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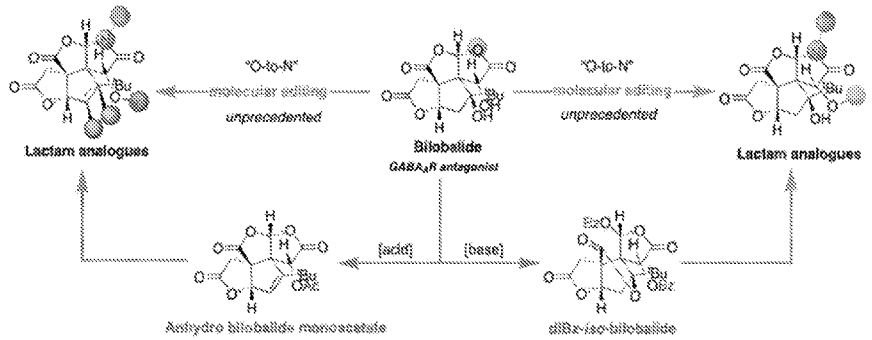
(54) Title: BILOBALIDE DERIVATIVE COMPOUNDS FOR TREATING NEUROLOGICAL DISEASES AND CANCERS

[Fig. 1A]



(57) Abstract: Provided herein are bilobalide derivative compounds, processes for making, methods of using, and uses thereof for preventing or treating neurological disease and cancer.

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Description

Title of Invention: BILOBALIDE DERIVATIVE COMPOUNDS FOR TREATING NEUROLOGICAL DISEASES AND CANCERS

[0001] CROSS-REFERENCE TO RELATED APPLICATION

[0002] This application claims benefit under 35 U.S.C. § 119 (e) of U.S. Provisional Application having Serial No. 63/517,627 filed on Aug 4, 2023 and U.S. Provisional Application having Serial No. 63/610,394 filed on Dec 14, 2023, the entire contents of which are hereby incorporated by reference herein.

FIELD OF INVENTION

[0003] This application relates to bilobalide derivative compounds, processes for making, methods of using, and uses of said compounds for preventing or treating cancers and neurological diseases.

BACKGROUND

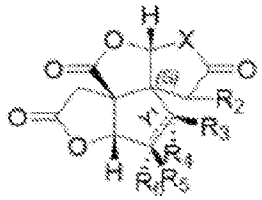
[0004] High-throughput screening of chemical libraries is a common starting point in modern drug discovery. Unfortunately, many existing libraries consist of planar molecules with minimal structural or stereochemical complexity, thereby impeding the process of drug discovery.

[0005] Terpene trilactones (TTLs) , such as ginkgolides and bilobalide, are polyoxygenated diterpenoids isolated from the Ginkgo tree. Bilobalide is not acutely toxic and has been demonstrated to exert a broad range of biological activities. However, the therapeutic potential of bilobalide is limited and its effects on the mammalian central nervous system, neurological diseases or cancers are not fully corroborated because of its instability. Due to the synthetic challenges for structural modification of bilobalide, no synthetic routes exist that enable facile access to bilobalide analogues for systematic structure-activity relationship (SAR) studies. As such, no effective bilobalide compounds have been identified that are useful for treating diseases.

SUMMARY

[0006] Disclosed herein are novel compounds useful against cancers, processes for making, methods of using, and intermediates used in preparing the novel compounds.

[0007] In some embodiments, provided is a compound of Formula I:



(Formula I)

[0008] or a stereomer, a tautomer, or a pharmaceutically acceptable salt thereof,

[0009] wherein

[0010] X is -O-, -NR^1-, -N=CR^1-NH-, or -NR^1-NH-; wherein when X is -O-, R^1 is absent;

[0011] bond Y^1 is between R^4 and R^5 and is a single bond or a double bond;

[0012] R^1 is H, R^{1B}, or - $(L^1)_u$- $(Z^1)_v$; wherein

[0013] L^1 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, O, or S; wherein L^1 is optionally substituted with 1-3 occurrences of halo, CN, R, OR', or R^{1C};

[0014] u is 0 or 1;

[0015] v is 0 or 1;

[0016] Z^1 is a 5-16 membered aromatic or nonaromatic monocyclic, bicyclic, or tricyclic ring system having 0-7 heteroatoms selected from O, N, or S; wherein Z^1 is optionally substituted with 1-5 occurrences of R^{1A}, R^{1C} or combinations thereof;

[0017] R^{1A} is - $(L^2)_m$- $(Z^2)_w$; wherein

[0018] L^2 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si; wherein L^2 is optionally substituted with 1-3 occurrences of halo, CN, R, OR' or R^{1C};

[0019] m is 0 or 1;

[0020] w is 0 or 1;

[0021] Z^2 is a C_1-C_{10} aliphatic, or 3-16 membered aromatic or nonaromatic monocyclic, bicyclic or tricylic ring system having 0-7 heteroatoms selected from O, N, or S; wherein Z^2 is optionally substituted with 1-5 occurrences of R^{1B};

[0022] R^{1B} is H, halo, CN, R*, OR*, NRR*; or two R^{1B}, taken together with the atom to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms;

[0023] R^{1C} is H, halo, CN, a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system having 0-5 heteroatoms selected from O, N, or S; R*, OR*, NRR*; or two R^{1C}, taken together with the atom or atoms to which they are attached,

optionally form a 3-16 membered ring having 0-4 heteroatoms; wherein R^{1C} is optionally substituted with 1-3 occurrences of halo, CN, R' or OR';

[0024] R*is C_1-C_6 aliphatic wherein up to three methylene units of the C_1-C_6 aliphatic are optionally replaced by N, NR, O, S, C=O, SO, SO_2 or Si and wherein the C_1-C_6 aliphatic is optionally substituted with 1-3 occurrences of halo, CN, R' or OR';

[0025] R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, a C_1-C_{16} aliphatic, a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system, or – (C_1-C_{16} aliphatic) – (5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system) ; wherein up to five carbon atoms of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{2A} is optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR';

[0026] R^3 is OH, R^{3A}, or OR^{3A}; wherein R^{3A} is C_1-C_{10} aliphatic optionally substituted with 1-3 occurrences of halo, R or OR';

[0027] R^4 is OH, R^{4A}, OR^{4A}; or when bond Y^1 between R^4 and R^5 is a double bond, R^4 is absent; wherein R^{4A} is C_1-C_7 aliphatic and R^{4A} is optionally substituted with 1-3 occurrences of halo, R' or OR';

[0028] R^5 is H or OH;

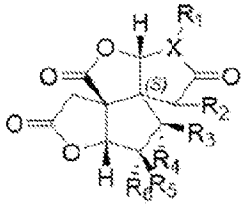
[0029] R^6 is H; or when bond Y^1 between R^4 and R^5 is a double bond, R^6 is absent;

[0030] R is H or C_1-C_6 aliphatic optionally substituted by 1-3 occurrences of F; or two R, taken together with the atom (s) to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms; and

[0031] R' is H, a C_1-C_6 aliphatic wherein up to three carbon atoms of the C_1-C_6 aliphatic are optionally replaced with O, NH, N (C_1-C_6alkyl) , C (O) , or S (O) $_2$; wherein said C_1-C_6 aliphatic is optionally substituted by 1-3 occurrences of F, OR, NH_2, NHR", or NR"$_2$, wherein R" is C_1-C_6 aliphatic or a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system having 0-5 heteroatoms selected from O, N, or S;

[0032] wherein when R^2 is OH, R^3 is tert-butyl, R^4 is OH, R^5 is H, and R^6 is H, X is not -O-.

[0033] In some embodiments, provided is a compound of Formula I:



(Formula I)

[0034] or a stereomer, a tautomer, or a pharmaceutically acceptable salt thereof,

[0035] wherein

[0036] X is -O-, -NR^1-, -N=CR^1-NH-, or -NR^1-NH-; wherein when X is -O-, R^1 is absent;

[0037] bond Y^1 is a single bond or a double bond;

[0038] R^1 is H, R^{1B}, or - $(L^1)_u$- $(Z^1)_v$; wherein

[0039] L^1 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, O, or S; wherein L^1 is optionally substituted with 1-3 occurrences of halo, CN, R, OR', or R^{1C};

[0040] u is 0 or 1;

[0041] v is 0 or 1;

[0042] Z^1 is a 5-16 membered aromatic or nonaromatic monocyclic, bicyclic, or tricyclic ring system having 0-7 heteroatoms selected from O, N, or S; wherein Z^1 is optionally substituted with 1-5 occurrences of R^{1A}, R^{1C} or combinations thereof;

[0043] R^{1A} is - $(L^2)_m$- $(Z^2)_w$; wherein

[0044] L^2 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si; wherein L^2 is optionally substituted with 1-3 occurrences of halo, CN, R, OR' or ; m is 0 or 1;

[0045] w is 0 or 1;

[0046] Z^2 is a C_1-C_{10} aliphatic, or 3-16 membered aromatic or nonaromatic monocyclic, bicyclic or tricylic ring system having 0-7 heteroatoms selected from O, N, or S; wherein Z^2 is optionally substituted with 1-5 occurrences of R^{1B};

[0047] R^{1B} is H, halo, CN, R*, OR*, NRR*; or two R^{1B}, taken together with the atom to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms;

[0048] R^{1C} is H, halo, CN, R*, OR*, NRR*; or two R^{1C}, taken together with the atom or atoms to which they are attached, optionally form a 3-16 membered ring having 0-4 heteroatoms;

[0049] R*is C_1-C_6 aliphatic wherein up to three methylene units of the C_1-C_6 aliphatic are optionally replaced by N, NR, O, S, C=O, SO, SO_2 or Si and wherein the C_1-C_6 aliphatic is optionally substituted with 1-3 occurrences of halo, CN, R' or OR';

[0050] R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, a C_1-C_{16} aliphatic, a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system, or – (C_1-C_{16} aliphatic) – (5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system) ; wherein up to five carbon atoms of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{2A} is optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR';

[0051] R^3 is OH, R^{3A}, or OR^{3A}; wherein R^{3A} is C_1-C_{10} aliphatic optionally substituted with 1-3 occurrences of halo, R or OR';

[0052] R^4 is OH, R^{4A}, OR^{4A}; or when bond Y^1 between R^4 and R^5 is a double bond, R^4 is absent; wherein R^{4A} is C_1-C_7 aliphatic and R^{4A} is optionally substituted with 1-3 occurrences of halo, R' or OR';

[0053] R^5 is H or OH;

[0054] R^6 is H; or when bond Y^1 between R^4 and R^5 is a double bond, R^6 is absent;

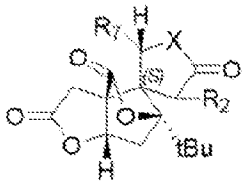
[0055] R is H or C_1-C_6 aliphatic optionally substituted by 1-3 occurrences of F; or two R, taken together with the atom (s) to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms; and

[0056] R' is H, a C_1-C_6 aliphatic optionally substituted by 1-3 occurrences of F, OR, NH_2, NHR", $NR"_2$, wherein R" is C_1-C_6 aliphatic, or a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system having 0-5 heteroatoms selected from O, N, or S;

[0057] wherein when R^2 is OH, R^3 is tert-butyl, R^4 is OH, R^5 is H, and R^6 is H, X is not -O-.

[0058] For the sake of clarity, when u is 0 or v is 0, then the bond before - $(L^1)_u$ or before - $(Z^1)_v$ is also absent, respectively. Likewise, when m and w is 0, the bond before - $(L^2)_m$ or before - $(Z^2)_w$ is also absent.

[0059] In some embodiments, provided is a compound of Formula II:



(Formula II)

[0060] or a stereomer, a tautomer, or a pharmaceutically acceptable salt thereof,

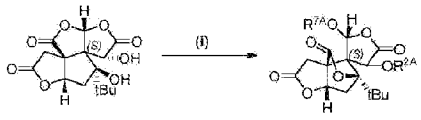
[0061] wherein

[0062] X is -O-, -NR^1-, -N=CR^1-NH-, or -NR^1-NH-; wherein R^1 is as defined herein;

[0063] R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, a C_1-C_{16} aliphatic or a 5-10 membered aroma tic or nonaromatic monocyclic or bicyclic ring system, wherein up to five carbon atom s of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromati c monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{2A} is optionally su bstituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR'; and

[0064] R^7 is R^{7A} or OR^{7A}, wherein R^{7A} is H, a C_1-C_{16} aliphatic or a 5-10 membered aroma tic or nonaromatic monocyclic or bicyclic ring system, wherein up to five carbon atom s of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromati c monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{7A} is optionally su bstituted with 1-5 occurrences of R^{7B}, wherein R^{7B} is halo, R' or OR'.

[0065] In some embodiments, provided is a process for preparing a compound as described herein, including at least the following steps: (i) treating bilobalide with R^{2A}-X in a suitable solvent to form protected product IIa



bilobalide protected product IIa ;

[0066] and (ii) treating protected product IIa with at least one base or an acceptable salt thereof to form aminated product IIb

protected product IIa aminated product IIb ;

[0067] wherein R^{2A} and R^{7A} are as defined in any one of the preceding embodim ents or described herein.

[0068] In some embodiments, provided is a method of treating or preventing cancer in a subject in need thereof, including administering to the subject a compoun d described herein.

[0069] In some embodiments, provided is a use of a compound described herei n for treating or preventing cancer.

[0070] In some embodiments, provided is a use of a compound described herei n for the manufacture of a medicament for treating or preventing cancer.

[0071] In some embodiments, provided is a method of inducing cell death in a cancer cell, in cluding contacting a compound described herein with the cancer cell.

[0072] In some embodiments, provided is a method of inhibiting cell growth in a cancer cell, including contacting a compound described herein with the cancer cell.

[0073] In some embodiments, provided is a method of treating or preventing neurological related disease in a subject in need thereof, including administering to the subject a compound of any one of the embodiments herein.

[0074] In some embodiments, provided is a use of a compound described herei n for treating or preventing Alzheimer's disease or Parkinson's disease.

[0075] In some embodiments, provided is a use of a compound described herei n for inhibiting ferroptosis by restoring glutathione peroxidase 4 (GPX4) , thereby m itigating GPX4 degradation induced by ferroptosis inducers.

[0076] In some embodiments, provided is a use of a compound described herei n for inhibiting ferroptosis by reducing intracellular reactive oxygen species (ROS l evel) .

[0077] In some embodiments, provided is a use of a compound described herei n for inhibiting ferroptosis by reducing lipid peroxidation.

[0078] In some embodiments, provided is a use of a compound described herei n for the manufacture of a medicament for treating or preventing Alzheimer's disease or Parkinson's disease.

[0079] There are many advantages of the invention. In certain embodiments, the methods and processes disclosed herein enable the synthesis of bilobalide (BB) co mpounds that can be used for SAR studies. In certain embodiments, th e novel compounds are particularly effective at treating or preventing cancer. In cer tain embodiments, the novel compounds are effective at inducing cell death in a cance r cell. In certain embodiments, the novel compounds are effective at inhibiting cell growth in a cancer cell. In other embodiments, the novel compounds h ave demonstrated surprising pan-anti-cancer effect against human and mo use cancer cells. In certain embodiments, the novel compositions are particularly eff ective reducing chemically-induced ferroptosis and/or chemically-induced oxidative stress. In other embodiments, the novel compounds have demonstrated surprising neuroprotective properties in mouse models.

[0080] BRIEF DESCRIPTION OF FIGURES

[0081] FIG. 1A is an illustration showing the overall molecular editing schemes of bilobalid e as disclosed herein.

[0082] FIG. 1B is an illustration of Scheme 12.

[0083] FIG. 1C is a plot showing the X-ray crystal structure of bilobalide analogue XBB-002.

[0084] FIG. 1D is a plot showing the X-ray crystal structure of bilobalide analogue XBB-003.

[0085] FIG. 1E is a plot showing the X-ray crystal structure of bilobalide analogue XBB-018.

[0086] FIG. 1F is a plot showing the X-ray crystal structure of bilobalide analogue JW072.

[0087] FIG. 1G is a plot showing the X-ray crystal structure of bilobalide analogue XBB-009.

[0088] FIG. 1H is a plot showing the X-ray crystal structure of bilobalide analogue XBB-010.

[0089] FIG. 2 is a heat map showing cell viability after treatment with 50 uM DW192 for 48 hours in A549 and Jurkat cells.

[0090] FIG. 3A is a plot showing the dose-response curve on A549 cells treated with DW192 for 48 hours.

[0091] FIG. 3B is a plot showing the dose-response curve on A549 cells treated with P-29 for 48 hours.

[0092] FIG. 3C is a plot showing the dose-response curve on A549 cells treated with P-21 for 48 hours.

[0093] FIG. 3D is a plot showing the dose-response curve on KP-1 cells treated with SCC506 for 48 hours.

[0094] FIG. 3E is a plot showing the dose-response curve on A549 cells treated with SCC363 for 48 hours.

[0095] FIG. 3F is a plot showing overlaid dose-dependent curves on Jurkat cells, A549 cells, KP-1 cells, and MCF-7 cells treated with DW192 for 48 hours.

[0096] FIG. 4A is a one-dose mean graph of percentage growth of cell lines across the NCI-60 cell line panel when treated DW192 (10uM, 48h) .

[0097] FIG. 4B is a plot showing the dose-response curves of leukemia cell lines treated with DW192.

[0098] FIG. 4C is a plot showing the dose-response curves of CNS cancer cell lines treated with DW192.

[0099] FIG. 4D is a plot showing the dose-response curves of renal cancer cell lines treated with DW192.

[0100] FIG. 4E is a plot showing the dose-response curves of NSCLC cell lines treated with DW192.

[0101] FIG. 4F is a plot showing the dose-response curves of melanoma cell lines treated with DW192.

[0102] FIG. 4G is a plot showing the dose-response curves of prostate cancer cell lines treated with DW192.

[0103] FIG. 4H is a plot showing the dose-response curves of colon cancer cell lines treated with DW192.

[0104] FIG. 4I is a plot showing the dose-response curves of ovarian cancer cell lines treated with DW192.

[0105] FIG. 4J is a plot showing the dose-response curves of breast cancer cell lines treated with DW192.

[0106] FIG. 4K shows the mean graphs of GI50, TGI and LC50 calculated from five-dose screen results.

[0107] FIG. 5A, is a chart showing the hydrolytic stabilities of bilobalide versus bilobalide analogue in buffer with pH=6.8.

[0108] FIG. 5B, is a chart showing the hydrolytic stabilities of bilobalide versus bilobalide analogue in buffer with pH=7.4.

[0109] FIG. 6A is a chart comparing the phenotypic screening of bilobalide and bilobalide analogue against RSL3-induced ferroptosis through 3 cell lines is shown.

[0110] FIG. 6B is a chart showing the dose-dependent curves of RSL3 on HT22 cell line treated with or without bilobalide or bilobalide analogue.

[0111] FIG. 6C is a chart showing the dose-dependent curves of RSL3 on HMC3 cell line treated with or without bilobalide or bilobalide analogue.

[0112] FIG. 6D is a chart showing the dose-dependent curves of RSL3 on BV-2 cell line treated with or without bilobalide or bilobalide analogue.

[0113] FIG. 6E is a chart comparing the fluorescent staining on HMC3 cell lines treated with RSL3 treated with or without bilobalide or bilobalide analogue.

[0114] FIG. 6F is a plot showing the normalization of ROS level against the Control based on the fluorescent intensity of CellROX.

[0115] FIG. 6G is a plot showing the normalization of ROS level in cells treated with various concentrations of XBB-037.

[0116] FIG. 6H is a plot showing the lipid peroxidation level (%) in cells treated with various concentrations of XBB-037.

[0117] FIG. 6I is a plot showing the lipid peroxidation level (%) in cells treated with various concentrations of bilobalide.

[0118] FIG. 7A is a chart showing the killing effect of ferroptosis inducer ML162 on HMC3 cells with or without bilobalide or bilobalide analogue.

[0119] FIG. 7B is a chart showing the killing effect of ferroptosis inducer ML210 on HMC3 cells with or without bilobalide or bilobalide analogue.

[0120] FIG. 7C is a chart showing the killing effect of ferroptosis inducer erastin on HMC3 cells with or without bilobalide or bilobalide analogue.

[0121] FIG. 7D is a chart showing the killing effect of ferroptosis inducer FIN56 on HMC3 cells with or without bilobalide or bilobalide analogue.

[0122] FIG. 7E is a chart of the Western-blot images showing the levels of GPX4 and β-actin at 0, 250, 500 or 750 nM RSL3.

[0123] FIG. 7F is a plot showing the normalized plot of GPX4 levels with or without bilobalide analogue XBB-037, according to FIG. 7E.

[0124] FIG. 7G is a chart of the Western-blot images showing the levels of GAPDH at 0 or 500 nM RSL3.

[0125] FIG. 7H is a chart of the Western-blot images showing the levels of GPX4 and β-actin at 0, 0.625, 1.25 and 2.5 μM FIN56.

[0126] FIG. 7I is a plot showing the normalized plot of GPX4 levels according to FIG. 7H.

[0127] FIG. 8A is a chart comparing the phenotypic screening of bilobalide, SXQ087-1 and XBB-037 against RSL3-induced ferroptosis through 3 cell lines.

[0128] FIG. 8B is a plot showing the dose-dependent cell viability (%) curves of SXQ087-1 or XBB-037 on HMC3 cell line treated with RSL3.

[0129] FIG. 8C is a plot showing the lipid peroxidation level (%) in cells treated with various concentrations of SXQ087-1.

[0130] FIG. 9A is a chart of the Western-blot images showing the levels of GPX4 and GAPDH at various concentrations of SXQ087-1 against RSL3.

[0131] FIG. 9B is a plot showing the normalized plot of GPX4 levels with various concentrations of SXQ087-1, according to FIG. 9A.

[0132] FIG. 9C is a chart of the Western-blot images showing the levels of LC3-II/LC3-I and GAPDH at various concentrations of SXQ087-1 against RSL3.

[0133] FIG. 9D is a plot showing the normalized plot of LC3-II/LC3-I level (%) levels according to FIG. 9C.

[0134] FIG. 10A is a chart showing the cell viability (%) curves of HMC3 cells treat with FIN56 or FIN56 + SXQ087-1.

[0135] FIG. 10B is a chart showing the cell viability (%) curves of HMC3 cells treat with ML162 or ML162 + SXQ087-1.

[0136] FIG. 10C is a chart showing the cell viability (%) curves of HMC3 cells treat with ML210 or ML210 + SXQ087-1.

[0137] FIG. 10D is a chart showing the cell viability (%) curves of HMC3 cells treat with Erastin or Erastin + SXQ087-1.

[0138] FIG. 11A is a chart showing the cell viability (%) curves of HMC3 cells treated with SXQ087-1, XBB-037 or bilobalide.

[0139] FIG. 11B is a chart showing the radical scavenging activity of SXQ087-1.

[0140] FIG. 12A is a plot showing the tumor volume measurements of C57BL/6 mice with B16 melanoma allograft treated with DW192 or vehicle.

[0141] FIG. 12B is a photograph of tumors after DW192 or vehicle treatment.

DETAILED DESCRIPTION

[0142] As used herein and in the claims, the terms "comprising" (or any related form such as "comprise" and "comprises") , "including" (or any related forms such as "include" o r "includes") , "containing" (or any related forms such as "contain" or "contains") , means including the following elements but not excluding others. It shall be under stood that for every embodiment in which the term "comprising" (or any related form s uch as "comprise" and "comprises") , "including" (or any related forms such as "incl ude" or "includes") , or "containing" (or any related forms such as "contain" or "co ntains") is used, this disclosure/application also includes alternate embodiments wh ere the term "comprising" , "including, " or "containing, " is replaced with "consist ing essentially of" or "consisting of" . These alternate embodiments that use "consis ting of" or "consisting essentially of" are understood to be narrower embodiments of the "comprising" , "including, " or "containing, " embodiments.

[0143] For example, alternate embodiments of "a composition comprising A, B , and C" would be "a composition consisting of A, B, and C" and "a c omposition consisting essentially of A, B, and C. " Even if the latter two embodiment s are not explicitly written out, this disclosure/application includes those embodime nts. Furthermore, it shall be understood that the scopes of the three embodiments lis ted above are different.

[0144] For the sake of clarity, "comprising" , including, and "containing" , and any related forms are open-ended terms which allows for additional elements or features beyond the named essential elements, whereas "consisting of" is a closed end term that is li mited to the elements recited in the claim and excludes any element, step, or ingredi ent not specified in the claim.

[0145] For the sake of clarity, "characterized by" or "characterized in" (together with thei r related forms as described above) , does not limit or change the nature of whether the list of terms following it are open or closed. For example, in a claim directed t owards "a composition comprising A, B, C, and characterized in D, E, and F" , the ele ments D, E, and F are still open-ended terms and the claim is meant to include other elements due to the use of the word "comprising" earlier in the claim.

[0146] "Consisting essentially of" limits the scope of a claim to the specified materials, c omponents, or steps ("essential elements") that do not materially affect the essent ial characteristic (s) of the claimed invention. In some embodiments, the essential c haracteristics are the basic and novel characteristic (s) of the claimed invention. F or example, in some embodiments, the essential elements of a composition of the discl osure can be "Xmg to Ymg" of compound A. Even if the composition inc ludes additional excipients, as long as the additional excipients do not materially a

ffect the essential characteristics of the compound, e.g., in compound A's cytotoxic effect against cancer cell lines, then such embodiment that "consists essentially of compound A" still includes compositions with the aforementioned addi tional excipients.

[0147] As used herein, the singular forms "a" , "an" and "the" are intended to include the p lural forms as well, unless the context clearly indicates otherwise. Where a range is referred in the specification, the range is understood to include each discrete poin t within the range. For example, 1-7 means 1, 2, 3, 4, 5, 6, and 7.

[0148] As used herein, the term "about" is understood as within a range of normal tolerance in the art and not more than ±10%of a stated value. By way of example only, about 50 means from 45 to 55 including all values in between. As used herein, the phrase "abou t" a specific value also includes the specific value, for example, about 50 includes 50.

[0149] As used herein and in the claims, an "effective amount" , is an amount that is effect ive to achieve at least a measurable amount of a desired effect. For example, the amo unt may be effective to cause cell death.

[0150] As used herein, the term "cancer" refers to a group of diseases characterized by the uncontrolled growth and spread of abnormal cells that tend to invade surrounding tiss ue or organs and to metastasize to other parts of the body through the bloodstream or lymphatic system. Examples of cancer include, but are not limited to bladder cancer, brain cancer, breast cancer, CNS cancer, colon cancer, colorectal cancer, hematopoi etic cancer, kidney cancer, leukemia (such as lymphocytic leukemia) , lung cancer (su ch as non-small cell lung cancer (NSCLC)) , melanoma, multiple myeloma, ovari an cancer, pancreatic cancer, prostate cancer, renal cancer and other cancers. In som e embodiments, NSCLC are associated with KRAS and/or P53 mutations.

[0151] As used herein and in the claims, a "subject" refers to animals such as mammals, incl uding, but not limited to, primates (e.g., humans) , cows, sheep, goats, horses, dogs , cats, rabbits, rats, mice and the like.

[0152] As used herein, the term "treat, " "treating" or "treatment" refers to methods of all eviating, abating or ameliorating a disease or condition symptoms, preventing additio nal symptoms, ameliorating or preventing the underlying metabolic ca uses of symptoms, inhibiting the disease or condition, arresting the development of t he disease or condition, relieving the disease or condition, causing regression of th e disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or ther apeutically.

[0153] In various aspects, the compounds disclosed herein further comprise their isotopicall y-labelled or isotopically-substituted variants, i.e., compounds identical to those described, but for the fact that one or more atoms are replaced by an atom havi

ng an atomic mass or mass number different from the atomic mass or m
ass number typically found in nature. For example, the isotopically-labelled or isoto
pically-substituted atom has one or more neutrons in the nucleus compared to
the natural atom. In some embodiments, the disclosed compounds comp
rise a mixture of natural atoms and their isotopically labeled variants. Examples of
isotopes that can be incorporated into the disclosed compounds include isotopes of hy
drogen, carbon, nitrogen, oxygen, sulfur, phosphorous, fluorine and chlorine, such as
^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds furthe
r comprise prodrugs thereof, and pharmaceutically acceptable salts of said compounds
or of said prodrugs which contain the aforementioned isotopes and/or other isotopes o
f other atoms are within the scope of this disclosure.

[0154] As used herein, the terms "halogen" or "halo" mean F, Cl, Br, or I (fluoro, chloro, b
romo, or iodo) .

[0155] As used herein, the term "aliphatic" , "aliphatic group" , "alkyl" or "alkyl group" ,
means a straight-chain (i.e., unbranched) , branched, or cyclic, substituted or unsub
stituted hydrocarbon chain that is completely saturated or that contains one or more
units of unsaturation that has a single point of attachment to the rest of the molecule.

[0156] In some embodiments, an aliphatic group contains 1-20 carbon atoms.
In some embodiments, an aliphatic group contains 1-10 carbon atoms.
In some embodiments, an aliphatic group contains 1-6 carbon atoms. I
n some embodiments, an aliphatic group contains 1-4 carbon atoms. I
n some embodiments, aliphatic groups are linear or branched, substituted or unsubstit
uted alkyl, alkenyl, or alkynyl groups. Specific examples include, but are not limite
d to, methyl, ethyl, isopropyl, isopropenyl, n-propyl, sec-butyl, vinyl. N-
butenyl, ethynyl, and tert-butyl. In some embodiments, aliphatic groups are cy
clic, or have a combination of linear or branched and cyclic groups, which are known
as "cyloalkyls" . Specific examples of such types of aliphatic groups or cycloalkyls
include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyc
lohexenyl, cyclooctyl, cyclobutylmethyl, cyclopropylmethyl, and -CHCH-
CH (CH) -cyclohexyl. Cyclic groups, (e.g. cycloaliphatic and heterocycles) ,
can be linearly fused, bridged, or spirocyclic, for example, 1- (bicyclo [2.2.1] hept-
5-en-2-yl) methyl, bicyclo [1.1.1] pentyl, 1-adamantanemethyl, norbornane and d
ecahydronaphthalene.

[0157] In some embodiments, carbon atom (s) of an aliphatic group are repla
ced by any number of non-carbon atoms such as N, O, S, B, P, Al, and Si. For
example, a C2 aliphatic where two carbon atoms are replaced by two nitrogens forms -
N=NH or -N=NR. In some embodiments, cycloalkyl is a "heterocyclic ring" which
is a 5-10 membered nonaromatic monocyclic, bicyclic or tricyclic ring having 0-

5 heteroatoms selected from N, O and/or S. In some embodiments, a heterocyclic ring i nclude a spirocyclic ring.

[0158] As used herein, the term "heteroatom" means one or more of N, O, S, B, P, Al, Si, or any oxidized forms thereof, such as SO and SO_2.

[0159] In some embodiments, aliphatic groups are "haloalkyls" which contain halogens. Specific examples of such types of aliphatic groups or haloalkyls include, but are not limited to, trifluoromethyl, flouromethyl, l, 2, 3, 4, 5-pentafluoro-phenyl. In some embodiments, haloalkyls include "perfluoro" compound s where at least two available hydrogens are substituted with fluorine. Examples of " perfluoro" compounds include, but are not limited to, perfluorophenyl (i.e., l, 2, 3, 4, 5-pentafluorophenyl) , perfluoromethane (i.e., l, l, l-trifluoromethyl) , and perfluoromethoxy (i.e., 1, 1, l-trifluoromethoxy) .

[0160] As used herein, the terms "aryl" , "aryl group" , or "aromatic" or "aromatic ring" refer to mono cyclic, bicyclic, and tricyclic ring systems having a total of 5 to 20 ring members, wherein at least one ring in the system is fully unsaturated (i.e., aromatic) , wherein the ring may be substituted or unsubstituted, wherein each ring in the system contains 3 to 7 ring members, and wherein the ring members may be heteroatoms. In some embodiments, the terms refer to a 5-10 membered aromatic monocyclic or bicyclic ring having 0-5 heteroatoms selected from oxygen, nitrogen, or sulfur. In some embodiments, the aryl is a "heteroaryl" , "heteroaryl group" , or "heterocyclic aromatic ring" . These refer to an "aryl" , "aryl group" , or "aromatic ring" wherein at least one ring in the mono cyclic, bicyclic, and tricyclic ring system includes a ring member that is a heteroatom. Examples of heteroaryl groups include, but are not limited to, optionally substituted phenyl, naphthyl, furanyl (e.g., 2-furanyl, 3-furanyl) , imidazolyl (e.g., N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl) , benzimidazolyl, isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl) , oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl) , pyrrolyl (e.g., N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl) , pyridyl (e.g., pyridinyl, 2-pyridyl, 3-pyridyl, 4-pyridyl) , pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl) , pyrazinyl (e.g., 4-pyrazinyl) , pyridazinyl (e.g., 3-pyridazinyl) , thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl) , tetrazolyl (e.g., 5-tetrazolyl) , triazolyl (e.g., 2-triazolyl and 5-triazolyl) , thienyl (e.g., 2-thienyl, 3-thienyl) , benzofuryl, benzothiophenyl, indolyl (e.g., 2-indolyl) , pyrazolyl (e.g., 2-pyrazolyl) , isothiazolyl, 1, 2, 3-oxadiazolyl, 1, 2, 5-oxadiazolyl, 1, 2, 4-oxadiazolyl, 1, 2, 3-triazolyl, 1, 2, 3-thiadiazolyl, 1, 3, 4-thiadiazolyl, 1, 2, 5-thiadiazolyl, purinyl, 1, 3, 5-triazinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-quinolinyl) , isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl) , tetrahydrothiophenyl, morpholino, quinuclidinyl, and l, 4-dioxa-8-aza-spiro [4.5] dec-8-yl. In some embodiments, aryl groups are optionally substituted by one or more

groups such as alkyl, alkoxy, aryl, hydroxy, halogen, cyano, amino, amino-alkyl, trifluoromethyl, alkylenedioxy (i.e., methylenedioxy or ethylenedioxy) and oxy-Cg-C3-alkylene (i.e., 2, 3-dihydrobenzofuran-5-yl) .

[0161] As used herein, the term "alkoxy" or "OR" refers to a group where th e attaching oxygen is bound to an R group. In some embodiments, the R group is an alkyl group defined in the preceding paragraphs. Examples of an alkoxy group include, but are not limited to, methoxy, ethoxy, propoxy, iso-propoxy, butoxy, 2-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, pentoxy, and hexoxy.

[0162] As used herein, the term "nonaromatic" refers to aliphatics that are fully saturated or partially saturated.

[0163] As used herein, the terms "carbonyl" or "C=O" refers to a group wher e a carbon is forms a double bond with an oxygen. Examples include, but are not limit ed to, aldehydes, ketones, carboxylic acids, esters, and amides.

[0164] Unless otherwise indicated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, geometric, conformational, and rotation al) forms of the structure.

[0165] The terms "stereomer" or "stereoisomer" include the R and S configur ations for each asymmetric center.

[0166] The term "tautomer" includes all the structural isomers resulted from interconversion . Examples of tautomers include, but are not limited to, keto-enol tautomers, a mine-imine tautomers, amide-imidic acid tautomers, and lactam-lactim tautomers. Unless otherwise indicated, all tautomeric forms of the compounds of the disclosure are within the scope of the invention.

[0167] The term "acceptable salt" refers to a compound which has a net charge of zero. In so me embodiments, an acceptable salt may be a salt of an acid or a salt of a base. Exam ples of acceptable salts include, but not limited to, fluorides (e.g., F^-) , chlorides (e. g., Cl^-) , bromides (e.g., Br^-) , iodides, carbonates, triflates (e.g., OTf^-) , hydroxides (e .g., OH^-) , formates, acetates (e.g., OAc^-) , oxides (e.g., O^{2-}) , sulfates, pyr osulfates, bisulfates, sulfites, bisulfites, phosphates (e.g., monohydrophosphates, d ihydrophosphates, metaphosphates, pyrophosphates) , fluoromethoxides (e.g., $[OCF_3]^-$, $[OCF_2R]^-$, $[OCFR_2]^-$) , propionates, butyrates (e.g., isobutyrates) , oxalates, malonate s, succinates, fumarates, maleates, benzoates (e.g., chlorobenzoates, methyl benzoate s, nitrobenzoates, hydroxybenzoates, methoxybenzoates) , phthalates, sulfonates, citr ates, lactates, glycolates, tartrates, ascorbate, acrylates, sulfides, phosphides, cy anides, azides, oxochlorides (ClO^-, ClO_2^-, $ClO_3^-ClO_4^-$) , tetrafluoroborates, tetrapheny lborates, hexafluorophosphates, and the like.

[0168] As used herein, the term "amine" refers to a compound having at leas t one or more nitrogen groups. In some embodiments, the nitrogen groups are primary, secondary or tertiary. In some embodiments, an amine is NH_3, NH_2R, NHR_2 , or NR_3, and its acceptable salt is referred as "ammounium" in the form of NH_4 $^+$, $[H_3NR]^+$, $[H_2NR_2]^+$, $[HNR_3]^+$, or $[NR_4]^+$, respectively. In some embodiment s, an amine is a carbamate, an amino acid, an amide, a hydrazine, or acceptable salts thereof. In some embodiments, an amine is a combination of the amine and its accepta ble salt. In some embodiments, an amine is ammonia, trimethylamine, triethylamine, diisopropylethylamine, tetramethylethylenediamine, ethyl amine, propyl amine, isopropyl amine, ethylenediamine, ethanolamine, other NH_2R^1, or combination thereof. In some embodiments, an amine is NH_2R^1, and its acceptable salt is $[H_3NR^1$] Cl. In some embodiments, an amine is a heterocyclic ring or a hetero aromatic ring as defined in the preceding paragraphs. Examples of a heterocyclic ring or a hetero a romatic ring include, but are not limited to, quinuclidine, N, N-methylphenylamine , aniline, 4-methylaniline, pyridine, pyrrolidine, piperdine, imidazole, pyridazi ne, pyrimidine, pyrazine 1, 5-Diazabicyclo [4.3.0] non-5-ene (DBN) , and 1, 8-Diazabicyclo [5.4.0] undec-7-ene (DBU) .

[0169] The term "base" refers to an electron donor which can share electron s with electron acceptors. In some embodiments, a base reacts with an electrophile to form a covalent bond. In some embodiments, a base reacts with acids to form salts. In some embodiments, the term "base" refers to an amine defined in th e preceding paragraph or an acceptable salt thereof.

[0170] As used herein, the terms "bilobalide" or "BB" refers to a terpenic trilactone substa nce.

[0171] As used herein, the terms "solvent" or "suitable solvent" refer to a substance which is capable of dissolving or dispersing other substances. In some emb odiments, a solvent is liquids, ionic liquids, gases, and supercritical fluids. In so me embodiments, a solvent is water, alcohols, ethers, hydrocarbons, and other organic and inorganic solvents. In some embodiments, the solvent or suitable solvent is dich loromethane (DCM) , dichloroethane (DCE) , chloroform, tetrahydrofur an (THF) , acetonitrile, toluene, chlorobenzene, benzene, pyridine, 2, 6-lutidine, dioxane (e.g., 1, 4-dioxane) , dimethyl sulfoxide (DMSO) , dimethylform amide (DMF) , ammonia, triethylamine, diisopropylethylamine, tetrame thylethylenediamine, hexanes, pentane, dimethyl ether, diethyl ether, petroleum ether , ethyl acetate, carbon tetrachloride, benzenethiol, cyclohexanethiol, 1-diethylaminoethanol, ethylene glycol, xylene, l, l, 2, 2-tetrachloroethane, phenol, 2-butanone, diglyme, N-methyl-Z-pyrrolidinone (NMP) , heptane, glycerin, hexamethyl

phosphorus triamide (HMPA) , methyl t-butyl ether (MTBE) , water, aceton e, methanol, ethanol, n-propanol, isopropanol, n-butanol (i.e., l-butanol, 2-butanol) , acetic acid, formic acid, nitromethane, or combination thereof. In some em bodiments, the solvent is anhydrous. In some embodiments, the solvent is degassed. In some embodiments, a solvent or a suitable solvent can be polar, aprotic, protic or non-polar. In some embodiments, a "protic solvent" is water, methanol, ethanol, isopropan ol, n-butanol, acetic acid, formic acid, nitromethane, or combination thereof.

[0172] As used herein, the term "protecting group" refers to a substituent that can be insta lled and removed selectively under certain reaction conditions. Examples of a protect ing group include, but are not limited to, acetate (OAc) , mesylate (OMs) , tosylate (OTs) , triflate (OTf) , substituted or non-substituted benzyl ether (OBn) , t ert-butyldimethylsilyl ether (OTBS) , triethylsilyl ether (OTES) , trime thylsilyl ether (OTMS) , methoxymethyl ether (OMOM) , ethoxyl methox yl ether (OEOM) , and t-butyl carbamate (-Nboc) . The term "R-X" refers to a su bstance which is used in a chemical reaction to introduce a protecting group, wherein R is a suitable protecting group selected from the examples above and other protecti ng groups known to one of skill in the art, and X is a leaving group such as halo (fl uoro, chloro, iodo) , or OCF_3. In some embodiments, R^2 is a protecting group. In some embodiments, R^2 is OBn, substituted OBn (e.g., p-bromobenzoate) , or OAc. In some embodiments, R^2-X used in the preparation is benzoyl chloride.

[0173] As used herein, the term "ligand" refers to an ion or neutral compou nd which bonds with a catalyst. In some embodiments, the ligand includes, but is not limited to, 1, 10-phenanthroline, 2, 2'-bipyridine, ammonia, triethylamine , diisopropylethylamine, tetramethylethylenediamine, or combinations thereof.

[0174] As used herein, the term "catalyst" refers to a substance which is used to increase t he rate of a chemical reaction. In some embodiments, the catalyst includes is a metal catalyst. In some embodiments, the catalyst includes, but is not limited to, CuOTf, $Cu(OAc)_2$, CuI, Cu_2O, CuBr, or $[CuOTf]_2$-toluene complex, or combinations thereof.

[0175] As used herein, the term "oxidizing agent" refers to a substance that gains an electr on in a redox chemical reaction. In some embodiments, the oxidizing agent is osmium (VIII) oxide.

[0176] As used herein, the term "alkali salt" refers to a substance which increases pH or ne utralizes acidity. In some embodiments, the alkali salt is potassium carbonate, potas sium bicarbonate, sodium acetate, sodium carbonate, sodium bicarbona te, cesium carbonate, cesium fluoride, potassium phosphate, potassium dihy drogen phosphate, potassium hydrogen phosphate, lithium hydroxide, s odium hydroxide, potassium hydroxide, lithium hexamethyldisilazide,

potassium hexamethyldisilazide, sodium hexamethyldisilazide, lithium hydride, sodium hydride, potassium hydride, or combinations thereof.

[0177] As used herein, the term "acid" refers to a substance which can donate a hydrogen proton (H^+), form a covalent bond with an electron pair, or decrease pH. In some embodiments, the acid is hydrochloric acid, sulfuric acid, acetic acid, formic acid, or combinations thereof. In some embodiments, an acid is an organic acid such as acetyl chloride or oxalyl chloride.

[0178] One skilled in the art will understand that the types listed or illustrated above are not exhaustive and that additional types within these specific terms can also be selected.

[0179] As used herein, the term "substituent" or "substituted" is used to describe an R group attached to a second group via at least one bond between the group and a portion of the second group. In some embodiments, when "a compound is substituted by an R group", it means that at least one atom of the compound forms a single, double or triple bond with the R group. In some embodiments, a compound can be substituted in two different positions by two R groups, wherein the two R groups, taken together with a portion of the compound, form a ring. For example, the compound bicyclo [2.2.1] hept-2-ene can be understood as a cyclopentane substituted with two R groups, wherein the two R groups, taken together, is a diene, and taken together with the cyclopentane, from bicyclo [2.2.1] hept-2-ene .

[0180] As used herein, the terms "benzene" and "phenyl" are used interchangeably to refer to an optionally substituted 6-membered aromatic (fully unsaturated) carbocyclic ring. One of skill in the art would understand, for example, that the phenyl group in the R^1 group 3, 5-difluorophenyl can also be described as having a formula of C_6H_3.

[0181] As used herein, compound names with "-yl" suffix are used to denote that the compound is a substituent or a group attached to another compound via at least one atom.

[0182] In some embodiments, the formula of an amine is written as NH_3, RNH_2, R_2NH, or R_3N, and acceptable salts thereof include the cations NH_4^+, $[RH_3N]^+$, $[R_2H_2N]^+$, $[R_3HN]^+$, or $[R_4N]^+$, respectively, together with one or more anions to form a salt. Examples of anions include, but are not limited to halides (F, Cl, I) , hydroxides, carbonates, phosphates, sulfates, sulfites, cyanides, azides, oxochlorides (ClO^-, ClO_2^-, ClO_3^- ClO_4^-) , tetrafluoroborates, tetraphenylborates, hexafluorophosphates, and the like.

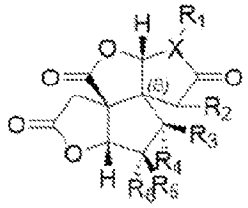
[0183] As used herein, the term "hindered base" refers to a subgroup of base as defined herein which are sterically hindered. Examples of hindered base include, but are not limi

ted to, triethylamine, diisopropylethylamine, tributylamine and tetramethylethylenedi amine.

[0184] Although the description referred to particular embodiments, the dis closure should not be construed as limited to the embodiments set forth herein.

[0185] Embodiments I

[0186] In some embodiments, provided is a compound of Formula I:



(Formula I)

[0187] or a stereomer, a tautomer, or a pharmaceutically acceptable salt thereof,

[0188] wherein

[0189] X is -O-, -NR^1-, -N=CR^1-NH-, or -NR^1-NH-; wherein when X is -O-, R^1 is absent;

[0190] bond Y^1 is a single bond or a double bond;

[0191] R^1 is H, R^{1B}, or - $(L^1)_u$- $(Z^1)_v$; wherein

[0192] L^1 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are op tionally replaced by N, O, or S; wherein L^1 is optionally substituted with 1-3 occurrences of halo, CN, R, OR', or R^{1C};

[0193] u is 0 or 1;

[0194] v is 0 or 1;

[0195] Z^1 is a 5-16 membered aromatic or nonaromatic monocyclic or bicyclic ring syst em having 0-5 heteroatoms selected from O, N, or S; wherein Z^1 is optionally su bstituted with 1-5 occurrences of R^{1A} , R^{1C} or combinations thereof;

[0196] R^{1A} is - $(L^2)_m$- $(Z^2)_w$; wherein

[0197] L^2 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are op tionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O , or Si; wherein L^2 is optionally substituted with 1-3 occurrences of halo, CN, R, OR' or ; m is 0 or 1;

[0198] w is 0 or 1;

[0199] Z^2 is a C_1-C_{10} aliphatic, or 3-16 membered aromatic or nonaromatic monocyclic or b icyclic ring system having 0-5 heteroatoms selected from O, N, or S; wherein Z^2 is optionally substituted with 1-5 occurrences of R^{1B};

[0200] R^{1B} is H, halo, CN, R*, OR*, NRR*; or two R^{1B}, taken together with the atom to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms;

[0201] R^{1C} is H, halo, CN, R*, OR*, NRR*; or two R^{1C}, taken together with the atom to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms;

[0202] R*is C_1-C_6 aliphatic wherein up to three methylene units of the C_1-C_6 aliphatic are optionally replaced by N, NR, O, S, C=O, SO, SO_2 or Si and wherein the C_1-C_6 aliphatic is optionally substituted with 1-3 occurrences of halo, CN, R' or OR';

[0203] R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, a C_1-C_{16} aliphatic, a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system, or – (C_1-C_{16} aliphatic) – (5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system) ; wherein up to five carbon atoms of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{2A} is optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR';

[0204] R^3 is OH, R^{3A}, or OR^{3A}; wherein R^{3A} is C_1-C_{10} aliphatic optionally substituted with 1-3 occurrences of halo, R or OR';

[0205] R^4 is OH, R^{4A}, OR^{4A}; or when bond Y^1 between R^4 and R^5 is a double bond, R^4 is absent; wherein R^{4A} is C_1-C_7 aliphatic and R^{4A} is optionally substituted with 1-3 occurrences of halo, R' or OR';

[0206] R^5 is H or OH;

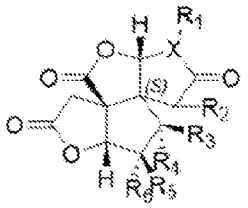
[0207] R^6 is H; or when bond Y^1 between R^4 and R^5 is a double bond, R^6 is absent;

[0208] R is H or C_1-C_6 aliphatic optionally substituted by 1-3 occurrences of F; or two R, taken together with the atom (s) to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms; and

[0209] R' is H, a C_1-C_6 aliphatic optionally substituted by 1-3 occurrences of F, or a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system having 0-5 heteroatoms selected from O, N, or S;

[0210] wherein when R^2 is OH, R^3 is tert-butyl, R^4 is OH, R^5 is H, and R^6 is H, X is not -O-.

[0211] In some embodiments, provided is a compound of Formula I:



(Formula I)

[0212] or a stereomer, a tautomer, or a pharmaceutically acceptable salt thereof,

[0213] wherein

[0214] X is -O-, -NR^1-, -N=CR^1-NH-, or -NR^1-NH-; wherein when X is -O-, R^1 is absent;

[0215] bond Y^1 is a single bond or a double bond;

[0216] R^1 is H, R^{1B}, or - $(L^1)_u$- $(Z^1)_v$; wherein

[0217] L^1 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, O, or S; wherein L^1 is optionally substituted with 1-3 occurrences of halo, CN, R, OR', or R^{1C};

[0218] u is 0 or 1;

[0219] v is 0 or 1;

[0220] Z^1 is a 5-16 membered aromatic or nonaromatic monocyclic, bicyclic, or tricyclic ring system having 0-7 heteroatoms selected from O, N, or S; wherein Z^1 is optionally substituted with 1-5 occurrences of R^{1A}, R^{1C} or combinations thereof;

[0221] R^{1A} is - $(L^2)_m$- $(Z^2)_w$; wherein

[0222] L^2 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si; wherein L^2 is optionally substituted with 1-3 occurrences of halo, CN, R, OR' or ; m is 0 or 1;

[0223] w is 0 or 1;

[0224] Z^2 is a C_1-C_{10} aliphatic, or 3-16 membered aromatic or nonaromatic monocyclic, bicyclic or tricylic ring system having 0-7 heteroatoms selected from O, N, or S; wherein Z^2 is optionally substituted with 1-5 occurrences of R^{1B};

[0225] R^{1B} is H, halo, CN, R*, OR*, NRR*; or two R^{1B}, taken together with the atom to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms;

[0226] R^{1C} is H, halo, CN, R*, OR*, NRR*; or two R^{1C}, taken together with the atom or atoms to which they are attached, optionally form a 3-16 membered ring having 0-4 heteroatoms;

[0227] R*is C_1-C_6 aliphatic wherein up to three methylene units of the C_1-C_6 aliphatic are optionally replaced by N, NR, O, S, C=O, SO, SO_2 or Si and wherein the C_1-C_6 aliphatic is optionally substituted with 1-3 occurrences of halo, CN, R' or OR';

[0228] R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, a C_1-C_{16} aliphatic, a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system, or – (C_1-C_{16} aliphatic) – (5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system) ; wherein up to five carbon atoms of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{2A} is optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR';

[0229] R^3 is OH, R^{3A}, or OR^{3A}; wherein R^{3A} is C_1-C_{10} aliphatic optionally substituted with 1-3 occurrences of halo, R or OR';

[0230] R^4 is OH, R^{4A}, OR^{4A}; or when bond Y^1 between R^4 and R^5 is a double bond, R^4 is absent; wherein R^{4A} is C_1-C_7 aliphatic and R^{4A} is optionally substituted with 1-3 occurrences of halo, R' or OR';

[0231] R^5 is H or OH;

[0232] R^6 is H; or when bond Y^1 between R^4 and R^5 is a double bond, R^6 is absent;

[0233] R is H or C_1-C_6 aliphatic optionally substituted by 1-3 occurrences of F; or two R, taken together with the atom (s) to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms; and

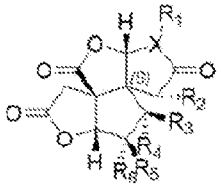
[0234] R' is H, a C_1-C_6 aliphatic optionally substituted by 1-3 occurrences of F, OR, NH_2, NHR", $NR"_2$, wherein R" is C_1-C_6 aliphatic, or a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system having 0-5 heteroatoms selected from O, N, or S;

[0235] wherein when R^2 is OH, R^3 is tert-butyl, R^4 is OH, R^5 is H, and R^6 is H, X is not -O-.

[0236] For the sake of clarity, when u is 0 or v is 0, then the bond before $-(L^1)_u$ or before $-(Z^1)_v$ is also absent, respectively. Likewise, when m and w is 0, the bond before $-(L^2)_m$ or before $-(Z^2)_w$ is also absent.

[0237] In some embodiments, X is $-NR^1-$, $-N=CR^1-NH-$, or $-NR^1-NH-$.

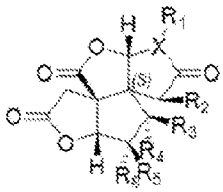
[0238] In some embodiments, the compound has the structure of Formula Ia:



(Formula Ia)

[0239] and R^1, R^2, R^3, R^4, R^5, and R^6 are as described herein. It shall be understood that superscripts and subscripts are interchangeable when referring to functional groups herein. For example R^1 is the same as R_1.

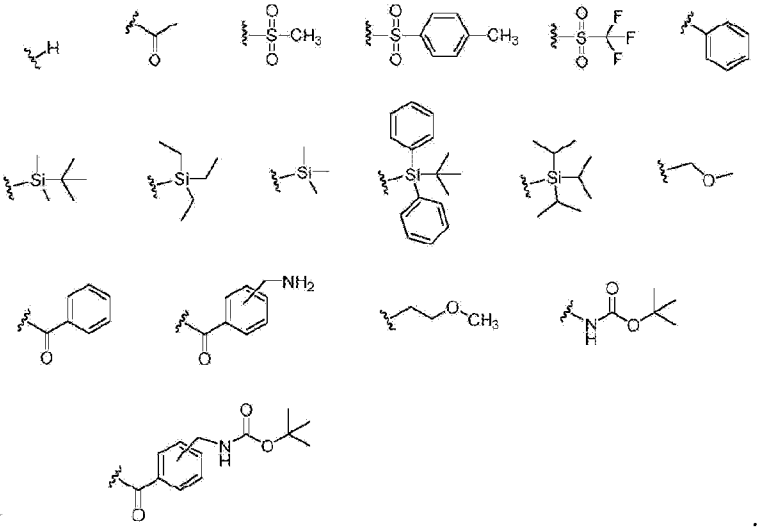
[0240] In some embodiments, the compound has the structure of Formula Ib:



(Formula Ib)

[0241] and R^1, R^2, R^3, R^4, R^5, and R^6 are as described herein.

[0242] In some embodiments, R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5, (C=O) $C_6H_4CH_2NH_2$, or NH (C=O) OC $(CH_3)_3$; wherein phenyl is optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR'; R^3 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or tert-butyl; the bond Y^1 between R^4 and R^5 is a single bond; R^4 is OH or OR^{4A}; and R^5 is H or OH. In some embodiments, R^{2A} is



or .

[0243] In some embodiments, R^1 is H.

[0244] In some embodiments, R^1 is $-(L^1)_u-(Z^1)_v$; wherein L^1 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, O, or S; Z^1 is phenyl, 1-methyl-1, 2, 3, 4-tetrahydronaphthalen-2-y, 1-methyl-2H-isoindol-2-yl, imidazol, indolyl, napthalenyl, adamantanyl, azetidinyl, bicyclo [1.1.1] pentyl, 1-oxa-8-azaspiro [4.5] decan-3-yl, cyclobutanyl, cyclohexanyl, cyclopentanyl, cyclopropanyl, norbornenyl, oxetanyl, piperazinyl, piperidinyl, pyridinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, or C_3-C_{12} cycloaliphatic having 0-5 heteroatoms selected from O, N, or S; u is 0 or 1; and v is 0 or 1; wherein Z^1 is optionally substituted with 1-5 occurrences of R^{1C}, morpholinyl, $-OCH_2O-$, -(C=O)-(pyrazinyl)-R^{1B}, -(C=O)-(phenyl)-R^{1B}, or $-(SO_2)$-(phenyl)-R^{1B}; wherein each independent occurrence of R^{1B} is H, halo, R*, OR*, or NRR*; wherein each independent occurrence of R^{1C} is H, halo, R*, OR*, or NRR*; and wherein each independent occurrence of R*is H, =N, -C≡CH, -N=N-, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, , -CN, $-CH_2O-$, $-CF_2O-$, $-CH_2CH_2O-$, or -Boc (-(C=O) OC $(CH_3)_3$).

[0245] In some embodiments, when Z^1 is phenyl, Z^1 is optionally substituted with 1-5 occurrences of morpholinyl or R^{1C}, wherein R^{1C} is halo, CH_3, -CH_2F, -CHF_2, -CF_3, -CN -OCH_3, -OCH_2O-, -OCF_2O-, -OCH_2CH_2O-, -NH_2, -NH (C=O) CH_3, or -N (Boc) (NH (C=O) OC (CH_3) $_3$) .

[0246] In some embodiments, when Z^1 is piperidinyl, Z^1 is optionally substituted with 1-2 occurrences of R^{1C}, wherein R^{1C} is tert-butoxylcarbonyl, 5- (difluoromethyl) pyrazine-2-carbonyl, 2, 2-difluoro-2H-1, 3-benzodioxole-5-carbonyl, 2, 3-dihydro-1, 4-benzodioxine-6-carbonyl, 2, 3-dihydro-1-benzofuran-5-sulfonyl, 4-chlorobenzoyl, 2, 3-dihydro-1-benzofuran-5-carbonyl, or prop-2-enoyl.

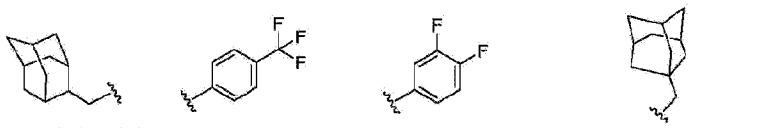
[0247] In some embodiments, when Z^1 is pyrrolidinyl, Z^1 is optionally substituted with 1-2 occurrences of R^{1C}, wherein R^{1C} is tert-butoxylcarbonyl.

[0248] In some embodiments, R^1 is H, 2, 4-dimethoxybenzyl, [1- (tert-butoxycarbonyl) piperidin-4-yl] methyl, piperidin-4-ylmethyl, 2- [1- (tert-butoxycarbonyl) piperidin-4-yl] ethyl, 2- (piperidin-4-yl) ethyl, 3- [1- (tert-butoxycarbonyl) piperidin-4-yl] propyl, 3- (piperidin-4-yl) propyl, 2- [4- (tert-butoxycarbonyl) piperazin-1-yl] ethyl, 2- (piperazin-1-yl) ethyl, 2- (3-methyl-1H-indol-2-yl) ethyl, 3- (1H-imidazol-1-yl) propyl, (R) - [1- (tertbutoxycarbonyl) pyrrolidin-3-yl] methyl, (S) - pyrrolidin-3-yl) methyl) , ((2R) -bicyclo [2.2.1] hept-5-en-2-yl) methyl, phenyl, 4-acetamidophenyl, 4- [(tert-butoxycarbonyl) amino] phenyl, 4-aminophenyl, 4-(morpholin-4-yl) phenyl, benzo [d] [1, 3] dioxol-5-yl, pyridin-3-yl, benzyl, methyl, bicyclo [1.1.1] pentyl, oxetan-3-yl, cyclobutyl methyl, cyclopropyl methyl, (oxetan-3-yl) methyl, adamantan-2-yl methyl, NH_2, cyclopropyl, 3-methoxy phenyl, 4-methoxy phenyl, naphthalen-2-yl, 3- (trifluoromethyl) phenyl, 4-cyano phenyl, 2-[3- (but-3-yn-1-yl) -3H-diazirin-3-yl] ethyl, cyclohexyl, 4-fluoro phenyl, 4-(trifluoromethyl) phenyl, 4-toluyl, 3-toluyl, 2-toluyl, (oxolan-2-yl) methyl, 2-methoxy-2-oxoethyl, (1- (5- (difluoromethyl) pyrazine-2-carbonyl) piperidin-4-yl) methyl, [1- (2, 3-dihydro-1-benzofuran-5-sulfonyl) piperidin-4-yl] methyl, (1-(2, 2-difluorobenzo [d] [1, 3] dioxole-5-carbonyl) piperidin-4-yl) methyl, (1-(2, 3-dihydrobenzo [b] [1, 4] dioxine-6-carbonyl) piperidin-4-yl) methyl, (1-(4-chlorobenzoyl) piperidin-4-yl) methyl, (1- (2, 3-dihydrobenzofuran-5-carbonyl) piperidin-4-yl) methyl, (1-acryloylpiperidin-4-yl) methyl, (1- (quinoxaline-6-carbonyl) piperidin-4-yl) methyl, (tetrahydro-2H-pyran-4-yl) methyl, (tetrahydro-2H-thiopyran-4-yl) methyl, 2- (1-methyl-1, 2, 3, 4-tetrahydronaphthalen-2-yl) ethyl, 2- (1-methyl-2H-isoindol-2-yl) ethyl, 2- (azetidin-1-yl) ethyl, 2-(trifluoromethyl) phenyl, 2-fluoro phenyl, 2-methoxy phenyl, 3, 4-difluoro phenyl, 3, 5-difluoro phenyl, 3-fluoro phenyl, 4-hydroxy phenyl, 8- (tert-butoxycarbonyl) -1-oxa-8-azaspiro [4.5] decan-3-yl, anilinyl, benzo [d] [1, 3] dioxol-4-yl,

cyclobutyl, cyclohexyl methyl, naphthalen-1-yl, piperidin-4-yl methyl, pyridi n-2-yl, or pyridin-4-yl. In some embodiments, R^1 is H, 2, 4-dimethoxybenzyl, [1- (tert-butoxycarbonyl) piperidin-4-yl] methyl, piperidin-4-ylmethyl, 2- [1- (tert-butoxycarbonyl) piperidin-4-yl] ethyl, 2- (piperidin-4-yl) ethyl, 3- [1- (tert-butoxycarbonyl) piperidin-4-yl] propyl, 3- (piperidin-4-yl) propyl, 2- [4- (tert-butoxycarbonyl) piperazin-1-yl] ethyl, 2- (piperazin-1-yl) ethyl, 2- (3-methyl-1H-indol-2-yl) ethyl, 3- (1H-imidazol-1-yl) propyl, [1- (tertbutoxycarbonyl) pyrrolidin-3-yl] methyl, (pyrrolidin-3-yl) methyl) , (bicyclo [2.2.1] hept-5-en-2-yl) methyl, pheny l, 4-acetamidophenyl, 4- [(tert-butoxycarbonyl) amino] phenyl, 4-aminophenyl, 4-(morpholin-4-yl) phenyl, benzo [d] [1, 3] dioxol-5-yl, pyridin-3-yl, benzyl, methy l, bicyclo [1.1.1] pentyl, oxetan-3-yl, cyclobutyl methyl, cyclopropyl methyl, (oxetan-3-yl) methyl, adamantan-2-yl methyl, NH_2, cyclopropyl, 3-methoxy phenyl, 4-methoxy phenyl, naphthalen-2-yl, 3- (trifluoromethyl) phenyl, 4-cyano phenyl, 2-[3- (but-3-yn-1-yl) -3H-diazirin-3-yl] ethyl, cyclohexyl, 4-fluoro phenyl, 4-(trifluoromethyl) phenyl, 4-toluyl, 3-toluyl, 2-toluyl, (oxolan-2-yl) methyl, 2-methoxy-2-oxoethyl, (1- (5- (difluoromethyl) pyrazine-2-carbonyl) piperidin-4-yl) methyl, [1- (2, 3-dihydro-1-benzofuran-5-sulfonyl) piperidin-4-yl] methyl, (1-(2, 2-difluorobenzo [d] [1, 3] dioxole-5-carbonyl) piperidin-4-yl) methyl, (1-(2, 3-dihydrobenzo [b] [1, 4] dioxine-6-carbonyl) piperidin-4-yl) methyl, (1- (4-chlorobenzoyl) piperidin-4-yl) methyl, (1- (2, 3-dihydrobenzofuran-5-carbonyl) piperid in-4-yl) methyl, (1-acryloylpiperidin-4-yl) methyl, (1- (quinoxaline-6-carbonyl) piperid in-4-yl) methyl, (tetrahydro-2H-pyran-4-yl) methyl, (tetrahydro-2H-thiopyran-4-yl) methyl, 2- (1-methyl-1, 2, 3, 4-tetrahydronaphthalen-2-yl) ethyl, 2- (1-methyl-2H-isoindol-2-yl) ethyl, 2- (azetidin-1-yl) ethyl, 2- (trifluoromethyl) phenyl, 2-fluoro phenyl, 2-methoxy phenyl, 3, 4-difluoro phenyl, 3, 4-dichloro phenyl, 3, 5-difluoro phenyl, 3-fluoro phenyl, 4-hydroxy phenyl, 8- (tert-butoxycarbonyl) -1-oxa-8-azaspiro [4.5] decan-3-yl, anilinyl, benzo [d] [1, 3] dioxol-4-yl, cyclobutyl, c yclohexyl methyl, naphthalen-1-yl, pyridin-2-yl, pyridin-4-yl, adamantan-1-yl methyl, 1- (tert-butoxycarbonyl) -1H-indol-5-yl, 1H-indol-5-yl, 3- [(tert-butoxycarbonyl) amino] phenyl, 4-Hydroxyphenyl ethyl, 1H-indole-3-ethyl, ((1R, 4aS , 10aR) -7-isopropyl-1, 4a-dimethyl-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl) methyl, [((tert-butoxycarbonyl) aminomethyl) adamantan-1-yl] methyl, (amin omethyl) adamantan-1-yl) methyl, 3, 5-di-tert butyl phenyl, 3, 4-dihydroxyphenyl e thyl, 3-methoxy, 4-hydroxyphenyl ethyl, 1H-indole-5-hydroxy-3-ethyl, 1H-indole-5-methoxy-3-ethyl, or 1H-indole-4-hydroxy-3-ethyl.

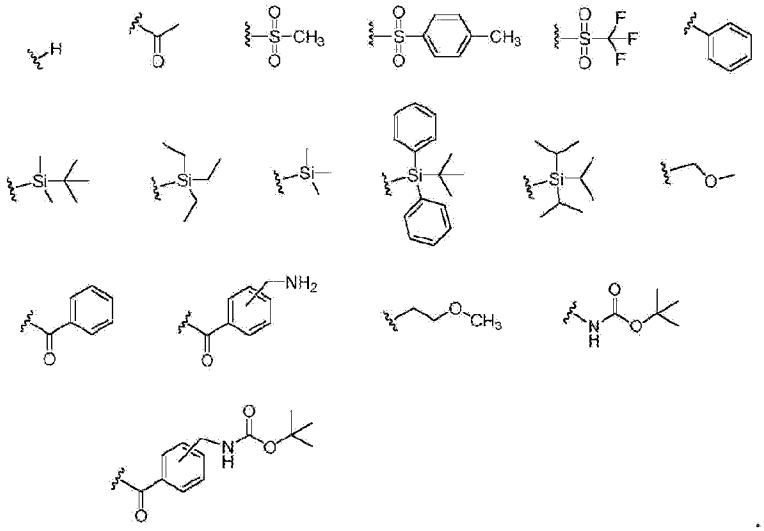
[0249] In some embodiments, R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3 , $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si (C

$_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5, (C=O) $C_6H_4CH_2NH_2$, or NH (C=O) OC $(CH_3)_3$; wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR'; R^3 is tert-butyl; the bond Y^1 between R^4 and R^5 is a single bond; R^4 is OH; R^5 is H; X is $-NR^1-$, $-N=CR^1-NH-$, or $-NR^1-NH-$; and R^1 is selected from



adamantan-2-yl methyl, 4-(trifluoromethyl) phenyl, 3,4-difluoro phenyl, or adamantan-1-yl methyl.

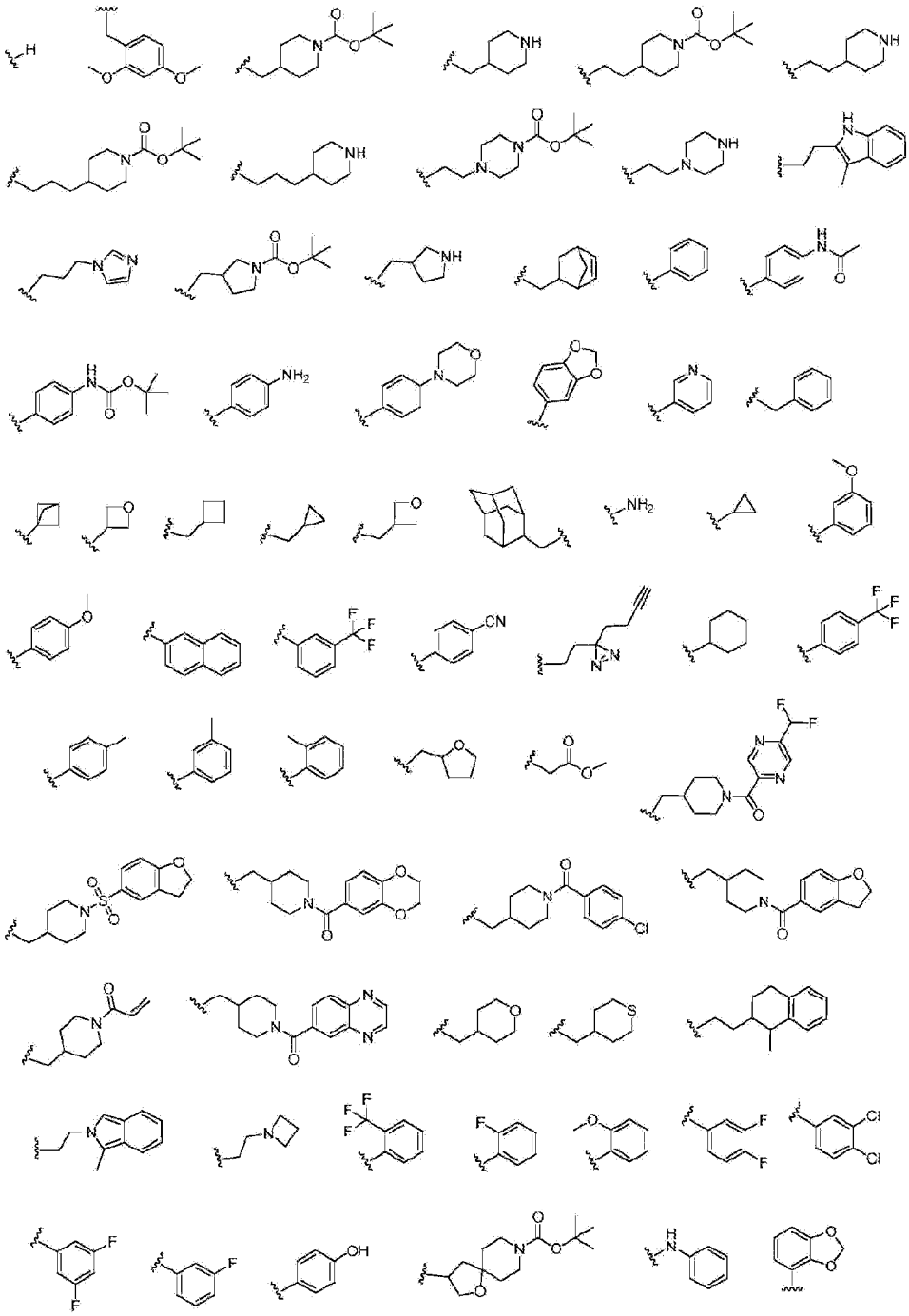
[0250] In some embodiments, R^{2A} is

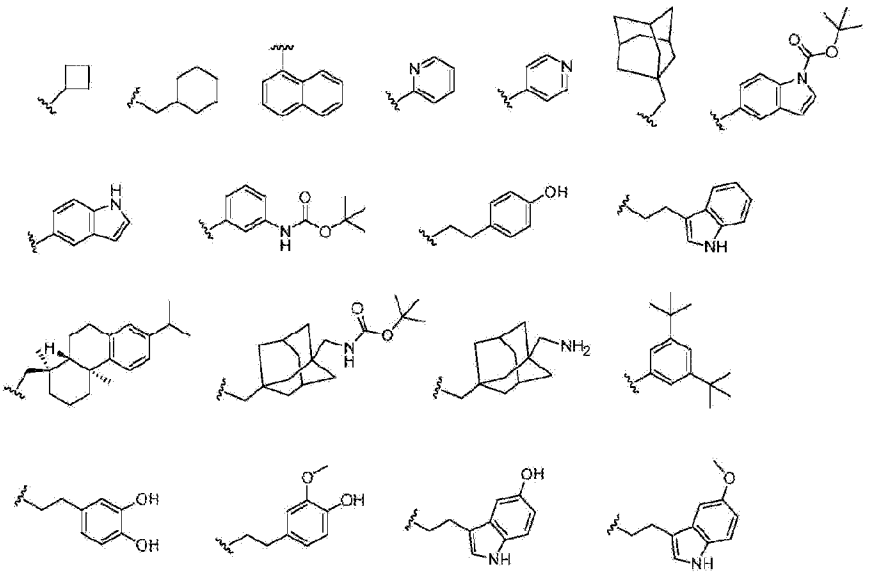


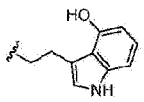
or

.

[0251] In some embodiments, R^1 is



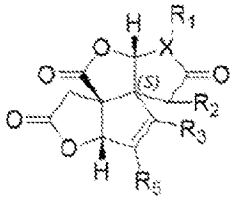


or  .

[0252] In some embodiments, the compound is selected from the group consisting of the compounds as described in Table 1d.

[0253] In some embodiments, the compound is DW192, P -29, P-21, P-30, P-33, JW093, XBB-023, P-28, JW107, XBB-039, JW094, P-34, XBB-045, JW081, XBB-028, XBB-038, XBB-037, XBB-054, XBB-025, XBB-029, XBB-024, DW172, XBB-004, XBB-042, XBB-068, XBB-040, XBB-006, JW072, DW189, P-8, DW191, DW168, XBB-013, XBB-037', XBB-009, XBB-060, XBB-016, DW182, XBB-010, SCC506, or SCC363.

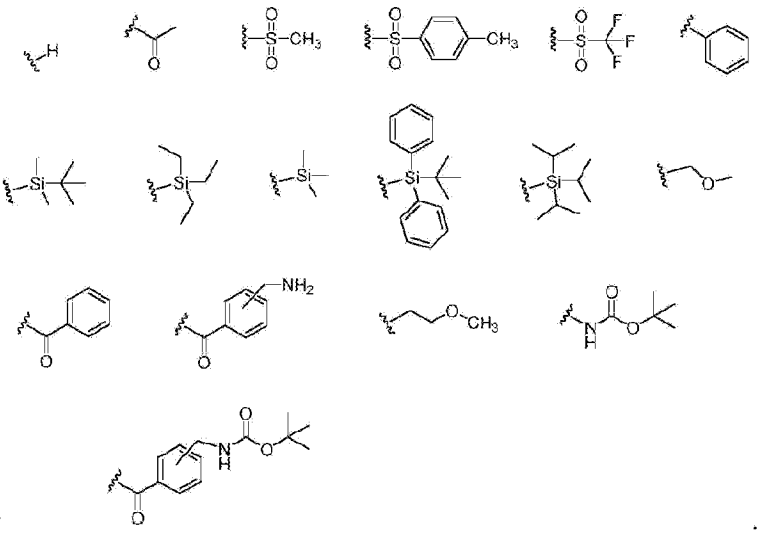
[0254] In some embodiments, the bond Y^1 is a double bond, having Formula I':

 (Formula I').

[0255] In some embodiments, X is -O-and R^1 is absent; R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5, (C=O) $C_6H_4CH_2NH_2$, or NH (C=O) OC $(CH_3)_3$; wherein phenyl is optionally sub

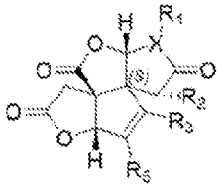
stituted with 1-5 occurrences of halo, R' or OR'; R^3 is tert-butyl; R^4 is absent; R^5 is H; and R^6 is absent.

[0256] In some embodiments, R^{2A} is



or .

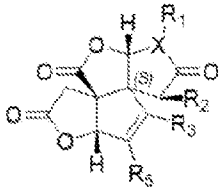
[0257] In some embodiments, the compound has a structure of Formula I'a:



(Formula I'a);

[0258] wherein R^1, R^2, R^3, and R^4 are as described herein.

[0259] In some embodiments, the compound has a structure of Formula I'b:

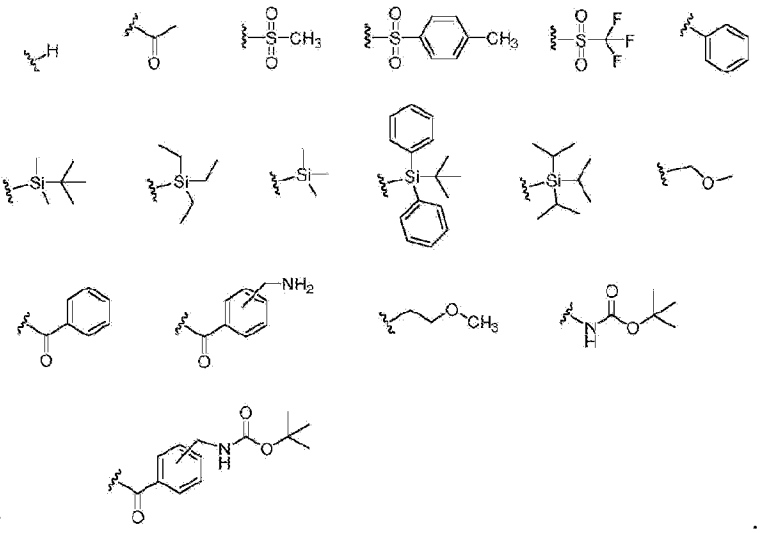


(Formula I'b);

[0260] wherein R^1, R^2, R^3, and R^4 are as described herein.

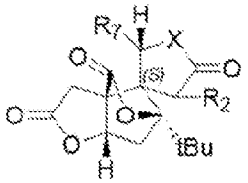
[0261] In some embodiments, X is -O-and R^1 is absent; bond Y^1 is a single bond; R^2 is OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5, (C=O) $C_6H_4CH_2NH_2$, or NH (C=O) OC $(CH_3)_3$; wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR'; R^3 is isopropenyl; R^4 is CH_3; R^5 is H; and R^6 is H.

[0262] In some embodiments, R^{2A} is



or .

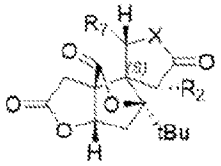
[0263] In some embodiments, provided is a compound of Formula II:



(Formula Ii)

[0264] or a stereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein X is -O-, -NR^1-, -N=CR^1-NH-, or -NR^1-NH-; wherein R^1 is as defined in any one of the p receding embodiments or described herein; R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, a C $_1$-C_{16} aliphatic or a 5-10 membered aromatic or nonaromatic monocyclic or b icyclic ring system, wherein up to five carbon atoms of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring syst em are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{2A} is optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR'; and R^7 is R^{7A} or OR^{7A} , wherein R^{7A} is H, a C_1-C_{16} aliphatic or a 5-10 membered aromatic or nonaromati c monocyclic or bicyclic ring system, wherein up to five carbon atoms of the C $_1$-C_{16} aliphatic or the 5-10 membered aromatic or nonaromatic monocyclic or b icyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2 , S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{7A} is optionally su bstituted with 1-5 occurrences of R^{7B}, wherein R^{7B} is halo, R' or OR'.

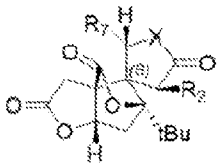
[0265] In some embodiments, the compound has a structure of Formula IIa:



(Formula IIa);

[0266] wherein R^2 and R^7 are as described herein.

[0267] In some embodiments, the compound has a structure of Formula IIb:

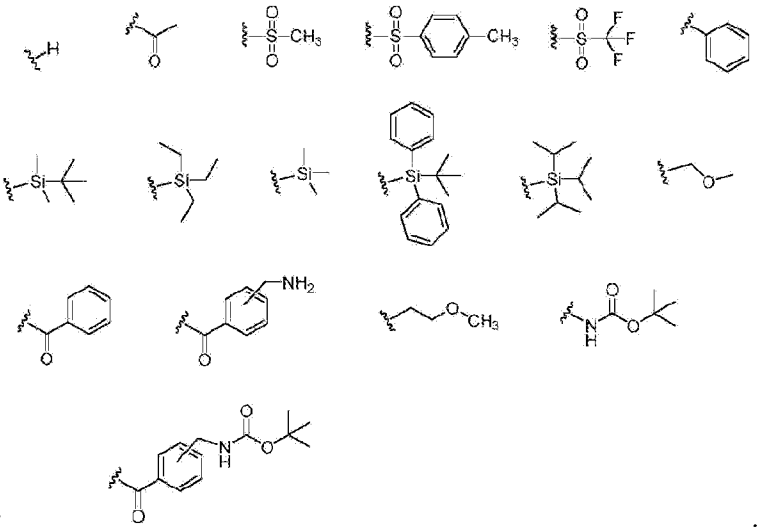


(Formula IIb)

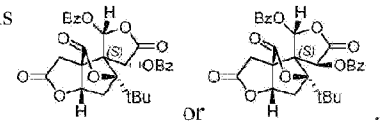
[0268] wherein R^2 and R^7 are as described herein.

[0269] In some embodiments, X is -O-; R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5, (C=O) $C_6H_4CH_2NH_2$ or NH (C=O) OC $(CH_3)_3$; wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR'; and R^7 is R^{7A} or OR^{7A}, wherein R^{7A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5, (C=O) $C_6H_4CH_2NH_2$ or NH (C=O) OC $(CH_3)_3$; wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR'.

[0270] In some embodiments, R^{2A} and/or R^{7A} is

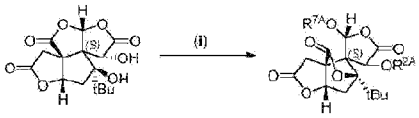


or .

[0271] In some embodiments, the compound is  or .

[0272] In some embodiments, provided is a process for preparing a compound as described herein, including at least the following steps:

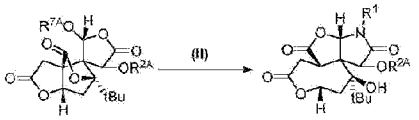
[0273] (i) treating bilobalide with R^{2A}-X in a suitable solvent to form protected product IIa



bilobalide protected product IIa ;

[0274] and

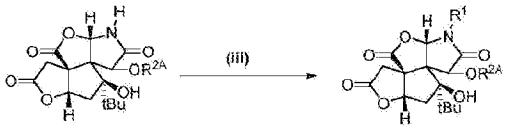
[0275] (ii) treating protected product IIa with at least one base or an acceptable salt ther eof to form aminated product IIb



protected product IIa aminated product IIb ;

[0276] wherein R^{2A} and R^{7A} are as defined in any one of the preceding embodim ents or described herein.

[0277] In some embodiments, wherein the aminated product IIb has the formul a of aminated product IIb', further comprising the step of: (iii) treating aminated p roduct IIb' with an $R^{1'}$-B $(OH)_2$ in the presence of a catalyst to form a N-arylated product IIc

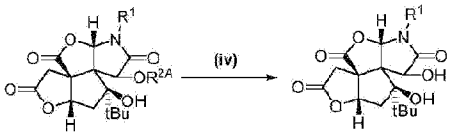


aminated product IIb' N-arylated product IIc ;

[0278] wherein R^1 and R^{2A} are as defined in any one of the preceding embodim ents or described herein. In some embodiments, a ligand is optionally added to the ca talyst. In some embodiments, the catalyst is a Cu catalyst. In some embodiments, Cu: ligand molar ratio is such that there is an excess of either Cu or the ligand. In som e embodiments, the Cu: ligand ratio is 5: 1, 4: 1, 3: 1, 2: 1, 1: 2, 1: 3, 1: 4, or 1 : 5. In some embodiments, the Cu: ligand ratio is A: B, wherein A is 1.1 to 10 and B is 1 A is 1 and B is 1.1 to 10. In some embodiments, the Cu: ligand ratio is not 1: 1.

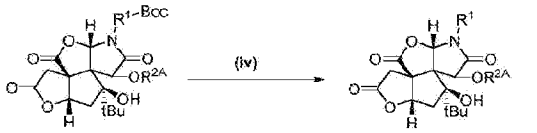
[0279] In some embodiments, the process further includes the step of:

[0280] (iv) treating the aminated product IIb of any one of the preceding embodiments or the N-arylated product IIc of any one of the preceding embodiments with an alkali salt or an acid in a protic solvent to form a deprotected product. In some em bodiments, the deprotected product is deprotected product IId and the alkali salt is K_2CO_3.



;

[0281] wherein R^1 and R^{2A} are as defined in any one of the preceding embodim ents or described herein. In some embodiments, the deprotected product is deprotected product IIe and the acid is an organic acid such as acetyl chloride or oxalyl chlori de, provided that R^1 contains other protecting groups such as tert-butoxycarbonyl (b oc) ; for example:



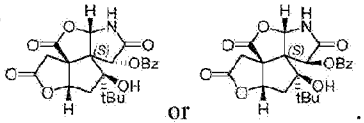
[0282] In some embodiments, R^{2A} and R^{7A} of the protected product IIa is as defined in any one of the preceding embodiments or described herein.

[0283] In some embodiments, R^{2A}-X is benzoyl chloride, and the suitable solvent is pyridine. In some embodiments, R^{2A}-X is 4- (Boc-aminomethyl) benzoic acid and the suitable solvent is DCM (dichloromethane) . In some embodiments, R^{2A}-X is benzoyl chloride or 4- (Boc-aminomethyl) benzoic acid and the suitable solvent is pyridine or DCM.

[0284] In some embodiments, R^1 and R^{2A} of aminated product IIb are as defined in any one of the preceding embodiments or described herein.

[0285] In some embodiments, R^1 and R^{2A} of the N-arylated product IIc are as define d in any one of the preceding embodiments or described herein.

[0286] In some embodiments, the at least one base is ammonia, and the amina ted product IIb is



or

.

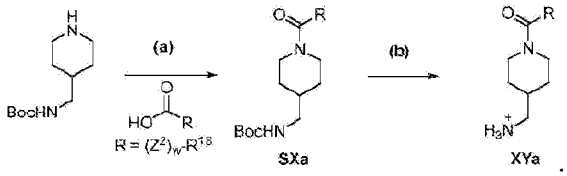
[0287] In some embodiments, the deprotected product, such as deprotected product IId or deprotected product IIe, is as defined in any one of the preceding embodiments or described herein.

[0288] In some embodiments, the at least one base is NH_2R^1. In some embodiments, the at least one base in step (ii) is $[H_3NR^1]^+$.

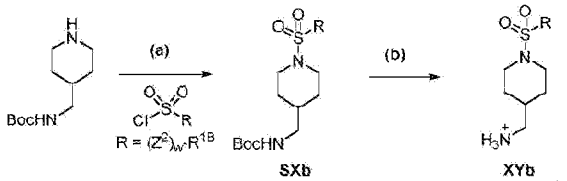
[0289] In some embodiments, the process further includes a second base in step (ii), wherein the second base is a hindered base such as triethylamine, diisopropylethylamine, tributylamine or tetramethylethylenediamine.

[0290] In some embodiments, the protected product IIa is as defined herein.

[0291] In some embodiments, the $[H_3NR^1]^+$ is provided as XYa prepared by the steps of: (a) treating R-COOH with 1-hydroxybenzotriazole, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, and tert-butyl (piperidin-4-ylmethyl) carbamate, to form a boc-protected product SXa, wherein $R = (Z^2)_w-R^{1B}$, wherein Z^2, w and R^{1B} are as defined in any one of the preceding embodiments or as described herein; and (b) treating the boc-protected product SXa with an acid in a solvent to form XYa



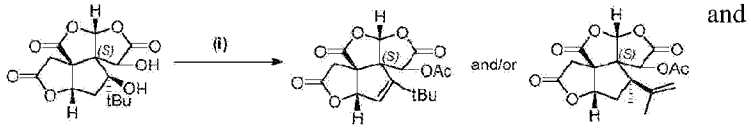
[0292] In some embodiments, the $[H_3NR^1]^+$ is provided as XYb prepared by the steps of: (a) treating R-SO_2 with tert-butyl (piperidin-4-ylmethyl) carbamate and triethylamine, to form a boc-protected product SXb, wherein $R = (Z^2)_w-R^{1B}$, wherein Z^2, w and R^{1B} are as defined in any one of the preceding embodiments or as described herein; and (b) treating the boc-protected product SXb with an acid in a solvent to form XYb



[0293] In some embodiments, provided is a process of preparing a compound as defined herein, which include the steps of:

[0294] (i) treating bilobalide with Ac_2O and an acid to form a protected product IVa and/or protected product Va

[0295]



and

;

[0296] (ii) treating protected product IVa and/or protected product Va with at least one bas e or an acceptable salt thereof to form aminated product IVb or aminated product Vb

[0297]

and/or

;

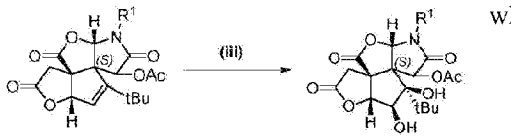
[0298]

wherein R^1 is as defined in

;

any one of the preceding embodiments or as described herein. In som e embodiments, the step (i) forms a mixture of protected product IVa and protected pr oduct Va which account for the total weight of the reaction product in a ratio (prote cted product IVa: protected product Va) of about 0: 100, 10: 90, 20: 80, 30: 70, 40: 60, 50: 50, 60: 40, 70: 30, 80: 20, 90: 10, or 100: 0. In some embodiments, the total weight of the reaction product in step (i) is 100%. In some embodiments, the step (i) forms protected product IVa or protected product Va.

[0299] In some embodiments, the process further includes the step of: (iii) treating the ami nated product IVb with an oxidizing agent and a solvent to form oxidized product VIc

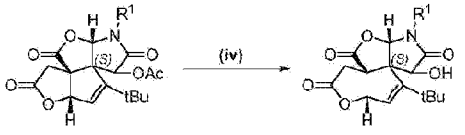


wherein R^1 is as defined in

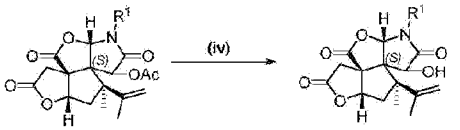
,

any one of the preceding embodiments or as described herein.

[0300] In some embodiments, the process further includes at least one of the steps of: (iv) treating the aminated product IVb or the aminated product Vb with an acid to form dep rotected product IVd or deprotected product Vd,



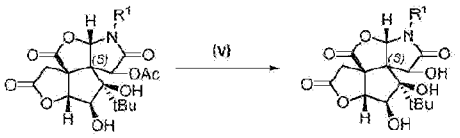
aminated product IVb deprotected product IVd ; or



aminated product Vb deprotected product Vd ;

wherein R^1 is as defined in any one of the preceding embodiments or as described herein.

[0301] In some embodiments, the process further includes the step of: (v) treating the oxidized product VIc with an acid to form deprotected product VId,



oxidized product VIc deprotected product VId ,

wherein R^1 is as defined in any one of the preceding embodiments or as described herein.

[0302] In some embodiments, provided is a method of treating or preventing cancer in a subject in need thereof, including administering to the subject a compound described herein.

[0303] In some embodiments, the cancer is bladder cancer, brain cancer, breast cancer, CNS cancer, colon cancer, hematopoietic cancer, kidney cancer, leukemia, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, or renal cancer.

[0304] In some embodiments, the cancer is leukemia, colon cancer, lung cancer, melanoma or renal cancer.

[0305] In some embodiments, the lung cancer is non-small cell lung cancer (NSCLC) .

[0306] In some embodiments, the leukemia is lymphocytic leukemia.

[0307] In some embodiments, provided is a use of a compound described herein for treating or preventing cancer.

[0308] In some embodiments, provided is a use of a compound described herein for the manufacture of a medicament for treating or preventing cancer.

[0309] In some embodiments, provided is a method of inducing cell death in a cancer cell, comprising contacting a compound of a compound described herein with the cancer cell.

[0310] In some embodiments, provided is a method of inhibiting cell growth in a cancer cell, comprising contacting a compound of a compound described herein wit h the cancer cell.

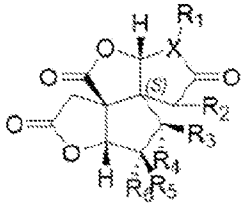
[0311] In some embodiments, the method is an in vitro method.

[0312] In some embodiments, the compound is DW192, P-29, P-21, P-30, P-33, JW093, XBB-023, P-28, JW107, XBB-039, JW094, P-34, XBB-045, JW081, XBB-028, XBB-038, XBB-037, XBB-054, XBB-025, XBB-029, XBB-024, DW172, XBB-004, XBB-042, XBB-068, XBB-040, XBB-006, JW072, DW189 , P-8, DW191, DW168, XBB-013, XBB-'37', XBB-009, XBB-060, XBB-016, DW182, XBB-010, SCC506, or SCC363.

[0313] In some embodiments, the compound is DW192, P-29, P-21, SCC506, or SCC363.

[0314] Embodiments II

[0315] In some embodiments, provided is a compound of Formula I:



(Formula I)

[0316] or a stereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein X is -O-, -NR^1-, -N=CR^1-NH-, or -NR^1-NH-; wherein when X is -O-, R^1 is absent; bond Y^1 is a single bond or a double bond; R^1 is H, R^{1B}, or - $(L^1)_u$- $(Z^1)_v$; wherein

[0317] L^1 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are op tionally replaced by N, O, or S; wherein L^1 is optionally substituted with 1-3 occurrences of halo, CN, R, OR', or R^{1C};

[0318] u is 0 or 1;

[0319] v is 0 or 1;

[0320] Z^1 is a 5-16 membered aromatic or nonaromatic monocyclic or bicyclic ring syst em having 0-5 heteroatoms selected from O, N, or S; wherein Z^1 is optionally su bstituted with 1-5 occurrences of R^{1A} , R^{1C} or combinations thereof;

[0321] R^{1A} is - $(L^2)_m$- $(Z^2)_w$; wherein

[0322] L^2 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are op tionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O , or Si; wherein L^2 is optionally substituted with 1-3 occurrences of halo, CN, R, OR' or ; m is 0 or 1;

[0323] w is 0 or 1;

[0324] Z^2 is a C_1-C_{10} aliphatic, or 3-16 membered aromatic or nonaromatic monocyclic or bicyclic ring system having 0-5 heteroatoms selected from O, N, or S; wherein Z^2 is optionally substituted with 1-5 occurrences of R^{1B};

[0325] R^{1B} is H, halo, CN, R*, OR*, NRR*; or two R^{1B}, taken together with the atom to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms;

[0326] R^{1C} is H, halo, CN, R*, OR*, NRR*; or two R^{1C}, taken together with the atom to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms;

[0327] R*is C_1-C_6 aliphatic wherein up to three methylene units of the C_1-C_6 aliphatic are optionally replaced by N, NR, O, S, C=O, SO, SO_2 or Si and wherein the C_1-C_6 aliphatic is optionally substituted with 1-3 occurrences of halo, CN, R' or OR';

[0328] R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, a C_1-C_{16} aliphatic, a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system, or – (C_1-C_{16} aliphatic) – (5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system) ; wherein up to five carbon atoms of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{2A} is optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR';

[0329] R^3 is OH, R^{3A}, or OR^{3A}; wherein R^{3A} is C_1-C_{10} aliphatic optionally substituted with 1-3 occurrences of halo, R or OR';

[0330] R^4 is OH, R^{4A}, OR^{4A}; or when bond Y^1 between R^4 and R^5 is a double bond, R^4 is absent; wherein R^{4A} is C_1-C_7 aliphatic and R^{4A} is optionally substituted with 1-3 occurrences of halo, R' or OR';

[0331] R^5 is H or OH;

[0332] R^6 is H; or when bond Y^1 between R^4 and R^5 is a double bond, R^6 is absent;

[0333] R is H or C_1-C_6 aliphatic optionally substituted by 1-3 occurrences of F; or two R, taken together with the atom (s) to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms; and

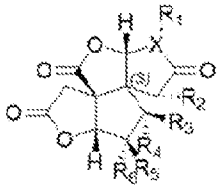
[0334] R' is H, a C_1-C_6 aliphatic optionally substituted by 1-3 occurrences of F, or a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system having 0-5 heteroatoms selected from O, N, or S;

[0335] wherein when R^2 is OH, R^3 is tert-butyl, R^4 is OH, R^5 is H, and R^6 is H, X is not -O-.

[0336] For the sake of clarity, when u is 0 or v is 0, then the bond before - $(L^1)_u$ or before - $(Z^1)_v$ is also absent, respectively. Likewise, when m and w is 0, the bond before - $(L^2)_m$ or before - $(Z^2)_w$ is also absent.

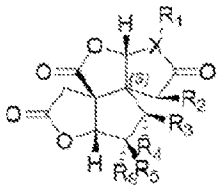
[0337] In some embodiments, X is -NR^1-, -N=CR^1-NH-, or -NR^1-NH-.

[0338] In some embodiments, the compound described in any one of the preceding embodiments has the structure of Formula Ia:



(Formula Ia).

[0339] In some embodiments, the compound described in any one of the preceding embodiments has the structure of Formula Ib:



(Formula Ib).

[0340] In some embodiments, R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, or N (C=O) OC $(CH_3)_3$; wherein phenyl is optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR'; R^3 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or tert-butyl; the bond Y^1 between R^4 and R^5 is a single bond; R^4 is OH or OR^{4A}; and R^5 is H or OH.

[0341] In some embodiments, R^1 is H.

[0342] In some embodiments, R^1 is - $(L^1)_u$- $(Z^1)_v$; wherein L^1 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, O, or S; Z^1 is phenyl, 1-methyl-1, 2, 3, 4-tetrahydronaphthalen-2-y, 1-methyl-2H-isoindol-2-yl, imidazol, indolyl, napthalenyl, adamantanyl, azetidinyl, bicyclo [1.1.1] pentyl, 1-oxa-8-azaspiro [4.5] decan-3-yl, cyclobutanyl, cyclohexanyl, cyclopentanyl, cyclopropanyl, norbornenyl, oxetanyl, piperazinyl, piperidinyl, pyridinyl, pyrrolidinyl, tetrahydrofuranyl,

[0343] tetrahydropyranyl, tetrahydrothiopyranyl, or C_3-C_{12} cycloaliphatic having 0-5 heteroatoms selected from O, N, or S; u is 0 or 1; and v is 0 or 1; wherein Z^1 is optionally substituted with 1-5 occurrences of R^{1C}, morpholinyl, -OCH_2O-, - (C=O) - (pyrazinyl) -R^{1B}, - (C=O) - (phenyl) -R^{1B}, or - (SO_2) - (phenyl) -R^{1B}; wherein each independent occurrence of R^{1B} is H, halo, R*, OR*, or NRR*; wherein each independent occurrence of R^{1C} is H, halo, R*, OR*, or NRR*; and w

herein each independent occurrence of R*is H, =N, -C≡CH, -N=N-, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, , -CN, $-CH_2O$-, $-CF_2O$-, $-CH_2CH_2O$-, or -Boc (- (C=O) OC $(CH_3)_3$) .

[0344] In some embodiments, when Z^1 is phenyl, Z^1 is optionally substituted with 1-5 occurrences of morpholinyl or R^{1C}, wherein R^{1C} is halo, CH_3, $-CH_2F$, $-CHF_2$, $-CF_3$, -CN $-OCH_3$, $-OCH_2O$-, $-OCF_2O$-, $-OCH_2CH_2O$-, $-NH_2$, -NH (C=O) CH_3, or -N (Boc) - (N (C=O) OC $(CH_3)_3$) .

[0345] In some embodiments, when Z^1 is piperidinyl, Z^1 is optionally substituted with 1-2 occurrences of R^{1C}, wherein R^{1C} is tert-butoxylcarbonyl, 5- (difluoromethyl) pyrazine-2-carbonyl, 2, 2-difluoro-2H-1, 3-benzodioxole-5-carbonyl, 2, 3-dihydro-1, 4-benzodioxine-6-carbonyl, 2, 3-dihydro-1-benzofuran-5-sulfonyl, 4-chlorobenzoyl, 2, 3-dihydro-1-benzofuran-5-carbonyl, or prop-2-enoyl.

[0346] In some embodiments, when Z^1 is pyrrolidinyl, Z^1 is optionally substituted with 1-2 occurrences of R^{1C}, wherein R^{1C} is tert-butoxylcarbonyl.

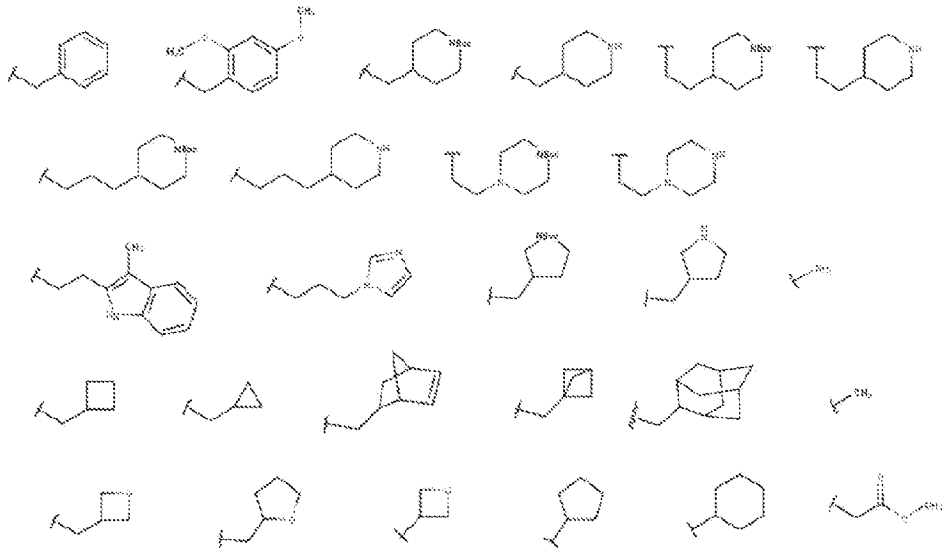
[0347] In some embodiments, R^1 is H, 2, 4-dimethoxybenzyl, [1- (tert-butoxycarbonyl) p iperidin-4-yl] methyl, piperidin-4-ylmethyl, 2- [1- (tert-butoxycarbonyl) piperidin-4-yl] ethyl, 2- (piperidin-4-yl) ethyl, 3- [1- (tert-butoxycarbonyl) piperidin-4-yl] propyl, 3- (piperidin-4-yl) propyl, 2- [4- (tert-butoxycarbonyl) piperazin-1-yl] ethyl, 2- (piperazin-1-yl) ethyl, 2- (3-methyl-1H-indol-2-yl) ethyl, 3- (1H-imidazol-1-yl) propyl, (R) - [1- (tertbutoxycarbonyl) pyrrolidin-3-yl] methyl, (S) - pyrrolidin-3-yl) methyl) , ((2R) -bicyclo [2.2.1] hept-5-en-2-yl) methyl, pheny l, 4-acetamidophenyl, 4- [(tert-butoxycarbonyl) amino] phenyl, 4-aminophenyl, 4-(morpholin-4-yl) phenyl, benzo [d] [1, 3] dioxol-5-yl, pyridin-3-yl, benzyl, methy l, bicyclo [1.1.1] pentyl, oxetan-3-yl, cyclobutyl methyl, cyclopropyl methyl, (oxetan-3-yl) methyl, adamantan-2-yl methyl, NH_2, cyclopropyl, 3-methoxy phenyl, 4-methoxy phenyl, naphthalen-2-yl, 3- (trifluoromethyl) phenyl, 4-cyano phenyl, 2-[3- (but-3-yn-1-yl) -3H-diazirin-3-yl] ethyl, cyclohexyl, 4-fluoro phenyl, 4-(trifluoromethyl) phenyl, 4-toluyl, 3-toluyl, 2-toluyl, (oxolan-2-yl) methyl, 2-methoxy-2-oxoethyl, (1- (5- (difluoromethyl) pyrazine-2-carbonyl) piperidin-4-yl) methyl, [1- (2, 3-dihydro-1-benzofuran-5-sulfonyl) piperidin-4-yl] methyl, (1-(2, 2-difluorobenzo [d] [1, 3] dioxole-5-carbonyl) piperidin-4-yl) methyl, (1-(2, 3-dihydrobenzo [b] [1, 4] dioxine-6-carbonyl) piperidin-4-yl) methyl, (1-(4-chlorobenzoyl) piperidin-4-yl) methyl, (1- (2, 3-dihydrobenzofuran-5-carbonyl) piperidin-4- yl) methyl, (1-acryloylpiperidin-4-yl) methyl, (1- (quinoxaline-6-carbonyl) piperidin-4-yl) methyl, (tetrahydro-2H-pyran-4-yl) methyl, (tetr ahydro-2H-thiopyran-4-yl) methyl, 2- (1-methyl-1, 2, 3, 4-tetrahydronaphtha len-2-yl) ethyl, 2- (1-methyl-2H-isoindol-2-yl) ethyl, 2- (azetidin-1-yl) ethyl, 2-(trifluoromethyl) phenyl, 2-fluoro phenyl, 2-methoxy phenyl, 3, 4-difluoro phenyl,

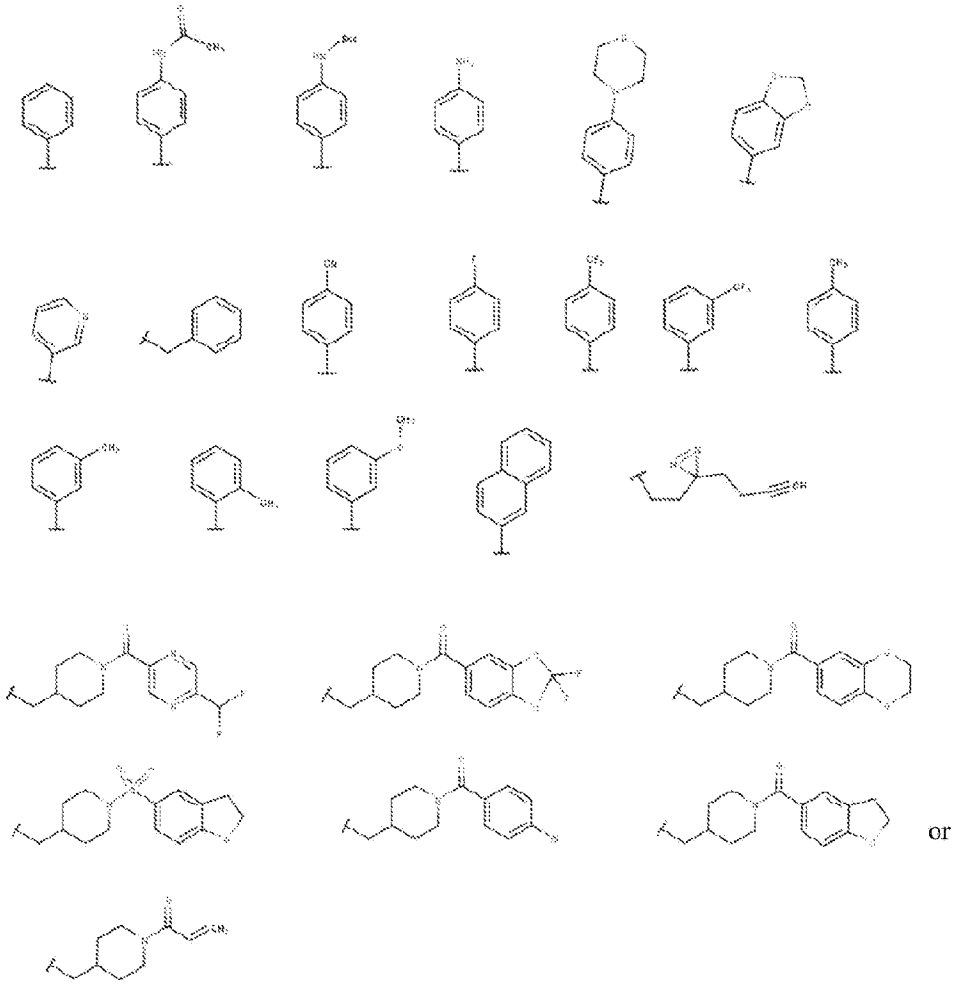
3, 5-difluoro phenyl, 3-fluoro phenyl, 4-hydroxy phenyl, 8- (tert-butoxycarbonyl) -1-oxa-8-azaspiro [4.5] decan-3-yl, anilinyl, benzo [d] [1, 3] dioxol-4-yl, cyclobutyl, cyclohexyl methyl, naphthalen-1-yl, piperidin-4-yl methyl, pyridin-2-yl, or pyridin-4-yl.

[0348] In some embodiments, R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, or N (C=O) OC $(CH_3)_3$; wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR'; R^3 is tert-butyl;

[0349] the bond Y^1 between R^4 and R^5 is a single bond; R^4 is OH; R^5 is H; X is $-NR^1-$, $-N=CR^1-NH-$, or $-NR^1-NH-$; and R^1 is selected from a group in Table 1a or Table 1b.

[0350] In some embodiments, R^1 is





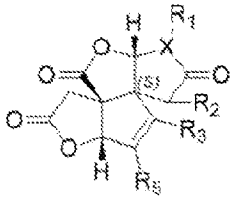
or

.

[0351] In some embodiments, the compound is selected from the group consisting of the compounds as described in Table 1d.

[0352] In some embodiments, the compound is XBB-037 or XBB-037'.

[0353] In some embodiments, the bond Y^1 is a double bond, having Formula I':

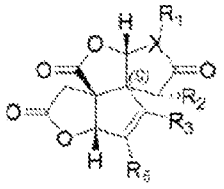


(Formula I').

[0354] In some embodiments, X is -O-and R^1 is absent; R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)$

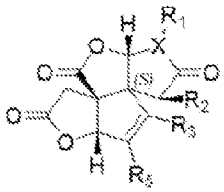
$_3$, Si (CH_2CH_3) $_3$, Si (CH_3) $_3$, Si (C_6H_5) $_2$C (CH_3) $_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, or N (C=O) OC (CH_3) $_3$; wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR'; R^3 is tert-butyl; R^4 is absent; R^5 is H; and R^6 is absent.

[0355] In some embodiments, the compound described in any one of the preceding embodiments has a structure of Formula I'a:



(Formula I'a).

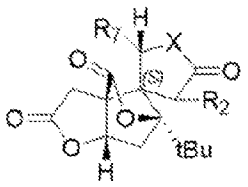
[0356] In some embodiments, the compound described in any one of the preceding embodiments has a structure of Formula I'b:



(Formula I'b).

[0357] In some embodiments, X is -O-and R^1 is absent; bond Y^1 is a single bond; R^2 is OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si (CH_3) $_2$C (CH_3) $_3$, Si (CH_2CH_3) $_3$, Si (CH_3) $_3$, Si (C_6H_5) $_2$C (CH_3) $_3$, Si (iPr) $_3$, CH_2OCH_3, or $CH_2CH_2OCH_3$; wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR'; R^3 is isopropenyl; R^4 is CH_3; R^5 is H; and R^6 is H.

[0358] In some embodiments, provided is a compound of Formula II:

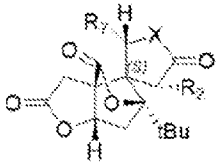


(Formula II)

[0359] or a stereomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein X is -O-, $-NR^1-$, $-N=CR^1-NH-$, or $-NR^1-NH-$; wherein R^1 is as defined in claim 1; R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, a C_1-C_{16} aliphatic or a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system, wherein up to five carbon atoms of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{2A} is optionally su

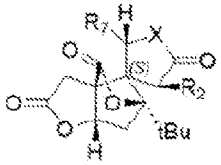
bstituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR'; and R^{7} is R^{7A} or OR^{7A}, wherein R^{7A} is H, a C_1-C_{16} aliphatic or a 5-10 membered aroma tic or nonaromatic monocyclic or bicyclic ring system, wherein up to five carbon atom s of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromati c monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{7A} is optionally su bstituted with 1-5 occurrences of R^{7B}, wherein R^{7B} is halo, R' or OR'.

[0360] In some embodiments, the compound described in any one of the precei ding embodiments has a structure of Formula IIa:



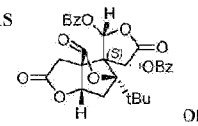
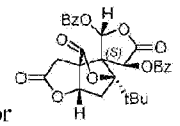
(Formula IIa).

[0361] In some embodiments, the compound described in any one of the preced ing embodiments has a structure of Formula IIb:

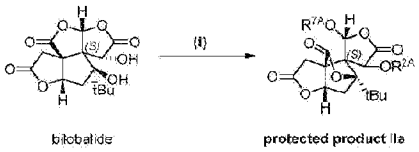


(Formula IIb).

[0362] In some embodiments, X is -O-; R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, or N (C=O) OC $(CH_3)_3$; wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR'; and R^{7} is R^{7A} or OR^{7A}, wherein R^{7A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, or N (C=O) OC $(CH_3)_3$; wherein phenyl is optionally sub stituted with 1-5 occurrences of halo, R' or OR'.

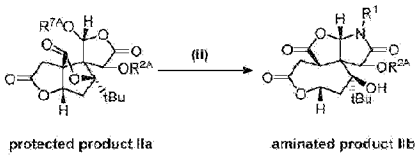
[0363] In some embodiments, the compound is  or  .

[0364] In some embodiments, provided is a process for preparing a compound of any one of the preceding embodiments, including at least the following steps: (i) treating bilobalide with R^{2A}-X in a suitable solvent to form protected product IIa



;

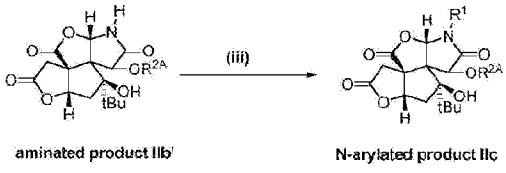
[0365] and (ii) treating protected product IIa with at least one base or an acceptable salt thereof to form aminated product IIb



;

[0366] wherein R^{2A} and R^{7A} are as defined in any one of the preceding embodiments.

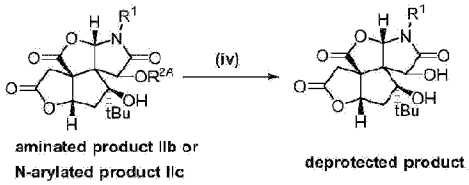
[0367] The process of claim 26, wherein the aminated product IIb has the fo rmula of aminated product IIb', further comprising the step of: (iii) treating aminat ed product IIb' with an $R^{1'}$-B $(OH)_2$ in the presence of a catalyst to form a N-arylated product IIc



;

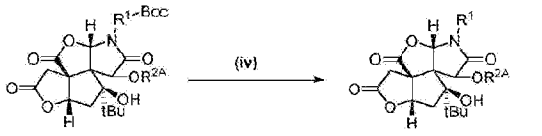
[0368] wherein R^1 and R^{2A} are as defined in any one of the preceding embodim ents. In some embodiments, a ligand is optionally added to the catalyst. In some embo diments, the catalyst is a Cu catalyst. In some embodiments, Cu: ligand molar ratio i s such that there is an excess of either Cu or the ligand. In some embodiments, the C u: ligand ratio is 5: 1, 4: 1, 3: 1, 2: 1, 1: 2, 1: 3, 1: 4, or 1: 5. In some embodim ents, the Cu: ligand ratio is A: B, wherein A is 1.1 to 10 and B is 1 A is 1 and B is 1.1 to 10. In some embodiments, the Cu: ligand ratio is not 1: 1.

[0369] In some embodiments, the process further include the step of: (iv) treating the amina ted product IIb of any one of the preceding embodiments or the N-arylated product IIc of any one of the preceding embodiments with an alkali salt or an acid in a proti c solvent to form a deprotected product. In some embodiments, the deprotected product is deprotected product IId and the alkali salt is K_2CO_3



;

[0370] wherein R^1 and R^{2A} are as defined in any one of the preceding embodim ents. In some embodiments, the deprotected product is deprotected product IIe and the acid is an organic acid such as acetyl chloride or oxalyl chloride, provided that R^1 contains other protecting groups such as tert-butoxycarbonyl (boc) ; for example:



aminated product IIb
or N-arylated product IIc

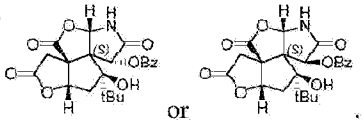
deprotected product IIe

[0371] In some embodiments, R^{2A} and R^{7A} of the protected product IIa is as defined in any one of the preceding embodiments.

[0372] In some embodiments, R^{2A}-X is benzoyl chloride, and the suitable solvent is pyridine.

[0373] In some embodiments, R^1 and R^{2A} of aminated product IIb are as defined in any one of the preceding embodiments.

[0374] In some embodiments, R^1 and R^{2A} of the N-arylated product IIc are as define d in any one of the preceding embodiments.

[0375] In some embodiments, the at least one base is ammonia, and the amina ted product IIb is  or .

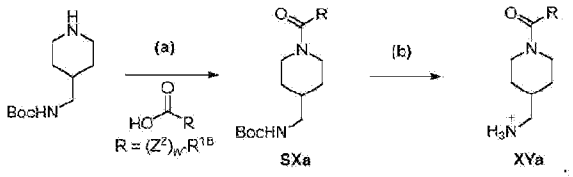
[0376] In some embodiments, the deprotected product, such as deprotected pr oduct IId or deprotected product IIe, is as defined in any one of the preceding embod iments.

[0377] In some embodiments, the at least one base is NH_2R^1.

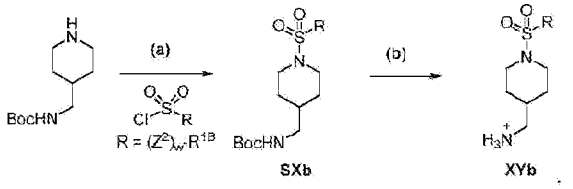
[0378] In some embodiments, the at least one base is $[H_3NR^1]^+$, triethylamine o r diisopropylethylamine.

[0379] In some embodiments, the protected product IIa is as defined in any one of the preceding embodiments.

[0380] The process of claim 33, wherein the $[H_3NR^1]^+$ is provided as XYa prepared by th e steps of: (a) treating R-COOH with 1-hydroxybenzotriazole, N- (3-dimethylaminopropyl) -N'-ethylcarbodiimide hydrochloride, and tert-butyl (piperidin-4-ylmethyl) carbamate, to form a boc-protected product SXa, wherein R = $(Z^2)_w$-R^{1B}, wherein Z^2, w and R^{1B} are as defined in claim 1; and (b) treating the boc-protected product SXa with an acid in a solvent to form XYa

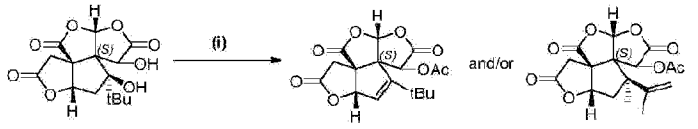


[0381] In some embodiments, the $[H_3NR^1]^+$ is provided as XYb prepared by th e steps of: (a) treating R-SO_2 with tert-butyl (piperidin-4-ylmethyl) carbama te and triethylamine, to form a boc-protected product SXb, wherein R = $(Z^2)_w$ -R^{1B}, wherein Z^2, w and R^{1B} are as defined in claim 1; and (b) treating the boc-protected product SXb with an acid in a solvent to form XYb



[0382] In some embodiments, provided is a process of preparing a compound o f claim 1, which include the steps of: (i) treating bilobalide with Ac_2O and an acid to form a protected product IVa

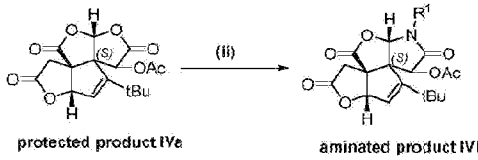
[0383]



and ;

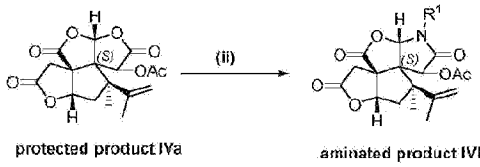
[0384] (ii) treating protected product IVa with at least one base or an acceptable salt ther eof to form aminated product IVb

[0385]



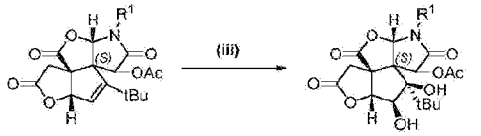
and/or ;

[0386]



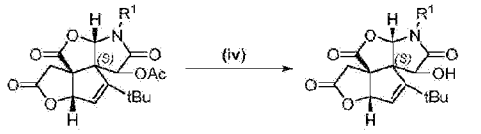
wherein R^1 is as defined in claim 1.

[0387] In some embodiments, the process further includes at least one of the steps of: (iii) treating the aminated product IVb with an oxidizing agent and a solvent to form oxid ized product IVc



aminated product IVb oxidized product IVc;

[0388] In some embodiments, the process further includes at least one of the steps of: (iv) treating the aminated product IVb or the oxidized product IVc with an acid to form de protected product IVd



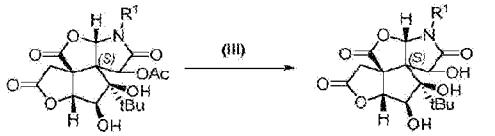
aminated product IVb deprotected product IVd;

[0389]

and/or

aminated product IVb deprotected product IVd;

[0390]



wherein R^1 is as defined in claim 1.

oxidized product IVc oxidized product IVc;

[0391] In some embodiments, provided is a method of treating or preventing neurological related disease in a subject in need thereof, comprising administering t o the subject a compound of any one of the preceding embodiments.

[0392] In some embodiments, the neurological related disease is a neurodege nerative disease.

[0393] In some embodiments, the neurodegenerative disease is caused by ferroptosis.

[0394] In some embodiments, the neurodegenerative disease is Alzheimer's di sease or Parkinson's disease.

[0395] In some embodiments, provided is a use of a compound of any one of t he preceding embodiments for treating or preventing Alzheimer's disease or Parkinson' s disease.

[0396] In some embodiments, provided is a use of a compound of any one of the preceding embodiments for inhibiting ferroptosis by restoring glutathione peroxidase 4 (GPX4) , thereby mitigating GPX4 degradation induced by ferroptosis inducers.

[0397] In some embodiments, the ferroptosis inducers are RSL3, FIN56, ML162 , ML210, or erastin.

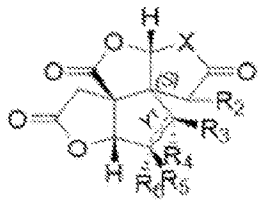
[0398] In some embodiments, provided is a use of a compound of any one of the preceding embodiments for inhibiting ferroptosis by reducing intracellular reactive oxygen species (ROS level) .

[0399] In some embodiments, provided is a use of a compound of any one of the preceding embodiments for inhibiting ferroptosis by reducing lipid peroxidation.

[0400] In some embodiments, provided is a use of a compound of any one of the preceding embodiments for the manufacture of a medicament for treating or preventing Alzheimer's disease or Parkinson's disease.

[0401] Embodiments III

[0402] In some embodiments, provided is a compound of Formula I:



(Formula I)

[0403] or a stereomer, a tautomer, or a pharmaceutically acceptable salt thereof,

[0404] wherein

[0405] X is -O-, -NR^1-, -N=CR^1-NH-, or -NR^1-NH-; wherein when X is -O-, R^1 is absent;

[0406] bond Y^1 is between R^4 and R^5 and is a single bond or a double bond;

[0407] R^1 is H, R^{1B}, or - $(L^1)_u$- $(Z^1)_v$; wherein

[0408] L^1 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, O, or S; wherein L^1 is optionally substituted with 1-3 occurrences of halo, CN, R, OR', or R^{1C};

[0409] u is 0 or 1;

[0410] v is 0 or 1;

[0411] Z^1 is a 5-16 membered aromatic or nonaromatic monocyclic, bicyclic, or tricyclic ring system having 0-7 heteroatoms selected from O, N, or S; wherein Z^1 is optionally substituted with 1-5 occurrences of R^{1A}, R^{1C} or combinations thereof;

[0412] R^{1A} is - $(L^2)_m$- $(Z^2)_w$; wherein

[0413] L^2 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si; wherein L^2 is optionally substituted with 1-3 occurrences of halo, CN, R, OR' or R^{1C};

[0414] m is 0 or 1;

[0415] w is 0 or 1;

[0416] Z^2 is a C_1-C_{10} aliphatic, or 3-16 membered aromatic or nonaromatic monocyclic, bicyclic or tricylic ring system having 0-7 heteroatoms selected from O, N, or S; wherein Z^2 is optionally substituted with 1-5 occurrences of R^{1B};

[0417] R^{1B} is H, halo, CN, R*, OR*, NRR*; or two R^{1B}, taken together with the atom to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms;

[0418] R^{1C} is H, halo, CN, a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system having 0-5 heteroatoms selected from O, N, or S; R*, OR*, NRR*; or two R^{1C}, taken together with the atom or atoms to which they are attached, optionally form a 3-16 membered ring having 0-4 heteroatoms; wherein R^{1C} is optionally substituted with 1-3 occurrences of halo, CN, R' or OR';

[0419] R*is C_1-C_6 aliphatic wherein up to three methylene units of the C_1-C_6 aliphatic are optionally replaced by N, NR, O, S, C=O, SO, SO_2 or Si and wherein the C_1-C_6 aliphatic is optionally substituted with 1-3 occurrences of halo, CN, R' or OR';

[0420] R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, a C_1-C_{16} aliphatic, a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system, or – (C_1-C_{16} aliphatic) – (5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system) ; wherein up to five carbon atoms of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{2A} is optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR';

[0421] R^3 is OH, R^{3A}, or OR^{3A}; wherein R^{3A} is C_1-C_{10} aliphatic optionally substituted with 1-3 occurrences of halo, R or OR';

[0422] R^4 is OH, R^{4A}, OR^{4A}; or when bond Y^1 between R^4 and R^5 is a double bond, R^4 is absent; wherein R^{4A} is C_1-C_7 aliphatic and R^{4A} is optionally substituted with 1-3 occurrences of halo, R' or OR';

[0423] R^5 is H or OH;

[0424] R^6 is H; or when bond Y^1 between R^4 and R^5 is a double bond, R^6 is absent;

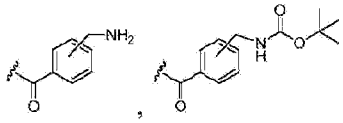
[0425] R is H or C_1-C_6 aliphatic optionally substituted by 1-3 occurrences of F; or two R, taken together with the atom (s) to which they are attached, form a 3-6 membered ring having 0-4 heteroatoms; and

[0426] R' is H, a C_1-C_6 aliphatic wherein up to three carbon atoms of the C_1-C_6 aliphatic are optionally replaced with O, NH, N (C_1-C_6 alkyl) , C (O) , or S (O) $_2$; wherein said C_1-C_6 aliphatic is optionally substituted by 1-3 occurrences of F, OR, NH_2, NHR", or NR"$_2$, wherein R" is C_1-C_6 aliphatic or a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system having 0-5 heteroatoms selected from O, N, or S;

[0427] wherein when R^2 is OH, R^3 is tert-butyl, R^4 is OH, R^5 is H, and R^6 is H, X is not -O-.

[0428] In some embodiments, R^2 is

[0429] R^{2A} or OR^{2A}, wherein R^{2A} is H, C=O (C_{1-10} aliphatic) , SO_2 (C_{1-10} aliphatic) , SO_2 (phenyl) , phenyl, Si (C_{1-10} aliphatic) $_{1-2}$, Si (phenyl) $_{1-2}$, (C_{1-10} aliphatic) O (C_{1-10} aliphatic) -, (C=O) (phenyl) , NH (C=O) (C_{1-10} aliphatic) or NH (C=O) O (C_{1-10} aliphatic) ; wherein each R^{2A}



is independently and optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR';

[0430] R^3 is C_{1-10} aliphatic;

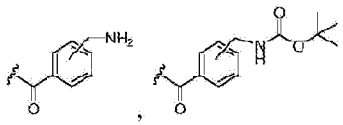
[0431] the bond Y^1 between R^4 and R^5 is a single bond;

[0432] R^4 is OH or OR^{4A};

[0433] and R^5 is H or OH.

[0434] In some embodiments, R^2 is

[0435] R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si (CH_3) $_2$C (CH_3) $_3$, Si (CH_2CH_3) $_3$, Si (CH_3) $_3$, Si (C_6H_5) $_2$C (CH_3) $_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5, or NH (C=O) OC (CH_3) $_3$; wherein phenyl, C_6H_4, and C_6H_5 are each independently and optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR';



[0436] R^3 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or tert-butyl;

[0437] the bond Y^1 between R^4 and R^5 is a single bond;

[0438] R^4 is OH or OR^{4A};

[0439] and R^5 is H or OH.

[0440] In some embodiments, R^1 is

[0441] H,

[0442] 2, 4-dimethoxybenzyl,

[0443] [1- (tert-butoxycarbonyl) piperidin-4-yl] methyl,

[0444] piperidin-4-yl methyl,

[0445] 2- [1- (tert-butoxycarbonyl) piperidin-4-yl] ethyl,

[0446] 2- (piperidin-4-yl) ethyl,

[0447] 3- [1- (tert-butoxycarbonyl) piperidin-4-yl] propyl,

[0448] 3- (piperidin-4-yl) propyl,

[0449] 2- [4- (tert-butoxycarbonyl) piperazin-1-yl] ethyl,

[0450] 2- (piperazin-1-yl) ethyl,

[0451] 2- (3-methyl-1H-indol-2-yl) ethyl,

[0452] 3- (1H-imidazol-1-yl) propyl,

[0453] [1- (tertbutoxycarbonyl) pyrrolidin-3-yl] methyl,

[0454] (pyrrolidin-3-yl) methyl,

[0455] (bicyclo [2.2.1] hept-5-en-2-yl) methyl,

[0456] phenyl,

[0457] 4-acetamidophenyl,

[0458] 4- [(tert-butoxycarbonyl) amino] phenyl,

[0459] 4-aminophenyl,

[0460] 4- (morpholin-4-yl) phenyl,

[0461] benzo [d] [1, 3] dioxol-5-yl,

[0462] pyridin-3-yl,

[0463] benzyl,

[0464] methyl,

[0465] bicyclo [1.1.1] pentyl,

[0466] oxetan-3-yl,

[0467] cyclobutyl methyl,

[0468] cyclopropyl methyl,

[0469] (oxetan-3-yl) methyl,

[0470] adamantan-2-yl methyl,

[0471] NH_2,

[0472] cyclopropyl,

[0473] 3-methoxy phenyl,

[0474] 4-methoxy phenyl,

[0475] naphthalen-2-yl,

[0476] 3- (trifluoromethyl) phenyl,
[0477] 4-cyano phenyl,
[0478] 2- [3- (but-3-yn-1-yl) -3H-diazirin-3-yl] ethyl,
[0479] cyclohexyl,
[0480] 4-fluoro phenyl,
[0481] 4- (trifluoromethyl) phenyl,
[0482] 4-toluyl,
[0483] 3-toluyl,
[0484] 2-toluyl,
[0485] (oxolan-2-yl) methyl,
[0486] 2-methoxy-2-oxoethyl,
[0487] (1- (5- (difluoromethyl) pyrazine-2-carbonyl) piperidin-4-yl) methyl,
[0488] [1- (2, 3-dihydro-1-benzofuran-5-sulfonyl) piperidin-4-yl] methyl,
[0489] (1- (2, 2-difluorobenzo [d] [1, 3] dioxole-5-carbonyl) piperidin-4-yl) methyl,
[0490] (1- (2, 3-dihydrobenzo [b] [1, 4] dioxine-6-carbonyl) piperidin-4-yl) methyl,
[0491] (1- (4-chlorobenzoyl) piperidin-4-yl) methyl,
[0492] (1- (2, 3-dihydrobenzofuran-5-carbonyl) piperidin-4-yl) methyl,
[0493] (1-acryloylpiperidin-4-yl) methyl,
[0494] (1- (quinoxaline-6-carbonyl) piperidin-4-yl) methyl,
[0495] (tetrahydro-2H-pyran-4-yl) methyl,
[0496] (tetrahydro-2H-thiopyran-4-yl) methyl,
[0497] 2- (1-methyl-1, 2, 3, 4-tetrahydronaphthalen-2-yl) ethyl,
[0498] 2- (1-methyl-2H-isoindol-2-yl) ethyl,
[0499] 2- (azetidin-1-yl) ethyl,
[0500] 2- (trifluoromethyl) phenyl,
[0501] 2-fluoro phenyl,
[0502] 2-methoxy phenyl,
[0503] 3, 4-difluoro phenyl,
[0504] 3, 4-dichloro phenyl,
[0505] 3, 5-difluoro phenyl,
[0506] 3-fluoro phenyl,
[0507] 4-hydroxy phenyl,
[0508] 8- (tert-butoxycarbonyl) -1-oxa-8-azaspiro [4.5] decan-3-yl,
[0509] anilinyl,
[0510] benzo [d] [1, 3] dioxol-4-yl,
[0511] cyclobutyl,
[0512] cyclohexyl methyl,
[0513] naphthalen-1-yl,

[0514] pyridin-2-yl,

[0515] pyridin-4-yl,

[0516] adamantan-1-yl methyl,

[0517] 1- (tert-butoxycarbonyl) -1H-indol-5-yl,

[0518] 1H-indol-5-yl,

[0519] 3- [(tert-butoxycarbonyl) amino] phenyl,

[0520] 4-Hydroxyphenyl ethyl,

[0521] 1H-indole-3-ethyl,

[0522] ((1R, 4aS, 10aR) -7-isopropyl-1, 4a-dimethyl-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl) methyl,

[0523] [((tert-butoxycarbonyl) aminomethyl) adamantan-1-yl] methyl,

[0524] (aminomethyl) adamantan-1-yl) methyl,

[0525] 3, 5-di-tert butyl phenyl,

[0526] 3, 4-dihydroxyphenyl,

[0527] 3-methoxy-4-hydroxyphenyl ethyl,

[0528] 1H-indole-5-hydroxy-3-ethyl,

[0529] 1H-indole-5-methoxy-3-ethyl,

[0530] 1H-indole-4-hydroxy-3-ethyl,

[0531] piperonyl,

[0532] 2- (4-Imidazolyl) ethyl (histamine) ,

[0533] 2, 2-diphenylethyl,

[0534] 3-hydroxy-4-methoxyphenyl ethyl,

[0535] 3, 4-methylenedioxyphenyl ethyl,

[0536] 1H-indole-5-hydroxy-3-ethyl (serotonin) ,

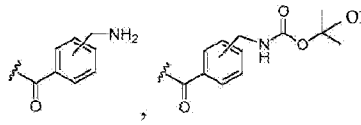
[0537] 3, 4-dihydroxyphenyl ethyl (dopamine) ,

[0538] 1H-indole-3-ethyl (tryptamine) ,

[0539] 3-methoxy-4-hydroxyphenyl ethyl (3-O-methyldopamine) , or

[0540] methylenedioxyphenyl.

[0541] In some embodiments, R^2 is

[0542] R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5,  or NH (C=O) OC $(CH_3)_3$;

[0543] wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR';

[0544] R^3 is tert-butyl;

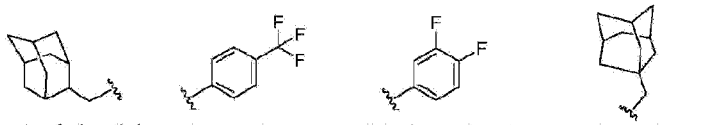
[0545] the bond Y^1 between R^4 and R^5 is a single bond;

[0546] R^4 is OH;

[0547] R^5 is H;

[0548] X is $-NR^1-$, $-N=CR^1-NH-$, or $-NR^1-NH-$; and.

[0549] R^1 is selected from



adamantan-2-yl methyl, 4-(trifluoromethyl) phenyl, 3,4-difluoro phenyl, adamantan-1-yl methyl,

[0550] 2- (4-imidazolyl) ethyl (histamine) ,

[0551] 1H-indole-5-hydroxy-3-ethyl (serotonin) ,

[0552] 3, 4-dihydroxyphenyl ethyl (dopamine) ,

[0553] 1H-indole-3-ethyl (tryptamine) , or

[0554] 3-methoxy-4-hydroxyphenyl ethyl (3-O-methyldopamine) .

[0555] In some embodiments,

[0556] In some embodiments, provided is a method of treating or preventing cancer in a subject in need thereof, including administering to the subject a compoun d described herein.

[0557] In some embodiments, the cancer is bladder cancer, brain cancer, bre ast cancer, CNS cancer, colon cancer, hematopoietic cancer, kidney cancer, leukemia, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, or renal c ancer.

[0558] In some embodiments, the cancer is leukemia, colon cancer, lung canc er, melanoma or renal cancer.

[0559] In some embodiments, the lung cancer is non-small cell lung cancer (NSCLC) .

[0560] In some embodiments, the leukemia is lymphocytic leukemia.

[0561] In some embodiments, provided is a use of a compound described herei n for treating or preventing cancer.

[0562] In some embodiments, provided is a use of a compound described herei n for the manufacture of a medicament for treating or preventing cancer.

[0563] In some embodiments, provided is a method of inducing cell death in a cancer cell, in cluding contacting a compound described herein with the cancer cell.

[0564] In some embodiments, a method of inhibiting cell growth in a cancer cell, including c ontacting a compound described herein with the cancer cell.

[0565] In some embodiments, the method is an in vitro method.

[0566] In some embodiments, the compound is DW192, P-29, P-21, P-30, P-33, JW093, XBB-023, P-28, JW107, XBB-039, JW094, P-34, XBB-

045, JW081, XBB-028, XBB-038, XBB-037, XBB-054, XBB-025, XBB-029, XBB-024, DW172, XBB-004, XBB-042, XBB-068, XBB-040, XBB-006, JW072, DW189, P-8, DW191, DW168, XBB-013, XBB-037', XBB-009, XBB-060, XBB-016, DW182, XBB-010, SCC506, SCC363, or SXQ087-1.

[0567] In some embodiments, the compound is DW192, P-29, P-21, SCC506, SCC363, or SXQ087-1.

[0568] In some embodiments, provided is a method of treating or preventing neurological related disease in a subject in need thereof, including administering to the subject a compound of any one of the embodiments here.

[0569] In some embodiments, the neurological related disease is caused by ferroptosis.

[0570] In some embodiments, the neurological related disease is Alzheimer's disease or Parkinson's disease.

[0571] In some embodiments, provided is a use of a compound described herein for treating or preventing Alzheimer's disease or Parkinson's disease.

[0572] In some embodiments, provided is a use of a compound described herein for inhibiting ferroptosis by restoring glutathione peroxidase 4 (GPX4), thereby mitigating GPX4 degradation induced by ferroptosis inducers.

[0573] In some embodiments, provided is a use of a compound described herein for inhibiting ferroptosis by reducing intracellular reactive oxygen species (ROS level).

[0574] In some embodiments, provided is a use of a compound described herein for inhibiting ferroptosis by reducing lipid peroxidation.

[0575] In some embodiments, provided is a use of a compound described herein for the manufacture of a medicament for treating or preventing Alzheimer's disease or Parkinson's disease.

[0576] In some embodiments, the compound is DW192, P-29, P-21, P-30, P-33, JW093, XBB-023, P-28, JW107, XBB-039, JW094, P-34, XBB-045, JW081, XBB-028, XBB-038, XBB-037, XBB-054, XBB-025, XBB-029, XBB-024, DW172, XBB-004, XBB-042, XBB-068, XBB-040, XBB-006, JW072, DW189, P-8, DW191, DW168, XBB-013, XBB-037', XBB-009, XBB-060, XBB-016, DW182, XBB-010, SCC506, SCC363, or SXQ087-1.

[0577] In some embodiments, the compound is DW192, P-29, P-21, SCC506, SCC363, or SXQ087-1.

[0578] In some embodiments, the compounds in the current disclosure include those wherein R^1 is derived from a neurotransmitter or derivatives thereof. For example, the compounds SXQ087-1, SXQ090-1, SXQ092-1, SXQ091-1, SXQ125-2, and SXQ128-1 are compounds wherein R^1 is derived from a neurotransmitte

r or derivatives thereof. Being "derived from a neurotransmitter or derivatives there of" means that the structure of R^1 includes the structure of a neurotransmitter or at least a portion of the structure of a neurotransmitter. In some example embodiments, the neurotransmitter is a monoamine neurotransmitter, and R^1 is the portion o f the molecule without the amine (see, for example, SXQ091-1 and serotonin) ,

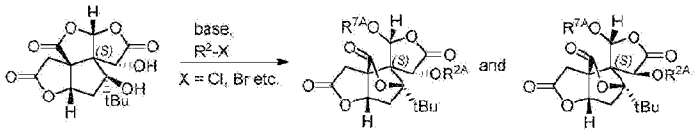
[0579] In some embodiments, R^1 is derived from dopamine, 3-O-methyldopamine, s erotonin, 5-hydroxytryptamin, tryptamine or histamine.

[0580] The compounds of the disclosure may be prepared in light of the specification using s teps generally known to those of ordinary skill in the art. Those compounds may be an alyzed by known methods, including but not limited to HRMS-ESI (high resolut ion mass spectrometry with electrospray ionization) and NMR (nuclear magnetic resonance) .

[0581] Generic Schemes

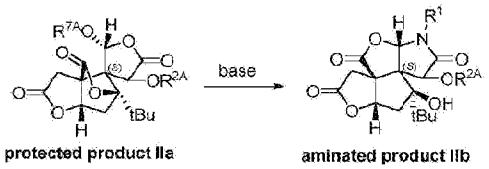
[0582] The following generic schemes and examples illustrate how to prepare the compounds of the present disclosure. The examples are for the purpose of illustr ation only and are not to be construed as limiting the scope of the invention in any way. FIG. 1A is an illustration showing the overall molecular editing schemes of bilo balide as disclosed herein.

[0583] Scheme 1: Synthesis of protected product IIa



[0584] To a solution of bilobalide (1 equiv.) , a suitable anhydrous solvent, R^{2A}-X (3-15 equiv.) and a base (0-6 equiv.) are added. In some examples, the base is a sterically hindered base. After stirring at a temperature of 20-80°C for 16-72 h, the reaction solution is treated with the steps generally known to those of ord inary skill in the art. Purification using silica gel column chromatography afforded di-protected iso-bilobalides, wherein $R^2 = R^7$ (protected product IIa) .

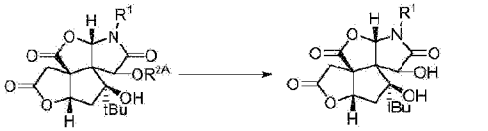
[0585] Scheme 2: Synthesis of aminated product IIb



[0586] To a solution of protected product IIa (1 equiv) in a suitable anhydrous solvent is a dded a base (2 equiv) . In some embodiments, the base is NH_2R^1. The resulting s

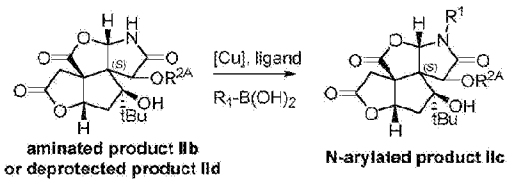
olution is then stirred for 15-60 minutes at room temperature. The reaction is dil uted with dichloromethane and treated with the steps generally known to those of ordi nary skill in the art to afford aminated product IIb.

[0587] Scheme 3: Synthesis of deprotected product IId



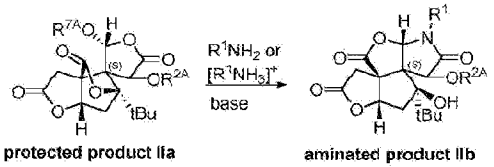
[0588] To a solution of aminated product IIb (1.0 equiv) in a protic solvent, a basic alkali salt (2 equiv.) is added. The resulting mixture is stirred at room temperature for 2 hours. The reaction mixture is then treated with the steps generally known to those of ordinary skill in the art to afford deprotected product IId.

[0589] Scheme 4: Synthesis of N-arylated product IIc



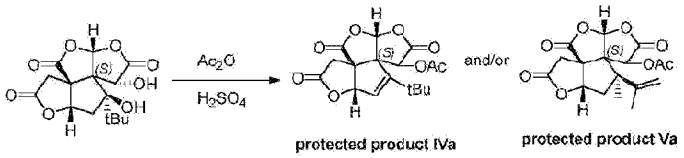
[0590] An oven-dried round-bottom flask is charged with aminated product IIb o r deprotected product IId (1 equiv) , R^1-B (OH) $_2$ (1.5-2 equiv) , a catalyst (10-100 mol %) , optionally a ligand (30-50 mol%) , and a suitable solvent. The reaction mix ture is stirred at room temperature under open air for 12-72 hours. The cru de reaction mixture is then treated with the steps generally known to those of ordina ry skill in the art to provide N-arylated product IIc. The N-arylated product IIc can be treated with the same procedure described in Scheme 3 to afford deprotecte d product IId.

[0591] Scheme 5: General procedure for the further derivatives (aminated product IIb)



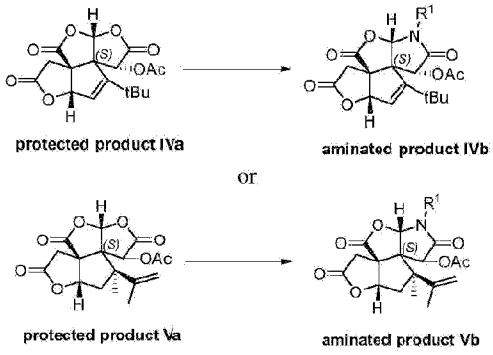
[0592] To a solution of protected product IIa (1 equiv) in a suitable anhydrous solvent is a dded R^1NH_2 or $[R^1NH_3]^+$ (1-2 equiv) together with a suitable hindered base (0-3 equiv) . The resulting solution is then stirred for 15 minutes up until 24 h at room temperature. The crude reaction mixture is then treated with the steps gene rally known to those of ordinary skill in the art to provide aminated product IIb.

[0593] Scheme 6: Synthesis of protected product Iva and/or protected product Va



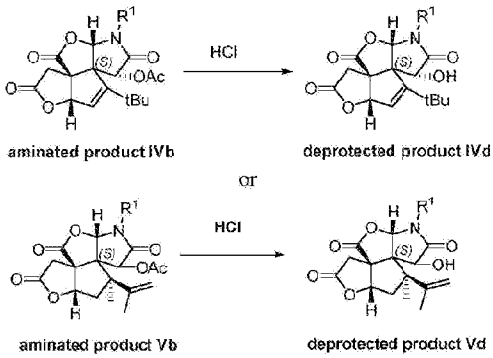
[0594] To a solution of Bilobalide in acetic anhydride is added a trace of concentrated sulf uric acid. The resulting solution is stirred at 50°C for 3 h. The reaction solution is then treated with the steps generally known to those of ordinary skill in the art to yield protected product IVa and/or protected product Va.

[0595] Scheme 7: Synthesis of aminated product IVb and/or protected product Vb



[0596] To a solution of protected product IVa (1.0 equiv) or protected product Va (1.0 equiv) in an anhydrous solvent is added a base (2.0 equiv) . The resulting solution is the n allowed to be stirred for 30 min at room temperature. The reaction is diluted with dichloromethane and treated with the steps generally known to those of ordinary skill in the art to afford aminated product IVb and/or aminated product Vb.

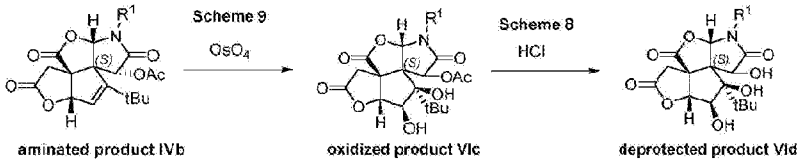
[0597] Scheme 8: Synthesis of deprotected product IVd and/or deprotected product Vd



[0598] To a round-bottom flask is added aminated product IVb and/or aminated product V b and a strong acid in H_2O. The resulting solution is allowed to be stirred under reflux condition for 12 h. the reaction solution is then treated with the steps

generally known to those of ordinary skill in the art to give deprotected product IV d and/or deprotected product Vd.

[0599] Scheme 9: Synthesis of oxidized product VIc and/or deprotected product VId

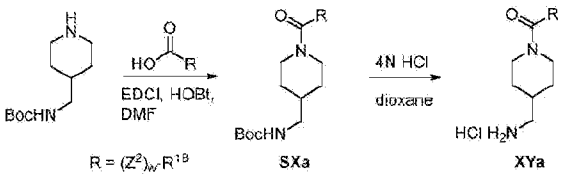


[0600] To a round-bottom flask is added aminated product IVb (1.0 equiv.) and a suitable solvent, followed by the addition of pyridine and osmium (VIII) oxide. The resulting solution is allowed to be stirred at room temperature for 18 h. The resulting solution is treated with the steps generally known to those of ordinary skill in the art to give oxidized product VIc. The oxidized product VIc can be treated with the same procedure described in Scheme 8 to afford deprotected product VId.

[0601] Scheme 10 Synthesis of $[H_3NR^1]^{\pm}$ salts from SXb (Amide derivatives)

[0602] Syntheses of other $[H_3NR^1]^+$ salts for use in Scheme 5 are described herein.

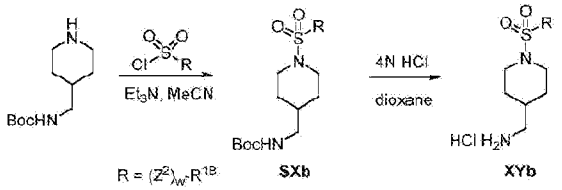
Scheme 10



[0603] A solution of R-substituted carboxylic acid, wherein R = $(Z^2)_w$-R^{1B} (1.0 equiv.) , in a suitable solvent is treated with 1-hydroxybenzotriazole (HOBt) (1.1 equiv.) , and N- (3-dimethylaminopropyl) -N′-ethylcarbodiimide hydrochloride (EDCI) (1.1 equiv.) . This mixture was stirred for 30 minutes at room temperature, then tert-butyl (piperidin-4-ylmethyl) carbamate (1.0 equiv.) is added. The crude reaction mixture is then treated with the steps generally known to those of ordinary skill in the art to afford a SXa. Then, SXa is treated with 4 N HCl in dioxane. The resulting solution is stirred at room temperature for 1 h. The reaction solution is then treated with the steps generally known to those of ordinary skill in the art to afford $[H_3NR^1]^+$ XYa.

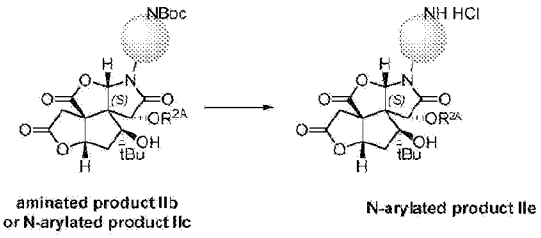
[0604] Scheme 11 Synthesis of $[H_3NR^1]^{\pm}$ salts from SXb (Sulfonamide derivatives)

Scheme 11



[0605] To a solution of tert-butyl (piperidin-4-ylmethyl) carbamate (1.0 equiv.) in a suitable solvent is added R-substituted sulfonyl chloride, wherein R = $(Z^2)_w$-R^{1B} (1.1 equiv.) , and triethylamine. The resulting mixture is stirred at room temperature for 4 h. The reaction solution treated with the steps generally known to those of ordinary skill in the art to afford SXb. Then, SXb is treated with 4 N HCl in dioxane. The resulting solution is stirred at room temperature for 1 h. The reaction solution is then treated with the steps generally known to those of ordinary skill in the art to afford $[H_3NR^1]^+$ XYb.

[0606] Scheme 12 Further modifications of aminated product IIb.



[0607] Aminated product IIb or N-arylated product IIc having the indicated structure (i.e., when R^1 is Boc-protected, 1 equiv.) is dissolved in a solution of HCl (2-4 N) in an appropriate solvent (MeOH or dioxane) . The reaction is stirred at room temperature until complete conversion (1-24h) . The volatiles are removed, and the resulting N-arylated product IIe can be crystallized as HCl salt. FIG. 1B is an illustration of Scheme 12.

[0608] EXAMPLES

[0609] Provided herein are examples that describe in more detail certain embodiments of the present disclosure. The examples provided herein are merely for illustrative purposes and are not meant to limit the scope of the invention in any way. All references given below and elsewhere in the present application are hereby included by reference.

[0610] Example 1.0: Example bilobalide analogues

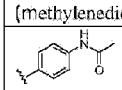
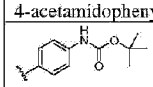
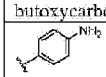
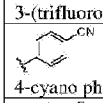
[0611] Provided herein are bilobalide analogues synthesized according to the methods in the present disclosure. The example bilobalide analogues and side chains (i.e., X, R^1, R^2, R^3, R^4, R^5, R^6 and R^7) thereof below are provided for illustration purpo

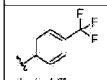
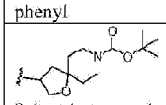
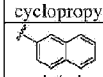
ses only and should not be construed as an exhaustive list of all possible bilobalide analogues. It shall be understood that terms such as "benzene" and pyrazine" , when used in a chart or table herein, are interchangeable with the terms such as "phenyl" and "pyrazinyl" , and refer to functional groups that may be optionally substituted.

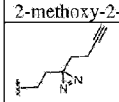
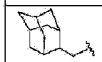
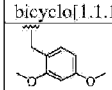
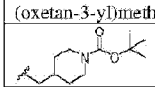
[0612] In some embodiments, R^2 is OH or O (C=O) R^{2B}, wherein R^{2B} is $-C_6H_5$ or $-CH_3$, R_3 is tert-butyl, bond Y1 between R^4 and R^5 is a single bond, R^4 is OH, R^5 is H, X is $-NR^1-$, and R^1 is $-(L^1)_u-(Z^1)_v$; wherein L^1, Z^1, u, and v correspond as shown in Table 1a and 1b:

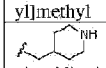
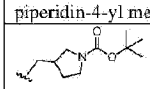
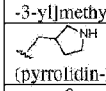
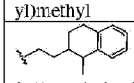
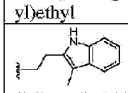
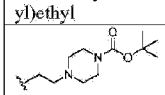
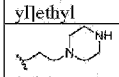
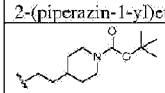
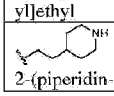
[0613] Table 1a: List of example R^1 groups where R^1 is $-(L^1)_u-(Z^1)_v$ and Z^1 is substituted with R^{1C}

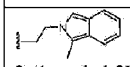
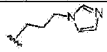
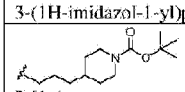
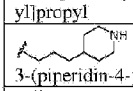
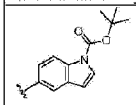
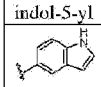
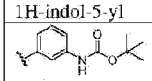
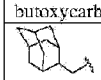
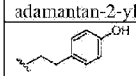
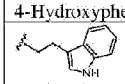
[0614] Two dashed lines “--” denotes that the group is absent.

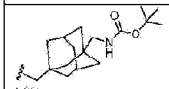
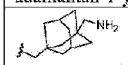
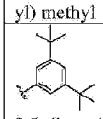
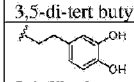
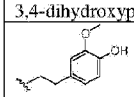
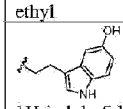
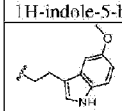
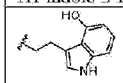
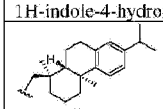
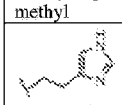
R^1	L^1	u	Z^1	v	R^{1C}	R*	R/R'
 benzo[d][1,3]dioxol-5-yl (methylenedioxyphenyl)	--	0	piperonyl	1	--	--	--
 3,4-difluoro phenyl	--	0	phenyl	1	-F	--	--
 3,4-dichloro phenyl	--	0	phenyl	1	-Cl	--	--
 3,5-difluoro phenyl	--	0	phenyl	1	-F	--	--
 3-fluoro phenyl	--	0	phenyl	1	-F	--	--
 benzo[d][1,3]dioxol-4-yl (methylenedioxyphenyl)	--	0	piperonyl	1	--	--	--
 4-acetamidophenyl	--	0	phenyl	1	NRR*	-(C=O)CH_3	H
 4-[(tert-butoxycarbonyl)amino]phenyl	--	0	phenyl	1	NRR*	-(C=O)$OC(CH_3)_3$	H
 4-aminophenyl	--	0	phenyl	1	NRR*	H	H
 3-methoxy phenyl	--	0	phenyl	1	OR*	-CH_3	--
 4-methoxy phenyl	--	0	phenyl	1	OR*	-CH_3	--
 3-(trifluoromethyl) phenyl	--	0	phenyl	1	-CF3	--	--
 4-cyano phenyl	--	0	phenyl	1	R*	-CN	--
	--	0	phenyl	1	R*	F	--

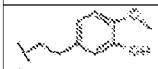
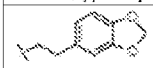
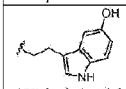
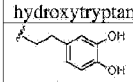
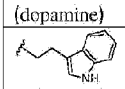
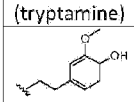
R^1	L^1	u	Z^1	v	R^{1C}	R*	R/R'
4-fluoro phenyl							
 4-(trifluoromethyl) phenyl	--	0	phenyl	1	R*	CF_3	--
 4-toluyl	--	0	phenyl	1	R*	CH_3	--
 3-toluyl	--	0	phenyl	1	R*	CH_3	--
 2-toluyl	--	0	phenyl	1	R*	CH_3	--
 2-(trifluoromethyl) phenyl	--	0	phenyl	1	R*	CF_3	--
 2-fluoro phenyl	--	0	phenyl	1	-F	--	--
 2-methoxy phenyl	--	0	phenyl	1	R*	OCH_3	--
 4-hydroxy phenyl	--	0	phenyl	1	R*	OH	--
 phenyl	--	0	phenyl	1	--	--	--
 8-(tert-butoxycarbonyl)-1-oxa-8-azaspiro[4.5]decan-3-yl	--	0	1-oxa-8-azaspiro[4.5]decan-3-yl	1	R*	$(C=O)OC(CH_3)_3$	--
 cyclobutyl	--	0	cyclobutanyl	1	--	--	--
 cyclohexyl	--	0	cyclohexanyl	1	--	--	--
 cyclopropyl	--	0	cyclopentanyl	1	--	--	--
 naphthalen-2-yl	--	0	napthalenyl	1	OR*	CH_3	--
 naphthalen-1-yl	--	0	napthalenyl	1	OR*	CH_3	--

R^1	L^1	u	Z^1	v	R^{1C}	R*	R/R'
 oxetan-3-yl	--	0	oxetanyl	1	--	--	--
 pyridin-4-yl	--	0	pyridinyl	1	--	--	--
 pyridin-2-yl	--	0	pyridinyl	1	--	--	--
 pyridin-3-yl	--	0	pyridinyl	1	--	--	--
 2-methoxy-2-oxoethyl	$CH_2(C=O)OCH_3$	1	--	0	--	--	--
 2-[3-(but-3-yn-1-yl)-3H-diazirin-3-yl] ethyl	$CH_2CH_2C(N=N)H_2CH_2CH_2CCH$	1	--	0	--	--	--
methyl	CH_3	1	--	0	--	--	--
NH_2	NH_2	1	--	0	--	--	--
 adamantan-2-yl methyl	CH_2	1	adamantanyl	1	--	--	--
 bicyclo[1.1.1]pentyl	CH_2	1	bicyclo[1.1.1]pentyl	1	--	--	--
 2,4-dimethoxybenzyl	CH_2	1	phenyl	1	OR*	CH_3	--
 benzyl	CH_2	1	phenyl	1	--	--	--
 cyclobutyl methyl	CH_2	1	cyclobutanyl	1	--	--	--
 cyclohexyl methyl	CH_2	1	cyclohexanyl	1	--	--	--
 cyclopropyl methyl	CH_2	1	cyclopropanyl	1	--	--	--
 (bicyclo[2.2.1]hept-5-en-2-yl)methyl	CH_2	1	norbornenyl	1	--	--	--
 (oxetan-3-yl)methyl	CH_2	1	oxetanyl	1	--	--	--
	CH_2	1	piperidinyl	1	R*	$(C=O)OC(CH_3)_3$	--

R^1	L^1	u	Z^1	v	R^{1C}	R*	R/R'
[1-(tert-butoxycarbonyl)piperidin-4-yl]methyl							
 piperidin-4-yl methyl	CH_2	1	piperidinyl	1	R*	H	--
 [1-(tertbutoxycarbonyl)pyrrolidin-3-yl]methyl	CH_2	1	pyrrolidinyl	1	R*	$(C=O)OC(CH_3)_3$	--
 (pyrrolidin-3-yl)methyl	CH_2	1	pyrrolidinyl	1	R*	H	--
 (oxolan-2-yl)methyl	CH_2	1	tetrahydrofuranyl	1	--	--	--
 (tetrahydro-2H-pyran-4-yl)methyl	CH_2	1	tetrahydropyranyl	1	--	--	--
 (tetrahydro-2H-thiopyran-4-yl)methyl	CH_2	1	tetrahydrothiopyranyl	1	--	--	--
 2-(1-methyl-1,2,3,4-tetrahydronaphthalen-2-yl)ethyl	CH_2CH_2	1	1-methyl-1,2,3,4-tetrahydronaphthalen-2-y	1	--	--	--
 2-(3-methyl-1H-indol-2-yl)ethyl	CH_2CH_2	1	indolyl	1	R*	CH_3	--
 2-[4-(tert-butoxycarbonyl)piperazin-1-yl]ethyl	CH_2CH_2	1	piperazinyl	1	R*	$(C=O)OC(CH_3)_3$	--
 2-(piperazin-1-yl)ethyl	CH_2CH_2	1	piperazinyl	1	R*	H	--
 2-[1-(tert-butoxycarbonyl)piperidin-4-yl]ethyl	CH_2CH_2	1	piperidinyl	1	R*	$(C=O)OC(CH_3)_3$	--
 2-(piperidin-4-yl)ethyl	CH_2CH_2	1	piperidinyl	1	R*	H	--

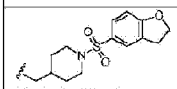
R^1	L^1	u	Z^1	v	R^{1C}	R*	R/R'
 2-(1-methyl-2H-isoindol-2-yl)ethyl	CH_2CH_2	1	1-methyl-2H-isoindol-2-yl	1	--	--	--
 2-(azetidin-1-yl)ethyl	CH_2CH_2	1	azetidinyl	1	--	--	--
 3-(1H-imidazol-1-yl)propyl	$CH_2CH_2CH_2$	1	imidazol	1	--	--	--
 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]propyl	$CH_2CH_2CH_2$	1	piperidinyl	1	R*	$(C=O)OC(CH_3)_3$	--
 3-(piperidin-4-yl)propyl	$CH_2CH_2CH_2$	1	piperidinyl	1	R*	H	--
 anilinyl	NH	1	phenyl	1	--	--	--
 adamantan-1-yl methyl	CH_2	1	adamantanyl	1		--	--
 1-(tert-butoxycarbonyl)-1H-indol-5-yl	--	1	indolyl	1	R*	$(C=O)OC(CH_3)_3$	
 1H-indol-5-yl	--	0	indolyl	1	R*	H	--
 3-[(tert-butoxycarbonyl)amino]phenyl	--	0	phenyl	1	NRR*	$(C=O)OC(CH_3)_3$	H
 adamantan-2-yl methyl	CH_2	1	adamantanyl	1	--	--	--
 4-Hydroxyphenyl ethyl	CH_2CH_2	1	phenyl	1	OR*	H	--
 1H-indole-3-ethyl	CH_2CH_2	1	indolyl	1	R*	H	--

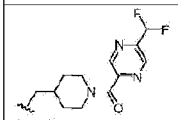
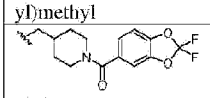
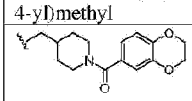
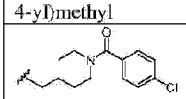
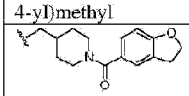
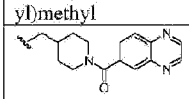
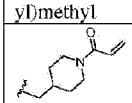
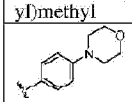
R^1	L^1	u	Z^1	v	R^{1C}	R*	R/R'
 [((tert-butoxycarbonyl)aminomethyl) adamantan-1-yl] methyl	CH_2	1	adamantanyl	1	R*	NH(C=O)OC(CH3)3	--
 (aminomethyl)adamantan-1-yl) methyl	CH_2	1	adamantanyl	1	NRR*	H	--
 3,5-di-tert butyl phenyl	--	0	phenyl	1	R*	$C(CH_3)_3$	--
 3,4-dihydroxyphenyl ethyl	--	0	phenyl	1	OR*	H	--
 3-methoxy-4-hydroxyphenyl ethyl	CH_2CH_2	1	phenyl	1	OR*	H or CH_3	--
 1H-indole-5-hydroxy-3-ethyl	CH_2CH_2	1	indolyl	1	OR*	H	--
 1H-indole-5-methoxy-3-ethyl	CH_2CH_2	1	indolyl	1	OR*	CH_3	--
 1H-indole-4-hydroxy-3-ethyl	CH_2CH_2	1	indolyl	1	OR*	H	--
 ((1R,4aS,10aR)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl) methyl	CH_2	1	 1,2,3,4,4a,9,10,10a-octahydrophenanthrenyl	1	R*	CH_3 or isopropyl	--
 2-(4-Imidazolyl)ethyl (histamine)	CH_2CH_2	1	imidazol	1	--	--	--
	CH_2CH_2	1	Phenyl (C6H5)	1	phenyl	--	--

R^1	L^1	u	Z^1	v	R^{1C}	R*	R/R'
2,2-diphenylethyl							
 3-hydroxy-4-methoxyphenyl ethyl	CH_2CH_2	1	Phenyl (C6H3)	1	OR*	H or CH_3	--
 3,4-Methylenedioxyphenyl ethyl	CH_2CH_2	1	piperonyl	1	--	--	--
 1H-indole-5-hydroxy-3-ethyl (serotonin, or 5-hydroxytryptamin)	CH_2CH_2	1	indolyl	1	OR*	H	--
 3,4-dihydroxyphenyl ethyl (dopamine)	CH_2CH_2	1	phenyl	1	OR*	H	--
 1H-indole-3-ethyl (tryptamine)	CH_2CH_2	1	indolyl	1	R*	H	--
 3-methoxy-4-hydroxyphenyl ethyl (3-O-Methyldopamine)	CH_2CH_2	1	phenyl	1	OR*	H or CH_3	--

[0615] Table 1b: List of example R^1 groups where R^1 is $-(L^1)_u-(Z^1)_v$ and Z^1 is substituted with R^{1A}, wherein R^{1A} is $-(L^2)_m-(Z^2)_w-R^{1B}$

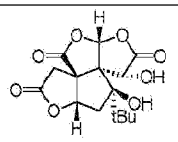
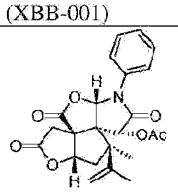
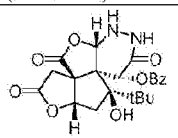
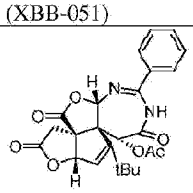
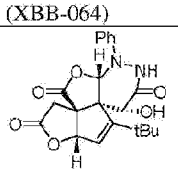
[0616] Two dashed lines "--" denotes that the group is absent.

R1	L^1	u	Z^1	v	L^2	m	Z^2	w	R^{1B}	R*	R/R'
 [1-(2,3-dihydro-1-benzofuran-5-sulfonyl)piperidin-4-yl]methyl	CH_2	1	piperidinyl	1	SO_2	1	dihydro benzofuran	1	--	--	--

R1	L^1	u	Z^1	v	L^2	m	Z^2	w	R^{1B}	R*	R/R'
 (1-(5-(difluoromethyl)pyrazine-2-carbonyl)piperidin-4-yl)methyl	CH_2	1	piperidinyl	1	C=O	1	 pyrazinyl	1	R*	$-CF_2$	--
 (1-(2,2-difluorobenzo[d][1,3]dioxole-5-carbonyl)piperidin-4-yl)methyl	CH_2	1	piperidinyl	1	C=O	1	piperonyl	1	F	--	--
 (1-(2,3-dihydrobenzo[b][1,4]dioxine-6-carbonyl)piperidin-4-yl)methyl	CH_2	1	piperidinyl	1	C=O	1	dihydrobenzodioxine	1	--	--	--
 (1-(4-chlorobenzoyl)piperidin-4-yl)methyl	CH_2	1	piperidinyl	1	C=O	1	phenyl	1	Cl	--	--
 (1-(2,3-dihydrobenzofuran-5-carbonyl)piperidin-4-yl)methyl	CH_2	1	piperidinyl	1	C=O	1	dihydrobenzofuran	1	--	--	--
 (1-(quinoxaline-6-carbonyl)piperidin-4-yl)methyl	CH_2	1	piperidinyl	1	C=O	1	 quinoxalinyl	1	--	--	--
 (1-acryloylpiperidin-4-yl)methyl	CH_2	1	piperidinyl	1	C=O	1	$-CH=CH_2$	1	--	--	--
 4-(morpholin-4-yl)phenyl	--	0	phenyl	1	--	0	morpholinyl	1	--	--	--

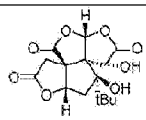
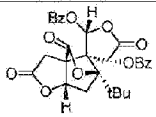
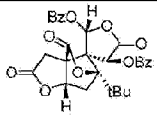
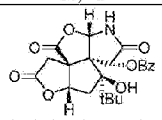
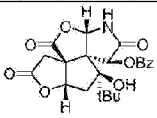
[0617] According to the methods in the present disclosure, the X group on a bilobalide analogue can be modified to yield lactam rings of various sizes (5-7 membered) . Examples are provided in Table 1c for illustration purposes only and should not be construed as an exhaustive list of all possible bilobalide analogues.

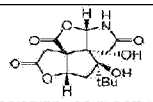
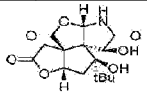
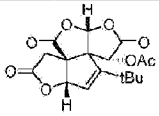
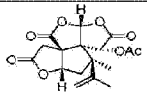
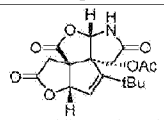
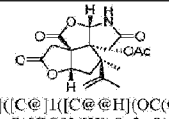
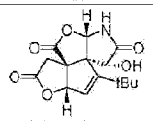
[0618] Table 1c: Examples of X groups

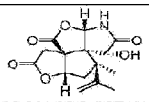
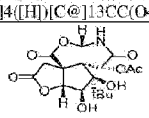
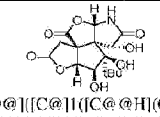
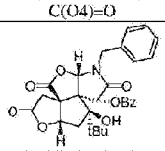
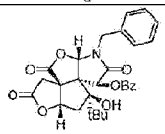
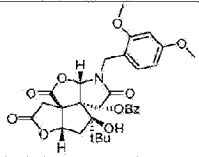
X	Example structure	R^1
-O-	 (XBB-001)	absent
$-NR^1-$	 (XBB-050)	Phenyl
-NH-NH-	 (XBB-051)	H
$-N=CR^1-NH-$	 (XBB-064)	phenyl
$-NR^1-NH-$	 (XBB-062)	Phenyl

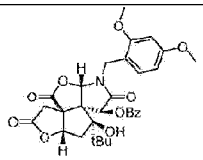
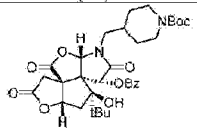
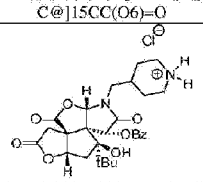
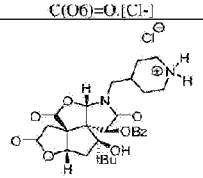
[0619] Table 1d provides a list of example bilobalide analogs prepared according to the methods of the present disclosure. The examples below are provided for illustration purposes only and should not be construed as an exhaustive list of all possible bilobalide analogues. In some embodiments, the compounds of Table 1d that are described as salts, e.g., HCl or chloride salts, are in their free base form. In some embodiments, the compounds of Table 1d that are described as free bases or neutral, e.g., compounds with $-NH_2$ groups, are in their salt forms, e.g., $-NH_2 \cdot HCl$.

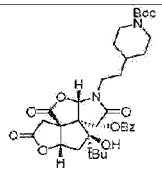
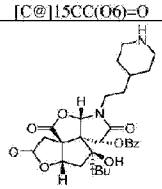
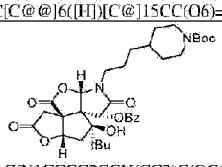
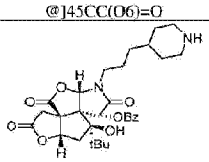
[0620] Table 1d: Structures of Compounds

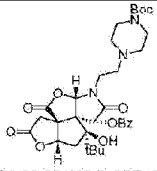
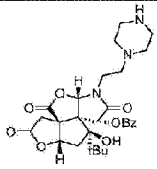
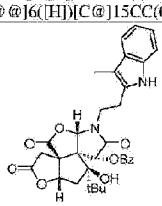
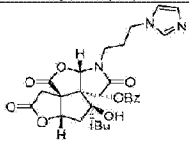
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-001 (Bilobalide)	 O[C@@]([C@]1([C@@H](O)C(O2)=O)[C@]2([H])OC3=O)(C(C)(C)C)C[C@@]4([H])[C@]13CC(O4)=O	O	--	OH	OH	 tBu	H	H	--
XBB-002	 O=C(O1)[C@H](OC(C2=CC=CC=C2)=O)[C@]3([C@]1([H])OC(C4=CC=CC=C4)=O)[C@](O5)(C(C)(C)C)C[C@@]6([H])[C@]3(C5=O)CC(O6)=O	O	--	 OBz	--	 tBu	H	H	 OBz
XBB-003	 O=C(O1)[C@@H](OC(C2=CC=CC=C2)=O)[C@]3([C@]1([H])OC(C4=CC=CC=C4)=O)[C@](O5)(C(C)(C)C)C[C@@]6([H])[C@]3(C5=O)CC(O6)=O	O	--	 OBz	--	 tBu	H	H	 OBz
XBB-004	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3)=O)[C@]3([H])OC4=O)(C(C)(C)C)C[C@@]5([H])[C@]14cC(O5)=O	N	H	 OBz	OH	 tBu	H	H	--
XBB-005	 O[C@@]([C@]1([C@H](OC(C2=CC=CC=C2)=O)C(N3)=O)[C@]3([H])OC4=O)(C(C)(C)C)C[C@@]5([H])[C@]14CC(O5)=O	N	H	 OBz	OH	 tBu	H	H	--

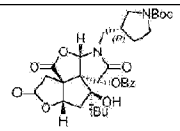
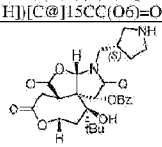
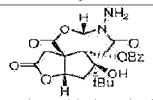
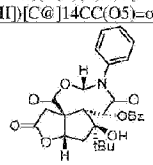
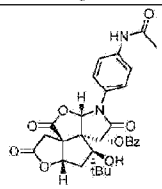
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-006	 O[C@@]([C@]1([C@@H](O)C(N2)=O)[C@]2([H])OC3=O)(C(C)(C)C)C[C@@]4([H])[C@]13CC(O4)=O	N	H	OH	OH	tBu	H	H	--
XBB-007	 O[C@@]([C@]1([C@H](O)C(N2)=O)[C@]2([H])OC3=O)(C(C)(C)C)C[C@@]4([H])[C@]13CC(O4)=O	N	H	OH	OH	tBu	H	H	--
XBB-008	 O=C(O1)[C@H](OC(C)=O)C2([C@]1([H])OC3=O)C(C(C)(C)C)=C[C@@]4([H])[C@]23CC(O4)=O	O	--	 OAc	tBu	--	H	--	--
XBB-009	 C[C@](C@]1([C@@H](OC(C)=O)C(O2)=O)[C@]2([H])OC3=O)(C(C)=C)C[C@@]4([H])[C@]13CC(O4)=O	O	--	OAc	isopropenyl	Me	H	H	--
XBB-010	 O=C(N1)[C@H](OC(C)=O)[C@]2([C@]1([H])OC3=O)C(C(C)(C)C)=C[C@@]4([H])[C@]23CC(O4)=O	N	H	OAc	tBu	--	H	--	--
XBB-011	 C[C@](C@]1([C@@H](OC(C)=O)C(N2)=O)[C@]2([H])OC3=O)(C(C)=C)C[C@@]4([H])[C@]13CC(O4)=O	N	H	OAc	isopropenyl	--	H	--	--
XBB-012	 O=C(N1)[C@H](O)C2([C@]1([H])OC3=O)C(C(C)(C)C)=C[C@@]4([H])[C@]23CC(O4)=O	N	H	OH	tBu	--	H	--	--

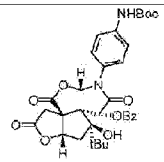
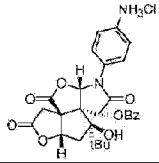
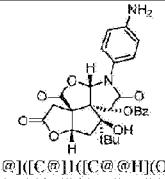
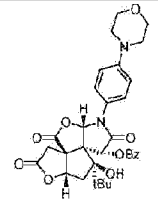
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-013	 C[C@](C@]1([C@@H](O)C(N2)=O)[C@]2([H])OC3=O)(C(C)=C)C[C@@]4([H])[C@]13CC(O4)=O	N	H	OH	isopropenyl	Me	H	H	--
XBB-014	 O[C@@](C@]1([C@@H](OC(C)=O)C(N2)=O)[C@]2([H])OC3=O)(C(C)(C)C)[C@@H](O)[C@@]4([H])[C@]13CC(O4)=O	N	H	OAc	OH	tBu	OH	H	--
XBB-015	 O[C@@](C@]1([C@@H](O)C(N2)=O)[C@]2([H])OC3=O)(C(C)(C)C)[C@@H](O)[C@@]4([H])[C@]13CC(O4)=O	N	H	OH	OH	tBu	OH	H	--
XBB-016	 O[C@@](C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3CC4=CC=CC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 benzyl	OBz	OH	tBu	H	H	--
XBB-017	 O[C@@](C@]1([C@H](OC(C2=CC=CC=C2)=O)C(N3CC4=CC=Cc=C4)=O)[c@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 benzyl	OBz	OH	tBu	H	H	--
XBB-018	 O[C@@]4([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3CC4=CC=C(OC)C=C4OC)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2,4-dimethoxybenzyl	OBz	OH	tBu	H	H	--

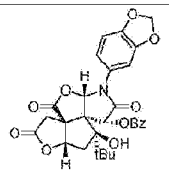
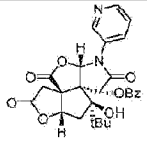
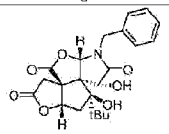
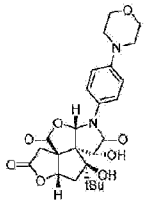
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-019	 O[C@@](C[C@]1([C@H](OC(C2=CC=CC=C2)=O)C(N3CC4=CC=C(C3)C=C4OC)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2,4-dimethoxybenzyl	OBz	OH	tBu	H	H	--
XBB-020	 O[C@@](C[C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3CC4CCN(CC4)C(OC(C)(C)C)=O)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 [1-(tert-butoxycarbonyl)piperidin-4-yl]methyl	OBz	OH	tBu	H	H	--
XBB-021	 O[C@@](C[C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3CC4CC[N+](CC4)C3)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O.[Cl-]	N	 piperidin-4-ylmethyl hydrochloride	OBz	OH	tBu	H	H	--
XBB-022	 O[C@@](C[C@]1([C@H](OC(C2=CC=CC=C2)=O)C(N3CC4CC[N+](CC4)C3)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O.[Cl-]	N	 piperidin-4-ylmethyl hydrochloride	OBz	OH	tBu	H	H	--

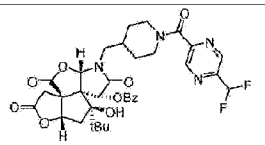
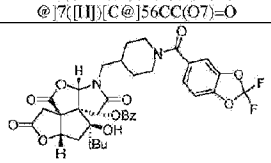
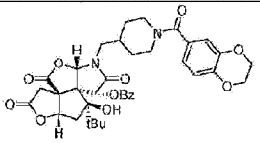
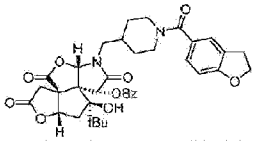
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-023	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3CCC4CCN(CC4)C(OC(C)(C)C)=O)=O)[C@]3([h])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2-[1-(tert-butoxycarbonyl)piperidin-4-yl]ethyl	OBz	OH	tBu	H	H	--
XBB-024	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3CCC4CCNCC4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2-(piperidin-4-yl)ethyl	OBz	OH	tBu	H	H	--
XBB-025	 O=C(N1CCCC2CCN(CC2)C(OC(C)(C)C)=O)[C@H](OC(C3=CC=CC=C3)=O)[C@]4([e@]1([h])OC5=O)[C@](O)(C(C)(C)C)C[C@@]6([H])[C@]45CC(O6)=O	N	 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]propyl	OBz	OH	tBu	H	H	--
XBB-026	 O=C(N1CCCC2CCNCC2)[C@H](OC(c3=CC=CC=C3)=O)[C@]4([C@]1([H])OC5=O)[C@](O)(C(C)(C)C)C[C@@]6([H])[C@]45CC(O6)=O	N	 3-(piperidin-4-yl)propyl	OBz	OH	tBu	H	H	--

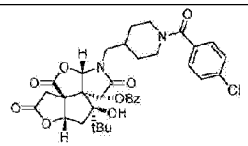
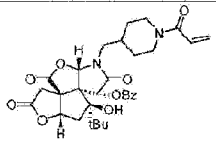
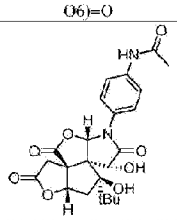
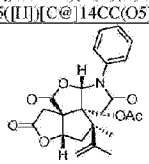
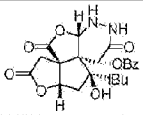
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-027	 O[C@@]([C@]11([C@@H](OC(C2=CC=CC=C2)=O)C(N3CCN4CCN(CC4)C(OC(C)(C)C)=O)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2-[4-(tert-butoxycarbonyl)piperazin-1-yl]ethyl	OBz	OH	tBu	H	H	--
XBB-028	 O[C@@]([C@]11([C@@H](OC(C2=CC=CC=C2)=O)C(N3CCN4CCNCC4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2-(piperazin-1-yl)ethyl	OBz	OH	tBu	H	H	--
XBB-029	 O[C@@]([C@]11([C@@H](OC(C2=CC=CC=c2)=O)C(N3CCC4=C(C)C5=C(C=CC=C5)N4)=O)[C@]3([H])OC6=O)(C(C)(C)C)C[C@@]7([H])[C@]16CC(O7)=O	N	 2-(3-methyl-1H-indol-2-yl)ethyl	OBz	OH	tBu	H	H	--
XBB-030	 O[C@@]([C@]11([C@@H](OC(C2=CC=CC=C2)=O)C(N3CCCN4C=NC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 3-(1H-imidazol-1-yl)propyl	OBz	OH	tBu	H	H	--

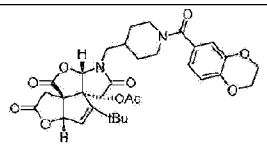
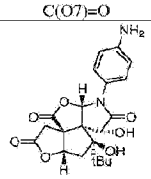
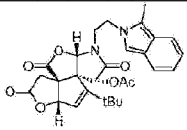
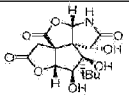
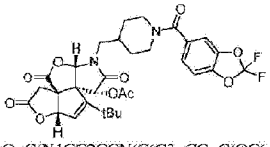
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-031	 O[C@@](C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C[C@H]4CCN(C4)C(OC(C)(C)C)=O)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 [1-(tertbutoxycarbonyl)pyrrolidin-3-yl]methyl	OBz	OH	tBu	H	H	--
XBB-032	 O[C@@](C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C[C@H]4CCNC4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 (pyrrolidin-3-yl)methyl	OBz	OH	tBu	H	H	--
XBB-033	 O[C@@](C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3N)=O)[C@]3([H])OC4=O)(C(C)(C)C)C[C@@]5([H])[C@]14CC(O5)=O	N	 NH_2	OBz	OH	tBu	H	H	--
XBB-034	 O[C@@](C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=CC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 phenyl	OBz	oH	tBu	H	H	--
XBB-035	 O[C@@](C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=C(NC(C)=O)C=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 4-acetamidophenyl	OBz	OH	tBu	H	H	--

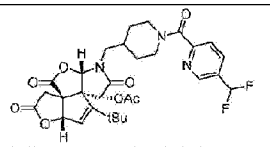
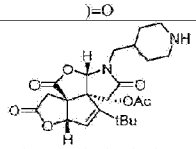
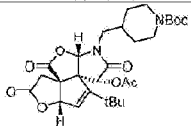
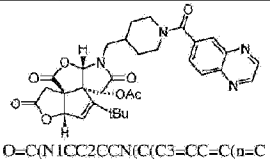
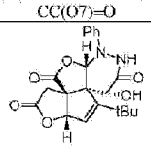
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-036	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=C(NC(Oc(C)(C)C)=O)C=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 4-[(tert-butoxycarbonyl)amino]phenyl	OBz	OH	tBu	H	H	--
XBB-037		N	 4-aminophenyl hydrochloride	OBz	OH	tBu	h	H	--
XBB-037'	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=C(N)C=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 4-aminophenyl	OBz	OH	tBu	H	H	--
XBB-038	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=C(N5CCOCC5)C=C4)=O)[C@]3([H])OC6=O)(C(C)(C)C)C[C@@]7([H])[C@]16CC(O7)=O	N	 4-(morpholin-4-yl)phenyl	OBz	OH	tBu	H	H	--

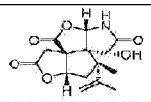
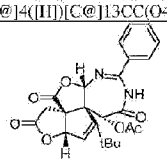
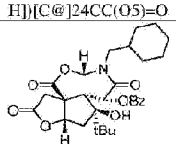
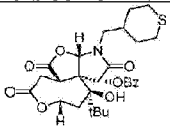
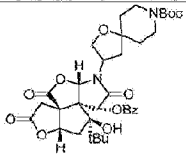
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-039	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC(OCO5)=C5C=C4)=O)[C@]3([H])OC6=O)(C(C)(C)C)C[C@@]7([H])[c@]16CC(O7)=O	N	 benzo[*d*][1,3]dioxol-5-yl	OBz	OH	tBu	H	H	--
XBB-040	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=CN=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 pyridin-3-yl	OBz	OH	tBu	H	H	--
XBB-041	 O[C@@]([C@]1([C@@H](O)C(N2CC3=CC=CC=C3)=O)[C@]2([H])OC4=O)(C(C)(C)C)C[C@@]5([H])[C@]14CC(O5)=O	N	 benzyl	OH	OH	tBu	H	H	--
XBB-042	 O[C@@]([C@]1([C@@H](O)C(N2C3=CC=C(N4CCOCC4)C=C3)=O)[C@]2([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 4-(morpholin-4-yl)phenyl	OH	OH	tBu	H	H	--

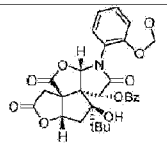
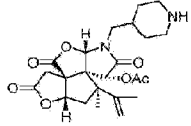
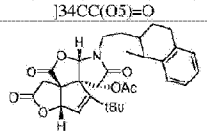
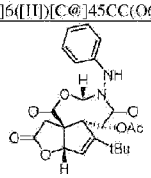
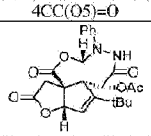
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-043	 O=C(N1CC2CCN(C(C3=CN=C(C(F)F)C=N3)=O)CC2)[C@H](OC(C4=CC=CC=C4)=O)[C@]5([C@]1([H])OC6=O)[C@](O)(C(C)(C)C)C[C@@]7([H])[C@]56CC(O7)=O	N	 (1-(5-(difluoromethyl)pyrazine-2-carbonyl)piperidin-4-yl)methyl	OBz	OH	tBu	H	H	--
XBB-044	 O=c(N1CC2CCN(C(C3=CC=C(OC(F)(F)O4)C4=C3)=O)CC2)[C@H](OC(C5=CC=CC=C5)=O)[C@]6([C@]1([H])OC7=O)[C@](O)(C(C)(C)C)C[C@@]8([H])[C@]67CC(O8)=O	N	 (1-(2,2-difluorobenzo[*d*][1,3]dioxole-5-carbonyl)piperidin-4-yl)methyl	OBz	OH	tBu	H	H	--
XBB-045	 O=C(N1CC2CCN(C(C3=CC=C(OCCO4)C4=C3)=O)CC2)[C@H](OC(C5=CC=CC=C5)=O)[C@]6([C@]1([H])OC7=O)[C@](O)(C(C)(C)C)C[C@@]8([H])[C@]67CC(O8)=O	N	 (1-(2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbonyl)piperidin-4-yl)methyl	OBz	Oh	tBu	H	H	--
XBB-046	 O=C(N1CC2CCN(C(C3=CC=C(OCC4)C4=C3)=O)CC2)[C@H](OC(C5=CC=CC=C5)=O)[C@]6([C@]1([H])OC7=O)[C@](O)(C(C)(C)C)C[C@@]8([H])[C@]67CC(O8)=O	N	 (1-(2,3-dihydrobenzofuran-5-carbonyl)piperidin-4-yl)methyl	OBz	Oh	tBu	H	H	--

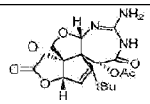
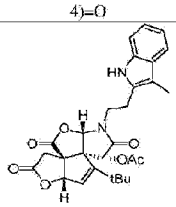
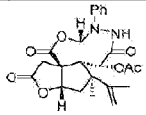
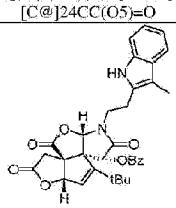
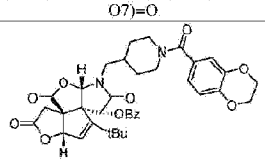
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-047	 O=C(N1CC2CCN(C(C3=CC=C(Cl)C=C3)=O)CC2)[C@H](OC(C4=CC=CC=C4)=O)[C@]5([C@]1([H])OC6=O)[C@](O)(C(C)(C)C)C[C@@]7([H])[C@]56CC(O7)=O	N	 (1-(4-chlorobenzoyl)piperidin-4-yl)methyl	OBz	OH	tBu	H	H	--
XBB-048	 O=C(N1CC2CCN(C(C=C)=O)CC2)[C@H](OC(C3=CC=CC=C3)=O)[C@]4([C@]1([H])OC5=O)[C@](O)(C(C)(C)C)C[C@@]6([H])[C@]45CC(O6)=O	N	 (1-acryloylpiperidin-4-yl)methyl	OBz	OH	tBu	H	H	--
XBB-049	 O[C@@](C@1([C@@H](O)C(N2C3=CC=C(NC(C)=O)C=C3)=O)[C@]2([H])OC4=O)(C(C)(C)C)C[C@@]5([H])[C@]14CC(O5)=O	N	 4-acetamidophenyl	OH	OH	tBu	H	H	--
XBB-050	 C[C@](C@1([C@@H](OC(C)=O)C(N2C3=CC=CC=C3)=O)[C@]2([H])OC4=O)(C(C)=C)C[C@@]5([H])[C@]14CC(O5)=O	N	phenyl	OAc	isopropenyl	Me	H	H	--
XBB-051	 O=C1[C@H](OC(C2=CC=CC=C2)=O)[C@]3([C@](NN1)([H])OC4=O)[C@](O)(C(C)(C)C)C[c@@]5([H])[C@]34CC(O5)=O	NH-NH	--	OBz	OH	tBu	H	H	--

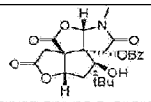
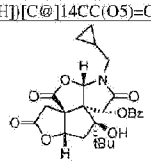
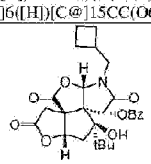
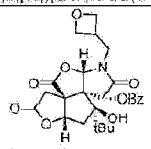
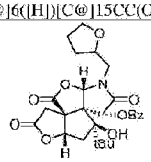
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-052	 O=C(N1CC2CCN(C(C3=CC=C(OCCO4)C4=C3)=O)CC2)[C@H](OC(C)=O)[C@]5([C@]1([H])OC6=O)C(C)(C)C)=C[C@@]7([H])[C@]56CC(O7)=O	N	 (1-(2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbonyl)piperidin-4-yl)methyl	OAc	tBu	--	H	--	--
XBB-053	 O[C@@]([C@]1([C@@H](o)C(N2C3=CC=C(N)C=C3)=O)[C@]2([H])OC4=O)(C(C)(C)C)C[C@@]5([H])[C@]14CC(O5)=O	N	 4-aminophenyl	OH	OH	tBu	H	H	--
XBB-054	 O=C(N1CCN2C=C(C=CC=C3)C3=C2C)[C@H](OC(C)=O)[C@]4([C@]1([H])OC5=O)C(C)(C)C)=C[C@@]6([H])[C@]45CC(O6)=O	N	 2-(1-methyl-2*H*-isoindol-2-yl)ethyl	OAc	tBu	--	H	--	--
XBB-055	[deleted]								
XBB-056	 O[C@@]([C@]1([C@@H](O)C(N2)=O)[C@]2([H])OC3=O)(C(C)(C)C)[C@@H](O)[C@@]4([H])[C@]13CC(O4)=O	N	H	OH	OH	tBu	OH	H	--
XBB-057	 O=C(N1CC2CCN(C(C3=CC=C(OC(F)(F)O4)C4=C3)=O)CC2)[C@H](OC(C)=O)[C@]5([C@]1([H])OC6=O)C(C)(C)C)=C[C@@]7([H])[C@]56CC(O7)=O	N	 (1-(2,2-difluorobenzo[*d*][1,3]dioxole-5-carbonyl)piperidin-4-yl)methyl	OAc	tBu	--	H	--	--

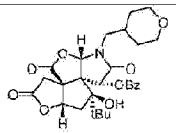
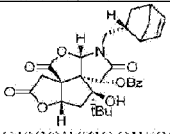
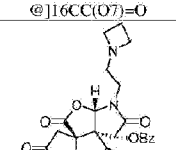
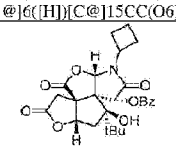
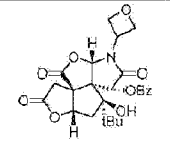
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-058	 O=C(N1CC2CCN(C(C3=NC=C(C(F)F)C=C3)=O)CC2)[C@H](OC(C)=O)[C@]4([C@]1([H])OC5=O)C(C)(C)C=C[C@@]6([H])[C@]45CC(O6)=O	N	 (1-(5-(difluoromethyl)pyrazine-2-carbonyl)piperidin-4-yl)methyl	OAc	tBu	--	H	--	--
XBB-059	 O=C(N1CC2CCNCC2)[C@H](OC(C)=O)[C@]3([C@]1([H])OC4=O)C(C)(C)C=C[C@@]5([H])[C@]34CC(O5)=O	N	 piperidin-4-yl methyl	OAc	tBu	--	H	--	--
XBB-060	 O=C(N1CC2CCN(CC2)C(OC(C)(C)C)=O)[C@H](OC(C)=O)[C@]3([C@]1([H])OC4=O)C(C)(C)C=C[C@@]5([H])[C@]34CC(O5)=O	N	 [1-(tert-butoxycarbonyl)piperidin-4-yl]methyl	OAc	tBu	--	H	--	--
XBB-061	 O=C(N1CC2CCN(C(C3=CC=C(n=CC=N4)C4=C3)=O)CC2)[C@H](OC(C)=O)[C@]5([C@]1([H])OC6=O)C(C)(C)C=C[C@@]7([H])[C@]56CC(O7)=O	N	 (1-(quinoxaline-6-carbonyl)piperidin-4-yl)methyl	OAc	tBu	--	H	--	--
XBB-062	 O=C1[C@H](O)[C@]2([C@](N(C3=CC=CC=C3)N1)([H])OC4=O)C(C)(C)C=C[C@@]5([H])[C@]24CC(O5)=O	NR1-NH	 phenyl	OAc	tBu	--	H	--	--

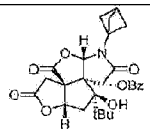
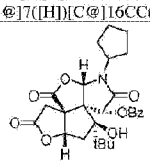
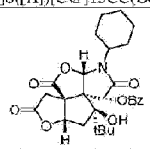
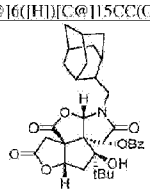
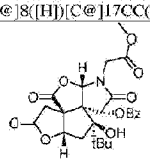
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-063	 C[C@@]1([C@]1([C@@H](O)C(N2)=O)[C@]2([H])OC3=O)(C(C)=C)C[C@@]4([H])[C@]13CC(O4)=O	N	H	OH	Me	isopropenyl	H	H	--
XBB-064	 O=C1[C@H](OC(C)=O)[C@]2([C@@]([H])(N=C(C3=CC=CC=C3)N1)OC4=O)C(C)(C)C=C[C@@]5([H])[C@]24CC(O5)=O	N=CR1-NH	 phenyl	OAc	tBu	--	H	--	--
XBB-065	 O=C(N1CC2CCCCC2)[C@H](OC(C3=CC=CC=C3)=O)[C@]4([C@]1([H])OC5=O)[C@](O)(C(C)(C)C)C[C@@]6([H])[C@]45CC(O6)=O	N	 cyclohexylmethyl	OBz	OH	tBu	H	H	--
XBB-066	 O=C(N1CC2CCSCC2)[C@H](OC(C3=CC=CC=C3)=O)[C@]4([C@]1([H])oC5=O)[C@](O)(C(C)(C)C)C[C@@]6([H])[C@]45CC(O6)=O	N	 (tetrahydro-2*H*-thiopyran-4-yl)methyl	OBz	OH	tBu	H	H	--
XBB-067	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4CC5(CCN(CC5)C(OC(C)(C)C)=O)OC4)=O)[C@]3([H])OC6=O)(C(C)(C)C)C[C@@]7([H])[C@]16CC(O7)=O	N	 8-(tert-butoxycarbonyl)-1-oxa-8-azaspiro[4.5]decan-3-yl	OBz	OH	tBu	H	H	--

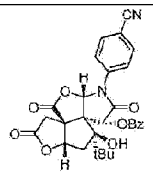
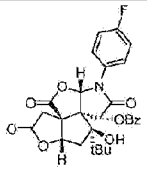
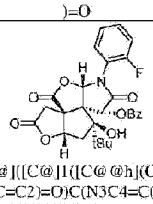
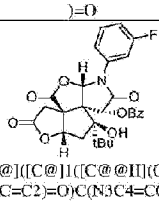
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-068	 O[C@@][([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=C(OCO5)C5=CC=C4)=O)[C@]3([H])OC6=O)(C(C)(C)C)C[C@@]7([H])[C@]16CC(O7)=O	N	 benzo[*d*][1,3]dioxol-4-yl	OBz	OH	tBu	H	H	--
XBB-069	 O=C(N1CC2CCNCC2)[C@H](OC(C)=O)[C@]3([C@]1([H])OC4=O)[C@](C(C)=C)(C)C[C@@]5([H])[C@]34CC(O5)=O	N	 piperidin-4-ylmethyl	OAc	isopropenyl	Me	H	H	--
XBB-070	 O=C(N1CCC2C(C)C(C=CC=C3)=C3CC2)[C@H](OC(C)=O)[C@]4([C@]1([H])OC5=O)C(c(C)(C)C)=C[C@@]6([H])[C@]45CC(O6)=O	N	 2-(1-methyl-1,2,3,4-tetrahydronaphthalen-2-yl)ethyl	OAc	tBu	--	H	--	--
XBB-071	 O=C(N1nC2=CC=CC=C2)[C@H](OC(C)=O)[C@]3([C@]1([H])OC4=O)C(C(C)(C)C)=C[C@@]5([H])[C@]34CC(O5)=O	N	 anilinyl	OAc	tBu	--	H	--	--
XBB-072	 O=C1[C@H](OC(C)=O)[C@]2([C@](n(C3=CC=CC=C3)N1)([H])OC4=O)C(C(C)(C)C)=C[C@@]5([H])[C@]24CC(o5)=O	NR1-NH	 phenyl	OAc	tBu	--	H	--	--

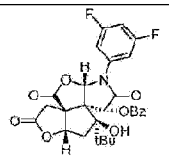
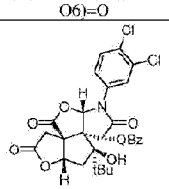
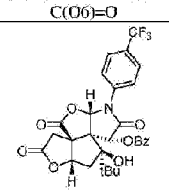
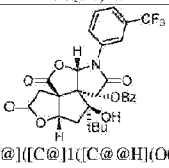
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XBB-073	 O=C1[C@H](OC(C)=O)[C@]2([C@@]([H])(N=C(N)N1)OC3=O)C(C(C)(C)C)=C[C@@]4([H])[C@]23CC(O4)=O	N=CR1-NH	NH_2	OAc	tBu	--	H	--	--
XBB-074	 O=C(N1CCC2=C(C)C3=CC=CC=C3N2)[C@H]((OC(C)=O)[C@]4([C@]1([H])OC5=O)C(C(C)(C)C)=C[c@@]6([H])[C@]45CC(O6)=O	N	 2-(3-methyl-1H-indol-2-yl)ethyl	OAc	tBu	--	H	--	--
XBB-075	 O=C1[C@H](OC(C)=O)[C@]2([C@](N(C3=CC=CC=C3)N1)([H])OC4=O)[C@](C(C)=C)(C)C[C@@]5([H])[C@]24CC(O5)=O	NR1-NH	 phenyl	OAc	isopropenyl	Me	H	h	--
XBB-076	 O=C(N1CCC2=C(C)C3=CC=CC=C3N2)[C@H](OC(C4=CC=CC=C4)=O)[C@]5([C@]1([H])OC6=O)C(C(C)(C)C)=C[C@@]7([H])[C@]56CC(O7)=O	N	 2-(3-methyl-1H-indol-2-yl)ethyl	OBz	tBu	--	H	--	--
XBB-077	 O=C(N1CC2CCN(C(C3=CC=C(OCCO4)C4=C3)=O)CC2)[C@H](OC(C5=CC=CC=C5)=O)[C@]6([C@]1([H])OC7=O)C(C(C)(C)C)=C[c@@]8([H])[C@]67CC(O8)=O	N	 (1-(2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbonyl)piperidin-4-yl)methyl	OBz	tBu	--	H	--	--

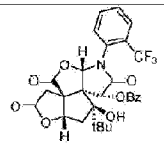
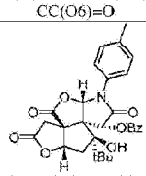
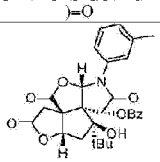
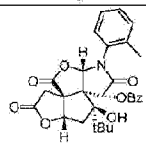
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
DW168	 O[C@@]([C@]1([C@@h]{OC(C2=CC=CC=C2)=O)C(N3C)=O)[C@]3([H])OC4=O)(C(C)(C)C)C[C@@]5([H])[C@]14CC(O5)=O	N	methyl (CH_3)	OBz	OH	tBu	H	H	--
DW189	 O[C@@]([C@]1([C@@H](OC(C2=Cc=CC=C2)=O)C(N3CC4CC4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 cyclopropyl methyl	OBz	OH	tBu	H	H	--
DW184	 O[C@@]([c@]1([C@@H](OC(c2=CC=CC=C2)=O)C(N3CC4CCC4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 cyclobutyl methyl	OBz	OH	tBu	H	H	--
DW191	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3CC4COC4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 (oxetan-3-yl)methyl	OBz	OH	tBu	H	H	--
P-5	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3CC4OCCC4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 (oxolan-2-yl)methyl	OBz	OH	tBu	H	H	--

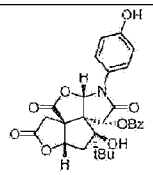
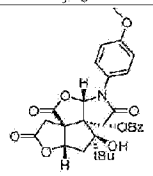
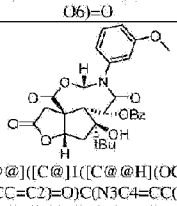
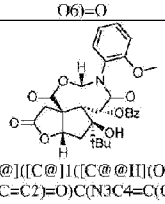
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
P-3	 O[C@@](C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3CC4CCOCC4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 (tetrahydro-2*H*-pyran-4-yl)methyl	OBz	OH	tBu	H	H	--
DW190	 O[C@@](C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3c[C@@]4([H])C(C5)C=CC5C4)=O)[C@]3([H])OC6=O)(c(C)(C)C)C[C@@]7([H])[C@]16CC(O7)=O	N	 (bicyclo[2.2.1]hept-5-en-2-yl)methyl	OBz	OH	tBu	H	H	--
P-10	 O[C@@](C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3CCN4CCC4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2-(azetidin-1-yl)ethyl	OBz	OH	tBu	H	H	--
DW163	 O[C@@](C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4CCC4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 cyclobutyl	OBz	OH	tBu	H	H	--
DW182	 O[C@@](C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4COC4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 oxetan-3-yl	OBz	OH	tBu	h	H	--

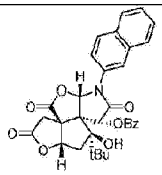
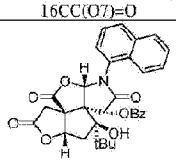
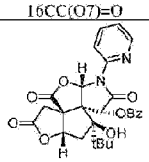
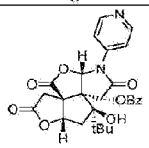
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
DW172	 O[C@@]([C@]12[C@@H](OC(C3=CC=CC=C3)=O)C(N4C5(CC6CC5C6)C4=O)[C@]7([H])OC8=O)(C(C)(C)C)C[C@@]79[H])[C@]18CC(O9)=O	N	 bicyclo[1.1.1]pentyl	OBz	OH	tBu	H	H	--
JW081	 O[C@@]([C@]12[C@@H](OC(C3=CC=CC=C3)=O)C(N4C5(CCCC5)C4=O)[C@]6([H])OC7=O)(C(C)(C)C)C[C@@]68[H])[C@]19CC(O8)=O	N	 cyclopropyl	OBz	OH	tBu	H	H	--
P-12	 O[C@@]([C@]12[C@@H](OC(C3=CC=CC=C3)=O)C(N4C5(CCCCC5)C4=O)[C@]6([H])OC7=O)(C(C)(C)C)C[C@@]69[H])[C@]18CC(O9)=O	N	 cyclohexyl	OBz	OH	tBu	H	H	--
DW192	 O[C@@]([C@]12[C@@H](OC(C3=CC=CC=C3)=O)C(N4CC5[C@@H]6C[C@@H]5C[C@@H]4C6)C7=O)[C@]8([H])OC9=O)(C(C)(C)C)C[C@@]89[H])[C@]17CC(O8)=O	N	 adamantan-2-yl methyl	OBz	OH	tBu	H	H	--
P-8	 O[C@@]([C@]12[C@@H](OC(C3=CC=CC=C3)=O)C(N4CC(NC4=O)=O)C5=O)[C@]6([H])OC7=O)(C(C)(C)C)C[C@@]69[H])[C@]18CC(O9)=O	N	 2-methoxy-2-oxoethyl	OBz	OH	tBu	H	H	--

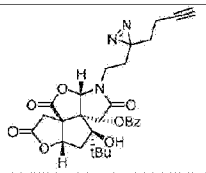
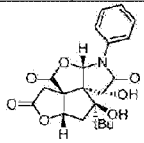
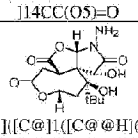
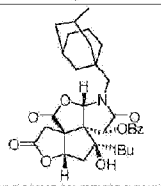
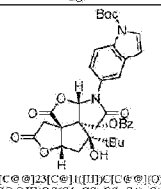
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
JW107	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=C(C#N)C=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 4-cyano phenyl	OBz	OH	tBu	H	H	--
P-28	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=C(F)C=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 4-fluoro phenyl	OBz	oH	tBu	H	H	--
JW098	 O[C@@]([C@]1([C@@h](OC(C2=CC=CC=C2)=O)C(N3C4=C(F)C=CC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2-fluoro phenyl	OBz	OH	tBu	H	H	--
JW099	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC(F)=CC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 3-fluoro phenyl	OBz	OH	tBu	H	H	--

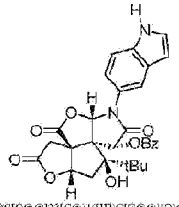
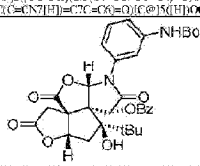
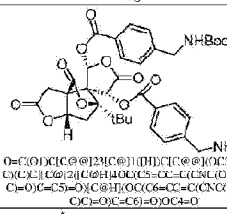
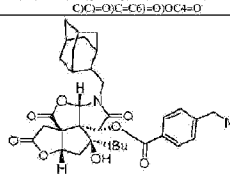
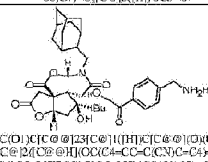
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
P-19	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC(F)=CC(F)=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 3,5-difluoro phenyl	OBz	OH	tBu	H	H	--
P-21	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC(Cl)=C(Cl)C=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 3,4-dichloro phenyl	OBz	OH	tBu	H	H	--
P-29	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=C(C(F)(F)F)C=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 4-(trifluoromethyl) phenyl	OBz	OH	tBu	H	H	--
JW100	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC(C(F)(F)F)=CC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 3-(trifluoromethyl) phenyl	OBz	OH	tBu	H	H	--

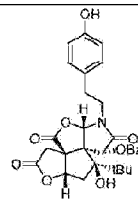
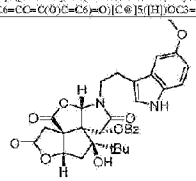
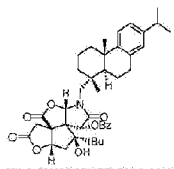
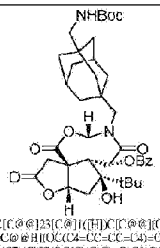
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
JW104	 O[C@@][C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=C(C(F)(F)F)C=CC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2-(trifluoromethyl)phenyl	OBz	OH	tBu	H	H	--
P-30	 O[C@@][C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=C(C)C=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 4-toluyl	OBz	OH	tBu	H	H	--
P-33	 O[C@@][C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC(C)=CC=C4)=O)[C@]3([H])Oc5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 3-toluyl	OBz	OH	tBu	H	H	--
P-34	 O[C@@][C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=C(C)C=CC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2-toluyl	OBz	OH	tBu	H	H	--

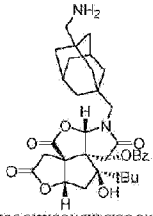
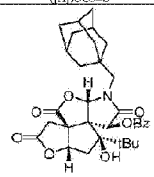
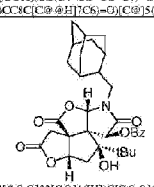
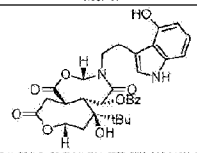
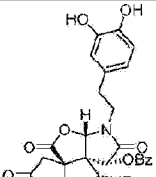
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
JW103	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=C(O)C=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 4-hydroxy phenyl	OBz	OH	tBu	H	H	--
JW093	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=C(OC)C=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 4-methoxy phenyl	OBz	OH	tBu	H	H	--
JW092	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC(OC)=CC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 3-methoxy phenyl	OBz	OH	tBu	H	H	--
JW095	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=C(OC)C=CC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2-methoxy phenyl	OBz	OH	tBu	H	H	--

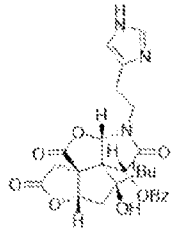
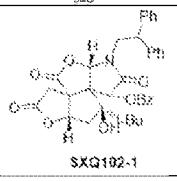
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
JW094	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC(C=CC=C5)=C5C=C4)=O)[C@]3([H])OC6=O)(C(C)(C)C)C[C@@]7([H])[C@]16CC(O7)=O	N	 naphthalen-2-yl	OBz	OH	tBu	H	H	--
JW097	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=C(C=CC=C5)C5=CC=C4)=O)[C@]3([H])OC6=O)(C(C)(C)C)C[C@@]7([H])[C@]16CC(O7)=O	N	 naphthalen-1-yl	OBz	OH	tBu	H	H	--
JW105	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=NC=CC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	pyridine-2-yl	OBz	OH	tBu	H	H	--
JW096	 O[C@@]([C@]1([C@@H](OC(C2=CC=CC=C2)=O)C(N3C4=CC=NC=C4)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	pyridine-4-yl	OBz	OH	tBu	H	H	--

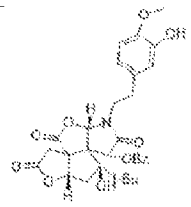
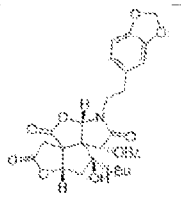
#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
JW120	 O[C@@](C@H](OC(C2=CC=CC=C2)=O)C(N3CCC4(N=N4)CCC#C)=O)[C@]3([H])OC5=O)(C(C)(C)C)C[C@@]6([H])[C@]15CC(O6)=O	N	 2-[3-(but-3-yn-1-yl)-3H-diazirin-3-yl] ethyl	OBz	OH	tBu	H	H	--
JW116	 O[C@@](C@]1([C@@H](O)C(N2C3=CC=CC=C3)=O)[C@]2([H])OC4=O)(C(C)(C)C)C[C@@]5([H])[C@]14CC(O5)=O	N	phenyl	OH	OH	tBu	H	H	--
JW072	 O[C@@](C@]1([C@@H](O)C(N2N)=O)[C@]2([H])OC3=O)(C(C)(C)C)C[C@@]4([H])[C@]13CC(O4)=O	N	NH_2	OH	OH	tBu	H	H	--
SCC363	 O=C(O1)C[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@]2([C@@H][OC(C4=CC=CC=C4)=O)C(N5CC6(CC(C7)CB)CC8C[C@@H]7C6)=O)[C@]3([H])OC3=O	N	 adamantan-1-yl methyl	OBz	OH	tBu	H	H	--
SCC376	 O=C(O1)C[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@]2([C@@H][OC(C4=CC=CC=C4)=O)C(N5C6=CC(C=CN7C(OC(C)(C)C)=O)=C7C=C6)=O)[C@]3([H])OC3=O	N	 1-(tert-butoxycarbonyl)-1H-indol-5-yl	OBz	OH	tBu	H	H	--

#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
SCC382	 O=C(O1)C[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@]2(C@@H](OC(C4=CC=CC=C4)=O)C[N5C6=CC(C=CN7[H])=C7C=C6)=O)[C@]5([H])OC3=O	N	 1H-indol-5-yl	OBz	OH	tBu	H	H	--
SCC385	 O=C(O1)C[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@]2(C@@H](OC(C4=CC=CC=C4)=O)C[N5C6=CC(NC(OC(C)(C)C)=O)=CC=C6)=O)[C@]5([H])OC3=O	N	 3-[(tert-butoxycarbonyl)amino]phenyl	OBz	OH	tBu	H	H	--
SCC501	 O=C(O1)C[C@@]23[C@]1([H])C[C@@](OC3=O)(C(O)(C)C)[C@]2(C@H]4OC(C5=CC=C(CNC(OC(C)(C)C)=O)C=C5)=O)[C@H](OC(C6=CC=C(CNC(OC(C)(C)C)=O)C=C6)=O)OC4=O	O	--	 4-[(tert-butoxycarbonyl)aminomethyl)]benzoyl	--	tBu	H	H	 4-[[(tert-butoxycarbonyl)aminomethyl)]benzoyl
SCC505	 O=C(O1)C[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@]2([C@@H](OC(C4=CC=C(CNC(OC(C)(C)C)=O)C=C4)=O)C[N5CC6[C@@H]7CC8C[C@@H]6CC(C8)C7)=O)[C@]5([H])OC3=O	N	 adamantan-2-yl methyl	 4-[(tert-butoxycarbonyl)aminomethyl)]benzoyl	OH	tBu	H	H	--
SCC506	 O=C(O1)C[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@]2([C@@H](OC(C4=CC=C(CN)C=C4)=O)C(N5CC6[C@@H]7CC8C[C@@H]6CC(C8)C7)=O)[C@]5([H])OC3=O.Cl	N	 adamantan-2-yl methyl	4-(aminomethyl)benzoyl Hydrochloride	OH	tBu	H	H	--

#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
SCC545	 O=C(O1)C[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@]2([C@@H](OC(C4=CC=CC=C4)=O)C(NSCCC6=CC=C(O)C=C6)=O)[C@]5([H])OC3=O	N	 4-Hydroxyphenyl ethyl	OBz	OH	tBu	H	H	--
SCC555	 O=C(O1)C[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@]2([C@@H](OC(C4=CC=CC=C4)=O)C(NSCCC6=CNC7=C6C=C(OC)C=C7)=O)[C@]5([H])OC3=O	N	 1H-indole-5-methoxy-3-ethyl	OBz	OH	tBu	H	H	--
SCC558	 O=C(O1)C[C@@]23[C@@]1([H])C[C@@](O)(C(C)(C)C)[C@@]2([C@@H](OC(C4=CC=CC=C4)=O)C(NSC[C@]6(C)CCC[C@@]7(C)[C@@]6([H])CCC8=CC(C(C)C)=CC=C87)=O)[C@]5([H])OC3=O	N	 ((1*R*,4a*S*,10a*R*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl) methyl	OBz	OH	tBu	H	H	--
SCC564	 O=C(O1)C[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@@]2([C@@H](OC(C4=CC=CC=C4)=O)C(NSC[C@@]6(CC(C7)(CNC(OC(C)(C)C)=O)C8)CC8C[C@@H]7C6)=O)[C@]5([H])OC3=O	N	 [({(tert-butoxycarbonyl)aminomethyl} adamantan-1-yl] methyl	OBz	OH	tBu	H	H	--

#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
SCC567	 O=C(O[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@]2([C@@]1(OC(C4=CC=CC=C4)=O)C(NSC[C@@]6(CC(C7)(CN)C8)CC8C[C@@H]7C6)=O)[C@]5([H])OC3=O	N	 (aminomethyl)adamantan-1-yl) methyl	OBz	OH	tBu	H	H	--
SCB001	 O=C(O[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@@]2([C@@H](OC(C4=CC=CC=C4)=O)C(NSCC6(CC(C7)C8)CC8C[C@@H]7C6)=O)[C@]5([H])OC3=O	N	 adamantan-1-yl methyl	OBz	OH	tBu	H	H	--
SCB002	 O=C(O[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@@]2([C@@H](OC(C4=CC=CC=C4)=O)C(NSCC6(C@@H]7CC8C[C@@H](CC(C8)C7)=O)[C@]5([H])OC3=O	N	 adamantan-2-yl methyl	OBz	OH	tBu	H	H	--
SCB008	 O=C(O[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@@]2([C@@H](OC(C4=CC=CC=C4)=O)C(NSCCC6=CNC7=C6C(OC)=CC=C7)=O)[C@]5([H])OC3=O	N	 1H-indole-4-hydroxy-3-ethyl	OBz	OH	tBu	H	H	--
SXQ087-1	 O=C(O[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@@]2([C@@H](OC(C4=CC=CC=C4)=O)C(NSCCC6=CC=C(O)C(O)=C6)=O)[C@]5([H])OC3=O	N	 3,4-dihydroxyphenyl ethyl (dopamine)	OBz	OH	tBu	H	H	--

#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
SXQ090-1	O=C(O[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@@]2([C@@H]OC(C4=CC=CC=C4)=O)C(N5CCC6=CNC7=C6C=CC=C7)=O)[C@]5([H])OC3=O	N	1H-indole-3-ethyl (tryptamine)	OBz	OH	tBu	H	H	--
SXQ092-1	 SXQ092-1	N	2-(4-Imidazolyl)ethyl (histamine)	OBz	OH	tBu	H	H	--
SXQ094-1	O=C(O[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@@]2([C@@H](OC(C4=CC=CC=C4)=O)C(N5CCC6=CC(C(C)(C)C)=CC(C(C)(C)C)=C6)=O)[C@]5([H])OC3=O	N	3,5-di-tert butyl phenyl	OBz	OH	tBu	H	H	--
SXQ102-1	 SXQ102-1	N	2,2-diphenylethyl	OBz	OH	tBu	H	H	--
SXQ091-1	O=C(O[C@@]23[C@]1([H])C[C@@](O)(C(C)(C)C)[C@@]2([C@@H]OC(C4=CC=CC=C4)=O)C(N5CCC6=CNC7=C6C=C(O)C=C7)=O)[C@]5([H])OC3=O	N	1H-indole-5-hydroxy-3-ethyl (serotonin)	OBz	OH	tBu	H	H	--

#	Structure	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7
SXQ125-2	 SXQ125-2	N	 3-hydroxy-4-methoxyphenyl ethyl	OBz	OH	tBu	H	H	--
SXQ126-1	 SXQ126-1	N	 3,4-Methylenedioxyphenyl ethyl	OBz	OH	tBu	H	H	--
SXQ128-1	O=C(O)C[C@@]23[C@]1([H])C[C@@]3(O)C(C)(C)CC[C@]2([C@@H](OC)C4=CC=CC=C4)=O)C(N5CCC6=CC=C(O)C(OC)=C6)=O)[C@]5([H])OC3=O	N	 3-methoxy-4-hydroxyphenyl ethyl (3-O-Methyldopamine)	OBz	OH	tBu	H	H	--

[0621] Example modification conditions are summarized in Table 1e.

[0622] Initial investigation of the conditions for bilobalide benzoylation.

[0623] Table 1e: Example conditions for bilobalide benzoylation

Entry	Base	Solvent	Temperature	Reaction time	Isolated yields	
					XBB-002	XBB-003
1	pyridine (6.0 equiv)	dioxane	60 °C	24 h	53%	38%
2	EDCI (10 equiv.) DMAP (10 equiv.)	DCM	rt	24 h	60%	35%
3	pyridine	pyridine	50 °C	26 h	80%	18%
4	pyridine	pyridine	60 °C	26 h	35%	65%
5	pyridine	pyridine	80 °C	26 h	25%	75%
6	2,6-lutidine (6.0 equiv)	DCM	rt	26 h	76%	trace

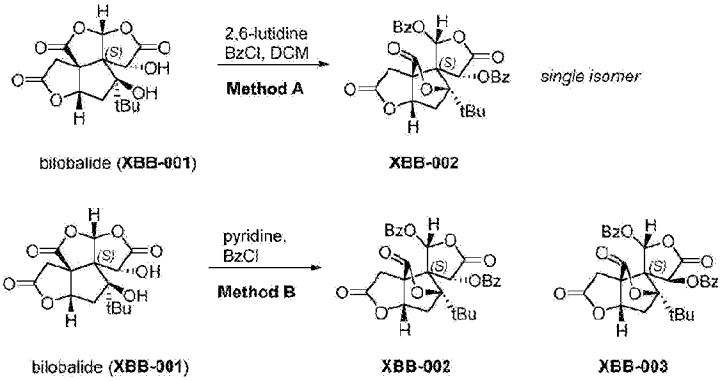
[0624] When conducting the reaction at 50 ℃, the major product XBB-002 was isolated in 80%yield (Entry 3, Table 1e) and the absolute structure was confirmed by X-ray crystallography. Unexpectedly, the absolute configuration of the minor product XBB-003 was the epimer of XBB-002 since only the configuration at C10 differs between XBB-002 and XBB-003. At lower temperature XBB-002 is the main product while at higher temperature XBB-003 is more favored (Entries 4-5, Table 1e) . Only a trace amount of XBB-003 was observed with 2, 6-lutidine as the base (Entry 6, Table 1e) .

[0625] Example 1.1: Synthesis of di-benzoylated iso-bilobalides XBB-002 and XBB-003 according to Scheme 1.

[0626] Unless otherwise stated, all syntheses and manipulations of air-and moisture-sensitive materials were carried out under nitrogen atmosphere using standard Schlenk techniques. All glassware was oven-dried immediately prior to use. For reaction setup dry solvents stored over molecular sieve (MS) were purchased from Me ryer (China) . Reactions were magnetically stirred and monitored by analytical thin-layer chromatography (TLC) . TLC was performed on Merck Kieselgel 60 F_{254} with 0.2 mm thickness and visualized by exposure to ultraviolet light and appropriat e staining. Organic solutions were concentrated by rotary evaporation at 20 –45 ℃.

[0627] All chemicals and reagents available from commercial sources were di rectly used without further purification unless otherwise stated. Chromatographic pur ification of products was accomplished using forced-flow chromatograp hy on silica gel (200 –300 mesh) . Melting points were measured on a n OptiMelt using open glass capillaries, and the data is uncorrected. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on an Bruker instruments at 400, 500 or 600 MHz frequency. ^{1}H NMR spectra are referred to the residual solvent signal. The data for ^{1}H NMR is represented as follows: chemical shift (δ, ppm) , multiplicity (s= singlet, d = doublet, t = triplet, m = multiplet, br = broad singlet, coupling constant (s) in Hz, integration) . $^{13}C\{^{1}H\}$ spectra are in ternally referenced to residual solvent signals. Data for ^{19}F and $^{13}C\{^{1}H\}$ are expressed in terms of chemical shift (δ, ppm) . High-resolution mass spectra (HRMS) wer e obtained on a Thermo Q ExactiveTM Focus Hybrid Quadrupole-OrbitrapTM Mass S pectrometer. X-ray crystallographic analysis was performed on Bruker D8ventur e Dif fractometer. Optical rotations were measured on Digital Polarimeter Jiao DIP-1010. Crystal structural data were collected by the single-crystal X-ray diffraction m ethod with a Bruker D8-Venture system.

[0628] Synthesis of (2R, 3S, 3a'S, 4R, 6'R, 7a'S) -6'- (tert-butyl) -2', 4', 5-trioxohexahydro-4'H, 6'H-spiro [furan-3, 8'- [3a, 6] methanofuro [3, 2-c] pyran] -2, 4-diyl dibenzoate (XBB-002) and (2R, 3S, 3a'S, 4S, 6'R, 7a'S) -6'- (tert-butyl) -2', 4', 5-trioxohexahydro-4'H, 6'H-spiro [furan-3, 8'- [3a, 6] methanofuro [3, 2-c] pyran] -2, 4-diyl dibenzoate (XBB-003) are discussed herein.



[0629] Method I: To a solution of bilobalide (6.00 g, 18.4 mmol, 1 equiv.) in anhydrous dic hloromethane (40 mL, 0.46 M) , benzoyl chloride (19.2 mL, 165.6 mmol , 9 equiv.) , and 2, 6-lutidine (12.9 mL, 110.4 mmol, 6 equiv.) was added . The reaction mixture was stirred at room temperature for 72 hours, then quenched wi th a saturated aqueous solution of sodium bicarbonate (40 mL) . The resultant mixture was extracted with ethyl acetate (3 x 20 mL) , dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude mixture is then eluted t hrough silica gel using a hexane/ethyl acetate/dichloromethane (3: 1: 1) mixture to r emove any residual benzoyl chloride. The product mixture is then purified using silic a gel column chromatography with dichloromethane to give the desired product XBB-002 (2.7 g, 28%) as a white solid.

[0630] Method II: To a solution of bilobalide (0.30 g, 0.920 mmol, 1.0 equiv.) and benzoyl chloride (1.940 g, 13.800 mmol, 15 equiv.) was added anhydrous pyri dine (5.0 mL) . After stirring at 50°C or 80°C for 16 h, the reaction solution was conc entrated under reduced pressure to remove pyridine. The residue was diluted with ethyl acetate and quenched with saturated sodium bicarbonate solution. T he combined organic layer was then washed with brine, dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The crude product was then purified by silica gel column chromatography (hexane/acetone = 6: 1) to afforded XBB-002 (50°C: 0.42 g, 85%; 80°C: 98 mg, 20%) and XBB-003 (50°C: 49 mg, 10%; 80°C: 0.38 g, 78%) both as white powder.

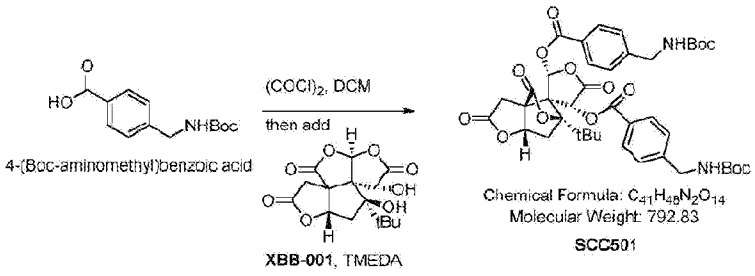
[0631] Method III: Bilobalide (1.0 eq., 1.53 mmol, 500 mg) was dried using MeCN co-evaporation and high vacuum. Then, dry DCM (20 mL) was added followe d by BzCl (3.0 eq., 4.60 mmol, 0.64 g, 0.53 mL) and TMEDA (3.0 eq., 4.60 mmol, 0.53 g, 0.69 mL) . The reaction was stirred until completion (18 h, o. n.) . Then NH_4Cl sat. solution was added (30 mL) and after phase separation, the a queous phase was extracted with DCM (2x 30 mL) . The combined organi c phases were washed with brine (40 mL) and dried over $MgSO_4$. Colum chromatog

raphy (SiO2, Hex/EA/DCM 3: 1: 1 to Hex/EA 1: 1) yielding XBB-002 in around 85-95%yield.

[0632] XBB-002: $R_f = 0.41$ (hexane: EtOAc, 3: 1) ; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 8.12 –8.06 (m, 2H) , 8.05 –8.01 (m, 2H) , 7.76 –7.71 (m, 1H) , 7.70 – 7.64 (m, 1H) , 7.61 –7.55 (m, 2H) , 7.54 –7.48 (m, 2H) , 7.36 (s, 1H) , 6.23 (s, 1H) , 4.46 (dd, J = 7.6, 4.5 Hz, 1H) , 3.37 (d, J = 18.0 Hz, 1H) , 3.09 (d, J = 18.0 Hz, 1H) , 2.94 –2.74 (m, 2H) , 1.28 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 169.60, 165.74, 165.52, 160.63, 160.59, 133.20, 132.87, 128.72, 128.62, 127.76, 127.30, 126.71, 126.31, 100.79, 94.46, 79.55, 69.00, 65.56, 64.44, 38.75, 37 .85, 35.49, 34.27, 29.92; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{26}O_{10}Na^+$ 557.14182, found 557.14142. The X-ray crystal structure of XBB-002 is shown in F IG. 1A.

[0633] XBB-003: $R_f = 0.43$ (hexane: EtOAc, 3: 1) ; mp = 172.4-173.0°C; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 8.06 (d, J = 7.7 Hz, 2H) , 8.01 (d, J = 7.8 Hz, 2H) , 7.75 –7.65 (m, 2H) , 7.61 –7.50 (m, 4H) , 7.35 (s, 1H) , 6.38 (s, 1H) , 4.46 (dd, J = 8.2, 3.6 Hz, 1H) , 3.27 (s, 2H) , 3.05 (dd, J = 14.9, 3.6 Hz, 1H) , 2.64 (dd, J = 14.9, 8.2 Hz, 1H) , 1.34 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 172.16, 169.07, 168.72, 163.91, 163.59, 134.84, 134.41, 130.17, 129.97, 129.16, 128.99, 127.68, 127.15, 101.45, 92.86, 79.03, 63.93, 62.75, 61.32, 35.34, 35 .03, 30.16, 26.87; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{26}O_{10}Na^+$ 557.14182, found 557.14182. The X-ray crystal structure of XBB-003 is shown in F IG. 1D.

[0634] Synthesis of (2R, 3S, 3a'S, 4R, 6'R, 7a'S) -6'- (tert-butyl) -2', 4', 5-trioxohexahydro-4'H, 6'H-spiro [furan-3, 8'- [3a, 6] methanofuro [3, 2-c] pyran] -2, 4-diyl bis (4-(((tert-butoxycarbonyl) amino) methyl) benzoate) (SCC501) .

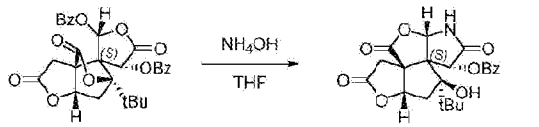


[0635] To a solution of 4- (Boc-aminomethyl) benzoic acid (4.0 equiv., 2.00 mmol, 5 02.1 mg) in DCM (25 mL) was added $(COCl)_2$ (4.0 equiv., 2.00 mmol, 253 mg, 1 71 μL) and one drop of DMF at 0°C. The reaction was stirred for 30 mi n. Then, at room temperature, tetramethylethylenediamine (TMEDA) (4. 0 equiv., 2.00 mmol, 232 mg, 300 μL) and bilobalide (1.0 equiv. 0.50

mmol, 163 mg) were added. The reaction was stirred for 19 h. Then sat. $NaHCO_3$ solution was added (20 mL) and the phases were separated. The aqueous phase was extracted with DCM (3x 20 mL) and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuuo. Column chromatography (SiO_2, hex/EtOAc/DCM 3: 1: 1) yielded in SCC501 as a white solid (215.6 mg, 54%) .

[0636] Example 1.2: Synthesis of bilobalide lactam analogues XBB-004 and XBB-005 according to Scheme 2 or Scheme 5.

[0637] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-004) is discussed herein.



Chemical Formula: $C_{29}H_{26}O_{10}$
Molecular Weight: 534.52

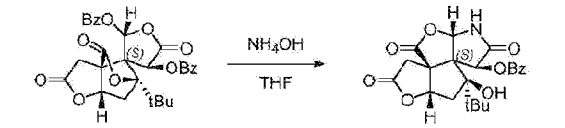
XBB-002

Chemical Formula: $C_{22}H_{23}NO_8$
Molecular Weight: 429.43

XBB-004

[0638] To a solution of XBB-002 (50 mg, 93.607 mmol, 1.0 equiv) in anhydrous THF (2 mL) was added 25%ammonia solution (13 mg, 0.187 mmol, 2.0 equiv) at 0°C. The resulting solution was then allowed to be stirred for 30 min at room temperature. The reaction was monitored by TLC and upon completion the reaction solution was diluted with ethyl acetate. The organic layer was washed with washed with saturated $NaHCO_3$ solution, and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified via column chromatography (hexane: EtOAc = 1: 1) to provide XBB-004 (76%yield, 31 mg) as a white powder. R_f = 0.34 (hexane: EtOAc, 1: 1) ; mp = 237.3-238.5°C; ^{1}H-NMR (500 MHz, MeOD) : δ [ppm] = 8.04 –7.89 (m, 2H) , 7.73 –7.61 (m, 1H) , 7.56 –7.40 (m, 2H) , 6.36 (s, 1H) , 6.08 (s, 1H) , 5.18 (t, J = 7.1 Hz, 1H) , 3.18 –2.94 (m, 2H) , 2.72 (dd, J = 13.7, 7.2 Hz, 1H) , 2.12 (dd, J = 13.7, 7.2 Hz, 1H) , 1.06 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, MeOD) : δ [ppm] = 179.93, 175.90, 171.03, 166.48, 135.23, 130.93, 130.82, 129.85, 129.45, 128.61, 87.45, 86.39, 85.49, 72.66, 65.87, 60.89, 43.14, 38.39, 37.44, 26.95; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{23}NO_8Na^+$ 452.13159, found 452.13155.

[0639] Synthesis of (3aS, 5aS, 8S, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-005)



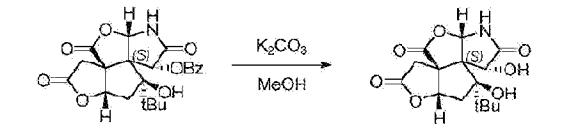
Chemical Formula: $C_{29}H_{26}O_{10}$
Molecular Weight: 534.52
XBB-003

Chemical Formula: $C_{22}H_{23}NO_8$
Molecular Weight: 429.43
XBB-005

[0640] To a solution of XBB-003 (50 mg, 93.6 μmol, 1.0 equiv) in anhydrous THF (2 mL) was added 25%ammonia solution (13 mg, 0.187 mmol, 2.0 equiv) at 0℃. The resulting solution was then allowed to be stirred for 30 min at room tempe rature. The reaction was monitored by TLC and upon completion the re action solution was diluted with ethyl acetate. The organic layer was washed with was hed with saturated $NaHCO_3$ solution, and the combined organic layers were dri ed over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified via column chromatography (hexane: EtOAc = 1: 1) to provide XBB-005 (72%yield, 29 mg) as a white powder. R_f = 0.35 (hexane: EtOAc, 1: 1) ; mp = 228.0-228.6℃; ^{1}H-NMR (400 MHz, MeOD) : δ [ppm] = 8.20 –8.06 (m, 2H) , 7.73 –7.64 (m, 1H) , 7.60 –7.50 (m, 2H) , 6.74 (s, 1H) , 5.76 (s, 1H) , 5.53 (t, J = 7.8 Hz, 1H) , 2.77 (d, J = 17.2 Hz, 1H) , 2.63 (dd, J = 15.3, 8.0 Hz, 1H) , 2.32 (d , J = 17.1 Hz, 1H) , 2.11 (dd, J = 15.3, 7.5 Hz, 1H) , 1.17 (s, 8H) ; ^{13}C {^{1}H} - NMR (100 MHz, MeOD) : δ [ppm] 182.53, 178.49, 173.63, 169.07, 137.82 , 133.51, 132.43, 132.05, 90.04, 88.98, 88.10, 75.25, 68.47, 63.48, 57.38, 45.73, 40. 99, 40.02, 29.52; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{23}NO_8Na^+$ 452.13159, found 452.13165.

[0641] <u>Example 1.3: Synthesis of bilobalide lactam analogues XBB-006 and XBB-007 according to Scheme 3</u>

[0642] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -8, 9-dihydroxytetrahydro-4H, 9Hfuro [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrole-2, 4, 7 (3H, 8H) -trione (XBB-006) is discussed herein.



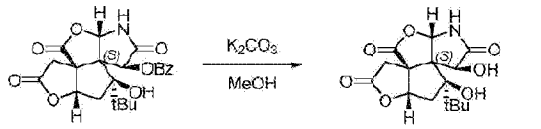
Chemical Formula: $C_{22}H_{23}NO_8$
Molecular Weight: 429.43
XBB-004

Chemical Formula: $C_{15}H_{15}NO_7$
Molecular Weight: 325.32
XBB-006

[0643] To a solution of XBB-004 (100 mg, 0.23 mmol, 1.0 equiv) in methanol was added potassium carbonate (64 mg, 0.46 mmol, 2.0 equiv) . The result ing mixture was allowed to be stirred at room temperature for 2 h. O nce the phenomenon of TLC plate indicated the completion of the reac

tion, the methanol was removed under reduced pressure. The residue w as then diluted with water and the pH value of the solution was adjusted to 7.0. The mixture was extracted with ethyl acetate and the organic layer was washed with brine. The combined organic layers were dried over anhydrous sodium sulfat e and concentrated under reduced pressure. The crude product was pur ified by column chromatography with elution system (hexane: EtOAc = 1: 1) to give XBB-006 (62 mg, 82%) as a white powder. R_f = 0.10 (hexane: EtOAc, 1: 1) ; mp = 128.4–128.9℃; ^{1}H-NMR (500 MHz, DMSO-d6) : δ [ppm] = 9 .19 (s, 1H) , 6.67 (d, J = 4.7 Hz, 1H) , 5.75 (s, 1H) , 5.18 (s, 1H) , 4.89 (t, J = 6 .9 Hz, 1H) , 4.65 (d, J = 4.7 Hz, 1H) , 2.84 (d, J = 17.9 Hz, 1H) , 2.70 (d, J = 18.0 Hz, 1H) , 2.56 –2.34 (m, 2H) , 2.09 (dd, J = 13.2, 6.8 Hz, 1H) , 1.01 (s, 9H) ; ^{13}C { ^{1}H} -NMR (125 MHz, DMSO-d6) : δ [ppm] = 178.44, 174.14, 173.59, 85.34, 84.4 3, 82.96, 69.00, 64.88, 58.96, 41.38, 36.98, 36.40, 26.64; HRMS (ESI) m/z: [M+Na] $^+$ Calcd for $C_{15}H_{19}NO_7Na^+$ 348.10537, found 348.10522.

[0644] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -8, 9-dihydroxytetrahydro-4H, 9Hfuro [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrole-2, 4, 7 (3H, 8H) -trione (XBB-007)



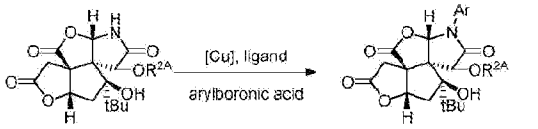
Chemical Formula: $C_{22}H_{23}NO_8$
Molecular Weight: 429.43
XBB-005

Chemical Formula: $C_{15}H_{19}NO_7$
Molecular Weight: 325.32
XBB-007

[0645] To a solution of XBB-005 (100 mg, 0.23 mmol, 1.0 equiv) in methanol was added potassium carbonate (64 mg, 0.46 mmol, 2.0 equiv) . The result ing mixture was allowed to be stirred at room temperature for 2 h. O nce the phenomenon of TLC plate indicated the completion of the reac tion, the methanol was removed under reduced pressure. The residue w as then diluted with water and the pH value of the solution was adjusted to 7.0. The mixture was extracted with ethyl acetate and the organic layer was washed with brine. The combined organic layers were dried with anhydrous sodium sulfat e and concentrate under reduced pressure. The crude product was puri fied by column chromatography with elution system (hexane: EtOAc = 1 : 1) to give XBB-007 (82%yield) as a white powder.

[0646] Example 1.4: Synthesis of N-arylated bilobalide lactam analogues according to S cheme 4

[0647] Chan-Evans-Lam coupling towards the synthesis of N-arylated bilobali de lactam analogues is discussed herein.



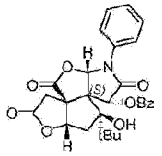
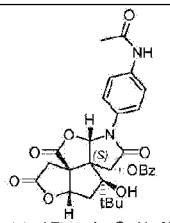
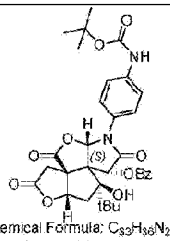
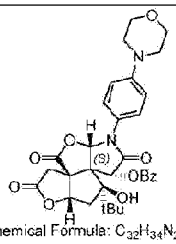
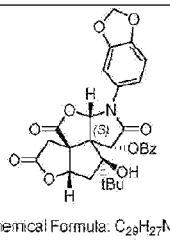
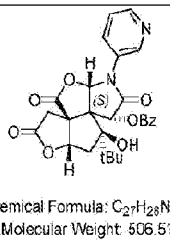
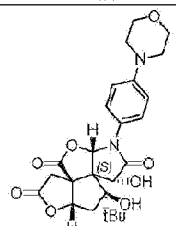
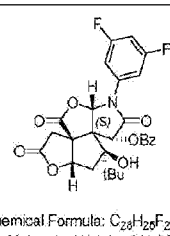
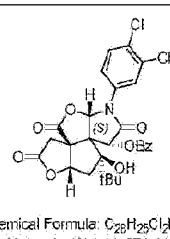
XBB-004
XBB-005
XBB-006
XBB-007

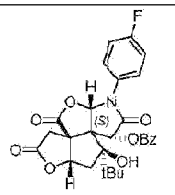
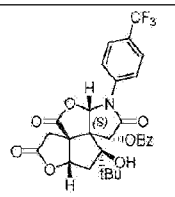
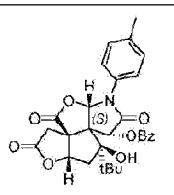
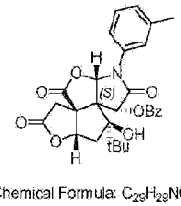
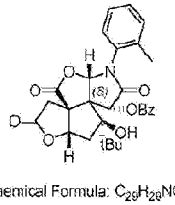
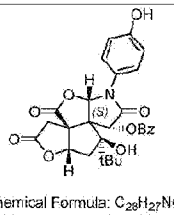
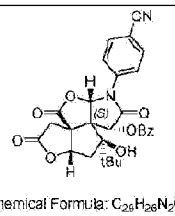
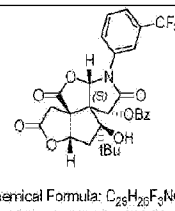
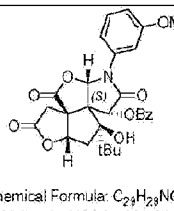
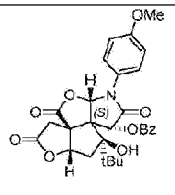
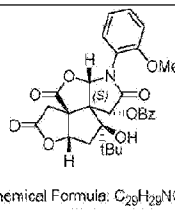
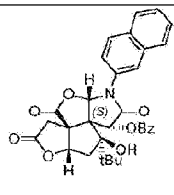
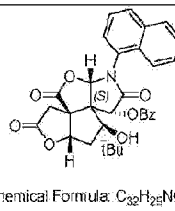
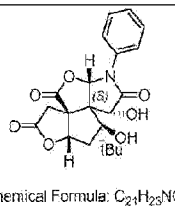
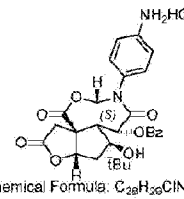
N-arylated products IIc

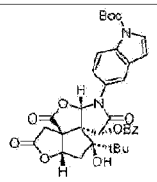
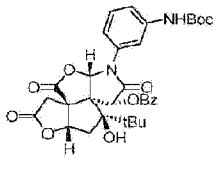
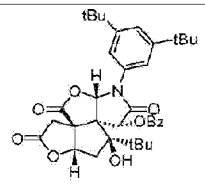
[0648] An oven-dried round-bottom flask was charged with XBB-004 (1.00 eq.) , arylboronic acid R^1-B (OH) $_2$ (1.5 eq.) , (CuOTf) $_2$-toluene (20 mol%) , ligand, and DMSO (0.1 M) . In some examples, 1, 10-phenanthroline (i n some embodiments, also referred to as '1, 10-phen') was used as the ligand. In some examples, no ligand is used. In some examples, XBB-004 was replaced with XBB-005, XBB-006, or XBB-007. The reaction mixture was stir red at room temperature under open air and monitored by TLC. Upon co mpletion of the reaction, the crude reaction mixture was diluted with ice cold water and extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product containing the N-arylated product IIc (i.e., N-arylated bilobali de lactam analogues) according to Table 1f was purified by column ch romatography to provide the desired product.

[0649] Examples of N-arylated bilobalide lactam analogues N-arylated products IIc are summarized in Table 1f.

[0650] Table 1f: Example N-arylated bilobalide lactam analogues

 Chemical Formula: $C_{28}H_{27}NO_8$ Molecular Weight: 505.52 **XBB-034**	 Chemical Formula: $C_{30}H_{30}N_2O_9$ Molecular Weight: 562.58 **XBB-035**	 Chemical Formula: $C_{33}H_{36}N_2O_{10}$ Molecular Weight: 620.66 **XBB-036**
 Chemical Formula: $C_{32}H_{34}N_2O_9$ Molecular Weight: 590.63 **XBB-038**	 Chemical Formula: $C_{29}H_{27}NO_{10}$ Molecular Weight: 549.53 **XBB-039**	 Chemical Formula: $C_{27}H_{28}N_2O_8$ Molecular Weight: 506.51 **XBB-040**
 Chemical Formula: $C_{29}H_{30}N_2O_8$ Molecular Weight: 486.52 **XBB-042**	 Chemical Formula: $C_{28}H_{25}F_2NO_8$ Molecular Weight: 541.50 **P-19**	 Chemical Formula: $C_{28}H_{25}Cl_2NO_8$ Molecular Weight: 574.41 **P-21**

 Chemical Formula: $C_{28}H_{28}FNO_8$ Molecular Weight: 523.51 **P-28**	 Chemical Formula: $C_{29}H_{28}F_3NO_8$ Molecular Weight: 573.52 **P-29**	 Chemical Formula: $C_{29}H_{29}NO_8$ Molecular Weight: 519.55 **P-30**
 Chemical Formula: $C_{29}H_{29}NO_8$ Molecular Weight: 519.55 **P-33**	 Chemical Formula: $C_{29}H_{29}NO_8$ Molecular Weight: 519.55 **P-34**	 Chemical Formula: $C_{28}H_{27}NO_9$ Molecular Weight: 521.52 **JW103**
 Chemical Formula: $C_{29}H_{26}N_2O_8$ Molecular Weight: 530.53 **JW107**	 Chemical Formula: $C_{29}H_{26}F_6NO_8$ Molecular Weight: 573.52 **JW100**	 Chemical Formula: $C_{29}H_{29}NO_9$ Molecular Weight: 535.55 **JW092**
 Chemical Formula: $C_{29}H_{29}NO_9$ Molecular Weight: 535.55 **JW093**	 Chemical Formula: $C_{29}H_{29}NO_9$ Molecular Weight: 535.55 **JW095**	 Chemical Formula: $C_{32}H_{29}NO_8$ Molecular Weight: 555.58 **JW094**
 Chemical Formula: $C_{32}H_{25}NO_8$ Molecular Weight: 555.58 **JW097**	 Chemical Formula: $C_{21}H_{23}NO_7$ Molecular Weight: 401.42 **JW116**	 Chemical Formula: $C_{28}H_{29}ClN_2O_8$ Molecular Weight: 557.00 **XBB-037**

		
SCC376	SCC385	SXQ094-1

[0651] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6-phenyloctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-034) . Using XBB-004 (100 mg, 0.23 mmol) , $(CuOTf)_2$-toluene (20 mol%, 46.6 μmol, 24.1 mg) , 1, 10-phenanthroline (40 mol%, 93.1 μmol , 16.8 mg) , and phenylboronic acid (1.5 equiv.) yielded XBB-034 as a white powder (94 mg, 81%) . R_f = 0.2 (hexane: EtOAc, 1: 1) ; mp = 125.7-126.4°C; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 8.07 –7.90 (m, 2H) , 7.71 –7.56 (m, 3H) , 7.56 –7.48 (m, 2H) , 7.47 –7.38 (m, 2H) , 7.34 –7.28 (m, 1H) , 6.47 (s, 1H) , 6.46 (s, 1H) , 5.22 (t, J = 7.1 Hz, 1H) , 3.30 (d, J = 18.8 Hz, 1H) , 2.95 (d, J = 18.9 Hz, 1H) , 2.68 (dd, J = 14.0, 7.2 Hz, 1H) , 2.28 (dd, J = 14.0, 7.1 Hz, 1H) , 1.13 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 177.75, 173.59, 166.34, 165.24, 135.32, 134.35, 133.85, 130.12, 129.46, 129.37, 128.83, 127.73, 127.32, 127.11, 121.82, 88.05, 87.46, 83.40, 70.99, 61.72, 59.36, 44.47, 42.76, 37.43, 36.27, 26.43.; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{27}NO_8Na^+$ 528.16289, found 528.16338.

[0652] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (4-acetamidophenyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-035) . Using XBB-004 (100 mg, 0.23 mmol) , $(CuOTf)_2$-toluene (20 mol%, 46.6 μmol, 24.1 mg) , 1, 10-phenanthroline (40 mol%, 93.1 μmol, 16.8 mg) , and 4-acetamidophenylboronic acid (1.5 equiv.) yielded XBB-035 as a white powder (92 mg, 71%) . R_f = 0.3 (hexane: EtOAc, 1: 1) ; mp = 185.7-186.2°C; ^{1}H-NMR (500 MHz, DMSO-d6) : δ [ppm] = 10.09 (s, 1H) , 8.02 –7.90 (m, 2H) , 7.78 –7.72 (m, 1H) , 7.72 –7.63 (m, 2H) , 7.60 –7.51 (m, 4H) , 6.49 (s, 1H) , 6.47 (s, 1H) , 5.12 (t, J = 7.1 Hz, 1H) , 3.28 (d, J = 19.2 Hz, 1H) , 2.98 (d, J = 19.2 Hz, 1H) , 2.73 (dd, J = 13.6, 7.2 Hz , 1H) , 2.11 –2.01 (m, 4H) , 1.07 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, DMSO-d6) : δ [ppm] = 177.87, 174.21, 168.90, 166.61, 164.96, 138.63, 134.93, 130.19, 129.95, 129.45, 128.24, 124.89, 119.70, 88.17, 86.66, 83.87, 71.78, 62.89, 59.31, 42.10, 40.85, 37.61, 36.11, 26.82, 24.45; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{30}N_2O_9Na^+$585.18435, found 585.18462.

[0653] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6- (4-pivalamidophenyl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-036) . Using XBB-004 (100 mg, 0.23 mmol) , $(CuOTf)_2$-toluene (20 mol%, 46.6 μmol, 24.1 mg) , 1, 10-phenanthroline (40 mol%, 93.1 μmol, 16.8 mg) , and a C- (1, 1-dimethylethyl) N- (4-boronophenyl) carbamate (2.0 eq, 0.46 mmol) yielded XBB-036 as a white powder (107 mg, 75%) . R_f = 0.4 (hexane: EtOAc, 4: 1) ; mp = 131.4-132.8℃; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 8.01 (d, J = 7.7 Hz, 2H) , 7.63 (t, J = 7.4 Hz, 1H) , 7.56 –7.46 (m, 4H) , 7.40 (d, J = 8.6 Hz, 2H) , 6.63 (s, 1H) , 6.46 (s, 1H) , 6.37 (s, 1H) , 5.21 (t, J = 7.0 Hz, 1H) , 3.29 (d, J = 18.8 Hz, 1H) , 2.95 (d, J = 18.8 Hz, 1H) , 2.66 (dd, J = 14.0, 7.1 Hz, 1H) , 2.27 (dd, J = 14.0, 7.1 Hz, 1H) , 1.52 (s, 9H) , 1.12 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 177.60, 173.48, 166.14, 165.24, 152.65, 137.31, 134.30, 130.14, 130.12, 128.80, 127.73, 122.96, 119.17, 88.24, 87.58, 83.27, 70.91, 61.74, 59.33, 42.97, 37.42, 36.31, 28.32, 26.43; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{33}H_{36}N_2O_{10}Na^+$ 643.22622, found 643.22659.

[0654] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6- (4-morpholinophenyl) -2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-038) . Using XBB-004 (100 mg, 0.23 mmol) , $(CuOTf)_2$-toluene (20 mol%, 46.6 μmol, 24.1 mg) , 1, 10-phenanthroline (40 mol%, 93.1 μmol, 16.8 mg) , and a C- (1, 1-dimethylethyl) N- (4-boronophenyl) carbamate (2.0 eq, 0.46 mmol) yielded XBB-038 as a white powder (124 mg, 91%) . R_f = 0.15 (hexane: EtOAc, 2: 1) ; mp = 160.8-161.2℃; ^{1}H-NMR (500 MHz, MeOD) : δ [ppm] 8.10 –7.95 (m, 2H) , 7.77 –7.64 (m, 1H) , 7.61 –7.49 (m, 2H) , 7.49 –7.36 (m, 2H) , 7.11 –6.90 (m, 2H) , 6.59 (s, 1H) , 6.42 (s, 1H) , 5.22 (t, J = 7.1 Hz, 1H) , 3.95 –3.69 (m, 4H) , 3.27 –3.07 (m, 6H) , 2.78 (dd, J = 13.7, 7.1 Hz, 1H) , 2.30 –2.12 (m, 1H) , 1.15 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, MeOD) : δ [ppm] 174.24, 170.85, 164.05, 161.99, 148.37, 132.32, 128.20, 127.17, 126.76, 125.41, 123.80, 114.86, 89.30, 87.06, 84.85, 72.62, 68.08, 64.56, 61.27, 51.26, 44.55, 40.14, 38.98, 29.17; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{32}H_{34}N_2O_9H^+$ 591.23371, found 591.23365.

[0655] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (benzo [d] [1, 3] dioxol-5-yl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-039) . Using XBB-004 (100 mg, 0.23 mmol) , $(CuOTf)_2$-toluene (20 mol%, 46.6 μmol, 24.1 mg) , 1, 10-phenanthroline (40 mol%, 93.1 μmol, 16.8 mg) , and a 3, 4-methylenedioxyphenylboronic acid (2.0 eq, 0.46 mmol) yielded XBB-

039 as a white powder (128 mg, 85%) . R_f = 0.2 (hexane: EtOAc, 2: 1) ; mp = 156.2-156.9°C; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.08 –7.90 (m, 2H) , 7.70 –7.59 (m, 1H) , 7.51 (t, J = 7.8 Hz, 2H) , 7.09 (d, J = 2.2 Hz, 1H) , 6.97 (dd, J = 8.4, 2.2 Hz, 1H) , 6.81 (d, J = 8.4 Hz, 1H) , 6.45 (s, 1H) , 6.31 (s, 1H) , 6.00 (s, 2H) , 5.21 (t, J = 7.1 Hz, 1H) , 3.28 (d, J = 18.9 Hz, 1H) , 2.96 (d, J = 18.9 H z, 1H) , 2.67 (dd, J = 14.0, 7.2 Hz, 1H) , 2.37 –2.17 (m, 1H) , 1.13 (s, 9H) ; ^{13}C {^{1} H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 177.84, 173.64, 166.38, 165.25, 148.2 3, 146.81, 134.35, 130.12, 128.83, 128.73, 127.74, 116.70, 108.39, 104.90, 101.84, 88 .62, 87.42, 83.41, 70.90, 61.96, 59.35, 42.76, 37.41, 36.26, 26.42; HRMS (ESI) m/z: [M+Na] $^+$ Calcd for $C_{29}H_{27}NO_{10}Na^+$572.15272, found 572.15255.

[0656] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo- 6- (pyridin-3-yl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] fur o [2, 3-b] pyrrol-8-yl benzoate (XBB-040) . Using XBB-004 (100 mg, 0.23 mmol) , $(CuOTf)_2$-toluene (20 mol%, 46.6 μmol, 24.1 mg) , 1, 10-phenanthroline (4 0 mol%, 93.1 μmol, 16.8 mg) , and pyridin-3-ylboronic acid (2.0 eq, 0.46 mmol) yielded XBB-040 as a white powder (92 mg, 78%) . R_f = 0.2 (hexane: E tOAc, 1: 1) ; mp = 269.4-270.1°C; ^{1}H-NMR (400 MHz, DMSO-d6) : δ [ppm] = 8 .90 (d, J = 2.6 Hz, 1H) , 8.53 (dd, J = 4.7, 1.5 Hz, 1H) , 8.10 (ddd, J = 8.4, 2.7, 1 .5 Hz, 1H) , 8.03 –7.84 (m, 2H) , 7.85 –7.64 (m, 1H) , 7.65 –7.44 (m, 3H) , 6.60 (s, 1H) , 6.53 (s, 1H) , 5.12 (t, J = 7.1 Hz, 1H) , 3.32 (d, J = 19.4 Hz, 1H) , 2.96 (d, J = 19.3 Hz, 1H) , 2.74 (dd, J = 13.6, 7.2 Hz, 1H) , 2.08 –1.95 (dd, J = 13.6, 7.2 Hz , 1H) , 1.07 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, DMSO-d6) : δ [ppm] = 1 77.72, 174.21, 167.00, 164.90, 148.00, 144.92, 134.96, 132.59, 131.06, 129.97, 129.45 , 128.17, 124.25, 87.56, 86.75, 83.87, 71.79, 62.90, 59.28, 42.08, 37.61, 36.13, 31.4 3, 31.12, 26.81, 22.54; HRMS (ESI) m/z: [M+Na] $^+$ Calcd for $C_{27}H_{26}N_2O_8H^+$ 507.17619, found 507.17663.

[0657] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -8, 9-dihydroxy- 6- (4-morpholinophenyl) tetrahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrole-2, 4, 7 (3H, 8H) -trione (XBB-042) . Using XBB- 006 (100 mg, 0.23 mmol) , $(CuOTf)_2$-toluene (20 mol%, 46.6 μmol, 24.1 mg) , 1, 10- phenanthroline (40 mol%, 93.1 μmol, 16.8 mg) , and 4- (morpholinopheny l) boronic acid (2.0 eq, 0.46 mmol) yielded XBB-042 as a white powder (66 mg, 80%) . R_f = 0.1 (hexane: EtOAc, 1: 2) ; mp = 175.6-176.1°C; ^{1}H-NMR (500 MHz, MeOD) : δ [ppm] = 7.45 –7.28 (m, 2H) , 7.09 –6.97 (m, 2H) , 6.21 (s, 1H) , 5.88 (s, 1H) , 5 .51 (s, 1H) , 5.09 (t, J = 7.0 Hz, 1H) , 5.07 (s, 1H) , 3.89 –3.80 (m, 4H) , 3.22 –3. 16 (m, 4H) , 3.14 (d, J = 18.0 Hz, 1H) , 2.81 (d, J = 17.9 Hz, 1H) , 2.66 (dd, J = 13 .5, 7.2 Hz, 1H) , 2.40 (dd, J = 13.5, 6.8 Hz, 1H) , 1.18 (s, 9H) ; ^{13}C {^{1}H} -

NMR (125 MHz, MeOD) : δ [ppm] = 179.97, 176.27, 174.29, 151.94, 128. 85, 126.19, 117.03, 90.22, 87.55, 85.26, 70.90, 67.87, 65.03, 60.87, 50.29, 43.03, 38 .58, 38.15, 27.36; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{30}N_2O_8Na^+$ 509.18944, found 509.18984.

[0658] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6- (3, 5-difluoro-phenyl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (P-19) . Using XBB-004 (50 mg, 0.12 mmol) , $(CuOTf)_2$-toluene (50 mol%, 0.06 mmol, 30.1 mg) , 1, 10-phenanthroline (5 0 mol%, 0.06 mmol, 10.5 mg) , and (2.0 eq, 0.46 mmol) yielded P-19 as a white pow der (26.7 mg, 42%) . ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 8.01 (d, J = 7.9 Hz, 2H) , 7.66 (t, J = 7.9 Hz, 1H) , 7.52 (t, J = 7.7 Hz, 2H) , 7.40 (d, J = 8.2 Hz, 2H) , 6.74 (t, J = 8.4 Hz, 1H) , 6.44 (s, 1H) , 6.41 (s, 1H) , 5.25 (t, J = 7.2 Hz, 1H) , 3.24 (d, J = 18.9 Hz, 1H) , 2.96 (d, J = 18.9 Hz, 1H) , 2.69 (dd, J = 7.3, 14.2 Hz, 1H) , 2.32 (dd, J = 7.0, 14.2 Hz, 1H) , 2.21 (s, 1H) , 1.15 (s, 9H) .

[0659] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6- (3, 4-dichloro-phenyl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (P-21) . Using XBB-004 (150 mg, 0.35 mmol) , $(CuOTf)_2$-toluene (20 mol%, 0.07 mmol, 36.1 mg) , 1, 10-phenanthroline (2 0 mol%, 0.07 mmol, 12.6 mg) , and (2.0 eq, 0.46 mmol) yielded P-21 as a white pow der (57.9 mg, 29%) . ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 8.01 (d, J = 7.9 Hz, 2H) , 7.90 (s, 1H) , 7.56-7.66 (m, 2H) , 7.45-7.55 (m, 3H) , 6.45 (s, 1H) , 6.40 (s, 1H) , 5.24 (t, J = 6.8 Hz, 1H) , 3.24 (d, J = 19.1 Hz, 1H) , 2.96 (d, J = 18.9 H z, 1H) , 2.68 (dd, J = 7.3, 13.7 Hz, 1H) , 2.31 (dd, J = 6.9, 13.7 Hz, 1H) , 2.28 (s, 1H) , 1.15 (s, 9H) .

[0660] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6- (4-fluorophenyl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (P-28) . Using XBB-004 (42.9 mg, 0.10 mmol) , $(CuOTf)_2$-toluene (20 mol%, 0.02 mmol, 10.3 mg) , 1, 10-phenanthroline (20 mol%, 0.02 mmol , 3.6 mg) , and (4-fluorophenyl) boronic acid (2.0 eq, 0.20 mmol) yielded P-28 as a white powder (48.9 mg, 38%) .

[0661] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6- (4- (trifluoromethyl) phenyl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3- b] pyrrol-8-yl benzoate (P-29) . Using XBB-004 (42.9 mg, 0.1 0 mmol) , $(CuOTf)_2$-toluene (20 mol%, 0.02 mmol, 10.3 mg) , and (4- (trifluoromethyl) phenyl) boronic acid (2.0 eq, 0.20 mmol) yielded P-29 as a white powder.

[0662] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6- (toluyl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-

b] pyrrol-8-yl benzoate (P-30) . Using XBB-004 (150.0 mg, 0.35 mmol) , (CuOTf) $_2$-toluene (20 mol%, 0.07 mmol, 36.1 mg) , and toluylboronic acid (2.0 eq, 0.70 mmol) yielded P-30 as a white powder (139.2 mg, 77%) .

[0663] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6- (3-methyl phenyl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (P-33) . Using XBB-004 (150.0 mg, 0. 35 mmol) , (CuOTf) 2-toluene (20 mol%, 0.07 mmol, 36.1 mg) , and toluylb oronic acid (2.0 eq, 0.70 mmol) yielded P-33 as a white powder (144.5 mg, 80%) .

[0664] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6- (2-methyl phenyl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (P-34) . Using XBB-004 (150.0 mg, 0. 35 mmol) , (CuOTf) $_2$-toluene (20 mol%, 0.07 mmol, 36.1 mg) , and (2-methyl phenyl) boronic acid (2.0 eq, 0.70 mmol) yielded P-34 as a white pow der (71.2 mg, 40%) .

[0665] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -6- (4-hydroxyphenyl) -9-hydroxy-2, 4, 7-trioxodecahydrofuro [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (JW103) . Using XBB-004 (153 mg, 0.35 mmol) , (CuOTf) $_2$-toluene (20 mol%, 0.07 mmol, 36.2 mg) , and 4-hydroxyphenyl phenylboronic acid (2.0 eq, 0.70 mmol) yielded JW103 as a white powder (0.16 g, 88%) .

[0666] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -6- (4-cyanophenyl) -9-hydroxy-2, 4, 7-trioxodecahydrofuro [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (JW107) . Using XBB-004 (153 mg, 0.35 mmol) , (CuOTf) $_2$-toluene (20 mol%, 0.07 mmol, 36.2 mg) , and 4-hydroxyphenyl phenylboronic acid (2.0 eq, 0.70 mmol) yielded JW107 as a white powder (0.12 g, 63%) . R $_f$ = 0.20 (hexane: EtOAc: DCM, 3: 1: 1) ; ^{1}H-NMR (400 MHz, DMSO-d6) : δ [ppm] = 7.96-8.03 (m, 2H) , 7.89-7.95 (m, 2H) , 7.77-7.84 (m, 2H) , 7.68-7.75 (m, 1H) , 7.50-7.57 (m, 2H) , 6.58 (s, 1H) , 6.50 (s, 1H) , 5.16 (t, J = 7.13 Hz, 1 H) , 3.68 (br. s, 1H) , 3.06 (d, J = 19 Hz, 1H) , 3.00 (d, J = 19 Hz, 1H) , 2.76 (dd, J = 1 4.0, 7.2 Hz, 1H) , 2.21 (dd, J = 14.0, 7.2 Hz, 1H) , 1.10 (s, 9H) .

[0667] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6- (3- (trifluoromethyl) phenyl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (JW100) . Using XBB-004 (153 mg, 0.35 mmol) , (CuOTf) $_2$-toluene (20 mol%, 0.07 mmol, 36.2 mg) , and (3- (trifluoromethyl) phenyl) boronic acid (2.0 eq, 0.70 mmol) yielded JW100 as a white powder (0.20 g, 6 9%) . R_f = 0.29 (hexane: EtOAc: DCM, 3: 1: 1) ; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 7.99-8.06 (m, 3H) , 7.88-7.94 (m, 1H) , 7.62-7.68 (m, 1H) , 7.49-7.59 (m, 4H) , 6.49 (s, 1H) , 6.48 (s, 1H) , 5.25 (t, J = 7.1 Hz, 1H) , 3.29 (d, J =

18.9 Hz, 1H) , 2.97 (d, J = 18.9 Hz, 1H) , 2.69 (dd, J = 14.2, 7.2 Hz, 1H) , 2.33 (dd , J = 14.2, 7.2 Hz, 1H) , 2.27 (s, 1H) , 1.16 (s, 9H) .

[0668] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6- (3-methoxyphenyl) -2, 4, 7-trioxodecahydrofuro [3", 2": 2', 3'] cyclopenta [1' , 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (JW092) . Using XBB-004 (150.3 mg, 0. 35 mmol) , $(CuOTf)_2$-toluene (20 mol%, 0.07 mmol, 36.2 mg) , 1, 10-phenanthroline (20 mol%, 0.07 mmol, 12.6 mg) and (3-methoxyphenyl) bo ronic acid (2.0 eq, 0.70 mmol) yielding in JW092 as a white powder (47.4 mg, 25%) . R_f = 0.26 (hexane: EtOAc: DCM, 3: 1: 1) ; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 8.00-8.05 (m, 2H) , 7.61-7.67 (m, 1H) , 7.48-7.54 (m, 2H) , 7.28-7.37 (m, 2H) , 7.14-7.21 (m, 1H) , 6.83 (dd, J = 8.2, 1.7 Hz, 1H) , 6.45 (s, 1H) , 6.44 (s, 1H) , 5.22 (t, J = 7.11 Hz, 1H) , 3.81 (s, 3H) , 3.29 (d, J = 18.8 Hz, 1H) , 2.95 (d, J = 18.8 Hz, 1H) , 2.67 (dd, J = 14.1, 7.2 Hz, 1H) , 2.47 (s, 1H) , 2.28 (dd, J = 14.1, 7.2 Hz, 1H) , 1.13 (s, 9H) .

[0669] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6- (4-methoxyphenyl) -2, 4, 7-trioxodecahydrofuro [3", 2": 2', 3'] cyclopenta [1' , 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (JW093) . Using XBB-004 (153 mg, 0.35 mmol) , $(CuOTf)_2$-toluene (20 mol%, 0.07 mmol, 36.2 mg) , 1, 10-phenanthroline (2 0 mol%, 0.02 mmol, 3.6 mg) , and (4-methoxyphenyl) boronic acid (2.0 e q, 0.70 mmol) (1.5 equiv.) yielded JW093 as a white powder (0.13 g, 68%) . R_f = 0.23 (hexane: EtOAc: DCM, 3: 1: 1) ; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 7.9 9-8.04 (m, 2H) , 7.60-7.66 (m, 1H) , 7.44-7.55 (m, 4H) , 6.90-6.96 (m, 2H) , 6. 47 (s, 1H) , 6.34 (s, 1H) , 5.23 (t, J = 7.1 Hz, 1H) , 3.81 (s, 3H) , 3.31 (d, J = 18 .9 Hz, 1H) , 2.97 (d, J = 18.9 Hz, 1H) , 2.66 (dd, J = 14.1, 7.3 Hz, 1H) , 2.29 (dd, J = 14.1, 7.3 Hz, 1H) , 2.27 (s, 1H) , 1.14 (s, 9H) .

[0670] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6- (2-methoxyphenyl) -2, 4, 7-trioxodecahydrofuro [3", 2": 2', 3'] cyclopenta [1' , 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (JW095) . Using XBB-004 (153 mg, 0.35 mmol) , $(CuOTf)_2$-toluene (20 mol%, 0.07 mmol, 36.2 mg) , 1, 10-phenanthroline (2 0 mol%, 0.02 mmol, 3.6 mg) , and (2-methoxyphenyl) boronic acid (2.0 e q, 0.70 mmol) (1.5 equiv.) yielded JW095 as a white powder (24.4 mg, 13%) . ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.01 (d, J = 7.8 Hz, 2H) , 7.62 (t, J = 7.5 Hz, 1H) , 7.50 (t, J = 8.1 Hz, 2H) , 7.38 (t, J = 7.6 Hz, 1H) , 7.19 (d, J = 8 .0 Hz, 1H) , 6.96-7.04 (m, 2H) , 6.54 (s, 1H) , 6.31 (s, 1H) , 5.23 (t, J = 7.2 Hz, 1H) , 3.83 (s, 3H) , 3.43 (d, J = 18.8 Hz, 1H) , 3.02 (d, J = 18.9 Hz, 1H) , 2.64 (dd, J = 14.2, 7.5 Hz, 1H) , 2.29 (dd, J = 13.9, 7.0 Hz, 1H) , 2.00 (s, 1H) , 1.17 (s, 9H) .

[0671] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6- (naphthalen-2-yl) -2, 4, 7-trioxodecahydrofuro [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (JW094) . Using XBB-004 (153 mg, 0.35 mmol) , $(CuOTf)_2$-toluene (20 mol%, 0.07 mmol, 36.2 mg) , 1, 10-phenanthroline (20 mol %, 0.02 mmol, 3.6 mg) , and (naphthalen-2-yl) boronic acid (2.0 eq, 0.70 mmo l) (1.5 equiv.) yielded JW094 as a white powder (0.14 g, 74%) . R_f = 0.23 (hexane: EtOAc: DCM, 3: 1: 1) ; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.11 (d, J = 1.9 Hz, 1H) , 8.00-8.07 (m, 2H) , 7.86 (d, J = 9.1 Hz, 1H) , 7.78-7.84 (m, 2H) , 7. 76 (dd, J = 9.0, 2.1 Hz, 1H) , 7.61-7.68 (m, 1H) , 7.46-7.55 (m, 4H) , 6. 56 (s, 1H) , 6.52 (s1H) , 5.23 (t, J = 7.1 Hz, 1H) , 3.35 (d, J = 19.0 Hz, 1H) , 2.99 (d, J = 19.0 Hz, 1H) , 2.66 (dd, J = 14.1, 7.2 Hz, 1H) , 2.56 (s, 1H) , 2.29 (dd, J = 14.1, 7.2 Hz, 1H) , 1.12 (s, 9H) .

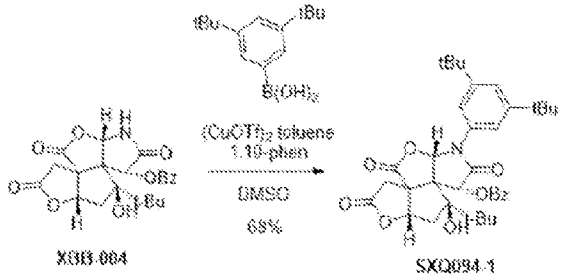
[0672] Synthesis of (3aS, 5aS, 8R, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6- (naphthalen-1-yl) -2, 4, 7-trioxodecahydrofuro [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (JW097) . Using XBB-004 (153 mg, 0.35 mmol) , $(CuOTf)_2$-toluene (20 mol%, 0.07 mmol, 36.2 mg) , 1, 10-phenanthroline (20 mol%, 0.02 mmol , 3.6 mg) , and (naphthalen-1-yl) boronic acid (2.0 eq, 0.70 mmol) (1.5 equiv.) yielded JW097 as a white powder (53.1 mg, 27%) .

[0673] Synthesis of tert-butyl 5- ((3aS, 5aS, 8R, 8aS, 9R, 10aS) -8- (benzoyloxy) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxohexahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) -1H-indole-1-carboxylate (SCC3 76) . Using XBB-004 (1.00 equiv., 0.16 mmol, 66.8 mg) , $(CuOTf)_2$-toluene (15 mol %, 23.3 μmol, 12.1 mg) , and (1- (tert-butoxycarbonyl) -1H-indol-5-yl) boronic acid (1.7 equiv., 0.26 mmol, 69.0 mg) yielded SCC376 as a white powder (6 0.3 mg, 60%) . R_f = 0.31 (hexane: EtOAc, 2: 1) ; ^{1}H-NMR (600 MHz, CDC l_3) : δ [ppm] = 8.16 (brs, 1H) , 8.02 (d, J = 7.6 Hz, 2H) , 7.75 (s, 1H) , 7.65-7.60 (m, 2H) , 7.50 (t, J = 7.1 Hz, 2H) , 7.44 (d, J = 8.9 Hz, 1H) , 6.54 (d, J = 3.5 Hz, 1H, 6.50 (s, 1H) , 6.42 (s, 1H) , 5.20 (t, J = 7.1 Hz, 1H) , 3.34 (d, J = 18.5 Hz, 1H) , 2.99 (d, J = 18.5 Hz, 1H) , 2.65 (dd, J = 7.1, 14.1 Hz, 1H) , 2.51 (s, 1H) , 2.27 (dd, J = 7.3, 14.1 Hz, 1H) , 1.67 (s, 9H) , 1.12 (s, 9H) .

[0674] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (3- ((tert-butoxycarbonyl) a mino) phenyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (SCC3 85) . Using XBB-004 (1.00 equiv., 89.9 μmol, 38.6 mg) , $(CuOTf)_2$-toluene (15 mol %, 13.5 μmol, 7.0 mg) , and (1- (tert-butoxycarbonyl) -1H-indol-5-yl) boronic acid (2.0 equiv., 0.18 mmol, 42.6 mg) yielded SCC385 as a white powder (3 2.1 mg, 57%) . R_f = 0.51 (hexane: EtOAc, 1: 1) ; ^{1}H-NMR (600 MHz, $CDCl_3$

) : δ [ppm] = 8.00 (d, J = 8.4 Hz, 1H) , 7.66-7.61 (m, 2H) , 7.50 (t, J = 8.1 Hz , 2H) , 7.37 (brs, 1H) , 7.33-7.27 (m, 2H) , 6.75 (s, 1H) , 6.44 (s, 1H) , 6.43 (s, 1H) , 5.20 (t, J = 7.1 Hz, 1H) , 3.27 (d, J = 18.7 Hz, 1H) , 2.94 (d, J = 19.0 Hz, 1H) , 2.71 (brs, 1H) , 2.66 (dd, J = 7.3, 14.2 Hz, 1H) , 2.24 (dd, J = 7.0, 13.8 Hz, 1H) , 1.48 (s, 9H) , 1.10 (s, 9H) .

[0675] Synthesis of SXQ094-1



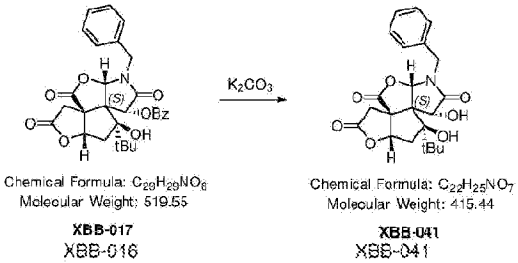
[0676] To an oven-dried flask containing a magnetic stir bar was added XBB-004 (20 mg, 0.0465 mmol, 1.0 equiv.) and 0.5 mL of DMSO, followed b y the addition of 1, 10-phen (4 mg, 0.0232 mmol, 0.5 equiv.) , $(CuOTf)_2$. toluene (12 mg, 0.0232 mmol, 0.5 equiv.) and (3, 5-Di-tert-butylphenyl) boro nic acid (22 mg, 0.093 mmol, 2 equiv.) . The resulting solution was allowed to be st irred at room temperature for 24 h. Once completion indicated by TLC, the resulting s olution was diluted with ethyl acetate and was quenched by the addition of saturated aqueous NH_4Cl (6 mL) . This mixture was extracted with EtOAc (3 × 10 mL) , the organic layers were combined, washed with saturated aqueous NaCl, an d dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo and this c rude product was purified by column chromatography (Hexane: EtOAc =2: 1, v/ v) to give SXQ094-1 (18 mg, 68%) as yellow powder. TLC: Rf = 0.5 (Hex ane/EtOAc = 2/1; strongly UV active, stains yellow upon $KMnO_4$ staining) . ^1H NMR (700 MHz, $CDCl_3$) δ 8.04 –8.01 (m, 2H) , 7.64 (t, J = 7.7 Hz, 1H) , 7.51 (t, J = 7.7 Hz, 2H) , 7.45 (d, J = 1.7 Hz, 2H) , 7.36 (d, J = 1.7 Hz, 1H) , 6.4 7 (m, 2H) , 5.23 (m, 1H) , 3.33 (d, J = 18.9 Hz, 1H) , 2.96 (d, J = 18.9 Hz, 1H) , 2. 69 (dd, J = 14.0, 7.2 Hz, 1H) , 2.48 (s, 1H) , 2.29 (dd, J = 14.0, 7.2 Hz, 1H) , 1.33 (s, 18H) , 1.15 (s, 9H) . ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 173.6, 166.4, 165.4, 15 2.3, 135.0, 134.4, 130.3, 128.9, 127.8, 121.4, 116.2, 88.4, 87.8, 83.3, 71.1, 61.8, 5 9.5, 43.1, 37.6, 36.4, 35.2, 35.2, 31.5, 26.6.

[0677] Example 1.5a: Further modification of bilobalide analogues via deben zylation according to Scheme 3

[0678] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -8, 9-dihydroxy-6-phenyltetrahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-

b] pyrrole-2, 4, 7 (3H, 8H) -trione (JW116) . Using XBB-034, K_2CO_3 yielding in JW11 6 as a white powder. ^{1}H-NMR (500 MHz, MeOD) : δ [ppm] = 7.57 (d, J = 7.6 Hz , 2H) , 7.45 (t, J = 8.1 Hz, 2H) , 7.32 (t, J = 7.6 Hz, 1H) , 6.32 (s, 1H) , 5.08 (t, J = 7.1 Hz, 1H) , 5.07 (s, 1H) , 3.13 (d, J = 18.3 Hz, 1H) , 2.80 (d, J = 17.8 Hz, 1 H) , 2.66 (dd, J = 7.1, 13.4 Hz, 1H) , 2.39 (dd, J = 7.1, 13.5 Hz, 1H) , 1.17 (s, 9H) .

[0679] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6-benzyl-9- (tert-butyl) -8, 9-dihydroxytetrahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrole-2, 4, 7 (3H, 8H) -trione (XBB-041)



Chemical Formula: $C_{29}H_{29}NO_8$
Molecular Weight: 519.55
XBB-017
XBB-016

Chemical Formula: $C_{22}H_{25}NO_7$
Molecular Weight: 415.44
XBB-041
XBB-041

[0680] To a solution of N-phenyl analogue XBB-016 (50 mg, 1 eq., 98.9 μmol) in m ethanol (10 mL) was added potassium carbonate (2.0 equiv, 27.3 mg, 0 .20 mmol) . The resulting solution was allowed to be stirred at room temperature for 4 h. Once the starting material was fully consumed, the reaction solution was concent rated under reduced pressure and then the residue was resuspended wi th water. The pH value of the resuspension was adjusted to 7.0 using 3 N HCl aqueous solution. The mixture was extracted with ethyl acetate and washed wi th brine. The combined organic layers were dried over anhydrous sodium s ulfate and concentrated under reduced pressure. The crude product was purified by col umn chromatography with elution system (hexane: ethyl acetate =1: 2) to give XBB-041 as white powder. R_f = 0.15 (hexane: EtOAc, 1: 2) ; mp = 191.2-191.8°C; ^{1}H-NMR (500 MHz, MeOD) : δ [ppm] = 7.39 –7.34 (m, 2H) , 7.33 –7.28 (m, 3H) , 5.59 (s, 1H) , 5.02 (t, J = 6.9 Hz, 1H) , 4.94 –4.87 (m, 2H) , 4.21 (d, J = 14. 7 Hz, 1H) , 2.99 (dd, J = 17.9, 1.3 Hz, 1H) , 2.65 (dd, J = 18.0, 1.4 Hz, 1H) , 2.58 (dd, J = 13.5, 7.2 Hz, 1H) , 2.29 (dd, J = 13.5, 6.8 Hz, 1H) , 0.99 (s, 9H) ; ^{13}C {^{1} H} -NMR (125 MHz, MeOD) : δ [ppm] = 180.17, 176.43, 174.65, 136.72, 130. 10, 129.67, 129.34, 88.52, 87.43, 85.41, 71.07, 65.32, 61.01, 45.38, 43.15, 38.48, 38 .37, 27.3.

[0681] Example 1.5b: Further modification of bilobalide analogues via Boc d eprotection according to Scheme 12

[0682] According to the method described in Scheme 12, MeOH (20 mL/mmol) wa s cooled to 0°C and acetyl chloride (10-15 eq.) was added. After 5 min Bo

c protected amine (1.00 eq) was added. The reaction is stirred at room temperature un til complete conversion. The volatiles are removed, and the product can be crystalliz ed as HCl salt.

[0683] Synthesis of 4- (((3aS, 5aS, 8R, 8aS, 9R, 10aS) -8- (benzoyloxy) -9- (tert-butyl) -9 -hydroxy-2, 4, 7 -trioxohexahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) methyl) piperidin-1-ium chloride (XBB -021) . Using XBB-020 (0.68 g, 1.07 mmol, 1.00 eq.) yielding in XBB-021 as a white powder (0.59 g, 84%) . R_f = 0.2 (DCM/MeOH, 10: 1) ; mp = 74.6-75.1℃; ^{1}H-NMR (400 MHz, MeOD) : δ [ppm] = 8.05 –7.92 (m, 2H) , 7.79 –7.65 (m, 1H) , 7.53 (t, J = 7.8 Hz, 2H) , 6.43 (s, 1H) , 6.11 (s, 1H) , 5.20 (t, J = 7.1 Hz, 1 H) , 3.54 –3.35 (m, 4H) , 3.15 –2.94 (m, 4H) , 2.77 (dd, J = 13.8, 7.2 Hz, 1H) , 2.16 (dd, J = 13.6, 7.2 Hz, 2H) , 1.97 –1.81 (m, 2H) , 1.60 –1.36 (m, 2H) , 1.10 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, MeOD) : δ [ppm] = 178.05, 174.33, 168.28, 165.13, 133. 96, 129.63, 128.54, 128.05, 88.58, 86.18, 84.09, 71.01, 63.02, 59.22, 46.75, 44.86, 4 4.82, 41.80, 37.07, 34.09, 29.97, 29.87, 25.64; HRMS (ESI) m/z: [M+Na] $^+$ Calcd for $C_{28}H_{34}N_2O_8H^+$ 527.23879, found 527.23860.

[0684] Synthesis of 4- (((3aS, 5aS, 8S, 8aS, 9R, 10aS) -8- (benzoyloxy) -9- (tert-butyl) -9 -hydroxy-2, 4, 7 -trioxohexahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) methyl) piperidin-1-ium chloride (XBB-022) . R_f = 0.15 (DCM/MeOH, 10: 1) ; mp = 78.4-79.2℃; ^{1}H-NMR (400 MHz, MeO D) : δ [ppm] = 8.03 –7.95 (m, 2H) , 7.70 (t, J = 7.5 Hz, 1H) , 7.53 (t, J = 7.7 Hz, 2H) , 6.43 (s, 1H) , 6.12 (s, 1H) , 5.22 (t, J = 7.1 Hz, 1H) , 3.54 –3.27 (m, 4H) , 3.16 – 2.93 (m, 4H) , 2.84 –2.69 (m, 1H) , 2.26 –2.09 (m, 2H) , 1.95 –1.82 (m, 2H) , 1.64 –1.41 (m, 2H) , 1.09 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 178 .14, 174.47, 168.59, 165.21, 134.14, 129.63, 128.64, 127.94, 88.75, 86.32, 84.16, 71. 09, 63.12, 59.33, 43.29, 41.79, 37.09, 36.12, 32.24, 26.52, 26.41, 25.72; HRMS (ESI) m/z: [M+Na] $^+$Calcd for $C_{28}H_{34}N_2O_8H^+$ 527.23879, found 527.23859.

[0685] Synthesis of 4- (2- ((3aS, 5aS, 8S, 8aS, 9R, 10aS) -8- (benzoyloxy) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxohexahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) ethyl) piperidin-1-ium chloride (XBB-024) . R_f = 0.15 (DCM/MeOH, 20: 1) ; mp = 220.3-221.2℃; ^{1}H-NMR (400 MHz, DMSO-d6) : δ [ppm] = 9.08 (s, 1H) , 7.95 –7.81 (m, 2H) , 7.78 –7.67 (m, 1H) , 7.54 (t, J = 7.7 Hz, 2H) , 6.23 (s, 1H) , 6.04 (s, 1H) , 5.69 (s, 1H) , 5.09 (t, J = 7.0 Hz, 1H) , 3.34 –3.05 (m, 5H) , 2.87 –2.62 (m, 4H) , 1.96 (d d, J = 13.6, 7.1 Hz, 1H) , 1.80 (t, J = 15.5 Hz, 2H) , 1.61 –1.28 (m, 5H) , 0.99 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, DMSO-d6) : δ [ppm] = 178.12, 174.16, 16 7.38, 165.03, 134.90, 129.90, 129.42, 128.23, 88.42, 86.30, 83.89, 71.55, 63.17, 59.3

5, 43.33, 42.07, 37.49, 36.20, 33.47, 31.33, 31.17, 28.41, 26.81.; HRMS (ESI) m/z: [M +H] $^{+}$ Calcd for $C_{29}H_{36}N_2O_8H^{+}$ 541.25444, found 541.25399.

[0686] Synthesis of 4- (3- ((3aS, 5aS, 8S, 8aS, 9R, 10aS) -8- (benzoyloxy) -9- (tert-butyl) -9 -hydroxy-2, 4, 7 -trioxohexahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) propyl) piperidin-1-ium chloride (XBB-0026) . R_f = 0.15 (DCM/MeOH, 20: 1) ; mp = 146.8-147.2℃; ^{1}H-NMR (400 MHz, MeOD) : δ [ppm] = 8.11 (s, 1H) , 8.05 –7.92 (m, 2H) , 7.76 –7.61 (m, 1H) , 7.53 (t, J = 7.8 Hz, 2H) , 7.25 (s, 1H) , 6.39 (s, 1H) , 6.11 (s , 1H) , 5.21 (t, J = 7.1 Hz, 1H) , 3.84 –3.57 (m, 1H) , 3.54 –3.44 (m, 1H) , 3.43 –3. 35 (m, 3H) , 3.11 –2.90 (m, 4H) , 2.84 –2.69 (m, 1H) , 2.22 –2.08 (m, 1H) , 1.99 – 1.86 (m, 2H) , 1.81 –1.5 6 (m, 3H) , 1.50 –1.24 (m, 3H) , 1.09 (s, 9H) ; ^{13}C {^{1} H} -NMR (100 MHz, MeOD) : δ [ppm] = 178.17, 174.38, 168.04, 165.17, 134. 63, 134.03, 129.61, 128.58, 128.02, 120.56, 88.35, 86.23, 84.13, 71.15, 63.15, 59.35, 43.87, 41.79, 41.16, 37.07, 36.13, 32.93, 32.75, 28.54, 25.67, 24.06; HRMS (ESI) m/z : [M+H] $^{+}$ Calcd for $C_{30}H_{38}N_2O_8H^{+}$ 555.27009, found 555.26993.

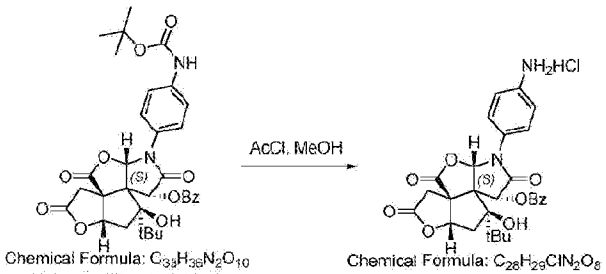
[0687] Synthesis of 4- (2- ((3aS, 5aS, 8S, 8aS, 9R, 10aS) -8- (benzoyloxy) -9- (tert-butyl) -9 -hydroxy-2, 4, 7 -trioxohexahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) ethyl) piperazin-1-ium chloride (XBB-028) . R_f = 0.20 (DCM/MeOH, 20: 1) ; mp = 136.5-137.2℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.05 –7.83 (m, 2H) , 7.68 –7.54 (m, 1H) , 7 .48 (t, J = 7.7 Hz, 2H) , 7.03 (s, 1H) , 6.35 (s, 1H) , 6.19 (s, 1H) , 5.20 (t, J = 7 .1 Hz, 1H) , 3.82 –3.65 (m, 1H) , 3.44 (s, 1H) , 3.40 –3.28 (m, 1H) , 3.14 (d, J = 19 .0 Hz, 1H) , 2.98 –2.78 (m, 5H) , 2.72 –2.38 (m, 7H) , 2.17 (dd, J = 13.8, 7.1 Hz, 1H) , 1.09 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 178.53, 173.97, 167. 34, 165.35, 134.21, 130.07, 128.77, 127.90, 88.56, 86.74, 83.76, 71.01, 62.79, 59.37, 55.65, 53.43, 42.47, 37.42, 36.95, 36.54, 26.65; HRMS (ESI) m/z: [M+H] $^{+}$ Calcd for $C_{28}H_{35}N_3O_8H^{+}$ 542.24969, found 542.24990.

[0688] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6- (((S) -pyrrolidin-3-yl) methyl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate hydrochloride (XBB-032) . R_f = 0.20 (DCM/MeOH, 20: 1) ; mp = 106.2-106.8℃; ^{1}H-NMR (400 MHz, MeO D) : δ [ppm] = 7.88 (d, J = 7.8 Hz, 3H) , 7.58 (t, J = 7.4 Hz, 1H) , 7.48 –7.20 (m, 2 H) , 6.31 (s, 1H) , 6.02 (s, 1H) , 5.09 (t, J = 7.0 Hz, 1H) , 3.64 (t, J = 5.5 Hz, 1H) , 3.51 –3.36 (m, 3H) , 3.36 –3.11 (m, 3H) , 3.07 –2.84 (m, 3H) , 2.79 – 2.52 (m, 2H) , 2.23 –1.87 (m, 3H) , 0.98 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, MeO D) : δ [ppm] = 177.98, 174.33, 168.57, 165.20, 134.21, 129.70, 128.72, 127.96, 88.82, 86.40, 84.10, 72.22, 71.17, 71.09, 66.82, 63.17, 60.87, 59.35, 48.76, 45.14, 44.01,

42.68, 41.83, 37.33, 37.11, 36.17, 28.30, 25.85; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{32}N_2O_8H^+$ 513.22314, found 513.22286.

[0689] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (((1S, 3S) -adamantan-2-yl) methyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl 4- (aminomethyl) benzoate hydrochloride (SCC506) . From SCC505 (90.1 μmol, 63.7 mg) in 3M HCl in MeOH yielded SCC506 (100%) . ^{1}H-NMR (600 MHz, MeOD-d4) : δ [ppm] = 8.05 (d, J = 8.4 Hz, 1H) , 7.61 (d, J = 8.2 Hz, 2H) , 6.42 (s, 1H) , 6.13 (s, 1H) , 5.17 (t, J = 6.9 Hz, 1H) , 4.22 (s, 2H) , 3.39 (d, J = 14.9 Hz, 1H) , 3.00 (d, J = 19.0 Hz, 1H) , 2.95 (d, J = 19.0 Hz, 1H) , 2.86 (d, J = 14.5 Hz, 1H) , 2.75 (dd, J = 7.1, 13.6 Hz, 1H) , 2.10 (dd, J = 7.0, 13.3 Hz, 1H) , 2.01 (brs, 3H) , 1.79 (m, 3H) , 1.69 (m, 3H) , 1.62 (m, 6H) , 1.11 (s, 9H) .

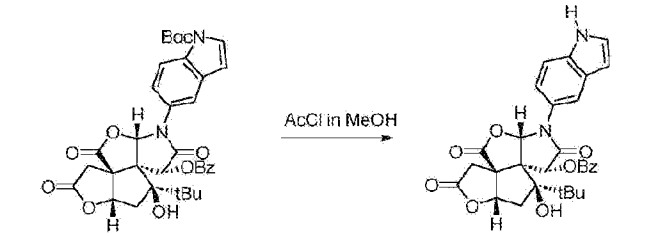
[0690] Synthesis of 4- (3aS, 5aS, 8R, 9R, 10aS) -8- (benzoyloxy) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxohexahydro -4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) benzenaminium chloride (XBB-037)



[0691] Acetyl chloride (0.35 mL, 4.95 mmol, 15 equiv.) was added dropwise to methanol (10 mL) while cooled in an ice bath. The solution is stirred at room temperature for 15 minutes to generate a 0.5 M HCl solution. XBB-036 (207 mg, 0.33 mmol, 1 equiv.) was added to the HCl solution and allowed to stir for 18 hours at room temperature. On completion, the reaction mixture is concentrated under reduced pressure to give a yellow residue. The residue is then suspended in a mixture of hexane/ethyl acetate (1: 1, 10 mL) and sonicated to reach homogeneity, before being filtered through a sintered funnel. The resultant residue is washed several times with hexane/ethyl acetate (1: 1) to produce the desired XBB-037 as HCl salt (155 mg, 85%) as a white solid. mp = 115.4-116.3℃; ^{1}H-NMR (400 MHz, MeOD) : δ [ppm] = 8.04 –7.98 (m, 2H) , 7.94 –7.84 (m, 2H) , 7.72 –7.65 (m, 1H) , 7.59 –7.48 (m, 4H) , 6.65 (s, 1H) , 6.60 (s, 1H) , 5.24 (t, J = 7.1 Hz, 1H) , 5.04 (s, 2H) , 3.23 –3.00 (m, 2H) , 2.82 (dd, J = 13.8, 7.2 Hz, 1H) , 2.22 (dd, J = 13.8, 7.2 Hz, 1H) , 1.13 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, MeOD) : δ [ppm] = 176.35, 173.07, 165

.86, 163.80, 134.82, 132.87, 128.41, 127.73, 127.37, 126.97, 126.65, 126.07, 122.54, 86.56, 85.34, 82.87, 65.49, 61.15, 59.54, 57.99, 41.27, 40.55, 35.91, 34.67, 24.47; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{28}N_2O_8Na^+$ 543.17379, found 543.17396.

[0692] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6- (1H-indol-5-yl) -2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (SCC382)



Chemical Formula: $C_{35}H_{38}N_2O_{10}$
Molecular Weight: 644.68

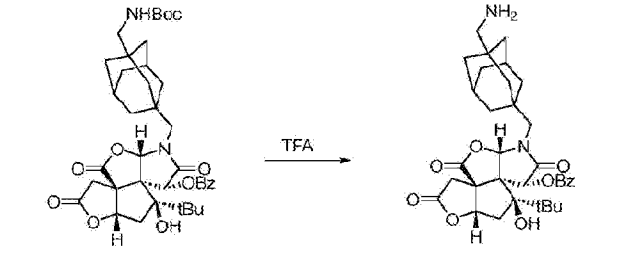
SCC376

Chemical Formula: $C_{30}H_{28}N_2O_8$
Molecular Weight: 544.56

SCC382

[0693] Acetyl chloride (0.43 mL, 6 mmol) was added dropwise to methanol (1.6 mL) while cooled in an ice bath resulting in a 3M HCl solution in Methanol/MeOAc. This solution is added to SCC376 (28.3 mg, 43.9 μmol) and allowed to stir for 22 hours at room temperature. On completion, sat. $NaHCO_3$ solution (10 mL) was added followed by EtOAc (10 mL) . After phase separation, the aqueous phase was extracted with EtOAc (10 mL) . The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (SiO2, EtOAc: hexane 1: 1) yielded the desired SCC382 (14.3 mg, 60%) as a white solid. ^{1}H-NMR (600 MHz, $CDCl_3$) : δ [ppm] = 8.41 (s, 1H) , 8.05 (d, J = 7.2 Hz, 2H) , 7.73 (s, 1H) , 7.65 (t, J = 7.2 Hz, 1H) , 7.52 (t, J = 8.1 Hz, 2H) , 7.36 (d, J = 8.6 Hz, 1H) , 7.25 (t, J = 2.7 Hz, 1H) , 7.21 (dd , J = 2.2, 9.0 Hz, 1H) , 6.56 (s, 1H) , 6.54 (s, 1H) , 6.39 (s, 1H) , 5.24 (t, J = 7.1 Hz, 1H) , 3.40 (d, J = 19.0 Hz, 1H) , 3.03 (d, J = 18.6 Hz, 1H) , 2.65 (dd, J = 7.1 , 13.8 Hz, 1H) , 2.30 (dd, J = 7.2, 14.0 Hz, 1H) , 2.29 (s, 1H) , 1.15 (s, 9H) .

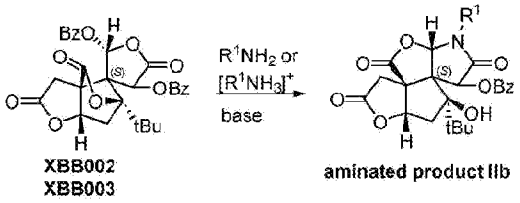
[0694] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (((1S, 5S) -3- (aminomethyl) adamantan-1-yl) methyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (SCC567)



[0695] SCC564 (0.10 mmol, 70.1 mg) was dissolved in DCM/TFA (2.5 mL, 5: 1) and stirred at room temperature. After 5h, the solvent was removed and the residue wa s re-dissolved in DCM (5 mL) and sat. $NaHCO_3$ (10 mL) was added. After phase se paration, the aqueous phase was extracted with DCM (4x 10 mL) . The combined organic layers were washed with brine (15 mL) , dried over MgSO4. The removal of the volatiles yielded in SCC567 (41.2 mg, 68%) .

[0696] Example 1.6: Synthesis of N-alkylated bilobalide lactam analogues according to Scheme 2 or Scheme 5

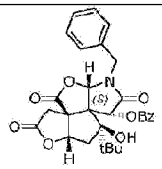
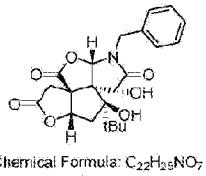
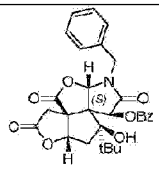
[0697] Synthesis of N-alkylated bilobalide lactam analogues according to the method descri bed in Scheme 2 or Scheme 5 is described herein.

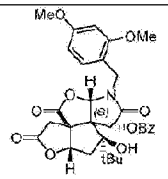
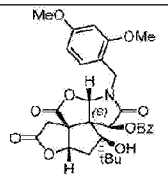
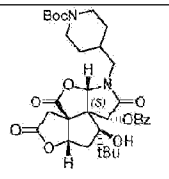
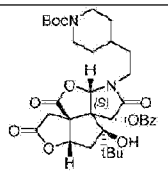
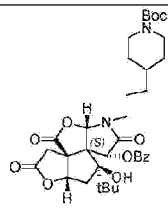
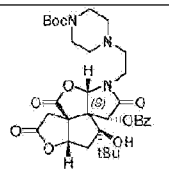
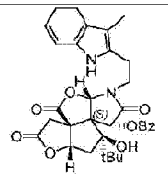
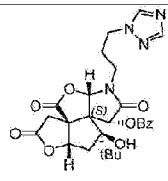
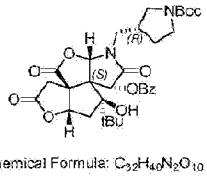
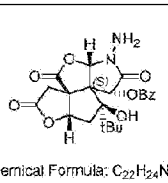
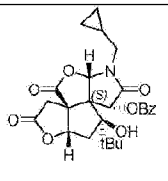
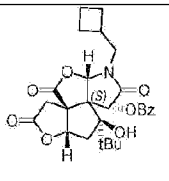
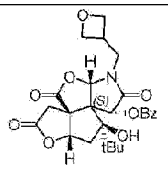
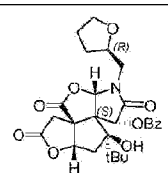
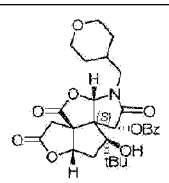


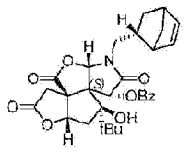
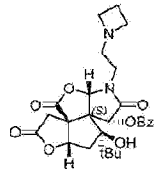
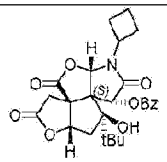
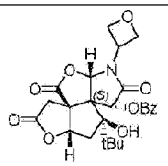
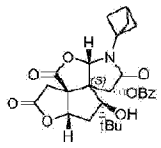
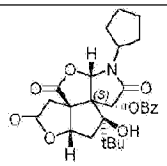
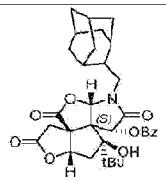
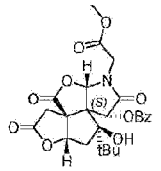
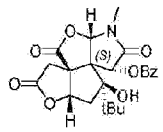
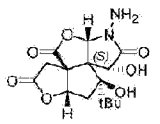
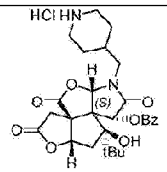
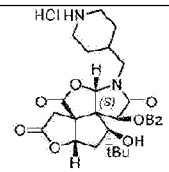
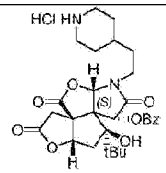
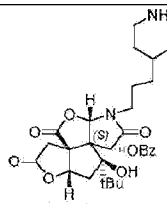
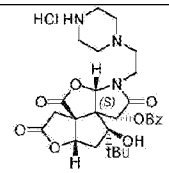
[0698] To a solution of XBB-002 or XBB-003 in anhydrous tetrahydrofuran or CH_3Cl (1%EtOH) was added R_1NH_2 or $[R_1NH_3]$ + at 0°C. In some embodiments, th e reaction mixture further included Et_3N or DIPEA. The resulting solution was warmed to room temperature and stirred for 30 min up to 24h. Up on completion indicated by TLC, the reaction solution was concentrated in vacuo. The residue was dissolved in saturated NH_4Cl or saturated $NaHCO_3$ solution and DCM or EtOAc. After phase separation, the aqueous phase was extracted w ith DCM or EtOAc. The combined organic layers were washed with brine , dried over Na_2SO_4, filtered and concentrated in vacuo. The crude pro duct was purified via column chromatography to provide the correspon ding aminated product IIb (i.e., N-alkylated bilobalide analogues according to Table 1 g) as a white powder.

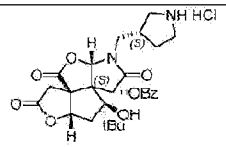
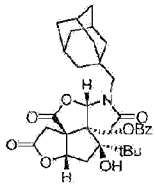
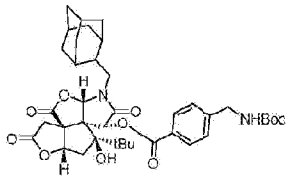
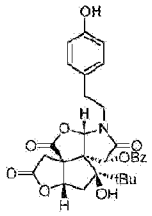
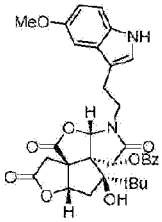
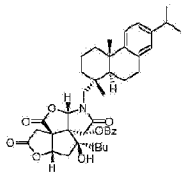
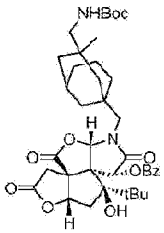
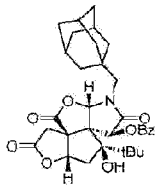
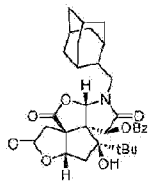
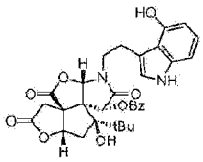
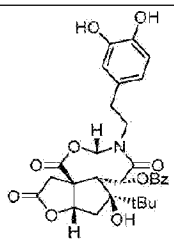
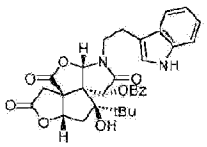
[0699] Examples of N-alkylated bilobalide analogues are summarized in Table 1g.

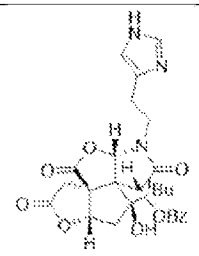
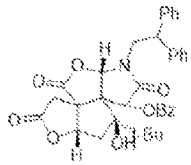
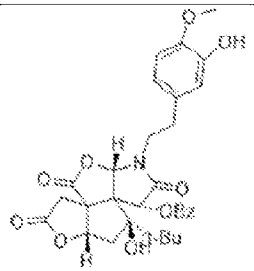
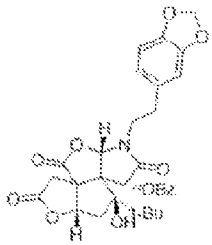
[0700] Table 1g: Example N-alkylated bilobalide lactam analogues

 Chemical Formula: $C_{29}H_{29}NO_8$ Molecular Weight: 519.55 **XBB-016**	 Chemical Formula: $C_{22}H_{25}NO_7$ Molecular Weight: 415.44 **XBB-041**	 Chemical Formula: $C_{29}H_{29}NO_8$ Molecular Weight: 519.55 **XBB-017**

 Chemical Formula: $C_{31}H_{33}NO_{10}$ Molecular Weight: 579.60 **XBB-018**	 Chemical Formula: $C_{31}H_{33}NO_{10}$ Molecular Weight: 579.60 **XBB-019**	 Chemical Formula: $C_{33}H_{42}N_2O_{10}$ Molecular Weight: 626.70 **XBB-020**
 Chemical Formula: $C_{34}H_{44}N_2O_{10}$ Molecular Weight: 640.73 **XBB-023**	 Chemical Formula: $C_{35}H_{46}N_2O_{10}$ Molecular Weight: 654.76 **XBB-025**	 Chemical Formula: $C_{33}H_{43}N_2O_{10}$ Molecular Weight: 641.72 **XBB-027**
 Chemical Formula: $C_{31}H_{35}N_2O_8$ Molecular Weight: 586.64 **XBB-029**	 Chemical Formula: $C_{27}H_{30}N_4O_8$ Molecular Weight: 538.56 **XBB-030**	 Chemical Formula: $C_{32}H_{40}N_2O_{10}$ Molecular Weight: 612.68 **XBB-031**
 Chemical Formula: $C_{22}H_{24}N_2O_8$ Molecular Weight: 444.44 **XBB-033**	 Chemical Formula: $C_{26}H_{29}NO_8$ Molecular Weight: 483.52 **DW189**	 Chemical Formula: $C_{27}H_{31}NO_8$ Molecular Weight: 497.54 **DW184**
 Chemical Formula: $C_{25}H_{29}NO_9$ Molecular Weight: 499.52 **DW191**	 Chemical Formula: $C_{27}H_{31}NO_9$ Molecular Weight: 513.54 **P-5**	 Chemical Formula: $C_{28}H_{33}NO_9$ Molecular Weight: 527.57 **P-3**

 Chemical Formula: $C_{30}H_{33}NO_8$ Molecular Weight: 535.59 **DW190**	 Chemical Formula: $C_{27}H_{32}N_2O_8$ Molecular Weight: 512.56 **P-10**	 Chemical Formula: $C_{26}H_{29}NO_8$ Molecular Weight: 483.52 **DW163**
 Chemical Formula: $C_{26}H_{27}NO_8$ Molecular Weight: 485.49 **DW182**	 Chemical Formula: $C_{27}H_{29}NO_8$ Molecular Weight: 495.53 **DW172**	 Chemical Formula: $C_{27}H_{31}NO_8$ Molecular Weight: 497.54 **JW081**
 Chemical Formula: $C_{35}H_{35}NO_8$ Molecular Weight: 577.67 **DW192**	 Chemical Formula: $C_{28}H_{27}NO_{10}$ Molecular Weight: 601.49 **P-8**	 Chemical Formula: $C_{23}H_{25}NO_8$ Molecular Weight: 443.45 **DW-168**
 Chemical Formula: $C_{15}H_{20}N_2O_7$ Molecular Weight: 340.33 **JW072**	 Chemical Formula: $C_{28}H_{35}ClN_2O_8$ Molecular Weight: 563.04 **XBB-021**	 Chemical Formula: $C_{28}H_{35}ClN_2O_8$ Molecular Weight: 563.04 **XBB-022**
 Chemical Formula: $C_{29}H_{37}ClN_2O_8$ Molecular Weight: 577.07 **XBB-024**	 Chemical Formula: $C_{30}H_{39}ClN_2O_8$ Molecular Weight: 591.10 **XBB-026**	 Chemical Formula: $C_{28}H_{35}ClN_2O_8$ Molecular Weight: 578.06 **XBB-028**

 Chemical Formula: $C_{27}H_{33}ClN_2O_8$ Molecular Weight: 549.02 **XBB-032**	 **SCC363**	 **SCC505**
 **SCC545**	 Chemical Formula: $C_{33}H_{34}N_2O_9$ Molecular Weight: 602.64 **SCC555**	 **SCC558**
 **SCC564**	 **SCB001**	 **SCB002**
 **SCB008**	 **SXQ090-1**	 **SXQ087-1**

 SXQ092-1	 SXQ102-1	SXQ091-1
 SXQ125-2	 SXQ126-1	SXQ128-1

[0701] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6-benzyl-9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-016) . Using XBB-002 (50.0 mg, 93.6 μmol, 1.00 eq.) , benzylamine (2.00 eq.) in THF (2 mL) yielding in XBB-016 as a white po wder (41 mg, 84%) . R_f = 0.30 (hexane: EtOAc, 3: 1) ; mp = 181.4-182.3℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.16 –7.90 (m, 2H) , 7.69 –7.60 (m, 1H) , 7.56 –7.45 (m, 2H) , 7.43 –7.31 (m, 5H) , 6.36 (s, 1H) , 5.73 (s, 1H) , 5.20 (t, J = 7.1 Hz, 1H) , 5.02 (d, J = 14.5 Hz, 1H) , 4.21 (d, J = 14.5 Hz, 1H) , 3.20 (d, J = 18.9 Hz, 1H) , 2.87 (d, J = 18.9 Hz, 1H) , 2.62 (dd, J = 14.0, 7.2 Hz, 1H) , 2.23 (dd, J = 14.0, 7. 1 Hz, 1H) , 1.00 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 178 .17, 173.80, 166.94, 165.32, 134.32, 134.21, 133.67, 130.16, 130.12, 129.12, 128.80, 128.60, 128.51, 127.76, 87.17, 87.00, 83.48, 70.97, 62.51, 59.40, 44.61, 42.71, 37.21 , 36.40, 26.28; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{29}NO_8Na^+$ 542.17854, found 542.17839.

[0702] Synthesis of (3aS, 5aS, 8S, 8aS, 9R, 10aS) -6-benzyl-9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-017) . Using XBB-003 (50.0 mg, 93.6 μmol, 1.00 eq.) , benzylamine (2.00 eq.) in THF (2 mL) yielding in XBB-017 as a white po wder (39 mg, 80%) . R_f = 0.35 (hexane: EtOAc, 3: 1) ; mp = 181.4-182.3℃; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 7.96 –7.90 (m, 2H) , 7.58 (t, J = 7.5 Hz, 1H) , 7.43 (t, J = 7.6 Hz, 2H) , 7.37 –7.31 (m, 2H) , 7.26 –7.21 (m, 3H) , 6.46 (s, 1H) , 5.43 (s, 1H) , 4.57 (d, J = 14.4 Hz, 1H) , 4.41 (d, J = 14.2 Hz, 1H) , 4.07

–3.99 (m, 1H) , 3.34 (d, J = 14.1 Hz, 1H) , 2.76 (d, J = 14.0 Hz, 1H) , 2.39 –2.30 (m, 1H) , 2.27 –2.15 (m, 1H) , 0.89 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 176.90, 175.00, 170.03, 165.99, 135.13, 133.34, 129.72, 129.64, 129.55, 128.71, 128.64, 128.15, 100.47, 83.07, 77.29, 77.03, 76.78, 70.07, 67.23, 66.11, 60. 84, 45.22, 38.53, 35.11, 32.90, 27.00; HRMS (ESI) m/z: [M+Na] $^{+}$Calcd for $C_{29}H_{29}NO_8$ Na^{+} 542.17854, found 542.17850.

[0703] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (2, 4-dimethoxy-benzyl- 9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-018) . Using XBB-002 (50.0 mg, 93.6 μmol, 1.00 eq.) , 2, 4-dimethoxybenzylamine (2.00 eq.) i n THF (2 mL) yielding in XBB-018 as a white powder (49 mg, 90%) . R_f = 0.2 (hexane: EtOAc, 3: 1) ; mp = 102.3-102.9°C; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 7.99 (d, J = 7.7 Hz, 2H) , 7.62 (t, J = 7.3 Hz, 1H) , 7.48 (t, J = 7.7 Hz, 2H) , 7.21 (d, J = 8.8 Hz, 1H) , 6.51 –6.43 (m, 2H) , 6.24 (s, 1H) , 5.72 (s, 1H) , 5.17 (t, J = 7.1 Hz, 1H) , 4.97 (d, J = 14.3 Hz, 1H) , 4.08 (d, J = 14.4 Hz, 1H) , 3.85 (s, 3H) , 3.82 (s, 3H) , 3.21 (d, J = 19.0 Hz, 1H) , 2.90 (d, J = 19.0 Hz, 1H) , 2.62 (dd, J = 13.9, 7.1 Hz, 1H) , 2.15 (dd, J = 13.9, 7.2 Hz, 1H) , 0.95 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 178.45, 173.79, 166.90, 165.26, 161.3 8, 158.68, 134.14, 132.23, 130.06, 128.72, 127.92, 114.19, 104.10, 98.69, 87.25, 87.1 2, 83.44, 70.90, 61.84, 60.52, 59.46, 55.45, 55.37, 42.77, 41.11, 37.14, 36.45; HRMS (ESI) m/z: [M+Na] $^{+}$ Calcd for $C_{31}H_{33}NO_{10}Na^{+}$ 602.19967, found 602.19967. The X-ray crystal structure of XBB-018 is shown in FIG. 1E.

[0704] Synthesis of (3aS, 5aS, 8S, 8aS, 9R, 10aS) -6- (2, 4-dimethoxy-benzyl- 9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-019) . Using XBB-003 (50.0 mg, 93.6 μmol, 1.00 eq.) , 2, 4-dimethoxybenzylamine (2.00 eq.) i n THF (2 mL) yielding in XBB-019 as a white powder (47 mg, 86%) . R_f = 0.2 (hexane: EtOAc, 3: 1) ; mp = 106.2-107.1°C; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] =7.80 (d, J = 7.6 Hz, 2H) , 7.60 (t, J = 7.5 Hz, 1H) , 7.42 (t, J = 7.7 H z, 2H) , 7.24 (d, J = 8.2 Hz, 1H) , 6.50 (s, 1H) , 6.42 (dd, J = 8.3, 2.3 Hz, 1H) , 6 .03 (s, 1H) , 5.80 (s, 1H) , 5.16 (t, J = 7.1 Hz, 1H) , 4.87 (d, J = 14.2 Hz, 1H) , 4 .19 (s, 1H) , 3.82 (s, 3H) , 3.76 (s, 3H) , 2.99 (s, 2H) , 2.61 (dd, J = 14.3, 7.1 Hz , 1H) , 2.13 (dd, J = 14.3, 7.2 Hz, 1H) , 0.95 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, C DCl_3) : δ [ppm] = 177.85, 172.26, 167.15, 164.99, 161.26, 158.70, 133.99 , 132.25, 130.15, 128.67, 128.57, 114.73, 104.17, 98.68, 90.98, 90.49, 83.54, 71.21, 61.09, 60.40, 55.58, 55.43, 42.62, 39.98, 37.26, 35.18, 26.69; HRMS (ESI) m/z: [M +Na] $^{+}$ Calcd for $C_{31}H_{33}NO_{10}Na^{+}$ 602.19967, found 602.19961.

[0705] Synthesis of tert-butyl 4- (((3aS, 5aS, 8R, 8aS, 9R, 10aS) -8- (benzoyloxy) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxohexahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) methyl) piperidine-1-carboxylate (XBB-020) . Using XBB-002 (50.0 mg, 93.6 μmol, 1.00 eq.) , 1-Boc-4- (aminomethyl) piperidine (2.00 eq.) in THF (2 mL) yielding in XBB-020 as a white powder (42 mg, 72%) . R_f = 0.2 (hexane: EtOAc, 2: 1) ; mp = 156.7-157.4℃; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 7.98 (d, J = 7.7 Hz, 2H) , 7.63 (t, J = 7.5 Hz, 1H) , 7.49 (t, J = 7.7 Hz, 2H) , 6.36 (s, 1H) , 5.95 (s, 1H) , 5.19 (t, J = 7.2 Hz, 1H) , 4.21 –3.92 (m, 3H) , 3.45 (d, J = 12.5 Hz, 1H) , 3.23 –2.95 (m, 3H) , 2.87 (d, J = 18.8 Hz, 1H) , 2.76 –2.61 (m, 3H) , 2.26 –2.16 (m, 1H) , 1.95 (q, J = 10.5, 9.9 Hz, 1H) , 1.85 –1.71 (m, 1H) , 1.57 (m, 1H) , 1.45 (d, J = 2.0 Hz, 9H) , 1.10 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 177.89, 173.49, 173.46, 167.45, 165.26, 154.74, 134.27, 130.07, 128.77, 127.75, 87.21, 87.19, 87.17, 83.36, 83.34, 79.75, 70.67, 62.73, 62.71, 59.27, 42.87, 42.85, 42.83, 37.42, 36.46, 34.37, 29.81, 28.42, 26.46; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{33}H_{42}N_2O_{10}Na^+$ 649.27317, found 649.27258.

[0706] Synthesis of tert-butyl 4- (2- ((3aS, 5aS, 8R, 8aS, 9R, 10aS) -8- (benzoyloxy) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxohexahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) ethyl) piperidine-1-carboxylate (XBB-023) . Using XBB-002 (50.0 mg, 93.6 μmol, 1.00 eq.) , 1-Boc-4- (aminoethyl) piperidine (2.00 eq.) in THF (2 mL) yielding in XBB-023 as a white powder (51 mg, 86%) . R_f = 0.2 (hexane: EtOAc, 2: 1) ; mp = 136.7-137.4℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.04 –7.91 (m, 2H) , 7.67 –7.56 (m, 1H) , 7.55 –7.41 (m, 2H) , 6.32 (s, 1H) , 5.95 (s, 1H) , 5.20 (t, J = 7.1 Hz, 1H) , 4.20 –3.98 (m, 2H) , 3.60 (ddd, J = 13.8, 9.5, 6.2 Hz, 1H) , 3.32 (ddd, J = 14.3, 9.4, 5.7 Hz, 1H) , 3.16 (d, J = 18.8 Hz, 1H) , 2.87 (d, J = 18.8 Hz, 1H) , 2.76 –2.57 (m, 4H) , 2.27 –2.19 (m, 1H) , 2.18 (s, 1H) , 1.68 (d, J = 8.2 Hz, 3H) , 1.65 –1.49 (m, 2H) , 1.45 (s, 9H) , 1.10 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 178.01, 173.70, 167.15, 165.29, 154.91, 134.25, 130.06, 128.77, 127.81, 87.81, 86.96, 83.56, 79.61, 70.93, 62.87, 59.31, 42.60, 38.89, 37.41, 36.44, 33.81, 33.71, 31.72, 28.45, 26.49; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{34}H_{44}N_2O_{10}Na^+$ 663.28882, found 663.28809.

[0707] Synthesis of (tert-butyl 4- (3- ((3aS, 5aS, 8R, 8aS, 9R, 10aS) -8- (benzoyloxy) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxohexahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) propyl) piperidine-1-carboxylate (XBB-025) . Using XBB-002 (50.0 mg, 93.6 μmol, 1.00 eq.) , 1-Boc-4- (3-aminopropyl) piperidine (2.00 eq.) in THF (2 mL) yielding in XBB-025 as a white powder (48 mg, 78%) . R_f = 0.2 (hexane: EtOAc, 2: 1) ; mp

= 127.8-128.6℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.04 –7.91 (m, 2H) , 7.67 –7.58 (m, 1H) , 7.49 (t, J = 7.8 Hz, 2H) , 6.33 (s, 1H) , 5.97 (s, 1H) , 5.20 (t, J = 7.1 Hz, 1H) , 4.05 (d, J = 13.1 Hz, 2H) , 3.60 –3.47 (m, 1H) , 3.33 –3.21 (m, 1H) , 3.16 (d, J = 18.9 Hz, 1H) , 3.03 –2.95 (m, 1H) , 2.87 (d, J = 18.7 Hz, 1H) , 2. 75 –2.54 (m, 2H) , 2.22 (dd, J = 13.9, 7.1 Hz, 1H) , 1.83 –1.77 (m, 1H) , 1.73 –1.53 (m, 4H) , 1.45 (s, 9H) , 1.42 –1.35 (m, 1H) , 1.26 –1.20 (m, 2H) , 1.10 (s, 9H) ; ^{13}C { ^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 178.08, 173.80, 167.22, 165.35, 155.0 0, 134.26, 130.07, 128.77, 127.81, 87.88, 86.95, 83.60, 79.58, 70.97, 62.85, 60.57, 5 9.34, 42.62, 41.31, 37.41, 36.45, 35.49, 33.51, 32.02, 28.46, 26.50, 24.33; HRMS (ESI) m/z: [M+Na] $^+$ Calcd for $C_{35}H_{46}N_2O_{10}Na^+$ 677.30447, found 677.30410.

[0708] Synthesis of tert-butyl 4- (2- ((3aS, 5aS, 8R, 8aS, 9R, 10aS) -8- (benzoyloxy) - 9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxohexahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) ethyl) piperazine-1- carboxylate (XBB-027) . Using XBB-002 (50.0 mg, 93.6 μmol, 1.00 eq.) , 1- boc-4- (2-aminoethyl) piperazine (2.00 eq.) in THF (2 mL) yielding in XBB- 027 as a white powder (51 mg, 85%) . R_f = 0.1 (hexane: EtOAc, 2: 1) ; mp = 134.4- 135.1℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.03 –7.95 (m, 2H) , 7.62 (t, J = 7.4 Hz, 1H) , 7.49 (t, J = 7.8 Hz, 2H) , 6.36 (s, 1H) , 6.20 (s, 1H) , 5.21 (t, J = 7.1 Hz, 1H) , 3.80 (dt, J = 14.7, 5.5 Hz, 1H) , 3.60 –3.21 (m, 5H) , 3.17 (d, J = 18.9 Hz , 1H) , 2.90 (d, J = 18.9 Hz, 1H) , 2.81 (s, 1H) , 2.71 –2.58 (m, 3H) , 2.55 –2.30 (m , 5H) , 2.23 (dd, J = 13.9, 7.1 Hz, 1H) , 1.46 (s, 9H) , 1.11 (s, 9H) ; ^{13}C {^{1}H} - NMR (100 MHz, $CDCl_3$) : δ [ppm] = 178.28, 173.68, 167.09, 165.30, 154.7 9, 134.20, 130.08, 128.75, 127.85, 88.37, 87.13, 83.45, 79.97, 70.91, 62.48, 59.31, 5 5.33, 52.68, 42.84, 37.41, 36.75, 36.57, 28.40, 26.51; HRMS (ESI) m/z: [M+H] $^+$ Calcd for $C_{33}H_{43}N_3O_{10}H^+$642.30212, found 642.30203.

[0709] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6- (2- (3- methyl-1H-indol-2-yl) ethyl) -2, 4, 7-trioxooctahydro -4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-029) . Using XBB- 002 (50.0 mg, 93.6 μmol, 1.00 eq.) , 2- (3-methyl-1H-indol-2-yl) ethylamine (2 .00 eq.) in THF (2 mL) yielding in XBB-029 as a white powder (45 mg, 82%) . R_f = 0.15 (hexane: EtOAc, 2: 1) ; mp = 143.2-144.1℃; ^{1}H-NMR (500 MHz, MeO D) : δ [ppm] = 7.97 (d, J = 7.7 Hz, 2H) , 7.71 –7.59 (m, 1H) , 7.49 (t, J = 7.6 Hz, 3 H) , 7.27 –7.17 (m, 1H) , 7.10 –6.92 (m, 2H) , 6.05 (s, 1H) , 5.19 (s, 1H) , 5.05 (t, J = 7.1 Hz, 1H) , 3.81 (ddd, J = 14.2, 6.8, 3.2 Hz, 1H) , 3.55 (ddd, J = 14.1, 10.5, 6.1 Hz, 1H) , 3.28 (ddd, J = 14.5, 8.3, 4.6 Hz, 1H) , 3.01 –2.74 (m, 3H) , 2.56 (dd, J = 13.7, 7.2 Hz, 1H) , 2.42 (s, 3H) , 2.00 –1.90 (m, 1H) , 0.62 (s, 9H) ; ^{13}C {^{1} H} -NMR (125 MHz, MeOD) : δ [ppm] = 179.48, 175.81, 169.40, 166.43, 137.

22, 135.24, 133.86, 130.92, 129.90, 129.46, 121.83, 120.19, 118.25, 111.70, 107.24, 90.32, 87.35, 85.36, 72.45, 64.50, 60.48, 42.95, 42.45, 37.97, 37.17, 26.54, 22.22, 11.44; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{33}H_{34}N_2O_8Na^+$609.22074, found 609.22060.

[0710] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (3- (1H-1, 2, 4-triazol-1-yl) propyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-030) . Using XBB-002 (50.0 mg, 93.6 μmol, 1.00 eq.) , 3- (1H-1, 2, 4-triazol-1-yl) propylamine (2.00 eq.) in THF (2 mL) yielding in XBB-030 as a white powder (38 mg, 75%) . R_f = 0.2 (hexane: EtOAc, 3: 1) ; mp = 163.2-163.5℃; ^{1}H-NMR (400 MHz, DMSO-d6) : δ [ppm] = 8.02 –7.87 (m, 2H) , 7.78 –7.68 (m, 1H) , 7.64 (t, J = 1.1 Hz, 1H) , 7.55 (t, J = 7.8 Hz, 2H) , 7.20 (d, J = 1.3 Hz, 1H) , 6.90 (t, J = 1.0 Hz, 1H) , 6.26 (s, 1H) , 6.03 (s, 1H) , 5.61 (s, 1H) , 5.07 (t, J = 7.1 Hz, 1H) , 4.00 (t, J = 6.9 Hz, 2H) , 3.25 –3.07 (m, 3H) , 2.79 (d, J = 19.2 Hz, 1H) , 2.69 (d, J = 6.5 Hz, 1H) , 2.20 –1.69 (m, 3H) , 1.00 (s, 9H) ; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{30}N_3O_8H^+$ 538.21839, found 538.21835.

[0711] Synthesis of tert-butyl (R) -3- (((3aS, 5aS, 8R, 8aS, 9R, 10aS) -8- (benzoyloxy) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxohexahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-6 (5aH) -yl) methyl) pyrrolidine-1-carboxylate (XBB-031) . Using XBB-002 (50.0 mg, 93.6 μmol, 1.00 eq.) , (R) -2- (Aminomethyl) pyrrolidine (2.00 eq.) in THF (2 mL) yielding in XBB-031 as a white powder (48 mg, 82%) . R_f = 0.2 (hexane: EtOAc, 3: 1) ; mp = 126.7-127.2℃; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 8.11 –7.88 (m, 2H) , 7.61 (t, J = 7.5 Hz, 2H) , 7.48 (t, J = 7.7 Hz, 2H) , 6.30 (s, 1H) , 5.96 (s, 1H) , 5.03 (t, J = 7.0 Hz, 1H) , 3.87 (dd, J = 14.2, 4.8 Hz, 1H) , 3.59 –3.34 (m, 3H) , 3.29 –3.01 (m, 3H) , 2.96 –2.46 (m, 3H) , 2.24 –2.09 (m, 1H) , 2.01 –1.90 (m, 1H) , 1.79 –1.58 (m, 1H) , 1.47 (s, 9H) , 1.12 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 178.33, 173.77, 167.25, 165.28, 155.44, 134.20, 130.06, 128.76, 127.86, 87.96, 86.23, 83.76, 80.14, 70.79, 63.11, 59.24, 49.73, 45.77, 43.17, 42.24, 37.57, 37.32, 36.44, 29.17, 28.58, 28.50; HRMS (ESI) m/z: $[M+Na]^+$Calcd for $C_{32}H_{40}N_2O_{10}Na^+$ 635.25752, found 635.25714.

[0712] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6-amino-9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-033) . Using XBB-002 (50.0 mg, 93.6 μmol, 1.00 eq.) , hydrazine (2.00 eq.) in THF (2 mL) yielding in XBB-033 as a white powder (32 mg, 78%) . R_f = 0.1 (hexane: EtOAc, 2: 1) ; mp = 108.4℃; ^{1}H-NMR (400 MHz, MeOD) : δ [ppm] = 8.09 –7.93 (m, 2H) , 7.74 –7.61 (m,

1H) , 7.52 (t, J = 7.8 Hz, 2H) , 6.40 (s, 1H) , 5.97 (s, 1H) , 5.19 (t, J = 7.2 Hz, 1 H) , 3.35 (d, J = 17.7 Hz, 1H) , 3.03 (s, 2H) , 2.74 (dd, J = 13.7, 7.2 Hz, 1H) , 2.1 4 (dd, J = 13.7, 7.2 Hz, 1H) , 1.09 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, MeO D) : δ [ppm] = 178.44, 174.63, 166.93, 165.13, 133.92, 129.59, 128.51, 128.05, 89.70, 86.22, 84.13, 70.04, 62.50, 59.42, 41.79, 37.02, 36.19, 25.59; HRMS (ESI) m/z: [M +H] $^{+}$ Calcd for $C_{22}H_{24}N_2O_8H^+$ 445.16122, found 445.16126.

[0713] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -6- (cyclopropylmeth yl) -9-hydroxy-2, 4, 7 -trioxooctahydro -4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (DW189) . Using XBB-002 (150.0 mg, 0. 28 mmol, 1.00 eq.) , cyclopropylmethane amine (2.50 eq.) in THF (3 mL) yielding in DW189 as a white powder (78 mg, 57%) . ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 8.0 2 –7.97 (m, 2H) , 7.66 –7.59 (m, 1H) , 7.49 (t, J = 7.8 Hz, 2H) , 6.36 (s, 1H) , 6.14 (s, 1H) , 5.22 (t, J = 7.1 Hz, 1H) , 3.65 (dd, J = 14.3, 6.4 Hz, 1H) , 3.19 (d, J = 18.9 Hz, 1H) , 2.99 –2.89 (m, 2H) , 2.87 (s, 1H) , 2.62 (dd, J = 14.0, 7.2 Hz, 1H) , 2.26 (dd, J = 14.0, 7.2 Hz, 1H) , 1.57 (s, 6H) , 1.13 (s, 9H) , 1.10 –1.00 (m, 1H) , 0.67 –0.59 (m, 1H) , 0.59 –0.50 (m, 1H) , 0.43 (dq, J = 9.8, 4.9 Hz, 1H) , 0.26 (dq, J = 9.9, 5.0 Hz, 1H) .

[0714] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -6- (cyclobutyl meth yl) -9 -hydroxy-2, 4, 7 -trioxooctahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (DW184) . Using XBB-002 (150.0 mg, 0. 28 mmol, 1.00 eq.) , cyclobutylmethane amine hydrochloride (3.00 eq.) , Et_3 N (6.00 eq.) in $CHCl_3$ (3 mL, 1%EtOH) yielding in DW184 as a white powder (62 mg, 44%) . ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 8.01 –7.96 (m, 2H) , 7.65 –7.58 (m, 1H) , 7.53 –7.46 (m, 2H) , 6.32 (s, 1H) , 5.90 (s, 1H) , 5.20 (t, J = 7.1 Hz, 1H) , 3.61 (dd, J = 13.8, 8.0 Hz, 1H) , 3.31 (dd, J = 13.8, 7.7 Hz, 1H) , 3. 15 (s, 1H) , 2.89 (s, 1H) , 2.70 (hept, J = 8.0 Hz, 1H) , 2.61 (dd, J = 14.0, 7.1 Hz, 1H) , 2.25 (dd, J = 14.0, 7.2 Hz, 1H) , 2.13 –1.69 (m, 7H) , 1.10 (s, 9H) .

[0715] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -6- (1-oxetan- 3-yl methyl) -9-hydroxy-2, 4, 7 -trioxooctahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (DW191) . Using XBB-002 (150.0 mg, 0.28 mmol, 1.00 eq.) , 1- (oxetan-3-yl) methanamine (2.50 eq.) in THF (3 mL) yielding in DW191 as a white powder.

[0716] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7- trioxo-6- (((R) -tetrahydrofuran-2-yl) methyl) octahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (P-5) . Using XBB-002 (75.0 mg, 0.14 mmol, 1.00 eq.) , ((R) -tetrahydrofuran-2-yl) methane amine (2.50 eq.) in THF (3 mL) yielding in P-5 as a white powder (46.7 mg, 65%) .

[0717] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo-6 - ((tetrahydro-2H-pyran-4-yl) methyl) octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (P-3) . Using XBB-002 (75.0 mg, 0.14 mmol, 1.00 eq.) , tetrahydro-2H-pyran-4-ylmethane amine (2.50 eq.) in THF (3 mL) yielding in P-3 as a white powder (43.7 mg, 59%) .

[0718] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (((2R) -bicyclo [2.2.1] hept-5-en-2-yl) methyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (DW190) . Using XBB-002 (150.0 mg, 0.28 mmol, 1.00 eq.) , ((2R) -bicyclo [2.2.1] hept-5-en-2-yl) methane amine (2.50 eq.) in THF (3 mL) yielding in DW190 as a white powder (42 mg, 28%) . ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 7.98 (dt, J = 8.4, 1.6 Hz, 2H) , 7.66 –7.59 (m, 1H) , 7.49 (t, J = 7.8 Hz, 2H) , 6.33 (s, 1H) , 5.90 (s, 1H) , 5.20 (t, J = 7.1 Hz, 1H) , 4.80 (dd, J = 7.8, 6.5 Hz, 2H) , 4.49 (dt, J = 12.8, 6.3 Hz, 2H) , 3.75 (d, J = 7.1 Hz, 2H) , 3.31 (hept, J = 7.1 Hz, 1H) , 3.11 (s, 1H) , 2.88 (s, 1H) , 2.62 (dd, J = 14.1, 7.2 Hz, 1H) , 2.25 (dd, J = 14.1, 7.2 Hz, 1H) , 2.01 (s, 1H) , 1.33 –1.23 (m, 2H) , 1.10 (s, 6H) , 0.88 (t, J = 6.8 Hz, 2H) .

[0719] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (2- (azetidin-1-yl) ethyl) -9- (tert-butyl) -9 -hydroxy-2, 4, 7 -trioxooctahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (P-10) . Using XBB-002 (0.10 g, 0.19 mmol, 1.00 eq.) , 2- (azetidin-1-yl) ethylamine (2.50 eq.) in THF (2 mL) yielding in P-10 as a white powder (10.8 mg, 23%) .

[0720] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -6-cyclobutyl-9-hydroxy-2, 4, 7 -trioxooctahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (DW163) . Using XBB-002 (80.0 mg, 0.15 mmol, 1.00 eq.) , cyclobutylamine (1.50 eq.) in THF (2 mL) yielding in DW163 (54%) . ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 7.98 (d, J = 7.1 Hz, 2H) , 7.62 (t, J = 7.3 Hz, 1H) , 7.49 (t, J = 8.1 Hz, 2H) , 6.28 (s, 1H) , 6.05 (s, 1H) , 5.21 (t, J = 7.0 Hz, 1H) , 4.35 (p, J = 8.7 Hz, 1H) , 3.19 (d, J = 18.8 Hz, 1H) , 2.88 (d, J = 18.2 Hz, 1H) , 2.61 (dd, J = 7.1, 13.9 Hz, 1H) , 2.34-2.49 (m, 2H) , 2.20-2.31 (m, 3H) , 1.99 (s, 1H) , 1.70-1.89 (m, 2H) , 1.11 (s, 9H) .

[0721] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6-(oxetan-3-yl) -2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (DW182) . Using XBB-002 (0.10 g, 0.19 mmol, 1.00 eq.) , oxetan-3-ylamine (2.50 eq.) in THF (2 mL) yielding in DW182 . ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 7.98 (d, J = 7.4 Hz, 2H) , 7.63 (t, J = 7.3 Hz, 1H) , 7.50 (t, J = 7.9 Hz, 2H) , 6.32 (s, 1H) , 6.20 (s, 1H) , 5.21 (t, J

= 7.0 Hz, 1H) , 4.99-5.08 (m, 2H) , 4.82-4.93 (m, 3H) , 3.16 (d, J = 19.0 H z, 1H) , 2.89 (d, J = 18.7 Hz, 1H) , 2.65 (dd, J = 7.0, 14.0 Hz, 1H) , 2.26 (dd, J = 6.9, 13.7 Hz, 1H) , 2.24 (s, 1H) , 1.12 (s, 9H) .

[0722] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (bicyclo [1.1.1] pentan-1-yl) -9- (tert-butyl) -9 -hydroxy-2, 4, 7 -trioxooctahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (DW172) . Using XBB-002 (0.10 g, 0.19 mmol, 1.00 eq.) , bicyclo [1.1.1] pentylamine (2.00 eq.) , Et_3N (3.00 eq) in CH Cl_3 (2 mL, 1%EtOH) yielding in DW172 as a white powder (53 mg, 56%) . ^{1} H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 7.99 –7.96 (m, 2H) , 7.61 (t, J = 7.4 Hz, 1H) , 7.48 (t, J = 7.7 Hz, 2H) , 6.28 (s, 1H) , 5.93 (s, 1H) , 5.20 (t, J = 7.1 Hz, 1H) , 3.20 (d, J = 18.9 Hz, 1H) , 2.90 (d, J = 18.9 Hz, 1H) , 2.61 (dd, J = 14.0, 7.2 Hz, 1H) , 2.56 (s, 1H) , 2.23 (s, 7H) , 1.11 (s, 9H) .

[0723] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -6-cyclopentyl-9-hydroxy -2, 4, 7-trioxooctahydro -4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (JW081) . Using XBB-002 (0.16 g, 0.30 mmol, 1.00 eq.) , cyclopropylamine (2.50 eq.) in THF (2.5 mL) yielding in JW081 as a white powder (110 mg, 74%) . ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 7.9 7 (d, J = 7.1 Hz, 2H) , 7.61 (t, J = 7.2 Hz, 1H) , 7.48 (t, J = 7.6 Hz, 2H) , 6.28 (s , 1H) , 6.03 (s, 1H) , 5.18 (t, J = 6.4 Hz, 1H) , 4.07-4.16 (m, 1H) , 3.18 (d, J = 18.8 H z, 1H) , 2.86 (d, J = 19.1 Hz, 1H) , 2.62 (dd, J = 8.2, 14.1 Hz, 1H) , 2.38 (s, 1H) , 2.22 (dd, J = 7.5, 14.2 Hz, 1H) , 1.96-2.07 (m, 1H) , 1.75-1.95 (m, 3H) , 1.64-1.74 (m, 2H) , 1.54-1.65 (m, 2H) , 1.08 (s, 9H) .

[0724] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (((1S, 5R, 7S) -adamantan-2-yl) methyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (DW192) . Using XBB-002 (0.18 g, 0.33 mmol, 1.00 eq.) , adamantan-2-yl methylamine hydrochloride (3.00 eq.) , Et_3N (6.00 eq.) in $CHCl_3$ (4 mL, 1%EtOH) yielding in DW192 as a white powder (32 mg, 17%) . ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 8.02 – 7.96 (m, 2H) , 7.67 –7.58 (m, 1H) , 7.49 (t, J = 7.9 Hz, 2H) , 6.39 (s, 1H) , 6.08 (s, 1H) , 5.20 (t, J = 7.1 Hz, 1H) , 3.45 (d, J = 14.3 Hz, 1H) , 3.15 (s, 1H) , 2.87 (s, 1H) , 2.86 –2.79 (m, 1H) , 2.62 (dd, J = 14.0, 7.2 Hz, 1H) , 2.27 (dd, J = 14.0, 7.1 Hz, 1H) , 2.00 (s, 2H) , 1.88 (s, 1H) , 1.73 (d, J = 12.5 Hz, 2H) , 1.61 (d, J = 12.4 Hz, 3H) , 1.14 (s, 9H) .

[0725] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6- (2-(methylamino) –2 -oxoethyl) -2, 4, 7 -trioxooctahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (P-8) . Using XBB-002 (0.15 g, 0.28 mmol, 1.00 eq.) , glycine methyl ester hydrochloride hydrochloride

(3.00 eq.) , Et_3N (5.40 eq.) in $CHCl_3$ (3 mL, 1%EtOH) yielding in P-8 as a white powder (108.1 mg, 77%) .

[0726] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6-methyl-2, 4, 7 -trioxooctahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (DW168) . Using XBB-002 (0.10 g, 0.19 mmol, 1.00 eq.) , $MeNH_2$ (2M in THF, 1.50 eq.) THF (2 mL) yielding in DW168 as a white powder (53%) . ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 7.98 (m, 2H) , 7.62 (m, 1H) , 7.49 (m, 2H) , 6.32 (s, 1H) , 5.92 (s, 1H) , 5.19 (t, J = 6.3 Hz, 1H) , 3.13 (d, J = 19.9 Hz, 1H) , 2.99 (s, 3H) , 2.88 (d, J = 19.1 Hz, 1H) , 2.64 (m, 1H) , 2.53 (s, 1H) , 2.21 (m, 1H) , 1.08 (s, 9H) .

[0727] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6-amino-9- (tert-butyl) -8, 9-dihydroxytetrahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrole-2, 4, 7 (3H, 8H) -trione (JW072) . Using XBB-002 and hydrazine yielding in JW072 as a white powder. ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 7.92-7.97 (m, 2H) , 7.39-7.43 (m, 1H) , 7.33-7.39 (m, 2H) , 5.76 (s, 1H) , 5.05 (t, J = 7.0 Hz, 1H) , 4.88 (s, 1H) , 2.96 (d, J = 18.0 Hz, 1H) , 2.70 (d, J = 18.0 Hz, 1H) , 2.61 (dd, J = 13.5, 7.0 Hz, 1H) , 2.30 (dd, J = 13.5, 7.0 Hz, 1H) , 1.10 (s, 9H) . The X-ray crystal structure of JW072 is shown in FIG. 1F.

[0728] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (adamantan-1-ylmethyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (SCC363) . Using XBB-002 (1.0 equiv., 0.10 mmol, 53.5 mg) , 1- adamantanemethylamine (2.0 equiv., 0.20 mmol., 33.1 mg, 35 μL) in THF (1 mL) yielding SCC363 (46.9 mg, 81%) . ^{1}H-NMR (600 MHz, $CDCl_3$) : δ [ppm] = 7.98 (d, J = 7.9 Hz, 2H) , 7.61 (t, J = 7.9 Hz, 1H) , 7.48 (t, J = 8.1 Hz, 1H) , 6.38 (s, 1H) , 6.07 (s, 1H) , 5.17 (t, J = 7.2 Hz, 1H) , 3.44 (d, J = 14.4 Hz, 1H) , 3.14 (d, J = 18.3 Hz, 1H) , 2.84 (d, J = 18.6 Hz, 1H) , 2.81 (d, J = 13.4 Hz, 1H) , 2.64 (dd, J = 7.0, 13.8 Hz, 1H) , 2.47 (s, 1H) , 2.22 (dd, J = 7.3, 14.1 Hz, 1H) , 2.00 (s, 3H) , 1.72 (d, J = 11.2 Hz, 3H) , 1.61 (d, J = 11.4 Hz, 3H) , 1.56 (brs, 6H) , 1.11 (s, 9H) .

[0729] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (((1S, 3S) -adamantan-2-yl) methyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl 4- (((tert-butoxycarbonyl) amino) methyl) benzoate (SCC505) . Using SCC501 (1.0 equiv., 0.13 mmol, 100 mg) , adamantan-2-ylmethanamine hydrochloride (1.5 equiv., 0.19 mmol, 38.2 mg) , Et_3N (4.0 equiv., 0.50 mmol, 51.1 mg, 70 μL) in $CHCl_3$ (1%EtOH, 2 mL) yielding SCC505 (63.7 mg, 73%) . MS (ESI) : m/z = 729.4 $[M+Na]^+$.

[0730] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6- (4-hydroxyphenethyl) -2, 4, 7-trioxooctahydro-4H, 9H- furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (SCC545) . Using XBB-002 (1.0 equiv., 50 μmol, 26.7 mg) , tyramine (1.3 equiv., 64.9 μmol., 8.9 mg) , Et_3N (2.0 equiv., 0. 10 mmol, 10.1 mg, 14 μL) in THF (1 mL) yielding SCC545 (14.0 mg, 51%) . ^{1}H-NMR (700 MHz, MeOD-d4) : δ [ppm] = 7.96 (d, J = 8.2 Hz, 2H) , 7.67 (t, J = 7.9 Hz, 1H) , 7.50 (t, J = 7.8 Hz, 1H) , 7.10 (d, J = 8.5 Hz, 2H) , 6.75 (d, J = 8.2 Hz, 2H) , 6.16 (s, 1H) , 5.69 (s, 1H) , 5.10 (t, J = 7.2 Hz, 1H) , 4.65 (s, 1H) , 3.83 (dd, J = 5.9, 13.3 Hz, 1H) , 3.57 (dd, J = 7.4, 14.0 Hz, 1H) , 2.96 (dt, J = 7 .0, 13.9 Hz, 1H) , 2.89 (dt, J = 5.0, 12.6 Hz, 1H) , 2.84 (d, J = 19.0 Hz, 1H) , 2.80 (d, J = 19.0 Hz, 1H) , 2.67 (dd, J = 7.0, 13.8 Hz, 1H) , 2.05 (dd, J = 7.3, 14.1 Hz, 1H) , 0.92 (s, 9H) .

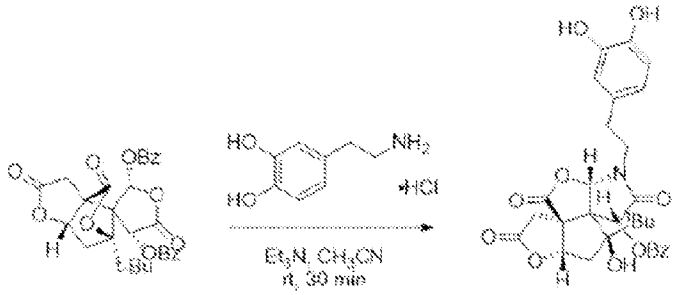
[0731] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (2- (5-methoxy-1H-indol-3-yl) ethyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (SCC555) . Using XBB-002 (1.0 equiv., 50 μmol, 26.7 mg) , 5-methoxytryptamine (1.3 equiv., 64. 9 μmol., 12.4 mg) , Et_3N (2.0 equiv., 0.10 mmol, 10.1 mg, 14 μL) in THF (1 mL) yielding SCC555 (16.7 mg, 55%) . ^{1}H-NMR (700 MHz, $CDCl_3$) : δ [ppm] = 8.0 9 (s, 1H) , 7.98 (d, J = 7.8 Hz, 2H) , 7.62 (t, J = 8.0 Hz, 1H) , 7.49 (t, J = 7.7 Hz , 1H) , 7.25 (d, J = 7.8 Hz, 1H) , 7.07 (d, J = 9.8 Hz, 2H) , 6.88 (dd, J = 2.3, 8.7 Hz, 1H) , 6.11 (s, 1H) , 5.54 (s, 1H) , 5.12 (t, J = 7.1 Hz, 1H) , 3.96 (dt, J = 6.5, 14.0 Hz, 1H) , 3.91 (s, 3H) , 3.64 (dt, J = 7.0, 14.2 Hz, 1H) , 3.22 (dt, J = 7.0, 1 4.9 Hz, 1H) , 3.08-30.3 (m, 1H) , 3.05 (d, J = 19.2 Hz, 1H) , 2.71 (d, J = 18.9 Hz, 1H) , 2.52 (dd, J = 7.2, 14.1 Hz, 1H) , 2.13 (dd, J = 7.3, 14.0 Hz, 1H) , 2.10 (brs, 1H) , 0.78 (s, 9H) .

[0732] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -9-hydroxy-6- (((1R, 4aS, 10aR) -7-isopropyl-1, 4a-dimethyl-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl) methyl) -2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (SCC5 58) . Using XBB002 (1.0 equiv., 75.0 μmol, 40.1 mg) , leelamine (1.3 equiv., 97.5 μmol, 26.1 mg) , Et_3N (2.0 equiv., 0.15 mmol, 15.2 mg, 21 μL) in THF (2 mL) yielding in SCC558 (29.7 mg, 57%) . ^{1}H-NMR (700 MHz, $CDCl_3$) : δ [ppm] = 7.97 (d, J = 7.2 Hz, 2H) , 7.61 (t, J = 7.0 Hz, 1H) , 7.48 (t, J = 7.1 Hz, 2H) , 7.14 (d, J = 8.2 Hz, 1H) , 6.98 (d, J = 8.2 Hz, 1H) , 6.89 (s, 1H) , 6.30 (s, 1H) , 6.05 (s, 1H) , 5.18 (t, J = 7.0 Hz, 1H) , 3.71 (d, J = 14.1 Hz, 1H) , 3.14 (d, J = 19.3 Hz, 1H) , 3.03-2.97 (m, 2H) , 2.89-2.79 (m, 3H) , 2.60 (dd, J = 7.1, 14.1 Hz, 1H) , 2.32 (d, J = 12.5 Hz, 1H) , 2.20 (dd, J = 7.0, 13.5 Hz, 1H) , 1.96-

1.91 (m, 1H) , 1.88-1.82 (m, 1H) , 1.76-1.65 (m, 2H) , 1.54 (d, J = 12.5 Hz, 1H) , 1.39-1.28 (m, 3H) , 1.22 (s, 3H) , 1.21 (s, 3H) , 1.20 (d, J = 7.1 Hz, 6H) , 1.00 (s, 3H) , 0.95 (s, 9H) .

[0733] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- (((1S, 5S) -3- (((tert-butoxycarbonyl) amino) methyl) adamantan-1-yl) methyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxo octahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (SCC564) . Using XBB002 (1.0 equiv., 0.16 mmol, 84 mg) , tert-butyl (((3S, 5R) -3- (aminomethyl) adamantan-1-yl) methyl) carba mate (1.2 equiv., 0.19 mmol, 55 mg) , Et3N (3.0 equiv., 0.47 mmol, 47.7 mg, 66 μL) in $CHCl_3$ (4 mL, 1%EtOH) yielding SCC564 (70.1 mg, 63%) . MS (ESI) : m/z = 729.2 (100%, $[M+Na]^+$) .

[0734] Synthesis of SXQ087-1

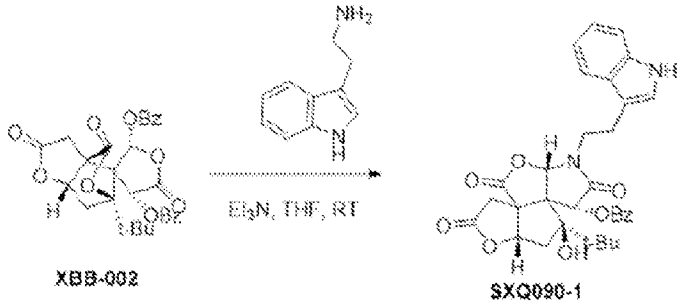


XBB-002 SXQ087-1

[0735] To an oven-dried flask containing a magnetic stir bar was added XBB-002 (20 mg, 0.037 mmol, 1.0 equiv.) and 0.3 mL of CH_3CN, followed by the addition of Et_3N (70 μL, 0.502 mmol, 14 equiv.) and dopamine hydrochloride (11 mg, 0.056 mmol, 1.5 equiv.) . The resulting solution was allowed to be stirred at room temperature for 30 min. Once completion indicated by TLC, the resulting solution was diluted with ethyl acetate and was quenched by the addition of saturated aqueous NH_4Cl (6 mL) . This mixture was extracted with EtOAc (3 × 10 mL) , the organic layers were combined, washed with saturated aqueous NaCl, and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo and this crude product was purified by column chromatography (hexane: EtOAc=2: 1, v/v) to give SXQ087-1 (16 mg, 76%) as white powder. TLC: Rf = 0.3 (Hexane/EtOAc = 1/1; strongly UV active, stains yellow upon $KMnO_4$ staining) . ^1H NMR (700 MHz, MeOD) δ 7.96 (d, J = 7.6 Hz, 2H) , 7.67 (t, J = 7.5 Hz, 1H) , 7.50 (t, J = 7.7 Hz, 2H) , 6.72 (d, J = 8.0 Hz, 1H) , 6.70 (d, J = 2.3 Hz, 1H) , 6.59 (dd, J = 8.0, 2.2 Hz, 1H) , 6.18 (s, 1H) , 5.65 (s, 1H) , 5.11 (t, J = 7.2 Hz, 1H) , 3.82 (m, 1H) , 3.55 –3.49 (m, 1H) , 2.87 (d, J = 3.1 Hz, 2H) , 2.82 (m, 1H) , 2.69 –2.63 (m, 1H) , 2.07 –2.03 (m, 1H) , 0.91 (s, 9H) . ^{13}C NMR (126 MHz, M

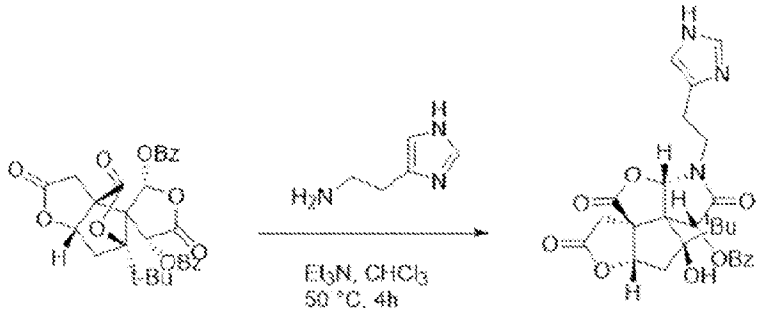
eOD) δ 179.4, 175.8, 169.3, 166.5, 146.7, 145.3, 135.3, 130.9, 130.5, 129.9, 129.5, 121.0, 116.9, 116.7, 89.9, 89.9, 87.5, 85.4, 72.4, 64.5, 60.6, 43.1, 42.9, 38.3, 37.2, 33.3, 26.9, 14.5.

[0736] Synthesis of SXQ090-1



[0737] To an oven-dried flask containing a magnetic stir bar was added XBB-002 (20 mg, 0.037 mmol, 1.0 equiv.) and 0.3 mL of THF, followed by the addition of Et_3N (11 μL, 0.075 mmol, 2 equiv.) and tryptamine (9 mg, 0.056 mmol, 1.5 equiv.) . The resulting solution was allowed to be stirred at room temperature for 3 h. Once completion indicated by TLC, the resulting solution was diluted with ethyl acetate and was quenched by the addition of saturated aqueous NH_4Cl (6 mL) . This mixture was extracted with EtOAc (3 × 10 mL) , the organic layers were combined, washed with saturated aqueous NaCl, and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo and this crude product was purified by column chromatography (hexane: EtOAc=1: 1, v/v) to give SXQ090-1 (18 mg, 85%) as white powder. TLC: Rf = 0.3 (Hexane/EtOAc = 2/1; strongly UV active, stains yellow upon $KMnO_4$ staining) . ^1H NMR (700 MHz, MeOD) δ 7.99 –7.95 (m, 2H) , 7.66 (tt, J = 7.3, 1.3 Hz, 1H) , 7.62 (dt, J = 7.6, 1.0 Hz, 1H) , 7.50 (dd, J = 8.3, 7.5 Hz, 2H) , 7.35 (dt, J = 8.0, 1.0 Hz, 1H) , 7.14 (s, 1H) , 7.11 (dddd, J = 21.8, 8.0, 7.0, 1.2 Hz, 3H) , 6.09 (s, 1H) , 5.42 (s, 1H) , 5.07 (t, J = 7.1 Hz, 1H) , 3.92 (ddd, J = 14.1, 6.6, 4.9 Hz, 1H) , 3.62 (ddd, J = 14.1, 9.3, 6.2 Hz, 1H) , 3.26 (ddd, J = 15.4, 9.3, 6.6 Hz, 1H) , 3.08 –3.03 (m, 1H) , 2.93 –2.81 (m, 2H) , 2.59 (dd, J = 13.8, 7.2 Hz, 1H) , 2.01 –1.98 (m, 1H) , 0.68 (s, 9H) . ^{13}C NMR (176 MHz, MeOD) δ 179.4, 175.8, 169.4, 166.5, 138.2, 135.2, 130.9, 129.9, 129.5, 128.7, 124.0, 122.7, 120.2, 119.2, 112.6, 111.8, 90.0, 87.4, 85.4, 72.5, 64.4, 60.5, 43.0, 42.8, 38.0, 37.2, 26.6, 23.4, 14.5.

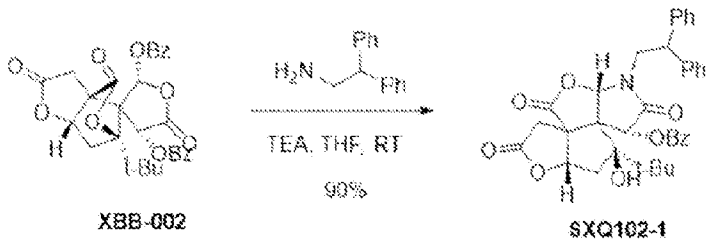
[0738] Synthesis of SXQ092-1



XBB-002 SXQ092-1

[0739] To an oven-dried flask containing a magnetic stir bar was added XBB-002 (20 mg, 0.037 mmol, 1.0 equiv.) and 0.3 mL of $CHCl_3$, followed by the addition of Et_3N (50 μL, 0.37 mmol, 10 equiv.) and histamine (7 mg, 0.056 mmol, 1. 5 equiv.) . The resulting solution was allowed to be stirred at 50 ℃ for 4h. Once co mpletion indicated by TLC, the resulting solution was diluted with ethyl acetate and was quenched by the addition of saturated aqueous NH_4Cl (6 mL) . This mixture was extracted with EtOAc (3 × 10 mL) , the organic layers we re combined, washed with saturated aqueous NaCl, and dried over anhydrous Na_2SO_4 . The solution was concentrated in vacuo and this crude product was purified by colum n chromatography (DCM: MeOH=30: 1, v/v) to give SXQ092-1 (5 mg, 26%) as white powder. TLC: Rf = 0.3 (DCM/MeOH = 30/1; strongly UV active, stains yellow upon $KMnO_4$ staining) . ^{1}H NMR (700 MHz, MeOD) δ 7.95 (d, J = 7.8 Hz, 2H) , 7.65 (t, J = 7.5 Hz, 1H) , 7.62 (s, 1H) , 7.49 (t, J = 7.7 Hz, 2H) , 6.89 (s, 1H) , 6.21 (s, 1H) , 5.74 (s, 1H) , 5.13 (t, J = 7.1 Hz, 1H) , 3.85 (m, 1H) , 3.63 (m, 1H) , 3.02 (m, 1H) , 2.95 –2.89 (m, 2H) , 2.85 (d, J = 19.1 Hz, 1H) , 2.6 8 (dd, J = 13.7, 7.2 Hz, 1H) , 2.08 (dd, J = 13.7, 7.2 Hz, 1H) , 0.96 (s, 9H) .

[0740] Synthesis of SXQ102-1

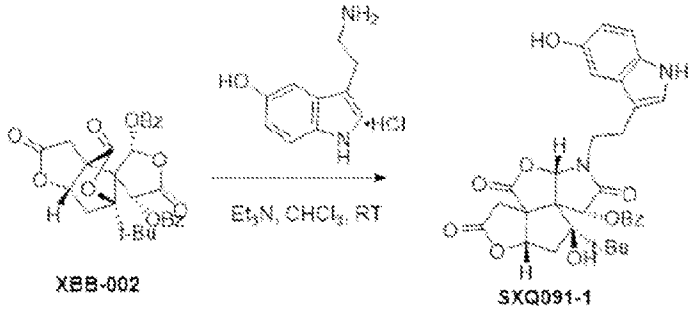


XBB-002 SXQ102-1

[0741] To an oven-dried flask containing a magnetic stir bar was added XBB-002 (20 mg, 0.037 mmol, 1.0 equiv.) and 0.4 mL of THF, followed by the addition of Et_3N (16 μL, 0.112 mmol, 3 equiv.) and 2, 2-diphenylethan-1-amine (11 mg, 0.056 mmol, 1.5 equiv.) . The resulting solution was allowed to be sti rred at room temperature for 15 h. Once completion indicated by TLC, the resulting so

lution was diluted with ethyl acetate and was quenched by the addition of saturated a queous NH_4Cl (6 mL) . This mixture was extracted with EtOAc (3 × 10 mL) , the organic layers were combined, washed with saturated aqueous NaCl, an d dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo and this c rude product was purified by column chromatography (hexane: EtOAc=2: 1, v/ v) to give SXQ102-1 (20 mg, 90%) as white powder. TLC: Rf = 0.3 (Hexa ne/EtOAc = 2/1; strongly UV active, stains yellow upon $KMnO_4$ staining) . ^{1} H NMR (700 MHz, $CDCl_3$) δ 8.13 –8.10 (m, 1H) , 7.98 –7.95 (m, 2H) , 7.62 (m, 1H) , 7.49 (t, J = 7.7 Hz, 3H) , 7.33 (m, 8H) , 7.27 –7.22 (m, 3H) , 6.02 (s, 1H) , 5.62 (s, 1H) , 5.12 (t, J = 7.1 Hz, 1H) , 4.60 (t, J = 8.9 Hz, 1H) , 4.19 (m, 1H) , 3.97 (m, 1H) , 2.86 (m, 1H) , 2.55 (dd, J = 14.1, 7.2 Hz, 1H) , 2.48 (m, 1H) , 2.13 (dd, J = 14.1, 7.1 Hz, 1H) , 0.82 (s, 9H) . ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 173.7, 167.2, 165.3, 140.8, 140.3, 134.4, 133.8, 130.3, 130.2, 129.1, 128.9, 128.6, 128.3, 127.9, 127.8, 127.5, 127.4, 88.2, 87.5, 83.2, 70.7, 62.4, 59.3, 48.7, 45.3, 43.0, 37. 2, 35.9, 26.2.

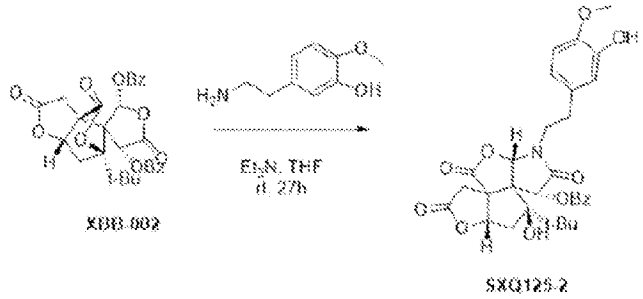
[0742] Synthesis of SXQ091-1



[0743] To an oven-dried flask containing a magnetic stir bar was added XBB-002 (20 mg, 0.037 mmol, 1.0 equiv.) and 0.5 mL of $CHCl_3$, followed by the addition of Et_3N (32 μL, 0.224 mmol, 6 equiv.) and serotonin hydrochloride (12 mg, 0.056 mmol, 1.5 equiv.) . The resulting solution was allowed to be stirred at room temperature for 19 h. Once completion indicated by TLC, the resulting solution was di luted with ethyl acetate and was quenched by the addition of saturated aqueous NH_4Cl (6 mL) . This mixture was extracted with EtOAc (3 × 10 mL) , the organic layers were combined, washed with saturated aqueous NaCl, an d dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo and this c rude product was purified by column chromatography (hexane: EtOAc=1: 1, v/ v) to give SXQ091-1 (6 mg, 28%) as white powder. TLC: Rf = 0.3 (Hexan e/EtOAc = 1/1; strongly UV active, stains yellow upon $KMnO_4$ staining) . ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.48 (t, J = 6.5 Hz, 2H) , 8.15 (t, J = 7.5 Hz,

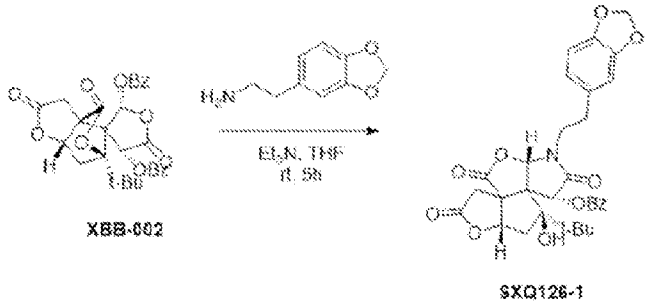
1H) , 8.01 (t, J = 7.7 Hz, 2H) , 7.75 –7.70 (m, 1H) , 7.59 –7.50 (m, 2H) , 7.28 (m, 1H) , 6.61 (s, 1H) , 6.03 (d, J = 5.3 Hz, 1H) , 5.64 (t, J = 7.1 Hz, 1H) , 4.42 (m, 1 H) , 4.07 (m, 1H) , 3.71 (m, 1H) , 3.59 –3.47 (m, 2H) , 3.30 (m, 1H) , 3.13 (m, 1H) , 2.59 –2.55 (m, 1H) , 1.24 (s, 9H) . ^{13}C NMR (176 MHz, $CDCl_3$) δ 178.3, 174.3, 167.7, 165.4, 150.0, 134.1, 131.3, 129.8, 129.7, 128.6, 128.6, 127.7, 127.6, 123.3, 123.2, 111.9, 109.6, 102.0, 88.5, 86.1, 83.9, 71.0, 62.8, 59.1, 41.7, 41.5, 36.8, 36. 0, 25.7, 22.2.

[0744] Synthesis of SXQ125-2



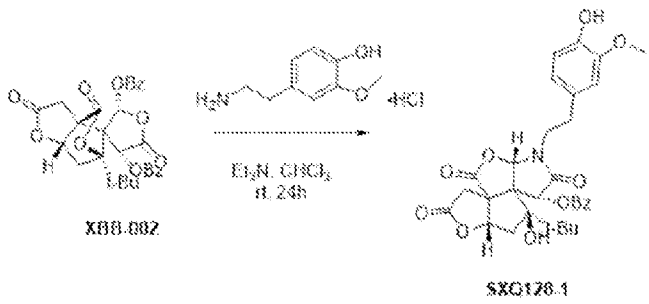
[0745] To an oven-dried flask containing a magnetic stir bar was added XBB-002 (30 mg, 0.056 mmol, 1.0 equiv.) and 0.5 mL of THF, followed by the addition of Et_3N (24 μL, 0.168 mmol, 3 equiv.) and 3-hydroxy-4-methoxyphenethylamine (14 mg, 0.084 mmol, 1.5 equiv.) . The resulti ng solution was allowed to be stirred at room temperature for 27 h. Once completion i ndicated by TLC, the resulting solution was diluted with ethyl acetate and was quench ed by the addition of saturated aqueous NH_4Cl (6 mL) . This mixture was extra cted with EtOAc (3 × 10 mL) , the organic layers were combined, wash ed with saturated aqueous NaCl, and dried over anhydrous Na_2SO_4. The solution wa s concentrated in vacuo and this crude product was purified by colum n chromatography (Hexane: EtOAc=1: 1, v/v) to give SXQ125-2 (19 mg, 60%) as white powder. TLC: Rf = 0.3 (Hexane/EtOAc = 1/1; strongly UV active , stains yellow upon $KMnO_4$ staining) . ^{1}H NMR (700 MHz, MeOD) δ 7.98 –7.95 (m, 2H) , 7.67 (m, 1H) , 7.50 (t, J = 7.7 Hz, 2H) , 6.87 (d, J = 8.2 Hz, 1H) , 6.74 (d, J = 2.1 Hz, 1H) , 6.71 (m, 1H) , 6.17 (s, 1H) , 5.66 (s, 1H) , 5.10 (t, J = 7.1 H z, 1H) , 3.83 (s, 3H) , 3.81 (q, J = 6.1, 5.2 Hz, 1H) , 3.56 (ddd, J = 14.4, 8.5, 6.3 Hz, 1H) , 2.92 (ddd, J = 14.8, 8.4, 6.5 Hz, 1H) , 2.84 (d, J = 4.9 Hz, 3H) , 2.66 (d d, J = 13.8, 7.2 Hz, 1H) , 2.08 –2.03 (m, 1H) , 0.91 (s, 9H) . ^{13}C NMR (176 MHz, M eOD) δ 179.4, 175.8, 169.3, 166.5, 148.1, 147.9, 135.3, 132.0, 130.9, 129.9, 129.4, 1 20.9, 116.9, 113.2, 89.9, 87.4, 85.4, 72.3, 64.5, 60.6, 56.5, 43.1, 43.0, 38.3, 37.2, 33.3, 26.9, 14.5.

[0746] Synthesis of SXQ126-1



[0747] To an oven-dried flask containing a magnetic stir bar was added XBB-002 (30 mg, 0.056 mmol, 1.0 equiv.) and 0.5 mL of THF, followed by the addition of Et_3N (24 μL, 0.168 mmol, 3 equiv.) and 3, 4-Methylenedioxyphe nethylamine (12 μL, 0.084 mmol, 1.5 equiv.) . The resulting solution was allowed to be stirred at room temperature for 5 h. Once completion indicated by TLC, the resulti ng solution was diluted with ethyl acetate and was quenched by the addition of satura ted aqueous NH_4Cl (6 mL) . This mixture was extracted with EtOAc (3 ×10 mL) , the o rganic layers were combined, washed with saturated aqueous NaCl, and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo and this c rude product was purified by column chromatography (Hexane: EtOAc=1: 1, v/ v) to give SXQ126-1 (22 mg, 68%) as white powder. TLC: Rf = 0.5 (Hexa ne/EtOAc = 1/1; strongly UV active, stains yellow upon $KMnO_4$ staining) . ^1H NMR (700 MHz, MeOD) δ 7.98 –7.95 (m, 2H) , 7.66 (tt, J = 7.5, 1.3 Hz, 1H) , 7.50 (dd, J = 8.4, 7.5 Hz, 2H) , 6.80 (d, J = 1.7 Hz, 1H) , 6.76 (d, J = 7. 9 Hz, 1H) , 6.72 (dd, J = 7.9, 1.7 Hz, 1H) , 6.19 (s, 1H) , 5.92 (s, 2H) , 5.73 (s, 1 H) , 5.11 (t, J = 7.2 Hz, 1H) , 3.81 (dt, J = 14.2, 6.3 Hz, 1H) , 3.57 (ddd, J = 14.4 , 8.1, 6.5 Hz, 1H) , 2.97 –2.92 (m, 1H) , 2.91 –2.86 (m, 1H) , 2.85 (d, J = 9.4 Hz, 2 H) , 2.67 (dd, J = 13.8, 7.2 Hz, 1H) , 2.08 –2.04 (m, 1H) , 0.94 (s, 9H) . ^{13}C NMR (176 MHz, MeOD) δ 179.4, 175.8, 169.3, 166.5, 149.5, 148.0, 13 5.3, 133.0, 131.0, 129.9, 129.4, 123.0, 110.1, 109.4, 102.3, 89.8, 87.5, 85.4, 72.3, 64.4, 60.6, 43.2, 43.1, 38.3, 37.2, 33.7, 26.9, 14.5.

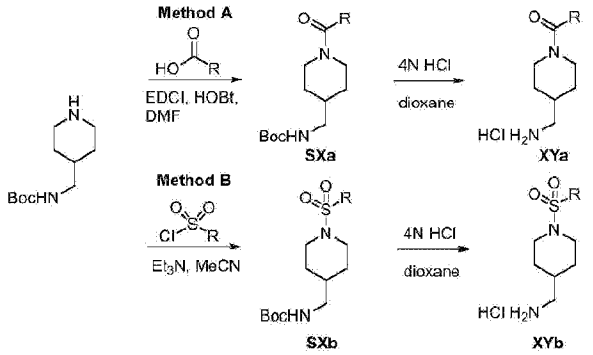
[0748] Synthesis of SXQ128-1

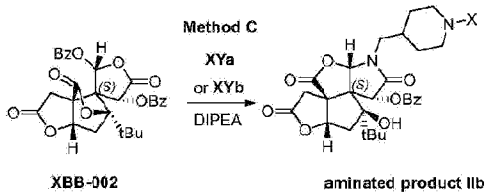


[0749] To an oven-dried flask containing a magnetic stir bar was added XBB-002 (30 mg, 0.056 mmol, 1.0 equiv.) and 0.5 mL of THF, followed by the addition of Et_3N (24 μL, 0.168 mmol, 3 equiv.) and 3-O-Methyldopamine hydrochloride (18 mg, 0.084 mmol, 1.5 equiv.) . The resulting solution was allowed to be stirred at room temperature for 24 h. Once completion indicated by TLC, the resulting solution was diluted with ethyl acetate and was quenched by the addition of saturated aqueous NH_4Cl (6 mL) . This mixture was extracted with EtOAc (3 × 10 mL) , the organic layers were combined, washed with saturated aqueous NaCl, and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo and this crude product was purified by column chromatography (Hexane: EtOAc=1: 1, v/v) to give SXQ128-1 (15 mg, 47%) as white powder. TLC: Rf = 0.4 (Hexane/EtOAc = 1/1; strongly UV active, stains yellow upon $KMnO_4$ staining) . ^1H NMR (700 MHz, MeOD) δ 7.98 –7.94 (m, 2H) , 7.68 –7.65 (m, 1H) , 7.50 (dd, J = 8.4, 7.4 Hz, 2H) , 6.84 (d, J = 1.9 Hz, 1H) , 6.75 (d, J = 8.0 Hz, 1H) , 6.71 (dd, J = 7.9, 1.9 Hz, 1H) , 6.13 (s, 1H) , 5.63 (s, 1H) , 5.10 (t, J = 7.2 Hz, 1H) , 3.89 (s, 3H) , 3.60 (ddd, J = 14.4, 8.4, 6.2 Hz, 1H) , 2.99 (ddd, J = 14.7, 8.5, 6.4 Hz, 1H) , 2.91 (dt, J = 14.5, 6.1 Hz, 1H) , 2.81 (q, J = 19.2 Hz, 2H) , 2.65 (dd , J = 13.8, 7.2 Hz, 1H) , 2.06 –2.02 (m, 1H) , 0.88 (s, 9H) .

[0750] ^{13}C NMR (176 MHz, MeOD) δ 179.4, 175.8, 169.3, 166.5, 149.3, 146.5, 135.3, 130.9, 130.3, 129.9, 129.4, 122.3, 116.5, 113.1, 89.9, 87.4, 85.4, 72.4, 64.4, 60.6, 56.3, 43.1, 42.6, 38.2, 37.1, 33.2, 26.9, 14.5.

[0751] Example 1.7: Synthesis of piperazine substituted-bilobalide lactam analogues, according to Schemes 5, 10 and 11





[0752] Method A (Scheme 10) : To a solution of substituted carboxylic acid (2 mmol, 1.0 equiv.) in DMF (20 mL) , 1-hydroxybenzotrizole (HOBt) (2.2 mmol, 1.1 equiv.) and N- (3-dimethylaminopropyl) -N′-ethylcarbodiimide hydrochloride (EDCI) (2.2 mmol, equiv.) were added. This mixture was stirred for 30 minutes at room temperature, then tert-butyl (piperidin-4-ylmethyl) carbamate (2 mmol, 1.0 equiv.) was added. Upon completion monitored by TLC , the crude reaction mixture was diluted with EtOAc (20 mL) and washed with water (20 mL x 3) and brine (20 mL x 3) . The combined organic layers were dried over Na_2SO_4. The solvents were then removed under reduced pressure. The crude residue was purified by silica gel column chromatography (hexane/EtOAc = 3: 1) to afford the desired Boc-protected amines (SXa1 through SXa4 according to Table 1h) . To an oven-dried flask was added compound and 4 N HCl in dioxane, respectively. The resulting solution was stirred at room temperature for 1 h. Once completed, the reaction solution was concentrated under reduced pressure to provide the respective alkyl amines XYa as a white powder, which was directly used for the next step without purification.

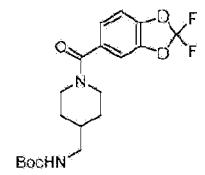
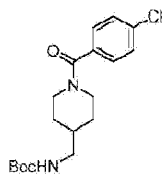
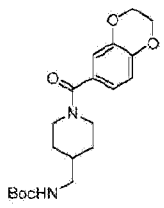
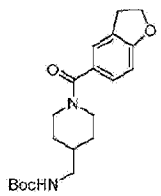
[0753] Method B (Scheme 11) : To a solution of tert-butyl (piperidin-4-ylmethyl) carbamate (2 mmol, 1.0 equiv.) in acetonitrile was added substituted sulfonyl chloride (2.2 mmol, 1.1 equiv.) and triethylamine, respectively. The resulting mixture was stirred at room temperature for 4 h. Upon completion monitored by TLC, the reaction solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3: 1

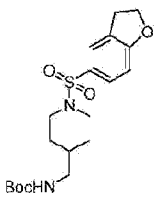
) to afford the desired Boc-protected amines (SXb1 according to Table 1h) . To an oven-dried flask was added compound and 4 N HCl in dioxane, respectively. The resulting solution was stirred at room temperature for 1 h. Once completed, the reaction solution was concentrated under reduced pressure to provide the respective a lkyl amines XYb white powder, which was directly used for the next step without purif ication.

[0754] Method C (Scheme 5) : To a solution of XBB-002 (100 mg, 1.0 equiv) in anhydro us tetrahydrofuran (2 mL) was added substituted alkyl amines XYa or XYb (1.1 equiv.) and DIPEA. The resulting solution was stirred at room temperature f or 1 h. Upon completion indicated by TLC, the reaction solution was concentrated in v acuo. The residue was dissolved with dichloromethane and the organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, filtered and co ncentrated in vacuo. The crude product was purified via column chrom atography with elution system (hexane: EtOAc = 3: 1) to provide the corresponding aminated product IIb according to Table 1i as a white powder.

[0755] Examples of Boc-protected amines are summarized in Table 1h.

[0756] Table 1h: Example Boc-protected amines

Method A (Scheme 10)			
			
SXa1	SXa2	SXa3	SXa4

Method B (Scheme 11)

SXb1

[0757] Synthesis of tert-butyl ((1- (2, 2-difluorobenzo [d] [1, 3] dioxole-5-carbonyl) piperid in-4-yl) methyl) carbamate (SXa1) . Method A (Scheme 10) . Colourless oil (0.76 g, 95%) . R_f = 0.30 (hexane/EtOAc, 5: 1) ; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 7.21 –7.12 (m, 2H) , 7.11 –7.02 (m, 1H) , 4.95 –4.26 (m, 2H) , 3.76 (s,

1H) , 3.22 –2.62 (m, 4H) , 1.75 (s, 2H) , 1.43 (s, 9H) , 1.34 –0.96 (m, 2H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 168.61, 156.09, 144.43, 143.63, 134.14, 132.14, 131.59, 129.04, 122.86, 109.39, 108.88, 79.39, 47.90, 45.75, 42.52, 36.94, 30.29, 28.38; HRMS (ESI) m/z: [M+Na] $^{+}$ Calcd for $C_{19}H_{24}F_2N_2O_5Na^{+}$ 421.15455, found 421.15424.

[0758] Synthesis of tert-butyl ((1- (4-chlorobenzoyl) piperidin-4-yl) methyl) carbamate (SXa2) . Method A (Scheme 10) . Colourless oil (0.64 g, 90%) . R_f = 0.40 (hexane/EtOAc, 6: 1) ; mp = 138.5-139.0℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 7.49 –7.31 (m, 4H) , 4.66 (s, 2H) , 3.76 (s, 1H) , 3.23 –2.63 (m, 4H) , 1.94 –1.64 (s, 2H) , 1.46 (s, 9H) , 1.35 –0.95 (m, 2H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 169.29, 156.11, 135.57, 134.53, 128.72, 128.41, 79.36, 47.71, 45.77, 42.27, 36.95, 30.37, 29.45, 28.40; HRMS (ESI) m/z: [M+Na] $^{+}$ Calcd for $C_{18}H_{25}ClN_2O_3Na^{+}$ 375.14459, found 375.14422.

[0759] Synthesis of tert-butyl ((1- (2, 3-dihydrobenzo [b] [1, 4] dioxine-6-carbonyl) piperidin-4-yl) methyl) carbamate (SXa3) . Method A (Scheme 10) . Colourless oil (0.66 g, 87%) . R_f = 0.30 (hexane/EtOAc, 5: 1) ; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 7.00 –6.92 (m, 1H) , 6.93 –6.83 (m, 2H) , 4.67 (s, 1H) , 4.29 (s, 4H) , 3.90 (s, 1H) , 3.23 –2.62 (m, 4H) , 1.75 (s, 2H) , 1.46 (s, 9H) , 1.20 (s, 2H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 169.89, 156.05, 144.78, 143.31, 129.34, 120.51, 117.19, 116.54, 79.39, 64.46, 64.31, 45.91, 37.02, 28.41; HRMS (ESI) m/z: [M+Na] $^{+}$ Calcd for $C_{20}H_{28}N_2O_5Na^{+}$ 399.20014, found 399.20010.

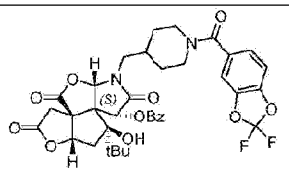
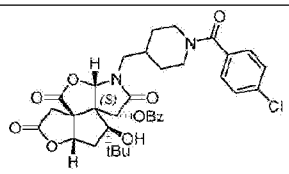
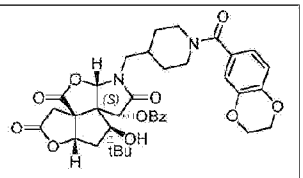
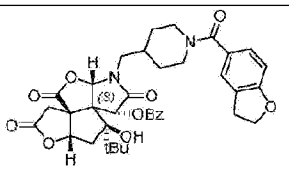
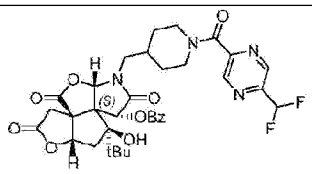
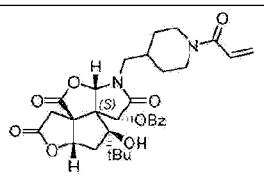
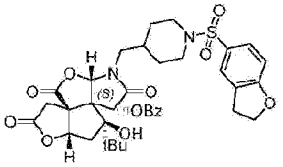
[0760] Synthesis of tert-butyl ((1- (2, 3-dihydrobenzofuran-5-carbonyl) piperidin-4-yl) methyl) carbamate (SXa4) . Method A (Scheme 10) . White powder (0.61 g, 84%) . R_f = 0.30 (hexane/EtOAc, 5: 1) ; mp = 138.7-139.5℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 7.30 (d, J = 1.7 Hz, 1H) , 7.18 (dd, J = 8.2, 1.8 Hz, 1H) , 6.78 (d, J = 8.2 Hz, 1H) , 4.68 (s, 1H) , 4.62 (t, J = 8.7 Hz, 2H) , 4.17 –3.64 (m, 1H) , 3.24 (t, J = 8.7 Hz, 2H) , 3.12 –2.70 (m, 4H) , 1.86 –1.61 (m, 3H) , 1.46 (s, 9H) , 1.32 –1.05 (m, 2H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 170.56, 161.21, 156.15, 128.22, 127.57, 127.25, 124.38, 108.75, 78.99, 71.52, 45.78, 36.96, 36.43, 29.34, 28.36; HRMS (ESI) m/z: [M+Na] $^{+}$ Calcd for $C_{15}H_{19}NO_8Na^{+}$ 364.10029, found 364.09999.

[0761] Synthesis of tert-butyl ((1- ((2, 3-dihydrobenzofuran-5-yl) sulfonyl) piperidin-4-yl) methyl) carbamate (SXb2) . Method B (Scheme 11) . White powder (0.70 g, 88%) . R_f = 0.20 (hexane/EtOAc, 5: 1) ; mp = 158.7-159.4℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 7.65 –7.49 (m, 2H) , 6.87 (d, J = 8.4 Hz, 1H) , 4.71 (t, J = 8.8 Hz, 2H) , 4.62 (s, 1H) , 3.78 (dt, J = 12.2, 3.4 Hz, 2H)

, 3.30 (t, J = 8.8 Hz, 2H) , 3.00 (t, J = 6.4 Hz, 2H) , 2.26 (td, J = 11.7, 2.5 Hz, 2 H) , 1.76 (dd, J = 12.7, 3.1 Hz, 2H) , 1.44 (s, 9H) , 1.39 –1.24 (m, 2H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 163.42, 155.56, 128.78, 127.82, 127.05, 124.42, 108.97, 78.86, 71.83, 45.65, 45.18, 35.35, 28.67, 28.59, 27.93; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{28}N_2O_5SNa^+$419.16111, found 419.16088.

[0762] Examples of piperazine substituted-bilobalide lactam analogues according to Method C as described in this example (Scheme 5) are summarized in Table 1i.

[0763] Table 1i: Example piperazine substituted-bilobalide lactam analogues

 Chemical Formula: $C_{36}H_{36}F_2N_2O_{11}$ Molecular Weight: 710.68 **XBB-044**	 Chemical Formula: $C_{35}H_{37}ClN_2O_9$ Molecular Weight: 665.14 **XBB-047**	 Chemical Formula: $C_{37}H_{40}N_2O_{11}$ Molecular Weight: 688.73 **XBB-045**
 Chemical Formula: $C_{37}H_{40}N_2O_{10}$ Molecular Weight: 672.73 **XBB-046**	 Chemical Formula: $C_{34}H_{36}F_2N_4O_9$ Molecular Weight: 682.68 **XBB-043**	 Chemical Formula: $C_{31}H_{36}N_2O_9$ Molecular Weight: 580.63 **XBB-048**
 Chemical Formula: $C_{38}H_{40}N_2O_{11}S$ Molecular Weight: 708.78 **XBB-078**		

[0764] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -6- ((1- (2, 2-difluorobenzo [d] [1, 3] dioxole-5-carbonyl) piperidin-4-yl) methyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-044) . Using method C (Scheme 5) and SXa1 yielding in XBB-044 as a white powder (93 mg, 70%) . R_f = 0.20 (DCM/MeOH, 10: 1) ; mp = 103.6-104.5°C; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.05 –7.94 (m, 2H) , 7.71 –7.63 (m, 1H) , 7.51 (t, J = 7.8 Hz, 2H) , 7.22 –7.08 (m, 3H) , 6.36 (s, 1H) , 5.95 (s, 1H) , 5.18 (t, J = 7.1 Hz, 1H) , 4.61 (m, 1H) , 3.79 (m, 1H

) , 3.62 –2.77 (m, 9H) , 2.70 (dd, J = 13.9, 7.2 Hz, 1H) , 2.23 (dd, J = 13.9, 7.1 Hz , 1H) , 2.13 (m, 2H) , 1.72 (m, 2H) , 1.11 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 177.90, 173.51, 168.93, 167.69, 165.27, 144.64, 143.71, 131.52, 130.06, 128.80, 127.71, 122.91, 109.60, 108.84, 86.93, 83.51, 70.69, 62.90, 59.25, 42.56, 37 .46, 36.45, 31.59, 26.48, 22.66.

[0765] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -6- ((1- (2, 2-difluorobenzo [d] [1, 3] dioxole-5-carbonyl) piperidin-4-yl) methyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] fur o [2, 3-b] pyrrol-8-yl benzoate (XBB-047) . Using method C (Scheme 5) a nd SXa2 yielding in XBB-047 as a white powder (97 mg, 78%) . R_f = 0.30 (DCM/ MeOH, 10: 1) ; mp = 137.3-137.9℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.0 3 –7.87 (m, 2H) , 7.62 (t, J = 7.4 Hz, 1H) , 7.48 (t, J = 7.7 Hz, 2H) , 7.40 (d, J = 8.1 Hz, 2H) , 7.32 (d, J = 8.2 Hz, 2H) , 6.33 (s, 1H) , 5.93 (s, 1H) , 5.13 (t, J = 7 .1 Hz, 1H) , 4.59 (s, 1H) , 4.06 –3.63 (m, 2H) , 3.58 –3.19 (m, 2H) , 3.18 – 3.08 (m, 2H) , 3.08 –2.75 (m, 2H) , 2.69 (dd, J = 14.0, 7.1 Hz, 1H) , 2.19 – 2.06 (m, 2H) , 1.80 –1.48 (m, 2H) , 1.43 –1.18 (m, 2H) , 1.05 (s, 9H) ; ^{13}C {^{1} H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 177.90, 173.59, 169.62, 167.71, 165.2 7, 135.97, 134.31, 133.92, 130.06, 128.93, 128.80, 128.38, 127.73, 86.84, 83.58, 70.7 1, 62.93, 59.24, 47.48, 46.04, 42.49, 42.07, 37.46, 36.47, 34.46, 30.29, 29.51, 26.50 . HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{35}H_{37}ClN_2O_9Na^+$ 687.20798, found 687.20744.

[0766] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -6- ((1- (2, 3-dihydrobenzo [b] [1, 4] dioxine-6-carbonyl) piperidin-4-yl) methyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-045) . Using method C (Scheme 5) and SXa3 yielding in XBB-045 as a white powder (77 mg, 66%) . R_f = 0.2 (DCM/MeOH, 10: 1) ; mp = 156.7-157.4℃; ^{1}H-NMR (400 MHz, MeOD) : δ [ppm] = 8.11 –7.87 (m, 2H) , 7.76 –7.59 (m, 1H) , 7.51 (t, J = 7.7 Hz, 2H) , 6.89 (d, J = 10.8 Hz, 3H) , 6.41 (s, 1H) , 6.08 (s, 1H) , 5.19 (t, J = 7.1 Hz, 1H) , 4.55 (s, 1H) , 4.26 (s, 4H) , 3.82 (s, 1H) , 3.42 (d d, J = 14.1, 7.5 Hz, 1H) , 3.27 (dd, J = 14.2, 7.3 Hz, 1H) , 3.05 (s, 1H) , 2.84 (s, 1H) , 2.74 (dd, J = 13.7, 7.1 Hz, 1H) , 2.13 (dd, J = 13.8, 7.2 Hz, 2H) , 1.86 –1.45 (m, 2H) , 1.37 –1.15 (m, 1H) , 1.08 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, MeO D) : δ [ppm] = 178.09, 174.35, 170.57, 168.29, 165.15, 145.26, 143.55, 133.99, 129.66 , 128.56, 128.43, 128.03, 120.00, 116.98, 116.03, 86.20, 84.05, 71.04, 64.38, 64.24, 63.04, 60.18, 59.31, 53.47, 41.80, 37.08, 36.14, 34.31, 30.35, 29.26, 25.67.

[0767] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -6- ((1- (2, 3-dihydrobenzofuran-5-carbonyl) piperidin-4-yl) methyl) -9-hydroxy-2, 4, 7-

trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-046) . Using method C (Scheme 5) and SXa4 yielding in XBB-046 as a white powder (85 mg, 68%) . R_f = 0.20 (DCM/MeOH , 10:1) ; mp = 142.5-143.3℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.04 –7.83 (m, 2H) , 7.70 –7.56 (m, 1H) , 7.49 (t, J = 7.8 Hz, 2H) , 7.26 (s, 1H) , 7.16 (dd, J = 8.2, 1.8 Hz, 1H) , 6.78 (d, J = 8.2 Hz, 1H) , 6.35 (s, 1H) , 5.94 (s, 1H) , 5.16 (t, J = 7.1 Hz, 1H) , 4.61 (t, J = 8.7 Hz, 2H) , 3.60 –3.37 (m, 1H) , 3.31 –3.04 (m, 5H) , 3.00 –2.79 (m, 3H) , 2.69 (dd, J = 13.8, 7.1 Hz, 1H) , 2.20 (dd, J = 14.0 , 7.1 Hz, 1H) , 2.15 –2.02 (m, 2H) , 1.72. –1.50 (s, 2H) , 1.44 –1.21 (m, 2H) , 1.10 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 177.90, 173.67, 171.02, 167.71, 165.28, 161.64, 134.25, 130.05, 128.77, 127.80, 127.75, 127.65, 127.47, 124.41, 109.07, 88.46, 86.68, 83.70, 71.73, 70.78, 62.99, 59.22, 53.53, 42.38, 37.48, 36.49, 34.55, 30.10, 29.40, 26.56; HRMS (ESI) m/z: $[M+K]^+$ Calcd for $C_{37}H_{40}N_2O_{10}K^+$ 711.25243, found: 711.25198.

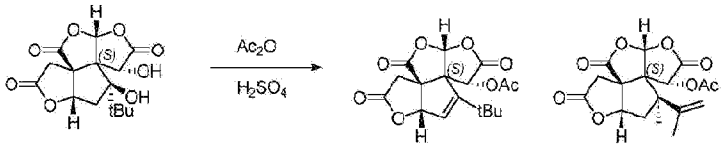
[0768] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -6- ((1- (5- (difluoromethyl) pyrazine-2-carbonyl) piperidin-4-yl) methyl) -9-hydroxy-2, 4, 7 -trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-043) . Using method C (Scheme 5) yielding in XBB-043 as a white powder (79 mg, 62%) . R_f = 0.20 (DCM/MeOH, 30: 1) ; mp = 84.5-85.2℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.97 –8.81 (m, 2H) , 7.95 (d, J = 7.8 Hz, 2H) , 7.61 (t, J = 7.5 Hz, 1H) , 7.53 –7.43 (m, 2H) , 6.99 –6.54 (m, 1H) , 6.33 (d, J = 5.2 Hz, 1H) , 5.94 (s, 1H) , 5.15 (q, J = 6.5 Hz, 1H) , 4.79 –4.56 (m, 1H) , 3.92 (d, J = 13.4 Hz, 1H) , 3.73 (d, J = 17.1 Hz, 1H) , 3.54 –3.36 (m, 1H) , 3.32 –3.18 (m, 1H) , 3.17 –3.05 (m, 2H) , 2.94 –2.80 (m, 2H) , 2.73 –2.62 (m, 1H) , 2.15 (dd, J = 13.9, 7.2 Hz, 2H) , 1.78 (d, J = 13.2 Hz, 1H) , 1.61 (d, J = 13.1 Hz, 1H) , 1.49 –1.25 (m, 2H) , 1.05 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 177.87, 173.54, 167.72, 167.64, 165.23, 164.53, 164.46, 150.91, 144.29, 140.03, 134.28, 130.03, 128.78, 127.72, 112.83 (t, J = 241.2 Hz) , 88.65, 88.30, 87.03, 86.98, 83.50, 70.69, 62.87, 59.24, 46.89, 46.68, 46.14, 42.57, 42.32, 37.42, 36.43, 34.48, 34.18, 30.41, 30.29, 29.50, 26.44; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{34}H_{36}F_2N_6O_9Na^+$ 705.23426, found: 705.23463.

[0769] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -6- ((1-acryloylpiperidin-4-yl) methyl) -9- (tert-butyl) -9-hydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-048) . Using method C (Scheme 5) yielding in XBB-048 as a white powder (54 mg, 50%) . R_f = 0.20 (DCM/MeOH, 5: 1) ; mp = 159.2-160.1℃; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.05 –7.91 (m, 2H) , 7.72 –7.59 (m, 1H) , 7.51 (t, J = 7.7 Hz, 2H) , 6.

70 –6.50 (m, 1H) , 6.37 (s, 1H) , 6.36 –6.20 (m, 1H) , 5.94 (s, 1H) , 5.84 –5.66 (m, 1H) , 5.24 –5.02 (m, 1H) , 4.59 (d, J = 13.1 Hz, 1H) , 4.19 –3.98 (m, 1H) , 3.64 –3.1 9 (m, 1H) , 3.17 –3.04 (m, 3H) , 2.95 –2.59 (m, 3H) , 2.29 –2.11 (m, 2H) , 1.77 – 1.63 (m, 2H) , 1.49 –1.30 (m, 2H) , 1.13 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 177.40, 173.07, 167.06, 165.36, 164.93, 133.84, 129.65, 128.35, 127.36, 126.71, 88.44, 86.12, 83.00, 70.27, 62.70, 58.76, 45.56, 41.86, 37.15, 35.90, 34.03, 29.53, 29.27, 28.77, 26.10; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{31}H_{36}N_2O_9Na^+$ 603.23130, found: 603.23116.

[0770] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10aS) -9- (tert-butyl) -6- ((1- ((2, 3-dihydrobenzofuran-5-yl) sulfonyl) piperidin-4-yl) methyl) -9 -hydroxy-2, 4, 7 -trioxooctahydro-4H, 9H -furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl benzoate (XBB-078) . Using method C (Scheme 5) yielding in XBB-078 as a white powder (99 mg, 75%) . R_f = 0.1 (DCM/MeOH, 10: 1) ; mp = 116.5-117.2°C; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ [ppm] = 8.13 –7.88 (m, 2H) , 7.64 (t, J = 7.5 Hz, 1H) , 7.60 –7.38 (m, 5H) , 6.95 –6.81 (m, 1H) , 6.33 (s, 1H) , 5.91 (s, 1H) , 5. 21 (t, J = 7.0 Hz, 1H) , 4.71 (t, J = 8.8 Hz, 2H) , 3.74 (d, J = 11.8 Hz, 2H) , 3.46 – 3.18 (m, 4H) , 3.15 (d, J = 18.6 Hz, 1H) , 2.86 (d, J = 18.8 Hz, 1H) , 2.74 –2.65 (m , 1H) , 2.62 (s, 1H) , 2.30 –2.08 (m, 2H) , 1.89 –1.73 (m, 2H) , 1.52 –1.29 (m, 2H) , 1.10 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, $CDCl_3$) : δ [ppm] = 177.93, 173.60, 167. 64, 165.24, 164.09, 134.31, 130.04, 129.22, 128.80, 128.66, 128.58, 127.72, 127.41, 1 27.01, 126.89, 124.83, 109.56, 88.58, 87.08, 83.54, 72.36, 70.69, 62.83, 59.25, 46.58 , 45.76, 42.59, 37.40, 36.44, 33.56, 29.22, 29.09, 26.48; HRMS (ESI) m/z: $[M+K]^+$ Calcd for $C_{37}H_{40}N_2O_{10}K^+$ 711.25243, found: 711.25198.

[0771] Example 1.8: Synthesis of other BB derivatives (XBB-008 and XBB-009) according to Scheme 6



bilobalide (XBB-001) XBB-008 XBB-009

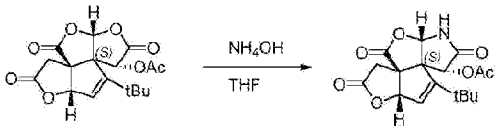
[0772] To a solution of bilobalide (1.0 g) in acetic anhydride (20 mL) was added a trace of concentrated sulfuric acid (20 μL) . The resulting solution was allowed to be stirred at 50°C for 3 h. Once the starting material was fully consumed, the reaction solution was quenched with saturated sodium bicarbonate solution. The mixtur e was extracted with ethyl acetate and the organic layer was washed with brine. The c ombined organic layers were dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The crude product was puri

fied by column chromatography with elution system (hexane: EtOAc = 8 : 1) to yield XBB-008 (54%) and XBB-009 (42%) .

[0773] XBB-008: R_f = 0.40 (hexane: EtOAc, 2: 1) ; mp = 127.1-128.0℃; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 6.57 (s, 1H) , 6.42 (s, 1H) , 6.16 (d , J = 2.8 Hz, 1H) , 5.24 (d, J = 2.8 Hz, 1H) , 3.10 (d, J = 17.9 Hz, 1H) , 2.97 (d, J = 17.9 Hz, 1H) , 2.17 (s, 3H) , 1.32 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 174.64, 171.95, 168.84, 166.64, 156.21, 129.16, 99.29, 86.09, 68.91, 67 .09, 58.35, 37.14, 35.05, 31.36, 19.90; HRMS (ESI) m/z: [M+Na] $^+$ Calcd for $C_{17}H_{18}O_8$ Na^+ 373.08939, found 373.08930.

[0774] XBB-009: R_f = 0.35 (hexane: EtOAc, 2: 1) ; mp = 170.5-171.2℃; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 6.06 (s, 1H) , 6.02 (s, 1H) , 5.16 (q , J = 1.4 Hz, 1H) , 5.00 (s, 1H) , 4.96 (dd, J = 5.6, 1.4 Hz, 1H) , 3.21 (d, J = 17.7 Hz, 1H) , 3.07 (d, J = 17.7 Hz, 1H) , 2.42 (dd, J = 15.4, 5.6 Hz, 1H) , 2.26 –2.17 (m, 4H) , 1.88 (d, J = 1.4 Hz, 3H) , 1.34 (s, 3H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 174.22, 172.60, 168.48, 167.19, 145.20, 115.93, 115.75, 101.10, 86.90, 69.23, 63.53, 61.57, 52.82, 41.21, 37.63, 24.49, 21.63, 20.44; HRMS (ESI) m/z: [M +Na] $^+$ Calcd for $C_{17}H_{18}O_8Na^+$ 373.08939, found 373.08945. The X-ray crystal structure of XBB-009 is shown in FIG. 1G.

[0775] Synthesis of (3aS, 5aS, 8R, 8aS, 10aS) -9- (tert-butyl) -2, 4, 7-trioxo-2, 3, 5a, 6, 7, 8-hexahydro-4H, 10aH-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl acetate (XBB-010)

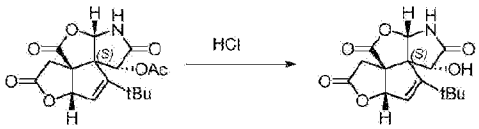


XBB-008 XBB-010

[0776] To a solution of XBB-008 (50 mg, 93.607 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (2 mL) was added 25%～28%ammonia solution (13 mg, 0.187 mmol, 2.0 equiv) at 0℃. The resulting solution was then allowed to be stirred for 30 min at room temperature. The reaction was monitored by TLC and upon completion the reaction solution was diluted ethyl acetate. The organic layer was washed with brine and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified via column chromatography (hexane: EtOAc = 1: 1) to provide XBB-010 as a white powder (86%yield, 43 mg) . The X-ray crystal structure of XBB-010 is shown in FIG. 1H. R_f = 0.15 (hexane: EtOAc, 1: 1) ; mp = 216.2-217.1℃; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 7.52 (s, 1H) , 6.13 (d, J = 2.7 Hz, 1

H) , 6.08 (s, 1H) , 5.24 (d, J = 2.7 Hz, 1H) , 5.01 (s, 1H) , 3.09 –2.90 (m, 2H) , 1. 74 (s, 3H) , 1.31 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 176 .89, 174.61, 174.57, 157.97, 127.58, 87.03, 85.60, 70.87, 67.83, 59.52, 37.82, 34.90, 31.51, 30.01; HRMS (ESI) m/z: [M+Na] $^{+}$ Calcd for $C_{17}H_{19}NO_7Na^{+}$ 372.10537, found 372.10513.

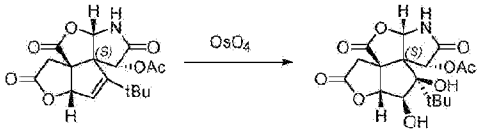
[0777] Synthesis of (3aS, 5aS, 8R, 10aS) -9- (tert-butyl) -8-hydroxy-5a, 6-dihydro-4H, 10aH-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrole-2, 4, 7 (3H, 8H) -trione (XBB-012)



XBB-010 XBB-012

[0778] To a round-bottom flask was added XBB-010 (100 mg) and 3 N HCl in H_2 O (10 mL) , respectively. The resulting solution was allowed to be stirred under refl ux condition for 12 h. Once the starting material was fully consumed, the reaction so lution was cooled down to room temperature and then the pH value was adjusted to 7.0 using saturated sodium bicarbonate solution. The mixture was extract ed with ethyl acetate and washed with brine. The combined organic la yers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromato graphy with elution system (hexane: EtOAc=1: 2) to give XBB-012 as a white po wder (70%yield, 62 mg) . R_f = 0.15 (hexane: EtOAc, 1: 2) ; mp = 230.4-231.0°C; ^{1}H-NMR (500 MHz, MeOD) : δ [ppm] = 6.19 (s, 1H) , 6.18 (d, J = 2.8 Hz, 1H) , 5.23 (s, 1H) , 5.14 (d, J = 2.8 Hz, 1H) , 2.86 (d, J = 17.5 Hz, 1H) , 2.77 (d, J = 17.5 Hz, 1H) , 1.31 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, MeOD) : δ [ppm] = 17 9.54, 176.67, 175.39, 159.30, 128.89, 88.00, 87.59, 71.41, 69.09, 60.94, 37.61, 36.10 , 31.87; HRMS (ESI) m/z: [M+Na] $^{+}$ Calcd for $C_{15}H_{17}NO_6Na^{+}$ 330.09445, found 330.09451.

[0779] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10S, 10aR) -9- (tert-butyl) -9, 10-dihydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl acetate (XBB-014)

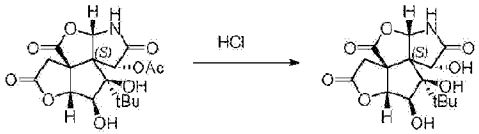


XBB-010 XBB-014

[0780] To a round-bottom flask was added XBB-010 (1.0 equiv, 200 mg) and 14 mL of acetone/H_2O (v/v=6: 1) , followed by the addition of pyridine (1 mL) and osmiu

m (VIII) oxide. The resulting solution was allowed to be stirred at room temperature for 18 h. Once completion indicated by TLC, acetone was removed unde r reduced pressure and the resultant was diluted with ethyl acetate and washed with 1 0%aqueous sodium sulfite solution and brine, respectively. The combi ned organic layers was dried over anhydrous sodium sulfate and conce ntrated under reduced pressure, and the residue was purified by colu mn chromatography with elution system (hexane: EtOAc=1: 2, v/v) to give XBB-014 as white powder (86%yield, 189 mg) . R_f = 0.1 (hexane: EtOAc, 1: 2) ; mp = 201.2-201.9℃; ^{1}H-NMR (500 MHz, MeOD) : δ [ppm] = 6.11 (s, 1H) , 6.07 (s, 1H) , 4.83 (d, J = 5.0 Hz, 1H) , 4.23 (d, J = 5.0 Hz, 1H) , 2.90 (q, J = 18.2 Hz , 2H) , 2.14 (s, 3H) , 1.16 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, MeOD) : δ [ppm] = 17 7.57, 174.17, 171.62, 169.85, 89.84, 84.64, 84.21, 81.34, 70.33, 62.52, 55.61, 53.42, 37.13, 36.73, 25.76, 19.47; HRMS (ESI) m/z: [M+Na] $^+$ Calcd for $C_{17}H_{21}NO_9Na^+$ 406.11085, found 406.11079.

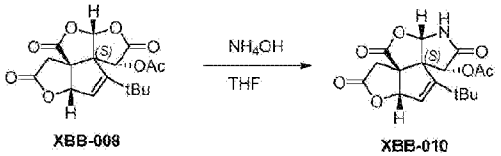
[0781] Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10S, 10aR) -9- (tert-butyl) -9, 10-dihydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl acetate (XBB-015)



[0782] To a round-bottom flask was added XBB-014 (100 mg) and 3 N HCl in H_2 O (10 mL) , respectively. The resulting solution was allowed to be stirred at 85℃ for 12 h. Once he starting material was fully consumed, the reaction solution was cooled down to room temperature and then the pH value was adjusted to 7.0 using saturated sodium bicarbonate solution. The mixture was extracted with ethyl ace tate and washed with brine. The combined organic layers were dried o ver anhydrous sodium sulfate and concentrated under reduced pressure . The crude product was purified by column chromatography with eluti on system (dichloromethane: MeOH=30: 1) to give XBB-015 as white powd er (86%yield, 71 mg) . R_f = 0.2 (DCM/MeOH = 30: 1) ; mp = 2061.7-207.5℃; ^{1}H-NMR (400 MHz, acetone-d6) : δ [ppm] = 8.29 (s, 1H) , 6.02 (s, 1H) , 5.90 (d, J = 3.6 Hz, 1H) , 5.30 (d, J = 5.9 Hz, 1H) , 4.97 (d, J = 3.7 Hz, 1H) , 4.71 (d, J = 5.1 Hz, 1H) , 4.62 (t, J = 5.5 Hz, 1H) , 4.31 (s, 1H) , 3.05 (d, J = 17.9 Hz, 1H) , 2.63 (d, J = 17.9 Hz, 1H) , 1.25 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, ace tone-d6) : δ [ppm] = 178.21, 173.67, 173.31, 89.65, 84.40, 81.18, 69.75,

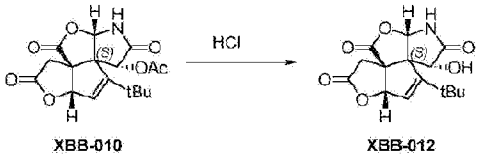
63.66, 55.06, 37.21, 36.86, 26.35; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{19}NO_8Na^+$ 364.10029, found 364.09999.

[0783] Example 1.9: Synthesis of (3aS, 5aS, 8R, 8aS, 10aS) -9- (tert-butyl) -2, 4, 7-trioxo-2, 3, 5a, 6, 7, 8-hexahydro-4H, 10aH-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl acetate (XBB-010) according to Scheme 7 (or Scheme 2)



[0784] To a solution of XBB-008 (50 mg, 93.607 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (2 mL) was added 25%~28%ammonia solution (13 mg, 0.187 mmol, 2.0 equiv) at 0℃. The resulting solution was then allowed to be stirred for 30 min at room temperature. The reaction was monitored by TLC and upon completion the reaction solution was diluted ethyl acetate. The organic layer was washed with brine and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified via column chromatography (hexane: EtOAc = 1: 1) to provide XBB-010 as a white powder (86%yield, 43 mg) . R_f = 0.15 (hexane: EtOAc, 1: 1) ; mp = 216.2-217.1℃; ^{1}H-NMR (500 MHz, $CDCl_3$) : δ [ppm] = 7.52 (s, 1H) , 6.13 (d, J = 2.7 Hz, 1H) , 6.08 (s, 1H) , 5.24 (d, J = 2.7 Hz, 1H) , 5.01 (s, 1H) , 3.09 –2.90 (m, 2H) , 1.74 (s, 3H) , 1.31 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, $CDCl_3$) : δ [ppm] = 176.89, 174.61, 174.57, 157.97, 127.58, 87.03, 85.60, 70.87, 67.83, 59.52, 37.82, 34.90, 31.51, 30.01; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}NO_7Na^+$ 372.10537, found 372.10513.

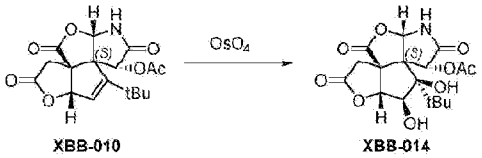
[0785] Example 1.10: Synthesis of (3aS, 5aS, 8R, 10aS) -9- (tert-butyl) -8-hydroxy-5a, 6-dihydro-4H, 10aH-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrole-2, 4, 7 (3H, 8H) -trione (XBB-012) according to Scheme 8



[0786] To a round-bottom flask was added XBB-010 (100 mg) and 3 N HCl in H_2O (10 mL) , respectively. The resulting solution was allowed to be stirred under reflux condition for 12 h. Once the starting material was fully consumed, the reaction solution was cooled down to room temperature and then the pH value was adjusted to 7.0 using saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate and washed with brine. The combined organic layers wer

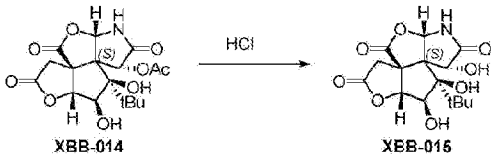
e dried over anhydrous sodium sulfate and concentrated under reduced pressure. The cr ude product was purified by column chromatography with elution syste m (hexane: EtOAc=1: 2) to give XBB-012 as a white powder (70%yield, 62 mg) . R $_f$ = 0.15 (hexane: EtOAc, 1: 2) ; mp = 230.4-231.0℃; ^{1}H-NMR (500 MHz, MeO D) : δ [ppm] = 6.19 (s, 1H) , 6.18 (d, J = 2.8 Hz, 1H) , 5.23 (s, 1H) , 5.14 (d, J = 2.8 Hz, 1H) , 2.86 (d, J = 17.5 Hz, 1H) , 2.77 (d, J = 17.5 Hz, 1H) , 1.31 (s, 9H) ; ^{13} C {^{1}H} -NMR (125 MHz, MeOD) : δ [ppm] = 179.54, 176.67, 175.39, 159.30, 128. 89, 88.00, 87.59, 71.41, 69.09, 60.94, 37.61, 36.10, 31.87; HRMS (ESI) m/z: [M+Na] $^+$ Calcd for $C_{15}H_{17}NO_6Na^+$ 330.09445, found 330.09451.

[0787] Example 1.11a: Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10S, 10aR) -9- (tert-butyl) - 9, 10-dihydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl acetate (XBB-014) according to Scheme 9



[0788] To a round-bottom flask was added XBB-010 (1.0 equiv, 200 mg) and 14 mL of acetone/H_2O (v/v=6: 1) , followed by the addition of pyridine (1 mL) and osmiu m (VIII) oxide. The resulting solution was allowed to be stirred at room temperature for 18 h. Once completion indicated by TLC, acetone was removed unde r reduced pressure and the resultant was diluted with ethyl acetate and washed with 1 0%aqueous sodium sulfite solution and brine, respectively. The combi ned organic layers was dried over anhydrous sodium sulfate and conce ntrated under reduced pressure, and the residue was purified by colu mn chromatography with elution system (hexane: EtOAc=1: 2, v/v) to give XBB- 014 as white powder (86%yield, 189 mg) . R_f = 0.1 (hexane: EtOAc, 1: 2) ; mp = 201.2-201.9℃; ^{1}H-NMR (500 MHz, MeOD) : δ [ppm] = 6.11 (s, 1H) , 6.07 (s, 1H) , 4.83 (d, J = 5.0 Hz, 1H) , 4.23 (d, J = 5.0 Hz, 1H) , 2.90 (q, J = 18.2 Hz , 2H) , 2.14 (s, 3H) , 1.16 (s, 9H) ; ^{13}C {^{1}H} -NMR (125 MHz, MeOD) : δ [ppm] = 17 7.57, 174.17, 171.62, 169.85, 89.84, 84.64, 84.21, 81.34, 70.33, 62.52, 55.61, 53.42 , 37.13, 36.73, 25.76, 19.47; HRMS (ESI) m/z: [M+Na] $^+$ Calcd for $C_{17}H_{21}NO_9Na^+$ 406.11085, found 406.11079.

[0789] Example 1.11b: Synthesis of (3aS, 5aS, 8R, 8aS, 9R, 10S, 10aR) -9- (tert-butyl) - 9, 10-dihydroxy-2, 4, 7-trioxooctahydro-4H, 9H-furo [3", 2": 2', 3'] cyclopenta [1', 2': 3, 4] furo [2, 3-b] pyrrol-8-yl acetate (XBB-015) according to Scheme 8



[0790] To a round-bottom flask was added XBB-014 (100 mg) and 3 N HCl in H_2O (10 mL) , respectively. The resulting solution was allowed to be stirred at 85℃ for 12 h. Once he starting material was fully consumed, the reaction solution was cooled down to room temperature and then the pH value was adjusted to 7.0 using saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate and washed with brine. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure . The crude product was purified by column chromatography with elution system (dichloromethane: MeOH=30: 1) to give XBB-015 as white powder (86%yield, 71 mg) . R_f = 0.2 (DCM/MeOH = 30: 1) ; mp = 2061.7-207.5℃; ^{1}H-NMR (400 MHz, acetone-d6) : δ [ppm] = 8.29 (s, 1H) , 6.02 (s, 1H) , 5.90 (d, J = 3.6 Hz, 1H) , 5.30 (d, J = 5.9 Hz, 1H) , 4.97 (d, J = 3.7 Hz, 1H) , 4.71 (d, J = 5.1 Hz, 1H) , 4.62 (t, J = 5.5 Hz, 1H) , 4.31 (s, 1H) , 3.05 (d, J = 17.9 Hz, 1H) , 2.63 (d, J = 17.9 Hz, 1H) , 1.25 (s, 9H) ; ^{13}C {^{1}H} -NMR (100 MHz, acetone-d6) : δ [ppm] = 178.21, 173.67, 173.31, 89.65, 84.40, 81.18, 69.75, 63.66, 55.06, 37.21, 36.86, 26.35; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{19}NO_8Na^+$ 364.10029, found 364.09999.

[0791] Example 2: Initial screening results of bilobalide analogues

[0792] In this example, the anti-cancer properties of the BB analogues described in Table 1d were evaluated. Single-dose screening approach is used for initial testing to assess the cytotoxic effect of the BB analogues (also referred to as 'BB compounds') on Jurkat cells (human T cell leukaemia cells) and A549 cells (human lung cancer cells) . Cell viability was measured using cell counting kit-8 (CCK-8) (MCE) .

[0793] Method for adherent cells (A549 cells)

[0794] In this example, 5000 cells/100uL were seeded in 96-well plates and incubate at 37℃ + 5%CO_2 overnight. Media were replaced with 100uL of 50uM compound per well in 6 replicates. The following controls were prepared.

[0795] Blank control: 100uL 0.1%DMSO in media with no cells per well.

[0796] Positive control: 100uL of 10uM 5-flurouracil per well.

[0797] Negative control: 100uL of 0.1%DMSO in media per well.

[0798] Each 96-well plate included 7 compounds and the complete set of controls (in 6 replicates) .

[0799] Cells were incubated at 37°C + 5%CO_2 for 46 hours. 10uL of CCK8 solution was added to each well. Cells were then incubated at 37°C + 5%CO_2 for 2 hours. Absorbance at 450 nm was measured using a multiplate reader.

[0800] Viability was calculated using the equation: $\%Viability = \frac{Test-Blank}{Negative-Blank} \times 100\%$

[0801] Method for suspension cells (Jurkat cells)

[0802] 5000 cells/90uL were seeded in 96-well plates. 10uL of 500uM compound (10X) was added to each well in 6 replicates. The following controls were prepared.

[0803] Blank control: 10uL 1%DMSO in media with no cells per well.

[0804] Positive control: 10uL of 100uM 5-flurouracil (10X) per well.

[0805] Negative control: 10uL of 1%DMSO in media (10X) per well.

[0806] Each 96-well plate included 7 BB analogues and the complete set of controls (in 6 replicates) .

[0807] Cells were incubated at 37°C + 5%CO_2 for 46 hours. 10uL of CCK8 solution was added to each well. Cells were then incubated at 37°C + 5%CO_2 for 2 hours. Absorbance at 450 nm was measured using a multiplate reader.

[0808] Viability was calculated using the equation: $\%Viability = \frac{Test-Blank}{Negative-Blank} \times 100\%$

[0809] The benchmark in Table 2 was used to define the activities of each compound.

[0810] Table 2a: Benchmark for determining activities

% Viability	Interpretation
<50	Excellent activity
50-70	Good activity
70-90	Moderate activity
>90	No detectable activity at 50uM in two cell lines

[0811] Results

[0812] Now referring to FIG. 2, a heat map of viability after DW192 treatment (50uM, 48h) in A549 and Jurkat cells. In which, 50uM DW192 treatment for 48 hours could achieve 53%and 43%viability on A549 and Jurkat cells respectively. Out of all the compounds according to Table 1d, DW192 and several other compounds exhibited significant cytotoxic effect against both cell lines, and the results are shown in Table 2b. The compounds showing sensitivities towards the A549 and Jurkat cell lines with S.D. <10 were chosen for further studies.

[0813] Table 2b: Initial screening of BB analogues

Compound	% Viability (50uM, 48h)		Average (%)	S.D.
	A549	Jurkat		
DW192	53.19	43.26	48.23	7.02
P-29	46.68	59.58	53.13	9.12
P-21	56.46	53.47	54.97	2.11
P-30	56.94	61.34	59.14	3.11
P-19	50.19	70.24	60.22	14.18
JW100	53.95	68.25	61.10	10.11
JW092	53.73	69.31	61.52	11.02
P-33	61.07	66.01	63.54	3.49
JW093	68.66	66.26	67.46	1.70
XBB-036	52.41	88.84	70.63	25.76
XBB-023	72.06	71.32	71.69	0.52
XBB-034	56.03	89.07	72.55	23.36
P-28	76.16	69.16	72.66	4.95
JW107	75.21	70.22	72.72	3.53
XBB-039	78.4	69.71	74.06	6.14
JW094	76.52	76.91	76.72	0.28
XBB-035	66.87	86.96	76.92	14.21
P-34	80.18	73.78	76.98	4.53
JW095	87.24	68.98	78.11	12.91
DW184	93.46	68.66	81.06	17.54
XBB-075	67.44	100.51	83.98	23.38
XBB-045	87.04	84.83	85.94	1.56
XBB-073	66.54	106.54	86.54	28.28
P-5	98.68	75.67	87.18	16.27
JW081	89.54	87.09	88.32	1.73
XBB-028	88.81	90.5	89.66	1.20
XBB-038	95.35	84.84	90.10	7.43
XBB-037	95	85.97	90.49	6.39
XBB-054	88.83	92.95	90.89	2.91

JW116	77.69	104.79	91.24	19.16
XBB-025	100.11	83.29	91.70	11.89
JW103	102.25	82.22	92.24	14.16
XBB-018	86.48	102.42	94.45	11.27
XBB-058	79.92	109.59	94.76	20.98
XBB-029	96.12	93.43	94.78	1.90
XBB-024	94.65	97.83	96.24	2.25
DW172	98.73	94.39	96.56	3.07
XBB-004	98.48	94.96	96.72	2.49
XBB-042	95.61	97.85	96.73	1.58
XBB-068	93.56	101.43	97.50	5.56
XBB-040	99.63	98.39	99.01	0.88
XBB-006	96.37	101.93	99.15	3.93
JW072	103.19	97.19	100.19	4.24
DW189	106.83	95.26	101.05	8.18
P-8	107.89	94.47	101.18	9.49
DW191	100.58	104.53	102.56	2.79
DW168	105.02	101.27	103.15	2.65
XBB-013	100.03	107.43	103.73	5.23
XBB-037'	110.02	98.42	104.22	8.20
XBB-009	103.22	107.25	105.24	2.85
XBB-060	107.73	103.52	105.63	2.98
XBB-016	104.59	106.82	105.71	1.58
DW182	113.77	101	107.39	9.03
XBB-010	112.02	115.08	113.55	2.16

[0814] Example 3: Dose-dependent screening

[0815] In this example, dose-dependent CCK8 Viability assay was performed to determine the IC50 (the concentration of compound to achieve 50%viability) of several of the hit compounds identified from Example 2. A variety of cell lines were used:

[0816] Jurkat cells: Human leukemia

[0817] A549 cells: Human NSCLC

[0818] KP-1 cells: Mouse NSCLC with KRAS and P53 mutations

[0819] MCF-7 cells: Human breast cancer

[0820] Method for adherent cells (A549, MCF-7 and KP-1 cells)

[0821] 5000 cells/100uL were seeded in 96-well plates and incubate at 37°C + 5%CO_2 overnight. Media were replaced with 100uL of compound per well in 6 replicates in a series of 2-fold dilutions. The following controls were prepared.

[0822] Blank control: 100uL 0.1%DMSO in media with no cells per well.

[0823] Positive control: 100uL of 10uM 5-flurouracil per well.

[0824] Negative control: 100uL of 0.1%DMSO in media per well.

[0825] Each 96-well plate included 1 compound in 7 concentrations and a complete set of controls (in 6 replicates) .

[0826] Cells were incubated at 37°C + 5%CO_2 for 46 hours. 10uL of CCK8 soluti on was added to each well. Cells were incubated at 37°C + 5%CO_2 for 2 hours. Abs orbance at 450 nm was measured using a multiplate reader.

[0827] Viability was calculated using the equation: $\%Viability = \frac{Test-Blank}{Negative-Blank} \times 100\%$

[0828] Method for suspension cells (Jurkat cells)

[0829] 5000 cells/90uL were seeded in 96-well plates. 10uL of compound (10X) in various concentrations was added to each well in 6 replicates. The following con trols were prepared.

[0830] Blank control: 10uL 1%DMSO in media with no cells per well.

[0831] Positive control: 10uL of 100uM 5-flurouracil (10X) per well.

[0832] Negative control: 10uL of 1%DMSO in media (10X) per well.

[0833] Note: Each 96-well plate can test 1 compound in 7 concentrations with a complete s et of controls (in 6 replicates)

[0834] Cells were incubated at 37°C + 5%CO_2 for 46 hours. 10uL of CCK8 soluti on was added to each well. Cells were incubated at 37°C + 5%CO_2 for 2 hours. Abs orbance at 450 nm was measured using a multiplate reader.

[0835] Viability was calculated using this equation: $\%Viability = \frac{Test-Blank}{Negative-Blank} \times 100\%$

[0836] Results

[0837] Now referring to FIGs. 3A-3E, plots showing the dose-response curve on A549 and KP-1 cells treated with the compounds DW192, P-29, P-21, SCC506, and S CC363 for 48 hours, respectively. BB analogue DW192 exhibited cytoto xic effect towards A549 cells with an IC_{50} value of 21.92 μM, as shown in FI G. 3A. BB analogue P-29 exhibited cytotoxic effect towards A549 cells with an IC $_{50}$ value of 5.84 μM, as shown in FIG. 3B. BB analogue P-21 exhibited cyto toxic effect towards A549 cells with an IC_{50} value of 17.92 μM, as shown in FI G. 3C. BB analogue SCC506 exhibited cytotoxic effect towards KP-1 cells with an I C_{50} value of 17.15 μM, as shown in FIG. 3D. BB analogue SCC363 exhibite d cytotoxic effect towards A549 cells with an IC_{50} value of 9.987 μM, as shown in FI G. 3E. The IC_{50} values in μM are summarized in Table 3. These results in dicate that the compounds DW192, P-29, P-21, SCC506, and SCC363 are therape utically effective against human NSCLC.

[0838] Table 3: Calculated IC_{50} values towards A549 and KP-1 cells

Compound	Cell lines	IC_{50} (μM)
DW192	A549	21.92 μM
P-29	A549	5.84 μM
P-21	A549	17.92 μM
SCC506	KP-1	17.15 μM
SCC363	A549	9.987 μM

[0839] Now referring to FIG. 3F, a plot showing overlaid dose-dependent curves on Jurkat cells, A549 cells, KP-1 cells, and MCF-7 cells treated with DW192 for 48 hours. The IC_{50} is 21.92 μM, 16.40 μM, 15.83 μM and 19.56 μM respe ctively. These results indicate that the compound DW192 is therapeutically effective against several cancer cell lines, including human leukemia, NSCLC, breast cancer, as well as mouse NSCLC cell lines with KRAS and P53 mutations.

[0840] Example 4: NCI-60 human tumor cell line screen

[0841] In this example, the cytotoxic effect of DW192 was assess via the NCI-60 Human Tumor Cell Lines Screen, provided by the Developmental Ther apeutics Program (DTP) of the National Cancer Institute (NCI) in the United States. T his screening helps to identify and characterize the cytotoxic effect of compounds on 60 different human cancer cell lines, including leukemia, melanoma, and cancers of t he lung, colon, brain, ovary, breast, prostate and kidneys. The screening comprised o f two assays: one-dose screen and five-dose screen. In one-dose screen, 10uM of DW192 was tested for 48 hours. In five-dose screen, four, 10-fold of 1/2 log s erial dilutions were tested for 48 hours.

[0842] Method (extracted from the NCI-60 website)

[0843] Cells were seeded into 96-well plates in 100uL at plating densities ranging f rom 5,000 to 40,000 cells/well depending on the doubling time of individual cell line s. Plates were incubated at 37℃ + 5%CO_2 + 95%air + 100%relative humidity for 24 hours before adding compounds. Two plates of each cell line were fixed in situ with TCA, to represent a measurement of the cell population for each cell line at th e time of drug addition (Tz) . 100uL of compounds in four, 10-fold of 1/2 log s erial dilutions were added to the wells already containing 100uL of medium. Plates we re incubated at 37℃ + 5%CO_2 + 95%air + 100%relative humidity for an additional 48 hours.

[0844] To terminate the assay, adherent cells were fixed in situ by the gentle addition of 5 0uL of cold 50% (w/v) TCA (final concentration, 10%TCA) and incubate d for 60 min at 4℃. For suspension cells, 50uL of 80%TCA (final conc entration, 16%TCA) was used.

[0845] Supernatant was discarded, and the plates were wash five times with tap water and air dried.

[0846] Sulforhodamine B (SRB) solution (100uL) at 0.4% (w/v) in 1%acetic ac id was added to each well, and the plates were incubated for 10 min at room temp. The plates were washed five times with 1%acetic acid and air dried.

[0847] Remaining stained cells were solubilized with 10mM trizma base. Abso rbance at 515 nm was measured.

[0848] Percentage growth was calculated using the following equations:

[0849] $\frac{Ti-Tz}{C-Tz} \times 100$ for which Ti≥Tz; and

[0850] $\frac{Ti-Tz}{Tz} \times 100$ for which Ti<Tz,

[0851] where Tz = absorbance at time zero, C = absorbance of control growth , Ti = absorbance of test growth in the presence of drug at the five concentration levels.

[0852] In five-dose screen, three dose response parameters were calculated with the steps below (extracted from NCI-60 website) :

[0853] Growth inhibition of 50% (GI50) : $\frac{Ti-Tz}{C-Tz} \times 100 = 50$, which is the drug concentration resulting in a 50%reduction in the net protein increase (as measured by SRB staining) in control cells during drug incubation.

[0854] Total growth inhibition (TGI) : Ti = Tz

[0855] Lethality (LC50) : $\frac{Ti-Tz}{Tz} \times 100 = -50$, concentration of drug resulting in a 50%reduction in the measured protein at the end of drug treatment as compared to that at the beginning, indicating a net loss of cells after treatment.

[0856] Results

[0857] Now referring to FIG. 4A, showing a one-dose mean graph of percentage growth of cell lines across the NCI-60 cell line panel when treated with 10 μM DW192 for 48 hours. The one-dose data was reported as a mean graph of the percent growth of treated cells, detecting both growth inhibition (values between 0 and 100) and lethality (values less than 0) . As shown in FIG. 4A, DW192 exhibits cytotoxic effects towards multiple cell lines of different cancer type, including leukemia (such as HL-60 (TB)) , NSCLC (such as HCI-H460) , colon cancer (such as COLO 205) , CNS cancer (such as SF-295) , melanoma (such as SK-MEL-2, SK-MEL-5, UACC-62) , ovarian cancer (such as OVCAR-3) , renal cancer (such as RXF 393 , SN12C) , and breast cancer (such as BT-529) . The most sensitive cell line against DW192 is COLO205 (colon cancer) , achieving 66.18%lethality. The comparatively less sensitive cell line is HOP62 (NSCLC) , achieving 50.22%growth inhibition. The dose-response curves of cell lines across the NCI-60 cell line panel when treated with DW192 for 48 hours are shown in FIGs. 4B-4J for leukemia, CNS cancer, renal cancer, NSCLC, melanoma, prostate cancer, colon cancer, ovarian cancer and breast cancer, respectively. FIG. 4K shows the mean graphs of GI50, TGI and LC50 calculated from five-dose screen results (Unit: Molar) . These results have demonstrated the pan-anti-cancer effect of DW192 against most of the human cell lines with various mutation profiles.

[0858] Example 5: Stability of bilobalide analogues.

[0859] Now referring to FIGS. 5A-5B, the hydrolytic stabilities of bilobalide and BB analogue (XBB-006) monitored using LC-MS/MS in buffer with pH=6.8 and 7.4 are shown, respectively. As shown in FIG. 5A, under the pH of 6.8, the concentration of bilobalide has dropped to below 20%after 20 hours whereas the concentration of XBB-006 has remained at about 80%. As shown in FIG. 5B, under the pH of 7.4, the concentration of bilobalide has dropped to below 20%within the first 10 hours whereas the concentration of XBB-006 has remained above 80%. These results showed a much higher hydrolytic stability of bilobalide analogue with respect to bilobalide at physiological pH values.

[0860] Example 6: Activities as a ferroptosis inhibitor.

[0861] In this example, the anti-ferroptotic properties of the BB analogues described in preceding examples were evaluated by a RSL3-induced ferroptosis model. RSL3 is an allosteric covalent inhibitor of GSH-dependent enzyme GSH peroxidase 4 (GPX4) , which is responsible for removing ROS from cells. By covalently binding to GPX4 protein, RSL3 induces the degradation of this antioxidant enzyme, leading to an accumulation of ROS and causing oxidative damage to cellular proteins. Cell lines derived from the central nervous system, such as the hippocampal cell line HT22, and the microglial cell lines HMC3 and BV-2, are highly sensitive to RSL3-induced lethality. To evaluate the anti-ferroptosis activity of BB analogues, we developed a phenotypic screening based on RSL3-induced ferroptosis model on HT22 mouse hippocampal cell line, HMC3 microglial cell line and BV-2 murine microglial cell line which were co-treated or pre-treated with RSL3 and BB analogues for 2-24 h, and the cell viability was subsequently measured. Compounds which showed significant rescue effects against ferroptosis were selected as hits. Dose-response studies were carried out for the hits, which will be discussed in the next example.

[0862] General Methods

[0863] HMC3 cell line was maintained in Minimum Essential Medium (MEM, Gibco) supplemented with 1x non-essential amino acid (Gibco) , 1 mM sodium pyruvate (Gibco) , 10%fetal bovine serum (FBS) (Gibco) and and 1%penicillin/streptomycin (Gibco) . BV-2 cell line was maintained in Roswell Park Memorial Institute (RPMI) 1640 medium (Gibco) supplemented with 10%FBS and 1%penicillin/streptomycin, and HT22 cell line was maintained in Dulbecco's Modified Eagle's Medium (DMEM) (Gibco) supplemented with 10%FBS and 1%penicillin/streptomycin. All cells were incubated at 37 °C in a humidified atmosphere under 5%CO2.

[0864] For phenotypic screening of bilobalide (BB) analogues, 5,000 cells per well (100 μL volume) of HT22, HMC3 or BV-2 cells were placed in 96-

well plate and allowed to adhere for 22 h. After which, cells were pre-treated with 200 nM (on HT22, HMC3) or 500 nM (on BV-2) of RSL3 (Bidepharm) for 2 h respectively. Medium was then replaced by 50 μM BB analogues and followed by 22 h incubation subsequently. Cell viability was measured using cell counting kit-8 (CCK-8) (MCE) . For dose-response of BB analogues, RSL3, HT22 and HMC3 cells (seeded on 96-well plates at 5,000 cells per well) were treated with multiple doses of RSL3 for 2 h. Medium was then replaced by DMSO (0.1%) only, XBB-037 (50 μM) or bilobalide (50 μM) . BV-2 cells (seeded on 96-well plates at 5,000 cells per well) were co-treated with multiple doses of RSL3 and DMSO (0.1%) only, XBB-037 (50 μM) , bilobalide (50 μM) for 24 h. Cell viability was measured after 22 h treatment by CCK-8. For evaluation of ferroptosis inducers, HMC3 cells (seeded on 96-well plates at 5,000 cells per well for 24 h) was pre-treated with multiple concentrations of erastin (MCE) , ML210 (MCE) , ML162 (MCE) or FIN56 (MCE) , for 2 h prior the 22 h treatment with DMSO (0.1%) only, XBB-037 (50 μM) , bilobalide (50 μM) . Cell viability was measured by CCK-8 using CLARIOstar monochromator multimode plate reader under 450 nm wavelength.

[0865] For flow cytometry, HMC3 cells (seeded 50,000 cells per well on 24-well plate one day prior to the experiment) were pretreated with 50 nM RSL3 for 2 h. After RSL3 treatment, medium was replaced by DMSO (0.1%) only, XBB-037 (50, 25 or 12.5 μM) , bilobalide (50, 25 or 12.5 μM) or ferrostatin-1 (1 μM, MCE) following by 3 h treatment. After which medium was replaced with BODIPY™ 581/591C11 (10 μM, Invitrogen) or CellROX™ Green (5 μM, Invitrogen) for 30 min staining. Cells were then washed 3 times with PBS and collected. Fluorescence was measured by BD FACSympgony A5.2 SORP Flow Cell Analyzer (BD Biosciences) .

[0866] For fluorescent imaging, 10,000 cells per well of HMC3 were laid on cover slip and incubated overnight. After the same compound treatment as described above in this section, cells were subsequently incubated with CellROX™ Green and Hoechst 34580 (MCE) for 30 min. After incubation, cells were washed 3 times gently with PBS. Cover slips were then attached to glass slides by Anti-Fade Fluorescence Mounting Medium (Abcam) and imaged via ECLIPSE Ti fluorescence microscope (Nikon) . Fluorescent intensity was quantified using imageJ software.

[0867] All data were plotted as mean ± s.d., ns, no significance, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$. Statistical analyses were performed by one-way ANOVA with mu

ltiple comparisons using Tukey's multiple comparisons test. The statistical analysis of all test groups was compared to the NR group respectively.

[0868] Now referring to FIG. 6A, a chart comparing the phenotypic screening of unmodified bilobalide and a bilobalide analogue against RSL3-induced ferroptos is through 3 cell lines is shown. In this example, the cells were pre-treated with RSL3 (200 nM for HT22 and HMC3, 500 nM for BV-2) for two hours, followed by bilo balide analogues treatment (50 μM) for 22 hours. Cell viability was measured using ce ll counting kit-8 (CCK-8) ; n = 5 technical replicates. In this example, t he bilobalide analogue was XBB-037 described in preceding example s, which was found to effectively inhibit ferroptosis across 3 cell lines, as shown i n FIG. 6A. The result suggested that N-arylated analogue such as XBB-037 effectively inhibited RSL3-induced ferroptosis. Such effect was further investig ated by treating the cell lines with various doses of RSL3.

[0869] Now referring to FIGS. 6B-6D, the dose-dependent curves of RSL3 with or w ithout treatment of bilobalide (50 μM) or XBB-037 (50 μM) on HT22, HMC3 and BV-2 cell lines, respectively, are shown (n = 3 technical replicates) . As shown in FIGS . 6B-6D, treatments of 50 μM bilobalide analogue (RSL3+XBB-037) displayed anti-ferroptotic activity in a dose-dependent manner, compared to the control group whi ch was not treated with XBB-037 or bilobalide (RSL3) and the sample group treat ed with unmodified bilobalide (RSL3+Bilobalide) . Consistent with th e phenotypic screening result shown in FIG. 6A, treatment with bilobalide analogue (R SL3+XBB-037) diminished RSL3 lethality in 3 cell lines compared to the treat ment with no bilobalide analogue (RSL3) and the treatment with unmod ified bilobalide (RSL3+Bilobalide) . Intriguingly, the curve shifts post BB treatment were relatively marginal, which indicated the modification brought new pharmacological effects (such as anti-ferroptotic effects) to bilobalide analogues.

[0870] To further evaluate the anti-ferroptotic properties of bilobalide analogues, we tested its effect on the total level of intracellular reactive oxygen species (ROS) , we performed fluorescent staining on the HMC3 cell line using CellR OX, which is a probe which can emit green fluorescence after reacting with ROS. In th is experiment, HMC3 cells were pre-treated with 50 nM RSL3 for two ho urs, and subsequently treated with 50 μM bilobalide analogue (XBB-037) or bilobalid e for three hours. A control of untreated HMC3 cells, as well as a comparative condit ion NR containing HMC3 cells treated with RSL3 where RSL3 doubled th e ROS level but not treated with any bilobalide or bilobalide analogues, were also pr epared. The conditions are summarized in Table 4. Now referring to FIG. 6E, a chart c omparing the fluorescent staining on HMC3 cell lines under the conditions according t o Table 4 is shown (sale bars = 100 μm) . ROS was stained with CellR

OX and the cell nucleus was stained with Hoechst 34580. FIG. 6F shows the normalization of ROS level against the Control based on the fluorescent intensity of CellROX (n = 3 technical replicates) . Based on the data shown in FIGS. 6E-6F, the treatment with 50 μM XBB-037 significantly reduced intracellular ROS level. By contrast, treatment with 50 μM unmodified bilobalide showed no reduction in ROS level.

[0871] Table 4: Example conditions for the evaluation of ROS level

Condition	[RSL3] (nM)	Rescuer/inhibitor
Control	--	--
NR	50	--
Bilobalide analogue	50	XBB-037
Bilobalide	50	Bilobalide

[0872] Now referring to FIG. 6G, a plot showing the normalization of ROS level (%) in cells pre-treated with 50 nM of RSL3 for 2 hours, and then treated with various concentrations of XBB-037 for 3 hours, is presented. ROS level was measured by flow cytometry using CellROX.

[0873] The results further indicated a dose-dependent reduction in ROS levels following treatment with bilobalide analogue, as shown in FIG. 6G, where disruptions of ROS level were observed.

[0874] Disequilibrium ROS level acts as a direct initiator of lipid peroxidation, which is one of the major hallmarks of ferroptosis. In this example, HMC3 cells according to the conditions in Table 4 were subjected to measurement of lipid peroxidation level using flow cytometry and the lipid peroxidation sensor C11-BODIPY.

[0875] Now referring to FIG. 6H, a chart showing the lipid peroxidation level (%) measured by flow cytometry using C11-BODIPY is presented (n = 3 technical replicates) . Compared to the control and NR groups, the groups treated with 50, 25 and 12.5 μM bilobalide analogue XBB-037 showed significant down-regulation of RSL3-induced lipid peroxidation accumulation in a dose-dependent manner. However, no significant alteration was found after treatment with the same concentrations of bilobalide (12.5, 25 and 50 μM) as lipid peroxidation in samples treated with bilobalide were higher than the Control, NR and Fer-1, as shown in FIG. 6I.

[0876] Example 7: Mechanistic studies.

[0877] To further explore how bilobalide analogues regulated ferroptosis, we tested their protection against various ferroptosis inducers (Class I-III) and their me

chnisms in the glutathione peroxidase 4 (GPX4) pathway, which is crucial for reducing hydroperoxides during ferroptosis.

[0878] Class II ferroptosis inducers ML162 and ML210 are GPX4 covalent inhi bitors. As shown in FIG. 7A, the treatment of 50 μM bilobalide analo gue (ML162+XBB-037) alleviated the lethality of ML162, compared to the contr ol group which was not treated with XBB-037 or bilobalide (ML162) and the sample group treated with unmodified bilobalide (ML162+Bilobalide) . Consistently, as shown in FIG. 7B, the treatment of 50 μM bilobalid e analogue (ML210+XBB-037) alleviated the lethality of ML210, compared to the control group (ML210) and the sample group treated with 50 μM u nmodified bilobalide (ML210+Bilobalide) . These results demonstrated the ability of b ilobalide analogues to alleviate the lethality of Class II ferroptosis inducers such as ML162 and ML210.

[0879] As shown inFIG. 7C, albeit the drift in cell viability within the range of 10^{1}-10^{2} nM erastin, the treatment of 50 μM bilobalide analogue (Erastin+XBB -037) suppressed erastin-induced lethality, compared to the control group (E rastin) and the sample group treated with 50 μM unmodified bilobalide (Erastin +Bilobalide) . Collectively, our observation on system Xc-inhibitors reflec ted that the mechanism of bilobalide analogue XBB-037 may directly interact with fer roptosis.

[0880] Lastly, FIN56 is a class III ferroptosis inducer, which induces ferroptosis via the d epletion of GPX4 instead of acting as a GPX4 binder. As shown inFIG. 7D, the treatment of 50 μM bilobalide analogue (FIN56+XBB-037) effectively suppressed FIN56-induced cell death, compared to the control group (FIN56) and the sample group treated with 50 μM unmodified bilobalide (FIN56+Bilobalide) . Intriguingly, the results showed that bilobalide analogue effec tively repressed FIN56-induced cell death, suggesting its utility effect o n the regulation of GPX4 level.

[0881] Aside from the GPX4 inhibition, RSL3 has also been reported to degra de GPX4 through inhibiting the mammalian target of rapamycin (mTOR) and enhancing chaperone-mediated autophagy (CMA) . As mentioned above, RSL3 treatment results in an oxidized environment in cells, which promotes the CMA to sca venge damaged proteins including GPX4 or glyceraldehyde-3-phosphate dehydro genase (GAPDH) , a well-known CMA substrate. To gain insights into the mech anism of action of bilobalide analogue XBB-037 against the RSL3-induced ferroptos is, HMC3 cells were pre-treated with RSL3, followed by treatment with or wi thout bilobalide analogue XBB-037.

[0882] In FIN56 assay, HMC3 (300,000 cells per well on 6-well plate) was p re-treated with FIN56 (2.5, 1.25, 0.625 μM) for 2 h, followed by 8 h tr eatment of DMSO only (0.1%) or XBB-037 (50 μM) . In RSL3 assay, HMC3 (300,000 cells per well on 6-well plate) was pre-treated with RSL3 (750, 500, 250 nM) for 2 h, followed by 4 h or 8 h treatment of DMSO only (0.1%) or XBB-037 (50 μM) . After incubation, cells were washed 3 times with ice-cold PBS and lysed in RIPA buffer containing 1x protease inhibitor c ocktail (MCE) and nuclease (Biyotime) on ice for 30 min. All samples were centrifuged and then quantified by bicinchoninic acid (BCA) as say (Pierce) . Cell lysates were diluted with Laemmli Sample Buffer (Bio-Rad) and heated at 95 °C for 10 min. Samples were separated by 12%SDS -PAGE and transferred to a polyvinylidene difluoride membrane. Membra ne was incubated with 3%bovine serum albumin (BSA, Sigma-Aldrich) for 1 h, and subsequently incubated with indicated primary antibody overnigh t at 4 °C. After incubation, membrane was washed by wash buffer (cont aining 20 mM Tris, 150 mM NaCl and 0.1%Tween 20) , and incubated wit h peroxidase-conjugated secondary antibody at room temperature for 1 h. Antibodie s for GPX4 (52455, CST) was used at 1: 500 dilution, β-Actin (AC026, ABc lonal) was used at 1: 400,000 dilution, GAPDH (AC035, ABclonal) was used at 1: 3000 dilution. Anti-mouse IgG HRP-linked antibody (7076, CST) and an ti-rabbit IgG HRP-linked antibody (7074, CST) was used at 1: 6000. Bl ot was washed and visualized using Clarity Western ECL Substrate (Bio-Rad) with ChemiDoc MP Imaging System (Bio-Rad) . Band intensity was normaliz ed by image lab software.

[0883] Now referring to FIGS. 7E-7F, GPX4 levels in HMC3 cells pre-treated with RSL3 are shown. Protein levels of GPX4 and β-actin at 0, 250, 500 or 750 nM RSL 3 were measured by Western-blot. HMC3 cells were pretreated with RSL3 for 2 ho urs and then treated with or without 50 μM bilobalide analogue XBB-037 for 4 hours. We found that RSL3 diminished the GPX4 level, and R SL3-induced GPX4 degradation was reduced after the treatment of bilobali de analogue XBB-037. As shown inFIG. 7E, higher RSL3 concentrations clearly diminished the GPX4 in the control without bilobalide analogue treatment. On the other hand, the GPX4 remained constant at all four RSL3 concentrations (0, 250, 500 and 750 nM) in the sample group treated with 50 μM bilobalide analogue XBB-037, as seen in FIG. 7F, where the normalized GPX4 levels with or without bilobalide analogue XBB-037 treatment is shown. These data revealed that RSL3-induced GPX4 degradation was blocked after bilobalide analogue treatment.

[0884] RSL3 also induced the degradation of glycer-aldehyde-3-phosphate dehydro genase (GAPDH) , a ferroptosis-related marker. Interestingly, as shown in FIG. 7G, when HMC3 cells were pre-treated with 0 (-) or 500 (+) nM RSL3 for 2 hours, then treated with various concentrations of XBB-037 (0, 0, 1, 50 and 100 μM) for 8 hours, it was observed that XBB-037 restored the level of GAPDH accordingly. This o bservation reflected the governing of GPX4 by bilobalide analogue XBB-037, which played an important role in the mechanism against RSL3-induced ferroptos is.

[0885] In addition to GPX4, FIN56 was further used to investigate the GPX4 regulation of bilobalide analogue XBB-037. As mentioned above, FIN56 is a Class III ferroptosis inducer, which causes the depletion of cellular GPX4 levels w ithout affecting GPX4 activity. In this experiment, HMC3 cells were pretreated with F IN56 for 2 hours and then treated with or without 50 μM XBB-037 for 8 hours. Protein levels were measured by Western-blotting using indicated antibodie s. Data were plotted as mean ± s.d., n = 3 technical replicates. **p < 0.01. Statisti cal analyses were performed by two-way ANOVA with multiple comparison s using Two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli mu ltiple comparisons test.

[0886] Now referring to FIGS. 7H-7I, GPX4 levels in HMC3 cells pre-treated with FIN5 6 were shown. Protein levels of GPX4 and β-actin at 0, 0.625, 1.25 and 2.5 μM FIN56 were measured by Western-blot, as shown in FIG. 7H. The nor malized plot of GPX4 levels are shown in FIG. 7I.

[0887] The results showed the treatment of bilobalide analogue XBB-037 significantly restored GPX4 level against depletion by different concentrations of FIN56, supporti ng the role of bilobalide analogue XBB-037in regulating the GPX4 level. O ur results suggest that bilobalide analogue could selectively inhibit ferroptosis ind uced by class I, II, and/or III ferroptosis inducers. By restoring GPX4 level under f erroptotic environment, cell viability against ferroptosis was maintained.

[0888] In conclusion, the results have shown that bilobalide analogues such as XBB-037 significantly reduce key ferroptosis markers, such as ROS levels and lipid peroxi dation, and notably counteracted GPX4 degradation induced by RSL3 an d FIN56, highlighting the therapeutic potential of bilobalide analogues against neuro logical diseases (e.g., neurodegenerative diseases) by inhibiting ferroptosis.

[0889] Example 8: Activities as a ferroptosis inhibitor.

[0890] In this example, the anti-ferroptotic properties of the BB analogues describe d in preceding examples were evaluated by a RSL3-induced ferroptosis model similar to the conditions as discussed in Example 6 herein. For the sake of brevity and simpl icity of the present disclosure, the full discussion is not reproduced here.

[0891] For phenotypic screening of bilobalide (BB) analogues, 5,000 cells p er well (100 μL volume) of HT22, HMC3 or BV-2 cells were placed in 96-well plate and allowed to adhere for 22 h. After which, cells were pre-treated with 200 nM (on HT22, HMC3) or 500 nM (on BV-2) of RSL3 (Bidepharm) for 2 h res pectively. Medium was then replaced by 50 μM BB analogues and follow ed by 22 h incubation subsequently. Cell viability was measured using cell counting k it-8 (CCK-8) (MCE) . For dose-response of SXQ087-1 and XBB-037 (HMC3 cells w ere seeded on 96-well plates at 5,000 cells per well) were treated with 200 nM of RSL 3 for 2 h. Medium was then replaced by multiple concentrations of SXQ087-1 or XBB-037. Cell viability was measured after 22 h treatment by CCK-8. For evaluation of ferroptosis inducers, HMC3 cells (seeded on 96-well plates at 5, 000 cells per well for 24 h) was pre-treated with multiple concentratio ns of ML210 (MCE) , ML162 (MCE) or FIN56 (MCE) , for 2 h prior the 2 2 h treatment with DMSO (0.1%) only or SXQ087-1 (10 μM) . For erastin, HMC3 cell s were co-treated with multiple concentration of erastin with DMSO (0.1%) only or SXQ087-1 (10 μM) . Cell viability was measured by CCK-8 using CLARIOsta r monochromator multimode plate reader under 450 nm wavelength.

[0892] For flow cytometry, HMC3 cells (seeded 50,000 cells per well on 24-well plate one day prior to the experiment) were pretreated with 50 nM RSL3 for 2 h. After RSL3 treatment, medium was replaced by DMSO (0.1%) only, SXQ08 7-1 (10, 5 and 2.5 μM) , following by 3 h treatment. After which mediu m was replaced with BODIPY™ 581/591C11 (10 μM, Invitrogen) for 30 min staining . Cells were then washed 3 times with PBS and collected. Fluorescenc e was measured by BD FACSympgony A5.2 SORP Flow Cell Analyzer (BD Bi osciences) .

[0893] All data were plotted as mean ± s.d., ns, no significance; *<0.05, **p < 0.01, ***p < 0.001, and ****p <0.0001. Statistical analyses were performed by one-way ANOVA with multiple comparisons.

[0894] Now referring to FIG. 8A, a chart comparing the phenotypic screening of unmodified bilobalide, SXQ087-1 and XBB-037 against RSL3-induced ferroptos is through 3 cell lines is shown. In this example, the cells were pre-treated with RSL3 (200 nM for HT22 and HMC3, 500 nM for BV-2) for two hours, followed by bilo balide analogues treatment (50 μM) for 22 hours. Cell viability was measured using ce ll counting kit-8 (CCK-8) ; n = 5 technical replicates. In this example, t he bilobalide analogues were SXQ087-1 and XBB-037 described in preceding example s, which was found to effectively inhibit ferroptosis across 3 cell lines, as shown i n FIG. 8A. The result suggested that N-alkylated and N-arylated BB analo

gues such as SXQ087-1 and XBB-037, respectively, inhibited RSL3-induced ferroptos is effectively.

[0895] Now referring to FIG. 8B, a plot showing the dose-dependent cell viability (%) curve s of RSL3 on HMC3 cell line treated with SXQ087-1 or XBB-037.

[0896] Lipid peroxidation is one of the major hallmarks of ferroptosis. In this example, HMC3 cells according to the conditions in Table 5 were subjected to measurement of lipid peroxidation level using flow cytometry and the li pid peroxidation sensor C11-BODIPY.

[0897] Table 5: Example conditions for the evaluation of lipid peroxidation level

Condition	[RSL3] (nM)	Rescuer/inhibitor
Control	--	--
NR	50	--
Bilobalide analogue	50	SXQ087-1

[0898] Now referring to FIG. 8C, a chart showing the lipid peroxidation lev el (%) measured by flow cytometry using C11-BODIPY is presented (n = 3 technic al replicates) . Compared to the control and NR groups, the groups treated with 10, 5 and 2.5 μM bilobalide analogue SXQ087-1 showed significant down-regulation of RSL3-induced lipid peroxidation accumulation in a dose-dependent manner.

[0899] Example 9: Mechanistic studies.

[0900] Aside from the GPX4 inhibition, RSL3 has also been reported to degra de GPX4 through inhibiting the mammalian target of rapamycin (mTOR) and enhancing chaperone-mediated autophagy (CMA) . In this example, HMC3 ce lls (100,000 cells per well on 12-well plate) were co-treated with RSL3 (1 μM) and SXQ087-1 (10, 5, 2.5, 0 μM) for 3 h. After incubation, cel ls were washed 3 times with ice-cold PBS and lysed in RIPA buffer containing 1x pro tease inhibitor cocktail (MCE) and nuclease (Biyotime) on ice for 30 min. All samples were centrifuged and then quantified by bicinchoninic acid (BC A) assay (Pierce) . Cell lysates were diluted with Laemmli Sample Buffer (Bio-Rad) and heated at 95 °C for 5 min. Samples were separated by 12%SDS-PAGE and transferred to a polyvinylidene difluoride membrane. Membra ne was incubated with 3%bovine serum albumin (BSA, Sigma-Aldrich) for 1 h, and subsequently incubated with indicated primary antibody overnigh t at 4 °C. After incubation, membrane was washed by wash buffer (cont aining 20 mM Tris, 150 mM NaCl and 0.1%Tween 20) , and incubated wit h peroxidase-conjugated secondary antibody at room temperature for 1 h. Antibodie

s for GPX4 (52455, Cell Signaling Technology) was used at 1: 500 dil ution, GAPDH (sc-32233, Santacruz) was used at 1: 3000 dilution, LC3 B (A19665, ABclonal) was used at 1: 1000 dilution. Goat anti-rabbit IgG HRP-linked antibody (7074, CST) was used at 1: 2500 dilution, goat anti-mouse IgG (H +L) secondary antibody DyLight™ 488 (35502, Invitrogen) was used at 1: 5000 diluti on. Blot was washed and visualized using Clarity Western ECL Substrate (Bio-Rad) with ChemiDoc MP Imaging System (Bio-Rad) . Band intensity was normaliz ed by image J software.

[0901] Now referring to FIGs. 9A-9B, Western-blot images showing the levels of GPX4 and GAPDH at various concentrations of SXQ087-1 (10, 5, 2.5, 0 μM) against RSL3 (1 μM) and a normalized GPX4 level (%) plot of are shown. In this example, GAPDH was a reference protein. The results s howed that RSL3 diminished the GPX4 level, and RSL3-induced GPX4 degr adation was reduced after the treatment of bilobalide analogue SXQ087-1 compared to GAPDH.

[0902] Now referring to FIGs. 9C-9D, Western-blot images showing the levels of LC3-II/LC3-I and GAPDH at various concentrations of SXQ087-1 (10, 5, 2.5, 0 μM) against RSL3 (1 μM) and a normalized LC3-II/LC3-I level (%) plot of are shown. The results showed that RSL3 significantly increased the autophagy rela ted protein LC3-II/LC3-I ratio, which indicated the up regulation of autop hagy, as seen in FIGS. 9C-9D. The increasing LC3-II/LC3-I ratio was also reduced after the treatment of bilobalide analogue SXQ087-1, indicating the potential inhibition activity of SXQ087-1 on autophagy to protect GPX4 fro m degradation.

[0903] Example 10: Further mechanistic studies.

[0904] In this example, the protection effect of bilobalide analogues against various ferrop tosis inducers (Class I-III) , their mechanisms in the glutathione peroxidase 4 (GPX4) pathway, cytotoxicity and antioxidative activity were studied by the procedures similar to those as discussed in Example 8 herein. For the sake of brevity and simpl icity of the present disclosure, the full discussion is not reproduced here.

[0905] Now referring to FIGs. 10A-10D, charts showing the protection effect of biloba lide analogues against various ferroptosis inducers (Class I-III) . FIN56 is a class III ferroptosis inducer, which induces ferroptosis via the depletion of GPX4 i nstead of acting as a GPX4 binder. As shown in FIG. 10A, the treatme nt of 10 μM bilobalide analogue (FIN56 + SXQ087-1) effectively suppressed FIN56-induced cell death, compared to the control group (FIN56) .

[0906] Class II ferroptosis inducers ML162 and ML210 are GPX4 covalent inhi bitors. As shown in FIG. 10B, the treatment of 10 μM bilobalide anal

ogue (ML162 + SXQ087-1) alleviated the lethality of ML162, compared to t he control group which was not treated with SXQ087-1 (ML162) . Consi stently, as shown in FIG. 10C, the treatment of 10 μM bilobalide ana logue (ML210 + SXQ087-1) alleviated the lethality of ML210, compared to t he control group (ML210) These results demonstrated the ability of bilobalide analogu es to alleviate the lethality of Class II ferroptosis inducers such as ML162 and ML210.

[0907] As shown in FIG. 10D, the treatment of 10 μM bilobalide analogue (Er astin +SXQ087-1) suppressed erastin-induced lethality, compared to the control group (Erastin) . Collectively, our observation on system X_c^- inhibitors reflec ted that the mechanism of bilobalide analogue SXQ087-1 may directly in teract with ferroptosis.

[0908] Now referring to FIGs 11A, a chart showing the cell viability (%) of HMC3 cells treated with SXQ087-1, XBB-037 or bilobalide. As shown in FIG . 11A, after 24 h treatment of SXQ087-1, XBB-037 or bilobalide, no significant cytotoxicity was observed in HMC3 cells.

[0909] The mechanism of the antioxidative activity of SXQ087-1 is also demonst rated herein by further evaluating the radical scavenging activity of SXQ087- 1 using a cell free radical assay. FIG. 11B is a chart showing the relative radical l evel (%) of SXQ087-1. As shown in FIG. 11B, SXQ087-1 demonstrated a significant dose-dependent radical scavenging activity.

[0910] In conclusion, bilobalide analogue SXQ087-1 was shown to significantly reduc e key ferroptosis markers lipid peroxidation, and notably counteracted GPX4 degradati on and LC3-II/LC3-I ratio induction induced by RSL3. The results in t his example highlight the therapeutic utility of bilobalide analogues against neurolo gical diseases (e.g., neurodegenerative diseases) by inhibiting ferroptosis.

[0911] Example 11: Animal studies.

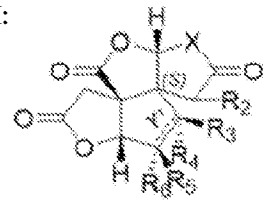
[0912] In the example, C57BL/6 mice were subcutaneously injected with B16 m elanoma cells. Tumor cells were allowed to develop for one week, after that mice were treated with daily subcutaneous injections of vehicle or DW192 (40mg/ kg) for 21 days. FIG. 12A is a plot showing the tumor growth curves. As shown in FI G. 12A, the tumor volume is lowered in mice treated with DW192 40mg/ kg daily. FIG. 12B is a photograph of the tumors collected from vehi cle and DW192 treated mice after the 21-day treatment, where tumors from m ice treated with DW192 were significantly smaller compared to those from mice treated with vehicle. From the results, DW192 significantly reduced the gro wth and size of melanoma tumors.

[0913] The exemplary embodiments of the present invention are thus fully de scribed. Although the description referred to particular embodiments, it will be clea

r to one skilled in the art that the present invention may be practiced with variatio n of these specific details. Hence this invention should not be construed as limited to the embodiments set forth herein.

Claims

[Claim 1] A compound of Formula I:



(Formula I)

or a stereomer, a tautomer, or a pharmaceutically acceptable salt th ereof,

wherein

X is -O-, -NR^1-, -N=CR^1-NH-, or -NR^1-NH-; wherein when X is -O-, R^1 is absent;

bond Y^1 is between R^4 and R^5 and is a single bond or a double bond;

R^1 is H, R^{1B}, or - $(L^1)_u$- $(Z^1)_v$; wherein

L^1 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, O, or S; wherein L^1 is optionally substituted with 1-3 occurrences of halo, CN, R, OR', or R^{1C};

u is 0 or 1;

v is 0 or 1;

Z^1 is a 5-16 membered aromatic or nonaromatic monocyclic, bic yclic, or tricyclic ring system having 0-7 heteroatoms sel ected from O, N, or S; wherein Z^1 is optionally substituted with 1-5 occurrences of R^{1A}, R^{1C} or combinations thereof;

R^{1A} is - $(L^2)_m$- $(Z^2)_w$; wherein

L^2 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si; wherein L^2 is optionally substituted with 1-3 occurrences of halo, CN, R, OR' or R^{1C};

m is 0 or 1;

w is 0 or 1;

Z^2 is a C_1-C_{10} aliphatic, or 3-16 membered aromatic or nonaromati c monocyclic, bicyclic or tricylic ring system having 0-

7 heteroatoms selected from O, N, or S; wherein Z^2 is optionally su bstituted with 1-5 occurrences of R^{1B};

R^{1B} is H, halo, CN, R*, OR*, NRR*; or two R^{1B}, taken together with the atom to which they are attached, form a 3-6 membered ring h aving 0-4 heteroatoms;

R^{1C} is H, halo, CN, a 5-10 membered aromatic or nonaromati c monocyclic or bicyclic ring system having 0-5 heteroatoms sel ected from O, N, or S; R*, OR*, NRR*; or two R^{1C}, taken together with the atom or atoms to which they are attached, optionally form a 3-16 membered ring having 0-4 heteroatoms; wherein R^{1C} is optionally su bstituted with 1-3 occurrences of halo, CN, R' or OR';

R*is C_1-C_6 aliphatic wherein up to three methylene units of the C_1-C_6 aliphatic are optionally replaced by N, NR, O, S, C=O, SO, SO_2 or Si and wherein the C_1-C_6 aliphatic is optionally substituted with 1-3 occurrences of halo, CN, R' or OR';

R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, a C_1-C_{16} aliphatic, a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring syst em, or – (C_1-C_{16} aliphatic) – (5-10 membered aromatic or nonaromati c monocyclic or bicyclic ring system) ; wherein up to five carbon at oms of the C_1-C_{16} aliphatic or the 5-10 membered aroma tic or nonaromatic monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{2A} is optionally su bstituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR';

R^3 is OH, R^{3A}, or OR^{3A}; wherein R^{3A} is C_1-C_{10} aliphatic option ally substituted with 1-3 occurrences of halo, R or OR';

R^4 is OH, R^{4A}, OR^{4A}; or when bond Y^1 between R^4 and R^5 is a double bond, R^4 is absent; wherein R^{4A} is C_1-C_7 aliphatic and R^{4A} is optionally substituted with 1-3 occurrences of halo, R' or OR';

R^5 is H or OH;

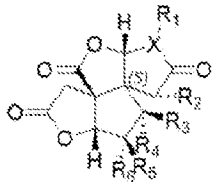
R^6 is H; or when bond Y^1 between R^4 and R^5 is a double bond, R^6 is absent;

R is H or C_1-C_6 aliphatic optionally substituted by 1-3 occurrences of F; or two R, taken together with the atom (s) to which they are atta ched, form a 3-6 membered ring having 0-4 heteroatoms; and

R' is H, a C_1-C_6 aliphatic wherein up to three carbon atoms of the C_1-C_6 aliphatic are optionally replaced with O, NH, N (C_1-C_6 alkyl) , C (O) , or S $(O)_2$; wherein said C_1-C_6 aliphatic is optionally substituted by 1-3 occurrences of F, OR, NH_2, NHR", or $NR"_2$, wherein R" is C_1-C_6 aliphatic or a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system having 0-5 heteroatoms selected from O, N, or S; wherein when R^2 is OH, R^3 is tert-butyl, R^4 is OH, R^5 is H, and R^6 is H, X is not -O-.

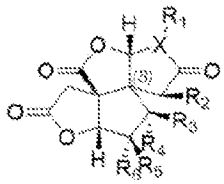
[Claim 2] The compound of claim 1, wherein X is $-NR^1-$, $-N=CR^1-NH-$, or $-NR^1-NH-$.

[Claim 3] The compound of claim 1, having Formula Ia:

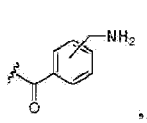


(Formula Ia).

[Claim 4] The compound of claim 1, having Formula Ib:



(Formula Ib).

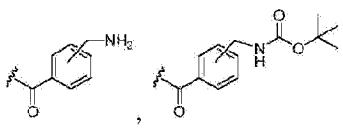
[Claim 5] The compound of any one of claims 2-4, wherein R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, C=O (C_{1-10} aliphatic) , SO_2 (C_{1-10} aliphatic) , SO_2 (phenyl) , phenyl, Si (C_{1-10} aliphatic) $_{1-2}$, Si (phenyl) $_{1-2}$, $^-$ (C_{1-10} aliphatic) O (C_{1-10} aliphatic) -, (C=O) (phenyl) , NH (C=O) (C_{1-10} aliphatic)  or NH (C=O) O (C_{1-10} aliphatic) ; wherein each R^{2A} is independently and optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR';

R^3 is C_{1-10} aliphatic;

the bond Y^1 between R^4 and R^5 is a single bond;

R^4 is OH or OR^{4A};

and R^5 is H or OH.

[Claim 6] The compound of any one of claims 2-4, wherein R^2 is R^{2A} or OR ^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5,  or NH (C=O) OC $(CH_3)_3$; wherein phenyl, C_6H_4, and C_6H_5 are each independently and optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR';

R^3 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or tert-butyl;

the bond Y^1 between R^4 and R^5 is a single bond;

R^4 is OH or OR^{4A};

and R^5 is H or OH.

[Claim 7] The compound of any one of claims 2-4, wherein R^1 is H.

[Claim 8] The compound of any one of claims 2-4, wherein R^1 is - $(L^1)_u$- $(Z^1)_v$; wherein

L^1 is C_1-C_{10} aliphatic wherein up to three carbon atoms of the C_1-C_{10} aliphatic are optionally replaced by N, O, or S;

Z^1 is phenyl, 1-methyl-1, 2, 3, 4-tetrahydronaphthalen-2-y, 1-methyl-2H-isoindol-2-yl, imidazol, indolyl, napthalenyl, adamantanyl, azetidinyl, bicyclo [1.1.1] pentyl, 1-oxa-8-azaspiro [4.5] decan-3-yl, cyclobutanyl, cyclohexanyl, cyclopentanyl, cyclopropanyl, norbornenyl, oxetanyl, piperazinyl, piperidinyl, pyridinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, or C_3-C_{12} cycloaliphatic having 0-5 heteroatoms selected from O, N, or S;

u is 0 or 1; and

v is 0 or 1; wherein Z^1 is optionally substituted with 1-5 occurrences of R^{1C}, morpholinyl, -OCH_2O-, - (C=O) - (pyrazinyl) -R^{1B}, - (C=O) - (phenyl) -R^{1B}, or - (SO_2) - (phenyl) -R^{1B}; wherein each independent occurrence of R^{1B} is H, halo, R*, OR*, or NRR*; wherein each independent occurrence of R^{1C} is H, halo, R*, OR*, or NRR*; and wherein each independent occurrence of R*is H, =N, -C≡CH, -N=N-, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, , -CN, -CH_2O-, -CF_2O-, -CH_2CH_2O-, or -Boc (- (C=O) OC $(CH_3)_3$) .

[Claim 9] The compound of claim 7, wherein when Z^1 is phenyl, Z^1 is optionally substituted with 1-5 occurrences of morpholinyl or R^{1C}, wherein R^{1C} is halo, CH_3, $-CH_2F$, $-CHF_2$, $-CF_3$, -CN $-OCH_3$, $-OCH_2O-$, $-OCF_2O-$, $-OCH_2CH_2O-$, $-NH_2$, -NH (C=O) CH_3, or-NH (Boc) (NH (C=O) OC $(CH_3)_3$) .

[Claim 10] The compound of claim 7, wherein when Z^1 is piperidinyl, Z^1 is optionally substituted with 1-2 occurrences of R^{1C}, wherein R^{1C} is tert-butoxylcarbonyl, 5- (difluoromethyl) pyrazine-2-carbonyl, 2, 2-difluoro-2H-1, 3-benzodioxole-5-carbonyl, 2, 3-dihydro-1, 4-benzodioxine-6-carbonyl, 2, 3-dihydro-1-benzofuran-5-sulfonyl, 4-chlorobenzoyl, 2, 3-dihydro-1-benzofuran-5-carbonyl, or prop-2-enoyl.

[Claim 11] The compound of claim 7, wherein when Z^1 is pyrrolidinyl, Z^1 is optionally substituted with 1-2 occurrences of R^{1C}, wherein R^{1C} is tert-butoxylcarbonyl.

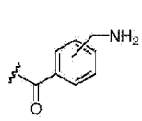
[Claim 12] The compound of claim 7, wherein R^1 is
H,
2, 4-dimethoxybenzyl,
[1- (tert-butoxycarbonyl) piperidin-4-yl] methyl,
piperidin-4-yl methyl,
2- [1- (tert-butoxycarbonyl) piperidin-4-yl] ethyl,
2- (piperidin-4-yl) ethyl,
3- [1- (tert-butoxycarbonyl) piperidin-4-yl] propyl,
3- (piperidin-4-yl) propyl,
2- [4- (tert-butoxycarbonyl) piperazin-1-yl] ethyl,
2- (piperazin-1-yl) ethyl,
2- (3-methyl-1H-indol-2-yl) ethyl,
3- (1H-imidazol-1-yl) propyl,
[1- (tertbutoxycarbonyl) pyrrolidin-3-yl] methyl,
(pyrrolidin-3-yl) methyl,
(bicyclo [2.2.1] hept-5-en-2-yl) methyl,
phenyl,
4-acetamidophenyl,
4- [(tert-butoxycarbonyl) amino] phenyl,
4-aminophenyl,
4- (morpholin-4-yl) phenyl,
benzo [d] [1, 3] dioxol-5-yl,
pyridin-3-yl,

benzyl,
methyl,
bicyclo [1.1.1] pentyl,
oxetan-3-yl,
cyclobutyl methyl,
cyclopropyl methyl,
(oxetan-3-yl) methyl,
adamantan-2-yl methyl,
NH_2,
cyclopropyl,
3-methoxy phenyl,
4-methoxy phenyl,
naphthalen-2-yl,
3- (trifluoromethyl) phenyl,
4-cyano phenyl,
2- [3- (but-3-yn-1-yl) -3H-diazirin-3-yl] ethyl,
cyclohexyl,
4-fluoro phenyl,
4- (trifluoromethyl) phenyl,
4-toluyl,
3-toluyl,
2-toluyl,
(oxolan-2-yl) methyl,
2-methoxy-2-oxoethyl,
(1- (5- (difluoromethyl) pyrazine-2-carbonyl) piperidin-4-yl) methyl,
[1- (2, 3-dihydro-1-benzofuran-5-sulfonyl) piperidin-4-yl] methyl,
(1- (2, 2-difluorobenzo [d] [1, 3] dioxole-5-carbonyl) piperidin-4-yl) methyl,
(1- (2, 3-dihydrobenzo [b] [1, 4] dioxine-6-carbonyl) piperidin-4-yl) methyl,
(1- (4-chlorobenzoyl) piperidin-4-yl) methyl,
(1- (2, 3-dihydrobenzofuran-5-carbonyl) piperidin-4-yl) methyl,
(1-acryloylpiperidin-4-yl) methyl,
(1- (quinoxaline-6-carbonyl) piperidin-4-yl) methyl,
(tetrahydro-2H-pyran-4-yl) methyl,
(tetrahydro-2H-thiopyran-4-yl) methyl,
2- (1-methyl-1, 2, 3, 4-tetrahydronaphthalen-2-yl) ethyl,
2- (1-methyl-2H-isoindol-2-yl) ethyl,

2- (azetidin-1-yl) ethyl,
2- (trifluoromethyl) phenyl,
2-fluoro phenyl,
2-methoxy phenyl,
3, 4-difluoro phenyl,
3, 4-dichloro phenyl,
3, 5-difluoro phenyl,
3-fluoro phenyl,
4-hydroxy phenyl,
8- (tert-butoxycarbonyl) -1-oxa-8-azaspiro [4.5] decan-3-yl,
anilinyl,
benzo [d] [1, 3] dioxol-4-yl,
cyclobutyl,
cyclohexyl methyl,
naphthalen-1-yl,
pyridin-2-yl,
pyridin-4-yl,
adamantan-1-yl methyl,
1- (tert-butoxycarbonyl) -1H-indol-5-yl,
1H-indol-5-yl,
3- [(tert-butoxycarbonyl) amino] phenyl,
4-Hydroxyphenyl ethyl,
1H-indole-3-ethyl,
((1R, 4aS, 10aR) -7-isopropyl-1, 4a-dimethyl-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthren-1-yl) methyl,
[((tert-butoxycarbonyl) aminomethyl) adamantan-1-yl] methyl,
(aminomethyl) adamantan-1-yl) methyl,
3, 5-di-tert butyl phenyl,
3, 4-dihydroxyphenyl,
3-methoxy-4-hydroxyphenyl ethyl,
1H-indole-5-hydroxy-3-ethyl,
1H-indole-5-methoxy-3-ethyl,
1H-indole-4-hydroxy-3-ethyl,
piperonyl,
2- (4-Imidazolyl) ethyl (histamine) ,
2, 2-diphenylethyl,
3-hydroxy-4-methoxyphenyl ethyl,
3, 4-methylenedioxyphenyl ethyl,

1H-indole-5-hydroxy-3-ethyl (serotonin) ,
3, 4-dihydroxyphenyl ethyl (dopamine) ,
1H-indole-3-ethyl (tryptamine) ,
3-methoxy-4-hydroxyphenyl ethyl (3-O-methyldopamine) , or
methylenedioxyphenyl.

[Claim 13] The compound of claim 11, wherein

R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5,  or NH (C=O) OC $(CH_3)_3$; wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR';

R^3 is tert-butyl;

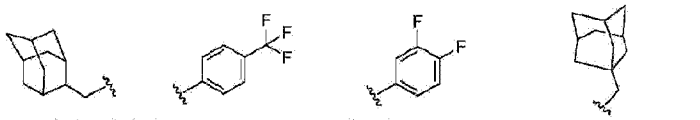
the bond Y^1 between R^4 and R^5 is a single bond;

R^4 is OH;

R^5 is H;

X is $-NR^1-$, $-N=CR^1-NH-$, or $-NR^1-NH-$; and.

R^1 is selected from



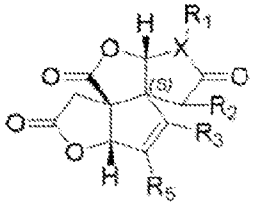
adamantan-2-yl methyl, 4-(trifluoromethyl) phenyl, 3,4-difluoro phenyl, adamantan-1-yl methyl,

2- (4-imidazolyl) ethyl (histamine) ,
1H-indole-5-hydroxy-3-ethyl (serotonin) ,
3, 4-dihydroxyphenyl ethyl (dopamine) ,
1H-indole-3-ethyl (tryptamine) , or
3-methoxy-4-hydroxyphenyl ethyl (3-O-methyldopamine) .

[Claim 14] The compound of claim 1, selected from a compound of Table 1d.

[Claim 15] The compound of claim 1, wherein the compound is DW192, P-29, P-21, P-30, P-33, JW093, XBB-023, P-28, JW107, XBB-039, JW094, P-34, XBB-045, JW081, XBB-028, XBB-038, XBB-037, XBB-054, XBB-025, XBB-029, XBB-024, DW172, XBB-004, XBB-042, XBB-068, XBB-040, XBB-006, JW072, DW189, P-8, DW191, DW168, XBB-013, XBB-037', XBB-009, XBB-060, XBB-016, DW182, XBB-010, SCC506, SCC363, or SXQ087-1.

[Claim 16] The compound of claim 1, wherein bond Y^1 is a double bond , having Formula I' :

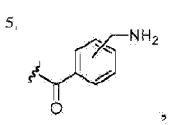


(Formula I').

[Claim 17] The compound of claim 15, wherein

X is -O-and R^1 is absent;

R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4$ CH_3, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H



or NH (C=O) OC $(CH_3)_3$;

wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR';

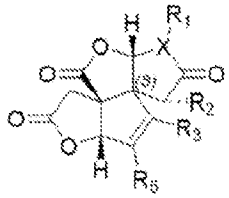
R^3 is tert-butyl;

R^4 is absent;

R^5 is H; and

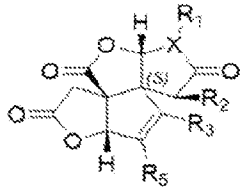
R^6 is absent.

[Claim 18] The compound of claim 1, having Formula I'a:



(Formula I'a).

[Claim 19] The compound of claim 1, having Formula I' b:

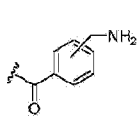
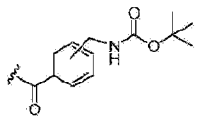


(Formula I'b).

[Claim 20] The compound of claim 1, wherein

X is -O-and R^1 is absent;

bond Y^1 is a single bond;

R^2 is OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, (C=O) C_6H_5,   $CH_2CH_2OCH_3$, or NH (C=O) OC $(CH_3)_3$;

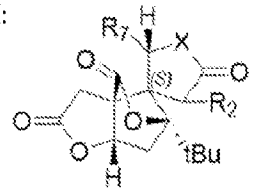
wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR';

R^3 is isopropenyl;

R^4 is CH_3;

R^5 is H; and

R^6 is H.

[Claim 21] A compound of Formula II: 

(Formula II)

or a stereomer, a tautomer, or a pharmaceutically acceptable salt thereof,

wherein

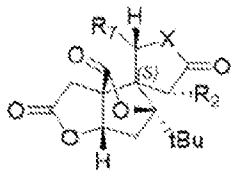
X is -O-, $-NR^1-$, $-N=CR^1-NH-$, or $-NR^1-NH-$; wherein R^1 is as defined in claim 1;

R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, a C_1-C_{16} aliphatic or a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system, wherein up to five carbon atoms of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO_2, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{2A} is optionally substituted with 1-5 occurrences of R^{2B}, wherein R^{2B} is halo, R' or OR'; and

R^7 is R^{7A} or OR^{7A}, wherein R^{7A} is H, a C_1-C_{16} aliphatic or a 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system, wherein up to five carbon atoms of the C_1-C_{16} aliphatic or the 5-10 membered aromatic or nonaromatic monocyclic or bicyclic ring system are optionally replaced by N, NR, O, S, C=O, SO

$_2$, S=O, (C=O) N, N (C=O) N, (C=O) O, or Si ; wherein R^{7A} is optionally substituted with 1-5 occurrences of R^{7B}, wherein R^{7B} is halo, R' or OR' .

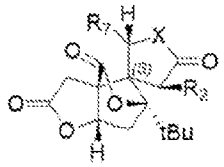
[Claim 22] The compound of claim 20, having Formula IIa:



(Formula IIa).

Rule 26, 02.09.2024

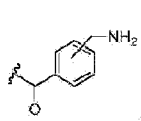
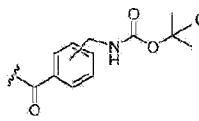
[Claim 23] The compound of claim 20, having Formula IIb:



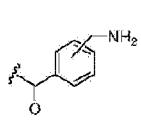
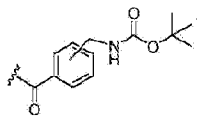
(Formula IIb).

[Claim 24] The compound of claim 20, wherein

X is -O-;

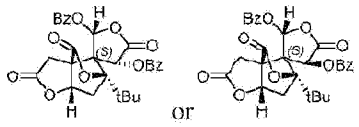
R^2 is R^{2A} or OR^{2A}, wherein R^{2A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5,  ,  or NH (C=O) OC $(CH_3)_3$;

wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR'; and

R^7 is R^{7A} or OR^{7A}, wherein R^{7A} is H, (C=O) CH_3, SO_2CH_3, $SO_2C_6H_4CH_3$, SO_2CF_3, phenyl, Si $(CH_3)_2C(CH_3)_3$, Si $(CH_2CH_3)_3$, Si $(CH_3)_3$, Si $(C_6H_5)_2C(CH_3)_3$, Si (iPr) $_3$, CH_2OCH_3, $CH_2CH_2OCH_3$, (C=O) C_6H_5,  ,  or NH (C=O) OC $(CH_3)_3$;

wherein phenyl is optionally substituted with 1-5 occurrences of halo, R' or OR' .

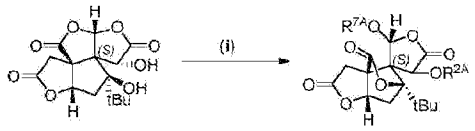
[Claim 25] The compound of claim 20, wherein the compound is



or

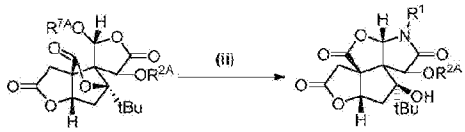
[Claim 26] A process for preparing a compound of claim 1, comprising at least t he following steps:

i) treating bilobalide with R^{2A}-X in a suitable solvent to form pr otected product IIa



bilobalide protected product IIa ; and

ii) treating protected product IIa with at least one base or an acce ptable salt thereof to form aminated product IIb

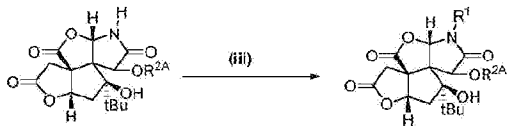


protected product IIa aminated product IIb ;

wherein R^{2A} and R^{7A} are as defined in claim 20.

[Claim 27] The process of claim 25, wherein the aminated product IIb is aminate d product IIb', further comprising the step of:

iii) treating the aminated product IIb' with R^{1}-B $(OH)_2$ in the presence of a catalyst to form a N-arylated product IIc



aminated product IIb' N-arylated product IIc ;

wherein R^{1} and R^{2A} are as defined in claim 1.

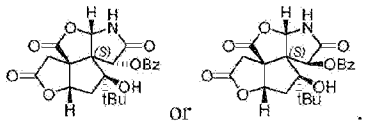
[Claim 27] The process of any one of claims 25-26, further comprising the step of:

iv) treating the aminated product IIb of claim 25 or the N-arylated product IIc of claim 26 in a protic solvent to form a depro tected product.

[Claim 28] The process of claim 25, wherein R^{2A} and R^{7A} of the protected product IIa is as defined in any one of claims 20-24.

[Claim 29] The process of claim 25, wherein the R^{2A}-X is benzoyl chloride, or 4- (Boc-aminomethyl) benzoic acid, and the suitable solvent is pyridine or dichloromethane.

[Claim 30] The process of claim 25, wherein the at least one base is ammonia, and the aminated product IIb is:



[Claim 31] The process of claim 27, wherein the deprotected product is as defined in claim 1.

[Claim 32] The process of claim 25, wherein the at least one base is NH_2R^1 or $[H_3NR^1]^+$.

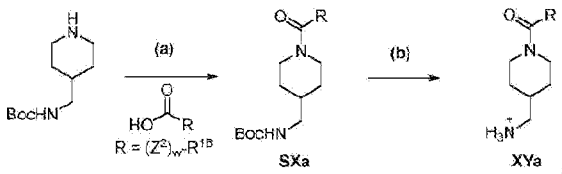
[Claim 33] The process of claim 32, further includes a second base in step (ii), wherein in the second base is a hindered base selected from triethylamine, diisopropylethylamine, tributylamine, or tetramethylethylenediamine.

[Claim 34] The process of claim 25, wherein the protected product IIa is as defined in claim 20.

[Claim 35] The process of claim 32, wherein the $[H_3NR^1]^+$ is provided as XYa prepared by the steps of:

a) treating R-COOH with 1-hydroxybenzotriazole, N- (3-dimethylaminopropyl) -N'-ethylcarbodiimide hydrochloride, and tert-butyl (piperidin-4-ylmethyl) carbamate, to form a boc-protected product SXa, wherein R = $(Z^2)_w$-R^{1B}, wherein Z^2, w and R^{1B} are as defined in claim 1; and

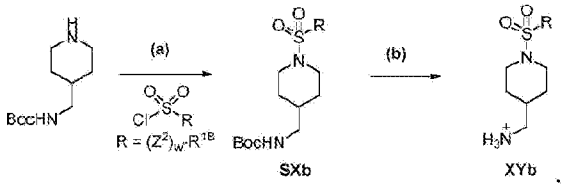
b) treating the boc-protected product SXa with an acid in a solvent to form XYa



[Claim 36] The process of claim 33, wherein the $[H_3NR^1]^+$ is provided as XYb prepared by the steps of:

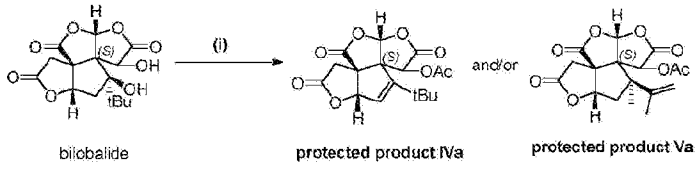
a) treating R-SO_2 with tert-butyl (piperidin-4-ylmethyl) carbamate and triethylamine, to form a boc-protected product SXb, wherein R = $(Z^2)_w$-R^{1B}, wherein Z^2, w and R^{1B} are as defined in claim 1; and

b) treating the boc-protected product SXb with an acid in a solvent to form XYb



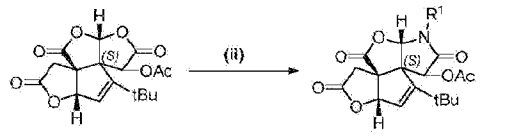
[Claim 37] A process of preparing a compound of claim 1, comprising at least on e of the steps of:

i) treating bilobalide with Ac_2O and an acid to form a protected product IVa and/or protected product Va

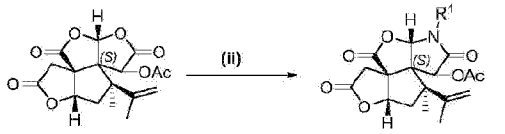


; and

ii) treating protected product IVa or protected product Va with at l east one base or an acceptable salt thereof to form aminated product IVb or aminated product Vb



or

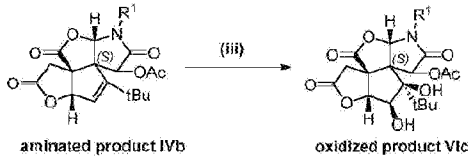


,

wherein R^1 is as defined in claim 1.

[Claim 38] The process of claim 37, further comprising the step of:

iii) treating the aminated product VIb with an oxidizing agent and a solvent to form oxidized product VIc

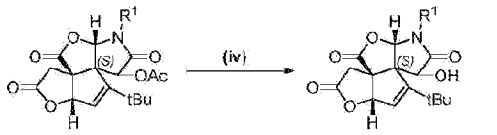


,

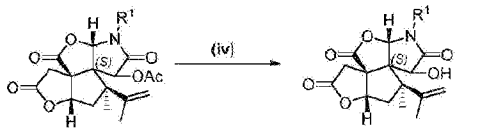
wherein R^1 is as defined in claim 1.

[Claim 39] The process of claim 37, further comprising at least one of the steps of:

iv) treating the aminated product IVb or the aminated product Vb wit h an acid to form deprotected product IVd or deprotected product Vd,



or

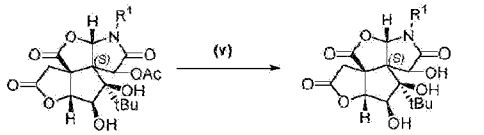


,

wherein R^1 is as defined in claim 1.

[Claim 40] The process of claim 38, further comprising the step of:

v) treating the oxidized product VIc with an acid to form deprotecte d product VId,



,

wherein R^1 is as defined in claim 1.

[Claim 41] A method of treating or preventing cancer in a subject in need there of, comprising administering to the subject a compound of any one of the preceding claims.

[Claim 42] The method of claim 41, wherein the cancer is bladder cancer, brain cancer, breast cancer, CNS cancer, colon cancer, hematopoietic cance r, kidney cancer, leukemia, lung cancer, melanoma, ovarian cancer, p ancreatic cancer, prostate cancer, or renal cancer.

[Claim 43] The method of claim 42, wherein the cancer is leukemia, colon cancer , lung cancer, melanoma or renal cancer.

[Claim 44] The method of claim 43, wherein the lung cancer is non-small cell lung cancer (NSCLC) .

[Claim 45] The method of claim 44, wherein the leukemia is lymphocytic leukemia .

[Claim 46] Use of a compound of claim 1 for treating or preventing cancer.

[Claim 47] Use of a compound of claim 1 for the manufacture of a medicament for treating or preventing cancer.

[Claim 48] A method of inducing cell death in a cancer cell, comprising contacting a compound of any one of the preceding claims with the cancer cell.

[Claim 49] A method of inhibiting cell growth in a cancer cell, comprising contacting a compound of any one of the preceding claims with the cancer cell.

[Claim 50] The method of claim 48 or claim 49, wherein the method is an in vitro method.

[Claim 51] The method of any one of claims 41-50, wherein the compound is DW192, P-29, P-21, P-30, P-33, JW093, XBB-023, P-28, JW107, XBB-039, JW094, P-34, XBB-045, JW081, XBB-028, XBB-038, XBB-037, XBB-054, XBB-025, XBB-029, XBB-024, DW172, XBB-004, XBB-042, XBB-068, XBB-040, XBB-006, JW072, DW189, P-8, DW191, DW168, XBB-013, XBB-037', XBB-009, XBB-060, XBB-016, DW182, XBB-010, SCC506, SCC363, or SXQ087-1.

[Claim 52] The method of claim 51, wherein the compound is DW192, P-29, P-21, SCC506, SCC363, or SXQ087-1.

[Claim 53] A method of treating or preventing neurological related disease in a subject in need thereof, comprising administering to the subject a compound of any one of the preceding claims.

[Claim 54] The method of claim 53, wherein the neurological related disease is caused by ferroptosis.

[Claim 55] The method of claim 54, wherein the neurological related disease is Alzheimer's disease or Parkinson's disease.

[Claim 56] Use of a compound of claim 1 for treating or preventing Alzheimer's disease or Parkinson's disease.

[Claim 57] Use of a compound of claim 1 for inhibiting ferroptosis by restoring glutathione peroxidase 4 (GPX4), thereby mitigating GPX4 degradation induced by ferroptosis inducers.

[Claim 58] The use of claim 57, wherein the ferroptosis inducers are RSL3, FIN56, ML162, ML210, or erastin.

[Claim 59] Use of a compound of claim 1 for inhibiting ferroptosis by reducing intracellular reactive oxygen species (ROS level).

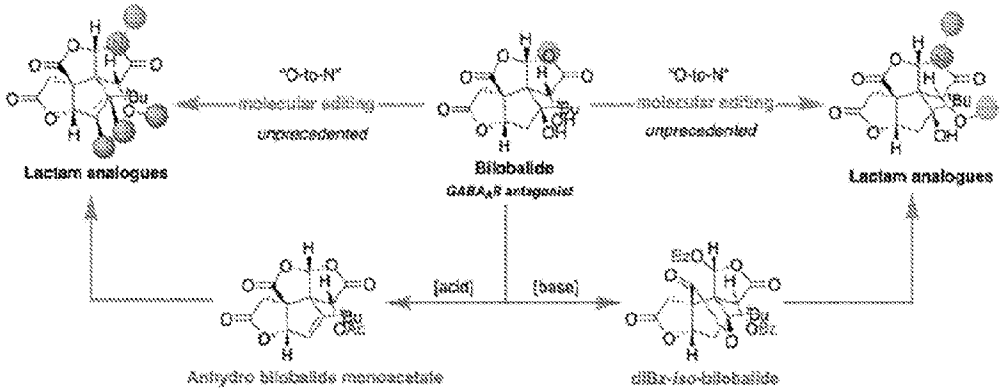
[Claim 60] Use of a compound of claim 1 for inhibiting ferroptosis by reducing lipid peroxidation.

[Claim 61] Use of a compound of claim 1 for the manufacture of a medicament for treating or preventing Alzheimer's disease or Parkinson's disease.

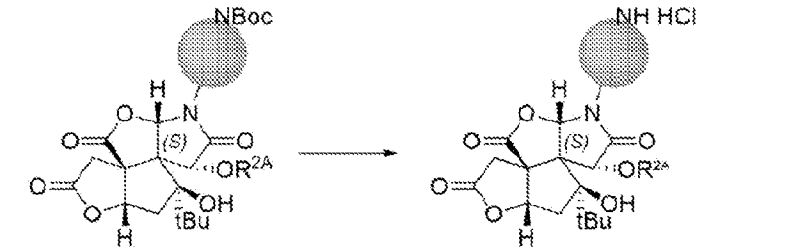
[Claim 62] The method of any one of claims 53-61, wherein the compound is DW192, P-29, P-21, P-30, P-33, JW093, XBB-023, P-28, JW107, XBB-039, JW094, P-34, XBB-045, JW081, XBB-028, XBB-038, XBB-037, XBB-054, XBB-025, XBB-029, XBB-024, DW172, XBB-004, XBB-042, XBB-068, XBB-040, XBB-006, JW072, DW189, P-8, DW191, DW168, XBB-013, XBB-037', XBB-009, XBB-060, XBB-016, DW182, XBB-010, SCC506, SCC363, or SXQ087-1.

[Claim 63] The method of claim 62, wherein the compound is DW192, P-29, P-21, SCC506, SCC363, or SXQ087-1.

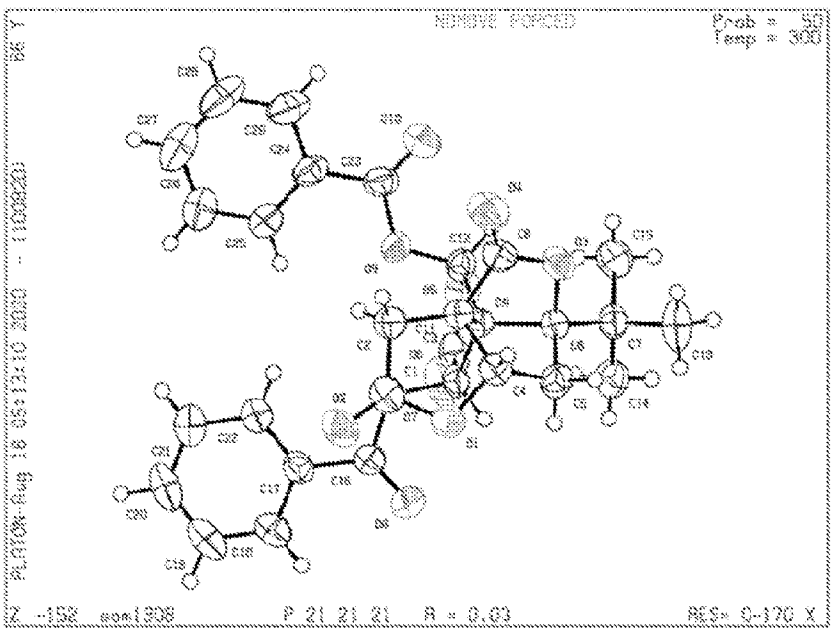
[Fig. 1A]



[Fig. 1B]

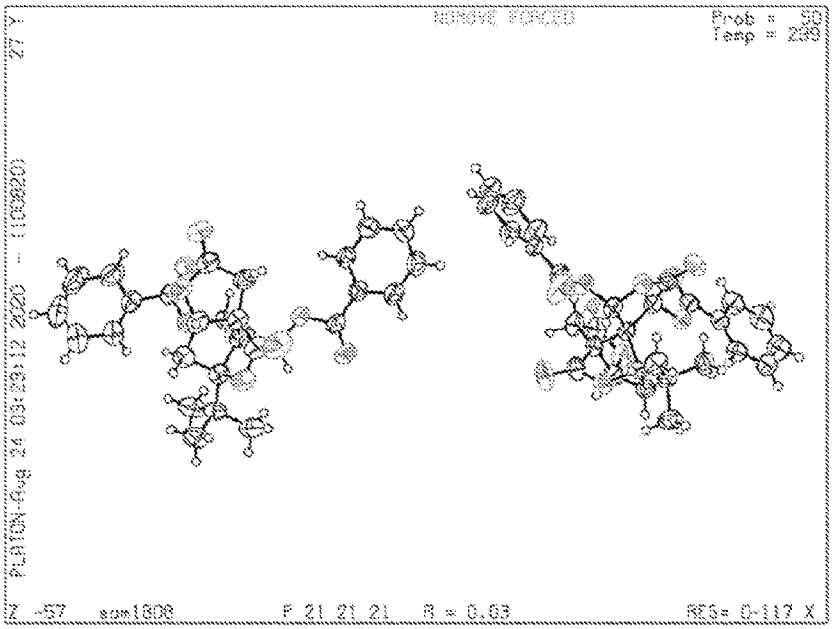


[Fig. 1C]



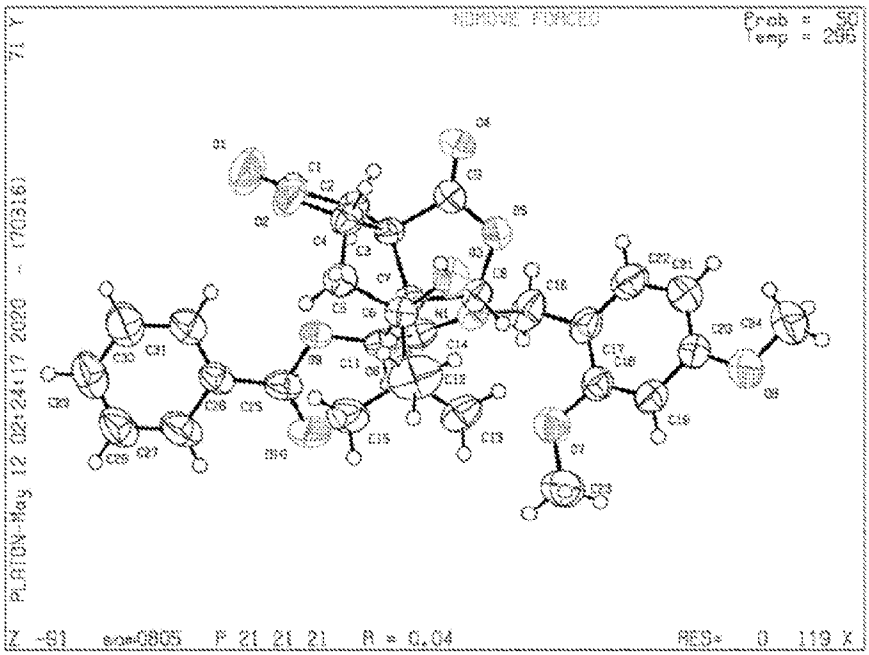
Rule 26, 02.09.2024

[Fig. 1D]



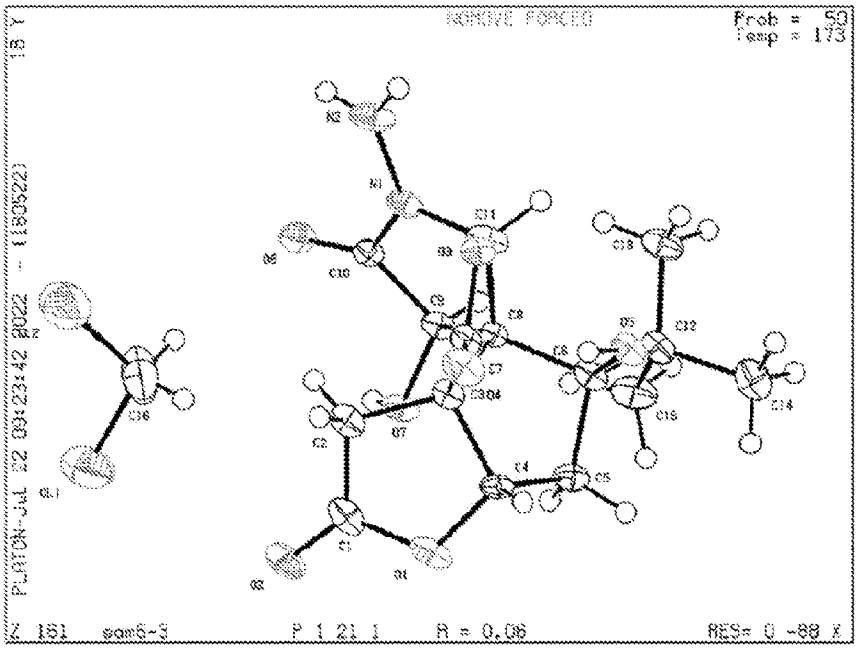
Rule 26, 02.09.2024

[Fig. 1E]



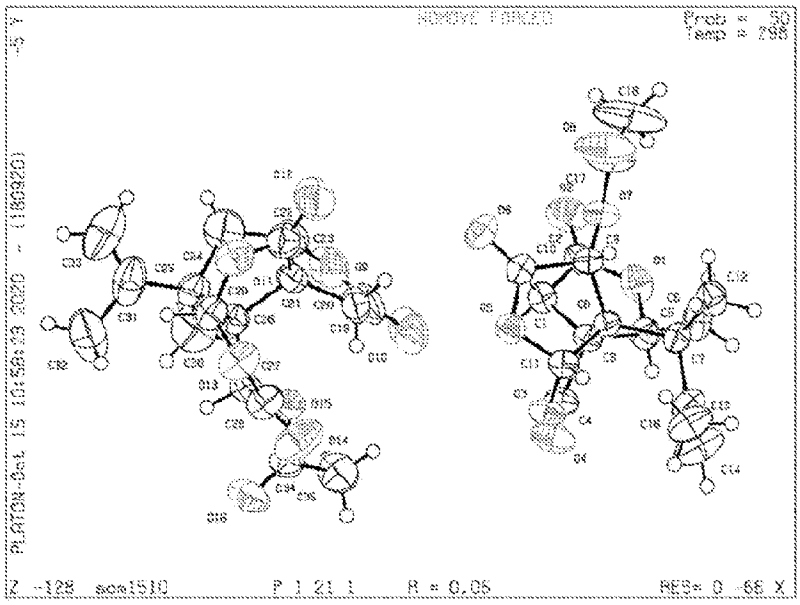
Rule 26, 02.09.2024

[Fig. 1F]



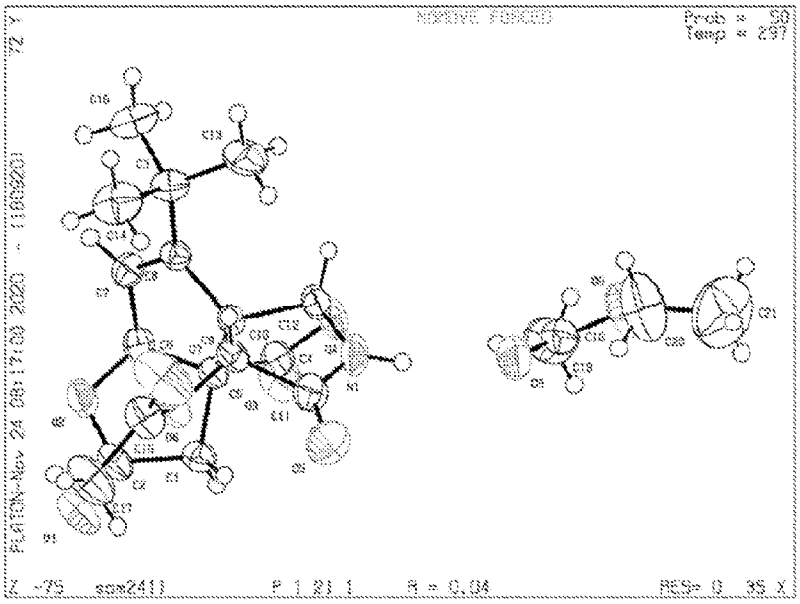
Rule 26, 02.09.2024

[Fig. 1G]



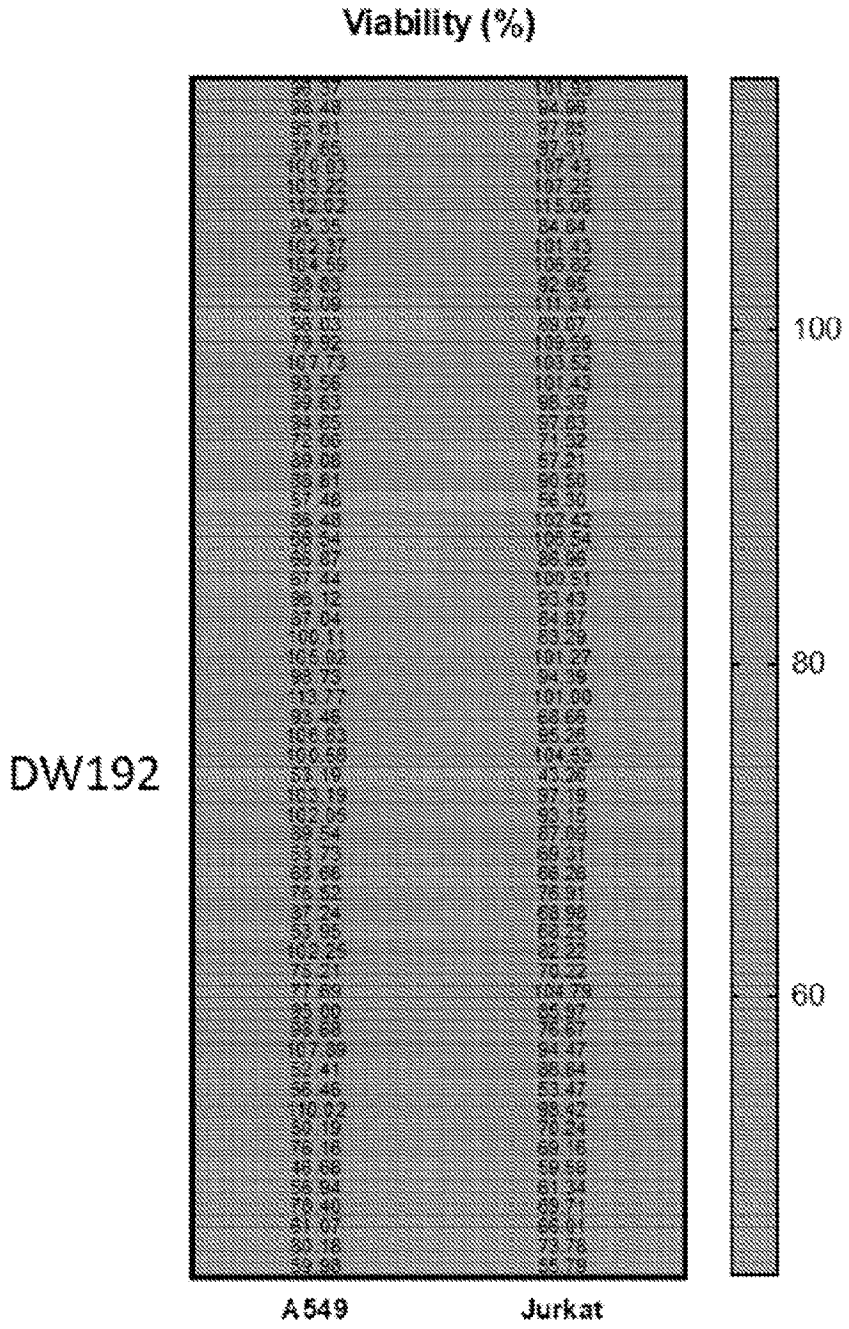
Rule 26, 02.09.2024

[Fig. 1H]

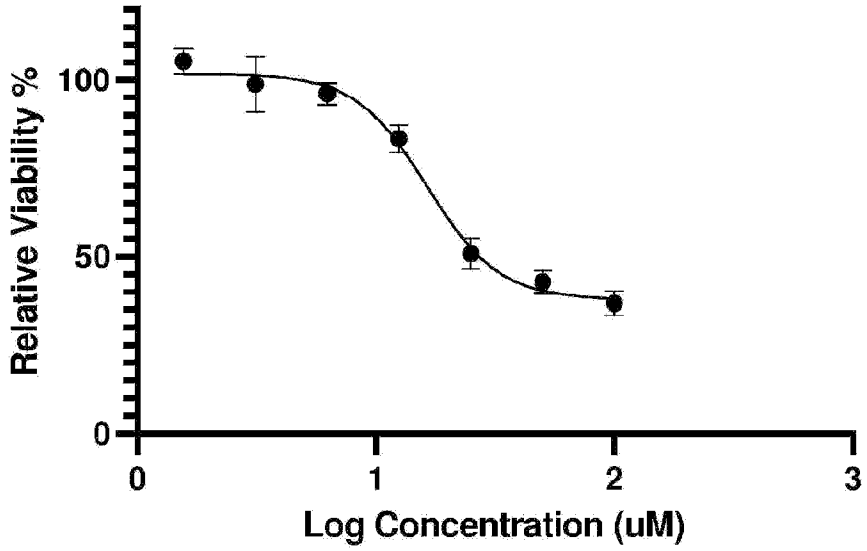


Rule 26, 02.09.2024

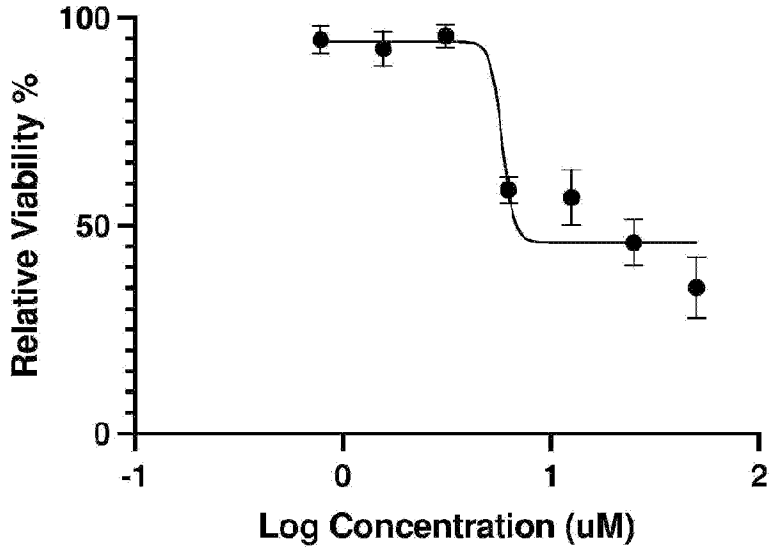
[Fig. 2]



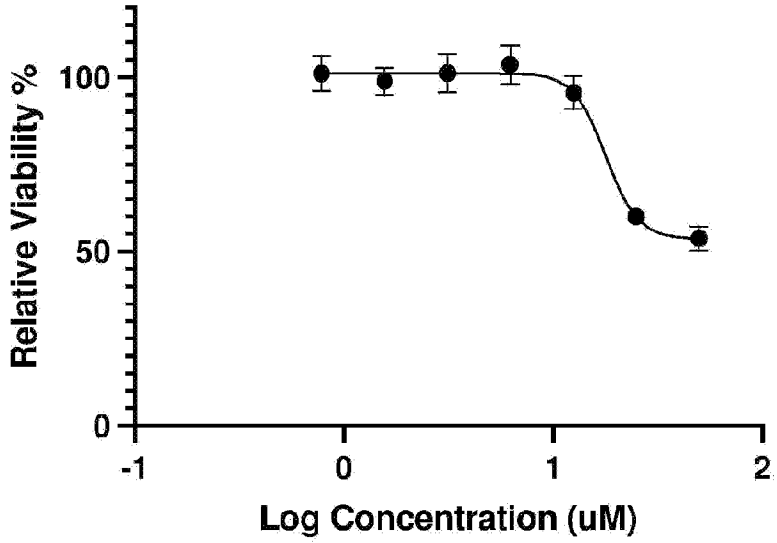
[Fig. 3A]


Relative Viability %
100
50
0
0
1
2
3
Log Concentration (uM)

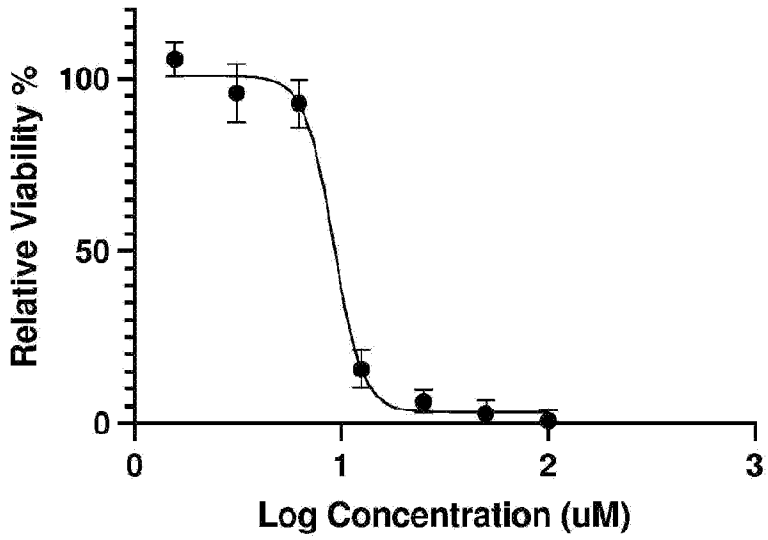
[Fig. 3B]


Relative Viability %
100
50
0
-1
0
1
2
Log Concentration (uM)

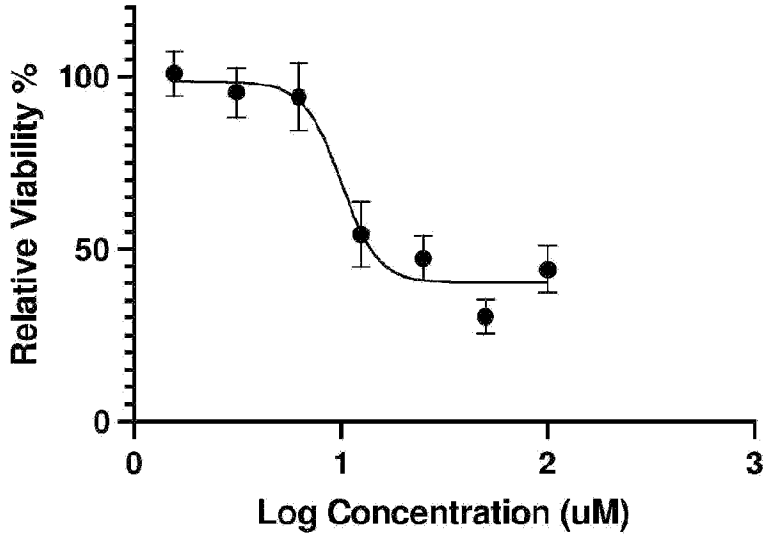
[Fig. 3C]


Relative Viability %
100
50
0
-1
0
1
2
Log Concentration (uM)

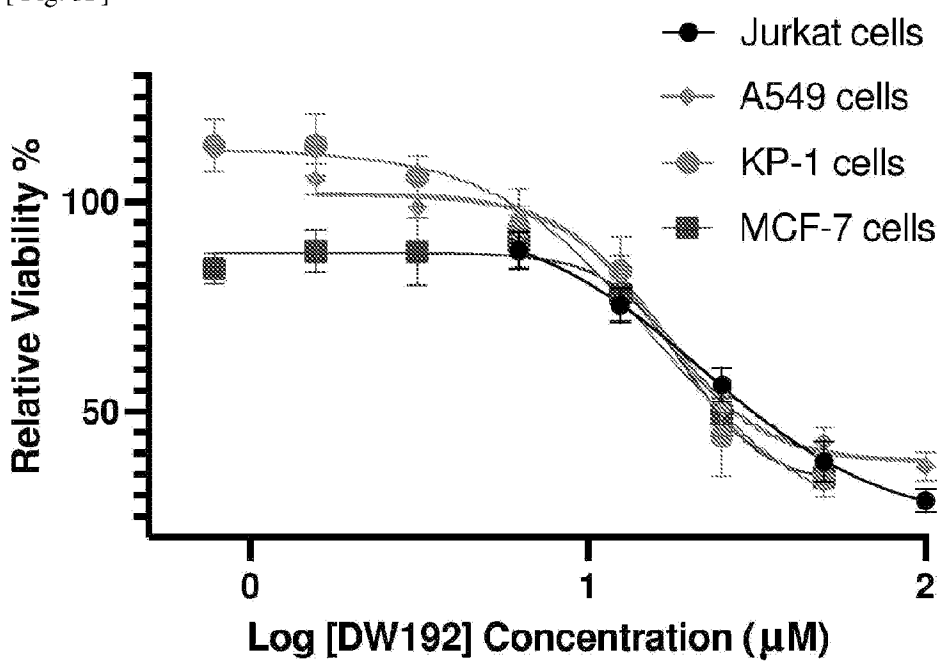
[Fig. 3D]


Relative Viability %
100
50
0
0
1
2
3
Log Concentration (uM)

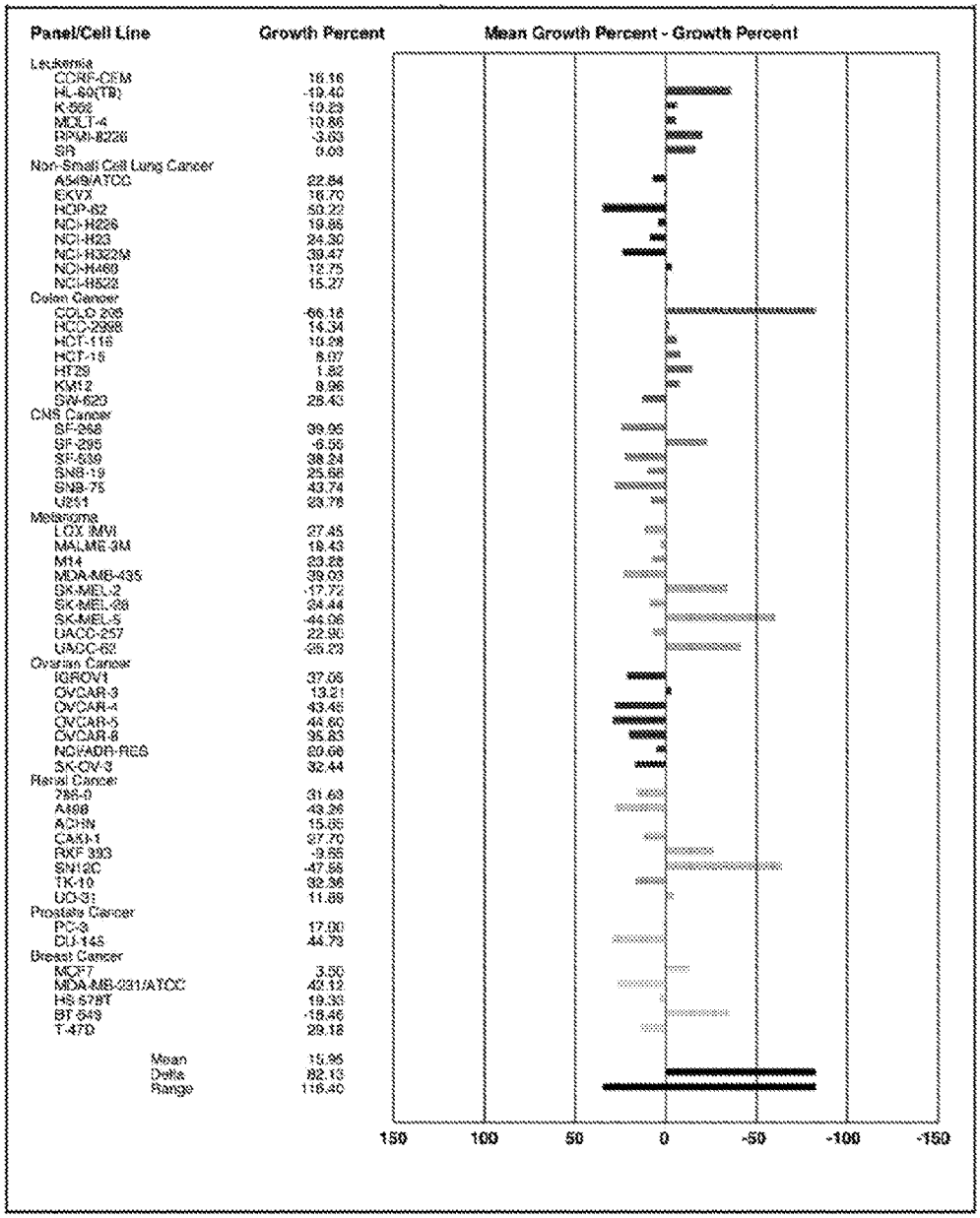
[Fig. 3E]


Relative Viability %
100
50
0
0
1
2
3
Log Concentration (uM)

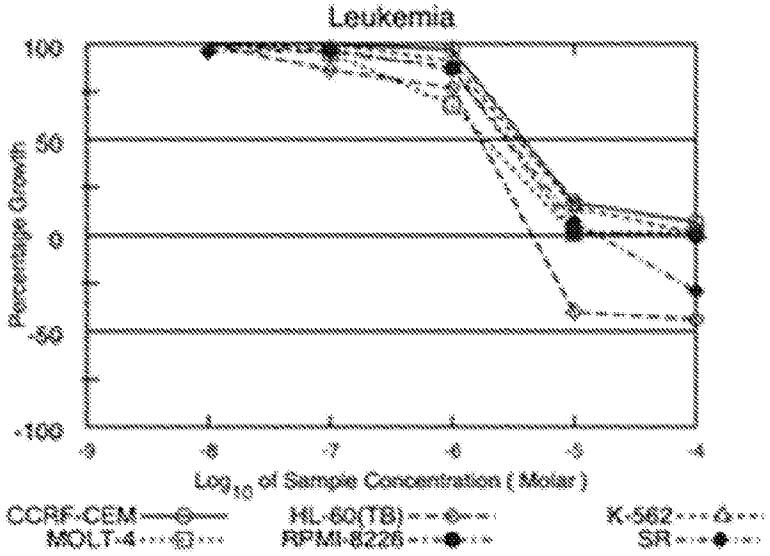
[Fig. 3F]


Jurkat cells
A549 cells
KP-1 cells
MCF-7 cells
Relative Viability %
100
50
0
1
2
Log [DW192] Concentration (μM)

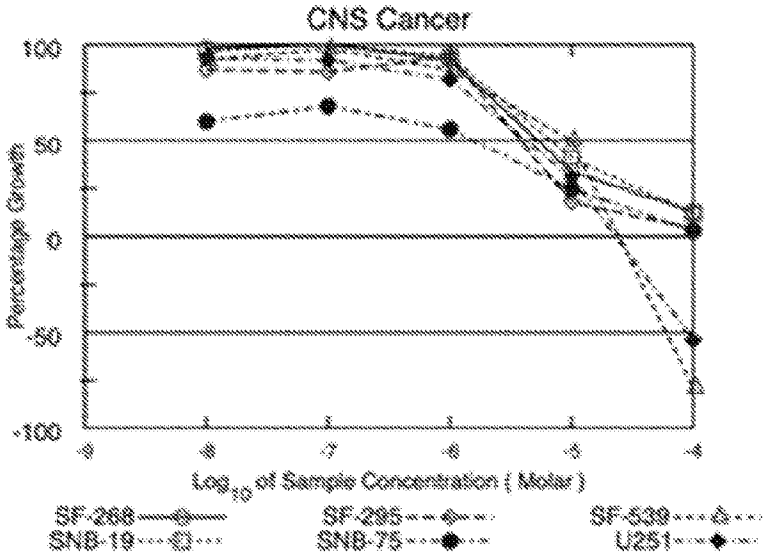
[Fig. 4A]


Panel/Cell Line
Growth Percent
Mean Growth Percent - Growth Percent
Leukemia
CCRF-CEM 16.16
HL-60(TB) -19.40
K-562 10.03
MOLT-4 10.86
RPMI-8226 -3.03
SR 9.09
Non-Small Cell Lung Cancer
A549/ATCC 22.84
EKVX 26.70
HOP-62 58.22
HOP-92 19.98
NCI-H226 34.26
NCI-H23 38.47
NCI-H322M 12.75
NCI-H460 15.27
Colon Cancer
COLO 205 -56.16
HCC-2998 14.04
HCT-116 16.28
HCT-15 8.07
HT29 1.82
KM12 8.96
SW-620 28.40
CNS Cancer
SF-268 99.95
SF-295 -9.56
SF-539 98.24
SNB-19 25.66
SNB-75 43.74
U251 33.78
Melanoma
LOX IMVI 37.45
MALME-3M 18.43
M14 23.28
MDA-MB-435 99.03
SK-MEL-2 -17.72
SK-MEL-28 24.44
SK-MEL-5 44.06
UACC-257 22.95
UACC-62 69.23
Ovarian Cancer
IGROV1 37.56
OVCAR-3 13.21
OVCAR-4 43.46
OVCAR-5 44.80
OVCAR-8 35.83
NCI/ADR-RES 80.68
SK-OV-3 32.44
Renal Cancer
786-0 31.63
A498 48.36
ACHN 15.66
CAKI-1 57.70
RXF 393 -9.95
SN12C 47.66
TK-10 92.36
UO-31 11.88
Prostate Cancer
PC-3 17.66
DU-145 44.78
Breast Cancer
MCF7 3.56
MDA-MB-231/ATCC 42.12
HS 578T 19.36
BT-549 -18.46
T-47D 29.18
Mean 15.96
Delta 82.13
Range 116.40
150
100
50
0
-50
-100
-150

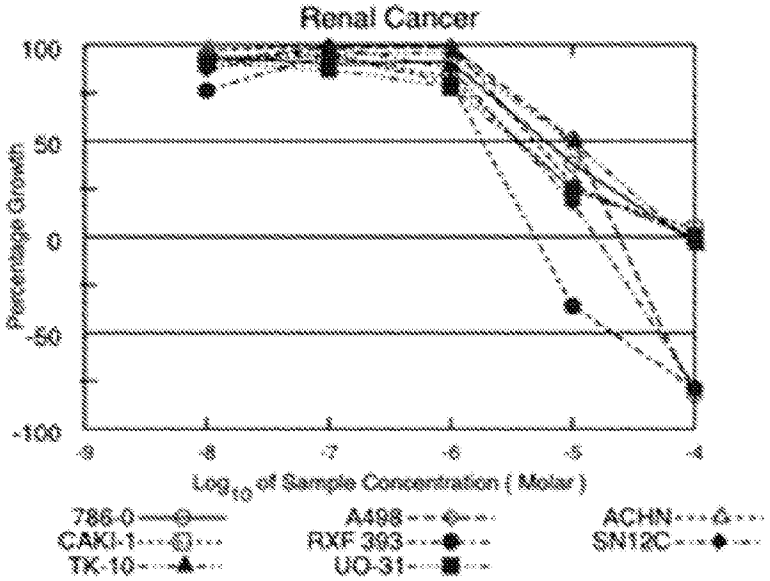
[Fig. 4B]


Leukemia
100
50
0
-50
-100
Percentage Growth
-9
-8
-7
-6
-5
-4
Log10 of Sample Concentration (Molar)
CCRF-CEM
MOLT-4
HL-60(TB)
RPMI-8226
K-562
SR

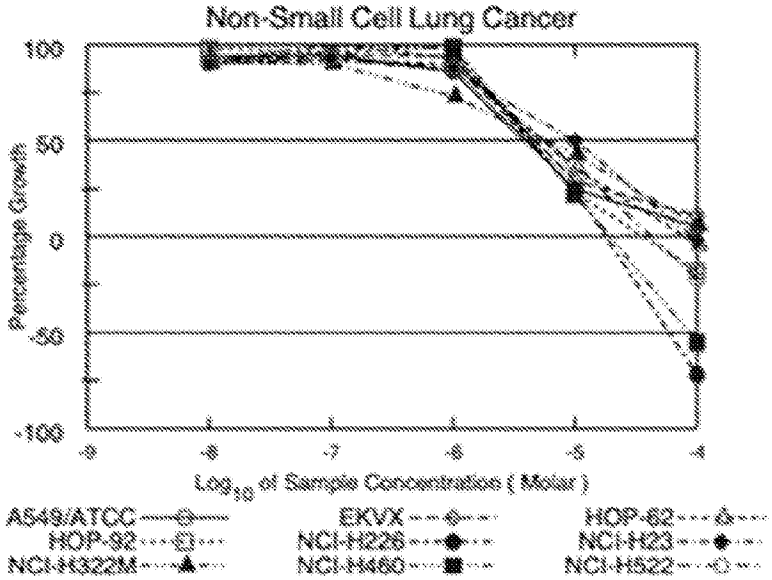
[Fig. 4C]


CNS Cancer
100
50
0
-50
-100
Percentage Growth
-9
-8
-7
-6
-5
-4
Log10 of Sample Concentration (Molar)
SF-268
SNB-19
SF-295
SNB-75
SF-539
U251

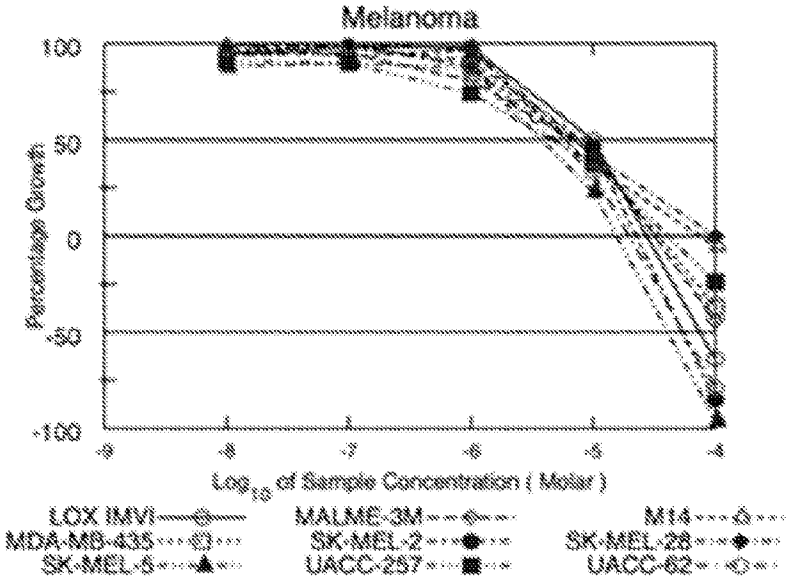
[Fig. 4D]


Renal Cancer
100
50
0
-50
-100
Percentage Growth
-9
-8
-7
-6
-5
-4
Log10 of Sample Concentration (Molar)
786-0
CAKI-1
TK-10
A498
RXF 393
UO-31
ACHN
SN12C

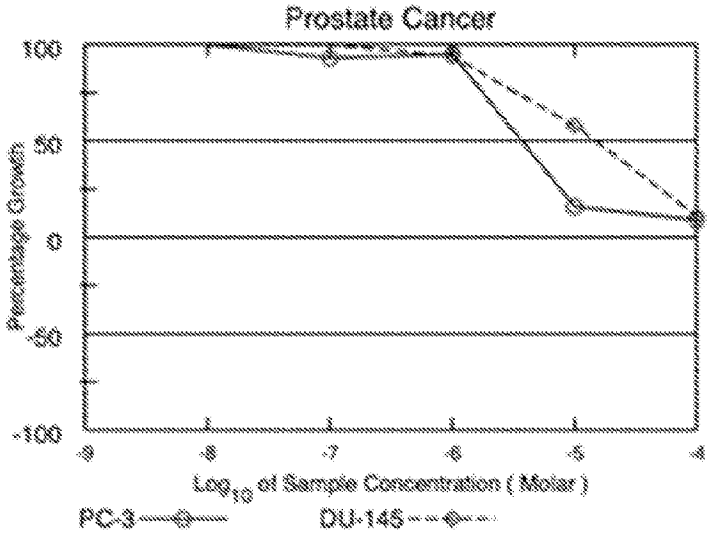
[Fig. 4E]


Non-Small Cell Lung Cancer
100
50
0
-50
-100
Percentage Growth
-9
-8
-7
-6
-5
-4
Log10 of Sample Concentration (Molar)
A549/ATCC
HOP-92
NCI-H322M
EKVX
NCI-H226
NCI-H460
HOP-62
NCI-H23
NCI-H522

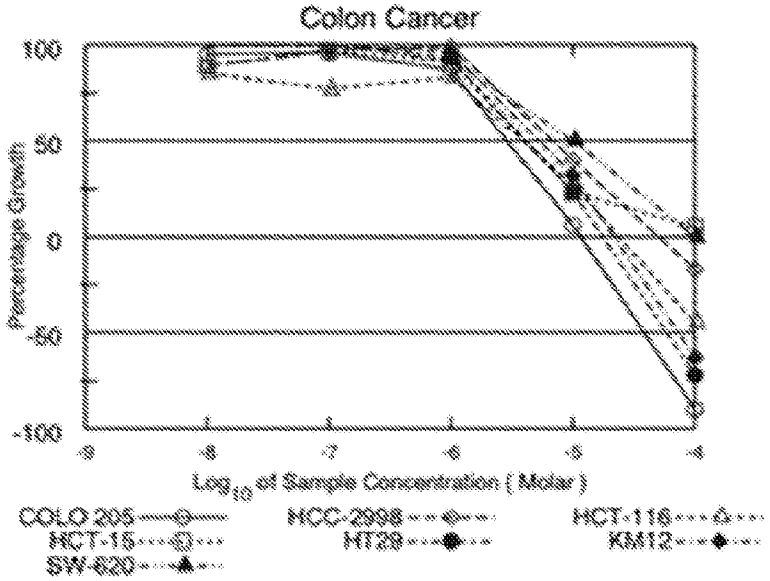
[Fig. 4F]


Melanoma
100
50
0
-50
-100
Percentage Growth
-9
-8
-7
-6
-5
-4
Log10 of Sample Concentration (Molar)
LOX IMVI
MDA-MB-435
SK-MEL-5
MALME-3M
SK-MEL-2
UACC-257
M14
SK-MEL-28
UACC-62

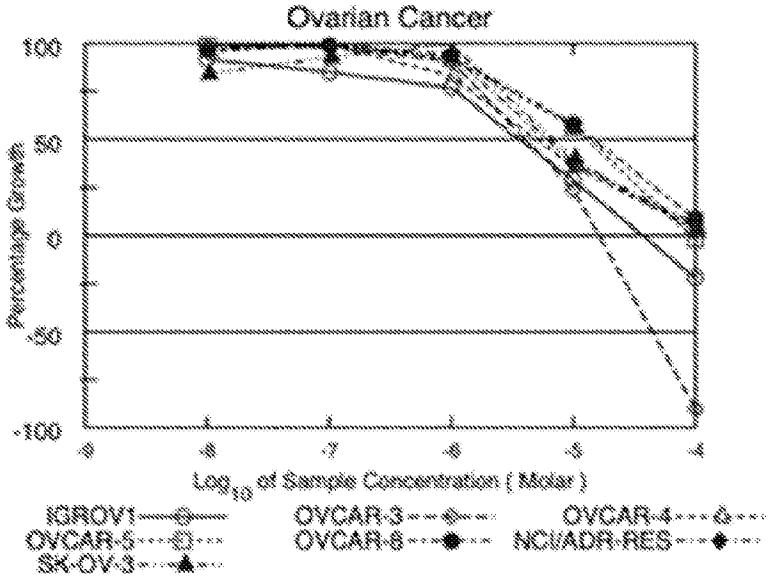
[Fig. 4G]


Prostate Cancer
100
50
0
-50
-100
Percentage Growth
-9
-8
-7
-6
-5
-4
Log10 of Sample Concentration (Molar)
PC-3
DU-145

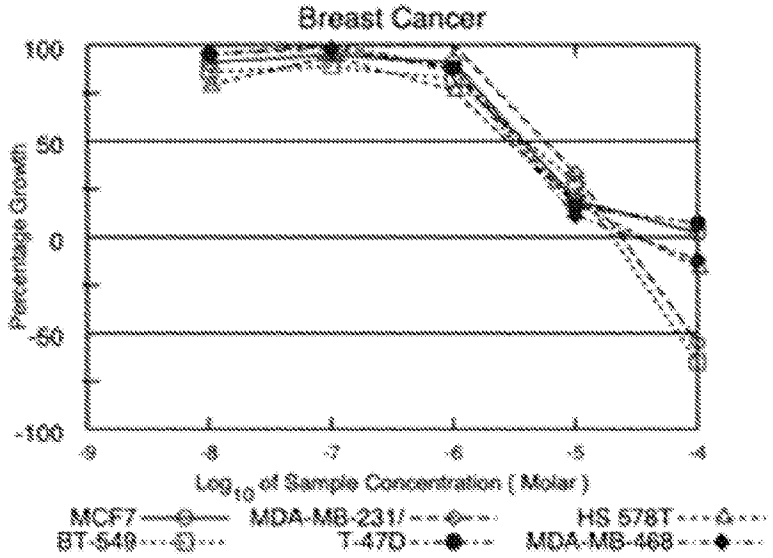
[Fig. 4H]


Colon Cancer
100
50
0
-50
-100
Percentage Growth
-9
-8
-7
-6
-5
-4
Log10 of Sample Concentration (Molar)
COLO 205
HCC-2998
HCT-116
HCT-15
HT29
KM12
SW-620

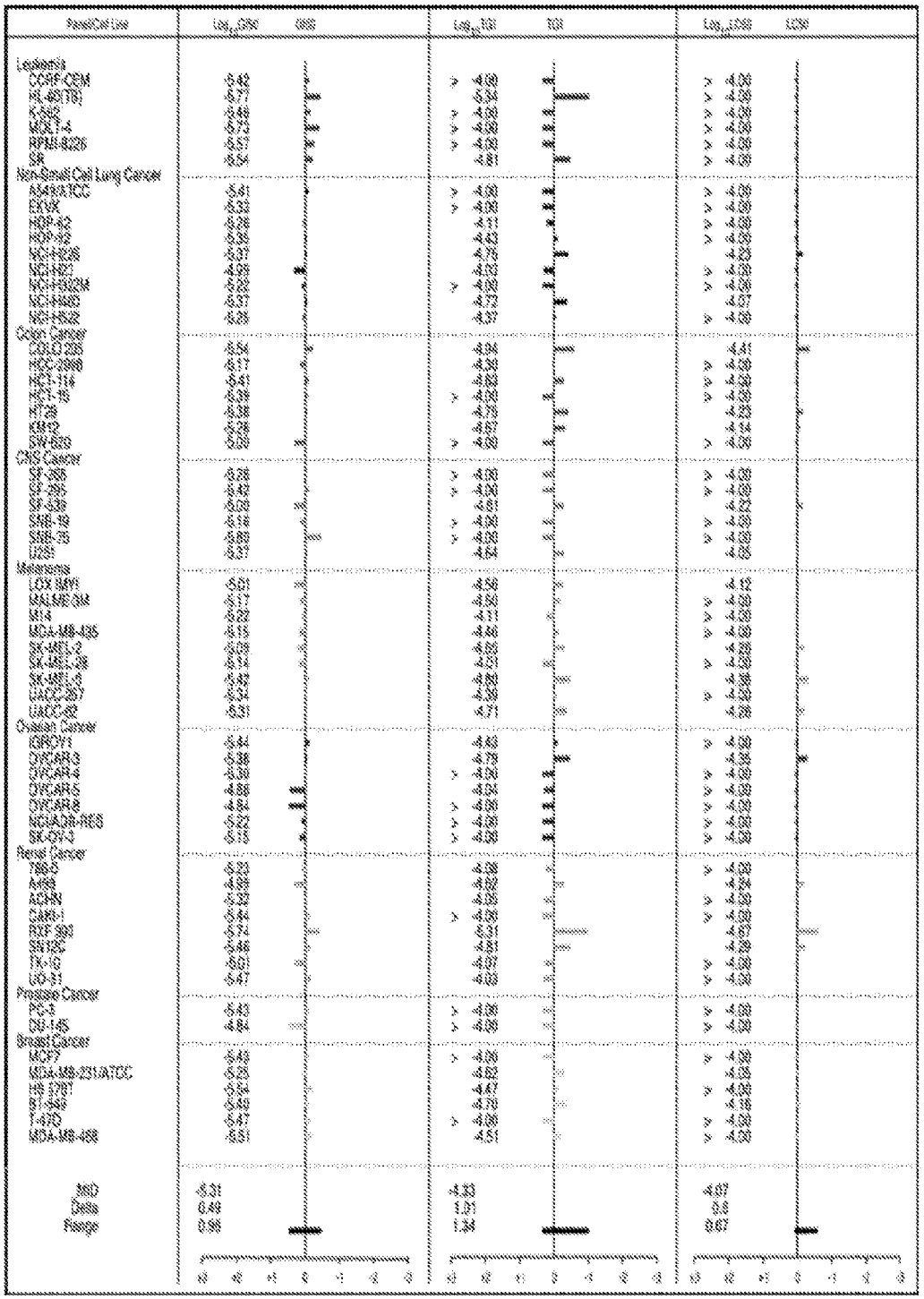
[Fig. 4I]


Ovarian Cancer
100
50
0
-50
-100
Percentage Growth
-9
-8
-7
-6
-5
-4
Log10 of Sample Concentration (Molar)
IGROV1
OVCAR-3
OVCAR-4
OVCAR-5
OVCAR-8
NCI/ADR-RES
SK-OV-3

[Fig. 4J]

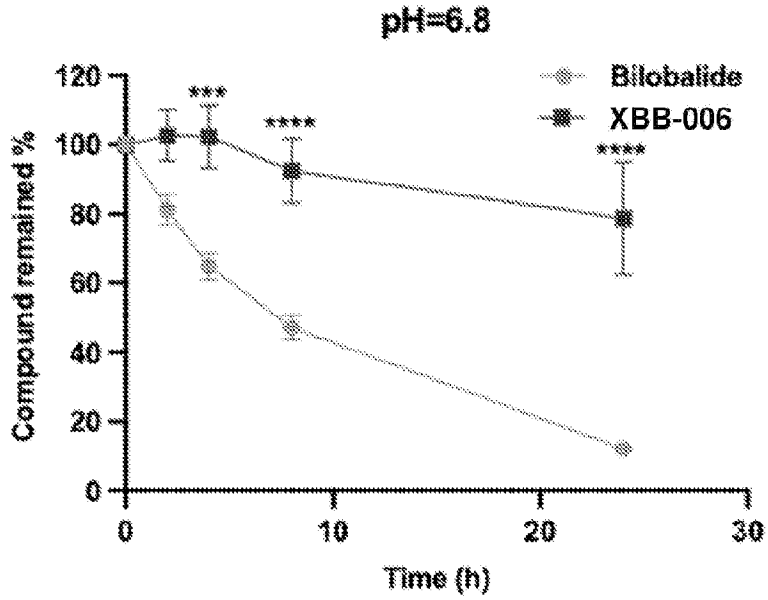

Breast Cancer
100
50
0
-50
-100
Percentage Growth
-9
-8
-7
-6
-5
-4
Log10 of Sample Concentration (Molar)
MCF7
MDA-MB-231
HS 578T
BT-549
T-47D
MDA-MB-468

[Fig. 4K]

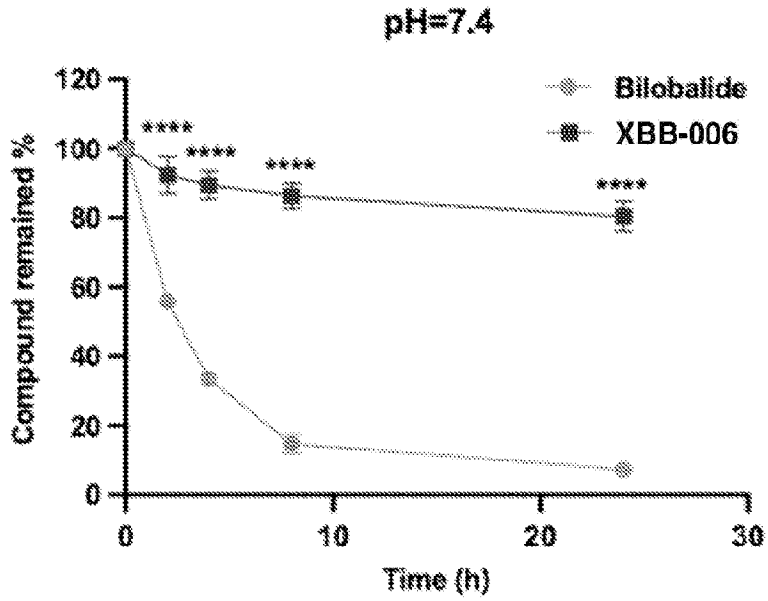


Rule 26, 02.09.2024

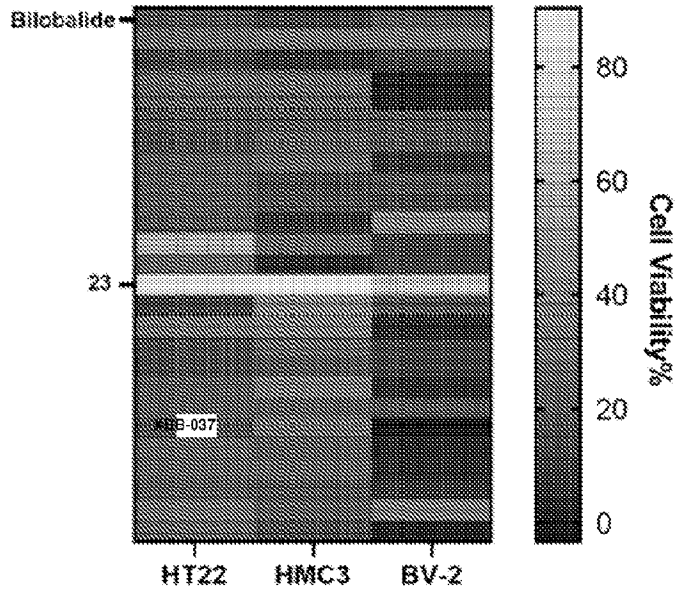
[Fig. 5A]


pH=6.8
Bilobalide
XBB-006
Compound remained %
Time (h)
0
20
40
60
80
100
120
0
10
20
30
***
****
****
****

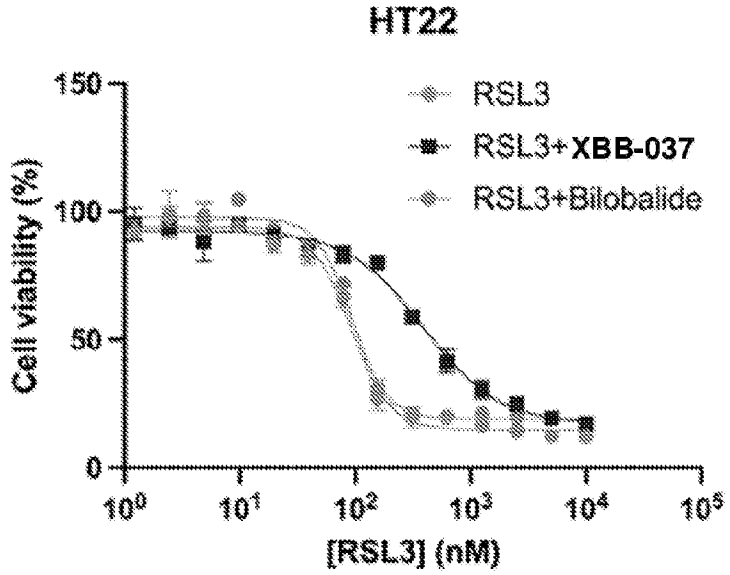
[Fig. 5B]


pH=7.4
Bilobalide
XBB-006
Compound remained %
Time (h)
0
20
40
60
80
100
120
0
10
20
30
****
****
****
****

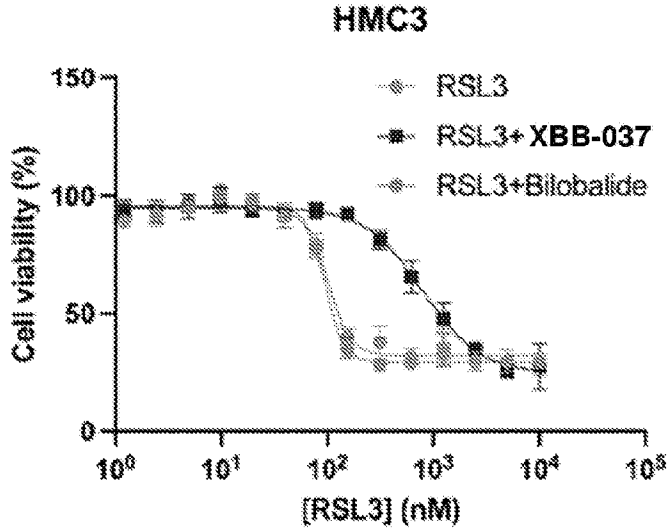
[Fig. 6A]


Bilobalide
23
XBB-037
HT22
HMC3
BV-2
80
60
40
20
0
Cell Viability%

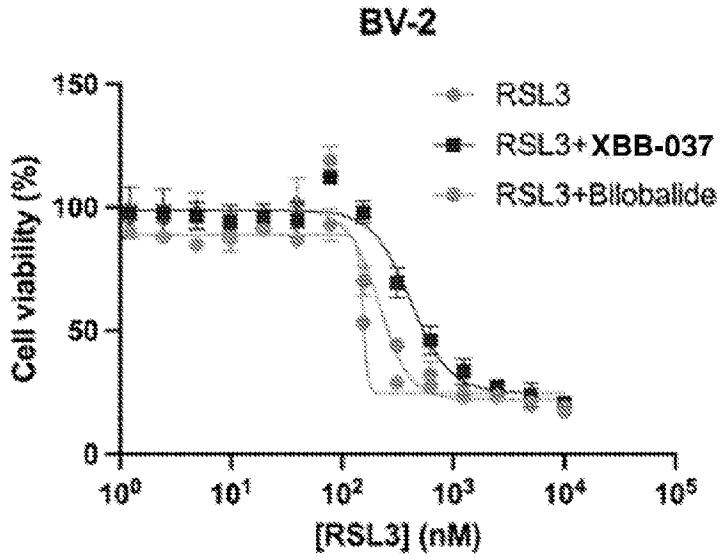
[Fig. 6B]


HT22
RSL3
RSL3+XBB-037
RSL3+Bilobalide
Cell viability (%)
150
100
50
0
10^0
10^1
10^2
10^3
10^4
10^5
[RSL3] (nM)

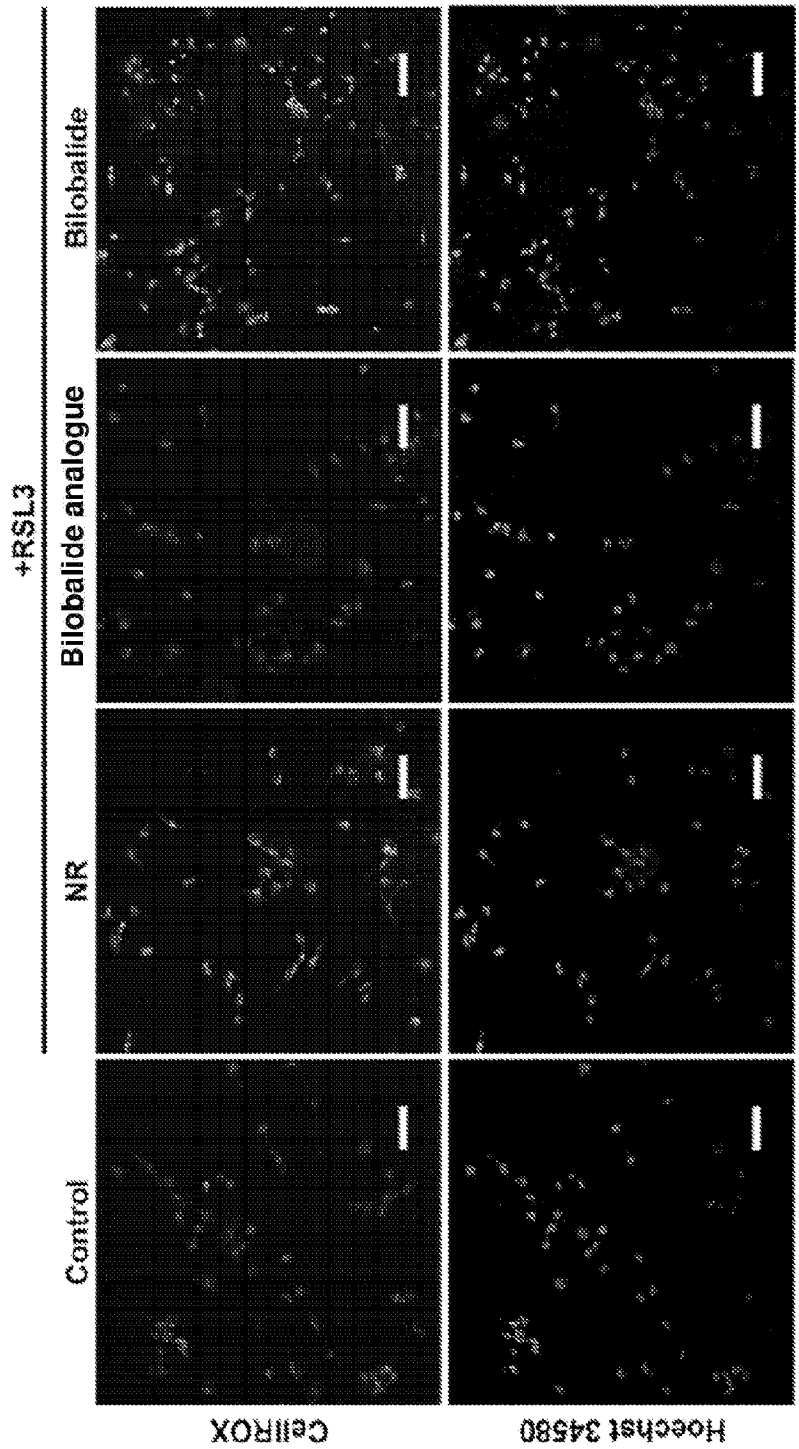
[Fig. 6C]


HMC3
RSL3
RSL3+XBB-037
RSL3+Bilobalide
Cell viability (%)
150
100
50
0
10^0
10^1
10^2
10^3
10^4
10^5
[RSL3] (nM)

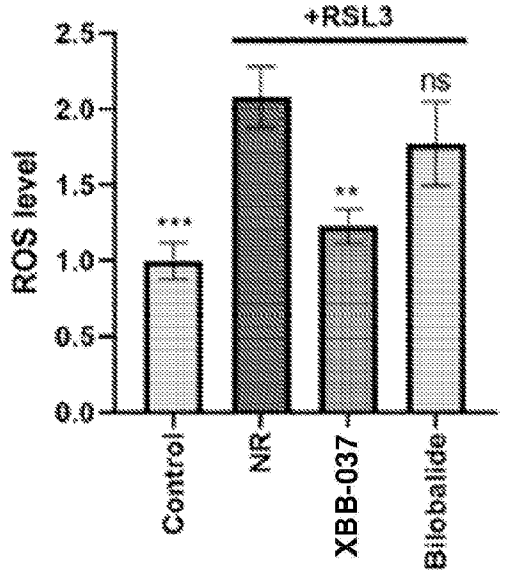
[Fig. 6D]


BV-2
RSL3
RSL3+XBB-037
RSL3+Bilobalide
Cell viability (%)
150
100
50
0
10^0
10^1
10^2
10^3
10^4
10^5
[RSL3] (nM)

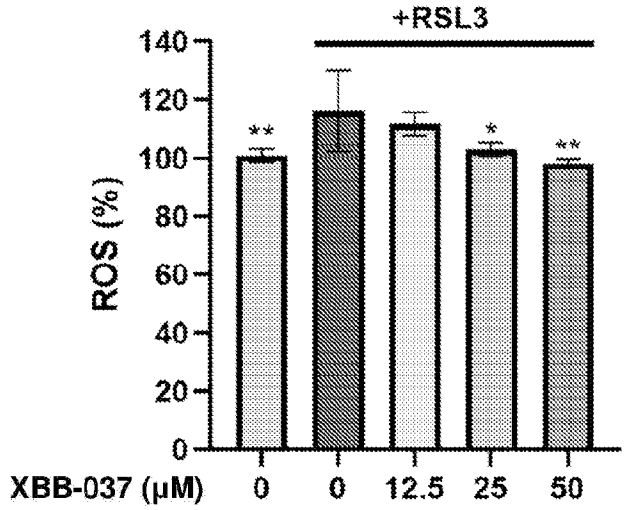
[Fig. 6E]


+RSL3
Bilobalide
Bilobalide analogue
NR
Control
CellROX
Hoechst 34580

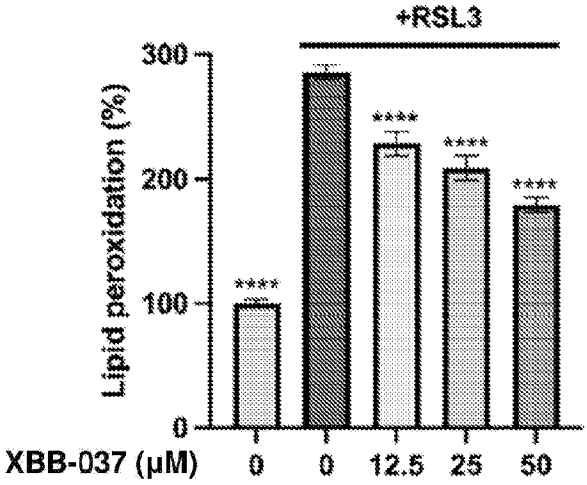
[Fig. 6F]


+RSL3
ROS level
2.5
2.0
1.5
1.0
0.5
0.0
***
**
ns
Control
NR
XBB-037
Bilobalide

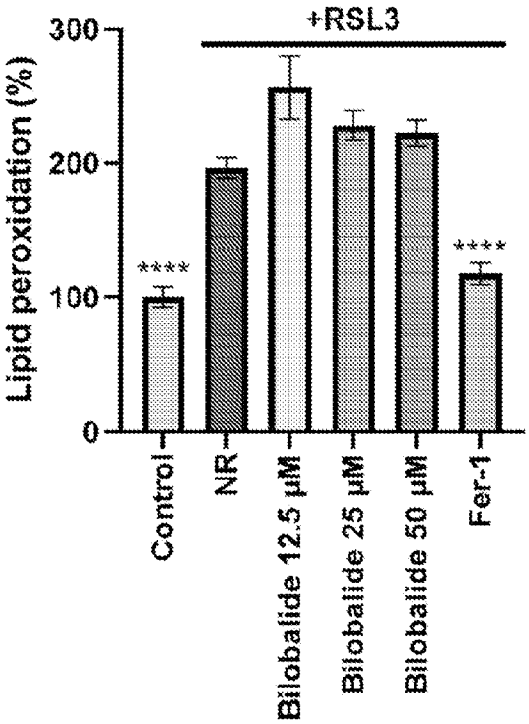
[Fig. 6G]


+RSL3
ROS (%)
140
120
100
80
60
40
20
0
**
*
**
XBB-037 (μM)
0
0
12.5
25
50

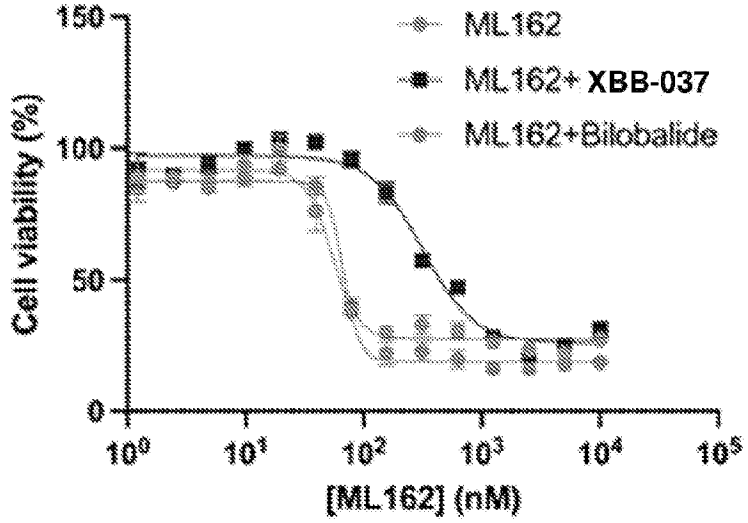
[Fig. 6H]


+RSL3
300
200
100
0
Lipid peroxidation (%)
****
****
****
****
XBB-037 (μM)
0
0
12.5
25
50

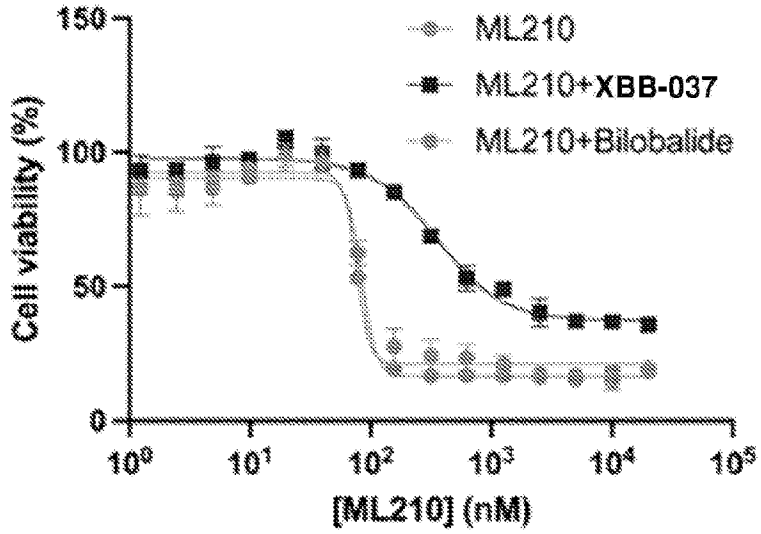
[Fig. 6I]


+RSL3
300
200
100
0
Lipid peroxidation (%)
****
****
Control
NR
Bilobalide 12.5 μM
Bilobalide 25 μM
Bilobalide 50 μM
Fer-1

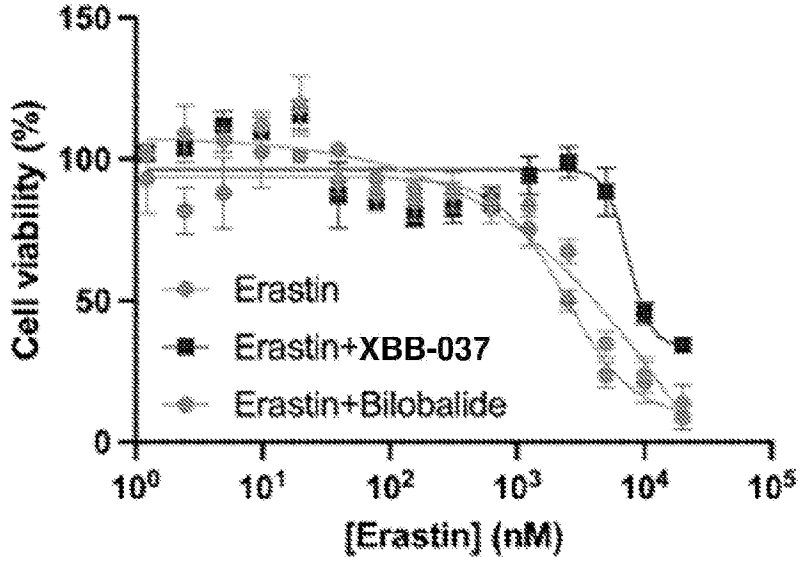
[Fig. 7A]


ML162
ML162+ XBB-037
ML162+Bilobalide
Cell viability (%)
150
100
50
0
10^0
10^1
10^2
10^3
10^4
10^5
[ML162] (nM)

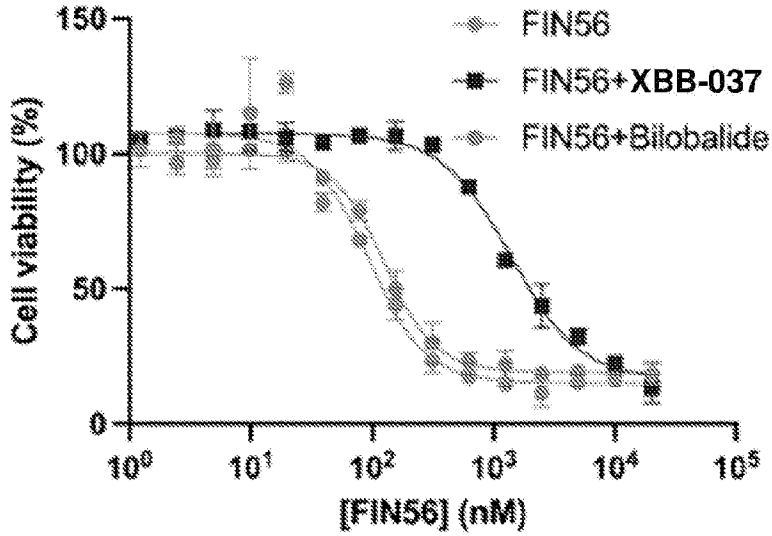
[Fig. 7B]


ML210
ML210+XBB-037
ML210+Bilobalide
Cell viability (%)
150
100
50
0
10^0
10^1
10^2
10^3
10^4
10^5
[ML210] (nM)

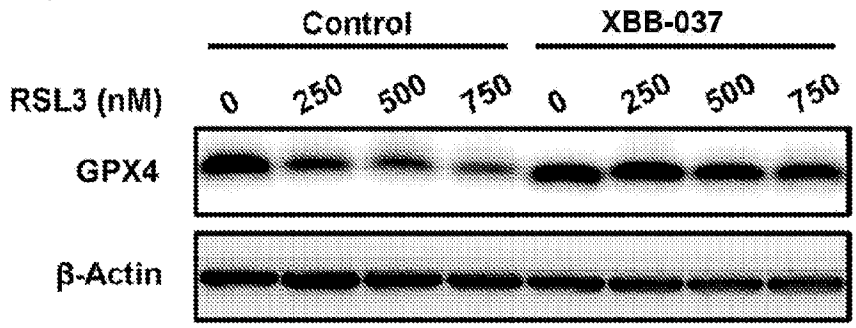
[Fig. 7C]



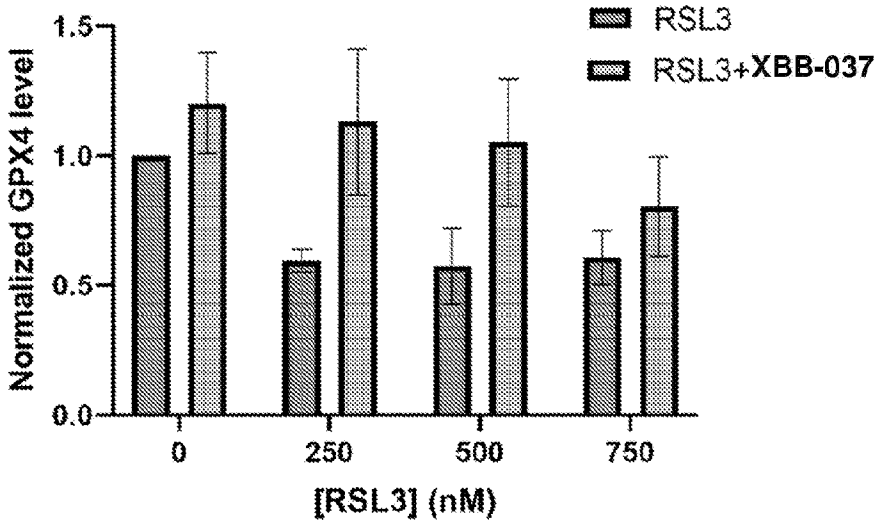
[Fig. 7D]



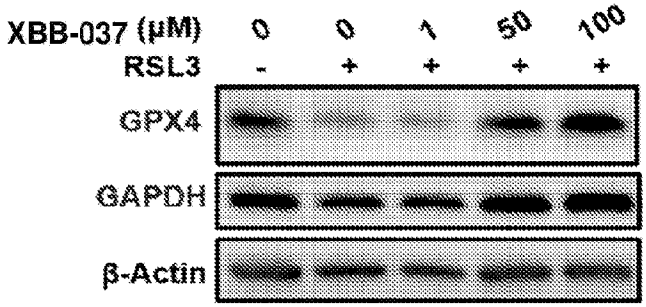
[Fig. 7E]



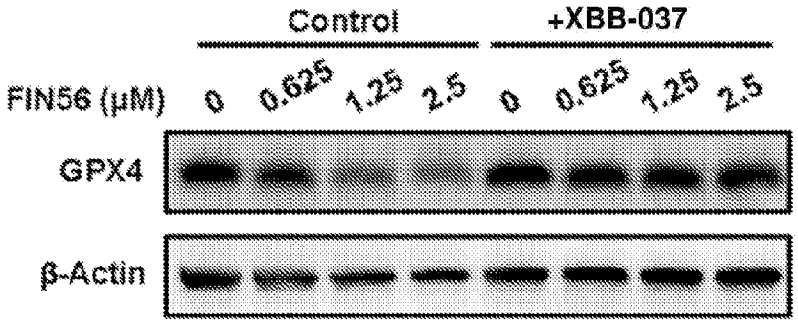
[Fig. 7F]



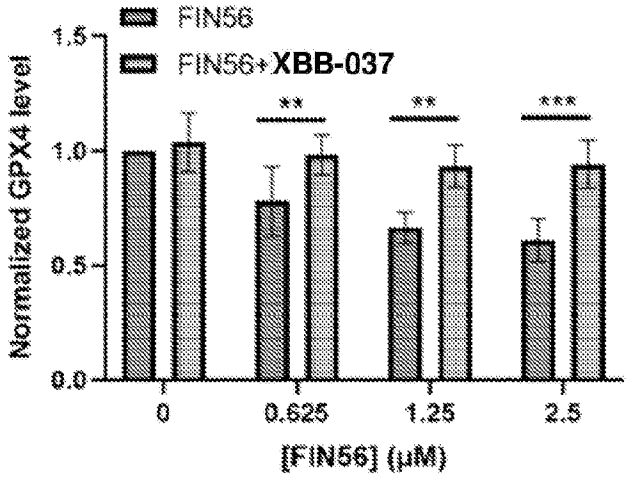
[Fig. 7G]



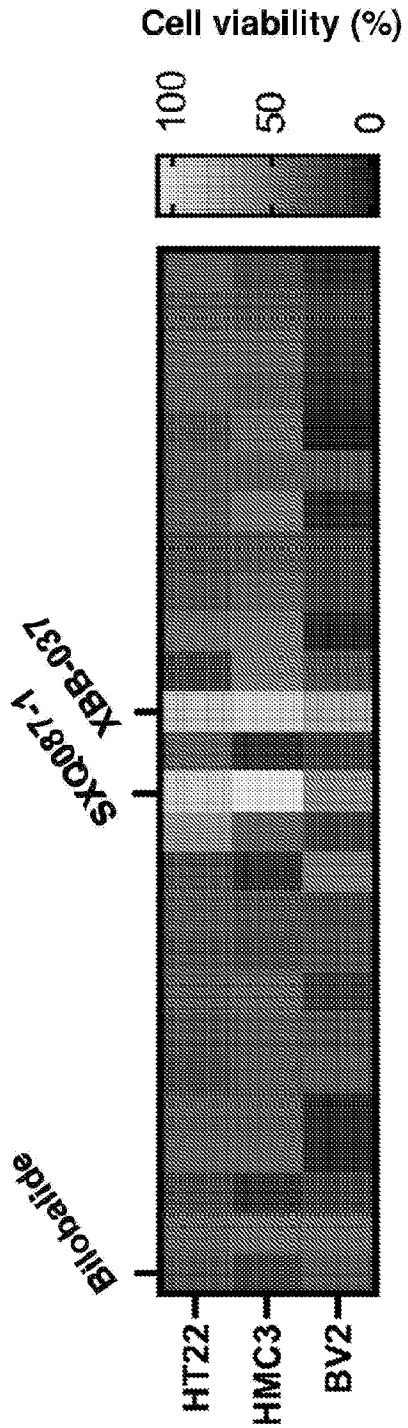
[Fig. 7H]



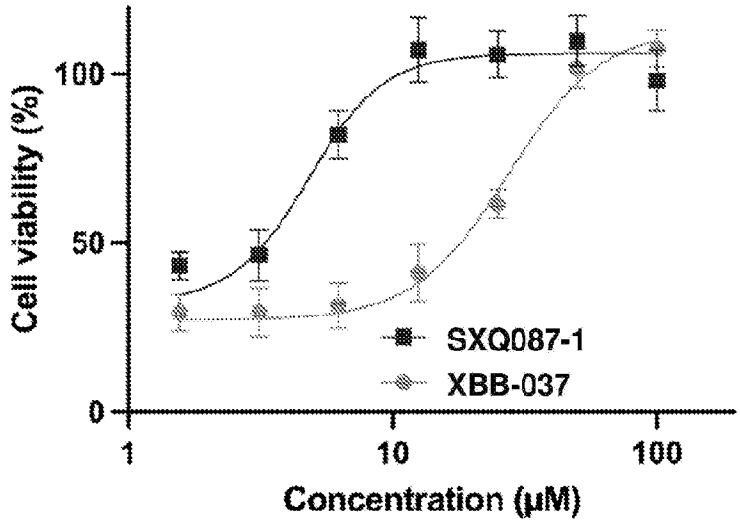
[Fig. 7I]


FIN56
FIN56+XBB-037
Normalized GPX4 level
1.5
1.0
0.5
0.0
**
**
***
0
0.625
1.25
2.5
[FIN56] (μM)

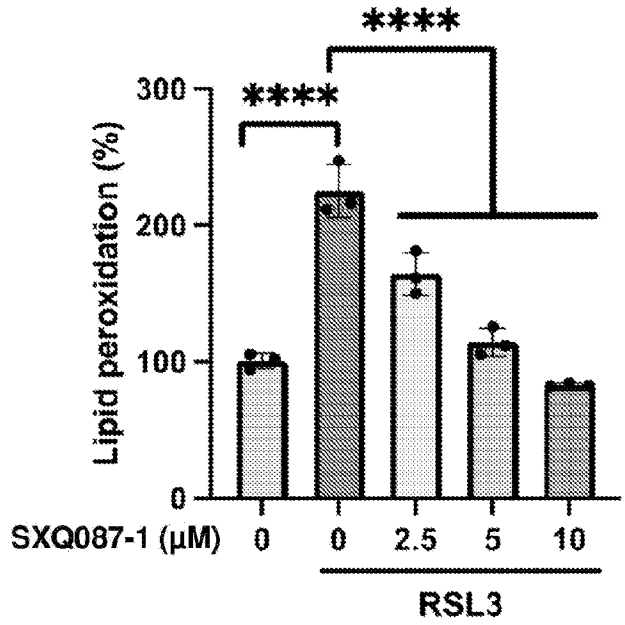
[Fig. 8A]


Cell viability (%)
100
50
0
XBB-037
SXQ087-1
Bilobalide
HT22
HMC3
BV2

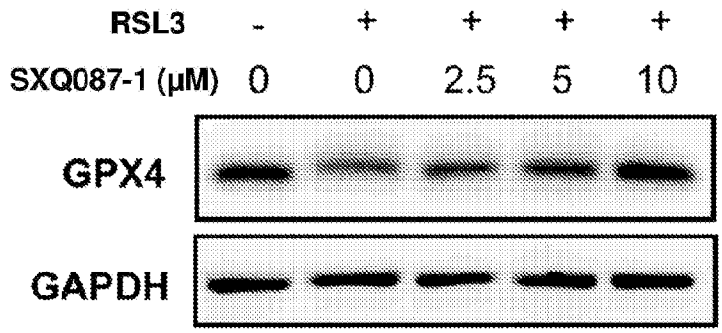
[Fig. 8B]



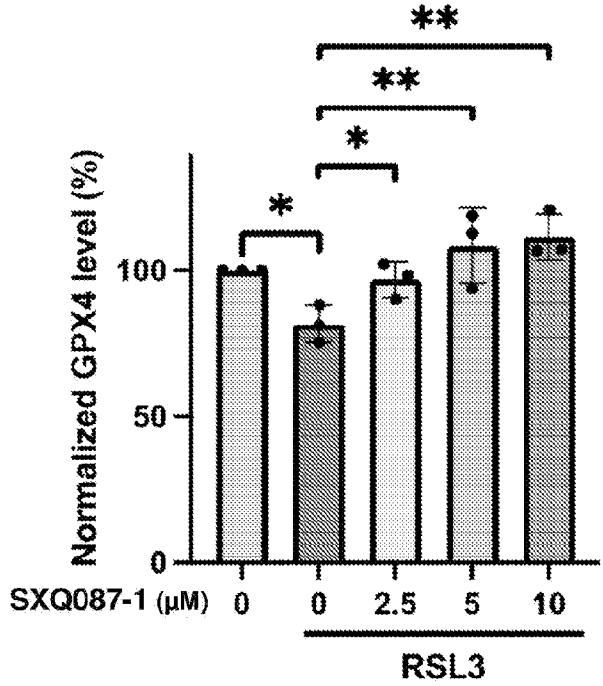
[Fig. 8C]



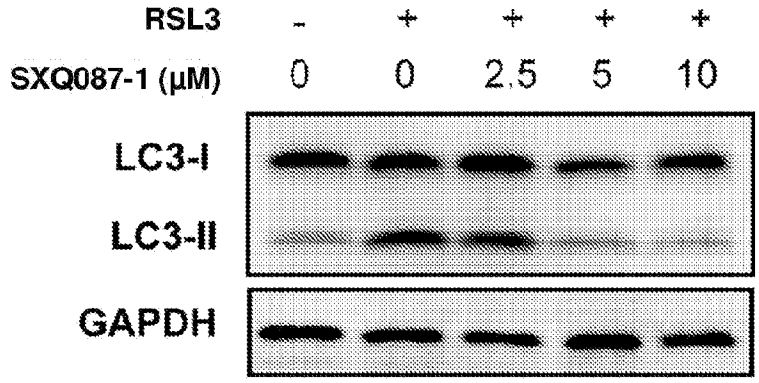
[Fig. 9A]



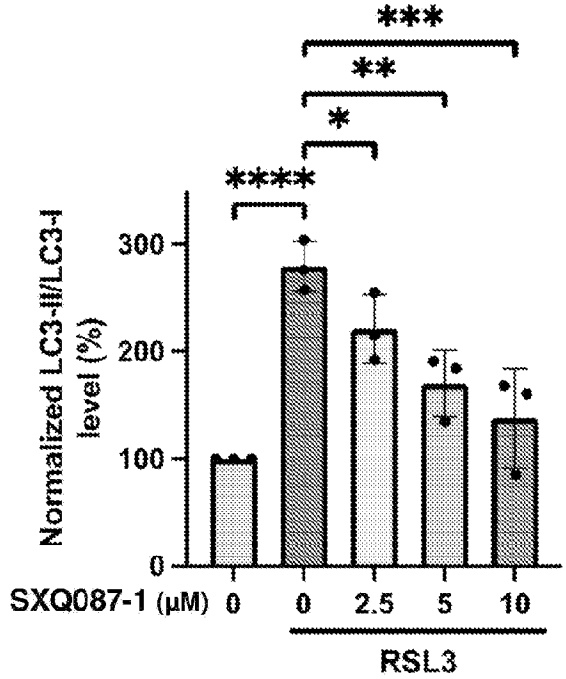
[Fig. 9B]


**
**
*
*
Normalized GPX4 level (%)
100
50
0
SXQ087-1 (μM) 0 0 2.5 5 10
RSL3

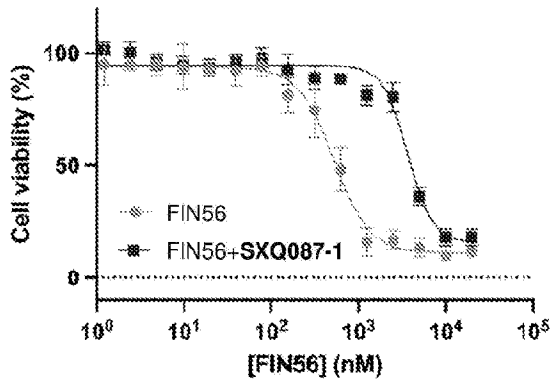
[Fig. 9C]


RSL3 - + + + +
SXQ087-1 (μM) 0 0 2.5 5 10
LC3-I
LC3-II
GAPDH

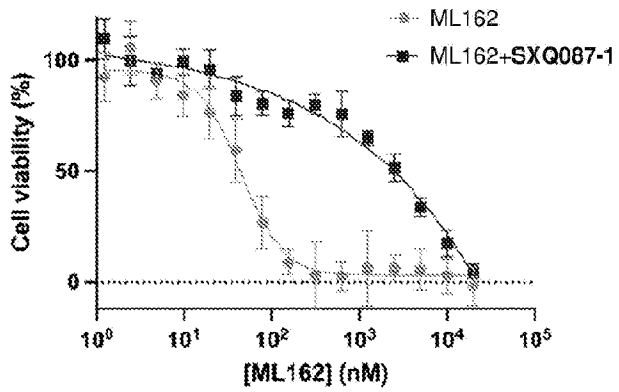
[Fig. 9D]



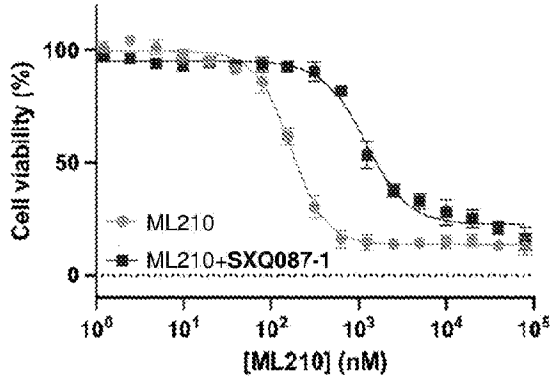
[Fig. 10A]



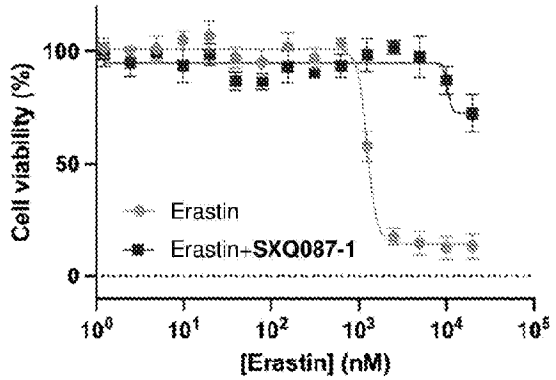
[Fig. 10B]



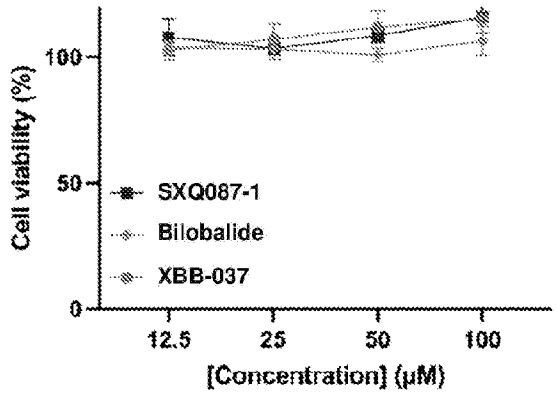
[Fig. 10C]



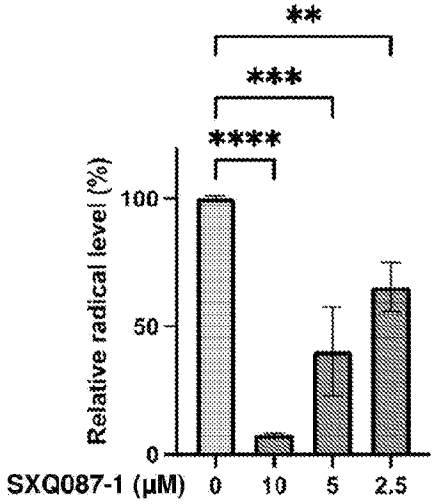
[Fig. 10D]



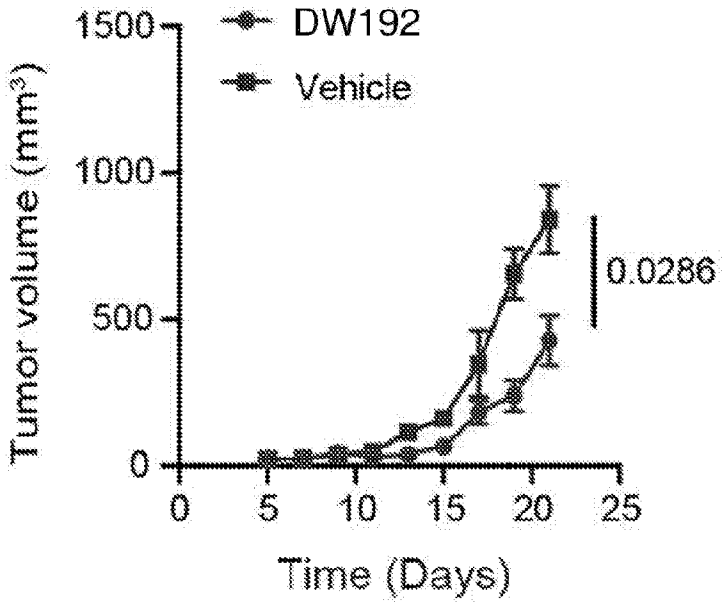
[Fig. 11A]



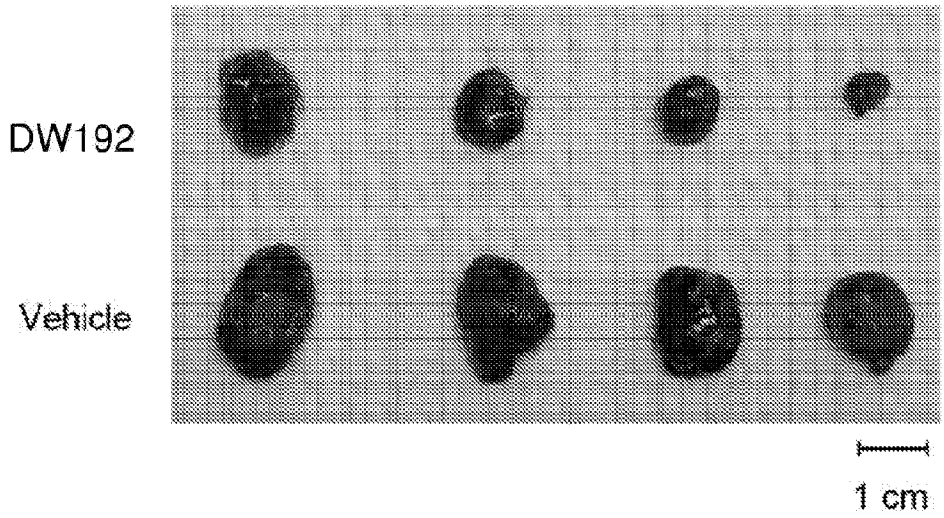
[Fig. 11B]



[Fig. 12A]



[Fig. 12B]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/109675

A. CLASSIFICATION OF SUBJECT MATTER

C07D307/93(2006.01)i; C07D493/20(2006.01)i; A61K31/365(2006.01)i; A61P35/00(2006.01)i; A61P25/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:C07D; A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DWPI, CNTXT, REGISTRY(STN), CAPLUS(STN), CNKI, ISI web of science: THE CHINESE UNIVERSITY OF HONG KONG, bilobalide, derivative, terpene trilactone?, TTLs, cancer?, tumor?, neurological, ferroptosis, GPX4, structural search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 115141169 A (Chengdu Baiyu Pharmaceutical Co., Ltd.) 04 October 2022 (2022-10-04) claims 3-6, pages 5-7 paragraphs 48-73	1, 4-6, 20, 53
X	CN 101829109 A (Shenyang Pharmaceutical University) 15 September 2010 (2010-09-15) claims 1-4, page 1 paragraph 3	1, 4-6, 20, 53
X	WEINGES Klaus et al. "Chemistry of ginkgolides. III. Bilobalide/isobilobalide. Structure determination by x-ray analysis" *Liebigs Annalen der Chemie*, Vol. 12, 31 December 1987 (1987-12-31), 1079-1085 page 1079	1, 4-6, 16-17, 19-24
X	COREY E. J. et al. "Total synthesis of a C15 ginkgolide, (±)-bilobalide" *Journal of the American Chemical Society*, Vol. 109, No. 24, 31 December 1987 (1987-12-31), 7534-7536 page 7535	1, 4-6, 16-18, 20

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 2024	**12 November 2024**
Name and mailing address of the ISA/CN **CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	Authorized officer **WANG,XinYue** Telephone No. **(+86) 010-53962173**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/109675

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DEMORET Robert M. et al. "Synthetic, Mechanistic, and Biological Interrogation of Ginkgo biloba Chemical Space En Route to (-)-Bilobalide" *Journal of the American Chemical Society*, Vol. 142, No. 43, 19 September 2020 (2020-09-19), 18599-18618 page 18611	1, 3-6, 20
A	CN 115141169 A (Chengdu Baiyu Pharmaceutical Co., Ltd.) 04 October 2022 (2022-10-04) claims 3-6, pages 5-7 paragraphs 48-73	2-3, 7-19, 21-52, 54-63
A	CN 101829109 A (Shenyang Pharmaceutical University) 15 September 2010 (2010-09-15) claims 1-4, page 1 paragraph 3	2-3, 7-19, 21-52, 54-63

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/109675

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **41-63**
because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claims 41-63 relates to methods for the treatment of human body by therapy as defined in PCT Rules 39.1(IV). This report has been carried out on the basis of the subject matter of the use in manufacture of medicaments for treating the alleged diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2024/109675

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
CN 115141169 A	04 October 2022	None	
CN 101829109 A	15 September 2010	None	