252 – Synthesis of Ethyl 4-bromoisoxazole-3-carboxylate (Intermediate 53)



[0488] To a mixture of ethyl isoxazole-3-carboxylate (2.0 g, 14.17 mmol) and NBS (7.57 g, 42.5 mmol) at 0 °C, trifluoromethanesulfonic acid (20 mL, 0.227 mol) was added dropwise. The mixture was stirred at 0 °C for 30 min and then at r.t. overnight. The reaction mixture was quenched at 0 °C with sat. aq. NaHCO_3 (50 mL) and neutralized with solid Na_2CO_3 . The mixture was diluted with EtOAc (30 mL) and Et₂O (30 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (2 x 60 mL). The combined organic layers were washed with brine (100 mL) dried over Na_2SO_4 , filtered and concentrated. The residue was purified by FCC (50 g SiO_2 cartridge, 0-50% EtOAc in heptane) to afford the title compound as a white solid (1.19 g, 100% purity, 38% Yield) as a white solid.

^1H NMR (500 MHz, DMSO) δ 9.49 (s, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H).

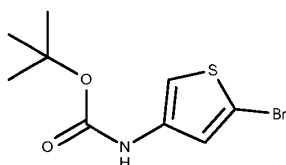
Example 253 – Synthesis of Methyl 5-bromo-2-(trifluoromethyl)thiazole-4-carboxylate



[0489] To a cooled (0 °C) solution of 5-bromo-2-(trifluoromethyl)thiazole-4-carboxylic acid (4.57 g, 16.56 mmol) in anhydrous MeOH (45 mL) was added thionyl chloride (6.0 mL, 82.7 mmol), dropwise. The reaction mixture was allowed to stir at 0 °C for 5 minutes before warming to r.t. and stirring for 17 h. The reaction mixture was quenched with water (100 mL)

and the product extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound as an off-white solid (4.58 g, 100% purity, 95% Yield). ^1H NMR (500 MHz, DMSO) δ 4.03 (s, 3H).

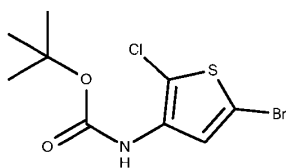
Example 254 – Synthesis of Tert-butyl N-(5-bromo-3-thienyl)carbamate (Intermediate 55)



[0490] To a solution of 5-bromothiophene-3-carboxylic acid (2.00 g, 9.66 mmol) in toluene (25 mL) was added DIPEA (2.0 mL, 11.5 mmol) 2-methylpropan-2-ol (11.7 mL, 123.28 mmol) and DPPA (2.5 mL, 11.7 mmol). The mixture was heated to 85 °C for 3 h. The mixture was cooled to r.t. and water (20 mL) was added and the aqueous layer was extracted with DCM (2 x 30 mL). The combined organic layers were washed with 1 M NaOH (20 mL) and brine (30 mL), passed through phase separator paper, and concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-20% EtOAc in heptane) to afford the title compound as a pale-yellow solid (1.97 g, 90% purity, 66% Yield). ^1H NMR (500 MHz, DMSO) δ 9.70 (s, 1H), 7.15 (s, 1H), 7.04 (d, J = 1.7 Hz, 1H), 1.46 (s, 9H).

LCMS: m/z = 221.8/223.8 [M-tButyl+H]⁺, (ESI⁻), RT = 1.06, Method D

Example 255 – Synthesis of Tert-butyl N-(5-bromo-2-chloro-3-thienyl)carbamate (Intermediate 56)

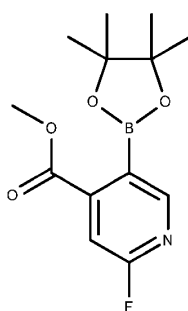


[0491] To a solution of *intermediate 55* (1.47 g, 4.76 mmol) in DMF (27 mL) was added 1-chloropyrrolidine-2,5-dione (700 mg, 5.24 mmol) and the reaction mixture was heated to 60 °C for 1.5 h. The reaction mixture was cooled to r.t. and water (30 mL) was added. The aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers were

washed with 1 M NaOH (30 mL) then brine (3 x 30 mL), passed through phase separator paper, and concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-20% EtOAc in heptane) to afford the title compound (1.41 g, 94% purity, 89% Yield) as an off white solid.

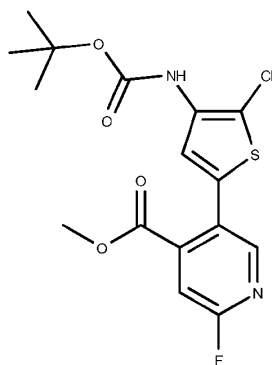
¹H NMR (400 MHz, MeOD) δ 7.26 (s, 1 H), 1.52 (s, 9 H). ¹H NMR (500 MHz, DMSO) δ 9.15 (s, 1H), 7.32 (s, 1H), 1.45 (s, 9H).

Example 256 – Synthesis of Methyl 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-4-carboxylate (Intermediate 57)



[0492] A mixture of bis(pinacolato)diboron (1.13 g, 4.45 mmol), *intermediate 8* (1.00 g, 4.27 mmol), and potassium acetate (1.26 g, 12.84 mmol) were combined in anhydrous 1,4-dioxane (20 mL). The reaction mixture was degassed with nitrogen for 10 mins then Pd(dppf)Cl₂ (314 mg, 0.428 mmol) was added and degassed for a further 5 mins. The reaction mixture was heated to 70 °C for 20 h. The mixture was allowed to cool to r.t. and then filtered through celite and washed with EtOAc (15 mL) with the solvent then removed under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-50% EtOAc in heptane) to afford the title compound (346 mg, 83% purity, 24% Yield) as colourless gum. ¹H NMR (500 MHz, DMSO) δ 8.42 (s, 1H), 7.55 – 7.49 (m, 1H), 3.89 (s, 3H), 1.32 (s, 12H). LCMS: m/z = 282.1 [M+H]⁺, (ESI⁺), RT = 0.95, Method D

Example 257 – Synthesis of Methyl 5-[4-(tert-butoxycarbonylamino)-5-chloro-2-thienyl]-2-fluoro-pyridine-4-carboxylate (Intermediate 58)

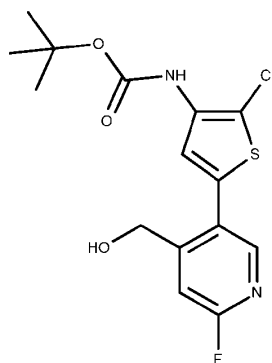


[0493] In a pressure vial, *intermediate 57* (700.0 mg, 2.49 mmol), *intermediate 56* (600 mg, 1.92 mmol) and potassium carbonate (800.0 mg, 5.79 mmol) were dissolved into a mixture of 1,4-dioxane (13 mL) and water (1.6 mL) and the solution was degassed with nitrogen for 10 minutes. To the mixture was added Pd(dppf)Cl₂ (145 mg, 0.198 mmol), before a further 5 mins' degassing. The mixture was heated to 70 °C for 16 h. The mixture was filtered through celite, washed with EtOAc (20 mL), and concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-40% EtOAc in heptane) to afford the title compound as an off-white gum (315 mg, 90% purity, 38% Yield).

¹H NMR (500 MHz, DMSO) δ 9.17 (s, 1H), 8.46 (s, 1H), 7.57 (d, J = 2.4 Hz, 1H), 7.31 (s, 1H), 3.83 (s, 3H), 1.46 (s, 9H).

LCMS: m/z = 331.0/333.0 [M-tButyl+H]⁺, (ESI⁺), RT = 1.10, Method D

Example 258 – Synthesis of Tert-butyl N-[2-chloro-5-[6-fluoro-4-(hydroxymethyl)-3-pyridyl]-3-thienyl]carbamate (Intermediate 59)

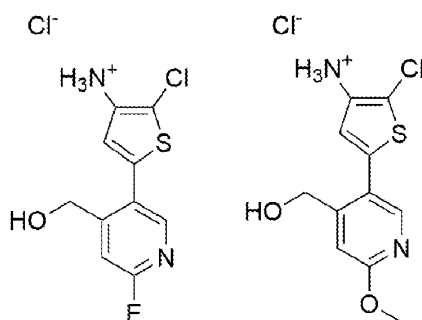


[0494] To a solution of *intermediate 58* (450.0 mg, 0.93 mmol) in THF (5.6 mL) and MeOH (0.8 mL) was added lithium borohydride (123 mg, 5.65 mmol) and the reaction mixture was stirred at r.t. for 30 mins. The reaction was quenched by slow addition of water (20 mL) and then concentrated to remove the THF/MeOH. The aqueous residue was extracted into EtOAc (3 x 30 mL), the combined organic phases were washed with brine (20 mL), passed through phase separator paper, and the solvent removed under reduced pressure to afford the title compound as a yellow oil (328 mg, 85% purity, 83% Yield).

¹H NMR (500 MHz, DMSO) δ 9.12 (s, 1H), 8.20 (s, 1H), 7.34 – 7.26 (m, 2H), 5.72 (t, J = 5.4 Hz, 1H), 4.61 (dd, J = 5.5, 1.0 Hz, 2H), 1.46 (s, 9H).

LCMS: m/z = 359.0/361.0 [M+H]⁺, (ESI⁺), RT = 0.96, Method D

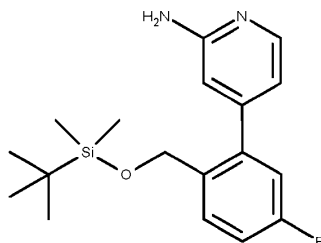
Example 259 – Synthesis of [2-Chloro-5-[6-fluoro-4-(hydroxymethyl)-3-pyridyl]-3-thienyl]ammonium chloride; [2-chloro-5-[4-(hydroxymethyl)-6-methoxy-3-pyridyl]-3-thienyl]ammonium chloride (1:1) (Intermediate 60)



[0495] To *intermediate 59* (328.0 mg, 0.78 mmol) was added 4 M HCl in 1,4-dioxane (2 mL, 8 mmol). The mixture was not in solution, so MeOH (2 mL) was added. The mixture was stirred at r.t. for 1.5 h. The mixture was then concentrated under reduced pressure to afford the title product mixture of [2-chloro-5-[4-(hydroxymethyl)-6-methoxy-3-pyridyl]-3-thienyl]ammonium chloride (380 mg, 0.3587 mmol, 46.168 % yield) and [2-chloro-5-[4-(hydroxymethyl)-6-methoxy-3-pyridyl]-3-thienyl]ammonium chloride (380 mg). The mixture was used directly in the next step without purification.

LCMS: m/z = 258.9/260.9 $[M+H]^+$, (ESI+), RT = 0.71; and 270.9/272.9 $[M+H]^+$, (ESI+), RT = 0.73, Method D

Example 260 – Synthesis of 4-[2-[[Tert-butyl(dimethyl)silyl]oxymethyl]-5-fluoro-phenyl]pyridin-2-amine (Intermediate 61)

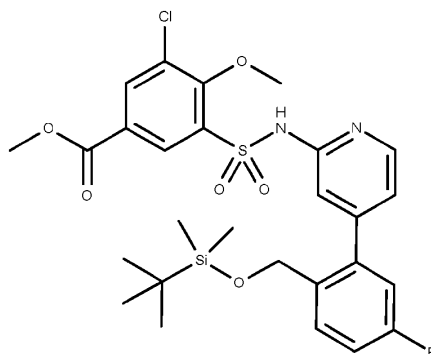


[0496] TBDMSCl (497 mg, 3.30 mmol) was added to a solution of [2-(2-amino-4-pyridyl)-4-fluoro-phenyl]methanol (*synthesised using a similar method to intermediate 3*, 600 mg, 2.75 mmol) and 1*H*-imidazole (234 mg, 3.44 mmol) in DMF (14 mL). The reaction was stirred for 1 hour then quenched into water. The aqueous layer was extracted into ethyl acetate (30 mL) three times, the combined organics washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by FCC (25 g SiO₂ cartridge, 0-20% EtOAc in heptane) to afford the title compound as a yellow oil (661 mg, 100% purity, 72% Yield) as a yellow oil.

¹H NMR (500 MHz, DMSO) δ 7.93 (dd, J = 5.2, 0.8 Hz, 1H), 7.54 (dd, J = 8.6, 6.0 Hz, 1H), 7.25 (td, J = 8.6, 2.8 Hz, 1H), 7.04 (dd, J = 9.6, 2.7 Hz, 1H), 6.48 (dd, J = 5.2, 1.5 Hz, 1H), 6.36 (s, 1H), 5.99 (s, 2H), 4.56 (s, 2H), 0.84 (s, 9H), -0.02 (s, 6H).

LCMS: m/z = 333.2 $[M+H]^+$, (ESI+), RT = 0.82, Method D

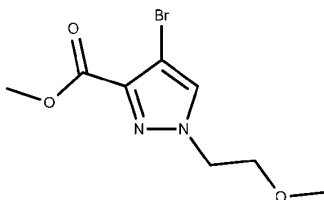
Example 261 – Synthesis of Methyl 3-[[4-[2-[[tert-butyl(dimethyl)silyl]oxymethyl]-5-fluoro-phenyl]-2-pyridyl]sulfamoyl]-5-chloro-4-methoxy-benzoate (Intermediate 62)



[0497] A solution of *intermediate 61* (660 mg, 1.99 mmol) in anhydrous THF (15 mL) was cooled to -78 °C and 1 M LiHMDS in THF (3.0 mL, 2.98 mmol) was added. The reaction was then stirred for 10 mins at -78 °C before a solution of *intermediate 1* (98%, 673 mg, 2.18 mmol) in anhydrous THF (4 mL) was added. The reaction was stirred for a further 3 h while warming to r.t. The mixture was carefully quenched with water (10 mL) and THF removed in vacuo. The aqueous residue was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by FCC (50 g SiO₂ cartridge, 0-40% EtOAc in heptane) to afford the title compound as a white solid (660 mg, 94% purity, 53% Yield).

¹H NMR (500 MHz, DMSO) δ 8.41 – 8.35 (m, 1H), 8.20 – 8.13 (m, 1H), 8.07 – 7.93 (m, 1H), 7.55 (dd, J = 8.6, 5.8 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.22 – 7.10 (m, 1H), 7.07 – 7.03 (m, 1H), 6.95 – 6.84 (m, 1H), 4.50 (s, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 0.74 (s, 9H), -0.14 (s, 6H).
LCMS: m/z = 595.2/597.2 [M+H]⁺, (ESI⁺), RT = 1.26, Method D

Example 262 – Synthesis of Methyl 4-bromo-1-(2-methoxyethyl)pyrazole-3-carboxylate (Intermediate 63)



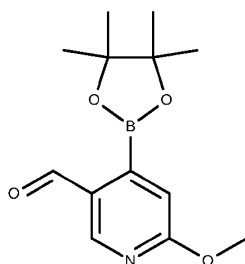
[0498] Sodium hydride (117 mg, 4.88 mmol) was added to a solution of methyl 4-bromo-1H-pyrazole-3-carboxylate (500 mg, 2.44 mmol) in THF (10 mL) at r.t. and stirred for 30

mins. 1-Bromo-2-methoxyethane (0.34 mL, 3.66 mmol) was added and the reaction left to stir for approximately 3 days. The reaction was quenched with pouring onto aq. sat. NaHCO_3 (25 mL). After extraction with EtOAc (2 x 20 mL), the combined org extracts were washed with brine (25 mL), dried (MgSO_4), filtered and concentrated. The residue was purified by FCC (25 g SiO_2 cartridge, 0-100% EtOAc in heptane) to afford the title compound (236 mg, 97% purity, 36% Yield) as a clear oil.

^1H NMR (500 MHz, DMSO) δ 8.12 (s, 1H), 4.33 (t, J = 5.2 Hz, 2H), 3.80 (s, 3H), 3.69 (t, J = 4.9 Hz, 2H), 3.22 (s, 3H).

LCMS: m/z = 285.0/287.0 $[\text{M}+\text{Na}]^+$, (ESI+), RT = 0.65, Method D

Example 263 – Synthesis of 6-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carbaldehyde (Intermediate 64)

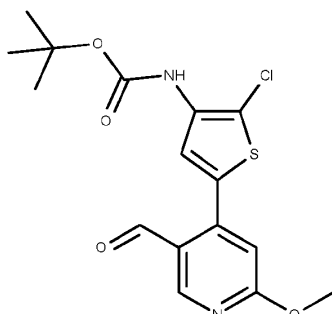


[0499] A mixture of bis(pinacolato)diboron (771 mg, 3.04 mmol), 4-chloro-6-methoxy-pyridine-3-carbaldehyde (500 mg, 2.91 mmol), and potassium acetate (860.0 mg, 8.76 mmol) were combined in anhydrous 1,4-dioxane (14 mL). The reaction mixture was degassed with nitrogen for 10 mins then XPhos (134 mg, 0.28 mmol) and $\text{Pd}_2(\text{dba})_3$ (133 mg, 0.15 mmol) were added and the mixture degassed for a further 5 mins. The reaction mixture was heated to 70 °C for 4 h. The reaction mixture was allowed to cool to r.t. and then filtered through celite and washed with EtOAc (15 mL) with the solvent then removed under reduced pressure. The residue was purified by FCC (25 g SiO_2 cartridge, 0-30% acetone in heptane) to afford the title compound (crude purity) as a dark red gum (706 mg, 42% Yield), which was used in the next step without further purification.

^1H NMR (400 MHz, DMSO) δ 10.04 (s, 1H), 8.75 (d, J = 0.8 Hz, 1H), 6.94 (d, J = 0.7 Hz, 1H), 3.96 (s, 3H), 1.34 (s, 12H).

LCMS: m/z = 182.0 $[\text{M}+\text{H}]^+$, (ESI+), RT = 0.35, Method D

Example 264 – Synthesis of Tert-butyl N-[2-chloro-5-(5-formyl-2-methoxy-4-pyridyl)-3-thienyl]carbamate (Intermediate 65)

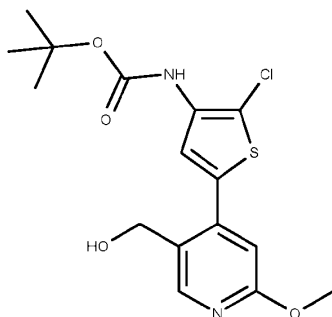


[0500] In a pressure vial, *intermediate 56* (473 mg, 1.51 mmol), *intermediate 63* (approx. 60% purity, 642 mg, 1.51 mmol) and potassium carbonate (672.0 mg, 4.86 mmol) were dissolved into a mixture of 1,4-dioxane (10 mL) and water (1 mL) and the solution was degassed with nitrogen for 10 minutes. To the mixture was added Pd(dppf)Cl₂ (112.0 mg, 0.15 mmol), before a further 5 mins' degassing. The mixture was heated to 70 °C for 1.5 h. The mixture was allowed to cool to r.t., diluted with EtOAc (20 mL), filtered through Celite (washing with EtOAc), and the filtrate concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-30% EtOAc in heptane) to afford the title compound as a colourless gum (382 mg, 71% purity, 49% Yield).

¹H NMR (500 MHz, DMSO) δ 10.05 (s, 1H), 8.74 (s, 1H), 6.94 (s, 1H), 3.96 (s, 3H), 1.33 (s, 12H).

LCMS: m/z = 369.0/371.0 [M+H]⁺, (ESI⁺), RT = 1.13, Method D

Example 265 – Synthesis of Tert-butyl N-[2-chloro-5-[5-(hydroxymethyl)-2-methoxy-4-pyridyl]-3-thienyl]carbamate (Intermediate 66)

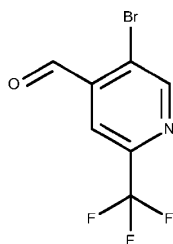


[0501] To a solution of *intermediate 65* (382 mg, 0.74 mmol) in THF (4 mL) and MeOH (0.7 mL) was added sodium borohydride (168 mg, 4.44 mmol) and the reaction mixture was stirred at r.t. for 30 mins. The reaction was quenched by slow addition of water (20 mL) and then concentrated to remove the THF/MeOH. The aqueous residue was extracted into DCM (3 x 30 mL), the combined organic phases were washed with brine (20 mL), passed through phase separator paper, and the solvent removed under reduced pressure to afford the title compound as a yellow solid (314 mg, 80% purity, 92% yield).

¹H NMR (500 MHz, DMSO) δ 9.10 (s, 1H), 8.23 (s, 1H), 7.66 (s, 1H), 6.81 (s, 1H), 5.35 (t, J = 5.1 Hz, 1H), 4.48 (d, J = 5.2 Hz, 2H), 3.87 (s, 3H), 1.46 (s, 9H).

LCMS: m/z = 371.0/373.0 [M+H]⁺, (ESI⁺), RT = 0.99, Method D

Example 266 – Synthesis of 5-Bromo-2-(trifluoromethyl)pyridine-4-carbaldehyde (Intermediate 67)

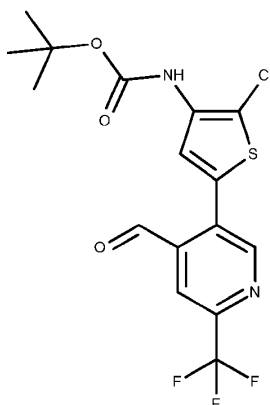


[0502] To a stirred solution of 2 M LDA (14 mL, 28.8 mmol) in THF (25 mL) was added 5-bromo-2-(trifluoromethyl)pyridine (5.00 g, 22.1 mmol) in THF (5 mL) slowly at -78 °C. The reaction mixture was left to stir at -78 °C for 1 h. Anhydrous DMF (2.44 mL, 28.7 mmol) was added dropwise and the mixture was stirred at -78 °C for 1 h. Sat. NH₄Cl (aq.) (50 mL) was added to the reaction mixture and then the product was extracted with EtOAc (3 x 50 mL), passed through phase separator paper, and concentrated. The residue was purified by FCC (50 g SiO₂ cartridge, 0-20% EtOAc in heptane) to afford the title compound as a red oil (3.35 g, 95% purity, 57% yield).

¹H NMR (400 MHz, DMSO) δ 10.18 (s, 1H), 9.19 (s, 1H), 8.10 (s, 1H).

LCMS: m/z = 271.9/273.9 [M+H]⁺, (ESI⁺), RT = 0.62, Method D

Example 267 – Synthesis of Tert-butyl N-[2-chloro-5-[4-formyl-6-(trifluoromethyl)-3-pyridyl]-3-thienyl]carbamate (Intermediate 68)



[0503] In a pressure vial, *intermediate 55* (550 mg, 1.76 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)pyridine-4-carbaldehyde (*synthesised from intermediate 67, using a similar method to intermediate 64*, 778 mg, 1.76 mmol) and potassium carbonate (780.0 mg, 5.64 mmol) were dissolved into a mixture of 1,4-dioxane (12 mL) and water (1.7 mL) and the solution was degassed with nitrogen for 10 minutes. To the mixture was added Pd(dppf)Cl₂ (129.0 mg, 0.18 mmol), before a further 5 mins' degassing. The mixture was heated to 70 °C for 16 h. The mixture was allowed to cool to r.t., diluted with EtOAc (20 mL), filtered through Celite (washing with EtOAc), and the filtrate concentrated under reduced pressure. The material was purified by FCC (25 g SiO₂ cartridge, 0-30% EtOAc in heptane) to afford the title compound as a yellow gum (330 mg, 62% purity, 29% Yield). Note: contains 31% wt of the des-chloro impurity.

Major component (title compound):

¹H NMR (500 MHz, DMSO) δ 10.18 (s, 1H), 9.27 (s, 1H), 9.07 (s, 1H), 8.11 (s, 1H), 7.62 (s, 1H), 1.47 (s, 9H).

LCMS: m/z = 405.1/407.1 [M-H]⁻, (ESI⁻), RT = 1.13, Method D

Minor component (des-chloro):

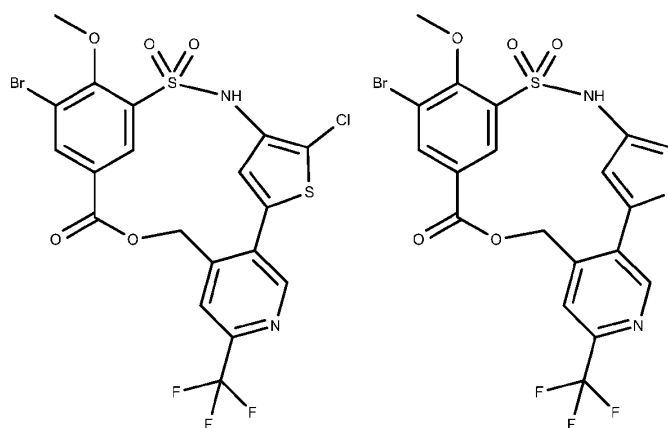
¹H NMR (500 MHz, DMSO) δ 10.18 (s, 1H), 9.84 (s, 1H), 9.08 (s, 1H), 8.06 (s, 1H), 7.55 (s, 1H), 7.34 (s, 1H), 1.48 (s, 9H).

LCMS: m/z = 373.1 [M+H]⁺, (ESI⁺), RT = 1.08, Method D

Example 268 – Synthesis of 19-Bromo-5-chloro-20-methoxy-2,2-dioxo-11-(trifluoromethyl)-15-oxa-2 λ 6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one (Intermediate 69)

and

Example 269 – Synthesis of 19-Bromo-20-methoxy-2,2-dioxo-11-(trifluoromethyl)-15-oxa-2 λ 6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one (Intermediate 70)



[0504] To a stirred solution of TCFH (185 mg, 0.659 mmol) and NMI (50.0 μ L, 0.630 mmol) in MeCN (40 mL) was added dropwise a mixture of 3-bromo-5-[[2-chloro-5-[4-(hydroxymethyl)-6-(trifluoromethyl)-3-pyridyl]-3-thienyl]sulfamoyl]-4-methoxy-benzoic acid (*synthesised from intermediate 68, using similar methods to intermediates 66 and 23*, 308 mg, 0.297 mmol, containing ~30% of the des-chloro species 3-bromo-5-[[5-[4-(hydroxymethyl)-6-(trifluoromethyl)-3-pyridyl]-3-thienyl]sulfamoyl]-4-methoxy-benzoic acid) and NMI (50 μ L, 0.630 mmol) in MeCN (10 mL). The reaction was stirred at r.t. for 1 h. The mixture was concentrated under reduced pressure and The residue was purified by FCC (10 g SiO₂ cartridge, 0-100% DCM in heptane, then 0-10% EtOAc in DCM) to afford two components:

The first eluting peak was and concentrated under reduced pressure to afford 19-bromo-5-chloro-20-methoxy-2,2-dioxo-11-(trifluoromethyl)-15-oxa-2 λ 6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one (Intermediate 69) (62 mg, 98% purity, 35% Yield) as a white solid.

¹H NMR (500 MHz, DMSO) δ 10.51 (s, 1H), 8.79 (s, 1H), 8.31 (d, J = 2.2 Hz, 1H), 8.19 (s, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.02 (s, 1H), 5.63 (s, 2H), 4.00 (s, 3H).

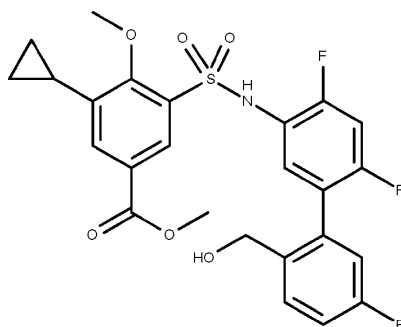
LCMS: m/z = 580.9/582.9/584.9 [M-H]⁻, (ESI⁻), RT = 1.10, Method D

The second eluting peak was combined and concentrated to afford 19-bromo-20-methoxy-2,2-dioxo-11-(trifluoromethyl)-15-oxa-2λ6,6-dithia-3,10-diazatetracyclo[15.3.1.14,7.08,13]docosa-1(21),4,7(22),8,10,12,17,19-octaen-16-one (Intermediate 70) (56.0 mg, 64% purity, 22% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 8.70 (s, 1H), 8.27 (d, J = 2.1 Hz, 1H), 7.70 (s, 1H), 7.46 (d, J = 2.1 Hz, 1H), 7.06 (s, 1H), 6.86 (s, 1H), 6.69 (s, 1H), 5.51 (s, 2H), 4.05 (s, 3H).

LCMS: m/z = 546.9/548.9 [M-H]⁻, (ESI⁻), RT = 1.07, Method D

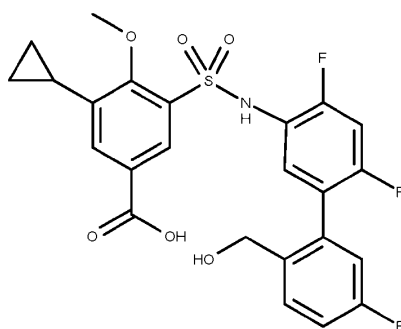
Example 270 – Synthesis of Methyl 3-cyclopropyl-5-[[2,4-difluoro-5-[5-fluoro-2-(hydroxymethyl)phenyl]phenyl]sulfamoyl]-4-methoxy-benzoate (Intermediate 71)



[0505] Methyl 3-bromo-5-[[2,4-difluoro-5-[5-fluoro-2-(hydroxymethyl)phenyl]phenyl]sulfamoyl]-4-methoxy-benzoate (*synthesised using a similar method to intermediate 22*, 400 mg, 0.714 mmol), cyclopropylboronic acid (92 mg, 1.07 mmol) and tripotassium phosphate (303 mg, 1.43 mmol) were dissolved in THF (7 mL) and water (0.7 mL). The mixture was degassed with N₂ for 5 mins and then palladium - triphenylphosphine (1:4) (42 mg, 0.0363 mmol) was added with a further 5 mins degassing. The mixture was heated to 70 °C for 16 h. Cyclopropylboronic acid (184 mg, 2.14 mmol) and Pd(dppf)Cl₂ (52 mg, 0.0711 mmol) were added and the mixture was degassed for 5 mins then heated to 70 °C for 4 h. The mixture was filtered through celite, washed with EtOAc, and concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-100% EtOAc in heptane, then 0-35% MeOH in EtOAc) to afford the title compound in crude purity, which was used in the next stage without further purification (529.0 mg). NMR not taken.

LCMS: m/z = 520.1 [M-H]⁻, (ESI⁻), RT = 1.01, Method D

Example 271 – Synthesis of 3-Cyclopropyl-5-[[2,4-difluoro-5-[5-fluoro-2-(hydroxymethyl)phenyl]phenyl]sulfamoyl]-4-methoxy-benzoic acid (Intermediate 72)

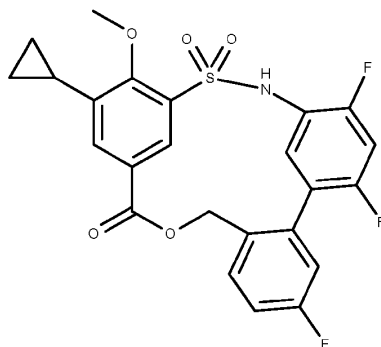


[0506] *Intermediate 71* (approx. 70% purity, 529 mg, 0.71 mmol) was dissolved in THF (10 mL) and 2 M aqueous sodium hydroxide (7.2 mL, 14.4 mmol) was added. The resulting solution was stirred at r.t. over the weekend. The THF was removed under reduced pressure and the aqueous layer was diluted with water (10 mL), extracted with DCM (3 x 15 mL) with the combined DCM layer discarded. The aqueous layer was acidified with 2 M HCl (8 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (25 mL), passed through phase separator paper, and concentrated under reduced pressure to afford the title compound as an off-white solid (270 mg, 88% purity, 66% Yield).

¹H NMR (500 MHz, DMSO) δ 13.25 (br. s, 1H), 10.12 (br. s, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.65 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = 8.7, 6.0 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.31 – 7.23 (m, 1H), 7.17 – 7.07 (m, 1H), 6.89 (dd, J = 9.4, 2.8 Hz, 1H), 5.14 (br. s, 1H), 4.15 (s, 2H), 3.93 (s, 3H), 2.19 – 2.10 (m, 1H), 1.12 – 1.04 (m, 2H), 0.75 (dt, J = 6.5, 3.2 Hz, 2H).

LCMS: m/z = 506.1 [M-H]⁻, (ESI⁻), RT = 0.88, Method D

Example 272 – Synthesis of 13-Cyclopropyl-4,19,21-trifluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.1.11,15.02,7]tricos-1(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Intermediate 73)

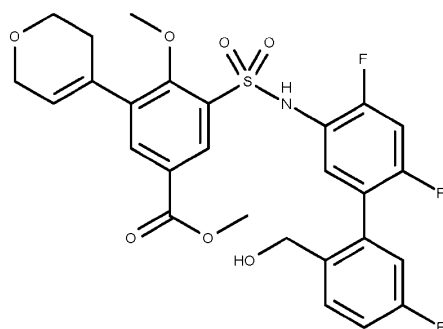


[0507] To a solution of *intermediate 72* (270 mg, 0.53 mmol) and DMAP (26 mg, 0.21 mmol) in DCM (30 mL) was added DCC (275 mg, 1.33 mmol) and the reaction mixture was stirred at r.t. for 3.5 h. The mixture was concentrated under reduced pressure and the residue was purified by FCC (25 g SiO₂ cartridge, 0-100% DCM in heptane) to afford the title compound as a colourless gum (88 mg, 93% purity, 31% Yield).

¹H NMR (500 MHz, DMSO) δ 10.14 (s, 1H), 7.63 (dd, J = 8.5, 5.8 Hz, 1H), 7.43 (d, J = 2.2 Hz, 1H), 7.41 – 7.22 (m, 4H), 7.02 – 6.95 (m, 1H), 5.40 (d, J = 12.8 Hz, 1H), 5.10 (d, J = 12.8 Hz, 1H), 3.98 (s, 3H), 2.22 – 2.13 (m, 1H), 1.08 – 0.99 (m, 2H), 0.78 – 0.68 (m, J = 4.8 Hz, 2H).

LCMS: m/z = 488.1 [M-H]⁻, (ESI⁻), RT = 1.08, Method D

Example 273 – Synthesis of Methyl 3-[[2,4-difluoro-5-[5-fluoro-2-(hydroxymethyl)phenyl]phenyl]sulfamoyl]-5-(3,6-dihydro-2H-pyran-4-yl)-4-methoxybenzoate (Intermediate 74)

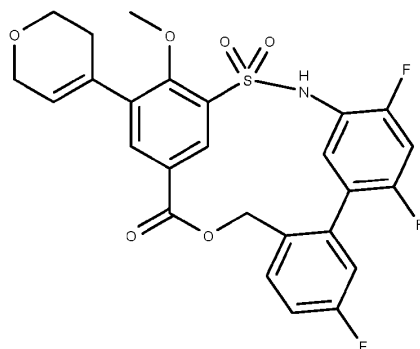


[0508] In a sealed vial methyl 3-chloro-5-[[2,4-difluoro-5-[5-fluoro-2-(hydroxymethyl)phenyl]phenyl]sulfamoyl]-4-methoxybenzoate (*synthesised using a similar method to intermediate 4*, 400 mg, 0.605 mmol) was dissolved in anhydrous 1,4-dioxane (4.2 mL), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran (140 mg, 0.666 mmol), water (0.4 mL) and caesium carbonate (789 mg, 2.42 mmol) were added. The reaction mixture was degassed with N₂ for 5 minutes then XPhos Pd G3 (53.0 mg, 0.06 mmol) was added and a further 5 minutes degassing. The reaction mixture was heated to 100 °C for 3.5 h. The mixture was filtered through celite, washing with EtOAc (20 mL). The organic layer was washed with water (2 x 20 mL), passed through phase separator paper, and concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-60% EtOAc in heptane) to afford the title compound as an off-white gum (305 mg, 80% purity, 72% Yield).

¹H NMR (500 MHz, DMSO) δ 10.18 (s, 1H), 8.14 (d, J = 2.2 Hz, 1H), 7.97 (d, J = 2.2 Hz, 1H), 7.59 (dd, J = 8.7, 6.0 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.30 – 7.25 (m, 1H), 7.21 – 7.13 (m, 1H), 6.94 (dd, J = 9.4, 2.8 Hz, 1H), 6.05 – 6.02 (m, 1H), 5.14 (t, J = 5.6 Hz, 1H), 4.23 (q, J = 2.7 Hz, 2H), 4.15 (d, J = 4.8 Hz, 2H), 3.85 (s, 3H), 3.81 (t, J = 5.3 Hz, 2H), 3.78 (s, 3H), 2.38 – 2.28 (m, 2H).

LCMS: m/z = 562.2 [M-H]⁻, (ESI⁻), RT = 0.97, Method D

Example 274 – Synthesis of 13-(3,6-Dihydro-2H-pyran-4-yl)-4,19,21-trifluoro-14-methoxy-16,16-dioxo-9-oxa-16 λ 6-thia-17-azatetracyclo[16.3.1.111,15.02,7]tricosal(21),2,4,6,11(23),12,14,18(22),19-nonaen-10-one (Intermediate 75)

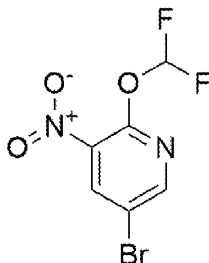


[0509] To a stirred solution of 3-[[2,4-difluoro-5-[5-fluoro-2-(hydroxymethyl)phenyl]phenyl]sulfamoyl]-5-(3,6-dihydro-2H-pyran-4-yl)-4-methoxybenzoic acid (*synthesised from intermediate 74, using a similar method to intermediate 72*, 80% purity, 281 mg, 0.41 mmol) in MeCN (32 mL) was added NMI (130 μ L, 1.64 mmol). TCFH (147.0 mg, 0.52 mmol) was added and the reaction was stirred at r.t. for 2 h. The mixture was concentrated under reduced pressure and the residue was purified by FCC (10 g SiO₂ cartridge, 0-20% DCM in EtOAc) to afford the title compound as a colourless gum (174 mg, 88% purity, 70% Yield).

¹H NMR (500 MHz, DMSO) δ 10.21 (s, 1H), 7.77 (d, J = 2.3 Hz, 1H), 7.68 – 7.60 (m, 1H), 7.41 (d, J = 2.3 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.28 (dd, J = 9.3, 2.7 Hz, 1H), 7.09 – 7.02 (m, 1H), 6.00 (tt, J = 2.8, 1.5 Hz, 1H), 5.41 (d, J = 13.2 Hz, 1H), 5.14 (d, J = 12.7 Hz, 1H), 4.21 (q, J = 2.8 Hz, 2H), 3.86 (s, 3H), 3.80 (t, J = 5.4 Hz, 2H), 2.40 – 2.35 (m, 2H).

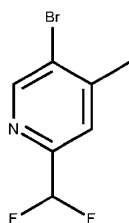
LCMS: m/z = 530.1 [M-H]⁻, (ESI⁻), RT = 1.04, Method D

Example 275 – Synthesis of 5-Bromo-2-(difluoromethoxy)-3-nitro-pyridine (Intermediate 76)



[0510] 5-bromo-3-nitropyridin-2-ol (1.00 g, 4.57 mmol) was dissolved in anhydrous MeCN (46 mL). To this was then added sodium hydride (512 mg, 12.8 mmol) in one rapid portion and the resulting mixture was stirred at r.t. for 10 min to afford a yellow suspension. Then, difluoro(fluorosulfonyl)acetic acid (0.850 mL, 8.22 mmol) was added neat and dropwise over a period of 5 min. After 1 h, further difluoro(fluorosulfonyl)acetic acid (1.20 mL, 11.6 mmol) was added over 5 mins and the mixture was stirred for 1 h. A final portion of difluoro(fluorosulfonyl)acetic acid (1.00 mL, 9.67 mmol) was added over 5 mins and the mixture was stirred for 1 h. The reaction was quenched with ice water (20 mL) and extracted with EtOAc (3 x 50 mL), the combined organic layers were washed with sat NaHCO₃ (30 mL) and brine (30 mL), passed through phase separator paper, and concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-20% EtOAc in heptane) to afford the title compound as a yellow oil (820 mg, 100% purity, 67% yield). ¹H NMR (400 MHz, DMSO) δ 8.91 (d, J = 2.3 Hz, 1H), 8.79 (d, J = 2.3 Hz, 1H), 7.77 (t, J = 70.8 Hz, 1H).

Example 276 – Synthesis of 5-Bromo-2-(difluoromethyl)-4-methyl-pyridine (Intermediate 77)



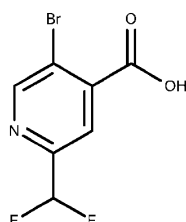
[0511] To a solution of 5-bromo-4-methylpicolinaldehyde (1.00 g, 5.00 mmol) in DCM (30.0 mL) at -78 °C was added DAST (2.00 g, 12.4 mmol). The reaction mixture was allowed

to warm up to r.t and stirred overnight. The reaction mixture was quenched with 2 M aq. NaOH (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-40% EtOAc in heptane) to afford the title compound (866 mg, 97% purity, 76% yield) as a brown liquid.

¹H NMR (400 MHz, DMSO) δ 8.77 (s, 1H), 7.73 (s, 1H), 6.93 (t, J = 54.8 Hz, 1H), 2.44 (s, 3H).

LCMS: m/z = 221.8/223.8 [M+H]⁺, (ESI⁺), RT = 0.89, Method D

Example 277 – Synthesis of 5-Bromo-2-(difluoromethyl)pyridine-4-carboxylic acid (Intermediate 78)

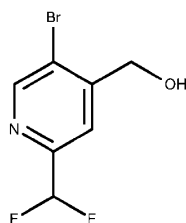


[0512] A solution of *intermediate 77* (800 mg, 3.50 mmol) and potassium permanganate (2.80 g, 17.7 mmol) in water (25.0 mL) was stirred at 90 °C for 24 hours. After cooling to room temperature, the reaction mixture was acidified with 2 M hydrochloric acid (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated to afford the title compound (231 mg, 93% purity, 24% yield) as a white solid.

¹H NMR (400 MHz, DMSO) δ 8.99 (s, 1H), 7.94 (s, 1H), 7.03 (t, J = 54.5 Hz, 1H).

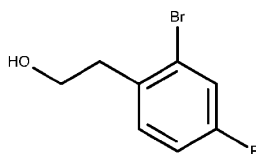
LCMS: m/z = 251.9/253.8 [M+H]⁺, (ESI⁺), RT = 0.47, Method D

Example 278 – Synthesis of [5-Bromo-2-(difluoromethyl)-4-pyridyl]methanol (Intermediate 79)



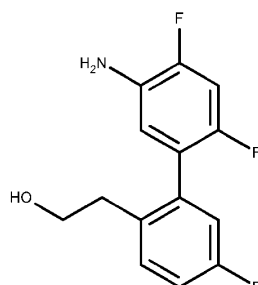
[0513] Sodium borohydride (90 mg, 2.38 mmol) was added over 5 minutes to an ice-cooled solution of *intermediate 78* (225 mg, 0.830 mmol) in anhydrous THF (5 mL). The reaction was stirred for 5 minutes before BF₃ etherate (0.14 mL, 1.13 mmol) was added (over 5 minutes). The reaction was stirred for 10 minutes then the cooling bath was removed and the reaction stirred for 3 h. The reaction was quenched by cautious addition of MeOH (cooling in ice/water) and 30 minutes stirring. The solvent volume was reduced by rotary evaporation (to approx. 5 mL) and the residue was taken up into water/ethyl acetate (1:1, ~50 mL). The biphasic mixture was separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL) before the combined organics were washed with brine (50 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by FCC (25 g SiO₂ cartridge, 0-80% EtOAc in heptane) to afford the title compound (66.0 mg, 100% purity, 33% yield) as a white solid. ¹H NMR (400 MHz, DMSO) δ 8.76 (d, J = 0.7 Hz, 1H), 7.81 (s, 1H), 7.01 (t, J = 54.8 Hz, 1H), 5.85 (s, 1H), 4.58 (s, 2H). LCMS: m/z = 238.1/240.1 [M+H]⁺, (ESI⁺), RT = 0.62, Method D

Example 279 – Synthesis of 2-(2-Bromo-4-fluoro-phenyl)ethanol (Intermediate 80)



[0514] Sodium borohydride (1.37 g, 36.1 mmol) was added over 5 minutes to an ice-cold solution of 2-(2-bromo-4-fluoro-phenyl)acetic acid (3.90 g, 16.7 mmol) in THF (31.2 mL). The reaction was stirred for 5 minutes then BF₃ etherate (2.15 mL, 17.4 mmol) was added over 5 minutes. The reaction was stirred for 10 minutes then the cooling bath removed and the reaction stirred for 1.5 hours. The reaction was quenched by cautious addition of MeOH (30 mL) (cooling in ice/water) and stirred for 30 minutes. The solvent was removed under reduced pressure and the residue taken up in water/EtOAc (1:1, 100 mL). The aqueous layer was extracted into EtOAc (2 x 50 mL), the combined organics washed with brine (50 mL), passed through phase separator paper, and the solvent removed under reduced pressure to afford the title compound (3.78 g, 94% purity, 97% yield) as colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.31 (dd, J = 8.3, 2.6 Hz, 1H), 7.25 (dd, J = 8.5, 6.0 Hz, 1H), 7.02 – 6.95 (m, 1H), 3.86 (t, J = 6.6 Hz, 2H), 3.00 (t, J = 6.6 Hz, 2H).

Example 280 – Synthesis of 2-[2-(5-Amino-2,4-difluoro-phenyl)-4-fluoro-phenyl]ethanol (Intermediate 81)

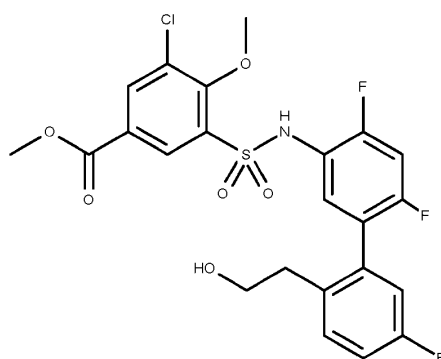


[0515] To a solution of *Intermediate 80* (1.0 g, 4.29 mmol) and *Intermediate 2* (1.46 g, 5.44 mmol) in 1,4-dioxane (31.7 mL) and water (7.9 mL) was added potassium carbonate (1.19 g, 8.6 mmol) and the mixture was degassed with N₂ for 10 mins. Pd(dppf)Cl₂ (0.317 g, 0.43 mmol) was added and the reaction mixture was degassed again for another 5 mins. The vessel was then sealed and its contents stirred at 100 °C for 18 h. The mixture was filtered through a pad of celite and concentrated in vacuo. The residue was purified by FCC (25 g SiO₂ cartridge, eluting with 0-75% EtOAc in heptane) to afford the title compound (1.55 g, 68% purity, 92% yield) as a colourless oil.

¹H NMR (400 MHz, DMSO) δ 7.42 – 7.34 (m, 1H), 7.21 – 7.06 (m, 2H), 7.02 – 6.94 (m, 1H), 6.69 – 6.60 (m, 1H), 5.10 (s, 2H), 4.59 (t, J = 5.2 Hz, 1H), 3.39 (td, J = 7.4, 5.3 Hz, 2H), 2.58 (t, J = 7.4 Hz, 2H).

LCMS: m/z = 268.2 [M+H]⁺, (ESI⁺), RT = 0.79, Method D

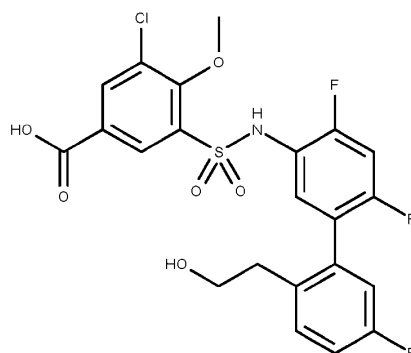
Example 281 – Synthesis of Methyl 3-chloro-5-[[2,4-difluoro-5-[5-fluoro-2-(2-hydroxyethyl)phenyl]phenyl]sulfamoyl]-4-methoxy-benzoate (Intermediate 82)



[0516] *Intermediate 81* (68% purity, 875 mg, 2.23 mmol) and *Intermediate 1* (98% purity, 695 mg, 2.28 mmol) were dissolved in anhydrous pyridine (17 mL) and the mixture was heated to 50 °C and stirred for 1 h in a pressure vial. The reaction mixture was allowed to cool to r.t. and then diluted with 1 M aq. HCl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), passed through a phase separator, and concentrated under reduced pressure. The crude material was purified by FCC (25 g SiO₂ cartridge, 0 - 100% EtOAc in heptane) to afford the title compound as a yellow oil (791 mg, 75% purity, 50% Yield).

¹H NMR (500 MHz, DMSO) δ 10.44 (s, 1H), 8.25 (d, J = 2.1 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 7.47 – 7.34 (m, 2H), 7.25 – 7.17 (m, 1H), 7.15 – 7.08 (m, 1H), 6.92 (dd, J = 9.4, 2.8 Hz, 1H), 4.51 (t, J = 5.2 Hz, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.30 (q, 2H), 2.44 (t, J = 7.1 Hz, 2H).
LCMS: m/z = 528.1/530.0 [M-H]⁻, (ESI⁻), RT = 1.00, Method D

Example 282 – Synthesis of 3-Chloro-5-[[2,4-difluoro-5-[5-fluoro-2-(2-hydroxyethyl)phenyl]phenyl]sulfamoyl]-4-methoxy-benzoic acid (Intermediate 83)

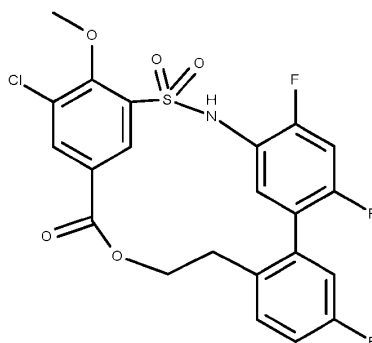


[0517] *Intermediate 82* (791 mg, 1.12 mmol) was dissolved in THF (5 mL) and 2 M sodium hydroxide (5.6 mL, 11.2 mmol) was added. The resulting solution was stirred at r.t. overnight. The THF was removed under reduced pressure and the remaining aqueous solution was added to DCM (25 mL) and acidified with 1 M HCl (50 mL). The layers were separated and the aqueous phase was extracted with additional DCM (3 x 25 mL), before the combined organic phases were washed with brine (50 mL), filtered and concentrated under reduced pressure to afford the title compound as an orange oil (775 mg, 70% purity, 94% Yield) as an orange oil.

¹H NMR (500 MHz, DMSO) δ 10.40 (s, 1H), 8.21 (d, J = 2.1 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 7.47 – 7.36 (m, 2H), 7.25 – 7.16 (m, 1H), 7.16 – 7.09 (m, 1H), 6.92 (dd, J = 9.4, 2.8 Hz, 1H), 4.51 (s, 1H), 3.95 (s, 3H), 2.46 (t, J = 7.0 Hz, 2H).

LCMS: m/z = 514.0/516.0 [M-H]⁻, (ESI⁻), RT = 0.88, Method D

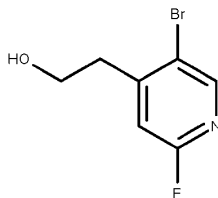
Example 283 – Synthesis of 14-Chloro-4,20,22-trifluoro-15-methoxy-17,17-dioxo-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.1.12,16.02,7]tetracos-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (Intermediate 84)



[0518] To a solution of DCC (434 mg, 2.10 mmol), *Intermediate 83* (70% purity, 775 mg, 1.05 mmol) in anhydrous DCM (20 mL) was added DMAP (32 mg, 0.263 mmol). The reaction mixture was stirred at r.t. for 3 h. NaHCO₃ (sat. aq., 50 mL) was added, the mixture was separated and the aqueous phase extracted with DCM (2 x 50 mL). The combined organic fractions were washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by FCC (25 g SiO₂ cartridge, 20 - 100% DCM in heptane) to afford the title compound as a white solid (216 mg, 99% purity, 41% Yield).

¹H NMR (400 MHz, DMSO) δ 10.16 (s, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.66 – 7.54 (m, 2H), 7.50 (d, J = 2.1 Hz, 1H), 7.32 – 7.22 (m, 1H), 6.89 (dd, J = 9.5, 2.8 Hz, 1H), 6.72 – 6.63 (m, 1H), 4.54 (t, J = 11.4 Hz, 1H), 4.29 (d, J = 10.8 Hz, 1H), 3.97 (s, 3H), 3.03 (d, J = 14.7 Hz, 1H), 2.80 (dd, J = 15.0, 12.1 Hz, 1H).

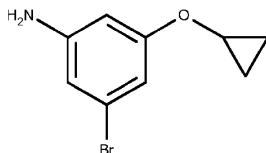
LCMS: m/z = 496.0/498.0 [M-H]⁻, (ESI⁻), RT = 1.04, Method D

Example 284 – Synthesis of 2-(5-Bromo-2-fluoro-4-pyridyl)ethanol (Intermediate 85)

[0519] To a solution of 5-bromo-2-fluoro-4-methylpyridine (2.5 g, 13.16 mmol) in anhydrous THF (25 mL) at -78 °C was added slowly 2 M LDA in THF/hexanes/ethylbenzene (16.45 mL, 32.89 mmol). The mixture was stirred at -78 °C for 1 h. Paraformaldehyde (1.07 g, 32.89 mmol) was added and the mixture was allowed to warm to r.t. overnight. The mixture was quenched with sat. aq. NH₄Cl (10 mL) and the THF removed under vacuum. Further sat. aq. NH₄Cl (50 mL) was added and the mixture extracted with EtOAc (3 x 50 mL). The combined organic was washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated. The residue was purified by FCC (28 g KP-Amino cartridge, 0-20% MeOH in DCM) to afford the title compound as a yellow oil (1.21 g, 94% purity, 39% Yield).

¹H NMR (500 MHz, DMSO) δ 8.38 (d, J = 0.8 Hz, 1H), 7.23 (d, J = 1.9 Hz, 1H), 4.85 (t, J = 5.3 Hz, 1H), 3.68 (td, J = 6.5, 5.2 Hz, 2H), 2.89 (t, J = 6.5 Hz, 2H).

LCMS: m/z = 219.9/221.9 [M+H]⁺, (ESI⁺), RT = 0.60, Method D

Example 285 – Synthesis of 3-Bromo-5-(cyclopropoxy)aniline (Intermediate 86)Step 1

[0520] To a solution of 1-bromo-3-fluoro-5-nitrobenzene (1.00 g, 4.55 mmol) in anhydrous DMF (20 mL) at r.t. were added dicaesium carbonate (2.221 g, 6.82 mmol) and cyclopropanol (343 mg, 5.91 mmol). The reaction mixture was stirred at 80 °C for 16 hours in a sealed tube. The mixture was taken up in EtOAc (50 mL) and the organics washed with 2 x 40 ml water then 1 x 40 ml saturated brine solution. The organic layer was dried (MgSO₄) before concentration to dryness. The crude was then purified by FCC (SiO₂ cartridge, 0-10% EtOAc in heptane) to afford the 1-bromo-3-(cyclopropoxy)-5-nitro-benzene as a yellow oil (483 mg, 90% purity, 37% Yield).

^1H NMR (500 MHz, CDCl_3) δ 7.98 (t, J = 1.8 Hz, 1H), 7.84 (t, J = 2.2 Hz, 1H), 7.48 (dd, J = 2.3, 1.7 Hz, 1H), 3.85 – 3.78 (m, 1H), 0.91 – 0.87 (m, 2H), 0.84 – 0.80 (m, 2H).

LCMS: m/z = 255.9/257.9 $[\text{M}+\text{H}]^+$, (ESI+), RT = 1.09, Method D

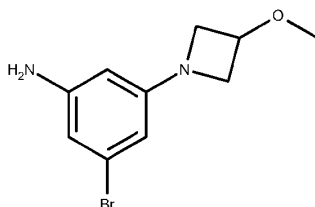
Step 2

[0521] 1-bromo-3-(cyclopropoxy)-5-nitro-benzene (480 mg, 1.86 mmol) was added to a mixture of iron (1.35 g, 24.18 mmol) and ammonium chloride (1.59 g, 29.8 mmol) in ethanol (12 mL) and water (4 mL). The reaction was heated to 80 °C for 1.5 h. The mixture was allowed to cool to r.t. and then filtered through a pad of celite, washing with EtOAc (20 mL). The filtrate was concentrated under reduced pressure. The crude material was taken up in EtOAc (50 mL) and the organics washed with 2 x 40 mL water then 1 x 40 mL saturated brine solution. The organic layer dried (MgSO_4) before concentration to dryness. The crude was then purified by FCC (25 g SiO_2 cartridge, 0-50% EtOAc in heptane) to afford the title compound (383 mg, 90% purity, 81% Yield) as a pale-yellow solid.

^1H NMR (500 MHz, DMSO) δ 6.35 (m, 1H), 6.33 (m, 1H), 6.21 (m, 1H), 5.40 (s, 2H), 3.75 – 3.68 (m, 1H), 0.75 – 0.69 (m, 2H), 0.66 – 0.55 (m, 2H).

LCMS: m/z = 227.9/229.9 $[\text{M}+\text{H}]^+$, (ESI+), RT = 0.88, Method D

Example 286 – Synthesis of 3-Bromo-5-(3-methoxyazetidin-1-yl)aniline (Intermediate 87)



Step 1

[0522] To a pressure vial was added 1-bromo-3-fluoro-5-nitrobenzene (500.0 mg, 2.27 mmol), 3-methoxyazetidine hydrochloride (1:1) (422.0 mg, 3.41 mmol), dipotassium carbonate (786.0 mg, 5.69 mmol), and DMF (7 mL). The mixture was heated to 100 °C for 3 h. The mixture was allowed to cool to r.t. and then diluted with water (20 mL) and EtOAc (30 mL). The aqueous layer was further extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (30 mL), passed through phase separator paper, and concentrated under reduced pressure. The residue was purified by FCC (25 g SiO_2 cartridge,

0-30% EtOAc in heptane) to afford 1-(3-bromo-5-nitro-phenyl)-3-methoxy-azetidine (371 mg, 98% purity, 56% Yield) as an orange oil.

^1H NMR (500 MHz, CDCl_3) δ 7.68 – 7.63 (m, 1H), 7.15 – 7.10 (m, 1H), 6.81 – 6.76 (m, 1H), 4.38 (tt, J = 6.2, 4.2 Hz, 1H), 4.20 – 4.13 (m, 2H), 3.85 – 3.78 (m, 2H), 3.35 (s, 3H).

LCMS: m/z = 286.9/288.9 $[\text{M}+\text{H}]^+$, (ESI+), RT = 1.03, Method D

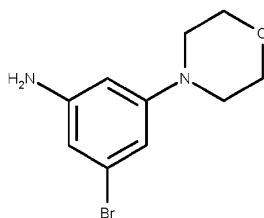
Step 2

[0523] 1-(3-bromo-5-nitro-phenyl)-3-methoxy-azetidine (371 mg, 1.29 mmol) was added to a solution of iron (0.99 g, 17.73 mmol) and ammonium chloride (1.14 g, 21.3 mmol) in ethanol (8 mL) and water (3 mL). The reaction was heated to 80 °C for 1 h, then diluted with EtOAc (15 mL), filtered through a pad of celite, washing with more EtOAc (20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by FCC (25 g SiO_2 cartridge, 0-50% EtOAc in heptane) to afford the title compound (306 mg, 99% purity, 91% Yield) as a yellow gum.

^1H NMR (500 MHz, DMSO) δ 6.11 – 6.07 (m, 1H), 5.77 – 5.72 (m, 1H), 5.59 – 5.55 (m, 1H), 5.18 (s, 2H), 4.25 (tt, J = 6.1, 4.2 Hz, 1H), 3.94 (ddd, J = 7.3, 6.1, 0.9 Hz, 2H), 3.55 – 3.47 (m, 2H), 3.22 (s, 3H).

LCMS: m/z = 256.9/258.9 $[\text{M}+\text{H}]^+$, (ESI+), RT = 0.72, Method D

Example 287 – Synthesis of 3-Bromo-5-morpholino-aniline (Intermediate 88)



Step 1

[0524] To a pressure vial was added 1-bromo-3-fluoro-5-nitrobenzene (500.0 mg, 2.27 mmol), morpholine (0.3 mL, 3.43 mmol), dipotassium carbonate (630.0 mg, 4.56 mmol), and DMF (7 mL). The mixture was heated to 100 °C for 5 h. The reaction was retreated with morpholine (0.4 mL, 4.57 mmol) and left to stir at 100 °C for a further 4 h before cooling to r.t. Water (20 mL) and EtOAc (50 mL) were added, the aqueous layer was further extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with brine (30 mL), passed through phase separator paper, and concentrated under reduced pressure. The residue

was purified by FCC (25 g SiO₂ cartridge, 0-30% EtOAc in heptane) to afford 4-(3-bromo-5-nitro-phenyl)morpholine (514 mg, 99% purity, 78% Yield) as a bright yellow solid.

¹H NMR (500 MHz, CDCl₃) δ 7.80 (t, J = 1.8 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.29 – 7.24 (m, 1H), 3.90 – 3.84 (m, 4H), 3.28 – 3.23 (m, 4H).

LCMS: m/z = 286.9/288.9 [M+H]⁺, (ESI⁺), RT = 0.98, Method D

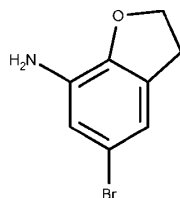
Step 2

[0525] 4-(3-bromo-5-nitro-phenyl)morpholine (99%, 514 mg, 1.77 mmol) was added to a solution of iron (1.36 g, 24.35 mmol) and ammonium chloride (1.56 g, 29.2 mmol) in ethanol (11 mL) and water (3.5 mL). The reaction was heated to 80 °C for 1 h. The mixture was allowed to cool to r.t. and then filtered through a pad of celite, washing with EtOAc (20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-50% EtOAc in heptane) to afford the title compound (480 mg, 95% purity, 100% Yield) as a colourless gum.

¹H NMR (500 MHz, DMSO) δ 6.27 – 6.20 (m, 2H), 6.10 – 6.06 (m, 1H), 5.20 (s, 2H), 3.72 – 3.64 (m, 4H), 3.03 – 2.98 (m, 4H).

LCMS: m/z = 257.0/259.0 [M+H]⁺, (ESI⁺), RT = 0.67, Method D

Example 288 – Synthesis of 5-Bromo-2,3-dihydrobenzofuran-7-amine (Intermediate 89)



Step 1

[0526] To a solution of 5-bromo-2,3-dihydro-1-benzofuran-7-carboxylic acid (350 mg, 1.44 mmol) in anhydrous toluene (3 mL) was added N-ethyl-N-(propan-2-yl)propan-2-amine (0.30 mL, 1.72 mmol) 2-methylpropan-2-ol (1.75 mL, 18.44 mmol), and diphenyl phosphoril azide (0.35 mL, 1.63 mmol). The mixture was heated to 85 °C for 2 h. The mixture was concentrated under reduced pressure, the residue was redissolved in EtOAc (20 mL) and washed with sat NaHCO₃ (30 mL) and the aqueous layer was further extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (30 mL), passed through phase separator paper, and concentrated under reduced pressure. The residue was purified by

FCC (25 g SiO₂ cartridge, 0-45% DCM in heptane) to afford tert-butyl N-(5-bromo-2,3-dihydrobenzofuran-7-yl)carbamate (314 mg, 97% purity, 67% Yield) as a colourless gum.

¹H NMR (500 MHz, DMSO) δ 8.58 (s, 1H), 7.49 (s, 1H), 7.14 – 7.10 (m, 1H), 4.55 (t, J = 8.8 Hz, 2H), 3.20 (t, J = 8.7 Hz, 2H), 1.43 (s, 9H).

LCMS: m/z = 312.0/313.9 [M-H]⁻, (ESI⁻), RT = 0.92, Method E

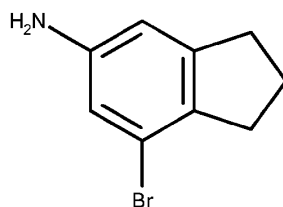
Step 2

[0527] To a solution of tert-butyl N-(5-bromo-2,3-dihydrobenzofuran-7-yl)carbamate (314.0 mg, 1.0 mmol) in DCM (5 mL) was added trifluoroacetic acid (1.0 mL, 13.06 mmol) and the mixture was stirred at r.t. for 45 mins. The mixture was diluted with DCM (20 mL) and sat. NaHCO₃ (20 mL) was added and the mixture was left to stir for 15 mins. The aqueous layer was then further extracted with DCM (2 x 30 mL). The combined organic layers were washed with brine (30 mL), passed through phase separator paper, and the solvent removed under reduced pressure to afford the title compound (224 mg, 93% purity, 97% Yield) as an off white solid.

¹H NMR (500 MHz, DMSO) δ 6.61 – 6.56 (m, 2H), 4.92 (s, 2H), 4.49 (t, J = 8.8 Hz, 2H), 3.15 – 3.08 (m, 2H).

LCMS: m/z = 213.9/215.9 [M+H]⁺, (ESI⁺), RT = 0.79, Method D

Example 289 – Synthesis of 7-Bromoindan-5-amine (Intermediate 90)

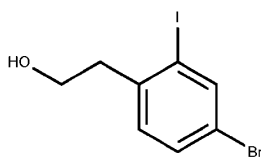


[0528] 5-Nitro-2,3-dihydro-1H-indene (2.0 g, 12.26 mmol) and aluminium trichloride (4.1 g, 30.75 mmol) were dissolved in anhydrous DCM (30 mL) and bromine (2.0 mL, 38.8 mmol) was added dropwise at 0 °C. The mixture was stirred at r.t. for 46 h. Further bromine (0.3 mL, 5.82 mmol) and aluminium trichloride (600.0 mg, 4.5 mmol) were added and stirring was continued at r.t. for 58 h. The mixture was quenched by the slow addition of an aqueous saturated solution of sodium thiosulfate (50 mL) at 0 °C and diluted with water (50 mL) and EtOAc (100 mL). The biphasic mixture was separated and the aqueous layer was further extracted with EtOAc (2 x 100 mL). The combined organic layers were then washed with brine (50 mL), passed through phase separator paper, and concentrated under reduced

pressure. The residue was purified by FCC (50 g SiO₂ cartridge, 0-25% EtOAc in heptane) followed by FCC (50 g SiO₂ cartridge, 0-100% DCM in heptane) to afford 4-bromo-6-nitro-indane (1.40 g, 46% purity, 22% Yield).

[0529] Iron (2.05 g, 36.7 mmol) was added to a solution of 4-bromo-6-nitro-indane (46%, 1.40 g, 2.66 mmol) and ammonium chloride (2.34 g, 43.7 mmol) in ethanol (16 mL) and water (5 mL) and the mixture was heated to 80 °C for 1.5 h. The mixture was allowed to cool to r.t. and then filtered through a pad of celite, washing with EtOAc. The filtrate was concentrated under reduced pressure, and then partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 30 mL) and the combined organics washed with brine (50 mL), passed through phase separator paper and concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-100% EtOAc in heptane) to afford the title compound (833 mg, 48% purity, 71% Yield).
¹H NMR (500 MHz, CDCl₃) δ 6.69 – 6.65 (m, 1H), 6.52 (d, J = 2.1 Hz, 1H), 3.60 (br s, 2H), 2.91 (t, J = 7.5 Hz, 2H), 2.86 – 2.77 (m, 2H), 2.10 – 1.99 (m, 2H).
LCMS: m/z = 212.1/214.1 [M+H]⁺, (ESI⁺), RT = 0.79, Method D

Example 290 – Synthesis of 2-(4-Bromo-2-iodo-phenyl)ethanol (Intermediate 91)



Step 1

[0530] Sodium borohydride (1.75 g, 46.3 mmol) was added over 5 minutes to an ice-cooled solution of 4-bromo-2-iodobenzoic acid (5.00 g, 15.3 mmol) in anhydrous THF (50 mL). The mixture was stirred for 5 minutes before BF₃ etherate (48%, 5.5 mL, 21.4 mmol) was added (over 5 minutes). The mixture was stirred for 10 minutes then the cooling bath removed and the mixture stirred for 3 hours. The reaction was quenched by cautious addition of methanol (cooling in ice/water) and 30 minutes' stirring. The solvent volume was reduced by rotary evaporation (to approx. 30 mL) and the residue was taken up into water/ethyl acetate (1:1, ~300 mL). The biphasic mixture was separated and the aqueous layer was extracted into ethyl acetate (2 x 100 mL) before the combined organics were washed with brine (100 mL), dried over Na₂SO₄ and concentrated in vacuo to afford (4-bromo-2-iodo-phenyl)methanol (4.27 g, 100% purity, 89% Yield) as an off-white solid.

¹H NMR (500 MHz, DMSO) δ 7.98 (d, J = 2.0 Hz, 1H), 7.62 (dd, J = 8.3, 2.0 Hz, 1H), 7.42 – 7.38 (m, 1H), 5.53 (t, J = 5.6 Hz, 1H), 4.36 (d, J = 5.5 Hz, 2H).

LCMS: m/z = 294.8/296.8 (ESI+), RT = 0.90, Method D

Step 2

[0531] Pyridinium chlorochromate (5.60 g, 29.8 mmol) was added to an ice-cooled solution of (4-bromo-2-iodo-phenyl)methanol (4.25 g, 13.6 mmol) in DCM (200 mL). The reaction was then stirred at r.t. for 18 h. The mixture was passed through a plug of celite (washings with ~500 mL DCM) and the filtrate was concentrated in vacuo. The residue was purified by FCC (100 g SiO₂ cartridge, 0 - 60% EtOAc in heptane) to afford 4-bromo-2-iodo-benzaldehyde (4.04 g, 100% purity, 96% Yield) as a white solid.

¹H NMR (500 MHz, DMSO) δ 9.91 (d, J = 0.7 Hz, 1H), 8.30 (d, J = 1.8 Hz, 1H), 7.80 (ddd, J = 8.2, 1.8, 0.7 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H).

Step 3

[0532] To a suspension of (methoxymethyl)(triphenyl)phosphonium chloride (4.4 g, 12.84 mmol) in anhydrous THF (25 mL) stirring at -78 °C was added sodium hydride (60 % in mineral oil) (520.0 mg, 13.0 mmol) in portions. The reaction mixture was allowed to warm to r.t. over 20 min, then cooled to -78 °C, after which 4-bromo-2-iodobenzaldehyde (3.3 g, 10.61 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was then taken into DCM (50 mL), washed with water (50 mL), and the aqueous phase extracted further with DCM (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by FCC (100 g SiO₂ cartridge, 0-60% EtOAc in heptane) and two isomeric products were collected:

4-bromo-2-iodo-1-[(Z)-2-methoxyvinyl]benzene (900 mg, 99% purity, 25% Yield) as a colourless oil.

¹H NMR (500 MHz, DMSO) δ 8.00 (d, J = 2.1 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.53 (dd, J = 8.5, 2.1 Hz, 1H), 6.51 (d, J = 7.2 Hz, 1H), 5.31 (d, J = 7.1 Hz, 1H), 3.78 (s, 3H).

4-bromo-2-iodo-1-[(E)-2-methoxyvinyl]benzene (850 mg, 98% purity, 23% Yield) crystallised on standing to a white solid.

¹H NMR (500 MHz, DMSO) δ 7.99 (d, J = 2.1 Hz, 1H), 7.48 (dd, J = 8.4, 2.1 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 12.7 Hz, 1H), 5.84 (d, J = 12.7 Hz, 1H), 3.68 (s, 3H).

Products were re-combined and taken on to the next step.

Step 4

[0533] 2 M HCl (3.0 mL, 6.0 mmol) was added to a solution of 4-bromo-2-iodo-1-(2-methoxyvinyl)benzene (1.4 g, 4.09 mmol) in acetone (50 mL). The mixture was heated to 60 °C and was stirred for 4 h. The mixture was cooled to r.t. and extracted with Et₂O (3 × 50 mL) and water (50 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ (50 mL) and brine (100 mL). The organic layer was then collected, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford 2-(4-bromo-2-iodo-phenyl)acetaldehyde (1.29 g, 95% purity, 92% Yield) as a yellow solid.

¹H NMR (500 MHz, DMSO) δ 9.71 (t, J = 1.1 Hz, 1H), 8.06 (d, J = 2.0 Hz, 1H), 7.60 (dd, J = 8.2, 2.1 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 3.96 – 3.94 (m, 2H).

LCMS: m/z = 322.8/324.9 [M-H]⁻, (ESI⁻), RT = 1.00, Method D

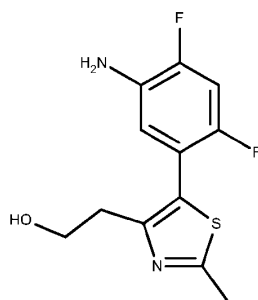
Step 5

[0534] Sodium borohydride (300 mg, 7.93 mmol) was added to a solution of 2-(4-bromo-2-iodo-phenyl)acetaldehyde (1.3 g, 3.8 mmol) in MeOH/THF (1:1, 20 mL) and the mixture was stirred at r.t. for 16 h. The reaction was quenched with water (50 mL), extracted with DCM (3 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated to afford the title compound (1.25 g, 95% purity, 96% Yield) as a pale-yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.99 (d, J = 2.1 Hz, 1H), 7.52 (dd, J = 8.2, 2.1 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 4.75 (t, J = 5.3 Hz, 1H), 3.55 (td, J = 7.0, 5.2 Hz, 2H), 2.80 (t, J = 7.0 Hz, 2H).

LCMS: m/z = 368.9/370.9 [M+MeCN+H]⁺, (ESI⁺), RT = 0.93, Method D

Example 291 – Synthesis of 2-[5-(5-Amino-2,4-difluoro-phenyl)-2-methyl-thiazol-4-yl]ethanol (Intermediate 92)



Step 1

[0535] (2-methyl-1,3-thiazol-4-yl)acetic acid (0.80 g, 5.09 mmol), was dissolved in anhydrous MeOH (25 mL). Thionyl dichloride (1.8 mL, 25.4 mmol) was added at 0 °C. The reaction mixture was slowly allowed to warm to r.t. and stirred for 3 h. The reaction was quenched by addition of water (10 mL) then most of the MeOH was removed under reduced pressure, remaining aq. layer basified with solid NaHCO₃ and extracted with ethyl acetate (20 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-70 % EtOAc in heptane) to afford methyl 2-(2-methylthiazol-4-yl)acetate (755 mg, 95% purity, 82% Yield) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.28 (s, 1H), 3.76 (s, 2H), 3.62 (s, 3H), 2.61 (s, 3H).

LCMS: m/z = 172.0 [M+H]⁺, (ESI⁺), RT = 0.52, Method D

Step 2

[0536] Methyl 2-(2-methylthiazol-4-yl)acetate (655 mg, 3.83 mmol), was dissolved in anhydrous DMF (30 mL). 1-bromopyrrolidine-2,5-dione (749 mg, 4.21 mmol) was added at r.t. The reaction mixture was heated to 70 °C for 1 h then concentrated in vacuo. The residue was diluted with ethyl acetate (30 mL) and water (30 mL). The organic phase was separated and dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by FCC (25 g SiO₂ cartridge, 0-50% EtOAc in heptane) to afford methyl 2-(5-bromo-2-methyl-thiazol-4-yl)acetate (805 mg, 95% purity, 80% Yield) as a yellow oil.

¹H NMR (500 MHz, DMSO) δ 3.74 (s, 2H), 3.63 (s, 3H), 2.61 (s, 3H).

LCMS: m/z = 249.9/251.9 [M+H]⁺, (ESI⁺), RT = 0.74, Method D

Step 3

[0537] Methyl 2-(5-bromo-2-methyl-thiazol-4-yl)acetate (600 mg, 2.40 mmol), Intermediate 2 (642 mg, 2.52 mmol) and potassium carbonate (663 mg, 4.80 mmol) were dissolved into a mixture of 1,4-dioxane (9 mL) and water (1.2 mL) and the solution was degassed with nitrogen for 10 minutes. To the mixture was added Pd(dppf)Cl₂ (176 mg, 0.240 mmol), before a further 5 mins degassing. The reaction mixture was heated at 100 °C for 16 h, before it was allowed to cool to r.t., filtered through a pad of celite and concentrated in vacuo. The residue was purified by FCC (25 g SiO₂ cartridge, 0-75% EtOAc in heptane) to afford methyl 2-[5-(5-amino-2,4-difluoro-phenyl)-2-methyl-thiazol-4-yl]acetate (762 mg, 70% purity, 75% Yield) as an off-white solid.

¹H NMR (500 MHz, DMSO) δ 7.19 (dd, J = 11.2, 9.8 Hz, 1H), 6.76 (dd, J = 9.8, 7.6 Hz, 1H), 5.20 (s, 2H), 3.61 (s, 2H), 3.58 (s, 3H), 2.64 (s, 3H).

LCMS: m/z = 299.0 [M+H]⁺, (ESI-), RT = 0.77, Method D

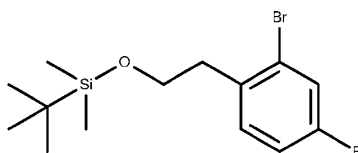
Step 4

[0538] To a solution of methyl 2-[5-(5-amino-2,4-difluoro-phenyl)-2-methyl-thiazol-4-yl]acetate (760.0 mg, 2.55 mmol) in THF (17 mL) and MeOH (2.5 mL) was added lithium borohydride (277.5 mg, 12.74 mmol). The reaction mixture was stirred at r.t. for 1 h. The reaction was quenched by slow addition of water (5 mL) and then concentrated to remove the THF/MeOH. Sat. aq. NaHCO₃ (10 mL) was added and the aqueous extracted with DCM (3 x 10 mL), the combined organics washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by FCC (50 g SiO₂ cartridge, 0-100% EtOAc in heptane) to afford the title compound as an off-white solid (560 mg, 99% purity, 81% Yield).

¹H NMR (500 MHz, DMSO) δ 7.17 (dd, J = 11.3, 9.8 Hz, 1H), 6.79 (dd, J = 9.9, 7.6 Hz, 1H), 5.16 (s, 2H), 4.59 (t, J = 5.5 Hz, 1H), 3.68 – 3.59 (m, 2H), 2.68 (t, J = 7.3 Hz, 2H), 2.63 (s, 3H).

LCMS: m/z = 271.0 [M+H]⁺, (ESI+), RT = 0.66, Method D

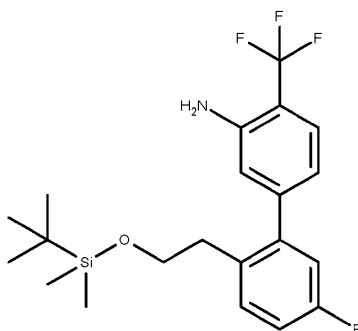
Example 292 – Synthesis of 2-(2-Bromo-4-fluoro-phenyl)ethoxy-tert-butyl-dimethyl-silane (Intermediate 93)



[0539] TBDMSCl (817 mg, 5.42 mmol) was added to a solution of *Intermediate 80* (1.00 g, 4.52 mmol) and 1*H*-imidazole (385 mg, 5.65 mmol) in DMF (20 mL). The reaction was stirred for 1 h then quenched into water. The aqueous layer was extracted with ethyl acetate (3 x 30 mL), the combined organics washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by FCC (25 g SiO₂ cartridge, 0-10% EtOAc in heptane) to afford the title compound (1.45 g, 95% purity, 91% Yield) as a colourless oil.

¹H NMR (500 MHz, DMSO) δ 7.53 (dd, J = 8.6, 2.6 Hz, 1H), 7.39 (dd, J = 8.6, 6.3 Hz, 1H), 7.23 – 7.17 (m, 1H), 3.76 (t, J = 6.7 Hz, 2H), 2.88 (t, J = 6.7 Hz, 2H), 0.81 (s, 9H), -0.06 (s, 6H).

Example 293 – Synthesis of 5-[2-[2-[Tert-butyl(dimethyl)silyl]oxyethyl]-5-fluorophenyl]-2-(trifluoromethyl)aniline (Intermediate 94)

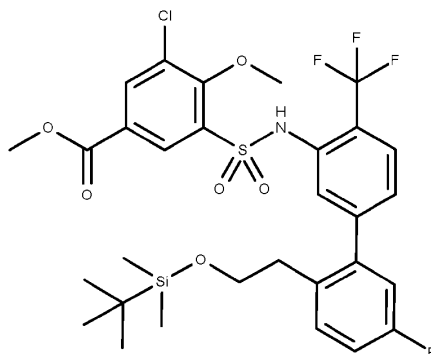


[0540] *Intermediate 93* (750 mg, 2.25 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)aniline (synthesised using a similar method to *Intermediate 2*, 646 mg, 2.25 mmol) and potassium carbonate (622 mg, 4.50 mmol) were dissolved into a mixture of 1,4-dioxane (9.5 mL) and water (1.3 mL) and the solution was degassed with nitrogen for 10 minutes. To the mixture was added Pd(dppf)Cl₂ (165 mg, 0.225 mmol), before a further 5 mins degassing. The reaction mixture was heated at 100 °C for 16 h, before it was allowed to cool to r.t., filtered through a pad of celite and concentrated in vacuo. The residue was purified by FCC (25 g SiO₂ cartridge, 0-15% EtOAc in heptane) to afford the title compound (830 mg, 96% purity, 86% Yield) as a pale orange oil.

¹H NMR (500 MHz, DMSO) δ 7.41 – 7.32 (m, 2H), 7.19 – 7.10 (m, 1H), 6.98 (dd, J = 9.6, 2.8 Hz, 1H), 6.75 (d, J = 1.6 Hz, 1H), 6.60 – 6.52 (m, 1H), 5.68 (s, 2H), 3.53 (t, J = 7.3 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H), 0.76 (s, 9H), -0.14 (s, 6H).

LCMS: m/z = 414.3 [M+H]⁺, (ESI⁺), RT = 1.25, Method F

Example 294 – Synthesis of Methyl 3-[[5-[2-[2-[tert-butyl(dimethyl)silyl]oxyethyl]-5-fluoro-phenyl]-2-(trifluoromethyl)phenyl]sulfamoyl]-5-chloro-4-methoxy-benzoate (Intermediate 95)

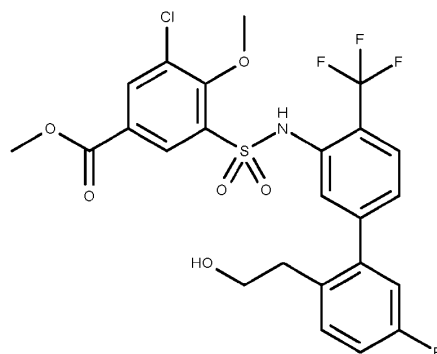


[0541] A solution of *Intermediate 94* (830 mg, 2.01 mmol) in anhydrous THF (15 mL) was cooled to -78 °C and 1 M LiHMDS in THF (3.0 mL, 3.01 mmol) was added. The mixture was then stirred for 10 mins at -78 °C before a solution of *Intermediate 1* (97% purity, 681 mg, 2.21 mmol) in anhydrous THF (4 mL) was added. The mixture was stirred for a further 3 h while warming to r.t. The mixture was carefully quenched with water (10 mL) and THF removed in vacuo. The aqueous residue was extracted with ethyl acetate (3 x 75 mL) and the combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by FCC (25 g SiO₂ cartridge, 0-15% EtOAc in heptane) to afford the title compound (1.09 g, 94% purity, 75% Yield) as a colourless oil.

¹H NMR (500 MHz, DMSO) δ 10.37 (s, 1H), 8.24 (d, J = 2.1 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.40 (dd, J = 8.6, 5.9 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.07 (d, J = 1.7 Hz, 1H), 6.85 (dd, J = 9.5, 2.8 Hz, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 3.49 (t, J = 6.7 Hz, 2H), 2.61 (t, J = 6.7 Hz, 2H), 0.71 (s, 9H), -0.20 (s, 6H).

LCMS: m/z = 674.2/676.2 [M-H]⁻, (ESI⁻), RT = 1.30, Method F

Example 295 – Synthesis of Methyl 3-chloro-5-[[5-[5-fluoro-2-(2-hydroxyethyl)phenyl]-2-(trifluoromethyl)phenyl]sulfamoyl]-4-methoxy-benzoate (Intermediate 96)

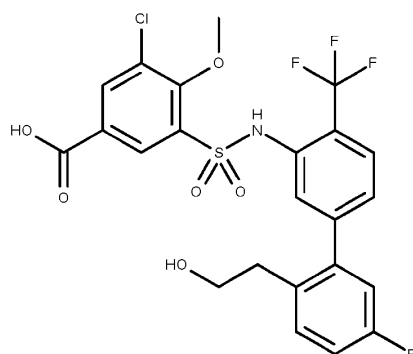


[0542] To a solution of *Intermediate 95* (1.00 g, 1.48 mmol) in MeOH (20 mL) was added *p*-toluenesulfonic acid monohydrate (28 mg, 0.148 mmol). The reaction mixture was stirred for 1 hour at r.t. and was then concentrated in vacuo. The residue was purified by FCC (25 g SiO₂ cartridge, 0-100% EtOAc in heptane) to afford the title compound (703 mg, 99% purity, 84% Yield) as a white solid.

¹H NMR (500 MHz, DMSO) δ 10.35 (s, 1H), 8.24 (d, *J* = 2.1 Hz, 1H), 8.18 (d, *J* = 2.1 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.45 (m, 1H), 7.39 (dd, *J* = 8.6, 5.9 Hz, 1H), 7.23 – 7.13 (m, 1H), 7.04 (d, *J* = 1.7 Hz, 1H), 6.82 (dd, *J* = 9.6, 2.8 Hz, 1H), 4.52 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.35 (t, *J* = 7.4 Hz, 2H), 2.52 (t, *J* = 5.9 Hz, 2H).

LCMS: *m/z* = 560.1/562.0 [M-H]⁻, (ESI⁻), RT = 1.06, Method D

Example 296 – Synthesis of 3-Chloro-5-[[5-[5-fluoro-2-(2-hydroxyethyl)phenyl]-2-(trifluoromethyl)phenyl]sulfamoyl]-4-methoxy-benzoic acid (Intermediate 97)

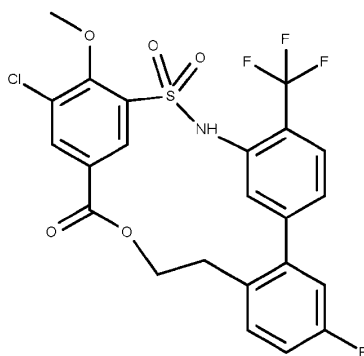


[0543] *Intermediate 96* (700 mg, 1.25 mmol) was dissolved in THF (18 mL) and 2 M sodium hydroxide (6.2 mL, 12.5 mmol) was added. The resulting solution was stirred at r.t. for 18 h. The THF was removed under reduced pressure and the remaining aqueous solution was acidified with 1 M HCl (25 mL), resulting white solid was extracted with EtOAc (50 mL), the aqueous phase was extracted with additional EtOAc (2 x 50 mL), before the combined organic phases were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (678 mg, 95% purity, 94% Yield) as a white solid.

¹H NMR (500 MHz, DMSO) δ 13.64 (s, 1H), 10.31 (s, 1H), 8.20 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.39 (dd, J = 8.6, 5.9 Hz, 1H), 7.23 – 7.14 (m, 1H), 7.07 (d, J = 1.7 Hz, 1H), 6.83 (dd, J = 9.5, 2.8 Hz, 1H), 4.51 (s, 1H), 3.91 (s, 3H), 3.38 (t, J = 6.9 Hz, 2H), 2.54 (t, J = 6.9 Hz, 2H).

LCMS: m/z = 546.0/548.0 [M-H]⁻, (ESI⁻), RT = 0.93, Method D

Example 297 – Synthesis of 14-Chloro-4-fluoro-15-methoxy-17,17-dioxo-20-(trifluoromethyl)-10-oxa-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracosan-1(22),2(7),3,5,12,14,16(24),19(23),20-nonaen-11-one (Intermediate 98)

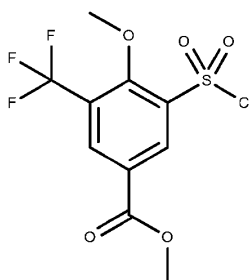


[0544] To a solution of DCC (621 mg, 3.01 mmol) and Intermediate 97 (660 mg, 1.20 mmol) in DCM (75 mL) was added DMAP (37 mg, 0.3 mmol). The mixture was stirred for 16 h at r.t. NaHCO₃ (sat. aq., 40 mL) was added, the mixture was separated and the aqueous phase extracted with DCM (2 x 30 mL). The combined organic fractions were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The crude material was purified by FCC (25 g SiO₂ cartridge, 20-100% DCM in heptane) to afford the title compound (420 mg, 98% purity, 64% Yield) as a white solid.

^1H NMR (500 MHz, DMSO) δ 10.32 (s, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.52 – 7.46 (m, 1H), 7.29 – 7.21 (m, 1H), 6.83 (dd, J = 9.6, 2.8 Hz, 1H), 6.61 – 6.52 (m, 1H), 4.71 – 4.57 (m, 1H), 4.35 – 4.17 (m, 1H), 3.98 (s, 3H), 3.19 – 3.06 (m, 1H), 3.01 – 2.89 (m, 1H).

LCMS: m/z = 528.1/530.0 $[\text{M-H}]^-$, (ESI-), RT = 1.09, Method D

Example 298– Synthesis of Methyl 3-chlorosulfonyl-4-methoxy-5-(trifluoromethyl)benzoate (Intermediate 99)



Step 1

[0545] To a solution of methyl 4-hydroxy-3-(trifluoromethyl)benzoate (5.0 g, 22.71 mmol) in DMF (227 mL) was added 1-bromopyrrolidine-2,5-dione (4.85 g, 27.25 mmol) and the reaction mixture was stirred at 30 °C for 1 h. The mixture was quenched with water (100 mL), extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by FCC (100 g SiO_2 cartridge, 0-10% EtOAc in heptane) to afford methyl 3-bromo-4-hydroxy-5-(trifluoromethyl)benzoate (4.50 g, 96% purity, 64% Yield) as a white solid.

^1H NMR (500 MHz, DMSO) δ 8.29 (d, J = 2.1 Hz, 1H), 8.04 (d, J = 2.1 Hz, 1H), 3.85 (s, 3H).

LCMS: m/z = 296.9/298.9 $[\text{M-H}]^-$, (ESI-), RT = 0.90, Method D

Step 2

[0546] To a suspension of methyl 3-bromo-4-hydroxy-5-(trifluoromethyl)benzoate (4.50 g, 15.04 mmol) and potassium carbonate (3.60 g, 26.06 mmol) in anhydrous DMF (40 mL) was added 2 M iodomethane (solution in tert-butyl methyl ether) (11.3 mL, 22.55 mmol) and the suspension was vigorously stirred for 18 h. The reaction mixture was then added to water (100 mL) and the organics diluted with EtOAc (100 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was

purified by FCC (50 g SiO₂ cartridge, 0-40% EtOAc in heptane) to afford methyl 3-bromo-4-methoxy-5-(trifluoromethyl)benzoate (3.35 g, 97% purity, 69% Yield) as a colourless oil that crystallised on standing.

¹H NMR (500 MHz, DMSO) δ 8.42 (d, J = 2.1 Hz, 1H), 8.13 (d, J = 2.1 Hz, 1H), 3.96 (s, 3H), 3.89 (s, 3H).

Step 3

[0547] To a solution of methyl 3-bromo-4-methoxy-5-(trifluoromethyl)benzoate (3.35 g, 10.38 mmol) in anhydrous 1,4-dioxane (25 mL) was added (4-tert-butylphenyl)methanethiol (2.0 mL, 10.71 mmol), Xantphos (367.0 mg, 0.63 mmol) and DIPEA (2.3 mL, 13.2 mmol). The solution was bubbled with N₂ for 10 mins, before Pd₂(dba)₃ (305.0 mg, 0.33 mmol) was added. The reaction mixture was bubbled with N₂ for a final 5 mins before it was heated to 100 °C and left to stir overnight. The mixture was allowed to cool to r.t. before it was added to water (100 mL) and extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by FCC (100 g SiO₂ cartridge, 0-100% EtOAc in heptane) to afford methyl 3-[(4-tert-butylphenyl)methylsulfanyl]-4-methoxy-5-(trifluoromethyl)benzoate (2.48 g, 85% purity, 49% Yield) as an orange oil.

¹H NMR (500 MHz, DMSO) δ 8.16 (d, J = 2.0 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.38 – 7.28 (m, 4H), 4.34 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 1.26 (s, 9H).

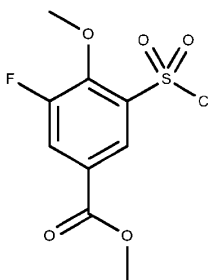
Step 4

[0548] Methyl 3-[(4-tert-butylphenyl)methylsulfanyl]-4-methoxy-5-(trifluoromethyl)benzoate (1.72 g, 3.54 mmol) was dissolved in a mixture of acetonitrile (20 mL), acetic acid (1.05 mL) and water (0.75 mL) and the resulting suspension was cooled to 0 °C in an ice bath. DCDMH (1.4 g, 7.11 mmol) was added portion-wise and the mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with 5% aq. Na₂CO₃ (3 x 30 mL) and brine (30 mL). The organic layer was dried using sodium sulfate, filtered, and concentrated in vacuo. The residue was diluted with 1:5 TBME:heptane (60 mL) and the solvent concentrated in vacuo a second time. The residue was then triturated in TBME (20 mL) leading to precipitation of a white solid. The solid was collected by filtration and discarded. The filtrate was purified by FCC (50 g SiO₂ cartridge, 0-20% TBME in heptane) to afford the title compound as a clear oil (432 mg, 95% purity, 35% Yield) as a clear oil.

¹H NMR (500 MHz, CDCl₃) δ 8.83 (d, J = 2.1 Hz, 1H), 8.64 (d, J = 2.2 Hz, 1H), 4.21 (s, 2H), 4.00 (s, 3H).

LCMS: $m/z = 313.0$ $[M-H]^-$, (ESI-), RT = 1.05, Method D

Example 299 – Synthesis of Methyl 3-chlorosulfonyl-5-fluoro-4-methoxy-benzoate (Intermediate 100)



Step 1

[0549] Methyl 3-fluoro-4-methoxybenzoate (475.0 mg, 2.58 mmol) and 1,3,5-tribromo-1,3,5-triazinane-2,4,6-trione (849.057 mg, 2.32 mmol) were dissolved in TFA (10 mL) and stirred at r.t. for 30 mins. The mixture was diluted with EtOAc (20 mL) and taken into sat. NaHCO_3 (20 mL). The layers were separated and the aqueous extracted with EtOAc (2 x 20 mL). The organics were combined and washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by FCC (25 g SiO_2 cartridge, 0-40% EtOAc in heptane) to afford methyl 3-bromo-5-fluoro-4-methoxybenzoate (547 mg, 95% purity, 77% Yield) as an orange oil.

^1H NMR (500 MHz, DMSO) δ 7.97 – 7.90 (m, 1H), 7.83 – 7.74 (m, 1H), 4.00 (d, $J = 2.5$ Hz, 3H), 3.86 (s, 3H).

Step 2

[0550] To a solution of (4-tert-butylphenyl)methanethiol (0.39 mL, 2.08 mmol) in anhydrous 1,4-dioxane (7 mL) was added methyl 3-bromo-5-fluoro-4-methoxybenzoate (547.0 mg, 2.08 mmol), Xantphos (73.418 mg, 0.13 mmol) and DIPEA (0.45 mL, 2.6 mmol). The solution was bubbled with N_2 for 10 mins, before $\text{Pd}_2(\text{dba})_3$ (61.2 mg, 0.07 mmol) was added. The reaction mixture was bubbled with N_2 for a final 5 mins before it was heated to 100 °C for 3 h. The mixture was allowed to cool to r.t. then added to water (100 mL) and extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by FCC (50 g SiO_2 cartridge, 0-100% EtOAc in heptane) to afford methyl 3-[(4-tert-butylphenyl)methylsulfanyl]-5-fluoro-4-methoxybenzoate (637 mg, 85% purity, 72% Yield) as an orange oil.

¹H NMR (500 MHz, DMSO) δ 7.71 – 7.65 (m, 1H), 7.59 (dd, J = 11.8, 2.0 Hz, 1H), 7.39 – 7.27 (m, 4H), 4.23 (s, 2H), 3.93 (d, J = 2.2 Hz, 3H), 3.84 (s, 3H), 1.26 (s, 9H).

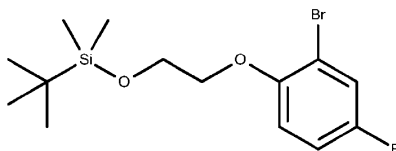
Step 3

[0551] Methyl 3-[(4-tert-butylphenyl)methylsulfanyl]-5-fluoro-4-methoxy-benzoate (500 mg, 1.17 mmol) was added to a mixture of acetonitrile (7 mL), acetic acid (0.35 mL) and water (0.25 mL) and the resulting suspension was cooled to 0 °C in an ice bath. DCDMH (462 mg, 2.34 mmol) was then added portion-wise (over approx. 15 mins) and the reaction mixture was stirred at 0 °C for 1 h. The mixture was diluted with EtOAc (50 mL) and washed with 5% aq. Na₂CO₃ (3 x 15 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and solvent concentrated in vacuo (water bath at 25 °C). The residue was diluted with TBME (10 mL) and heptane (50 mL) and triturated with a spatula for 5 mins leading to precipitation of a pale-yellow solid. The solid was removed by filtration and discarded. The filtrate was concentrated in vacuo and the residue was purified by FCC (25 g SiO₂ cartridge, 0-20% EtOAc in heptane) to afford the title compound as a yellow oil (224 mg, 88% purity, 59% Yield).

¹H NMR (500 MHz, DMSO) δ 8.16 – 8.11 (m, 1H), 7.73 (dd, J = 11.5, 2.2 Hz, 1H), 3.89 (d, J = 1.4 Hz, 3H), 3.84 (s, 3H).

LCMS: m/z = 262.9/265.0 [M-H]⁻, (ESI⁻), RT = 0.96, Method D

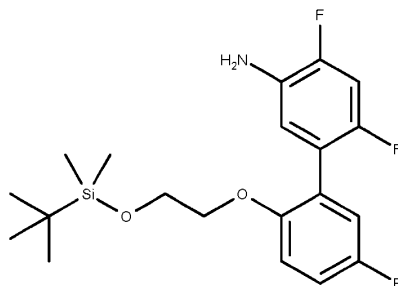
Example 300 – Synthesis of 2-(2-Bromo-4-fluorophenoxy)ethoxy-tert-butyl-dimethyl-silane (Intermediate 101)



[0552] To a solution of 2-bromo-4-fluorophenol (1.00 g, 5.24 mmol), 2-[(tert-butyl(dimethyl)silyl)oxy]ethanol (0.91 g, 5.16 mmol) and triphenylphosphine (1.37 g, 5.24 mmol) in anhydrous THF (20 mL) was added DIAD (1.06 g, 5.24 mmol) and the reaction was stirred at 40 °C for 24 h. The mixture was cooled to r.t. before copper (I) chloride (0.52 g, 5.24 mmol) was added and stirring continued at r.t. for 20 minutes. The mixture was then filtered through a pad of celite, washing with EtOAc (2 x 40 mL). The filtrate was concentrated under reduced pressure and purified by FCC (50 g SiO₂ cartridge, 0-20% EtOAc in heptane) to afford the title compound as a green oil (1.39 g, 85% purity, 65% Yield).

^1H NMR (400 MHz, DMSO) δ 7.50 – 7.41 (m, 1H), 7.18 – 7.03 (m, 2H), 4.03 (t, J = 4.6 Hz, 2H), 3.86 (t, J = 4.6 Hz, 2H), 0.79 (s, 9H), 0.00 (s, 6H).

Example 301 – Synthesis of 5-[2-[2-[Tert-butyl(dimethyl)silyl]oxyethoxy]-5-fluorophenyl]-2,4-difluoro-aniline (Intermediate 102)

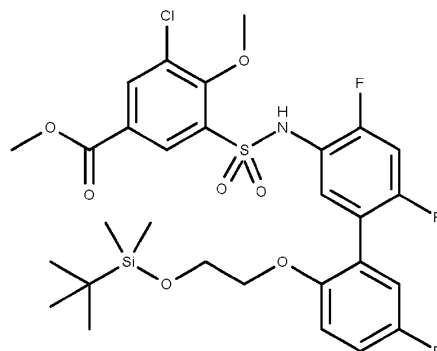


[0553] To a solution of *Intermediate 2* (94% purity, 0.98 g, 3.60 mmol) and *Intermediate 101* (85% purity, 1.37 g, 3.33 mmol) in 1,4-dioxane (17 mL) and water (3 mL) was added potassium carbonate (1.99 g, 14.4 mmol) and the mixture was degassed with N_2 for 15 mins. $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.25 g, 0.339 mmol) was added and the reaction mixture was degassed again for another 5 mins. The vessel was then sealed and its contents stirred at 100 °C overnight. The mixture was cooled to r.t., taken into EtOAc (75 mL) and added to water (75 mL). The layers were separated and the aqueous phase extracted further with EtOAc (2 x 75 mL). The organic layers were combined, washed with brine (100 mL), filtered and concentrated under reduced pressure. The residue was purified by FCC (50 g SiO_2 cartridge, 0-100% EtOAc in heptane) to afford the title compound as a yellow oil (1.29 g, 95% purity, 92% Yield).

^1H NMR (500 MHz, DMSO) δ 7.32 – 7.22 (m, 1H), 7.23 – 7.15 (m, 1H), 7.15 – 7.05 (m, 2H), 6.84 – 6.75 (m, 1H), 5.08 (s, 2H), 4.08 (t, J = 4.0 Hz, 2H), 3.88 (t, J = 4.1 Hz, 2H), 0.88 (s, 9H), 0.00 (s, 6H).

LCMS: m/z = 398.2 $[\text{M}+\text{H}]^+$, (ESI+), RT = 1.24, Method D

Example 302 – Synthesis of Methyl 3-[[5-[2-[2-[tert-butyl(dimethyl)silyl]oxyethoxy]-5-chloro-4-methoxy-benzoate
(Intermediate 103)

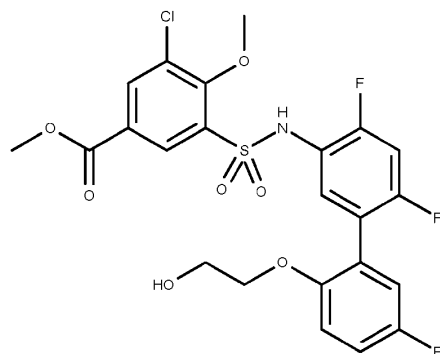


[0554] *Intermediate 1* (0.92 g, 3.08 mmol) and *Intermediate 102* (95% purity, 1.29 g, 3.08 mmol) were dissolved in anhydrous pyridine (24.5 mL) and the mixture was heated to 50 °C and stirred for 1 h. The mixture was allowed to cool to r.t. and then diluted with 1 M aq. HCl (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), passed through a phase separator, and concentrated under reduced pressure. The residue was purified by FCC (50 g SiO₂ cartridge, 0-100% EtOAc in heptane) to afford the title compound as a yellow oil (1.60 g, 88% purity, 69% Yield).

¹H NMR (500 MHz, DMSO) δ 10.61 (s, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.35 (d, J = 2.1 Hz, 1H), 7.53 – 7.44 (m, 1H), 7.44 – 7.37 (m, 2H), 7.34 – 7.25 (m, 1H), 7.20 – 7.14 (m, 1H), 4.17 – 4.14 (m, 5H), 4.03 (s, 3H), 3.91 (t, J = 4.6 Hz, 2H), 0.91 (s, 9H), 0.00 (s, 6H).

LCMS: m/z = 660.1/662.1 [M]⁻, (ESI⁻), RT = 1.32, Method D

Example 303 – Synthesis of Methyl 3-chloro-5-[[2,4-difluoro-5-[5-fluoro-2-(2-hydroxyethoxy)phenyl]phenyl]sulfamoyl]-4-methoxy-benzoate (Intermediate 104)

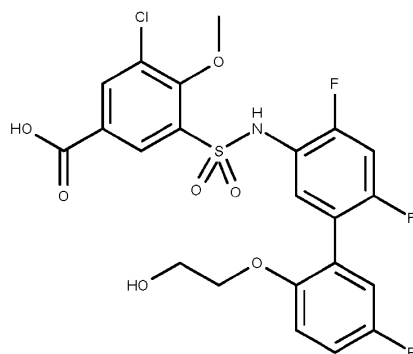


[0555] To a solution of *Intermediate 103* (88% purity, 1.60 g, 2.13 mmol) in MeOH (31.3 mL) was added *p*-toluenesulfonic acid monohydrate (44 mg, 0.230 mmol). The reaction mixture was stirred at r.t. for 1 h. Further *p*-toluenesulfonic acid monohydrate (242 mg, 1.27 mmol) was added and the mixture was stirred at r.t. for 1 h. The reaction mixture was concentrated in vacuo and purified by FCC (50 g SiO₂ cartridge, 0-50% EtOAc in heptane) to afford the title compound as a white solid (903 mg, 97% purity, 75% Yield).

¹H NMR (500 MHz, DMSO) δ 10.40 (s, 1H), 8.25 (d, *J* = 2.1 Hz, 1H), 8.17 (d, *J* = 2.1 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.29 – 7.20 (m, 2H), 7.20 – 7.14 (m, 1H), 7.02 – 6.96 (m, 1H), 4.68 (t, *J* = 5.5 Hz, 1H), 3.98 – 3.92 (m, 5H), 3.87 (s, 3H), 3.56 (q, *J* = 5.4 Hz, 2H).

LCMS: *m/z* = 544.0/546.0 [M-H]⁻, (ESI⁻), RT = 0.97, Method D

Example 304- Synthesis of 3-Chloro-5-[[2,4-difluoro-5-[5-fluoro-2-(2-hydroxyethoxy)phenyl]phenyl]sulfamoyl]-4-methoxy-benzoic acid (Intermediate 105)

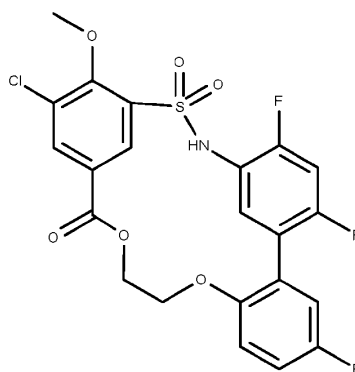


[0556] *Intermediate 104* (97% purity, 903 mg, 1.60 mmol) was dissolved in THF (24 mL) and 2 M sodium hydroxide (8.0 mL, 16.0 mmol) was added. The resulting solution was stirred at r.t. overnight. THF was removed under reduced pressure and the remaining aqueous solution was added to DCM (50 mL) and acidified with 1 M HCl (50 mL). The layers were separated and the aqueous phase was extracted with additional DCM (2 x 50 mL), before the combined organic phases were washed with brine (50 mL), filtered and concentrated under reduced pressure to give the title compound (843 mg, 95% purity, 94% Yield) as a white solid.

^1H NMR (500 MHz, DMSO) δ 13.67 (s, 1H), 10.36 (s, 1H), 8.21 (d, $J = 2.1$ Hz, 1H), 8.17 (d, $J = 2.1$ Hz, 1H), 7.39 – 7.31 (m, 1H), 7.29 – 7.20 (m, 2H), 7.19 – 7.14 (m, 1H), 7.02 – 6.96 (m, 1H), 4.68 (s, 1H), 3.98 – 3.93 (m, 5H), 3.57 (t, $J = 5.3$ Hz, 2H).

LCMS: $m/z = 530.0/532.0$ [M-H] $^-$, (ESI $^-$), RT = 0.84, Method D

Example 305 – Synthesis of 15-Chloro-4,21,23-trifluoro-16-methoxy-18,18-dioxo-8,11-dioxo-18 λ 6-thia-19-azatetracyclo[18.3.1.113,17.02,7]pentacos-1(23),2(7),3,5,13,15,17(25),20(24),21-nonaen-12-one (Intermediate 106)

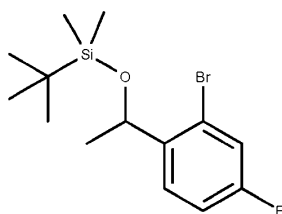


[0557] To a solution of DCC (636 mg, 3.08 mmol) and *Intermediate 105* (95% purity, 843 mg, 1.51 mmol) in anhydrous DCM (48 mL) was added DMAP (48 mg, 0.390 mmol). The mixture was stirred at r.t. for 4.5 h. NaHCO_3 (sat. aq., 50 mL) was added, the mixture was separated and the aqueous phase extracted with DCM (2 x 50 mL). The combined organic fractions were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (25 g SiO_2 cartridge, 0-100% DCM in heptane) to afford the title compound as a white solid (543 mg, 99% purity, 69% Yield).

^1H NMR (400 MHz, DMSO) δ 10.63 (s, 1H), 8.20 (d, J = 2.2 Hz, 1H), 7.52 (d, J = 2.2 Hz, 1H), 7.43 – 7.35 (m, 1H), 7.34 – 7.26 (m, 2H), 7.26 – 7.18 (m, 2H), 4.37 (t, J = 4.4 Hz, 2H), 4.29 (t, J = 4.4 Hz, 2H), 4.04 (s, 3H).

LCMS: m/z = 512.3/514.3 [M-H] $^-$, (ESI $^-$), RT = 1.04, Method D

Example 306 – Synthesis of 1-(2-Bromo-4-fluoro-phenyl)ethoxy-tert-butyl-dimethylsilane (Intermediate 107)



Step 1

[0558] Sodium borohydride (105 mg, 2.78 mmol) was added to a solution of 1-(2-bromo-4-fluoro-phenyl)ethanone (0.40 mL, 2.83 mmol) in MeOH (28 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h then stirred for another 1 hour at r.t. The reaction mixture was diluted with water (20 mL) and DCM (20 mL). The layers were separated and the aqueous phase further extracted with DCM (2 x 50 mL). The combined organics were then washed with sat. aqueous NH_4Cl (30 mL), dried over Na_2SO_4 and then concentrated in vacuo to give 1-(2-bromo-4-fluoro-phenyl)ethanol (457 mg, 98% purity, 72% Yield) as a colourless oil.

^1H NMR (400 MHz, DMSO) δ 7.62 (dd, J = 8.7, 6.4 Hz, 1H), 7.49 (dd, J = 8.6, 2.6 Hz, 1H), 7.32 – 7.24 (m, 1H), 5.44 (d, J = 3.9 Hz, 1H), 4.96 – 4.88 (m, 1H), 1.28 (d, J = 6.4 Hz, 3H).

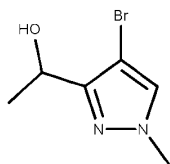
LCMS: m/z = 201.1/203.1 (ESI $^+$), RT = 0.79, Method D

Step 2

[0559] To a solution of 1-(2-bromo-4-fluoro-phenyl)ethanol (99%, 467 mg, 2.11 mmol) in anhydrous DMF (9 mL) was added imidazole (287 mg, 4.22 mmol) and the resulting solution was stirred at r. t. for 15 min. To the reaction mixture was then added tert-butyl(chloro)dimethylsilane (445 mg, 2.95 mmol) and the reaction was stirred at r. t. for 18 h. DMF was removed under vacuum and the residue was purified by FCC (25 g SiO_2 cartridge, 0-50% EtOAc in heptane) to give the title compound (502 mg, 91% purity, 65% Yield) as a colourless oil.

¹H NMR (500 MHz, DMSO) δ 7.58 (dd, J = 8.8, 6.3 Hz, 1H), 7.51 (dd, J = 8.6, 2.6 Hz, 1H), 7.34 – 7.28 (m, 1H), 5.09 (q, J = 6.2 Hz, 1H), 1.31 (d, J = 6.2 Hz, 3H), 0.85 (s, 10H), 0.04 (s, 3H), -0.05 (s, 3H).

Example 307 – Synthesis of 1-(4-Bromo-1-methyl-pyrazol-3-yl)ethanol (Intermediate 108)



Step 1

[0560] To a solution of methyl 4-bromo-1-methyl-pyrazole-3-carboxylate (500.0 mg, 2.28 mmol) in THF (8 mL) and MeOH (1.5 mL) was added lithium borohydride (300 mg, 13.77 mmol) and the mixture was stirred at r.t. for 1.5 h. Further lithium borohydride (500 mg, 23.0 mmol) was added and the mixture was stirred for another 30 mins at r.t. The reaction was quenched by slow addition of water (20 mL) and then concentrated to remove the THF/MeOH. The aqueous was extracted with EtOAc (3 x 40 mL), the combined organic phases were washed with brine (30 mL), passed through phase separator paper, and the solvent removed under reduced pressure to afford (4-bromo-1-methyl-pyrazol-3-yl)methanol (469 mg, 95% purity, quantitative yield) as a white solid.

¹H NMR (500 MHz, DMSO): 7.84 (s, 1H), 4.99 (t, J = 5.6 Hz, 1H), 4.33 (d, J = 5.5 Hz, 2H), 3.79 (s, 3H).

LCMS: m/z = 190.9/192.9 [M+H]⁺, (ESI⁺), RT = 0.42, Method D

Step 2

[0561] (4-bromo-1-methyl-pyrazol-3-yl)methanol (469 mg, 2.33 mmol) was dissolved in DCM (11.4 mL) and manganese dioxide (1.01 g, 11.6 mmol) was added and the mixture was heated to 40 °C for 16 h. The mixture was filtered through celite and washed through with DCM (20 mL). The filtrate was concentrated under reduced pressure to afford 4-bromo-1-methyl-pyrazole-3-carbaldehyde (393 mg, 100% purity, 89% Yield) as a yellow solid.

¹H NMR (500 MHz, DMSO): 9.84 (d, J = 0.7 Hz, 1H), 8.17 (d, J = 0.7 Hz, 1H), 3.97 (s, 3H).

LCMS: m/z = 188.9/190.9 [M+H]⁺, (ESI⁺), RT = 0.54, Method D

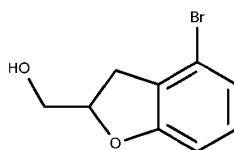
Step 3

[0562] To a solution of 4-bromo-1-methyl-pyrazole-3-carbaldehyde (397 mg, 2.10 mmol) in anhydrous THF (15 mL) at -78 °C under an atmosphere of nitrogen was introduced 3.4 M bromo(methyl)magnesium in 2-methyl THF (1.6 mL, 5.44 mmol) dropwise and the mixture was stirred for 1.5 h. The mixture was quenched by slow addition of sat. NH₄Cl (aq.) (15 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), passed through phase separator paper, and concentrated under reduced pressure to afford the title compound (392 mg, 90% purity, 82% Yield) as a pale-yellow oil.

¹H NMR (500 MHz, DMSO): 7.82 (s, 1H), 4.98 (d, J = 5.0 Hz, 1H), 4.70 (qd, J = 6.6, 5.0 Hz, 1H), 3.78 (s, 3H), 1.38 (d, J = 6.6 Hz, 3H).

LCMS: m/z = 204.9/206.9 [M+H]⁺, (ESI⁺), RT = 0.50, Method D

Example 308 – Synthesis of (4-Bromo-2,3-dihydrobenzofuran-2-yl)methanol (Intermediate 109)

Step 1

[0563] To a solution of 3-bromophenol (98%, 5.00 g, 28.3 mmol) in acetone (75 mL) was added K₂CO₃ (7.83 g, 56.6 mmol) and 3-bromoprop-1-ene (2.7 mL, 31.2 mmol). The suspension was stirred at r.t. overnight and then at 65 °C for 1 h. Further 3-bromoprop-1-ene (0.9 mL, 10.4 mmol) was added and the RM was stirred at 65 °C for 2.5 h. The mixture was cooled to r.t, then the solvent removed under vacuum, water (100 mL) added and the aqueous phase extracted with Et₂O (3 × 70 mL). The combined organic phase was washed with water (100 mL) and brine (100 mL), dried with magnesium sulfate, filtered, and the filtrate concentrated under vacuum to give 1-allyloxy-3-bromo-benzene (6.10 g, 98% purity, 99% Yield) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.24 (dd, J = 8.1, 8.1 Hz, 1H), 7.18 – 7.15 (m, 1H), 7.12 (ddd, J = 7.8, 1.9, 1.0 Hz, 1H), 7.00 – 6.93 (m, 1H), 6.02 (ddt, J = 17.3, 10.5, 5.2 Hz, 1H), 5.39 (ddt, J = 17.3, 1.7, 1.7 Hz, 1H), 5.26 (ddt, J = 10.6, 1.5, 1.5 Hz, 1H), 4.62 – 4.55 (m, 2H).

Step 2

[0564] A mixture of 1-allyloxy-3-bromo-benzene (6.10 g, 28.6 mmol) and *N,N*-diethylaniline (10 mL, 62.3 mmol) was heated under reflux for 3.5 h. The mixture was cooled to r.t., diluted with EtOAc (80 mL), and washed with 2 M aq. HCl (2 x 20 mL), water (20 mL), brine (10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by FCC (100 g SiO₂ cartridge, 0-100% EtOAc in heptane) to afford 2-allyl-3-bromo-phenol (1.15 g, 99% purity, 19% Yield) as a yellow oil.

¹H NMR (400 MHz, DMSO) δ 9.88 (br. s, 1H), 7.01 (dd, J = 8.0, 1.4 Hz, 1H), 6.96 (dd, J = 7.9, 7.9 Hz, 1H), 6.82 (dd, J = 7.8, 1.4 Hz, 1H), 5.85 (ddt, J = 16.5, 10.1, 6.1 Hz, 1H), 5.03 – 4.90 (m, 2H), 3.48 – 3.40 (m, 2H).

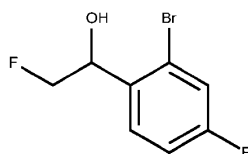
LCMS: m/z = 211.0/213.0 [M-H]⁻, (ESI⁻), RT = 3.32, Method A

Step 3

[0565] A mixture of 2-allyl-3-bromo-phenol (1.14 g, 5.35 mmol), mCPBA (2.64 g, 10.7 mmol) and DCM (50 mL) was stirred at r.t. for 4.5 h. K₂CO₃ (2218 mg, 16.1 mmol) and MeOH (30 mL) were added and the mixture was stirred at r.t. overnight. The mixture was concentrated under vacuum. The residue was taken up in water (50 mL) and DCM (50 mL), then the layers separated. The aqueous was extracted with further DCM (2 x 50 mL), then combined organic passed through a phase separator and then concentrated. The residue was purified by FCC (50 g SiO₂ cartridge, 0-50% EtOAc in heptane) to give the title compound (1.04 g, 94% purity, 79% Yield) as a pale-yellow oil.

¹H NMR (400 MHz, DMSO) δ 7.04 (dd, J = 7.8, 7.8 Hz, 1H), 6.99 (dd, J = 8.1, 1.1 Hz, 1H), 6.74 (dd, J = 7.7, 1.1 Hz, 1H), 5.03 (t, J = 5.5 Hz, 1H), 4.87 (dddd, J = 9.4, 7.3, 5.1, 4.1 Hz, 1H), 3.69 – 3.47 (m, 2H), 3.19 (dd, J = 16.1, 9.6 Hz, 1H), 2.99 (dd, J = 16.1, 7.3 Hz, 1H).

Example 309 – Synthesis of 1-(2-Bromo-4-fluorophenyl)-2-fluoro-ethanol (Intermediate 110)



[0566] A mixture of 1-(2-bromo-4-fluorophenyl)ethanone (1.00 g, 4.61 mmol), Selectfluor (3.26 g, 9.21 mmol) and MeOH (30 mL) was heated at 70 °C for 24 h. Conc. sulfuric acid (25 μ L, 0.466 mmol) was added and the RM heated at 70 °C for 24 h. The mixture was

concentrated under vacuum, the residue was taken up in EtOAc (50 mL) and washed with sat. aq. NH_4Cl (40 mL) and brine (40 mL), then dried (Na_2SO_4), filtered and concentrated under vacuum. The resulting yellow oil was combined with TFA (1.5 mL, 19.6 mmol), chloroform (7 mL) and water (1.5 mL) and the mixture was heated under reflux at 70 °C for 4 h. The mixture was diluted with sat. aq. NaHCO_3 (40 mL) and DCM (30 mL) stirred at r.t. for 10 min. The layers were separated and the aqueous extracted with further DCM (2 x 30 mL). The combined organic was passed through a phase separator and then concentrated. The residue was purified by FCC (100 g SiO_2 cartridge, 0-80% EtOAc in heptane) to afford 1-(2-bromo-4-fluoro-phenyl)-2-fluoro-ethanone (582 mg, 95% purity, quantitative yield) as a colourless oil.

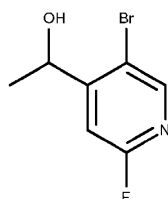
^1H NMR (500 MHz, CDCl_3) δ 7.56 (dd, J = 8.6, 5.9 Hz, 1H), 7.40 (dd, J = 8.1, 2.4 Hz, 1H), 7.14 (ddd, J = 8.6, 7.7, 2.4 Hz, 1H), 5.36 (d, J = 47.3 Hz, 2H).

Step 2

[0567] NaBH_4 (177 mg, 4.69 mmol) was added to a solution of 1-(2-bromo-4-fluoro-phenyl)-2-fluoro-ethanone (95%, 580 mg, 2.34 mmol) in MeOH (19 mL) at 0 °C. The mixture was stirred at r.t. for 1 h and then diluted with water (20 mL) and DCM (20 mL). The layers were separated and the aqueous phase further extracted with DCM (2 x 50 mL). The combined organics were then washed with sat. aqueous NH_4Cl (30 mL), dried over Na_2SO_4 and then concentrated in vacuo to give the title compound as a colourless oil (511 mg, 93% purity, 86% Yield).

^1H NMR (500 MHz, CDCl_3) δ 7.61 (dd, J = 8.7, 6.1 Hz, 1H), 7.30 (dd, J = 8.1, 2.6 Hz, 1H), 7.14 – 7.05 (m, 1H), 5.37 (ddt, J = 14.2, 8.0, 2.9 Hz, 1H), 4.62 (ddd, J = 46.5, 9.6, 2.7 Hz, 1H), 4.28 (ddd, J = 48.4, 9.6, 8.1 Hz, 1H), 2.60 (dd, J = 3.2, 1.3 Hz, 1H).

Example 310 – Synthesis of 1-(5-Bromo-2-fluoro-4-pyridyl)ethanol (Intermediate 111)



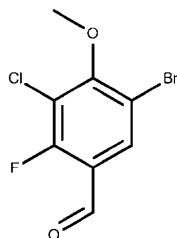
[0568] To a solution of 5-bromo-2-fluoro-pyridine-4-carbaldehyde (980 mg, 4.75 mmol) in anhydrous THF (30 mL) at -78 °C was added 3 M MeMgBr in THF (4.8 mL, 14.3 mmol). The mixture was allowed to warm up to r.t. overnight. The mixture was quenched slowly

with sat. aq. NH_4Cl (30 mL) and the THF removed under vacuum. The remaining aqueous was extracted with EtOAc (2 x 30 mL). The combined organic was washed with brine (40 mL), dried (Na_2SO_4), filtered and concentrated to give the title compound (1.01 g, 97% purity, 94% Yield) as a yellow oil.

^1H NMR (500 MHz, DMSO) δ 8.43 – 8.32 (m, 1H), 7.28 (d, J = 2.0 Hz, 1H), 5.78 (d, J = 4.4 Hz, 1H), 4.93 – 4.82 (m, 1H), 1.33 (d, J = 6.5 Hz, 3H).

LCMS: m/z = 219.9/221.9 $[\text{M}+\text{H}]^+$, (ESI+), RT = 0.67, Method D

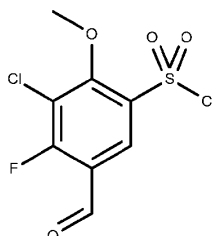
Example 311 – Synthesis of 5-Bromo-3-chloro-2-fluoro-4-methoxy-benzaldehyde (Intermediate 112)



[0569] A stirred solution of 1-bromo-3-chloro-4-fluoro-2-methoxy-benzene (25.0 g, 104.4 mmol) in dry THF (250 mL) was cooled to $-78\text{ }^\circ\text{C}$ under an atmosphere of nitrogen and LDA (78.0 mL of a 2 M solution in THF/ethylbenzene, 156.6 mmol) introduced dropwise over 15 minutes. After 60 minutes at this temperature, dry DMF (22.9 mL, 313.2 mmol) was introduced dropwise over 2 minutes. The reaction mixture was slowly warmed to $\sim 0\text{ }^\circ\text{C}$ over 2 hours, then held at $0\text{ }^\circ\text{C}$. After 15 minutes stirring at $\sim 0\text{ }^\circ\text{C}$, saturated aqueous ammonium chloride (150 mL) was introduced and stirring continued another 5 minutes. The reaction mixture was then transferred to a separating funnel containing tert-butyl methyl ether (1.0 L), the mixture shaken and the aqueous phase removed. The organic phase was washed with water (3 x 300 mL) and brine (1 x 300 mL) then dried over magnesium sulfate. Following filtration of the dried organic extract, the filtrate was concentrated in vacuo, re-dissolved in dichloromethane and adsorbed onto silica in-vacuo. Purification of the dry-loaded material by flash column chromatography (heptane then 10% ethyl acetate in heptane) furnished the title compound (22.78 g, 82.61 mmol, 79%) as a pale-yellow wax.

^1H NMR (400 MHz, CDCl_3) δ 10.23 (s, 1H), 8.00 (d, J = 7.1 Hz, 1H), 4.01 (s, 3H).

Example 312 – Synthesis of 3-Chloro-4-fluoro-5-formyl-2-methoxy-benzenesulfonyl chloride (Intermediate 113)



Step 1

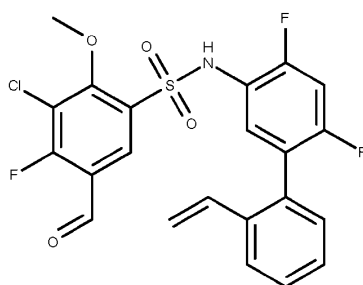
[0570] *Intermediate 112* (10 g) was dissolved in anhydrous 1,4-dioxane (215 mL) and added to a 500 mL pressure vessel containing Xantphos (1.73 g). Nitrogen was bubbled through the solution for 5 minutes before DIPEA (7.2 mL) was added. After another 5 mins, benzyl mercaptan (5.57 mL) was added and bubbling continued for several minutes. Finally, Pd₂dba₃ (1.37 g) was added, nitrogen bubble continued for 2 mins and close the pressure flask under nitrogen. The mixture was heated to 85 °C with stirring for 2 h. The mixture was diluted with EtOAc (1 L), washed with 2 x 200 mL water, then brine (100 mL). The organic phase was dried over magnesium sulfate, then filtered through a shallow bed of kieselguhr and concentrated the filtrate. The residue was purified by FCC (350 g SiO₂ cartridge, 0-15% EtOAc in heptane) to afford 5-benzylsulfanyl-3-chloro-2-fluoro-4-methoxy-benzaldehyde (11.4 g, 66% purity) as a pale-yellow oil, which was used in the next step without further purification.

Step 2

[0571] To a stirred solution of 5-benzylsulfanyl-3-chloro-2-fluoro-4-methoxy-benzaldehyde (4.54 g at 66% purity, 9.63 mmol) in acetonitrile (59 mL) at 0 °C was introduced water (1.80 mL) and acetic acid (2.64 mL). DCDMH (3.81 g, 19.31 mmol) was introduced portion-wise over 10 minutes. After 2.5 hours at 0 °C, the reaction mixture was concentrated in-vacuo (rotary evaporator bath = 30 °C). The residue diluted with dichloromethane (150 mL) and washed with saturated sodium bicarbonate (2 x 25 mL) and brine (1 x 25 mL), then dried over magnesium sulfate. Following filtration to remove the inorganics, the filtrate was concentrated in-vacuo and the residue purified by flash column chromatography (350 g SiO₂ cartridge, 5-25% gradient of ethyl acetate in heptane) to furnish the title compound (2.04 g, 6.75 mmol, 70%) as a colourless oil.

^1H NMR (500 MHz, CDCl_3) δ 10.28 (s, 1H), 8.45 (d, $J = 7.1$ Hz, 1H), 4.27 (s, 3H).

Example 313 – Synthesis of 3-Chloro-N-[2,4-difluoro-5-(2-vinylphenyl)phenyl]-4-fluoro-5-formyl-2-methoxy-benzenesulfonamide (Intermediate 114)

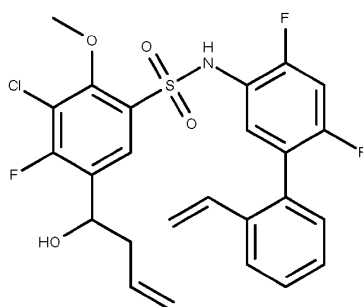


[0572] To a solution of *Intermediate 113* (2.04 g, 7.13 mmol) in anhydrous DCM (25 mL) at -15 to -20 °C under an atmosphere of nitrogen, was introduced a premixed solution of 2,4-difluoro-5-(2-vinylphenyl)aniline (*synthesised using a similar method to Intermediate 3*, 1.50 g, 6.49 mmol) and pyridine (1.03 g, 12.97 mmol) in dry DCM (9.0 mL) dropwise over 15 minutes. The reaction mixture was warmed to 0 °C over 60 minutes then held at this temperature for 2 hours, before warming to r.t. The reaction mixture was diluted with dichloromethane (100 mL) and washed with 1 M aqueous hydrochloric acid (2 x 25 mL). The organic phase was concentrated in-vacuo and the residue re-dissolved in methanol (20 mL) and the solution applied to an Isolute SCX-2 cartridge (20 g). The cartridge was eluted with methanol (5 x 20 mL), 9:1 methanol/water (6 x 20 mL) and 3.5 M ammonia in methanol (5 x 20 mL). The methanol fractions were concentrated in-vacuo, re-dissolved in acetonitrile (60 mL) and 1 M aqueous hydrochloric acid introduced (15 mL). After stirring for 60 minutes, the solution was concentrated in-vacuo to remove acetonitrile, additional acetonitrile introduced and the solution concentrated in-vacuo again. The aqueous acidic residue was diluted with water (15 mL), extracted with ethyl acetate (3 x 50 mL) and the combined ethyl acetate extracts dried over magnesium sulfate. After filtering the dried organic extracts, the filtrate was concentrated in-vacuo to furnish the title compound (2.03 g, 89% purity, 58% yield) as a pale brown solid.

^1H NMR (500 MHz, CDCl_3) δ 10.23 (s, 1H), 8.23 (d, $J = 7.3$ Hz, 1H), 7.68 – 7.62 (m, 1H), 7.45 (dd, $J = 8.7, 7.6$ Hz, 1H), 7.43 – 7.36 (m, 1H), 7.32 (td, $J = 7.5, 1.3$ Hz, 1H), 7.15 (d, $J = 7.6$ Hz, 1H), 7.09 (s, 1H), 6.82 (dd, $J = 9.9, 8.8$ Hz, 1H), 6.45 – 6.35 (m, 1H), 5.67 (dd, $J = 17.4, 0.9$ Hz, 1H), 5.20 (dd, $J = 11.0, 0.9$ Hz, 1H), 4.25 (s, 3H).

LCMS: $m/z = 480.2, 482.2$ $[M+H]^+$, (ESI+), $RT = 3.92$, Method C

Example 314 – Synthesis of 3-Chloro-N-[2,4-difluoro-5-(2-vinylphenyl)phenyl]-4-fluoro-5-(1-hydroxybut-3-enyl)-2-methoxy-benzenesulfonamide (Intermediate 115)

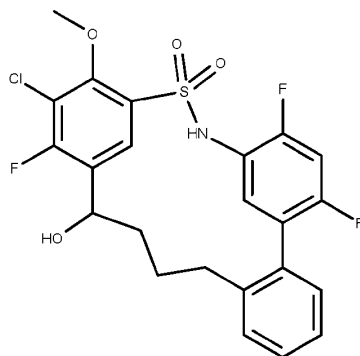


[0573] To a solution of *Intermediate 114* (2.03 g, 4.21 mmol) in 3:1 diethyl ether / THF (anhydrous, 100 mL) at $-78\text{ }^{\circ}\text{C}$ under an atmosphere of nitrogen was introduced allylmagnesium chloride (4.63 mL of a 2.0 M solution in tetrahydrofuran, 9.27 mmol) dropwise over three minutes. After 20 minutes, aqueous saturated ammonium chloride (10 mL) was introduced and the reaction warmed to r.t. Water (10 mL) and ethyl acetate (80 mL) were then added and the pH of the aqueous phase adjusted to 6-7 by dropwise addition of acetic acid. The ethyl acetate phase was separated and the aqueous phase extracted with additional ethyl acetate (80 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the filtrate concentrated in-vacuo. The filtrate residue was adsorbed onto silica (from a solution in dichloromethane) and the dry-loaded material purified by FCC (100 g SiO_2 cartridge, 5-50% gradient of ethyl acetate in heptane) to furnish the title compound (1.59 g, 93% purity, 67% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, $J = 7.6$ Hz, 1H), 7.64 (d, $J = 7.8$ Hz, 1H), 7.47 – 7.34 (m, 2H), 7.31 (td, $J = 7.5, 1.3$ Hz, 1H), 7.13 (s, 1H), 6.82 (dd, $J = 10.0, 8.8$ Hz, 1H), 6.48 – 6.36 (m, 1H), 5.77 – 5.62 (m, 2H), 5.20 (dd, $J = 11.0, 1.0$ Hz, 1H), 5.16 – 5.05 (m, 2H), 4.99 (dt, $J = 8.2, 4.3$ Hz, 1H), 4.15 (s, 3H), 2.56 – 2.45 (m, 1H), 2.41 – 2.29 (m, 1H), 2.12 (d, $J = 4.1$ Hz, 1H).

LCMS: $m/z = 522.2, 524.2$ $[M-H]^-$, (ESI-), $RT = 4.03$, Method C

Example 315 – Synthesis of 14-Chloro-13,20,22-trifluoro-15-methoxy-17,17-dioxo-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2,4,6,12,14,16(24),19(23),20-nonaen-11-ol (Intermediate 116)



Step 1

[0574] *Intermediate 115* (640 mg) was dissolved in anhydrous toluene (600 mL) and nitrogen was bubbled through for 30 mins. HG2 catalyst (77 mg) was added and bubbling was continued for a further 10 minutes. The mixture was warmed to 80 °C for 3 h under nitrogen, bubbling with nitrogen for 1 minute every 10-15 minutes. After cooling the mixture to r.t., the catalyst was quenched by air bubbling the solution for 10 mins. The mixture was then concentrated in vacuo and the residue was purified by FCC (50 g SiO₂ cartridge, 5-50% EtOAc in heptane) to afford (8E/Z)-14-chloro-13,20,22-trifluoro-15-methoxy-17,17-dioxo-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2,4,6,8,12,14,16(24),19(23),20-decaen-11-ol (0.53 g) as a pale brown oil. This was used directly in the next step.

Step 2

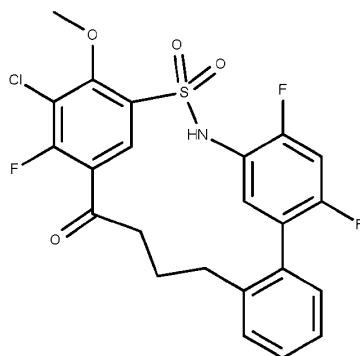
[0575] A solution of (8E/Z)-14-chloro-13,20,22-trifluoro-15-methoxy-17,17-dioxo-17 λ 6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2,4,6,8,12,14,16(24),19(23),20-decaen-11-ol (390 mg, 0.786 mmol) in ethanol (15 mL) and 10% Pd on carbon, (35 mg) was stirred at r.t. under 1 atmosphere of hydrogen for 3 h. The reaction mixture was filtered through a shallow bed of kieselguhr on a sintered glass funnel and the solid washed through with ethanol (5 mL). The filtrate was concentrated in-vacuo to furnish the title compound (373 mg, 91%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.79 (d, J = 7.5 Hz, 1H), 7.50 (dd, J = 9.0, 7.3 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.28 – 7.24 (m, 1H), 7.22 – 7.15 (m, 2H), 7.08 (d, J = 7.3 Hz, 1H), 6.74 (dd, J =

9.6, 8.7 Hz, 1H), 5.24 (d, J = 4.9 Hz, 1H), 4.10 (s, 3H), 2.45 – 2.30 (m, 2H), 1.96 (br. s, 1H), 1.92 – 1.83 (m, 1H), 1.34 – 1.23 (m, 1H), 1.11 – 1.02 (m, 2H).

LCMS: m/z = 496.2/498.2 [M-H]⁻, (ESI⁻), RT = 3.63, Method C

Example 316 – Synthesis of 14-chloro-13,20,22-trifluoro-15-methoxy-17,17-dioxo-17λ6-thia-18-azatetracyclo[17.3.1.112,16.02,7]tetracos-1(22),2,4,6,12,14,16(24),19(23),20-nonaen-11-one (Intermediate 117)

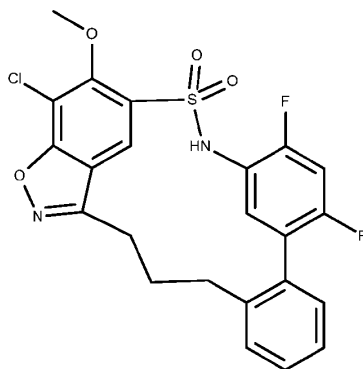


[0576] To a stirred solution of *Intermediate 116* (373 mg, 0.749 mmol) in dry DCM (15 mL) at r.t. was introduced DMP (413 mg, 0.974 mmol) in one portion. After 3 h, the mixture was diluted with DCM (10 mL), saturated aqueous sodium thiosulfate (5 mL) and saturated aqueous sodium bicarbonate (5 mL), and the two-phase mixture stirred for 30 minutes. After separating the organic phase, the aqueous was extracted with dichloromethane (15 mL) and the combined dichloromethane extracts dried over magnesium sulfate. Filtration and evaporation of the dried organic extract furnished the title compound (409 mg, 95% purity, quantitative yield) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.75 (d, J = 7.3 Hz, 1H), 7.37 (td, J = 7.5, 1.4 Hz, 1H), 7.30–7.19 (m, 3H), 7.11 (d, J = 6.7 Hz, 1H), 6.97 (s, 1H), 6.87 (dd, J = 9.8, 8.7 Hz, 1H), 4.17 (s, 3H), 2.87 – 2.76 (m, 1H), 2.67 – 2.56 (m, 1H), 2.47 – 2.30 (m, 2H), 1.76 – 1.66 (m, 1H), 1.54–1.41 (m, 1H).

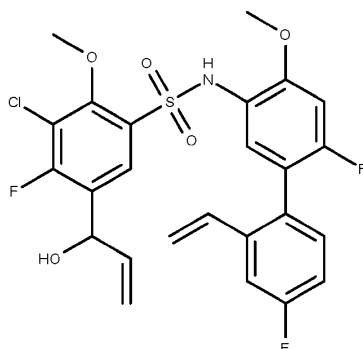
LCMS: m/z = 494.1, 496.1 [M-H]⁻, (ESI⁻), RT = 3.79, Method C

Example 317 – Synthesis of 22-Chloro-5,7-difluoro-23-methoxy-20-oxa-2λ6-thia-3,19-diazapentacyclo[16.5.2.14,8.09,14.021,25]hexacos-1(24),4(26),5,7,9,11,13,18,21(25),22-decaene 2,2-dioxide (Intermediate 118)



[0577] To a solution of acetoneoxime (83 mg, 1.13 mmol) in dry THF (4.0 mL) at 0 °C was introduced KOtBu (1.04 mL of a 1.0 M solution in tetrahydrofuran, 1.04 mmol) dropwise with stirring under nitrogen. This solution was allowed to warm to r.t. for three minutes. Separately, a stirred solution of *Intermediate 117* (200 mg, 0.403 mmol) in dry THF (5.0 mL) was cooled to 0 °C under an atmosphere of nitrogen, then the [acetone-oxime/KOtBu] suspension was introduced dropwise over 1-2 minutes. The resulting solution was stirred at r.t. for 60 minutes and 30 minutes at 50 °C. After cooling to r.t., saturated aqueous ammonium chloride was introduced and the mixture extracted with ethyl acetate (2 x 20 ml). The combined ethyl acetate extracts were dried over sodium sulfate, filtered and the filtrate concentrated in vacuo. The residue was dissolved in ethanol (5.0 mL) to which was introduced 1 M aqueous hydrochloric acid and the suspension warmed to 70 °C for 3 hours. After cooling, the mixture was concentrated in vacuo, re-dissolved in ethanol (5 mL) and evaporated again to furnish the title compound as an off-white solid (188 mg, 90% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.00 (s, 1H), 7.47 (dd, J = 8.7, 7.5 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.25 (td, J = 7.3, 1.7 Hz, 1H), 7.12 (br. s, 1H), 7.06 (dd, J = 7.4, 1.3 Hz, 1H), 6.57 (dd, J = 10.0, 8.3 Hz, 1H), 4.19 (s, 3H), 3.28 – 3.21 (m, 1H), 3.10 (dt, J = 15.3, 4.3 Hz, 1H), 2.35 (td, J = 13.3, 4.8 Hz, 1H), 2.22 – 2.08 (m, 1H), 2.03 (ddt, J = 18.6, 9.4, 3.9 Hz, 1H), 1.80 (td, J = 13.5, 4.0 Hz, 1H).

Example 318 – Synthesis of 3-Chloro-4-fluoro-N-[4-fluoro-5-(4-fluoro-2-vinyl-phenyl)-2-methoxy-phenyl]-5-(1-hydroxyallyl)-2-methoxy-benzenesulfonamide (Intermediate 119)



[0578] To a solution of 3-chloro-4-fluoro-N-[4-fluoro-5-(4-fluoro-2-vinyl-phenyl)-2-methoxy-phenyl]-5-formyl-2-methoxy-benzenesulfonamide (*synthesised using a similar method to Intermediate 114*, 66% purity, 0.898 g, 1.75 mmol) in anhydrous THF (17 mL) at -78 °C under an atmosphere of nitrogen was introduced 1 M bromo(ethenyl)magnesium (3.86 mL, 3.86 mmol) dropwise over 5 minutes. The mixture was stirred at -78 °C for 1 h and then quenched with aqueous saturated ammonium chloride (10 mL) and the reaction was warmed to r.t. Water (20 mL) and ethyl acetate (30 mL) were then added and organic layer was separated and passed through phase separator paper and then concentrated. The residue was purified by FCC (25 g SiO₂ cartridge, 0-30% EtOAc in heptane) to afford the title compound (691 mg, 72% purity, 80% Yield) as a yellow gum. NMR not taken.

LCMS: m/z = 538 & 540 [M-H]⁻, (ESI⁻), RT = 1.13, Method D

Example 319 – RF/MS hACYLase assay protocol

[0579] The final reaction volume is 20 µL and consists of buffer (50 mM Hepes pH 8.0, 10 mM MgCl₂, 0.003% BSA, 0.01% Brij35, 50 mM NaCl, 4 mM DTT) and 1 nM human ATP Citrate Lyase (hACYLase, EV12992, PP6692) using Greiner, 384 well small volume, deep well plates (Cat# 784201). A two-fold dilution series with a top concentration of 10 µM was used to record the pre-concentration response curve. Final DMSO-concentration was 1% (v/v). Compounds are pre-incubated for 30 min with the buffered enzyme solution at r.t. (20 °C), substrate solution is added (final concentrations: 15 µM Coenzyme A, 50 µM ATP and 50 µM citrate) to initiate the enzyme reaction and the enzyme reaction is incubated for additional 30 min at r.t. The reaction is quenched upon addition of 40 µL of 5% Formic acid in H₂O and centrifuged (4350 rpm at 20 °C for 10 min).

[0580] Product formation is quantified using a RF/MS-based method based on mass change of CoA (substrate) to Acetyl-CoA (product).

[0581] Table 2. A is less than 10 nM; B is at least 10 nM but less than 25 nM; C is at least 25 nM but less than 250 nM; and D is 250 nM or greater.

Table 2. RF/MS hACYLase assay data

Compound No.	RFMS IC50 GMean
1	B
2	C
3	B
4	D
5	A
6	B
7	C
8	A
9	C
10	C
11	A
12	C
13	B
14	A
15	C
16	A
17	A
18	A
19	D
20	B
21	A
22	C
23	C
24	A
25	A
26	D
27	C
28	D
29	C
30	C
31	C
32	B
33	A
34	B
35	B
36	C
37	B
38	B
39	B

Compound No.	RFMS IC50 GMean
40	B
41	B
42	B
43	B
44	C
45	C
46	C
47	A
48	A
49	A
50	A
51	B
52	B
53	B
54	A
55	B
56	B
57	C
58	C
59	C
60	A
61	B
62	B
63	B
64	B
65	C
66	C
67	D
68	A
69	B
70	D
71	D
72	C
73	D
74	A
75	D
76	C
77	B
78	B
79	B
80	B
81	B
82	B
83	A
84	A
85	D
86	B

Compound No.	RFMS IC50 GMean
87	B
88	B
89	A
90	A
91	B
92	B
93	A
94	B
95	A
96	C
97	A
98	A
99	D
100	C
101	C
102	A
103	D
104	D
105	B
106	A
107	C
108	B
109	A
110	A
111	C
112	B
113	A
114	A
115	C
120	A
126	B
127	C
128	B
129	B
130	D
131	D
132	B
133	B
134	B
135	C
136	C
137	C
138	C
139	D
140	C
141	D
142	D

Compound No.	RFMS IC50 GMean
143	C
144	C
145	D
146	B
147	C
148	C
149	B
150	D
151	A
152	C
153	D
154	C
155	A
156	C
157	C
158	B
159	B
160	B
161	A
162	C
163	C
164	C
165	C
166	C
167	B
168	C
169	B
170	B
171	C
172	D
173	D
174	D
175	C
176	D
177	A
178	D
179	A
180	D
181	A
182	A
183	D
184	D
185	B
186	D
187	A
188	C
189	C

Compound No.	RFMS IC ₅₀ GMean
190	C
191	C
192	C
193	B
194	C
195	C
196	B
197	A
198	D
199	D

Example 320 – InCell Pulse assay protocol

[0582] HEK293 cells transfected for 24 hours with pICP-ACLY(FL)-ePL (3 µg DNA per T25 flask) using FuGene HD (Promega Corp.) were harvested and cryopreserved. On the day of the assay, the frozen transfected cells were thawed at 37 °C and the storage medium (DMEM with 2 mM L-Glutamine, 10% FBS and a final concentration of DMSO 10%) was exchanged with assay medium (OptiMEM; Gibco™, ThermoFischer Scientific).

Compounds were 3-fold serially diluted in DMSO over 11-point concentration range. 100 nL of the corresponding dilutions were spotted into the assay plate (Greiner AG; 384 Well, PP, Small Volume, Deep Well, Natural, cat. no. 784201) followed by the addition of 20 µL of cell suspension adjusted with assay medium to 7.5E4 cells/mL. Subsequently, the plates were sealed and incubated for 1 hour at 37 °C. Afterwards, the plates were fixed upside down in a rack and incubated in a 55 °C water bath for 10 minutes. Following this heat pulse step, plates were allowed to reach room temperature for 10 minutes and centrifuged for a few seconds at 1000 rpm and room temperature. 25 µL EA detection solution (working solution: 0.0167x InCell EA Reagent, 0.15x InCell Dilution Buffer, 0.167x InCell Lysis Buffer; 0.667x InCell Substrate Reagent; InCell Hunter Detection kit; Eurofins DiscoverX; cat.no. 96-0079) were added to each well. Afterwards, 42 µL were transferred from the assay plate to the detection plate (Corning Inc., 384-well Low Flange Black Flat Bottom Polystyrene NBS Microplate, cat.no. 3575), followed by an incubation for 1 hour at room temperature, a centrifugation step for 1 minute at 1000 rpm and the detection of the luminescence signal using an EnVision microplate reader (Perkin Elmer Inc.). Concentration-response curve-fitting and IC₅₀ determination was performed using Evotec's in-house evaluation software APlus with a four-parameter non-linear regression fit model. Data was normalized to 0.5%

(final concentration) DMSO as low/negative control and 1 μ M (final concentration) NDI-094311 as high/positive control.

[0583] Table 3. A is less than 0.15 μ M; B is at least 0.15 μ M but less than 0.5 μ M; C is at least 0.5 μ M but less than 50 μ M; and D is 50 μ M or greater.

Table 3. InCell Pulse assay data

Compound No.	InCell Pulse IC50 GMean
1	B
2	B
3	C
4	D
5	A
6	A
7	D
8	A
9	D
10	C
11	B
12	D
13	C
14	A
15	C
16	B
17	A
18	A
19	D
20	B
21	A
22	B
23	C
24	C
25	A
26	D
27	D
28	D
29	B
30	B
31	A
32	A
33	A
34	C
35	B
36	D
37	C
38	A
39	A

Compound No.	InCell Pulse IC50 GMean
40	B
41	A
42	D
43	B
44	B
45	A
46	B
47	A
48	A
49	B
50	B
51	A
52	B
53	A
54	D
55	B
56	B
57	B
58	A
59	B
60	A
61	B
62	A
63	A
64	C
65	D
66	D
67	D
68	A
69	D
70	D
71	D
72	C
73	D
74	C
75	D
76	D
77	D
78	B
79	B
80	B
81	C
82	C
83	B
84	B
85	C
86	C

Compound No.	InCell Pulse IC50 GMean
87	A
88	C
89	B
90	C
91	C
92	A
93	B
94	C
95	A
96	D
97	A
98	A
99	D
100	C
101	C
102	A
103	D
104	D
105	A
106	A
107	B
108	A
109	A
110	A
120	A
126	B
127	B
128	B
129	B
130	D
131	C
132	C
133	C
134	B
135	B
136	A
137	C
138	B
139	D
140	C
141	D
142	D
143	C
144	C
145	C
146	C
147	B

Compound No.	InCell Pulse IC50 GMean
148	C
149	B
150	D
151	B
152	C
153	C
154	C
155	B
156	C
157	C
158	B
159	C
160	B
161	B
162	B
163	A
164	D
165	A
166	B
167	C
168	A
169	A
170	D
171	B
172	C
173	C
174	D
175	D
176	D
177	B
178	D
179	B
180	C
181	B
182	B
183	D
184	D
185	C
186	C
187	A
188	A
189	C
190	A
191	A
192	A
193	A
194	C

Compound No.	InCell Pulse IC50 GMean
195	B
196	A
197	A
198	D
199	D

Example 321 – Fatty acid synthesis (FAS) assay in HepG2 cells

[0584] HepG2 cells were seeded into white clear-bottom 96-well plates (50,000/well) coated with collagen and incubated at 37 °C for 16-24 hours. After that plates were washed once with 100 µL PBS (+CaCl₂ +MgCl₂) and 50 µL assay medium (RPMI 1860 containing 11 mM glucose, 10 mM HEPES and 1 nM Insulin) per well was added. Test substances in assay medium were added (10 µL, 0.5% DMSO) and incubated for 20 min at 37 °C. After that 10 µL assay medium containing 14C-citrate (final concentration 50 µM) and PrestoBlue reagent (1 x final concentration; ThermoFisher) were added and incubated for 90 min (37 °C, 5% CO₂). Cell viability was measured (Multiskan FC, microplate reader, absorbance 570 nm). Medium was removed by inverting the plate and cells were washed once with 100 µL ice-cold PBS. Cells were lysed with 50 µL lysis buffer (0.1 N NaOH, 0.1% Triton X-100) and plate was sealed with Tape Pads and vortexed. For the saponification reaction plates were incubated for 16-24 hours at 80 °C. Seals were removed and 200 µL 0.1 N HCl was added for neutralisation of the pH. 150 µL from each well was transferred into the corresponding wells of a 96-well Flash plate (Perkin Elmer) and sealed with TopSeal A (Perkin Elmer). Plates were incubated for 4 h at 70 °C and for 1 h at room temperature in the dark. Signal of 14C radioactivity was measured (TopCount). As a positive control 5 mM unlabelled citrate or C75 (Sigma, C5490) was applied.

[0585] Table 4. A is less than 1.5 µM; B is at least 1.5 µM but less than 3 µM; and C is 3 µM or greater.

Table 4. Fatty acid synthesis (FAS) assay data

Compound No.	FAS IC50 GMean
2	B
3	C
5	C
6	B
8	B
10	C
11	B
12	C

Compound No.	FAS IC50 GMean
13	C
14	B
18	A
20	C
21	A
22	C
23	C
25	A
26	C
27	C
29	C
30	C
31	A
32	B
38	A
39	A
47	A
48	A
49	C
51	A
68	A
74	C
75	C
78	B
83	B
87	A
89	C
95	A
126	B
129	B
132	C
134	B
136	A
138	C
144	B
151	B
162	C
163	B
165	C
166	C
169	B
177	B
179	C
185	C
191	A
193	A
195	A

Compound No.	FAS IC50 GMean
197	A

INCORPORATION BY REFERENCE

[0586] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

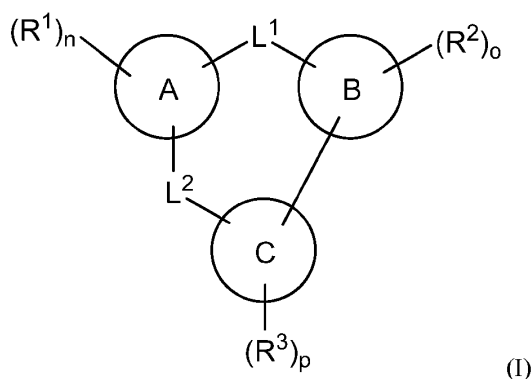
EQUIVALENTS

[0587] The disclosure may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the disclosure described herein. Scope of the disclosure is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

CLAIMS

WE CLAIM:

1. A compound of formula (I)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl or 9-membered bicyclic heteroaryl;

Ring B is phenyl or 5-6 membered heteroaryl;

Ring C is selected from the group consisting of phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, and 5-6 membered heteroaryl;

R^1 is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^2 is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkoxy, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from R^{2A} , or

optionally two R^2 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl, a 9-membered bicyclic heterocyclyl, or a 9-membered bicyclic heteroaryl;

R^3 is independently, for each occurrence, selected from the group consisting of cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and $-C(O)N(R^A)(R^B)$, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkoxy;

L^1 is $^*-S(O)_2N(R^C)-^{**}$, wherein $*$ denotes the point of attachment to Ring A and ** denotes the point of attachment to Ring B;

L^2 is selected from the group consisting of $\#-C(O)O-\#\#$, $\#-C(O)-(C_{1-6}alkyl)-\#\#$, $\#-C(O)O-(C_{1-6}alkyl)-\#\#$, $\#-C(O)O-(C_{1-6}alkyl)-O-\#\#$, $\#-C(O)O-(C_{1-6}haloalkyl)-\#\#$, and $C_{1-6}alkyl$, wherein $\#$ denotes the point of attachment to Ring A and $\#\#$ denotes the point of attachment to Ring C;

R^{2A} is halogen or $C_{1-6}alkoxy$;

R^A is hydrogen or $C_{1-6}alkyl$;

R^B is hydrogen or $C_{1-6}alkyl$;

R^C is hydrogen or $C_{1-3}alkyl$;

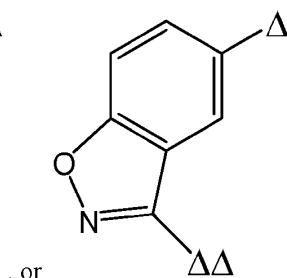
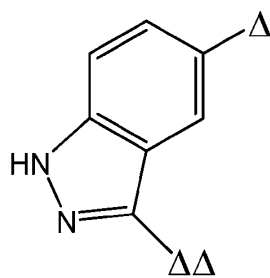
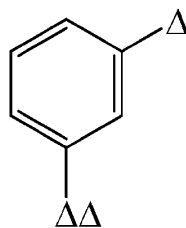
n is 2 or 3;

o is 0, 1, or 2; and

p is 0, 1, or 2.

2. The compound of claim 1, wherein Ring A is phenyl, indazolyl, or benzo[d]isoxazolyl.

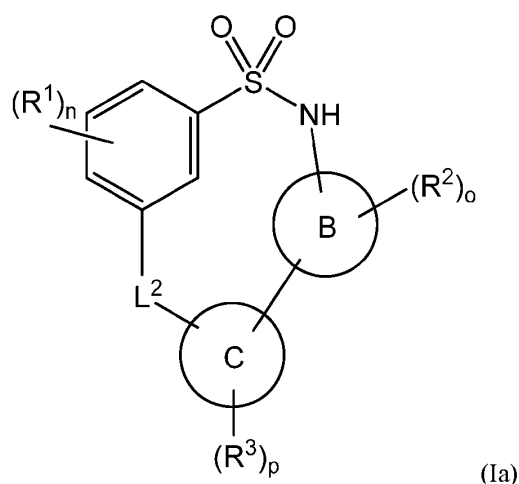
3. The compound of claim 1 or 2, wherein Ring A is



, or , wherein Δ denotes the point of attachment to L^1 and $\Delta\Delta$ denotes the point of attachment to L^2 .

4. The compound of any one of claims 1-3, wherein L^1 is $^*-S(O)_2N(H)-^{**}$, wherein * denotes the point of attachment to Ring A and ** denotes the point of attachment to Ring B.

5. A compound of formula (Ia)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring B is phenyl or 5-6 membered heteroaryl;

Ring C is selected from the group consisting of phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, and 5-6 membered heteroaryl;

R^1 is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^2 is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{1-6} haloalkoxy, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from R^{2A} ; or

optionally two R^2 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl, a 9-membered bicyclic heterocyclyl, or a 9-membered bicyclic heteroaryl;

R^3 is independently, for each occurrence, selected from the group consisting of cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and $-C(O)N(R^A)(R^B)$, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents independently selected from C_{1-6} alkoxy;

L^2 is selected from the group consisting of $\#-C(O)O-##$, $\#-C(O)-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-##$, $\#-C(O)O-(C_{1-6}alkyl)-O-##$, $\#-C(O)O-(C_{1-6}haloalkyl)-##$, and $C_{1-6}alkyl$, wherein # denotes the point of attachment to Ring A and ## denotes the point of attachment to Ring C;

R^{2A} is halogen or C_{1-6} alkoxy;

R^A is hydrogen or C_{1-6} alkyl;

R^B is hydrogen or C_{1-6} alkyl;

n is 2 or 3;

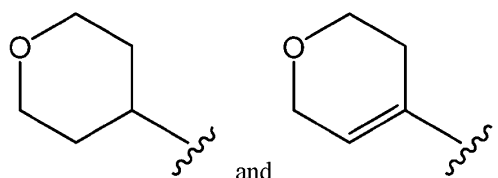
o is 1 or 2; and

p is 0, 1, or 2.

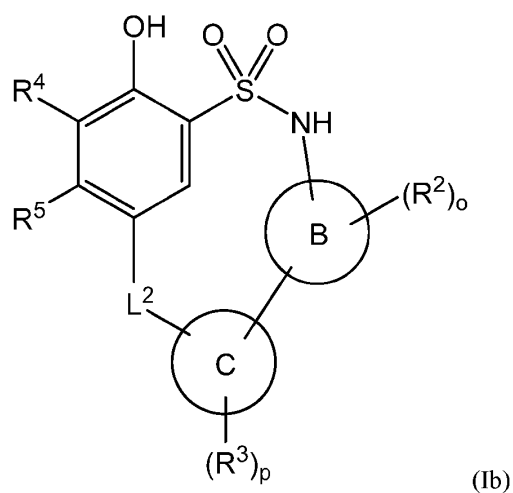
6. The compound of any one of claims 1-5, wherein n is 2.

7. The compound of any one of claims 1-5, wherein n is 3.

8. The compound of any one of claims 1-7, wherein R^1 is, independently, for each occurrence, selected from the group consisting of bromo, chloro, fluoro, hydroxyl, $-CH_3$, $-CF_3$, cyclopropyl,



9. A compound of formula (Ib)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring B is phenyl or 5-6 membered heteroaryl;

Ring C is phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, C₃₋₆cycloalkyl, or 5-6 membered heteroaryl;

R² is independently, for each occurrence, selected from the group consisting of halogen, hydroxyl, cyano, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₁₋₆haloalkoxy, -O-C₃₋₆cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from R^{2A}; or

optionally two R² may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl, a 9-membered bicyclic heterocyclyl, or a 9-membered bicyclic heteroaryl;

R³ is independently, for each occurrence, selected from the group consisting of cyano, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, and -C(O)N(R^A)(R^B), wherein the C₁₋₆alkyl is optionally substituted with one or more substituents independently selected from C₁₋₆alkoxy;

R⁴ is selected from the group consisting of halogen, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, and 6-membered heterocyclyl;

R⁵ is hydrogen or halogen;

L² is selected from the group consisting of #-C(O)O-##, #-C(O)-(C₁₋₆alkyl)-##, #-C(O)O-(C₁₋₆alkyl)-##, #-C(O)O-(C₁₋₆alkyl)-O-##, #-C(O)O-(C₁₋₆haloalkyl)-##, and C₁₋₆alkyl, wherein # denotes the point of attachment to Ring A and ## denotes the point of attachment to Ring C;

R^{2A} is halogen or C₁₋₆alkoxy;

R^A is hydrogen or C₁₋₆alkyl;

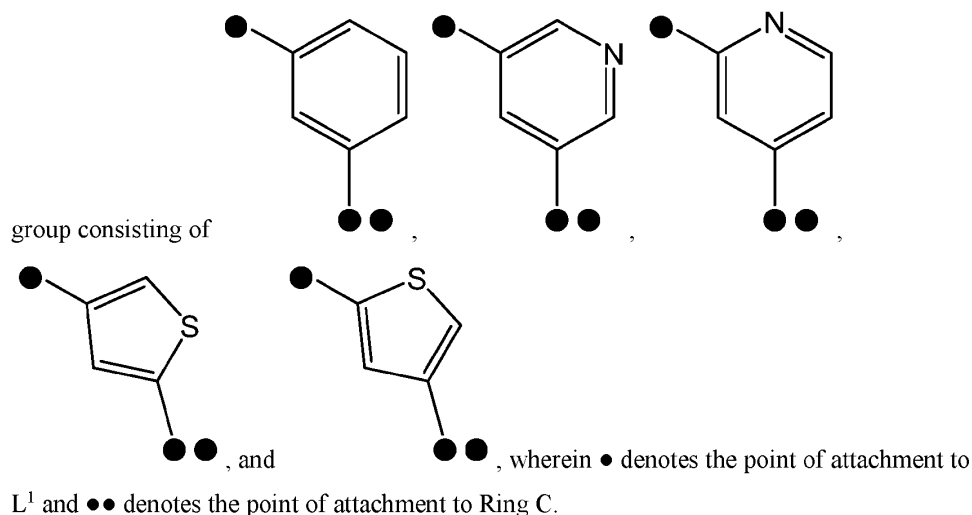
R^B is hydrogen or C₁₋₆alkyl;

o is 1 or 2; and

p is 0, 1, or 2.

10. The compound of any one of claims 1-9, wherein Ring B is phenyl, thiophenyl, or pyridinyl.

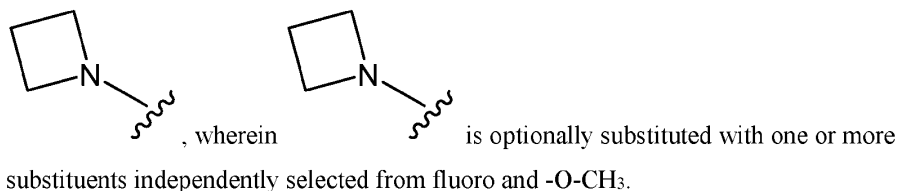
11. The compound of any one of claims 1-10, wherein Ring B is selected from the



12. The compound of any one of claims 1-11, wherein o is 1.

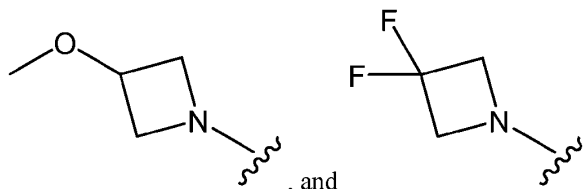
13. The compound of any one of claims 1-11, wherein o is 2.

14. The compound of any one of claims 1-13, wherein R^2 is, independently, for each occurrence, selected from the group consisting of chloro, fluoro, cyano, hydroxyl, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CH}_2\text{CH}_3$, $-\text{O}-\text{CHF}_2$, $-\text{O}-\text{CF}_3$, cyclopropyl, $-\text{O}-\text{cyclopropyl}$, morpholinyl, and



15. The compound of any one of claims 1-14, wherein R^2 is, independently, for each occurrence, selected from the group consisting of chloro, fluoro, cyano, hydroxyl, $-\text{CH}_3$, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CH}_2\text{CH}_3$, $-\text{O}-\text{CHF}_2$, $-\text{O}-\text{CF}_3$, cyclopropyl, $-\text{O}-\text{cyclopropyl}$, morpholinyl, and

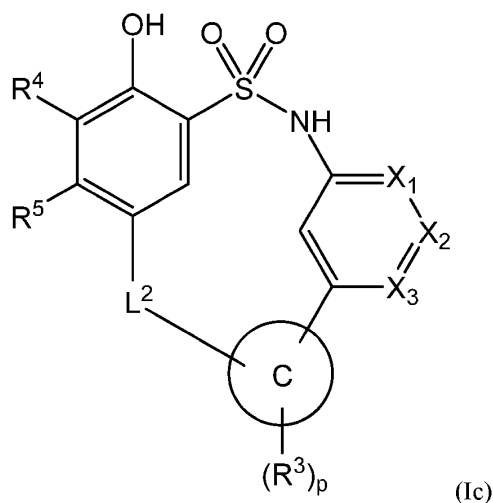
CF₃, -O-CH₃, -O-CH₂CH₃, -O-CHF₂, -O-CF₃, cyclopropyl, -O-cyclopropyl, morpholinyl,



16. The compound of any one of claims 1-11 and 13, wherein two R² groups on different carbon atoms are taken together, along with the atoms to which they are attached, to form a 5 membered carbocyclyl, a 5-membered heterocyclyl, or a 5-membered heteroaryl.

17. The compound of any one of claims 1-11, wherein o is 0.

18. A compound of formula (Ic)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

Ring C is selected from the group consisting of phenyl, 9-membered bicyclic heterocyclyl, 9-membered bicyclic carbocyclyl, and 5-6 membered heteroaryl;

R³ is independently, for each occurrence, selected from the group consisting of cyano, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₁₋₆haloalkoxy, and -C(O)N(R^A)(R^B), wherein the C₁₋₆alkyl is optionally substituted with one or more substituents independently selected from C₁₋₆alkoxy;

R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^5 is hydrogen or halogen;

X_1 is CR^6 or N;

X_2 is CR^7 or N;

X_3 is CR^8 or N;

R^6 is selected from the group consisting of hydrogen, cyano, halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from halogen;

R^7 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with C_{1-6} alkoxy; or

R^6 and R^7 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic heteroaryl or a 9-membered bicyclic heterocyclyl;

R^8 is hydrogen or halogen; or

R^7 and R^8 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl;

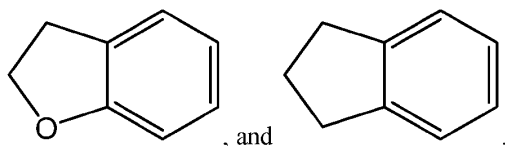
L^2 is selected from the group consisting of $\#-C(O)O-\##$, $\#-C(O)-(C_{1-6}alkyl)-\##$, $\#-C(O)O-(C_{1-6}alkyl)-\##$, $\#-C(O)O-(C_{1-6}alkyl)-O-\##$, $\#-C(O)O-(C_{1-6}haloalkyl)-\##$, and $C_{1-6}alkyl$, wherein # denotes the point of attachment to Ring A and ## denotes the point of attachment to Ring C;

R^A is hydrogen or $C_{1-6}alkyl$;

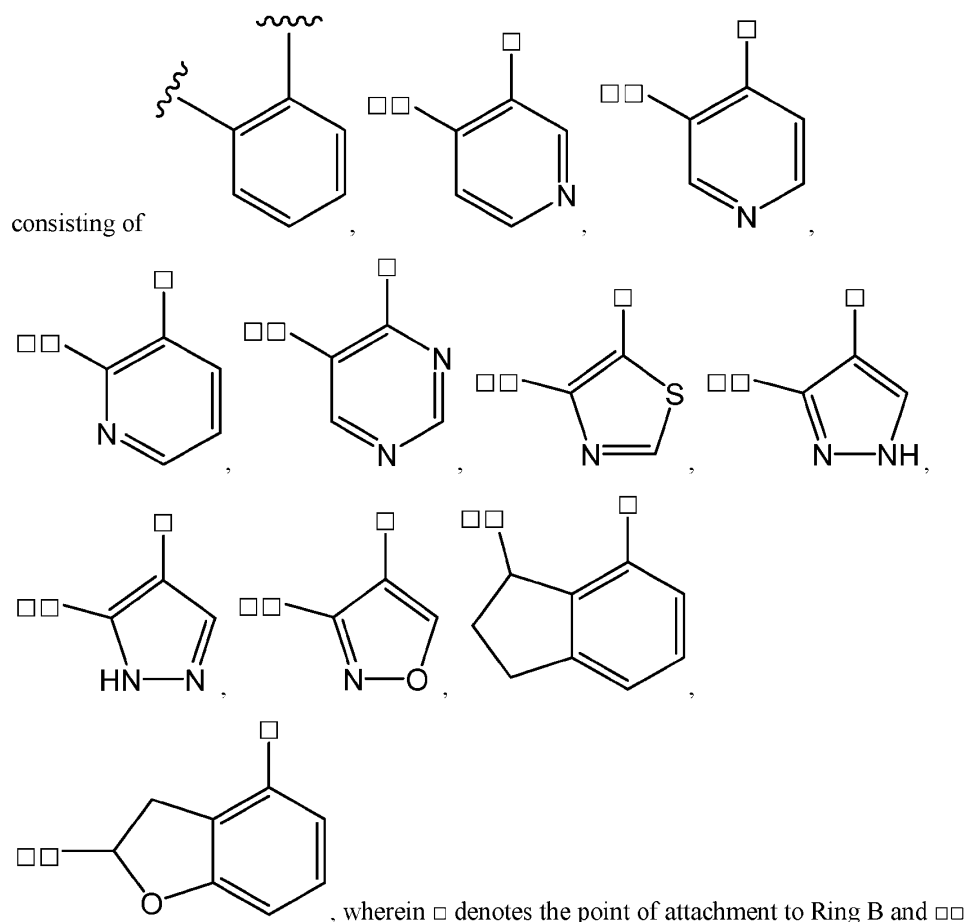
R^B is hydrogen or $C_{1-6}alkyl$; and

p is 0, 1, or 2.

19. The compound of any one of claims 1-18, wherein Ring C is selected from the group consisting of cyclopropyl, phenyl, pyridinyl, thiazolyl, pyrimidinyl, pyrazolyl, isoxazolyl,



20. The compound of any one of claims 1-19, wherein Ring C is selected from the group



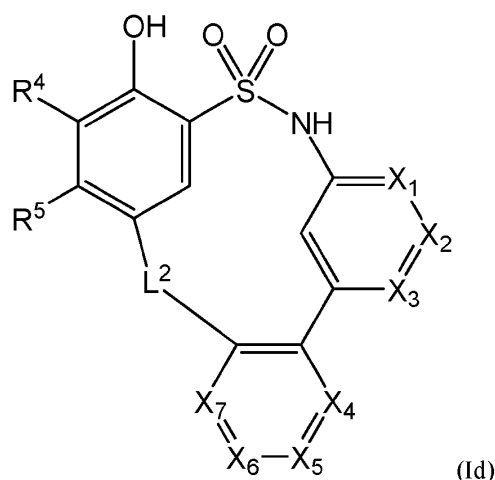
21. The compound of any one of claims 1-20, wherein p is 1.

22. The compound of any one of claims 1-20, wherein p is 2.

23. The compound of any one of claims 1-22, wherein R³ is, independently, for each occurrence, selected from the group consisting of cyano, bromo, fluoro, -CH₃, -CHF₂, -CF₃, -O-CH₃, -O-CHF₂, -CH₂CH₂-O-CH₃, -C(O)NH₂, and -CH₂CHF₂.

24. The compound of any one of claims 1-20, wherein p is 0.

25. A compound of formula (Id)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R^5 is hydrogen or halogen;

X_1 is CR^6 or N;

X_2 is CR^7 or N;

X_3 is CR^8 or N;

X_4 is CH or N;

X_5 is CR^9 or N;

X_6 is CR^{10} or N;

X_7 is CR^{11} or N;

R^6 is selected from the group consisting of hydrogen, cyano, halogen, hydroxyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from halogen;

R^7 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, $-O-C_{3-6}$ cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with C_{1-6} alkoxy; or

R^6 and R^7 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic heteroaryl or a 9-membered bicyclic heterocyclyl;

R^8 is hydrogen or halogen; or

R^7 and R^8 may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl;

R^9 is selected from the group consisting of hydrogen, cyano, halogen, C_{1-6} haloalkyl, $-C(O)N(R^A)(R^B)$, and C_{1-6} alkoxy;

R^{10} is selected from the group consisting of hydrogen, halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, and C_{1-6} alkoxy;

R^{11} is hydrogen, halogen, or C_{1-6} alkyl; and

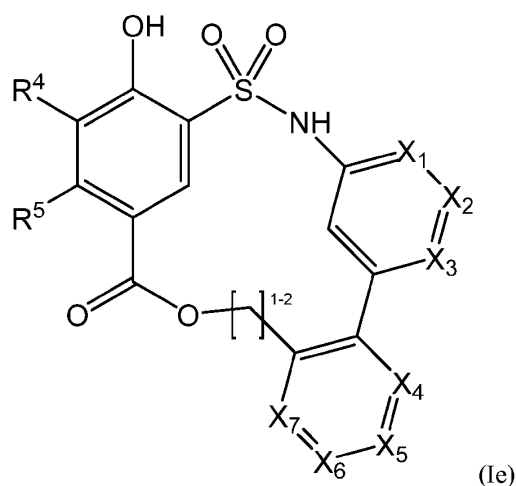
L^2 is selected from the group consisting of $\#-C(O)O-\#\#$, $\#-C(O)-(C_{1-6}alkyl)-\#\#$, $\#-C(O)O-(C_{1-6}alkyl)-\#\#$, $\#-C(O)O-(C_{1-6}alkyl)-O-\#\#$, $\#-C(O)O-(C_{1-6}haloalkyl)-\#\#$, and $C_{1-6}alkyl$, wherein $\#$ denotes the point of attachment to Ring A and $\#\#$ denotes the point of attachment to Ring C;

R^A is hydrogen or C_{1-6} alkyl; and

R^B is hydrogen or C_{1-6} alkyl.

26. The compound of any one of claims 1-25, wherein L^2 is selected from the group consisting of $\#-C(O)O-\#\#$, $\#-C(O)O-CH_2-\#\#$, $\#-C(O)O-C(CH_3)(H)-\#\#$, $\#-C(O)O-C(CH_2F)(H)-\#\#$, $\#-C(O)O-(CH_2)_2-\#\#$, $\#-C(O)O-(CH_2)_2-O-\#\#$, $-(CH_2)_2-$, $-(CH_2)_3-$, and $\#-C(O)-(CH_2)_3-\#\#$, wherein $\#$ denotes the point of attachment to Ring A and $\#\#$ denotes the point of attachment to Ring C.

27. A compound of formula (Ie)



or a stereoisomer and/or a pharmaceutically acceptable salt thereof, wherein:

R^4 is selected from the group consisting of halogen, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, and 6-membered heterocyclyl;

R⁵ is hydrogen or halogen;

X₁ is CR⁶ or N;

X₂ is CR⁷ or N;

X₃ is CR⁸ or N;

X₄ is CH or N;

X₅ is CR⁹ or N;

X₆ is CR¹⁰ or N;

X₇ is CR¹¹ or N;

R⁶ is selected from the group consisting of hydrogen, cyano, halogen, hydroxyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, C₃₋₆cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with one or more substituents independently selected from halogen;

R⁷ is selected from the group consisting of hydrogen, cyano, halogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, -O-C₃₋₆cycloalkyl, and 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl is optionally substituted with C₁₋₆alkoxy; or

R⁶ and R⁷ may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic heteroaryl or a 9-membered bicyclic heterocyclyl;

R⁸ is hydrogen or halogen; or

R⁷ and R⁸ may be taken together, along with the ring to which they are attached, to form a 9-membered bicyclic carbocyclyl;

R⁹ is selected from the group consisting of hydrogen, cyano, halogen, C₁₋₆haloalkyl, -C(O)N(R^A)(R^B), and C₁₋₆alkoxy;

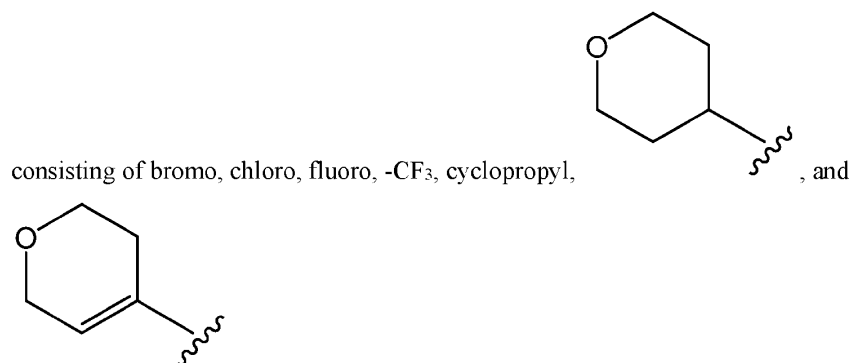
R¹⁰ is selected from the group consisting of hydrogen, halogen, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, and C₁₋₆alkoxy;

R¹¹ is hydrogen, halogen, or C₁₋₆alkyl;

R^A is hydrogen or C₁₋₆alkyl; and

R^B is hydrogen or C₁₋₆alkyl.

28. The compound of any one of claims 9-27, wherein R^4 is selected from the group



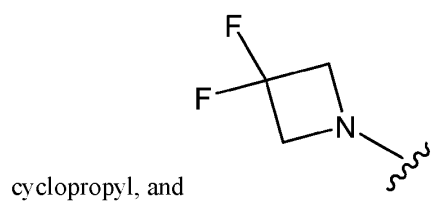
29. The compound of any one of claims 9-28, wherein R^5 is hydrogen or fluoro.

30. The compound of any one of claims 18-29, wherein X_1 is CR^6 , X_2 is CR^7 , and X_3 is CR^8 .

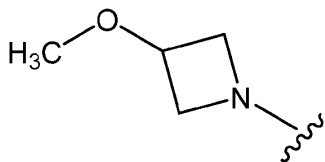
31. The compound of any one of claims 18-29, wherein X_1 is CR^6 , X_2 is N, and X_3 is CR^8 .

32. The compound of any one of claims 18-29, wherein X_1 is N, X_2 is CR^7 , and X_3 is CR^8 .

33. The compound of any one of claims 18-31, wherein R^6 is selected from the group consisting of hydrogen, cyano, chloro, fluoro, $-CF_3$, $-O-CH_3$, $-O-CH_2-CH_3$, $-O-CHF_2$, $-O-CF_3$,



34. The compound of any one of claims 18-30 and 32, wherein R^7 is selected from the group consisting of hydrogen, cyano, chloro, fluoro, $-CH_3$, $-CF_3$, cyclopropyl, $-O-$



cyclopropyl, morpholinyl, and

35. The compound of any one of claims 18-34, wherein R^8 is hydrogen or fluoro.

36. The compound of any one of claims 18-30, wherein R^6 and R^7 are taken together, along with the atoms to which they are attached, to form a 5 membered heteroaryl or a 5 membered heterocyclyl.

37. The compound of any one of claims 18-30, wherein R^7 and R^8 may be taken together, along with the atoms to which they are attached, to form a 5-6 membered carbocyclyl.

38. The compound of any one of claims 25-37, wherein X_4 is CH, X_5 is CR^9 , X_6 is CR^{10} , and X_7 is CR^{11} .

39. The compound of any one of claims 25-37, wherein X_4 is CH, X_5 is N, X_6 is CR^{10} , and X_7 is CR^{11} .

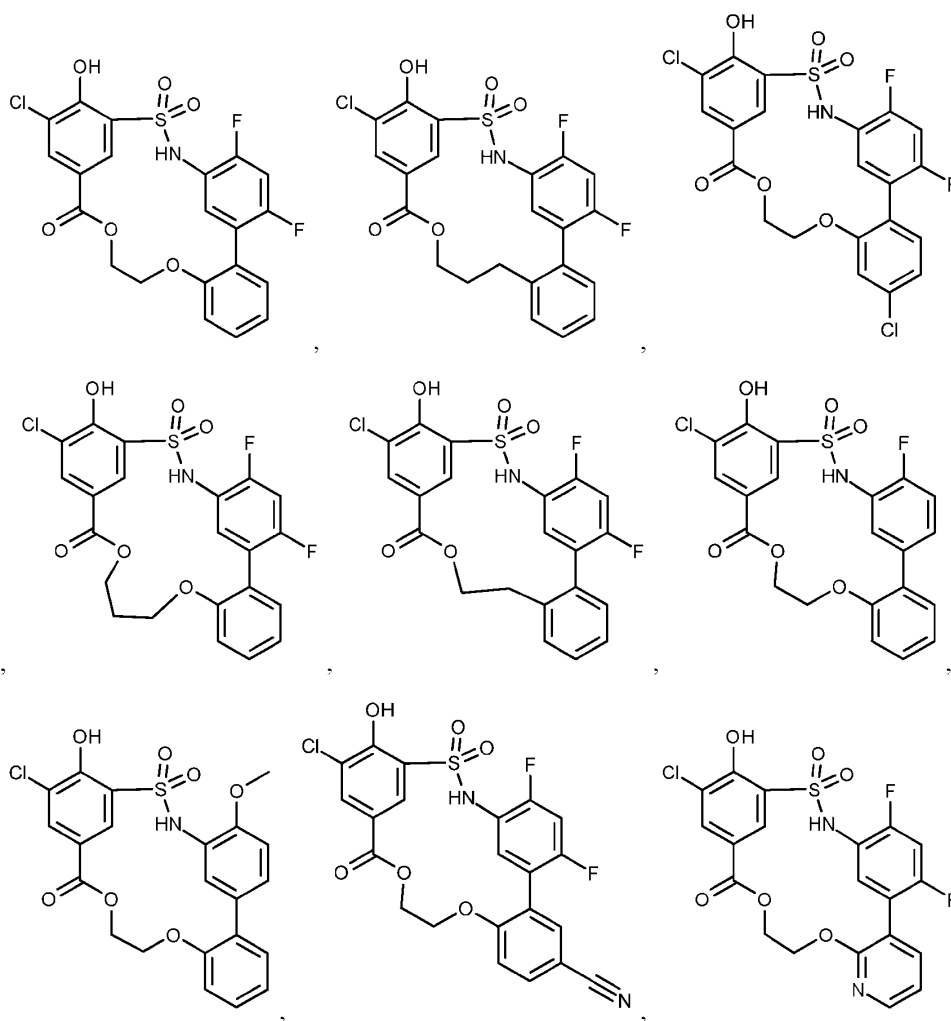
40. The compound of any one of claims 25-37, wherein X_4 is CH, X_5 is CR^9 , X_6 is N, and X_7 is CR^{11} .

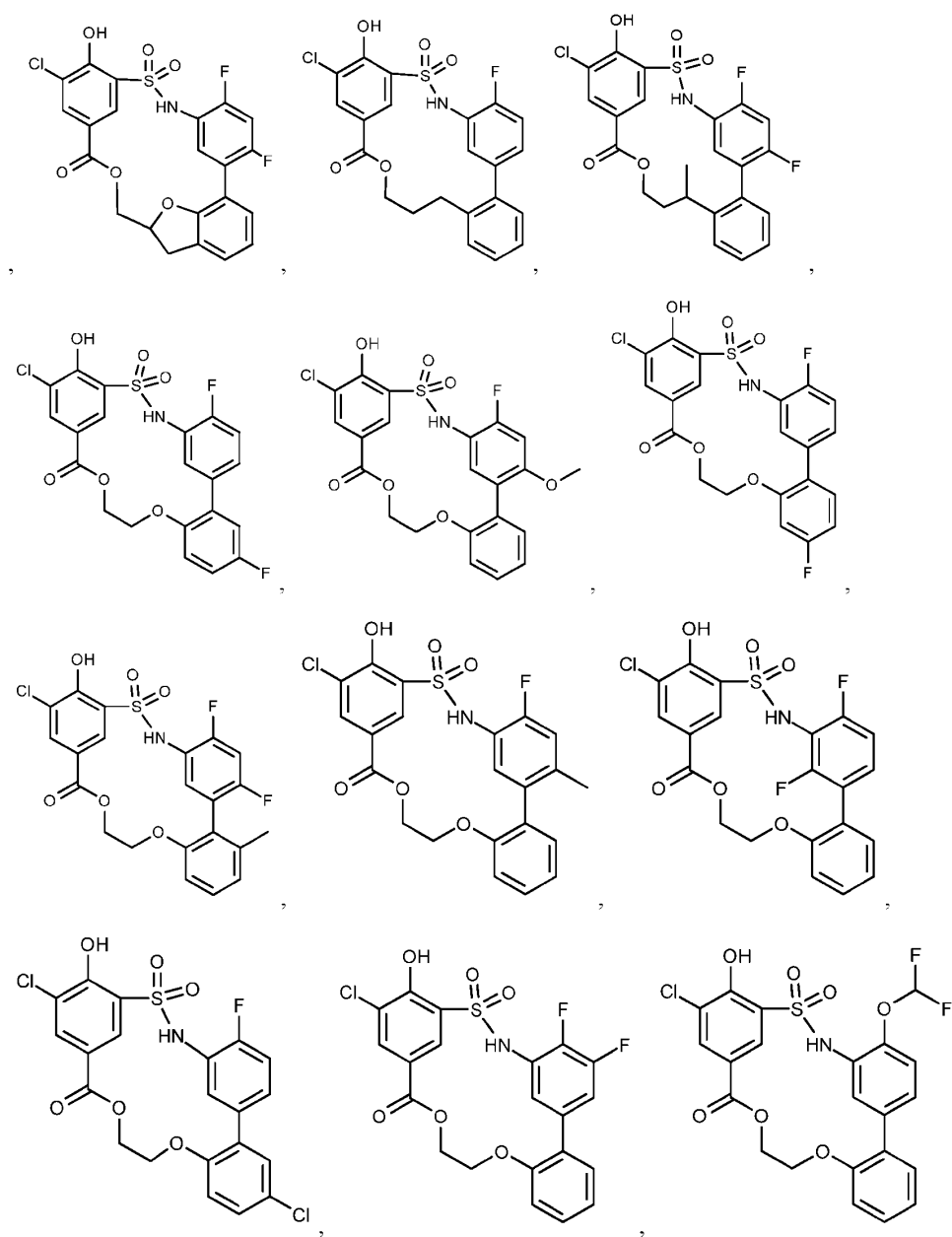
41. The compound of any one of claims 25-37, wherein X_4 is CH, X_5 is CR^9 , X_6 is CR^{10} , and X_7 is N.

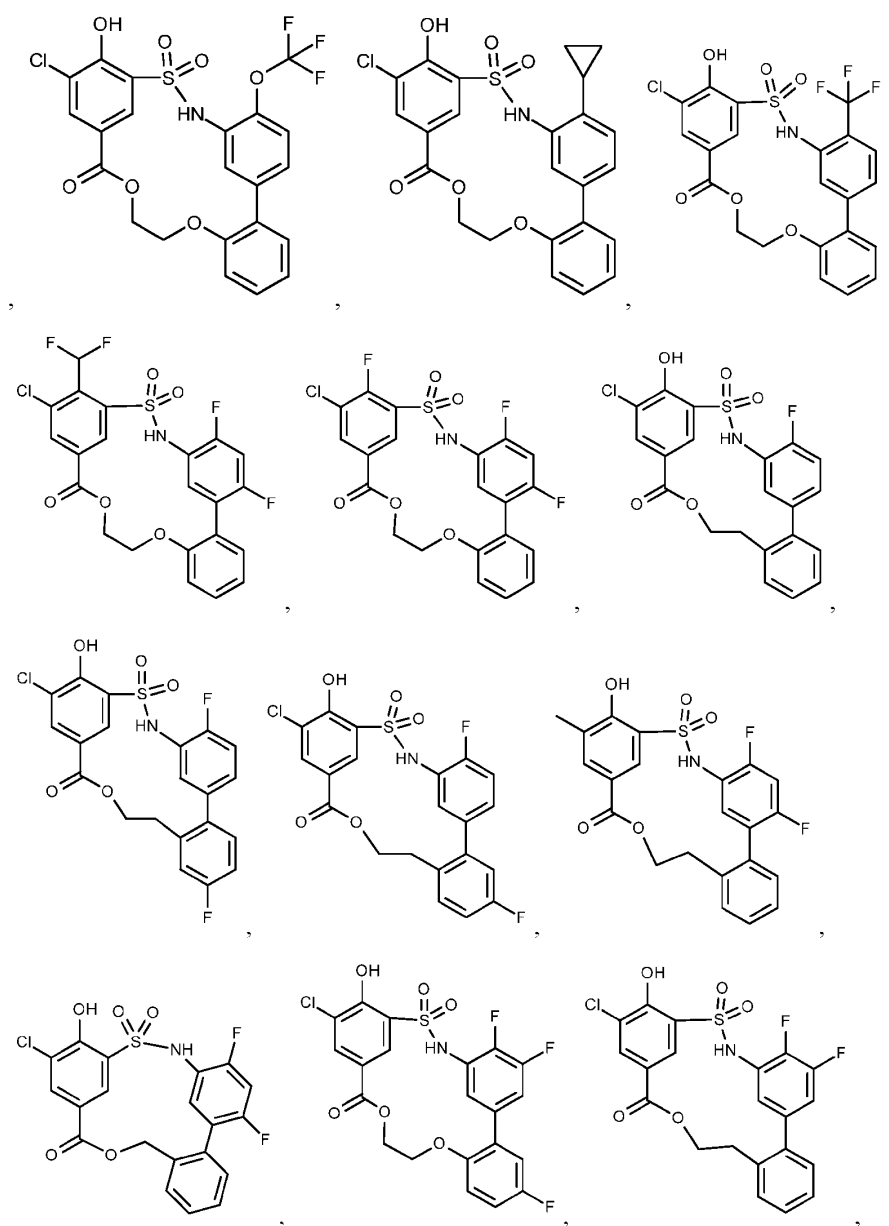
42. The compound of any one of claims 25-37, wherein X_4 is N, X_5 is CR^9 , X_6 is N, and X_7 is CR^{11} .

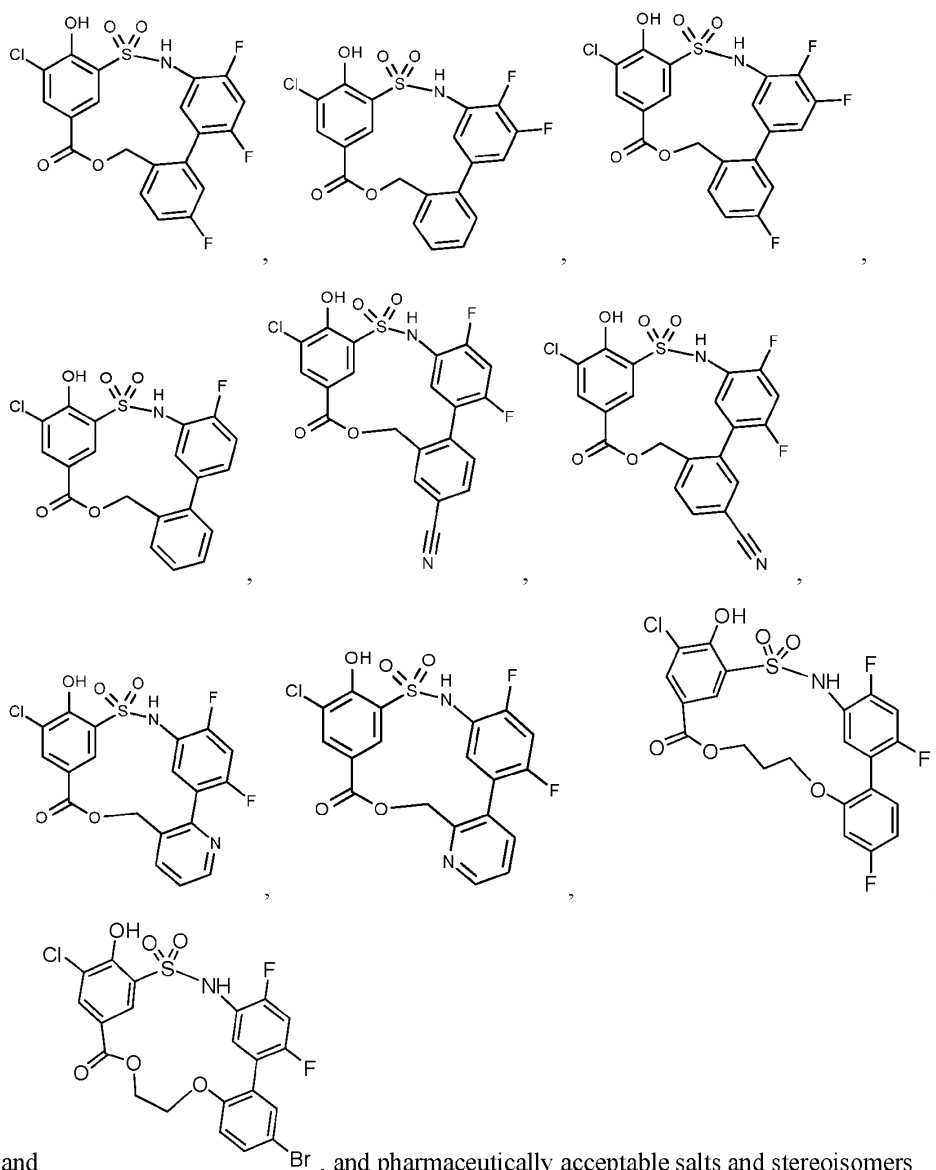
43. The compound of any one of claims 25-38 and 40-42, wherein R^9 is selected from the group consisting of hydrogen, cyano, bromo, fluoro, $-CF_3$, $-O-CH_3$, and $-C(O)NH_2$.

44. The compound of any one of claims 25-39 and 41, wherein R^{10} is selected from the group consisting of hydrogen, fluoro, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{O}-\text{CH}_3$, and $-\text{O}-\text{CHF}_2$.
45. The compound of any one of claims 25-40 and 42, wherein R^{11} is hydrogen, fluoro, or CH_3 .
46. The compound of any one of claims 1-42, wherein the compound of formula (I) is not a compound selected from the group consisting of:









and
thereof.

47. A compound selected from any compound set forth in Table 1, or a pharmaceutically acceptable salt thereof.

48. A pharmaceutical composition comprising a compound of any one of claims 1-47; and a pharmaceutically acceptable carrier.

49. A method of inhibiting ACLY in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-47 or a pharmaceutical composition of claim 48.
50. The method of claim 49, wherein the subject has a liver condition, disease, or disorder.
51. The method of claim 49, wherein the liver condition, disease, or disorder is NAFLD/MAFLD or NASH/MASH.
52. The method of claim 49, wherein the subject has type-2 diabetes.
53. The method of claim 49, wherein the subject has inflammation.
54. The method of claim 49, wherein the subject has chronic kidney disease.
55. The method of claim 49, wherein the subject has autoimmunity.
56. The method of claim 49, wherein the subject has cancer.
57. A method of treating NAFLD/MAFLD in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-47 or a pharmaceutical composition of claim 48.
58. A method of treating NASH/MASH in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-47 or a pharmaceutical composition of claim 48.
59. A method of treating type-2 diabetes in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-47 or a pharmaceutical composition of claim 48.

60. A method of treating inflammation in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-47 or a pharmaceutical composition of claim 48.
61. A method of treating chronic kidney disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-47 or a pharmaceutical composition of claim 48.
62. A method of treating autoimmunity in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-47 or a pharmaceutical composition of claim 48.
63. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-47 or a pharmaceutical composition of claim 48.
64. A method of treating a condition, disease, or disorder as described herein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-47 or of the pharmaceutical composition of claim 48.