

CARBOLINE COMPOUNDS AND USE THEREOF

FIELD

[0001] Provided herein are β -carboline compounds and their use to inhibit dihydroorotate dehydrogenase (DHODH).

BACKGROUND

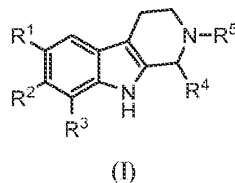
[0002] Dihydroorotate dehydrogenase (DHODH) is located on the inner membrane of mitochondria and acts in the *de novo* pyrimidine nucleotide synthesis pathway to catalyze dehydrogenation of dihydroorotate (DHO) to orotic acid (ORO), resulting in the generation of uridine monophosphate (UMP) (Munier-Lehmann et al., J Med Chem 2015; 58(2):860-877). UMP is subsequently converted to uridine (U) and cytosine (C) triphosphates to supply the cellular pool of pyrimidine nucleotides.

[0003] DHODH is a rate-limiting enzyme for the *de novo* synthesis of pyrimidine ribonucleotides. As such, inhibitors of DHODH have been used to treat autoimmune diseases and are in clinical trials for cancer and viral infections. In general, inhibitors of DHODH show beneficial immunosuppressive and antiproliferative activities, with pronounced effects on activated lymphocyte proliferation. Examples of such DHODH inhibitors include, for example, leflunomide, teriflunomide, brequinar, maritimus (FK 778), redoxal, BAY2402234, ASLAN003, and emvodostat (PTC299). DHODH is a rate-limiting enzyme for the *de novo* synthesis of pyrimidine ribonucleotides. As such, inhibitors of DHODH have been used to treat autoimmune diseases and are in clinical trials for cancer and viral infections. In general, inhibitors of DHODH show beneficial immunosuppressive and antiproliferative activities, with pronounced effects on activated lymphocyte proliferation. Many existing DHODH inhibitors have been reported including for example, leflunomide, teriflunomide, brequinar, maritimus (FK 778), redoxal, BAY2402234, ASLAN003, and emvodostat (PTC299).

[0004] Although several DHODH inhibitors currently in development show promise, there is an ongoing need for therapeutically beneficial compounds useful as DHODH inhibitors, and new compositions thereof.

SUMMARY

[0005] Provided herein is a compound of Formula (I):



[0006] or a form thereof, wherein:

[0007] R^1 is hydrogen, halo, hydroxy, C_{1-8} alkoxy, amino, or heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members, and, wherein heteroaryl is optionally substituted with one, two, or three R^{1A} substituents;

[0008] R^{1A} is C_{1-8} alkyl;

[0009] R^2 is hydrogen, halo, hydroxy, C_{1-8} alkyl, C_{1-8} alkoxy, or amino;

[0010] R^3 is hydrogen, hydroxy, or amino;

[0011] R^4 is halo, hydroxy, cyano, C_{1-8} alkyl, C_{1-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylthio, or thiocarbonyl; wherein C_{1-8} alkyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo, C_{1-8} alkoxy, C_{1-8} alkoxycarbonyl, aminocarbonyl, C_{1-8} alkylcarbonyloxy, carboxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, heteroaryl, or heterocyclyl; wherein C_{1-8} alkenyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, C_{1-8} alkoxycarbonyl, C_{3-8} cycloalkyl, or heterocyclyl; wherein C_{1-8} alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, heteroaryl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents;

[0012] R^{4A} is halo, hydroxy, cyano, oxo, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, or thiocarbonyl; wherein C_{1-8} alkyl is optionally substituted with one, two, or three substituents independently selected from halo; and, wherein C_{1-8} alkoxy is optionally substituted with one, two, or three substituents independently selected from halo;

[0013] R^5 is heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; and, wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents;

[0014] R^{5A} is halo, cyano, C_{1-8} alkyl, C_{1-8} alkylthio, C_{1-8} alkoxy, or heterocyclyl; wherein C_{1-8} alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C_{1-8} alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and wherein heterocyclyl is optionally substituted with one or two R^{5B} substituents;

[0015] R^{5B} is halo, hydroxy, cyano, oxo, C_{1-8} alkyl, C_{1-8} alkyl, C_{1-8} alkylthio, C_{1-8} alkoxy, or thiocarbonyl; wherein C_{1-8} alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C_{1-8} alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; and,

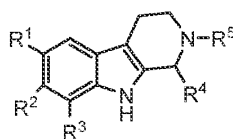
[0016] wherein the form of the compound is selected from the group consisting of a free acid, free base, salt, hydrate, solvate, anhydrous, racemate, enantiomer, diastereomer, stereoisomer, and tautomer thereof.

[0017] Another aspect provided herein is a pharmaceutical composition comprising a compound of Formula (I) or a form thereof, and a pharmaceutically acceptable excipient.

[0018] Another aspect provided herein is a method of treating a disease or disorder amenable to dihydroorotate dehydrogenase (DHODH) inhibition using a compound of Formula (I), or a form thereof, or pharmaceutical composition thereof.

DETAILED DESCRIPTION

[0019] In one aspect provided herein is a compound of Formula (I):



[0020] or a form thereof, wherein:

[0021] R^1 is hydrogen, halo, hydroxy, C_{1-8} alkoxy, amino, or heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; and, wherein heteroaryl is optionally substituted with one, two, or three R^{1A} substituents;

[0022] R^{1A} is C_{1-8} alkyl;

[0023] R² is hydrogen, halo, hydroxy, C₁₋₈alkyl, C₁₋₈alkoxy, or amino;

[0024] R³ is hydrogen, hydroxy, or amino;

[0025] R⁴ is halo, hydroxy, cyano, C₁₋₈alkyl, C₁₋₈alkenyl, C₂₋₈alkynyl, C₁₋₈alkoxy, C₁₋₈alkylthio, or thiocarbonyl; wherein C₁₋₈alkyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₈alkoxy, C₁₋₈alkoxycarbonyl, aminocarbonyl, C₁₋₈alkylcarbonyloxy, carboxy, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, heteroaryl, or heterocyclyl; wherein C₁₋₈alkenyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, C₁₋₈alkoxycarbonyl, C₃₋₈cycloalkyl, or heterocyclyl; wherein C₁₋₈alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, heteroaryl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents;

[0026] R^{4A} is halo, hydroxy, cyano, oxo, C₁₋₈alkyl, C₁₋₈alkoxy, C₁₋₈alkylthio, or thiocarbonyl; wherein C₁₋₈alkyl is optionally substituted with one, two, or three substituents independently selected from halo; and, wherein C₁₋₈alkoxy is optionally substituted with one, two, or three substituents independently selected from halo;

[0027] R⁵ is heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; and, wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents;

[0028] R^{5A} is halo, cyano, C₁₋₈alkyl, C₁₋₈alkylthio, C₁₋₈alkoxy, or heterocyclyl; wherein C₁₋₈alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C₁₋₈alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and wherein heterocyclyl is optionally substituted with one or two R^{5B} substituents;

[0029] R^{5B} is halo, hydroxy, cyano, oxo, C₁₋₈alkyl, C₁₋₈alkyl, C₁₋₈alkylthio, C₁₋₈alkoxy, or thiocarbonyl; wherein C₁₋₈alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C₁₋₈alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; and,

[0030] wherein the form of the compound is selected from the group consisting of a free acid, free base, salt, hydrate, solvate, anhydrous, racemate, enantiomer, diastereomer, stereoisomer, and tautomer thereof.

[0031] Another aspect provided herein is a pharmaceutical composition comprising a compound of Formula (I) or a form thereof, and a pharmaceutically acceptable excipient.

[0032] Another aspect provided herein is a method of treating a disease or disorder amenable to dihydroorotate dehydrogenase (DHODH) inhibition using a compound of Formula (I), or a form thereof, or pharmaceutical composition thereof.

[0033] Another aspect includes a compound of Formula (I) or form thereof, wherein the form is a salt thereof.

[0034] Another aspect includes a compound of Formula (I), wherein R^1 is hydrogen, halo, hydroxy, C_{1-3} alkoxy, amino, or heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; and, wherein heteroaryl is optionally substituted with one, two, or three R^{1A} substituents.

[0035] Another aspect includes a compound of Formula (I), wherein R^1 is hydrogen, halo, hydroxy, C_{1-3} alkoxy, or heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; and, wherein heteroaryl is optionally substituted with one R^{1A} substituent.

[0036] Another aspect includes a compound of Formula (I), wherein R^1 is halo selected from chloro, bromo, fluoro, or iodo.

[0037] Another aspect includes a compound of Formula (I), wherein R^1 is halo selected from chloro, bromo, or fluoro.

[0038] Another aspect includes a compound of Formula (I), wherein R^1 is C_{1-3} alkoxy selected from methoxy or ethoxy.

[0039] Another aspect includes a compound of Formula (I), wherein R^1 is C_{1-3} alkoxy selected from methoxy.

[0040] Another aspect includes a compound of Formula (I), wherein R^1 is heteroaryl; and, wherein heteroaryl is selected from a monocyclic ring having 5 ring members optionally substituted with one R^{1A} substituent.

[0041] Another aspect includes a compound of Formula (I), wherein R^1 is heteroaryl; and, wherein heteroaryl is a monocyclic ring having 5 ring members selected from triazolyl optionally substituted with one R^{1A} substituent.

[0042] Another aspect includes a compound of Formula (I), wherein R¹ is triazolyl selected from 1*H*-1,2,3-triazol-1-yl or 2*H*-1,2,3-triazol-2-yl optionally substituted with one R^{1A} substituent.

[0043] Another aspect includes a compound of Formula (I), wherein R^{1A} is C₁₋₃alkyl.

[0044] Another aspect includes a compound of Formula (I), wherein R^{1A} is C₁₋₃alkyl selected from methyl, ethyl, or propyl.

[0045] Another aspect includes a compound of Formula (I), wherein R^{1A} is C₁₋₃alkyl selected from methyl.

[0046] Another aspect includes a compound of Formula (I), wherein R¹ is hydrogen, halo, hydroxy, C₁₋₃alkoxy, or heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; wherein heteroaryl is optionally substituted with one R^{1A} substituent; and, wherein R^{1A} is C₁₋₃alkyl.

[0047] Another aspect includes a compound of Formula (I), wherein R¹ is hydrogen, chloro, bromo, fluoro, hydroxy, methoxy, 1*H*-1,2,3-triazolyl, or 2*H*-1,2,3-triazolyl; wherein 1*H*-1,2,3-triazolyl and 2*H*-1,2,3-triazolyl are optionally substituted with one R^{1A} substituent; and, wherein R^{1A} is methyl.

[0048] Another aspect includes a compound of Formula (I), wherein R¹ is hydrogen, chloro, bromo, fluoro, hydroxy, methoxy, 1*H*-1,2,3-triazol-1-yl, or 2*H*-1,2,3-triazol-2-yl; wherein 1*H*-1,2,3-triazol-1-yl and 2*H*-1,2,3-triazol-2-yl are optionally substituted with one R^{1A} substituent; and, wherein R^{1A} is methyl.

[0049] Another aspect includes a compound of Formula (I), wherein R² is hydrogen, halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, or amino.

[0050] Another aspect includes a compound of Formula (I), wherein R² is hydrogen or halo.

[0051] Another aspect includes a compound of Formula (I), wherein R² is halo selected from chloro, bromo, fluoro, or iodo.

[0052] Another aspect includes a compound of Formula (I), wherein R² is halo selected from fluoro.

[0053] Another aspect includes a compound of Formula (I), wherein R² is hydrogen or fluoro.

[0054] Another aspect includes a compound of Formula (I), wherein R³ is hydrogen, hydroxy or amino.

[0055] Another aspect includes a compound of Formula (I), wherein R³ is hydrogen, or amino.

[0056] Another aspect includes a compound of Formula (I), wherein R^2 is hydrogen or halo and R^3 is hydrogen or amino.

[0057] Another aspect includes a compound of Formula (I), wherein R^2 is hydrogen or fluoro and R^3 is hydrogen or amino.

[0058] Another aspect includes a compound of Formula (I), wherein R^4 is halo, hydroxy, cyano, C_{1-8} alkyl, C_{1-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylthio, or thiocarbonyl; wherein C_{1-8} alkyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo, C_{1-8} alkoxy, C_{1-8} alkoxycarbonyl, aminocarbonyl, C_{1-8} alkylcarbonyloxy, carboxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, heteroaryl, or heterocyclyl; wherein C_{1-8} alkenyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, C_{1-8} alkoxycarbonyl, C_{3-8} cycloalkyl, or heterocyclyl; wherein C_{1-8} alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, heteroaryl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents.

[0059] Another aspect includes a compound of Formula (I), wherein R^4 is hydroxy, C_{1-8} alkyl, C_{1-8} alkenyl, C_{2-8} alkynyl, or thiocarbonyl; wherein C_{1-8} alkyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo, C_{1-8} alkoxy, C_{1-8} alkoxycarbonyl, aminocarbonyl, C_{1-8} alkylcarbonyloxy, carboxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, or heterocyclyl; wherein C_{1-8} alkenyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, C_{1-8} alkoxycarbonyl, C_{3-8} cycloalkyl, or heterocyclyl; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents; and, wherein R^{4A} is oxo, C_{1-8} alkyl, thiocarbonyl, or hydroxy.

[0060] Another aspect includes a compound of Formula (I), wherein R^4 is C_{1-8} alkyl selected from methyl, ethyl, propyl, butyl, isobutyl, pentyl, hexyl, heptyl, (methyl)ethyl, (methyl)propyl, (methyl)butyl, or (methyl)pentyl optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo, C_{1-8} alkoxy, C_{1-8} alkoxycarbonyl, aminocarbonyl, C_{1-8} alkylcarbonyloxy, carboxy, C_{3-8} cycloalkyl,

C₃₋₈cycloalkenyl, or heterocyclyl; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, heteroaryl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents.

[0061] Another aspect includes a compound of Formula (I), wherein R⁴ is C₁₋₈alkyl selected from methyl, ethyl, propyl, butyl, isobutyl, pentyl, or (methyl)butyl optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₈alkoxy, C₁₋₈alkoxycarbonyl, aminocarbonyl, C₁₋₈alkylcarbonyloxy, carboxy, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, or heterocyclyl; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, heteroaryl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents.

[0062] Another aspect includes a compound of Formula (I), wherein R⁴ is C₁₋₈alkyl selected from methyl, ethyl, propyl, butyl, isobutyl, pentyl, or (2-methyl)butyl optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₈alkoxy, C₁₋₈alkoxycarbonyl, aminocarbonyl, C₁₋₈alkylcarbonyloxy, carboxy, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, or heterocyclyl; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, heteroaryl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents.

[0063] Another aspect includes a compound of Formula (I), wherein R⁴ is C₁₋₈alkyl; and, wherein C₁₋₈alkyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₈alkoxy, C₁₋₈alkoxycarbonyl, aminocarbonyl, C₁₋₈alkylcarbonyloxy, carboxy, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, or heterocyclyl; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, heteroaryl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents.

[0064] Another aspect includes a compound of Formula (I), wherein R⁴ is C₁₋₈alkyl selected from methyl, ethyl, propyl, butyl, isobutyl, pentyl, or (2-methyl)butyl optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo,

C₁₋₈alkoxy, C₁₋₈alkoxycarbonyl, aminocarbonyl, C₁₋₈alkylcarbonyloxy, carboxy, C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, or heterocyclyl; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, heteroaryl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents.

[0065] Another aspect includes a compound of Formula (I), wherein R⁴ is optionally substituted C₁₋₈alkyl selected from (2-oxo)propyl, (2,2-difluoro)ethyl, (2,2,2-trifluoro)ethyl, [(3-fluoro)(2-methyl)]propyl, [(6-chloro)(2,6-dimethyl)]heptyl, [(3,3,3-trifluoro)(2-methyl)]propyl, (2-cyano)ethyl, (2-cyano)propyl, [(2-hydroxy)(3-cyano)]propyl, [(2-hydroxy)(4-cyano)]butyl, (2-methoxy)propyl, (3-methoxy)butyl, (2,2-dimethoxy)ethyl, [3-(methoxy)-2-(methoxymethyl)]propyl, (2-methoxycarbonyl)ethyl, (2-methoxycarbonyl)propyl, (3-methoxycarbonyl)propyl, (4-methoxycarbonyl)butyl, (3-methoxycarbonyl)isobutyl, (5-methoxycarbonyl)pentyl, (2-ethoxycarbonyl)ethyl, (2,2-diethoxycarbonyl)ethyl, (2-methoxycarbonyl)propenyl, (3-methoxycarbonyl)propenyl, (2-aminocarbonyl)propyl, (3-aminocarbonyl)propyl, (4-aminocarbonyl)butyl, (5-aminocarbonyl)pentyl, [(2-methyl)(3-aminocarbonyl)]propyl, (2,3-dimethylcarbonyloxy)propyl, (2-hydroxy)propyl, (3-hydroxy)propyl, (2-hydroxy)butyl, (4-hydroxy)butyl, (2-hydroxy)isobutyl, (5-hydroxy)pentyl, (6-hydroxy)hexyl, (2,3-dihydroxy)propyl, (2,4-dihydroxy)butyl, (3,4-dihydroxy)butyl, (2-hydroxymethyl)propyl, [(1-hydroxy)(2-methyl)]propyl, [(2-hydroxy)(2-methyl)]propyl, [(4-hydroxy)(2-methyl)]butyl, [(5-hydroxy)(2-methyl)]pentyl, [(6-hydroxy)(2,6-dimethyl)]heptyl, [(5,6-dihydroxy)(2,6-dimethyl)]heptyl, [(3-hydroxy){(2-hydroxy)methyl}]propyl, [(3-methoxy)(2-hydroxy)]propyl, [(4-methoxy)(2-hydroxy)]butyl, [(3-methylcarbonyloxy)(2-hydroxy)]propyl, (5-carboxy)pentyl, (cyclopentenyl)methyl, (cyclopent-2-enyl)methyl, (oxetan-2-yl)methyl, (pyrrolidine-3-yl)methyl, (tetrahydrofuran-2-yl)methyl, (tetrahydrofuran-3-yl)methyl, (piperidin-3-yl)methyl, (piperidin-4-yl)methyl, (2-oxo-piperidin-3-yl)methyl, (tetrahydro-2H-pyran-2-yl)methyl, (tetrahydro-2H-pyran-3-yl)methyl, (tetrahydro-2H-pyran-4-yl)methyl, (1,4-dioxan-2-yl)methyl, (1,3-dioxan-2-yl)methyl, (1,3-dioxan-4-yl)methyl, (1,3-dioxan-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, (1,3-dioxolan-4-yl)methyl, (1,3-dioxan-2-on-5-yl)methyl, (3,6-dihydro-2H-pyran-2-yl)methyl, or (3,6-dihydro-2H-pyran-3-yl)methyl.

[0066] Another aspect includes a compound of Formula (I), wherein R^4 is optionally substituted C_{1-8} alkyl selected from (2-oxo)prop-1-yl, (2,2-difluoro)eth-1-yl, (2,2,2-trifluoro)eth-1-yl, [(3-fluoro)(2-methyl)]prop-1-yl, [(6-chloro)(2,6-dimethyl)]hept-1-yl, [(3,3,3-trifluoro)(2-methyl)]prop-1-yl, (2-cyano)eth-1-yl, (2-cyano)prop-1-yl, [(2-hydroxy)(3-cyano)]prop-1-yl, [(2-hydroxy)(4-cyano)]but-1-yl, (2-methoxy)prop-1-yl, (3-methoxy)but-1-yl, (2,2-dimethoxy)eth-1-yl, [3-(methoxy)-2-(methoxymethyl)]prop-1-yl, (2-methoxycarbonyl)eth-1-yl, (2-methoxycarbonyl)prop-1-yl, (3-methoxycarbonyl)prop-1-yl, (4-methoxycarbonyl)but-1-yl, (3-methoxycarbonyl)isobut-1-yl, (5-methoxycarbonyl)pent-1-yl, (2-ethoxycarbonyl)eth-1-yl, (2,2-diethoxycarbonyl)eth-1-yl, (2-methoxycarbonyl)prop-1-en-1-yl, (3-methoxycarbonyl)prop-2-en-1-yl, (2-aminocarbonyl)prop-1-yl, (3-aminocarbonyl)prop-1-yl, (4-aminocarbonyl)but-1-yl, (5-aminocarbonyl)pent-1-yl, [(2-methyl)(3-aminocarbonyl)]prop-1-yl, (2,3-dimethylcarbonyloxy)prop-1-yl, (2-hydroxy)prop-1-yl, (3-hydroxy)prop-1-yl, (2-hydroxy)but-1-yl, (4-hydroxy)but-1-yl, (2-hydroxy)isobut-1-yl, (5-hydroxy)pent-1-yl, (6-hydroxy)hex-1-yl, (2,3-dihydroxy)prop-1-yl, (2,4-dihydroxy)but-1-yl, (3,4-dihydroxy)but-1-yl, (2-hydroxymethyl)prop-1-yl, [(1-hydroxy)(2-methyl)]prop-1-yl, [(2-hydroxy)(2-methyl)]prop-1-yl, [(4-hydroxy)(2-methyl)]but-1-yl, [(5-hydroxy)(2-methyl)]pent-1-yl, [(6-hydroxy)(2,6-dimethyl)]hept-1-yl, [(5,6-dihydroxy)(2,6-dimethyl)]hept-1-yl, [(3-hydroxy){(2-hydroxy)methyl}]prop-1-yl, [(3-methoxy)(2-hydroxy)]prop-1-yl, [(4-methoxy)(2-hydroxy)]but-1-yl, [(3-methylcarbonyloxy)(2-hydroxy)]prop-1-yl, (5-carboxy)pent-1-yl, (cyclopentenyl)methyl, (cyclopent-2-enyl)methyl, (oxetan-2-yl)methyl, (pyrrolidine-3-yl)methyl, (tetrahydrofuran-2-yl)methyl, (tetrahydrofuran-3-yl)methyl, (piperidin-3-yl)methyl, (piperidin-4-yl)methyl, (2-oxo-piperidin-3-yl)methyl, (tetrahydro-2H-pyran-2-yl)methyl, (tetrahydro-2H-pyran-3-yl)methyl, (tetrahydro-2H-pyran-4-yl)methyl, (1,4-dioxan-2-yl)methyl, (1,3-dioxan-2-yl)methyl, (1,3-dioxan-4-yl)methyl, (1,3-dioxan-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, (1,3-dioxolan-4-yl)methyl, (1,3-dioxan-2-on-5-yl)methyl, (3,6-dihydro-2H-pyran-2-yl)methyl, or (3,6-dihydro-2H-pyran-3-yl)methyl.

[0067] Another aspect includes a compound of Formula (I), wherein R^4 is C_{1-8} alkenyl selected from ethenyl, propenyl, butenyl, isobutenyl, pentenyl, hexenyl, (methyl)ethenyl, (methyl)propenyl, (methyl)butenyl, (methyl)pentyl, (methyl)hexyl, (methyl)heptenyl, (cyclohexylidene)methyl, or (oxanylidene)methyl; and, wherein C_{1-8} alkenyl is optionally substituted with one, two, or three substituents is selected from halo, methoxycarbonyl, hydroxy.

[0068] Another aspect includes a compound of Formula (I), wherein R^4 is optionally substituted C_{1-8} alkenyl selected from ethenyl, propenyl, butenyl, isobutenyl, hexenyl, pentenyl, (methyl)propenyl, (methyl)butenyl, (methyl)heptenyl, (cyclohexylidene)methyl, or (oxanylidene)methyl; and, wherein C_{1-8} alkenyl is optionally substituted with one, two, or three substituents is selected from halo, methoxycarbonyl, hydroxy.

[0069] Another aspect includes a compound of Formula (I), wherein R^4 is C_{1-8} alkenyl selected from eth-1-en-1-yl, prop-2-en-1-yl, but-3-en-1-yl, isobut-1-en-1-yl, hex-3-en-1-yl, (2-methyl)prop-2-en-1-yl, (2-methyl)but-3-en-1-yl, (2,6-dimethyl)hept-5-en-1-yl, (cyclohexylidene)methyl, or (oxan-4-ylidene)methyl; and, wherein C_{1-8} alkenyl is optionally substituted with one, two, or three substituents is selected from halo, methoxycarbonyl, hydroxy.

[0070] Another aspect includes a compound of Formula (I), wherein R^4 is optionally substituted C_{1-8} alkenyl selected from (3-difluoro)prop-2-en-1-yl, (2-methoxycarbonyl)prop-1-en-1-yl, (3-methoxycarbonyl)prop-2-en-1-yl, (2-hydroxymethyl)prop-1-en-1-yl, [(3-hydroxy){(2-hydroxy)methyl}]prop-1-en-1-yl, (cyclohexylidene)methyl, or (oxan-4-ylidene)methyl;

[0071] Another aspect includes a compound of Formula (I), wherein R^4 is C_{2-8} alkynyl selected from ethynyl, propynyl, butynyl, isobutynyl, pentynyl, or hexynyl.

[0072] Another aspect includes a compound of Formula (I), wherein R^4 is C_{2-8} alkynyl selected from propynyl or butynyl.

[0073] Another aspect includes a compound of Formula (I), wherein R^4 is C_{2-8} alkynyl selected from prop-2-yn-1-yl, or but-3-yn-1-yl.

[0074] Another aspect includes a compound of Formula (I), wherein R^{4A} is halo, hydroxy, cyano, oxo, C_{1-8} alkyl, C_{1-8} alkylthio, C_{1-8} alkoxy, or thiocarbonyl; wherein C_{1-8} alkyl is optionally substituted with one, two, or three substituents independently selected from halo; and, wherein C_{1-8} alkoxy is optionally substituted with one, two, or three substituents independently selected from halo.

[0075] Another aspect includes a compound of Formula (I), wherein R^{4A} is hydroxy, oxo, C_{1-8} alkyl, or thiocarbonyl.

[0076] Another aspect includes a compound of Formula (I), wherein R^{4A} is C_{1-8} alkyl selected from methyl.

[0077] Another aspect includes a compound of Formula (I), wherein R^{4A} is hydroxy, oxo, methyl, or thiocarbonyl.

[0078] Another aspect includes a compound of Formula (I), wherein R^4 is hydroxy, C_{1-8} alkyl, C_{1-8} alkenyl, C_{2-8} alkynyl, or thiocarbonyl; wherein C_{1-8} alkyl is substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo, C_{1-8} alkoxy, C_{1-8} alkoxycarbonyl, aminocarbonyl, C_{1-8} alkylcarbonyloxy, carboxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, heteroaryl, or heterocyclyl; wherein C_{1-8} alkenyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, C_{1-8} alkoxycarbonyl, C_{3-8} cycloalkyl, or heterocyclyl; wherein C_{1-8} alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, heteroaryl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents; and, wherein R^{4A} is oxo, C_{1-8} alkyl, thiocarbonyl, or hydroxy.

[0079] Another aspect includes a compound of Formula (I), wherein R^4 is C_{1-8} alkyl selected from methyl, ethyl, propyl, butyl, isobutyl, pentyl, or (2-methyl)butyl; C_{1-8} alkenyl selected from eth-1-en-1-yl, prop-2-en-1-yl, but-3-en-1-yl, isobut-1-en-1-yl, hex-3-en-1-yl, (2-methyl)prop-2-en-1-yl, (2-methyl)but-3-en-1-yl, or (2,6-dimethyl)hept-5-en-1-yl; or, C_{2-8} alkynyl selected from prop-2-yn-1-yl or but-3-yn-1-yl; wherein optionally substituted C_{1-8} alkyl is selected from (2-oxo)prop-1-yl, (2,2-difluoro)eth-1-yl, (2,2,2-trifluoro)eth-1-yl, [(3-fluoro)(2-methyl)]prop-1-yl, [(6-chloro)(2,6-dimethyl)]hept-1-yl, [(3,3,3-trifluoro)(2-methyl)]prop-1-yl, (2-cyano)eth-1-yl, (2-cyano)prop-1-yl, [(2-hydroxy)(3-cyano)]prop-1-yl, [(2-hydroxy)(4-cyano)]but-1-yl, (2-methoxy)prop-1-yl, (3-methoxy)but-1-yl, (2,2-dimethoxy)eth-1-yl, [3-(methoxy)-2-(methoxymethyl)]prop-1-yl, (2-methoxycarbonyl)eth-1-yl, (2-methoxycarbonyl)prop-1-yl, (3-methoxycarbonyl)prop-1-yl, (4-methoxycarbonyl)but-1-yl, (3-methoxycarbonyl)isobut-1-yl, (5-methoxycarbonyl)pent-1-yl, (2-ethoxycarbonyl)eth-1-yl, (2,2-diethoxycarbonyl)eth-1-yl, (2-methoxycarbonyl)prop-1-en-1-yl, (3-methoxycarbonyl)prop-2-en-1-yl, (2-aminocarbonyl)prop-1-yl, (3-aminocarbonyl)prop-1-yl, (4-aminocarbonyl)but-1-yl, (5-aminocarbonyl)pent-1-yl, [(2-methyl)(3-aminocarbonyl)]prop-1-yl, (2,3-dimethylcarbonyloxy)prop-1-yl, (2-hydroxy)prop-1-yl, (3-hydroxy)prop-1-yl, (2-hydroxy)but-1-yl, (4-hydroxy)but-1-yl, (2-hydroxy)isobut-1-yl, (5-hydroxy)pent-1-yl, (6-hydroxy)hex-1-yl, (2,3-dihydroxy)prop-1-yl, (2,4-dihydroxy)but-1-yl, (3,4-dihydroxy)but-1-yl, (2-hydroxymethyl)prop-1-yl, [(1-hydroxy)(2-methyl)]prop-1-yl, [(2-hydroxy)(2-methyl)]prop-1-yl,

[(4-hydroxy)(2-methyl)]but-1-yl, [(5-hydroxy)(2-methyl)]pent-1-yl, [(6-hydroxy)(2,6-dimethyl)]hept-1-yl, [(5,6-dihydroxy)(2,6-dimethyl)]hept-1-yl, [(3-hydroxy){(2-hydroxy)methyl}]prop-1-yl, [(3-methoxy)(2-hydroxy)]prop-1-yl, [(4-methoxy)(2-hydroxy)]but-1-yl, [(3-methylcarbonyloxy)(2-hydroxy)]prop-1-yl, (5-carboxy)pent-1-yl, (cyclopentenyl)methyl, (cyclopent-2-enyl)methyl, (oxetan-2-yl)methyl, (pyrrolidine-3-yl)methyl, (tetrahydrofuran-2-yl)methyl, (tetrahydrofuran-3-yl)methyl, (piperidin-3-yl)methyl, (piperidin-4-yl)methyl, (2-oxo-piperidin-3-yl)methyl, (tetrahydro-2H-pyran-2-yl)methyl, (tetrahydro-2H-pyran-3-yl)methyl, (tetrahydro-2H-pyran-4-yl)methyl, (1,4-dioxan-2-yl)methyl, (1,3-dioxan-2-yl)methyl, (1,3-dioxan-4-yl)methyl, (1,3-dioxan-5-yl)methyl, (1,3-dioxolan-2-yl)methyl, (1,3-dioxolan-4-yl)methyl, (1,3-dioxan-2-on-5-yl)methyl, (3,6-dihydro-2H-pyran-2-yl)methyl, or (3,6-dihydro-2H-pyran-3-yl)methyl; wherein optionally substituted C₁₋₈alkenyl is selected from (3-difluoro)prop-2-en-1-yl, (2-hydroxymethyl)prop-1-en-1-yl, [(3-hydroxy)(2-hydroxymethyl)]prop-1-en-1-yl, (2-methoxycarbonyl)prop-1-en-1-yl, (3-methoxycarbonyl)prop-2-en-1-yl, (cyclohexylidene)methyl, or (oxan-4-ylidene)methyl.

[0080] Another aspect includes a compound of Formula (I), wherein R⁵ is heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; and, wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents.

[0081] Another aspect includes a compound of Formula (I), wherein R⁵ is heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members; and, wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents.

[0082] Another aspect includes a compound of Formula (I), wherein R⁵ is heteroaryl selected from oxadiazolyl, thiadiazolyl, triazinyl, tetrazolyl, pyridinyl, or pyrimidinyl; and, wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents.

[0083] Another aspect includes a compound of Formula (I), wherein R⁵ is heteroaryl selected from 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3,4-2H-tetrazolyl, pyridinyl, or pyrimidinyl; and, wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents.

[0084] Another aspect includes a compound of Formula (I), wherein R⁵ is heteroaryl selected from 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, 1,2,3,4-2H-tetrazol-5-yl, pyridin-2-yl, pyrimidin-2-yl, or pyrimidin-4-yl; and, wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents.

[0085] Another aspect includes a compound of Formula (I), wherein R^{5A} is selected from halo, cyano, C_{1-8} alkyl, C_{1-8} alkylthio, C_{1-8} alkoxy, or heterocyclyl; wherein C_{1-8} alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C_{1-8} alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and wherein heterocyclyl is optionally substituted with one or two R^{5B} substituents.

[0086] Another aspect includes a compound of Formula (I), wherein R^{5A} is halo selected from fluoro or chloro.

[0087] Another aspect includes a compound of Formula (I), wherein R^{5A} is C_{1-8} alkyl selected from methyl, ethyl, difluoromethyl, or trifluoromethyl.

[0088] Another aspect includes a compound of Formula (I), wherein R^{5A} is C_{1-8} alkylthio selected from methylthio.

[0089] Another aspect includes a compound of Formula (I), wherein R^{5A} is C_{1-8} alkoxy selected from methoxy or difluoromethoxy.

[0090] Another aspect includes a compound of Formula (I), wherein R^{5A} is heterocyclyl, wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members; and, wherein heterocyclyl is optionally substituted with one or two R^{5B} substituents.

[0091] Another aspect includes a compound of Formula (I), wherein R^{5A} is heterocyclyl selected from piperazinyl, or morpholinyl; and, wherein heterocyclyl is optionally substituted with one or two R^{5B} substituents.

[0092] Another aspect includes a compound of Formula (I), wherein R^{5A} is heterocyclyl selected from piperazin-1-yl or morpholin-4-yl; and, wherein heterocyclyl is optionally substituted with one R^{5B} substituent.

[0093] Another aspect includes a compound of Formula (I), wherein R^{5A} is selected from fluoro, chloro, methyl, ethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, methylthio, methoxy, piperazin-1-yl, or morpholin-4-yl; and, wherein piperazin-1-yl, or morpholin-4-yl are each optionally substituted with one R^{5B} substituent.

[0094] Another aspect includes a compound of Formula (I), wherein R^{5B} is selected from halo, hydroxy, cyano, oxo, C_{1-8} alkyl, C_{1-8} alkyl, C_{1-8} alkylthio, C_{1-8} alkoxy, or thiocarbonyl; wherein C_{1-8} alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C_{1-8} alkoxy is optionally substituted with one, two, or three substituents independently selected from halo.

[0095] Another aspect includes a compound of Formula (I), wherein R^{5B} is selected from C_1 -alkyl.

[0096] Another aspect includes a compound of Formula (I), wherein R^{5B} is C_1 -alkyl selected from methyl.

[0097] Another aspect includes a compound of Formula (I), wherein R^5 is heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents; wherein, R^{5A} is halo, cyano, C_1 -alkyl, C_1 -alkylthio, C_1 -alkoxy, or heterocyclyl; wherein C_1 -alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C_1 -alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7-8 ring members or a polycyclic ring having 13-16 ring members; wherein heterocyclyl is optionally substituted with one or two R^{5B} substituents; wherein, R^{5B} is halo, hydroxy, cyano, oxo, C_1 -alkyl, C_1 -alkyl, C_1 -alkylthio, C_1 -alkoxy, or thiocarbonyl; wherein C_1 -alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C_1 -alkoxy is optionally substituted with one, two, or three substituents independently selected from halo.

[0098] Another aspect includes a compound of Formula (I), wherein R^5 is heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents; ; wherein, R^{5A} is halo, cyano, C_1 -alkyl, C_1 -alkylthio, C_1 -alkoxy, or heterocyclyl; wherein C_1 -alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C_1 -alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; wherein heterocyclyl is optionally substituted with one or two R^{5B} substituents; wherein, R^{5B} is C_1 -alkyl; wherein C_1 -alkyl is optionally substituted with one, two, or three substituents independently selected from halo.

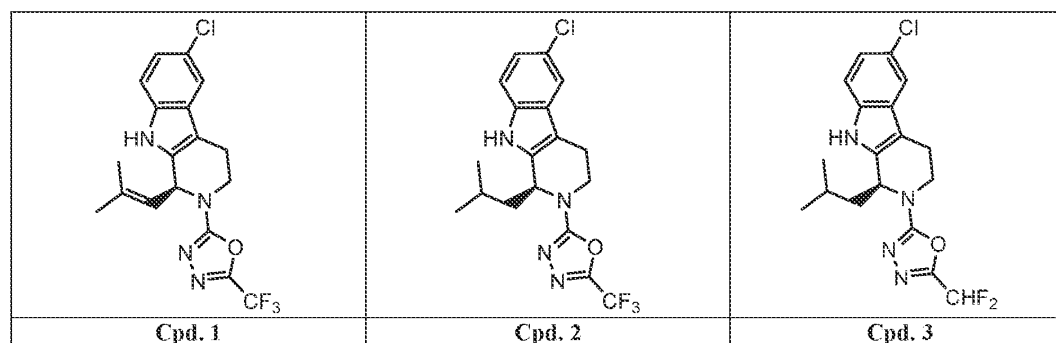
[0099] Another aspect includes a compound of Formula (I), wherein R^5 is heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members; wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents.

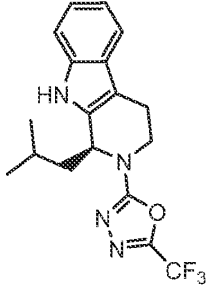
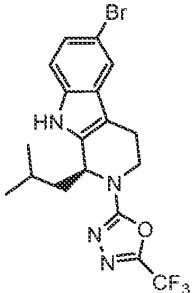
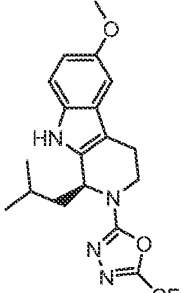
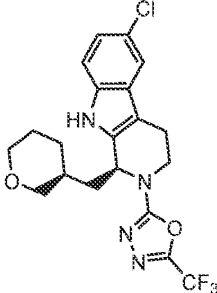
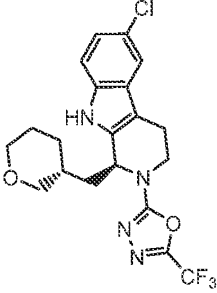
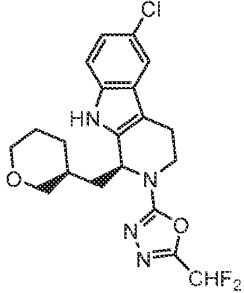
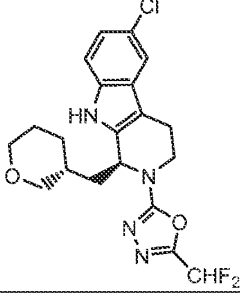
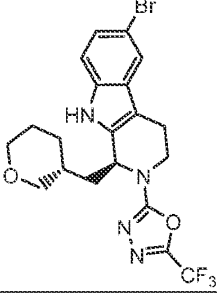
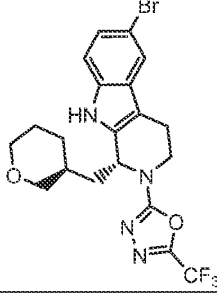
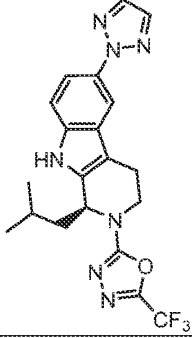
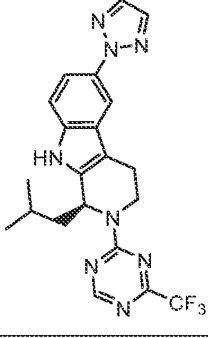
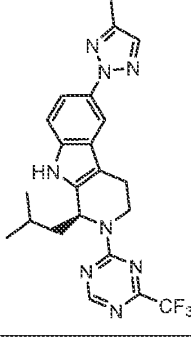
[0100] Another aspect includes a compound of Formula (I), wherein R^5 is heteroaryl selected from 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3,4-2*H*-tetrazolyl, 1,2,4-triazinyl, 1,3,5-triazinyl, pyridinyl, or pyrimidinyl; and, wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents; wherein R^{5A} is fluoro, chloro, cyano, methyl, ethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, methylthio, methoxy, piperazinyl, or morpholinyl; wherein piperazinyl and morpholinyl are each optionally substituted with one R^{5B} substituent; and wherein R^{5B} is C_1 -alkyl selected from methyl.

[0101] Another aspect includes a compound of Formula (I), wherein R^5 is heteroaryl selected from 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,2,3,4-2*H*-tetrazol-5-yl, 1,2,4-triazin-3-yl, 1,3,5-triazin-2-yl, pyridin-2-yl, pyrimidin-2-yl, or pyrimidin-4-yl; wherein heteroaryl is selected from a monocyclic ring having 5 to 8 ring members or a bicyclic ring having from 9 to 10 ring members; and, wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents; wherein R^{5A} is fluoro, chloro, cyano, methyl, ethyl, difluoromethyl, trifluoromethyl, difluoromethoxy, methylthio, methoxy, piperazin-1-yl, or morpholin-4-yl; wherein piperazin-1-yl and morpholin-4-yl are each optionally substituted with one R^{5B} substituent; and, wherein R^{5B} is C_1 -alkyl selected from methyl.

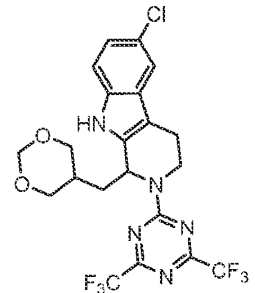
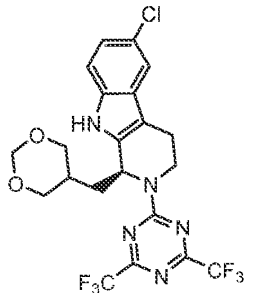
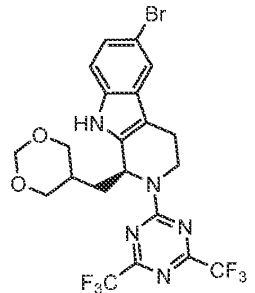
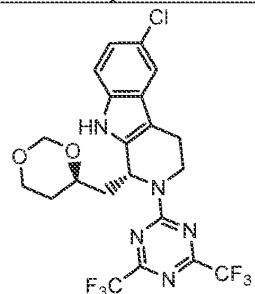
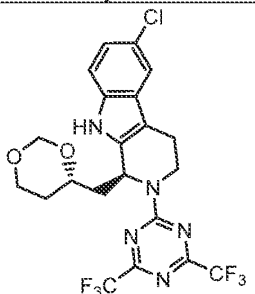
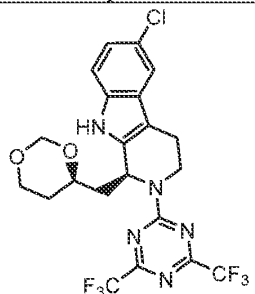
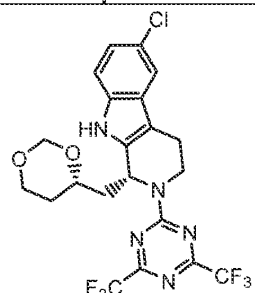
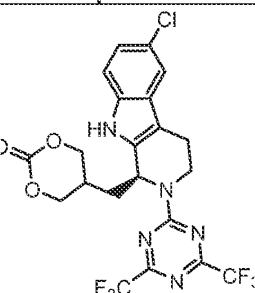
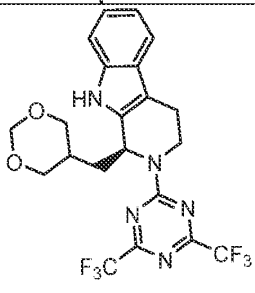
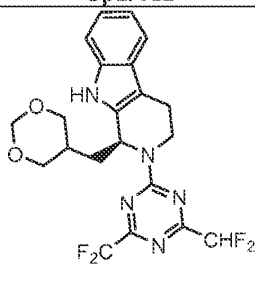
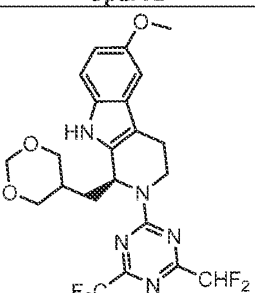
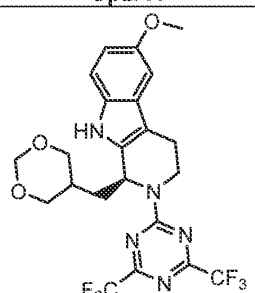
[0102] Another aspect includes a compound of Formula (I), wherein the form of the compound is selected from the group consisting of a free acid, free base, salt, hydrate, solvate, anhydrous, racemate, enantiomer, diastereomer, stereoisomer, and tautomer thereof.

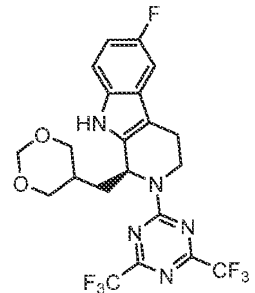
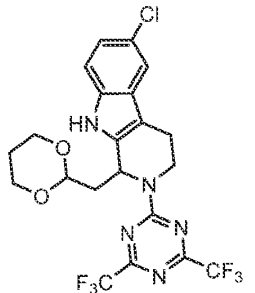
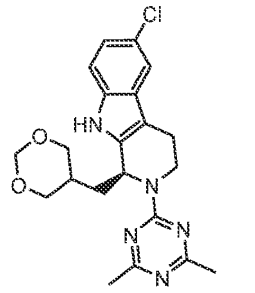
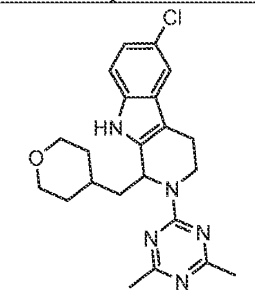
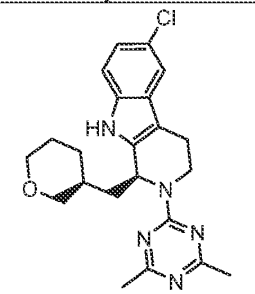
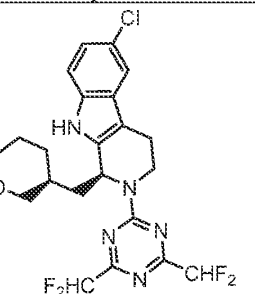
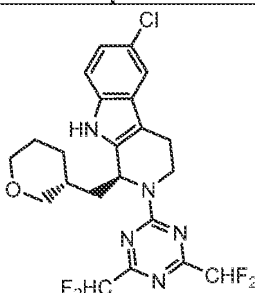
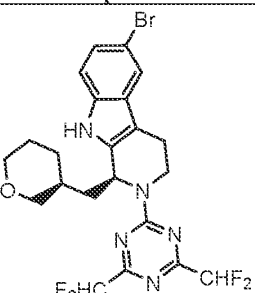
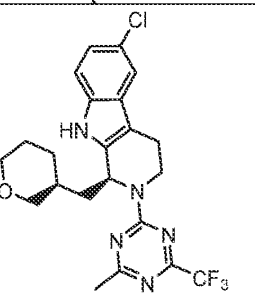
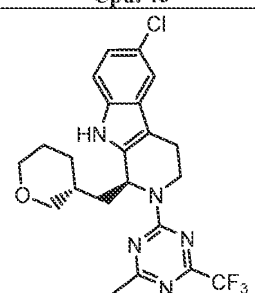
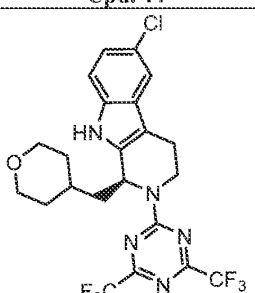
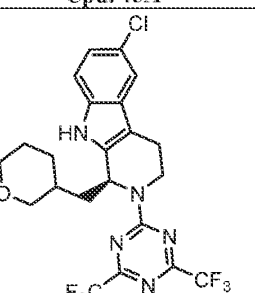
[0103] An aspect of the compound of Formula (I) or a form thereof includes a compound selected from the group consisting of:

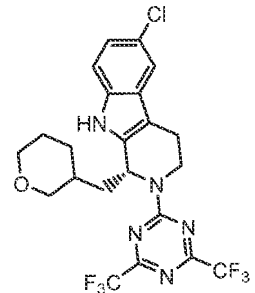
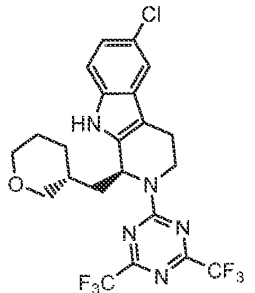
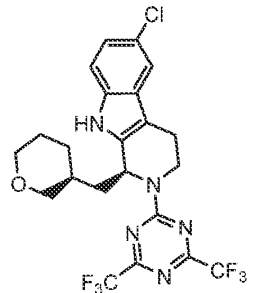
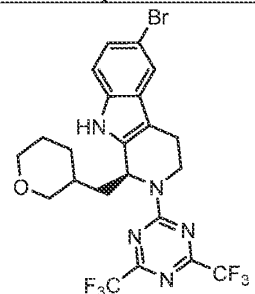
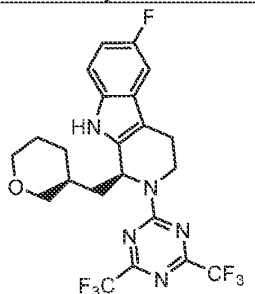
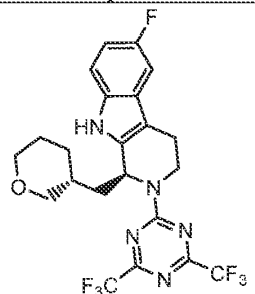
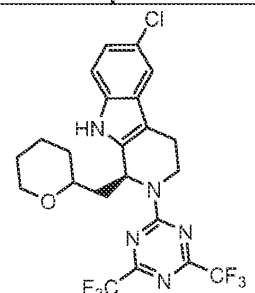
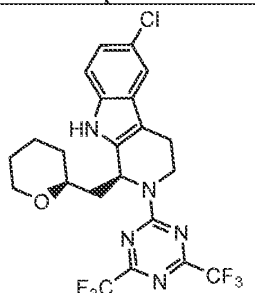
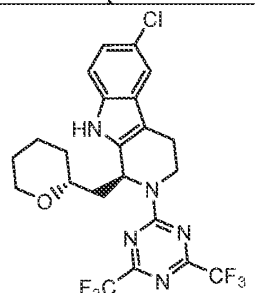
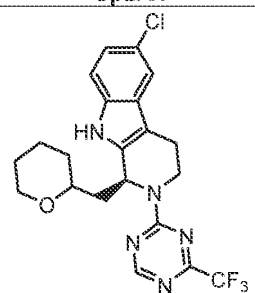
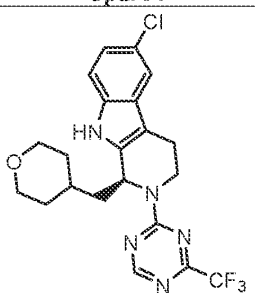
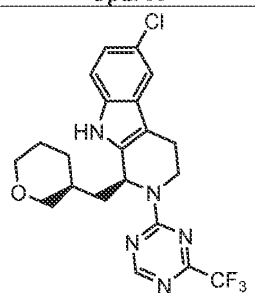


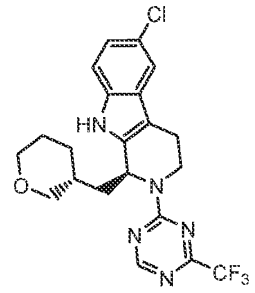
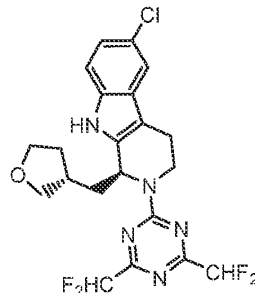
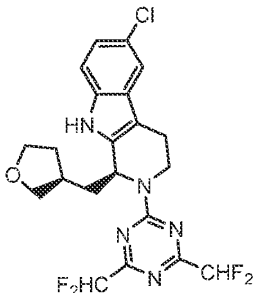
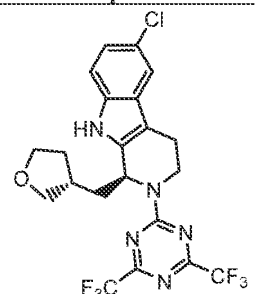
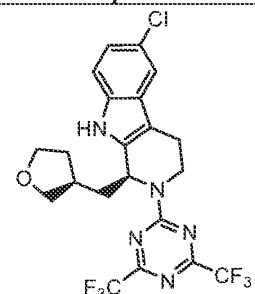
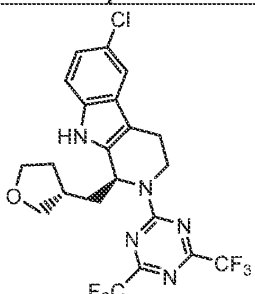
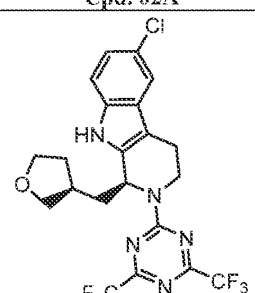
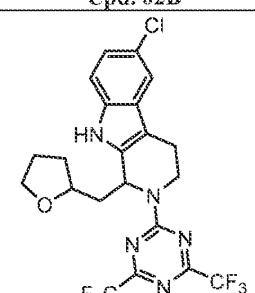
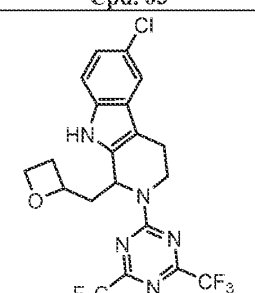
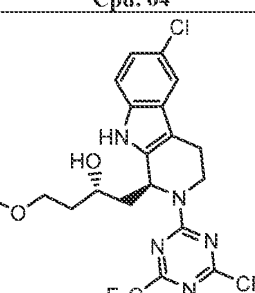
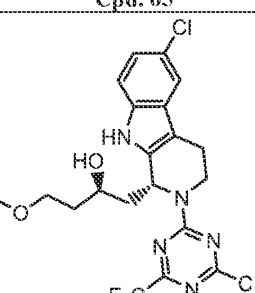
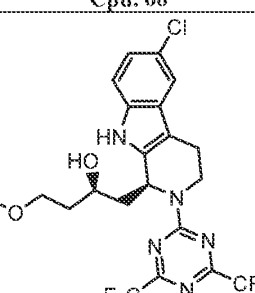
		
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Cpd. 10	Cpd. 11A	Cpd. 11B
		
Cpd. 12	Cpd. 13	Cpd. 14

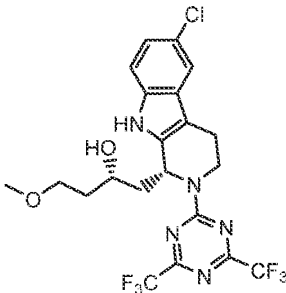
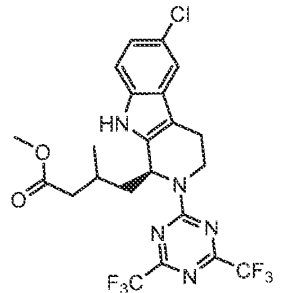
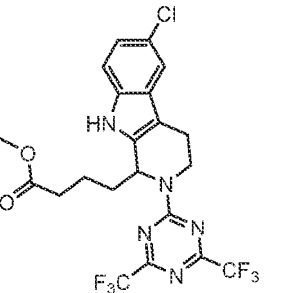
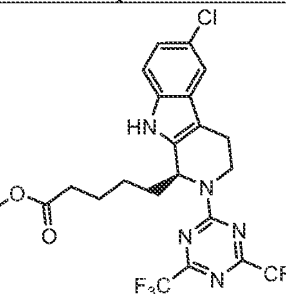
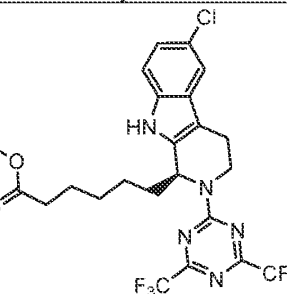
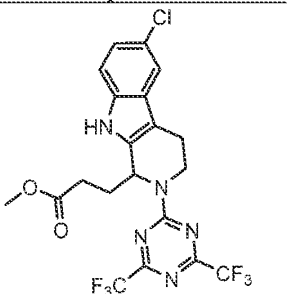
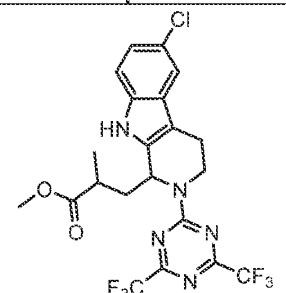
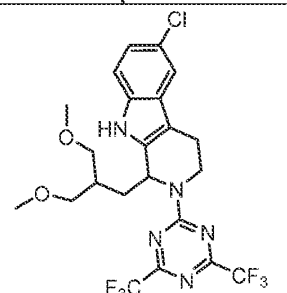
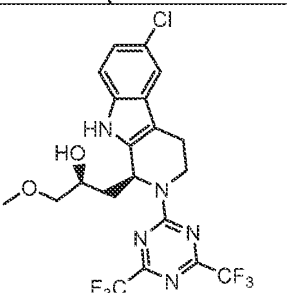
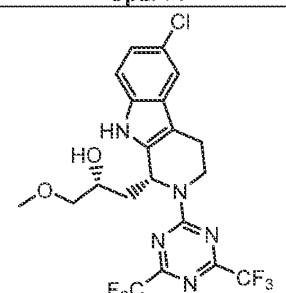
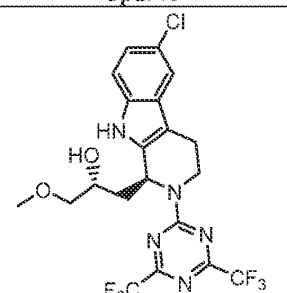
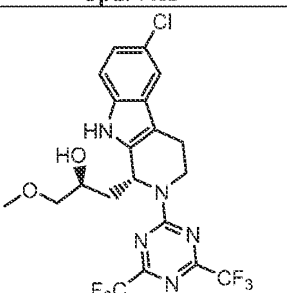
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Cpd. 21	Cpd. 22	Cpd. 23
Cpd. 24	Cpd. 25	Cpd. 26

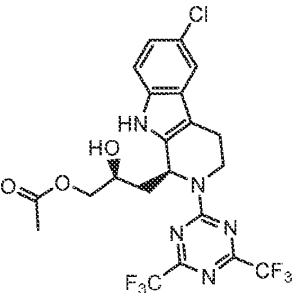
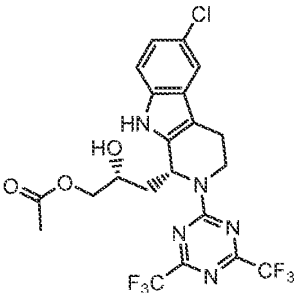
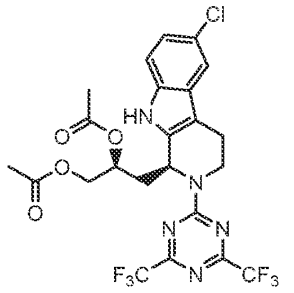
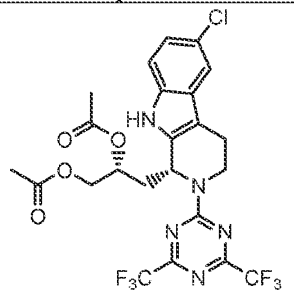
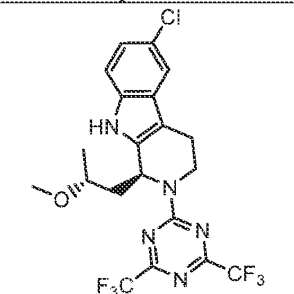
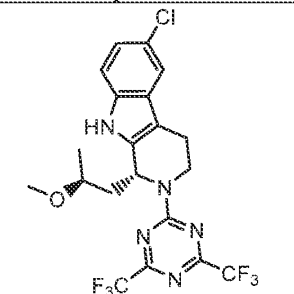
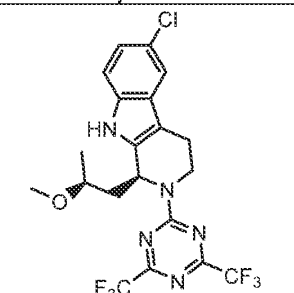
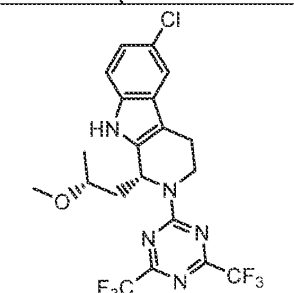
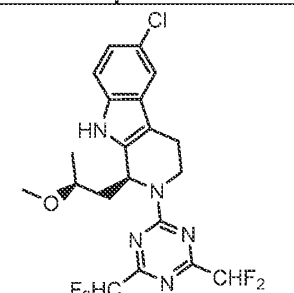
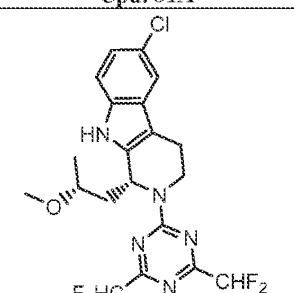
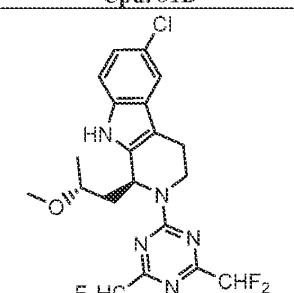
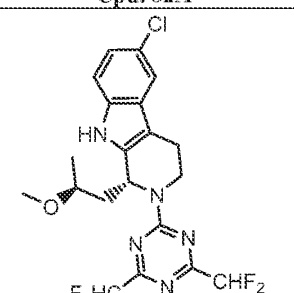
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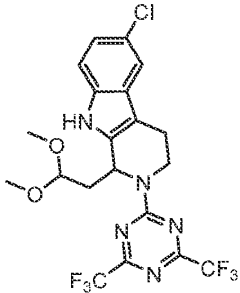
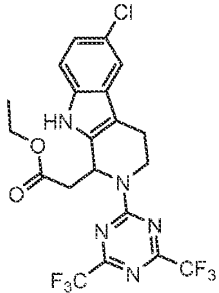
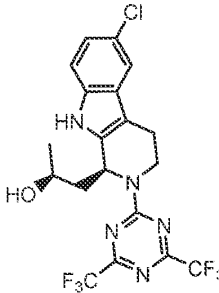
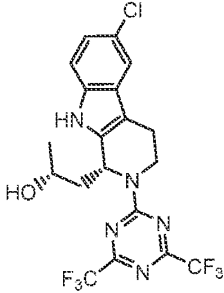
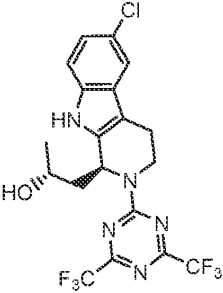
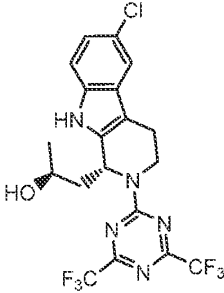
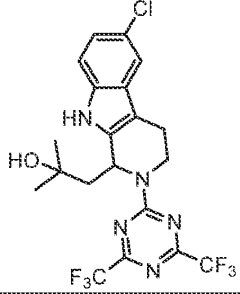
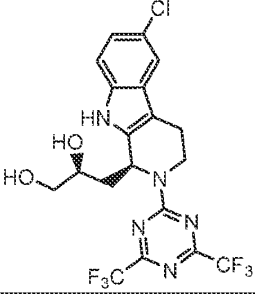
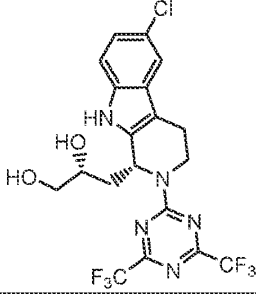
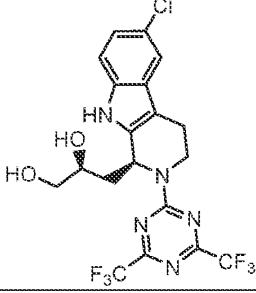
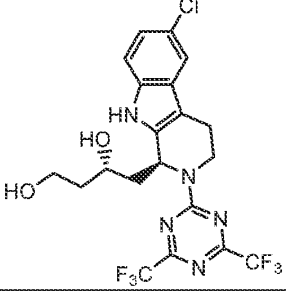
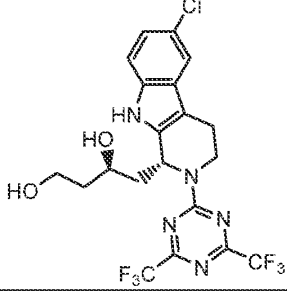
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 Cpd. 45B	 Cpd. 46	 Cpd. 47A

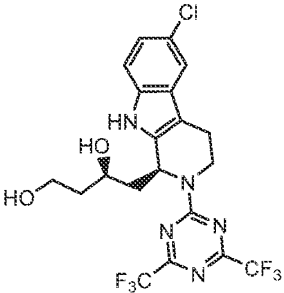
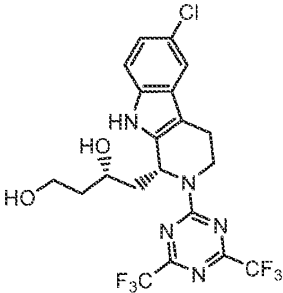
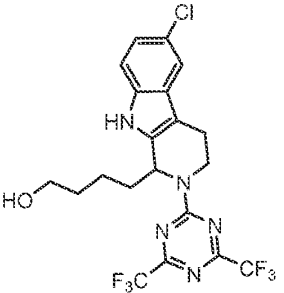
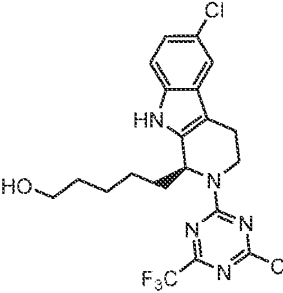
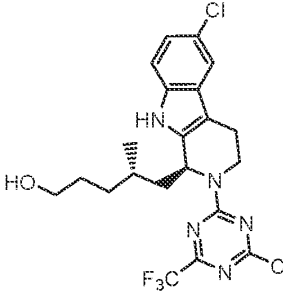
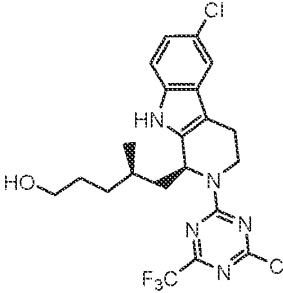
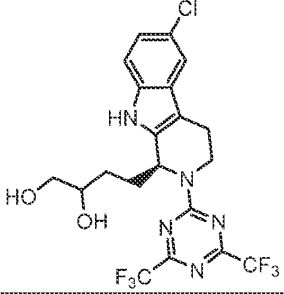
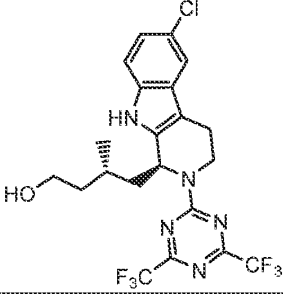
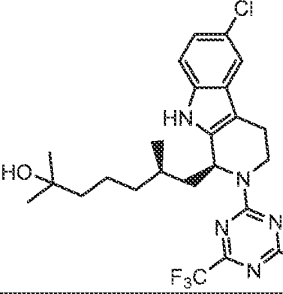
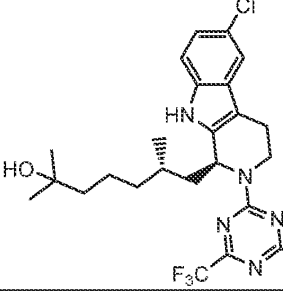
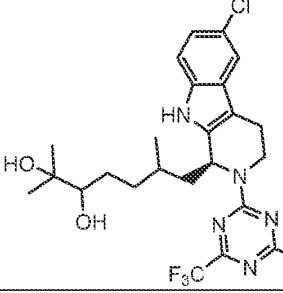
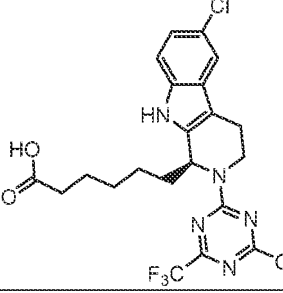
 Cpd. 47B	 Cpd. 48	 Cpd. 49
 Cpd. 50	 Cpd. 51	 Cpd. 52
 Cpd. 53	 Cpd. 54	 Cpd. 55
 Cpd. 56	 Cpd. 57	 Cpd. 58

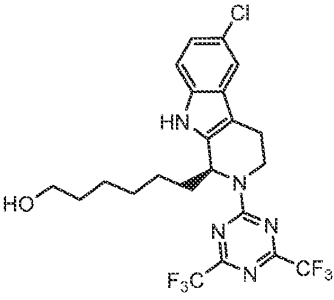
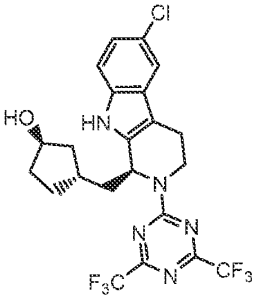
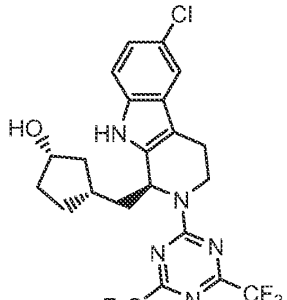
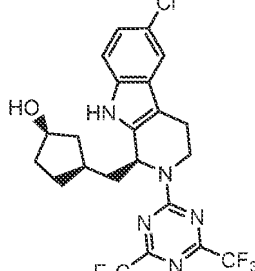
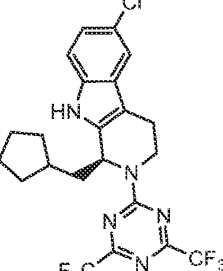
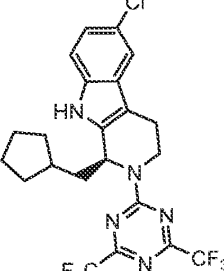
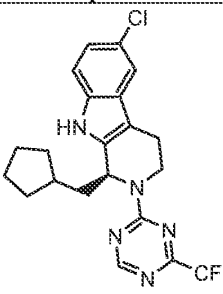
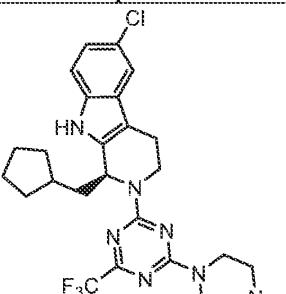
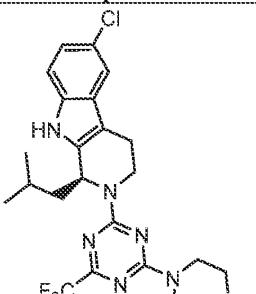
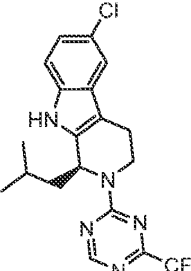
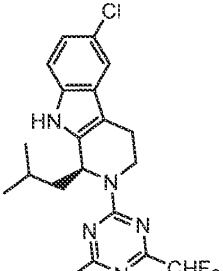
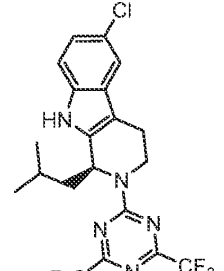
		
Cpd. 59	Cpd. 60	Cpd. 61
		
Cpd. 62A	Cpd. 62B	Cpd. 63
		
Cpd. 64	Cpd. 65	Cpd. 66
		
Cpd. 67A	Cpd. 67B	Cpd. 68A

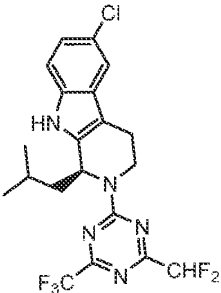
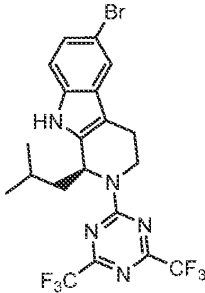
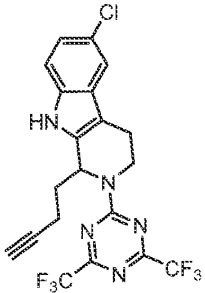
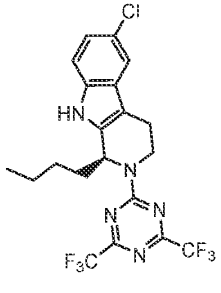
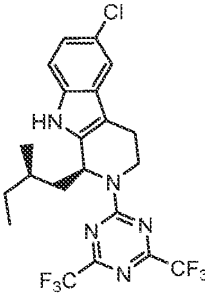
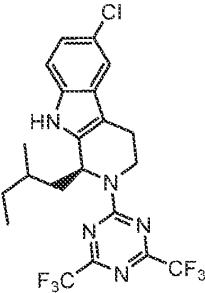
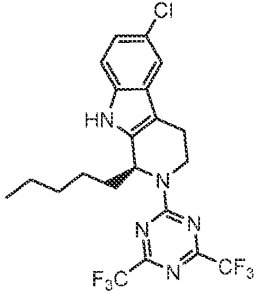
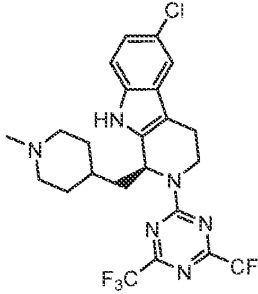
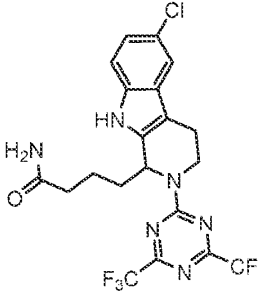
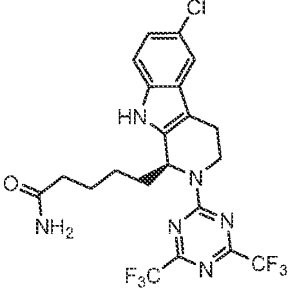
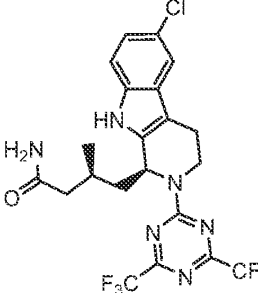
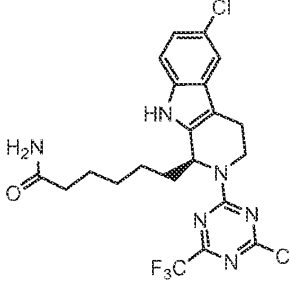
 Cpd. 68B	 Cpd. 69	 Cpd. 70
 Cpd. 71	 Cpd. 72	 Cpd. 73
 Cpd. 74	 Cpd. 75	 Cpd. 76A
 Cpd. 76B	 Cpd. 77A	 Cpd. 77B

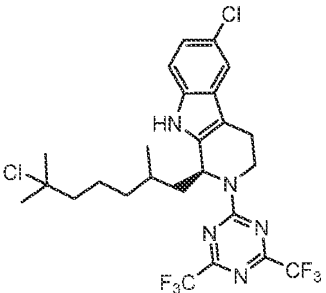
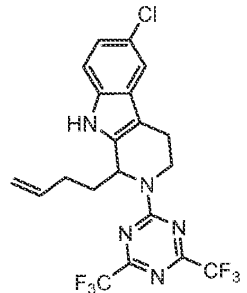
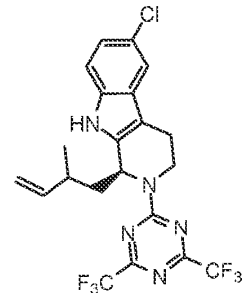
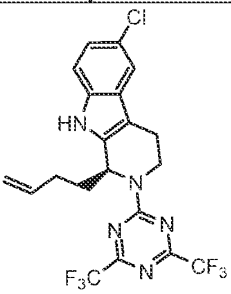
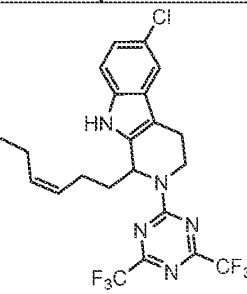
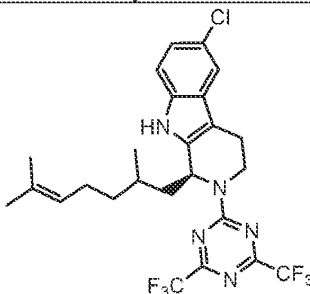
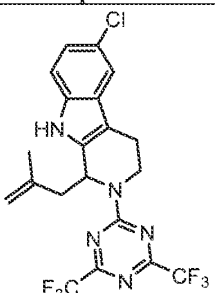
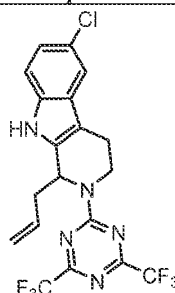
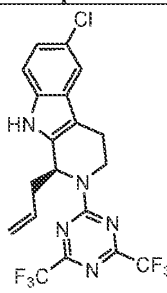
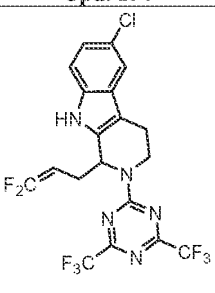
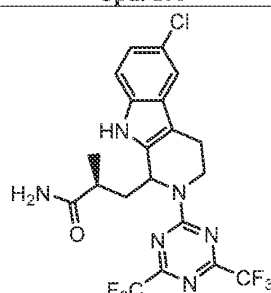
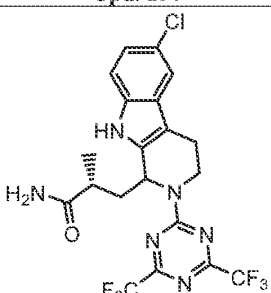
 Cpd. 78A	 Cpd. 78B	 Cpd. 79A
 Cpd. 79B	 Cpd. 80A	 Cpd. 80B
 Cpd. 81A	 Cpd. 81B	 Cpd. 82A
 Cpd. 82B	 Cpd. 83A	 Cpd. 83B

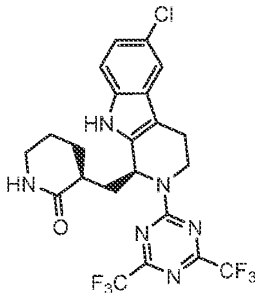
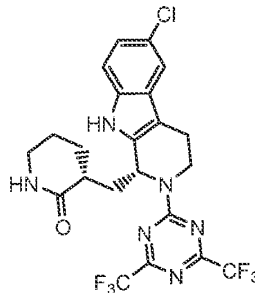
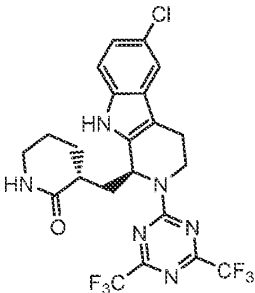
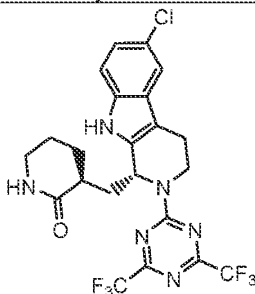
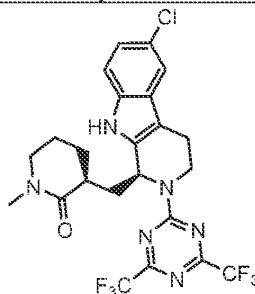
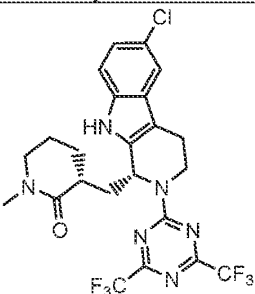
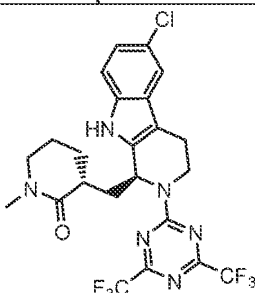
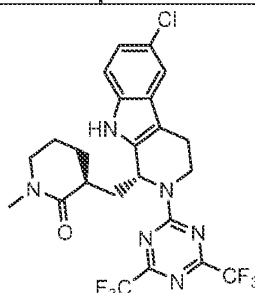
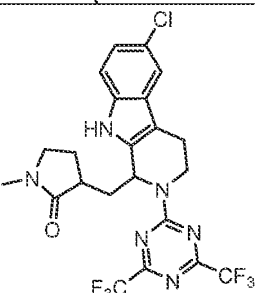
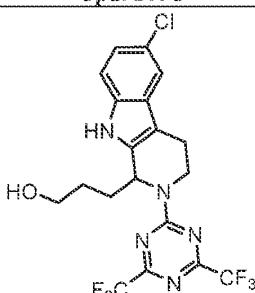
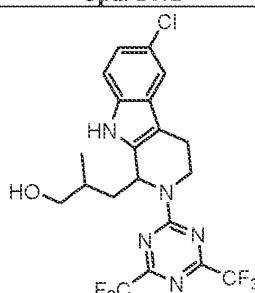
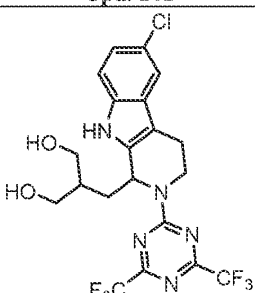
 Cpd. 84	 Cpd. 85	 Cpd. 86A
 Cpd. 86B	 Cpd. 87A	 Cpd. 87B
 Cpd. 88	 Cpd. 89A	 Cpd. 89B
 Cpd. 90	 Cpd. 92A	 Cpd. 92B

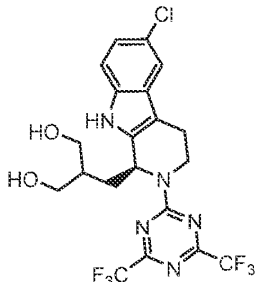
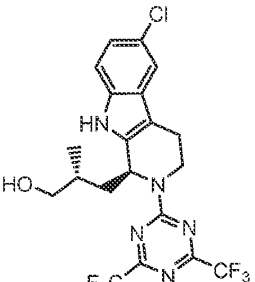
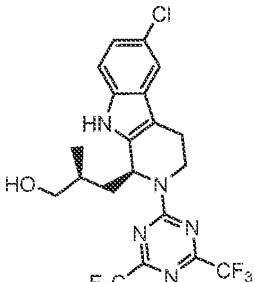
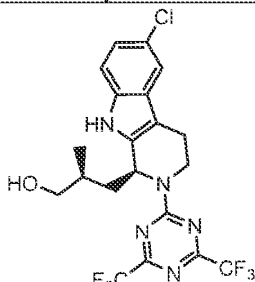
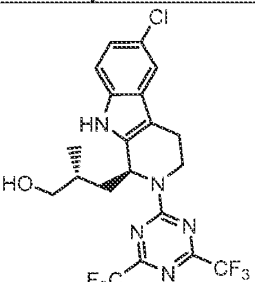
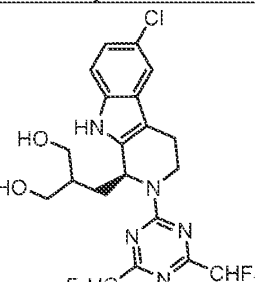
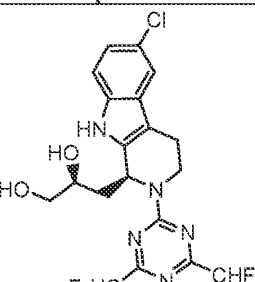
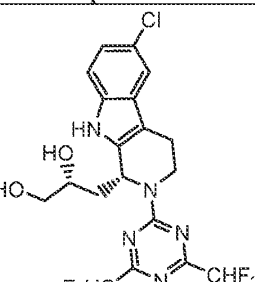
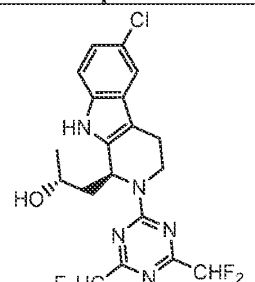
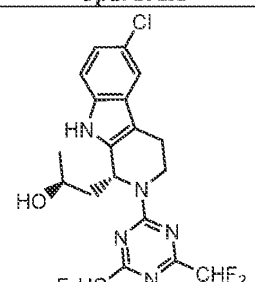
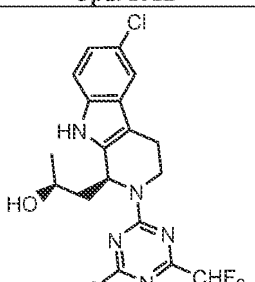
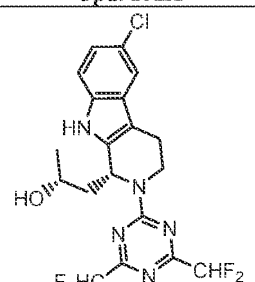
 Cpd. 93A	 Cpd. 93B	 Cpd. 94
 Cpd. 95	 Cpd. 96	 Cpd. 97
 Cpd. 98	 Cpd. 99	 Cpd. 100
 Cpd. 101	 Cpd. 102	 Cpd. 103

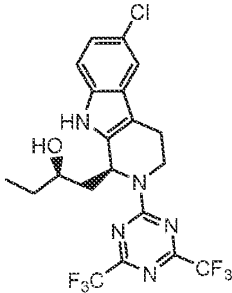
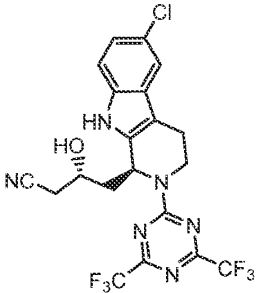
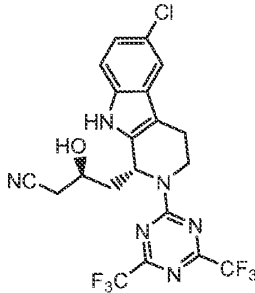
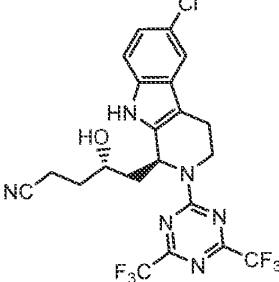
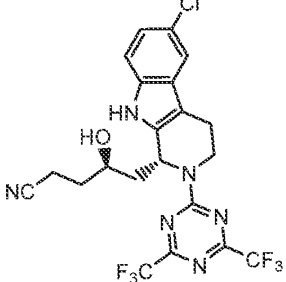
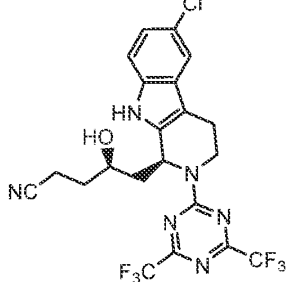
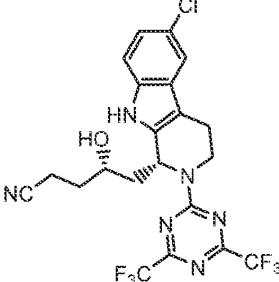
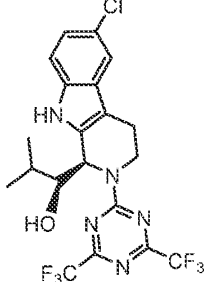
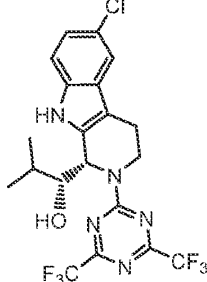
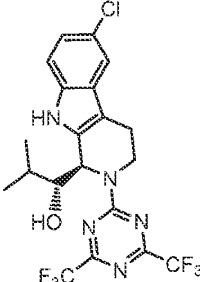
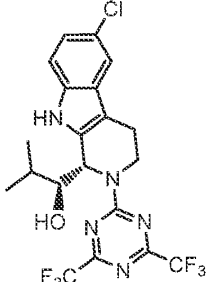
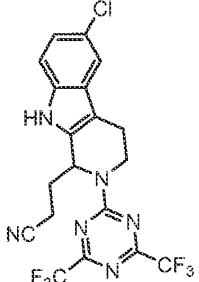
		
Cpd. 104	Cpd. 105	Cpd. 106
		
Cpd. 107	Cpd. 108	Cpd. 109
		
Cpd. 110	Cpd. 111	Cpd. 112
		
Cpd. 113	Cpd. 114	Cpd. 115

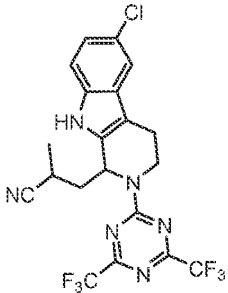
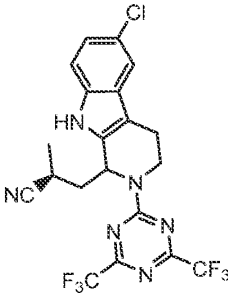
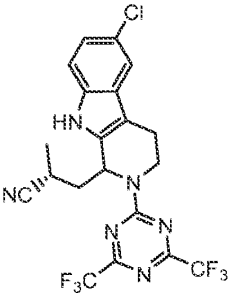
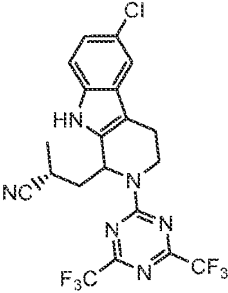
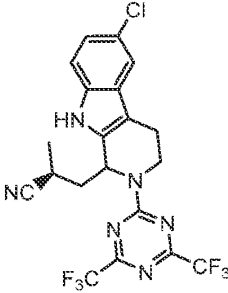
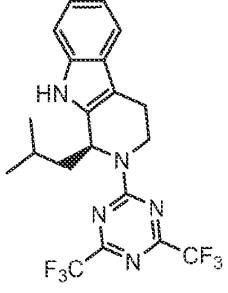
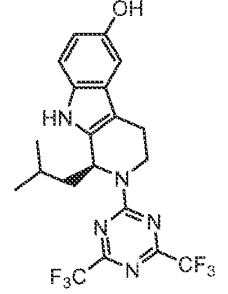
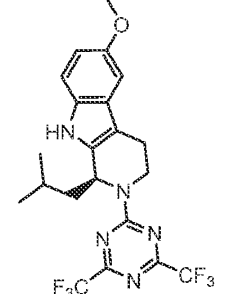
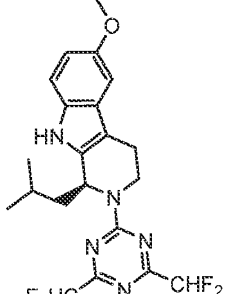
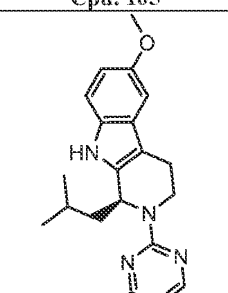
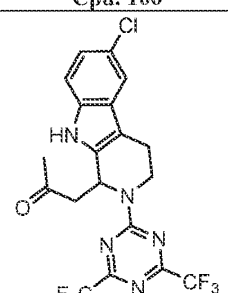
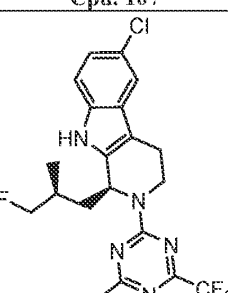
 Cpd. 116	 Cpd. 117	 Cpd. 118
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 Cpd. 125	 Cpd. 126	 Cpd. 127

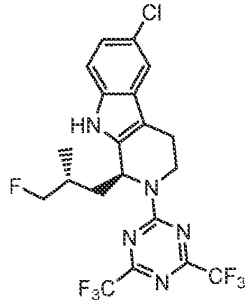
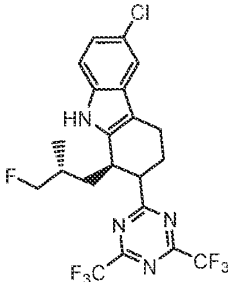
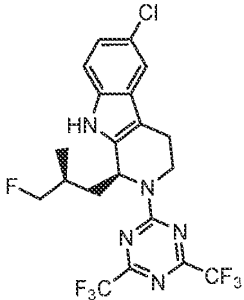
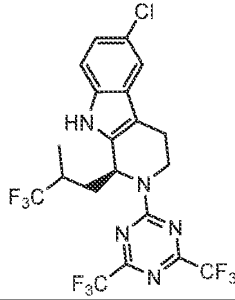
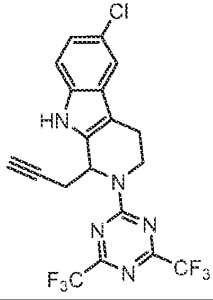
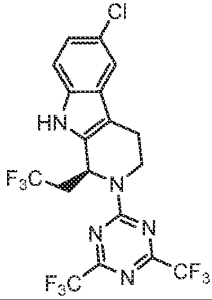
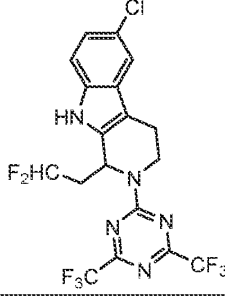
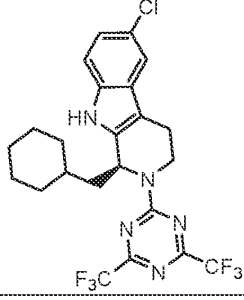
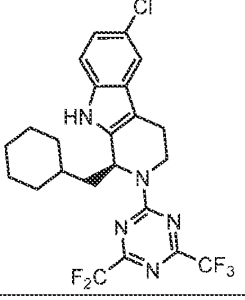
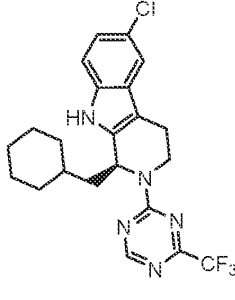
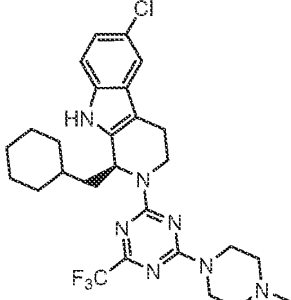
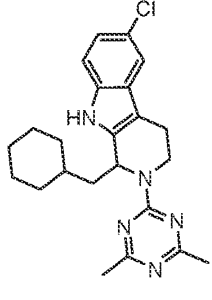
 Cpd. 128	 Cpd. 129	 Cpd. 130
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 Cpd. 134	 Cpd. 135	 Cpd. 136
 Cpd. 137	 Cpd. 138A	 Cpd. 138B

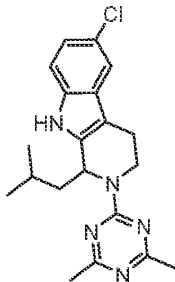
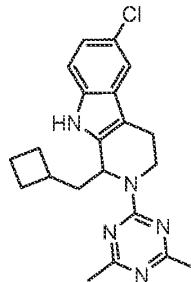
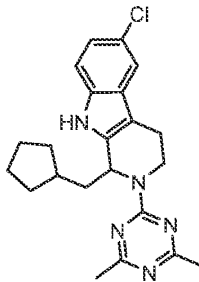
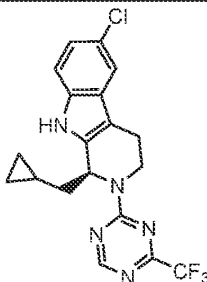
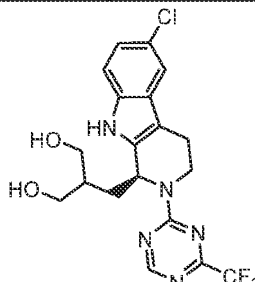
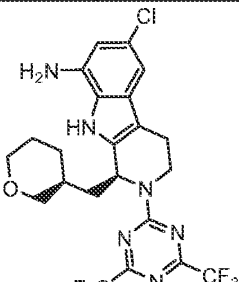
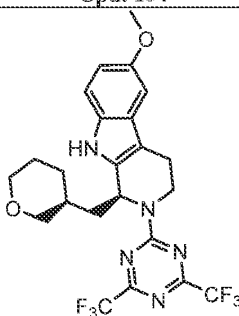
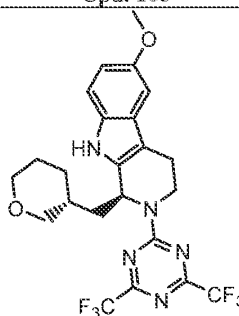
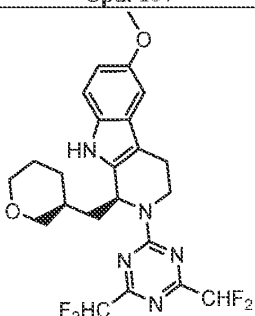
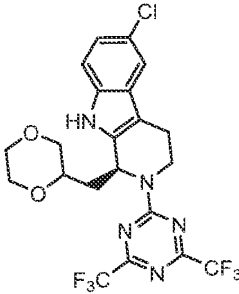
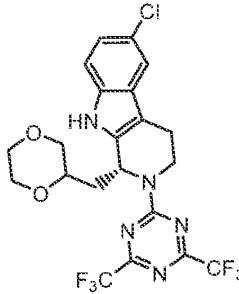
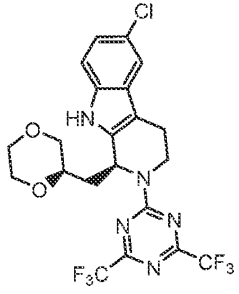
 Cpd. 139A	 Cpd. 139B	 Cpd. 139C
 Cpd. 139D	 Cpd. 140A	 Cpd. 140B
 Cpd. 140C	 Cpd. 140D	 Cpd. 141
 Cpd. 144	 Cpd. 145	 Cpd. 146

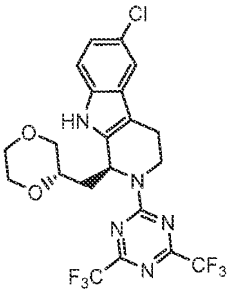
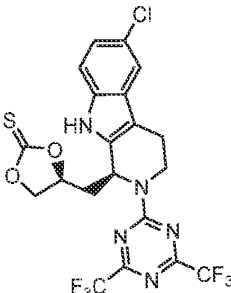
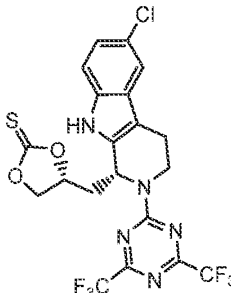
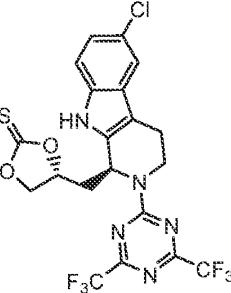
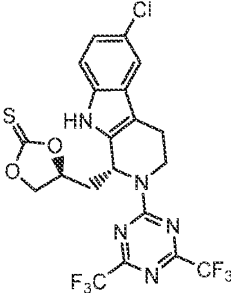
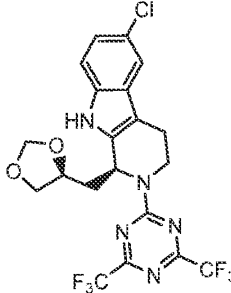
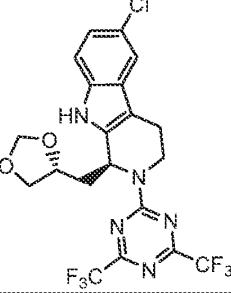
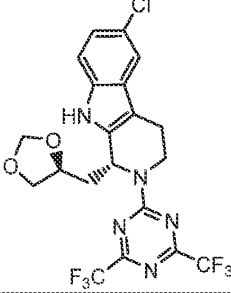
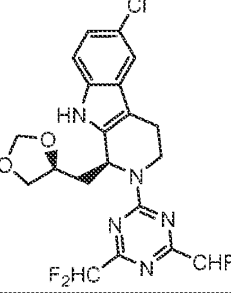
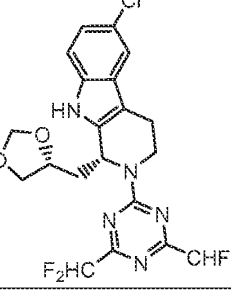
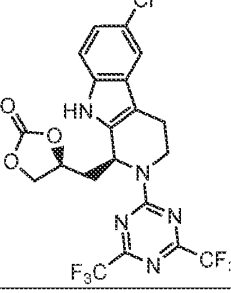
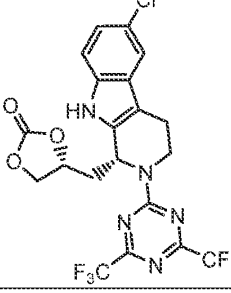
 Cpd. 147	 Cpd. 148A	 Cpd. 148B
 Cpd. 149A	 Cpd. 149B	 Cpd. 150
 Cpd. 151A	 Cpd. 151B	 Cpd. 152A
 Cpd. 152B	 Cpd. 153A	 Cpd. 153B

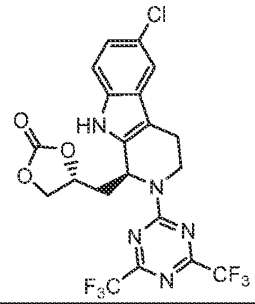
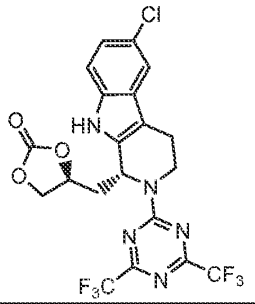
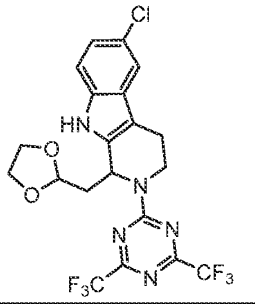
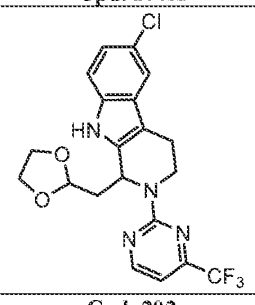
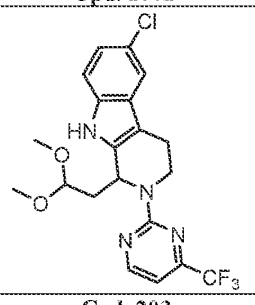
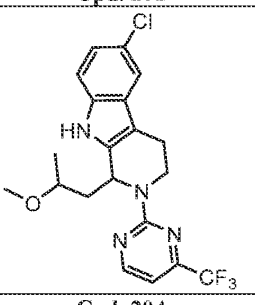
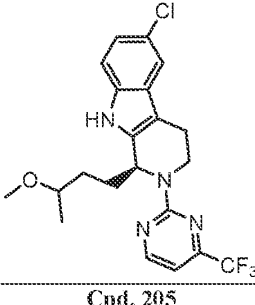
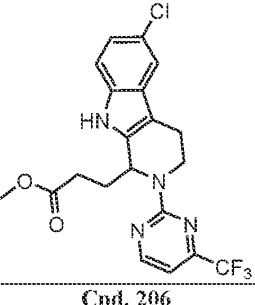
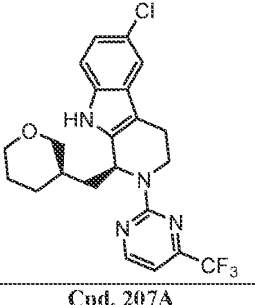
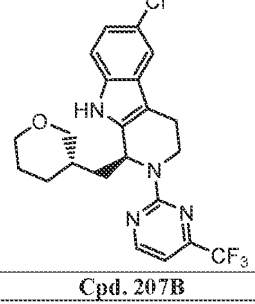
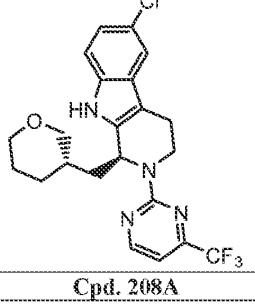
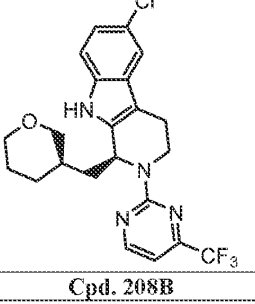
 Cpd. 154	 Cpd. 155A	 Cpd. 155B
 Cpd. 156A	 Cpd. 156B	 Cpd. 157A
 Cpd. 157B	 Cpd. 158A	 Cpd. 158B
 Cpd. 159A	 Cpd. 159B	 Cpd. 160

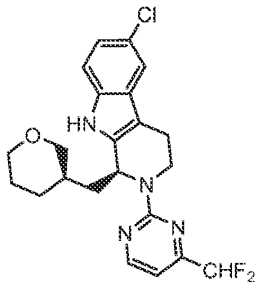
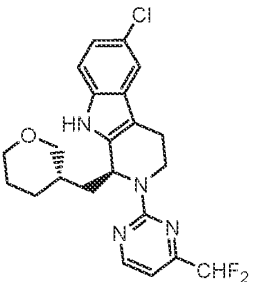
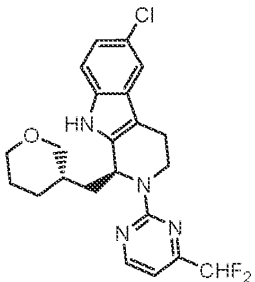
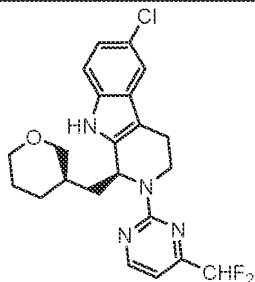
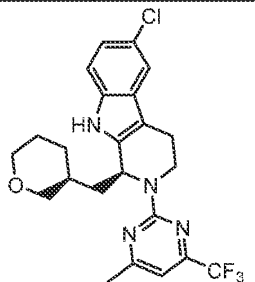
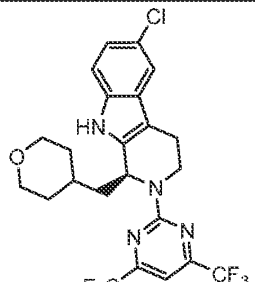
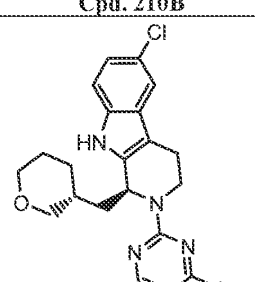
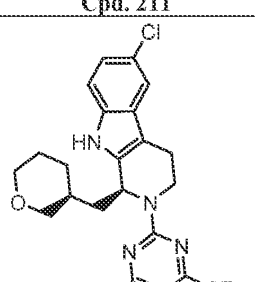
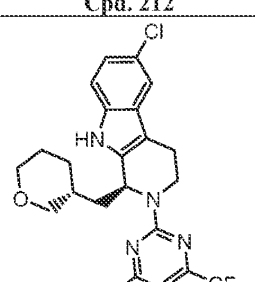
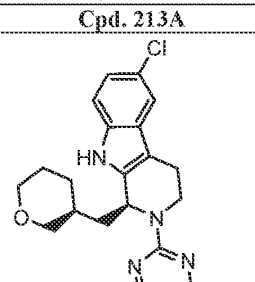
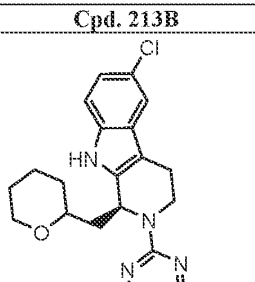
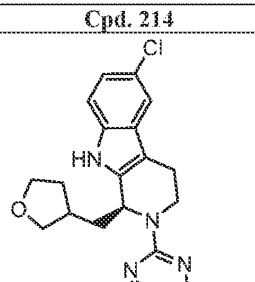
		
Cpd. 161	Cpd. 162A	Cpd. 162B
		
Cpd. 163A	Cpd. 163B	Cpd. 164
		
Cpd. 165	Cpd. 166	Cpd. 167
		
Cpd. 168	Cpd. 169	Cpd. 170A

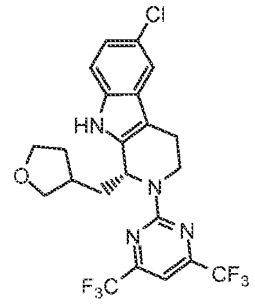
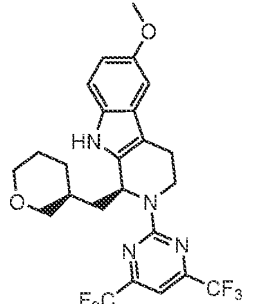
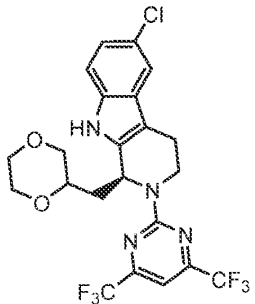
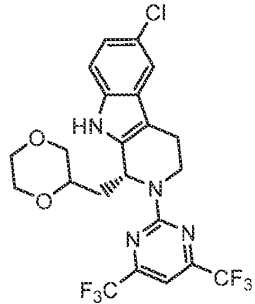
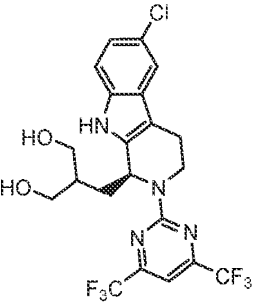
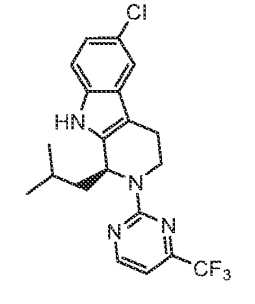
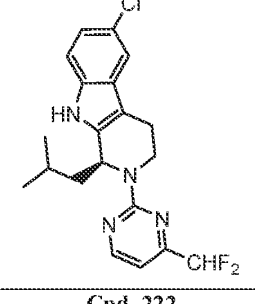
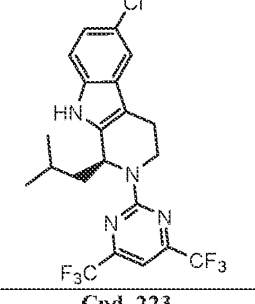
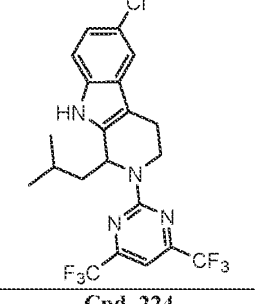
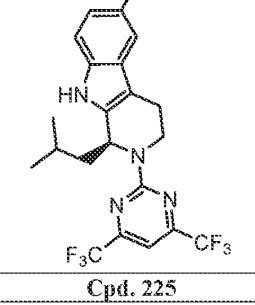
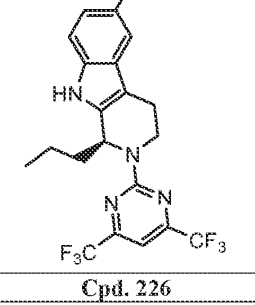
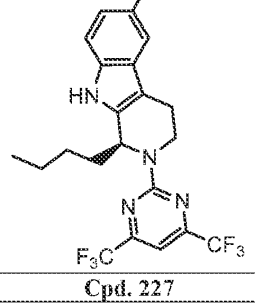
		
Cpd. 170B	Cpd. 171A	Cpd. 171B
		
Cpd. 172	Cpd. 173	Cpd. 174
		
Cpd. 175	Cpd. 176	Cpd. 177
		
Cpd. 178	Cpd. 179	Cpd. 180

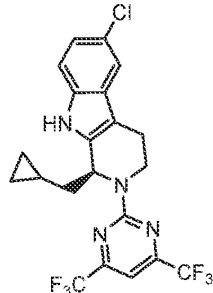
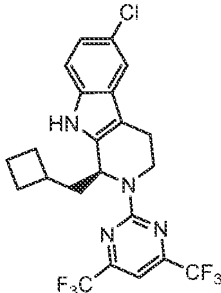
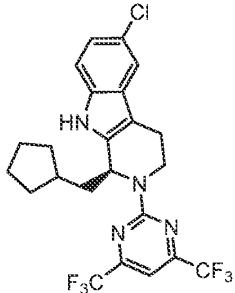
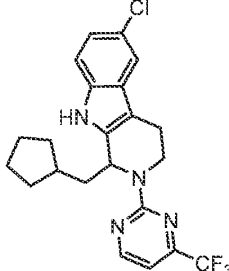
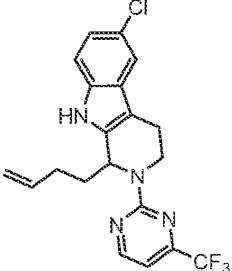
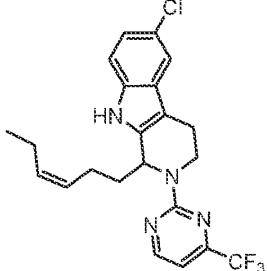
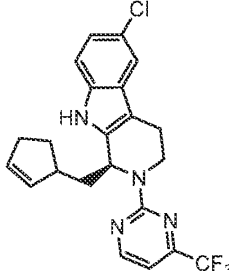
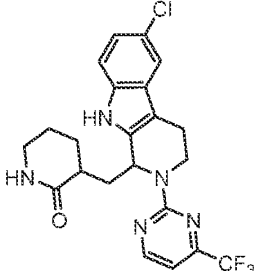
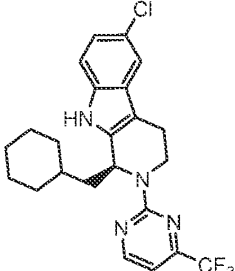
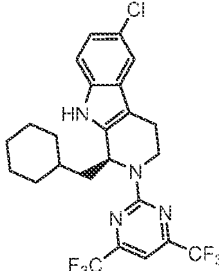
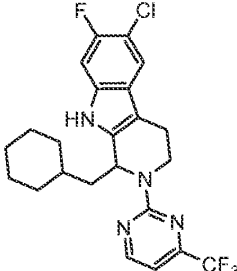
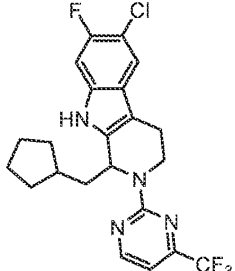
		
Cpd. 181	Cpd. 182	Cpd. 183
		
Cpd. 184	Cpd. 185	Cpd. 187
		
Cpd. 188	Cpd. 189	Cpd. 190
		
Cpd. 191A	Cpd. 191B	Cpd. 192

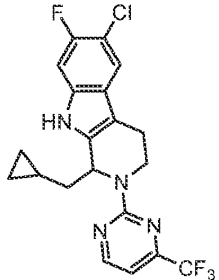
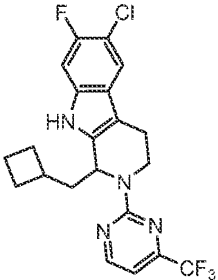
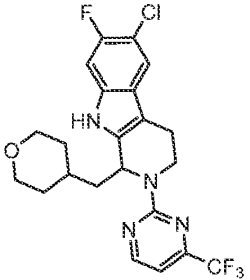
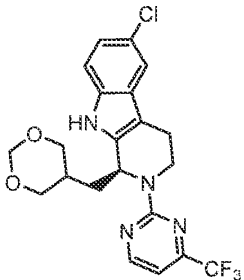
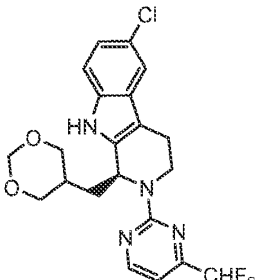
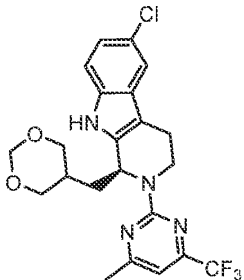
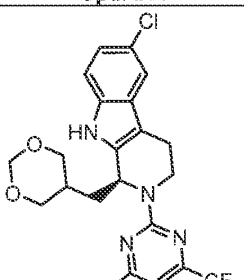
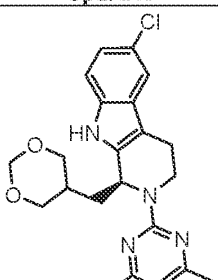
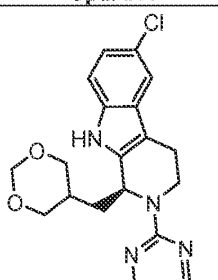
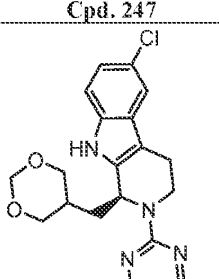
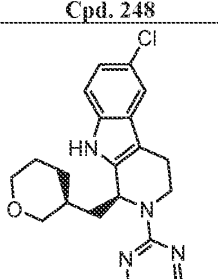
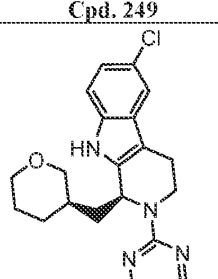
		
Cpd. 193	Cpd. 194A	Cpd. 194B
		
Cpd. 195A	Cpd. 195B	Cpd. 196
		
Cpd. 197A	Cpd. 197B	Cpd. 198A
		
Cpd. 198B	Cpd. 199A	Cpd. 199B

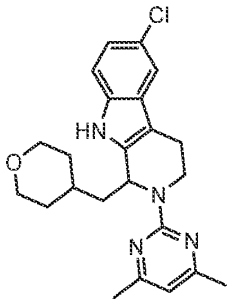
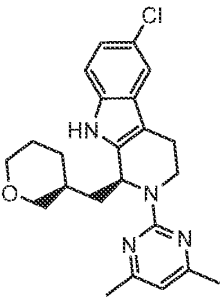
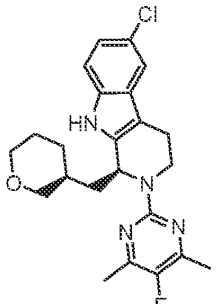
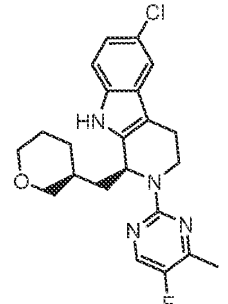
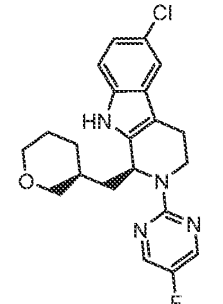
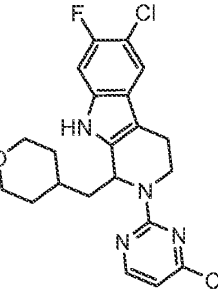
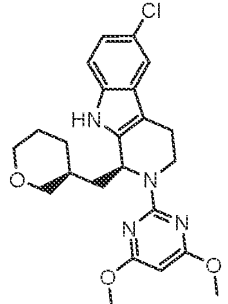
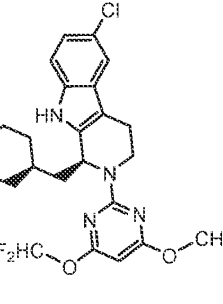
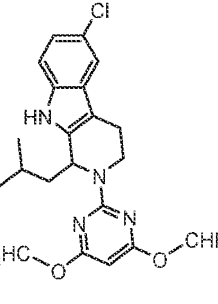
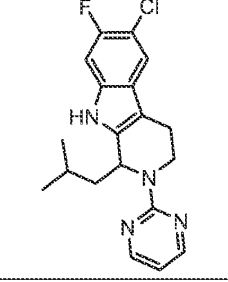
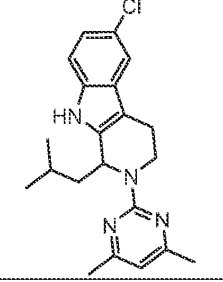
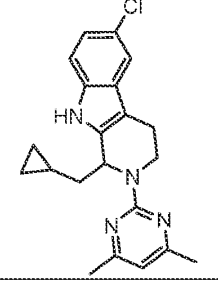
 Cpd. 200A	 Cpd. 200B	 Cpd. 201
 Cpd. 202	 Cpd. 203	 Cpd. 204
 Cpd. 205	 Cpd. 206	 Cpd. 207A
 Cpd. 207B	 Cpd. 208A	 Cpd. 208B

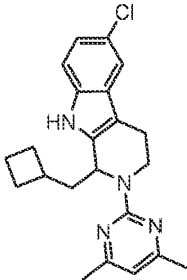
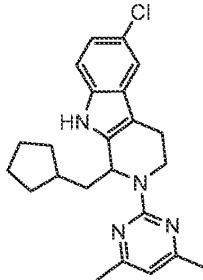
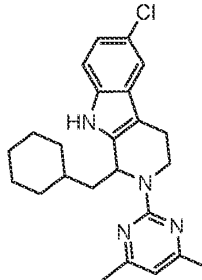
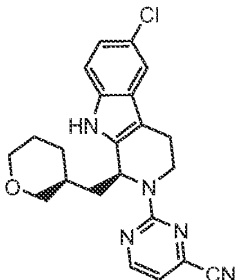
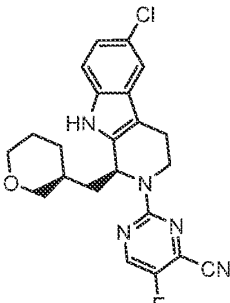
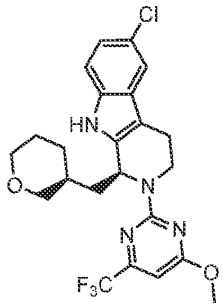
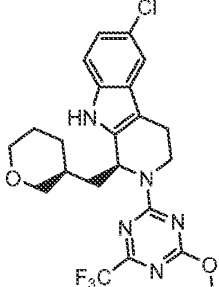
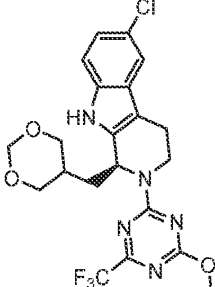
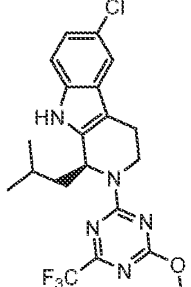
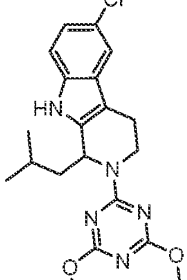
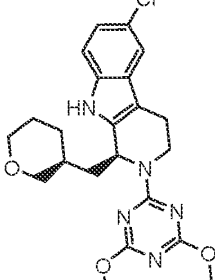
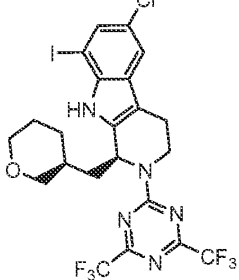
		
Cpd. 209A	Cpd. 209B	Cpd. 210A
		
Cpd. 210B	Cpd. 211	Cpd. 212
		
Cpd. 213A	Cpd. 213B	Cpd. 214
		
Cpd. 215	Cpd. 216	Cpd. 217A

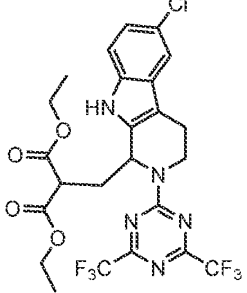
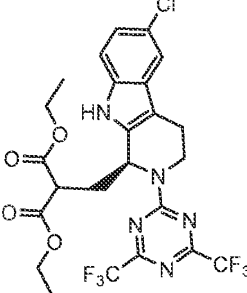
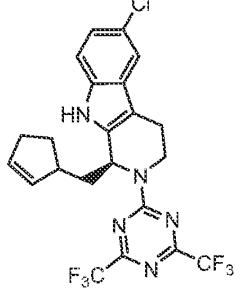
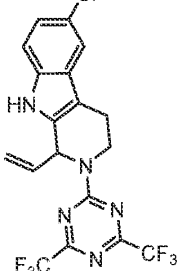
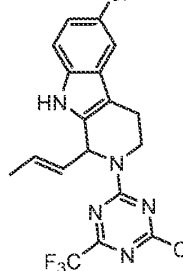
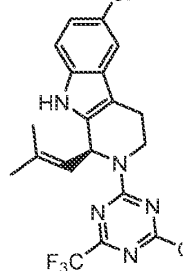
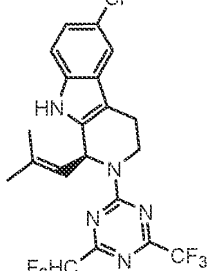
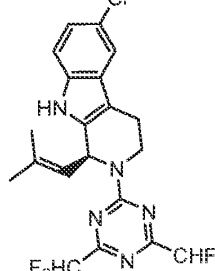
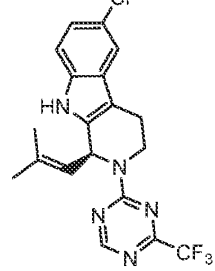
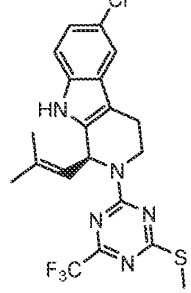
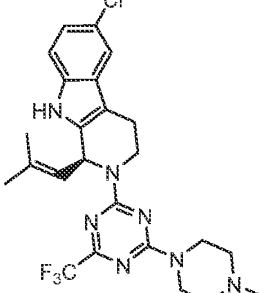
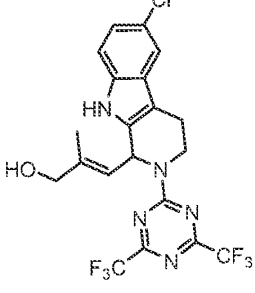
		
Cpd. 217B	Cpd. 218	Cpd. 219A
		
Cpd. 219B	Cpd. 220	Cpd. 221
		
Cpd. 222	Cpd. 223	Cpd. 224
		
Cpd. 225	Cpd. 226	Cpd. 227

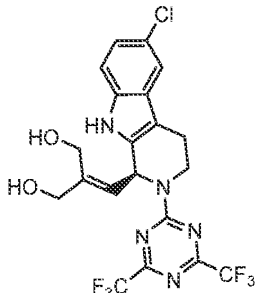
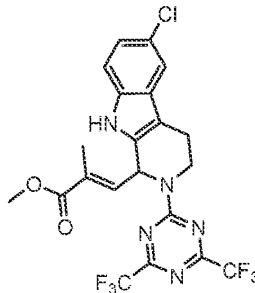
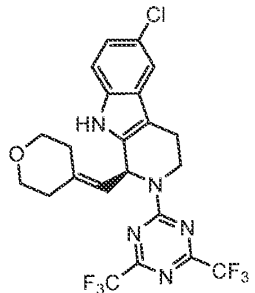
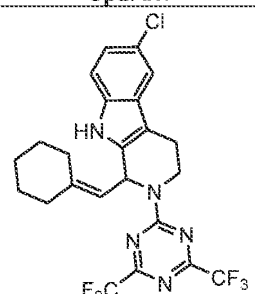
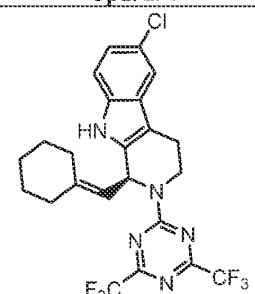
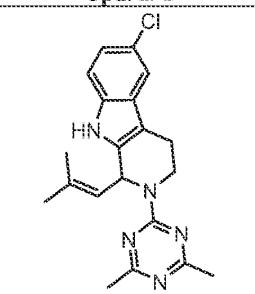
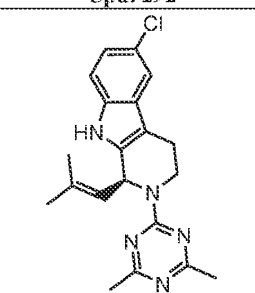
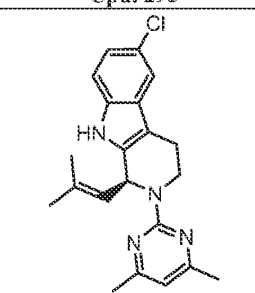
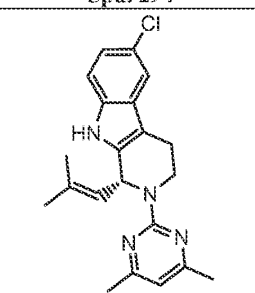
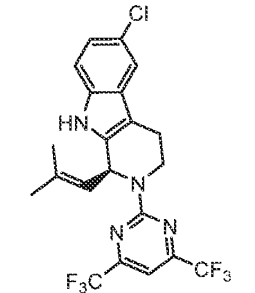
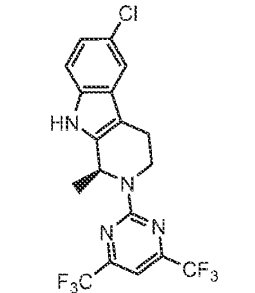
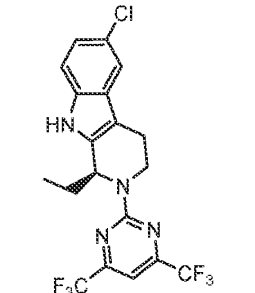
 Cpd. 228	 Cpd. 229	 Cpd. 230
 Cpd. 231	 Cpd. 232	 Cpd. 233
 Cpd. 234	 Cpd. 236	 Cpd. 237
 Cpd. 238	 Cpd. 239	 Cpd. 240

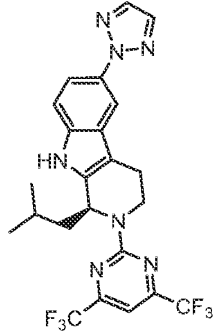
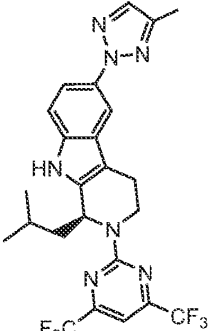
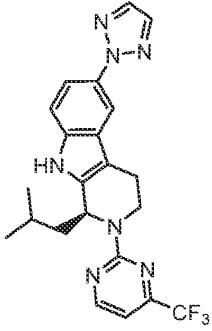
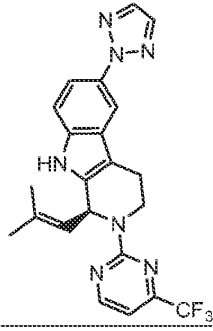
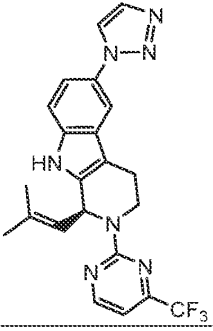
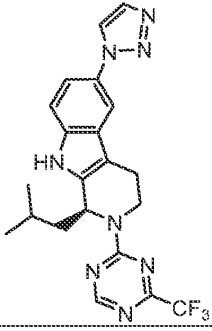
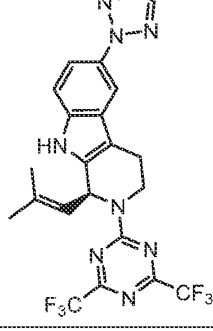
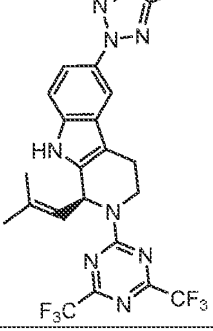
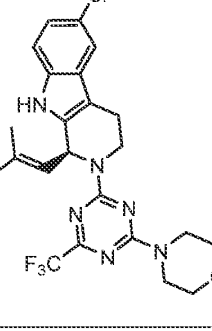
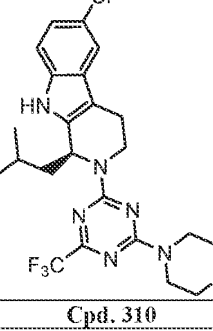
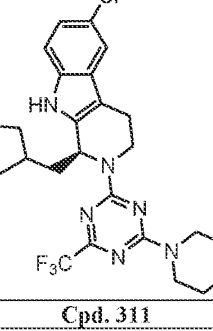
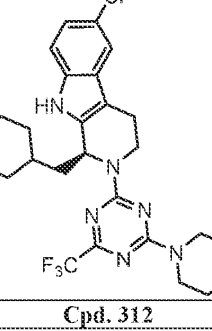
		
Cpd. 241	Cpd. 242	Cpd. 243
		
Cpd. 244	Cpd. 245	Cpd. 246
		
Cpd. 247	Cpd. 248	Cpd. 249
		
Cpd. 250	Cpd. 251	Cpd. 252

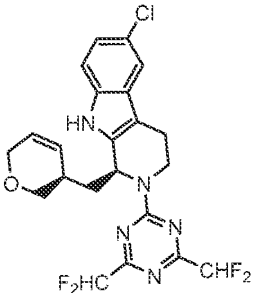
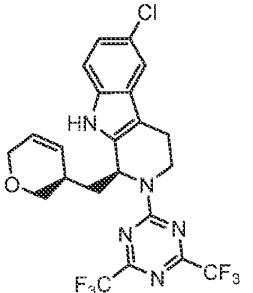
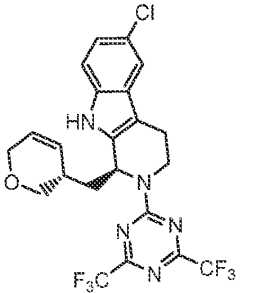
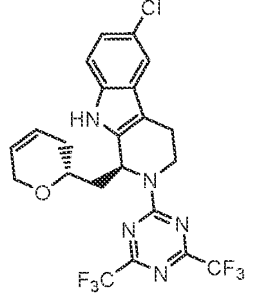
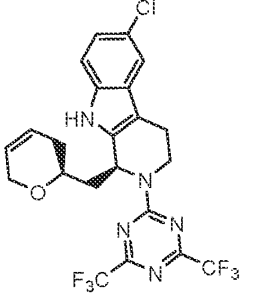
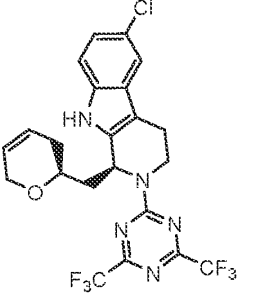
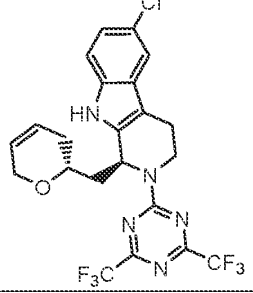
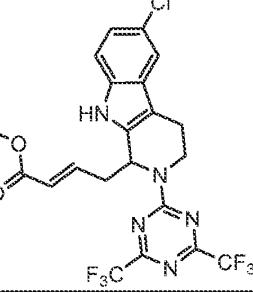
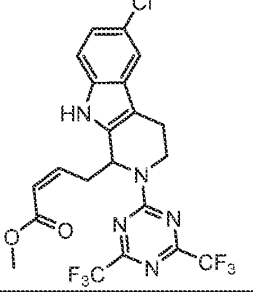
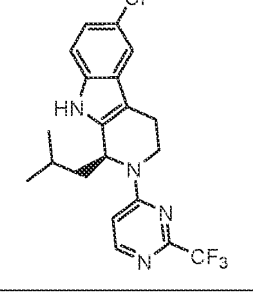
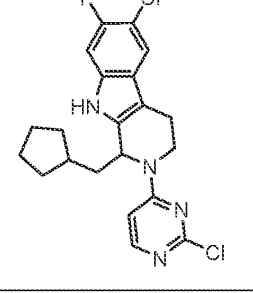
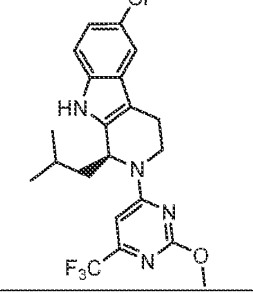
		
Cpd. 253	Cpd. 254	Cpd. 255
		
Cpd. 256	Cpd. 257	Cpd. 258
		
Cpd. 259	Cpd. 260	Cpd. 261
		
Cpd. 262	Cpd. 263	Cpd. 264

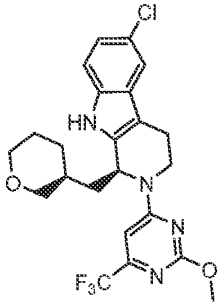
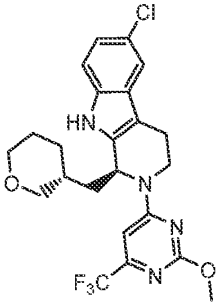
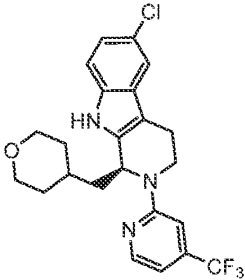
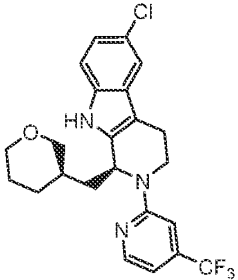
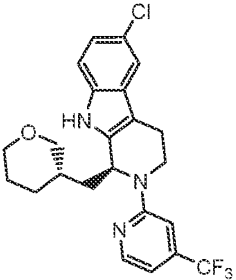
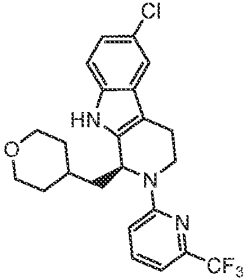
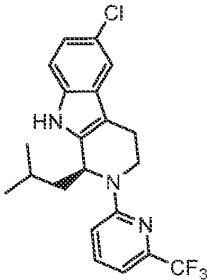
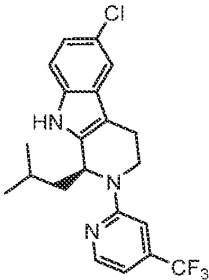
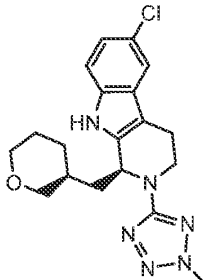
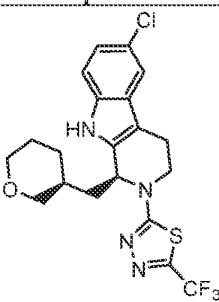
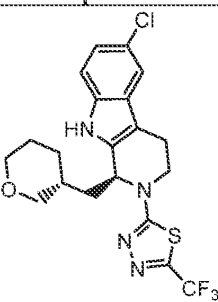
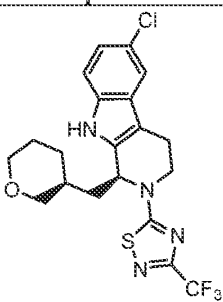
		
Cpd. 265	Cpd. 266	Cpd. 267
		
Cpd. 268	Cpd. 269	Cpd. 270
		
Cpd. 271	Cpd. 272	Cpd. 273
		
Cpd. 274	Cpd. 275	Cpd. 276

		
Cpd. 277	Cpd. 278	Cpd. 279
		
Cpd. 280	Cpd. 281	Cpd. 282
		
Cpd. 283	Cpd. 284	Cpd. 285
		
Cpd. 286	Cpd. 287	Cpd. 288

		
Cpd. 289	Cpd. 290	Cpd. 291
		
Cpd. 292	Cpd. 293	Cpd. 294
		
Cpd. 295	Cpd. 296	Cpd. 297
		
Cpd. 298	Cpd. 299	Cpd. 300

		
Cpd. 301	Cpd. 302	Cpd. 303
		
Cpd. 304	Cpd. 305	Cpd. 306
		
Cpd. 307	Cpd. 308	Cpd. 309
		
Cpd. 310	Cpd. 311	Cpd. 312

 Cpd. 313	 Cpd. 314	 Cpd. 315
 Cpd. 316A	 Cpd. 316B	 Cpd. 317A
 Cpd. 317B	 Cpd. 318	 Cpd. 319
 Cpd. 320	 Cpd. 321	 Cpd. 322

		
Cpd. 323	Cpd. 324	Cpd. 325
		
Cpd. 326	Cpd. 327	Cpd. 328
		
Cpd. 329	Cpd. 330	Cpd. 331
		
Cpd. 332	Cpd. 333	Cpd. 334

Cpd. 335	Cpd. 336	Cpd. 337
Cpd. 338	Cpd. 339	Cpd. 340
Cpd. 341		

[0104] wherein the form of the compound is selected from the group consisting of a free acid, free base, salt, hydrate, solvate, anhydrous, racemate, enantiomer, diastereomer, stereoisomer, and tautomer thereof.

[0105] An aspect of the compound of Formula (I) or a form thereof includes a compound (Cpd) selected from the group consisting of (wherein ¹Cpd# indicates the compound was isolated as a salt form):

Cpd	Name
1	(1S)-6-chloro-1-(2-methylprop-1-en-1-yl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2	(1S)-6-chloro-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
3	(1S)-6-chloro-2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

Cpd	Name
4	(1S)-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
5	(1S)-6-bromo-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6	(1S)-6-methoxy-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
7	(1S)-6-chloro-1-[(3S)-oxan-3-yl]methyl-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
8	(1S)-6-chloro-1-[(3R)-oxan-3-yl]methyl-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
9	(1S)-6-chloro-2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1-[(3S)-oxan-3-yl]methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
10	(1S)-6-chloro-2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1-[(3R)-oxan-3-yl]methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
11A and 11B	(1S)-6-bromo-1-[(3R)-oxan-3-yl]methyl-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-6-bromo-1-[(3S)-oxan-3-yl]methyl-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
12	(1S)-1-(2-methylpropyl)-6-(2H-1,2,3-triazol-2-yl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
13	(1S)-1-(2-methylpropyl)-6-(2H-1,2,3-triazol-2-yl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
14	(1S)-1-(2-methylpropyl)-6-(4-methyl-2H-1,2,3-triazol-2-yl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
15	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-6-(4-methyl-2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
16	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
17	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(3R)-oxan-3-yl]methyl-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
18	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-1-[(3S)-oxan-3-yl]methyl-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
19	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
20	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
21	(1S)-1-[(1,3-dioxan-5-yl)methyl]-6-(2H-1,2,3-triazol-2-yl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
22	(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
23	(1S)-6-bromo-1-[(1,3-dioxan-5-yl)methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
24	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
25	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
26	(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-methyl-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

Cpd	Name
27	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
28	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
29	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
30A and 30B	(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(4S)-1,3-dioxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(4R)-1,3-dioxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
31A and 31B	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(4S)-1,3-dioxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(4R)-1,3-dioxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
32	5-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl}-1,3-dioxan-2-one,
33	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
34	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
35	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
36	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
37	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-6-fluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
38	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
39	(1S)-6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
40	6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-[(oxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
41	(1S)-6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-[(3S)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
42	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3S)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
43	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3R)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
44	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-[(3S)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
45A or 45B	(1S)-6-chloro-2-[4-methyl-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(3S)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-6-chloro-2-[4-methyl-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(3R)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
46	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

Cpd	Name
47A and 47B	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
48	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
49	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
50	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-[(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
51	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-fluoro-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
52	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-fluoro-1-[(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
53	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
54	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-oxan-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
55	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-oxan-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
56	(1S)-6-chloro-1-[(oxan-2-yl)methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
57	(1S)-6-chloro-1-[(oxan-4-yl)methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
58	(1S)-6-chloro-1-[(3S)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
59	(1S)-6-chloro-1-[(3R)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
60	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3S)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
61	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3R)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
62A and 62B	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3S)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3R)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
63	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3S)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
64	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3R)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
65	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxolan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
66	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxetan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
67A and 67B	(2S)-1-[(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-4-methoxybutan-2-ol AND (2R)-1-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-4-methoxybutan-2-ol.

Cpd	Name
68A and 68B	(2S)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-methoxybutan-2-ol AND (2R)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-methoxybutan-2-ol,
69	methyl 4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-methylbutanoate,
70	methyl 4-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}butanoate,
71	methyl 5-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)pentanoate,
72	methyl 6-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)hexanoate,
73	methyl 3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propanoate,
74	methyl 3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanoate,
75	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[3-methoxy-2-(methoxymethyl)propyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
76A and 76B	(2S)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-methoxypropan-2-ol AND (2R)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-methoxypropan-2-ol,
77A and 77B	(2R)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-methoxypropan-2-ol AND (2S)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-methoxypropan-2-ol,
78A and 78B	(2S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-hydroxypropyl acetate AND (2R)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-hydroxypropyl acetate,
79A and 79B	(2S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diyl diacetate AND (2R)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diyl diacetate,
80A and 80B	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
81A and 81B	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
82A and 82B	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

Cpd	Name
83A and 83B	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
84	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2,2-dimethoxyethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.
85	ethyl {2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} acetate.
86A and 86B	(2S)-1-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]propan-2-ol AND (2R)-1-[(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]propan-2-ol.
87A and 87B	(2R)-1-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]propan-2-ol AND (2S)-1-[(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]propan-2-ol.
88	1-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropan-2-ol.
89A and 89B	(2S)-3-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]propane-1,2-diol AND (2R)-3-[(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]propane-1,2-diol.
90	(2S)-3-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]propane-1,2-diol.
92A and 92B	(3R)-4-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]butane-1,3-diol AND (3S)-4-[(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]butane-1,3-diol.
93A and 93B	(3S)-4-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]butane-1,3-diol AND (3R)-4-[(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]butane-1,3-diol.
94	4-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}butan-1-ol.
95	5-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]pentan-1-ol.
96	(4S)-5-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-4-methylpentan-1-ol.
97	(4R)-5-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-4-methylpentan-1-ol.
98	4-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]butane-1,2-diol.
99	(3R)-4-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-3-methylbutan-1-ol.
100	(6R)-7-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-2,6-dimethylheptan-2-ol.
101	(6S)-7-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-2,6-dimethylheptan-2-ol.

Cpd	Name
102	7-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2,6-dimethylheptane-2,3-diol,
103	6-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)hexanoic acid,
104	6-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)hexan-1-ol,
105	(1R,3S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)cyclopentan-1-ol,
106	(1S,3S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)cyclopentan-1-ol,
107	(1R,3R)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)cyclopentan-1-ol,
108	(1S)-6-chloro-1-(cyclopentylmethyl)-2-[4-(difluoromethyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
109	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(cyclopentylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
110	(1S)-6-chloro-1-(cyclopentylmethyl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
111	(1S)-6-chloro-1-(cyclopentylmethyl)-2-[4-(4-methylpiperazin-1-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
112	(1S)-6-chloro-2-[4-(4-methylpiperazin-1-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
113	(1S)-6-chloro-1-(2-methylpropyl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
114	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
115	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
116	(1S)-6-chloro-2-[4-(difluoromethyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
117	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
118	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(but-3-yn-1-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
119	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-butyl-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
120	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-2-methylbutyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
121	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylbutyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
122	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-pentyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
123	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1-methylpiperidin-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
124	4-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}butanamide,
125	5-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)pentanamide,

Cpd	Name
126	(3S)-4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-methylbutanamide,
127	6-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)hexanamide,
128	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(6-chloro-2,6-dimethylheptyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
129	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(but-3-en-1-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
130	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylbut-3-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
131	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(but-3-en-1-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
132	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3Z)-hex-3-en-1-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
133	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2,6-dimethylhept-5-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
134	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylprop-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
135	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(prop-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
136	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(prop-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
137	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(3,3-difluoroprop-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
138A or 138B	(2S)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanamide OR (2R)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanamide,
139A or 139B or 139C or 139D	(3S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)piperidin-2-one OR (3R)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)piperidin-2-one OR (3R)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)piperidin-2-one OR (3S)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)piperidin-2-one,
140A or 140 or 140B or 140C or 140D	(3S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1-methylpiperidin-2-one OR (3R)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1-methylpiperidin-2-one OR (3R)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1-methylpiperidin-2-one OR (3S)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1-methylpiperidin-2-one,
141	3-({2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1-methylpyrrolidin-2-one,
144	3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propan-1-ol,

Cpd	Name
145	3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropan-1-ol,
146	2-({2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}methyl)propane-1,3-diol,
147	2-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}methyl)propane-1,3-diol,
148A or 148B	(2R)-3-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropan-1-ol OR (2S)-3-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropan-1-ol,
149A or 149B	(2S)-3-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropan-1-ol OR (2R)-3-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropan-1-ol,
150	2-({(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}methyl)propane-1,3-diol,
151A and 151B	(2S)-3-({(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propane-1,2-diol AND (2R)-3-({(1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propane-1,2-diol,
152A and 152B	(2R)-1-({(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propan-2-ol AND (2S)-1-({(1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propan-2-ol,
153A and 153B	(2S)-1-({(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propan-2-ol AND (2R)-1-({(1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propan-2-ol,
154	(2R)-1-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}butan-2-ol,
155A and 155B	(3R)-4-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-3-hydroxybutanenitrile AND (3S)-4-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-3-hydroxybutanenitrile,
156A and 156B	(4S)-5-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-4-hydroxypentanenitrile AND (4R)-5-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-4-hydroxypentanenitrile,
157A and 157B	(4R)-5-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-4-hydroxypentanenitrile AND (4S)-5-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-4-hydroxypentanenitrile,
158A and 158B	(1S)-1-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropan-1-ol AND (1R)-1-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropan-1-ol,

Cpd	Name
159A and 159B	(1R)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol AND (1S)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol,
160	3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propanenitrile,
161	3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanenitrile,
162A or 162B	(2S)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanenitrile OR (2R)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanenitrile,
163A or 163B	(2R)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanenitrile OR (2S)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanenitrile,
164	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
165	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-6-ol,
166	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-methoxy-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
167	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-methoxy-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
168	(1S)-6-methoxy-1-(2-methylpropyl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
169	1-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propan-2-one,
170A or 170B	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-3-fluoro-2-methylpropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-3-fluoro-2-methylpropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
171A or 171B	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-3-fluoro-2-methylpropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-3-fluoro-2-methylpropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
172	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(3,3,3-trifluoro-2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
173	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(prop-2-yn-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
174	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
175	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2,2-difluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
176	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(cyclohexylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
177	(1S)-6-chloro-1-(cyclohexylmethyl)-2-[4-(difluoromethyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

Cpd	Name
178	(1S)-6-chloro-1-(cyclohexylmethyl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
179	(1S)-6-chloro-1-(cyclohexylmethyl)-2-[4-(4-methylpiperazin-1-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
180	6-chloro-1-(cyclohexylmethyl)-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
181	6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
182	6-chloro-1-(cyclobutylmethyl)-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
183	6-chloro-1-(cyclopentylmethyl)-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
184	(1S)-6-chloro-1-(cyclopropylmethyl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
185	2-({(1S)-6-chloro-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}methyl)propane-1,3-diol,
187	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(3S)-oxan-3-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-8-amine,
188	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-methoxy-1-{{(3S)-oxan-3-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
189	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-methoxy-1-{{(3R)-oxan-3-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
190	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-methoxy-1-{{(3S)-oxan-3-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
191A and 191B	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,4-dioxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,4-dioxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
192	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(2R)-1,4-dioxan-2-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
193	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(2S)-1,4-dioxan-2-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
194A and 194B	(4S)-4-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}methyl)-1,3-dioxolane-2-thione AND (4R)-4-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}methyl)-1,3-dioxolane-2-thione,
195A and 195B	(4R)-4-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}methyl)-1,3-dioxolane-2-thione AND (4S)-4-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}methyl)-1,3-dioxolane-2-thione,
196	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxolan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
197A and 197B	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(4R)-1,3-dioxolan-4-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(4S)-1,3-dioxolan-4-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

Cpd	Name
198A and 198B	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(4S)-1,3-dioxolan-4-yl)methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(4R)-1,3-dioxolan-4-yl)methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
199A and 199B	(4S)-4-[[{(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl]-1,3-dioxolan-2-one AND (4R)-4-[[{(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl]-1,3-dioxolan-2-one,
200A and 200B	(4R)-4-[[{(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl]-1,3-dioxolan-2-one AND (4S)-4-[[{(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl]-1,3-dioxolan-2-one,
201	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxolan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
202	6-chloro-1-[(1,3-dioxolan-2-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
203	6-chloro-1-(2,2-dimethoxyethyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
204	6-chloro-1-(2-methoxypropyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
205	(1S)-6-chloro-1-(3-methoxybutyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
206	methyl 3-{6-chloro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propanoate,
207A or 207B	(1S)-6-chloro-1-[[{(3R)-oxan-3-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-6-chloro-1-[[{(3S)-oxan-3-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
208A or 208B	(1S)-6-chloro-1-[[{(3S)-oxan-3-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-6-chloro-1-[[{(3R)-oxan-3-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
209A or 209B	(1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-[[{(3R)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-[[{(3S)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
210A or 210B	(1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-[[{(3S)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-[[{(3R)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
211	(1S)-6-chloro-2-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]-1-[[{(3S)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
212	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(oxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
213A and 213B	(S)-2-(4,6-bis(trifluoromethyl)pyrimidin-2-yl)-6-chloro-1-(((R)-tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (S)-2-(4,6-bis(trifluoromethyl)pyrimidin-2-yl)-6-chloro-1-(((S)-tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

Cpd	Name
214	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[[{(3R)-oxan-3-yl]methyl}]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
215	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[[{(3S)-oxan-3-yl]methyl}]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
216	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(oxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
217A and 217B	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(oxolan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(oxolan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
218	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-methoxy-1-[[{(3S)-oxan-3-yl]methyl}]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
219A and 219B	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(1,4-dioxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(1,4-dioxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
220	2-({(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}methyl)propane-1,3-diol,
221	(1S)-6-chloro-1-(2-methylpropyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
222	(1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
223	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
224	2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
225	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-bromo-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
226	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-propyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
227	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-1-butyl-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
228	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(cyclopropylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
229	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(cyclobutylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
230	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(cyclopentylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
231	6-chloro-1-(cyclopentylmethyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
232	1-(but-3-en-1-yl)-6-chloro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
233	6-chloro-1-[(3Z)-hex-3-en-1-yl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
234	(1S)-6-chloro-1-[(cyclopent-2-en-1-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
236	3-({6-chloro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}methyl)piperidin-2-one,

Cpd	Name
237	(1S)-6-chloro-1-(cyclohexylmethyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
238	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(cyclohexylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
239	6-chloro-1-(cyclohexylmethyl)-7-fluoro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
240	6-chloro-1-(cyclopentylmethyl)-7-fluoro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
241	6-chloro-1-(cyclopropylmethyl)-7-fluoro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
242	6-chloro-1-(cyclobutylmethyl)-7-fluoro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
243	6-chloro-7-fluoro-1-[(oxan-4-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
244	(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
245	(1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
246	(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
247	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
248	(1S)-6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
249	(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-(4-methylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
250	(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-(4-ethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
251	(1S)-6-chloro-2-(4-ethylpyrimidin-2-yl)-1-[(3S)-oxan-3-ylmethyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
252	(1S)-6-chloro-2-(4-methylpyrimidin-2-yl)-1-[(3S)-oxan-3-ylmethyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
253	6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-[(oxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
254	(1S)-6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-[(3S)-oxan-3-ylmethyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
255	(1S)-6-chloro-2-(5-fluoro-4,6-dimethylpyrimidin-2-yl)-1-[(3S)-oxan-3-ylmethyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
256	(1S)-6-chloro-2-(5-fluoro-4-methylpyrimidin-2-yl)-1-[(3S)-oxan-3-ylmethyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
257	(1S)-6-chloro-2-(5-fluoropyrimidin-2-yl)-1-[(3S)-oxan-3-ylmethyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
258	6-chloro-2-(4-chloropyrimidin-2-yl)-7-fluoro-1-[(oxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
259	(1S)-6-chloro-2-(4,6-dimethoxypyrimidin-2-yl)-1-[(3S)-oxan-3-ylmethyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
260	(1S)-2-[4,6-bis(difluoromethoxy)pyrimidin-2-yl]-6-chloro-1-[(3S)-oxan-3-ylmethyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

Cpd	Name
261	2-[4,6-bis(difluoromethoxy)pyrimidin-2-yl]-6-chloro-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
262	6-chloro-7-fluoro-1-(2-methylpropyl)-2-(pyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
263	6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
264	6-chloro-1-(cyclopropylmethyl)-2-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
265	6-chloro-1-(cyclobutylmethyl)-2-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
266	6-chloro-1-(cyclopentylmethyl)-2-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
267	6-chloro-1-(cyclohexylmethyl)-2-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
268	2-[(1S)-6-chloro-1-[(3S)-oxan-3-yl]methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl]pyrimidine-4-carbonitrile,
269	2-[(1S)-6-chloro-1-[(3S)-oxan-3-yl]methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl]-5-fluoropyrimidine-4-carbonitrile,
270	(1S)-6-chloro-2-[4-methoxy-6-(trifluoromethyl)pyrimidin-2-yl]-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
271	(1S)-6-chloro-2-[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
272	(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
273	(1S)-6-chloro-2-[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
274	6-chloro-2-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
275	(1S)-6-chloro-2-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
276	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-8-iodo-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
277	diethyl ((2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)propanedioate,
278	diethyl ((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)propanedioate,
279	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(cyclopent-2-en-1-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
280	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-ethenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
281	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1E)-prop-1-en-1-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
282	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
283	(1S)-6-chloro-2-[4-(difluoromethyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
284	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

Cpd	Name
285	(1S)-6-chloro-1-(2-methylprop-1-en-1-yl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
286	(1S)-6-chloro-1-(2-methylprop-1-en-1-yl)-2-[4-(methylsulfanyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
287	(1S)-6-chloro-2-[4-(4-methylpiperazin-1-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
288	(2E)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylprop-2-en-1-ol,
289	2-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methylidene)propane-1,3-diol,
290	methyl (2E)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylprop-2-enoate,
291	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxan-4-ylidene)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
292	2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(cyclohexylidenemethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
293	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(cyclohexylidenemethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
294	6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
295	(1S)-6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
296	(1S)-6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
297	(1R)-6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
298	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
299	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
300	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
301	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-1-(2-methylpropyl)-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
302	(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-1-(2-methylpropyl)-6-(4-methyl-2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
303	(1S)-1-(2-methylpropyl)-6-(2H-1,2,3-triazol-2-yl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
304	(1S)-1-(2-methylprop-1-en-1-yl)-6-(2H-1,2,3-triazol-2-yl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
305	(1S)-1-(2-methylprop-1-en-1-yl)-6-(1H-1,2,3-triazol-1-yl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
306	(1S)-1-(2-methylpropyl)-6-(1H-1,2,3-triazol-1-yl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
307	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylprop-1-en-1-yl)-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
308	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylprop-1-en-1-yl)-6-(4-methyl-2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

Cpd	Name
309	(1S)-6-chloro-1-(2-methylprop-1-en-1-yl)-2-[4-(morpholin-4-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
310	(1S)-6-chloro-1-(2-methylpropyl)-2-[4-(morpholin-4-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
311	(1S)-6-chloro-1-(cyclopentylmethyl)-2-[4-(morpholin-4-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
312	(1S)-6-chloro-1-(cyclohexylmethyl)-2-[4-(morpholin-4-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
313	(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3R)-3,6-dihydro-2H-pyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
314	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3R)-3,6-dihydro-2H-pyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
315	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3S)-3,6-dihydro-2H-pyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
316A or 316B	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-3,6-dihydro-2H-pyran-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-3,6-dihydro-2H-pyran-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
317A or 317B	(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-3,6-dihydro-2H-pyran-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-3,6-dihydro-2H-pyran-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
318	methyl (2E)-4-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}but-2-enoate,
319	methyl (2Z)-4-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}but-2-enoate,
320	(1S)-6-chloro-1-(2-methylpropyl)-2-[2-(trifluoromethyl)pyrimidin-4-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
321	6-chloro-2-(2-chloropyrimidin-4-yl)-1-(cyclopentylmethyl)-7-fluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
322	(1S)-6-chloro-2-[2-methoxy-6-(trifluoromethyl)pyrimidin-4-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
323	(1S)-6-chloro-2-[2-methoxy-6-(trifluoromethyl)pyrimidin-4-yl]-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
324	(1S)-6-chloro-2-[2-methoxy-6-(trifluoromethyl)pyrimidin-4-yl]-1-[(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
325	(1S)-6-chloro-1-[(oxan-4-yl)methyl]-2-[4-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
326	(1S)-6-chloro-1-[(3S)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
327	(1S)-6-chloro-1-[(3R)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
328	(1S)-6-chloro-1-[(oxan-4-yl)methyl]-2-[6-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
329	(1S)-6-chloro-1-(2-methylpropyl)-2-[6-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
330	(1S)-6-chloro-1-(2-methylpropyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

Cpd	Name
331	(1S)-6-chloro-2-(2-methyl-2H-tetrazol-5-yl)-1-[[{(3S)-oxan-3-yl]methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
332	(1S)-6-chloro-1-[[{(3S)-oxan-3-yl]methyl}-2-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
333	(1S)-6-chloro-1-[[{(3R)-oxan-3-yl]methyl}-2-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
334	(1S)-6-chloro-1-[[{(3S)-oxan-3-yl]methyl}-2-[3-(trifluoromethyl)-1,2,4-thiadiazol-5-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
335	(1S)-6-chloro-1-[[{(3R)-oxan-3-yl]methyl}-2-[3-(trifluoromethyl)-1,2,4-thiadiazol-5-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
336	(1S)-6-chloro-1-(2-methylpropyl)-2-[3-(trifluoromethyl)-1,2,4-thiadiazol-5-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
337	(1S)-6-chloro-1-(2-methylpropyl)-2-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
338	(1S)-6-chloro-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
339	(1S)-6-chloro-2-[5-(difluoromethyl)-1,2,4-oxadiazol-3-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
340	6-chloro-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,2,4-triazin-3-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole, and
341	6-chloro-7-fluoro-1-(2-methylprop-1-en-1-yl)-2-(pyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

[0106] wherein the form of the compound is selected from the group consisting of a free acid, free base, salt, hydrate, solvate, anhydrous, racemate, enantiomer, diastereomer, stereoisomer, and tautomer thereof.

[0107] One aspect provided herein is a pharmaceutical composition comprising a compound of Formula (I) or a form thereof, and a pharmaceutically acceptable excipient.

[0108] One aspect provided herein is a use of a compound of Formula (I), or a form thereof, or pharmaceutical composition thereof, to treat or ameliorate a disease or disorder by inhibiting dihydroorotate dehydrogenase.

[0109] Another aspect provided herein is a use of a compound of Formula (I), or a form thereof, to treat or ameliorate a disease or disorder by inhibiting dihydroorotate dehydrogenase.

[0110] Another aspect provided herein is a use of a pharmaceutical composition comprising a compound of Formula (I), or a form thereof, and a pharmaceutically acceptable excipient to treat or ameliorate a disease or disorder by inhibiting dihydroorotate dehydrogenase.

[0111] One aspect provided herein is a method of use of a compound of Formula (I), or a form thereof, or pharmaceutical composition thereof to treat or ameliorate a disease or disorder in a subject in need thereof comprising, administering to the subject an effective

amount of the compound of Formula (I), or a form thereof, or pharmaceutical composition thereof to inhibit dihydroorotate dehydrogenase.

[0112] Another aspect provided herein is a method of use of a compound of Formula (I), or a form thereof, to treat or ameliorate a disease or disorder in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I), or a form thereof, to inhibit dihydroorotate dehydrogenase.

[0113] Another aspect provided herein is a method of use of a pharmaceutical composition comprising a compound of Formula (I), or a form thereof, and a pharmaceutically acceptable excipient to treat or ameliorate a disease or disorder in a subject in need thereof comprising, administering to the subject an effective amount of the pharmaceutical composition to inhibit dihydroorotate dehydrogenase.

DEFINITIONS

[0114] The chemical terms used above and throughout the description herein, unless specifically defined otherwise, shall be understood by one of ordinary skill in the art to have the following indicated meanings.

[0115] As used herein, the term “C₁₋₄alkyl”, “C₁₋₆alkyl”, or “C₁₋₈alkyl” generally refers to saturated hydrocarbon radicals having from one to eight carbon atoms in a straight or branched chain configuration, including, but not limited to, methyl, ethyl, n-propyl (also referred to as propyl or propanyl), isopropyl, n-butyl (also referred to as butyl or butanyl), isobutyl, sec-butyl, tert-butyl, n-pentyl (also referred to as pentyl or pentanyl), n-hexyl (also referred to as hexyl or hexanyl), n-heptyl (also referred to as heptyl or heptanyl), n-octyl (also referred to as octyl or octanyl) and the like. A C₁₋₄alkyl, C₁₋₆alkyl, or C₁₋₈alkyl radical is optionally substituted with substituent species as described herein, where allowed by available valences.

[0116] As used herein, the term “C₁₋₄alkenyl”, “C₁₋₆alkenyl”, or “C₁₋₈alkenyl” generally refers to partially unsaturated hydrocarbon radicals having from two to eight carbon atoms in a straight or branched chain configuration and one or more carbon-carbon double bonds therein, including, but not limited to, methylenedene, ethenyl (also referred to as vinyl), allyl, propenyl and the like. A C₁₋₄alkenyl, C₁₋₆alkenyl, or C₁₋₈alkenyl radical is optionally substituted with substituent species as described herein, where allowed by available valences.

[0117] As used herein, the term “C₂₋₄alkynyl”, “C₂₋₆alkynyl”, or “C₂₋₈alkynyl” generally refers to partially unsaturated hydrocarbon radicals having from two to eight carbon atoms in a straight or branched chain configuration and one or more carbon-carbon triple bonds

therein, including, but not limited to, ethynyl, propynyl and the like. A C₂₋₄alkynyl, C₂₋₆alkynyl, or C₂₋₈alkynyl radical is optionally substituted with substituent species as described herein, where allowed by available valences.

[0118] As used herein, the term “C₁₋₄alkoxy”, “C₁₋₆alkoxy”, or “C₁₋₈alkoxy” generally refers to saturated hydrocarbon radicals having from one to eight carbon atoms in a straight or branched chain configuration of the formula: -O-C₁₋₄alkyl, -O-C₁₋₆alkyl, -O-C₁₋₈alkyl, including, but not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like. A C₁₋₄alkoxy, C₁₋₆alkoxy, C₁₋₈alkoxy radical is optionally substituted with substituent species as described herein, where allowed by available valences.

[0119] As used herein, the term “C₃₋₈cycloalkyl” generally refers to a saturated monocyclic, bicyclic or polycyclic hydrocarbon ring system radical, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. In certain aspects, C₃₋₈cycloalkyl includes, but is not limited to C₃cycloalkyl, C₄cycloalkyl, C₅-cycloalkyl and the like. A C₃₋₈cycloalkyl ring system radical is optionally substituted with substituent species as described herein, where allowed by available valences.

[0120] As used herein, the term “(C₃₋₈cycloalkyl)C₁₋₈alkyl” refers to a radical of the formula: -C₁₋₈alkyl-C₃₋₈cycloalkyl. In certain aspects, (C₃₋₈cycloalkyl)C₁₋₈alkyl includes but is not limited to (C₃₋₈cycloalkyl)methyl and the like. The C₃₋₈cycloalkyl portion of (C₃₋₈cycloalkyl)C₁₋₈alkyl is optionally substituted with substituent species as described herein, where allowed by available valences.

[0121] As used herein, the term “C₃₋₈cycloalkenyl” generally refers to a partially unsaturated monocyclic, bicyclic or polycyclic hydrocarbon ring system radical, including, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. In certain aspects, C₃₋₈cycloalkenyl includes, but is not limited to C₃cycloalkenyl, C₄cycloalkenyl, C₅-cycloalkenyl and the like. A C₃₋₈cycloalkenyl ring system radical is optionally substituted with substituent species as described herein, where allowed by available valences.

[0122] As used herein, the term “aryl” generally refers to a monocyclic, bicyclic or polycyclic aromatic carbon atom ring system radical, including, but not limited to, phenyl, naphthyl, anthracenyl, fluorenyl, azulenyl, phenanthrenyl and the like. In certain aspects, the aryl monocyclic, or bicyclic ring system radical is phenyl, or naphthyl, respectively. An aryl ring system radical is optionally substituted with substituent species as described herein where allowed by available valences.

[0123] As used herein, the term “heteroaryl” generally refers to an aromatic ring system selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members, wherein the ring members are independently selected from C (carbon), N (nitrogen), O (oxygen), or S (sulfur); and, wherein one or more ring members may be selected from one or more N, O or S, where allowed by structural stability, with the remaining ring members selected from C. In certain aspects, a heteroaryl ring system radical may be optionally substituted on a C or N ring member with one, two, or three substituents where allowed by available valences. In certain aspects, the term “heteroaryl” may refer to a monocyclic ring having 5 to 8 ring members or a bicyclic ring having from 9 to 10 ring members; wherein heteroaryl may be optionally substituted with one, two, or three substituents where allowed by available valences.

[0124] In certain aspects, a heteroaryl radical may include a ring system radical such as, but not limited to, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, 1,3-thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, 1,2,3,4-*2H*-tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, indolyl, indazolyl, indolizynyl, isoindolyl and the like.

[0125] In certain aspects, the nomenclature for a heteroaryl radical may differ, such as in non-limiting examples where furanyl may also be referred to as furyl, thienyl may also be referred to as thiophenyl, and pyridinyl may also be referred to as pyridyl.

[0126] In certain aspects, the term for a heteroaryl radical may also include other regioisomers, such as in non-limiting examples where the term pyrrolyl may also include *1H*-pyrrolyl, *2H*-pyrrolyl, *3H*-pyrrolyl and the like; the term pyrazolyl may also include *1H*-pyrazolyl and the like; the term imidazolyl may also include *1H*-imidazolyl and the like; the term triazolyl may also include *1H*-1,2,3-triazolyl, *2H*-1,2,3-triazolyl, 1,2,4-triazolyl and the like; the term oxadiazolyl may also include 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl and the like; the term thiadiazolyl may also include 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl and the like; the term tetrazolyl may also include *1H*-tetrazolyl, *2H*-tetrazolyl, 1,2,3,4-*2H*-tetrazolyl and the like; the term indolyl may also include *1H*-indolyl and the like; the term indazolyl may also include *1H*-indazolyl, *2H*-indazolyl and the like; the term triazinyl may also include 1,2,4-*1H*-triazinyl, 1,3,5-*1H*-triazinyl, 2,4,6-*1H*-triazinyl and the like; the term benzoimidazolyl may also include *1H*-benzoimidazolyl; and the term purinyl may also include *9H*-purinyl and the like.

[0127] As used herein, the term “heterocyclyl” generally refers to a saturated or partially unsaturated monocyclic ring system having 3-7 ring members, a bicyclic ring system having

6-10 ring members, a bicyclic ring system having 7 or 8 ring members or a polycyclic ring system having 13-16 ring members, wherein the ring members are independently selected from C (carbon), N (nitrogen), O (oxygen), or S (sulfur), wherein one or more ring members may be selected from one or more N, O or S, where allowed by structural stability, with the remaining ring members selected from C. In certain aspects, a heterocyclyl ring system radical may be optionally substituted on a C or N ring member with one, two, or three substituents where allowed by available valences.

[0128] In certain aspects, the term “heterocyclyl” may refer to a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; wherein heterocyclyl may be optionally substituted with one, two, or three substituents where allowed by available valences.

[0129] In certain aspects, a heterocyclyl radical may include a ring system radical such as, but not limited to, oxiranyl, oxetanyl, azetidiny, tetrahydrofuranyl, pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, isoxazolinyl, isoxazolidinyl, isothiazolinyl, isothiazolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, triazolinyl, triazolidinyl, oxadiazolinyl, oxadiazolidinyl, thiadiazolinyl, thiadiazolidinyl, tetrazolinyl, tetrazolidinyl, pyranyl, 2*H*-pyranyl, dihydro-2*H*-pyranyl, tetrahydro-2*H*-pyranyl, thiopyranyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, 1,2,5,6-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,4-diazepanyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl, 2,3-dihydro-1,4-benzodioxinyl, hexahydropyrrolo-[3,4-*b*]pyrrol-(1*H*)-yl, (3*aS*,6*aS*)hexahydropyrrolo-[3,4-*b*]pyrrol-(1*H*)-yl, (3*aR*,6*aR*)hexahydropyrrolo-[3,4-*b*]pyrrol-(1*H*)-yl, hexahydropyrrolo-[3,4-*b*]pyrrol-(2*H*)-yl, (3*aS*,6*aS*)hexahydropyrrolo-[3,4-*b*]pyrrol-(2*H*)-yl, (3*aR*,6*aR*)hexahydropyrrolo-[3,4-*b*]pyrrol-(2*H*)-yl, hexahydropyrrolo-[3,4-*c*]pyrrol-(1*H*)-yl, (3*aR*,6*aS*)hexahydropyrrolo-[3,4-*c*]pyrrol-(1*H*)-yl, (3*aR*,6*aR*)hexahydropyrrolo-[3,4-*c*]pyrrol-(1*H*)-yl, octahydro-5*H*-pyrrolo[3,2-*c*]pyridinyl, octahydro-6*H*-pyrrolo[3,4-*b*]pyridinyl, (4*aR*,7*aR*)octahydro-6*H*-pyrrolo[3,4-*b*]pyridinyl, (4*aS*,7*aS*)octahydro-6*H*-pyrrolo[3,4-*b*]pyridinyl, hexahydropyrrolo[1,2-*a*]pyrazin-(1*H*)-yl, (7*R*,8*aS*)hexahydropyrrolo-[1,2-*a*]pyrazin-(1*H*)-yl, (8*aS*)hexahydropyrrolo-[1,2-*a*]pyrazin-(1*H*)-yl, (8*aR*)hexahydropyrrolo-[1,2-*a*]pyrazin-(1*H*)-yl, (8*aS*)octahydropyrrolo-[1,2-*a*]pyrazin-(1*H*)-yl, (8*aR*)octahydropyrrolo-[1,2-*a*]pyrazin-(1*H*)-yl, hexahydropyrrolo-[1,2-*a*]pyrazin-(2*H*)-one,

octahydro-2*H*-pyrido[1,2-*a*]pyrazinyl, 3-azabicyclo[3.1.0]hexyl, (1*R*,5*S*)-3-azabicyclo[3.1.0]hexyl, 3-oxa-8azabicyclo[3.2.1]-octanyl, 8-azabicyclo[3.2.1]octyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]octyl, 8-azabicyclo[3.2.1]oct-2-enyl, (1*R*,5*S*)-8-azabicyclo[3.2.1]oct-2-enyl, 9-azabicyclo[3.3.1]nonyl, (1*R*,5*S*)-9-azabicyclo[3.3.1]nonyl, 2,5-diazabicyclo[2.2.1]heptyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, (1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptanyl, (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptanyl, (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptyl, 2,5-diazabicyclo[2.2.2]octyl, 3,8-diazabicyclo[3.2.1]octyl, (1*R*,5*S*)-3,8-diazabicyclo[3.2.1]octyl, 1,4-diazabicyclo[3.2.2]nonyl, 4,7-diazaspiro[2.5]-octanyl, azaspiro[3.3]heptyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptyl, 2,7-diazaspiro[3.5]nonyl, 5,8-diazaspiro[3.5]nonyl, 2,7-diazaspiro[4.4]nonyl, 6,9-diazaspiro[4.5]decyl and the like.

[0130] In certain aspects, a heterocyclyl radical may also include other regioisomers, including non-limiting examples where the term pyranyl may also include 2*H*-pyranyl, 3,6-dihydro-2*H*-pyranyl, tetrahydro-2*H*-pyranyl, oxanyl, and the like; the term tetrahydrofuranlyl may also include oxolanyl and the like; the term 1,3-dioxolanyl may also include 1,3-dioxanyl; the term triazolyl may also include 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1,2,4-triazolyl and the like; the term oxadiazolyl may also include 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl and the like; the term thiadiazolyl may also include 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl and the like; the term tetrazolyl may also include 1*H*-tetrazolyl, 2*H*-tetrazolyl, 1,2,3,4-2*H*-tetrazolyl and the like; the term indolyl may also include 1*H*-indolyl and the like; the term indazolyl may also include 1*H*-indazolyl, 2*H*-indazolyl and the like; the term triazinyl may also include 1*H*-1,2,4-triazinyl, 1*H*-2,4,6-triazinyl and the like; the term benzoimidazolyl may also include 1*H*-benzoimidazolyl; and the term purinyl may also include 9*H*-purinyl and the like.

[0131] As used herein, the term “C₁-salkoxycarbonyl,” “(C₁-salkoxycarbonyl),” or “(C₁-salkoxy)carbonyl” refers to a radical of the formula: -C(=O)-O-C₁-salkyl. In certain aspects, C₁-salkoxycarbonyl includes, but is not limited to methoxycarbonyl and the like.

[0132] As used herein, the term “C₁-salkylcarbonyloxy” refers to a radical of the formula: -O-C(=O)-C₁-salkyl. In certain aspects, C₁-salkylcarbonyloxy includes, but is not limited to methylcarbonyloxy and the like.

[0133] As used herein, the term “C₁-salkylthio” refers to a radical of the formula: -S-C₁-salkyl. C₁-salkylthio includes but is not limited to methylthio and the like.

[0134] As used herein, the term “aminocarbonyl” refers to a radical of the formula: -C(=O)-NH_2 .

[0135] As used herein, the term “carbonyl” refers to a radical of the formula: -C(=O)- , wherein C(=O) is a linking structure having additional atoms attached to the carbon atom.

[0136] As used herein, the term “carboxy” refers to a radical of the formula: -C(=O)-OH .

[0137] As used herein, the term “cyano” refers to a radical of the formula: $\text{-C}\equiv\text{N}$, or -CN .

[0138] As used herein, the term “halo” or “halogen” generally refers to a halogen atom radical, including fluoro, chloro, bromo and iodo.

[0139] As used herein, the term “hydroxy” refers to a radical of the formula: -OH .

[0140] As used herein, the term “nitro” refers to a radical of the formula: -NO_2 .

[0141] As used herein, the term “oxo” refers to a radical of the formula: =O .

[0142] As used herein, the term “thiocarbonyl” refers to a radical of the formula: -C(=S)- .

[0143] As used herein, the term “substituent” means positional variables on the atoms of a core molecule that are substituted at a designated atom position, replacing one or more hydrogens on the designated atom, provided that the designated atom’s normal valency is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. A person of ordinary skill in the art should note that any carbon as well as heteroatom with valences that appear to be unsatisfied as described or shown herein is assumed to have a sufficient number of hydrogen atom(s) to satisfy the valences described or shown. In certain instances one or more substituents having a double bond (e.g., “oxo” or “=O”) as the point of attachment may be described, shown or listed herein within a substituent group, wherein the structure may only show a single bond as the point of attachment to the core structure of Formula (I). A person of ordinary skill in the art would understand that, while only a single bond is shown, a double bond is intended for those substituents.

[0144] As used herein, the term “and the like,” with reference to the definitions of chemical terms provided herein, means that variations in chemical structures that could be expected by one skilled in the art include, without limitation, isomers (including chain, branching or positional structural isomers), hydration of ring systems (including saturation or partial unsaturation of monocyclic, bicyclic or polycyclic ring structures) and all other variations where allowed by available valences which result in a stable compound.

[0145] For the purposes of this description, where one or more substituent variables for a compound of Formula (I) or a form thereof encompass functionalities incorporated into a

compound of Formula (I), each functionality appearing at any location within the disclosed compound may be independently selected, and as appropriate, independently and/or optionally substituted.

[0146] As used herein, the terms “independently selected,” or “each selected” refer to functional variables in a substituent list that may occur more than once on the structure of Formula (I), the pattern of substitution at each occurrence is independent of the pattern at any other occurrence. Further, the use of a generic substituent variable on any formula or structure for a compound described herein is understood to include the replacement of the generic substituent with species substituents that are included within the particular genus, *e.g.*, aryl may be replaced with phenyl or naphthalenyl and the like, and that the resulting compound is to be included within the scope of the compounds described herein.

[0147] As used herein, the term “optionally substituted” means optional substitution with the specified substituent variables, groups, radicals or moieties.

COMPOUND FORMS

[0148] As used herein, the term “form” means a compound of Formula (I) having a form selected from the group consisting of a free acid, free base, salt, hydrate, solvate, anhydrous, racemate, enantiomer, diastereomer, stereoisomer, and tautomer thereof.

[0149] In certain aspects described herein, the form of the compound of Formula (I) is a free acid, free base or salt thereof.

[0150] In certain aspects described herein, the form of the compound of Formula (I) is a salt thereof.

[0151] In certain aspects described herein, the form of the compound of Formula (I) is a hydrate, solvate, or anhydrous form thereof.

[0152] In certain aspects described herein, the form of the compound of Formula (I) is a stereoisomer, racemate, enantiomer or diastereomer thereof.

[0153] In certain aspects described herein, the form of the compound of Formula (I) is a tautomer thereof.

[0154] In certain aspects described herein, the form of the compound of Formula (I) is a pharmaceutically acceptable form.

[0155] In certain aspects described herein, the compound of Formula (I) or a form thereof is isolated for use.

[0156] As used herein, the terms “dihydroorotate dehydrogenase inhibition” or “DHODH inhibition” refer to inhibition of pyrimidine synthesis via the *de novo* pathway in the presence of a DHODH inhibitor such as those compounds disclosed herein.

[0157] As used herein, the term “isolated” means the physical state of a compound of Formula (I) or a form thereof after being isolated and/or purified from a synthetic process (*e.g.*, from a reaction mixture) or natural source or combination thereof according to an isolation or purification process or processes described herein or which are well known to the skilled artisan (*e.g.*, chromatography, recrystallization and the like) in sufficient purity to be characterized by standard analytical techniques described herein or well known to the skilled artisan.

[0158] As used herein, the term “protected” means that a functional group in a compound of Formula (I) or a form thereof is in a form modified to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T.W. Greene *et al.*, *Protective Groups in organic Synthesis* (1991), Wiley, New York. Such functional groups include hydroxy, phenol, amino and carboxylic acid. Suitable protecting groups for hydroxy or phenol include trialkylsilyl or diarylalkylsilyl (*e.g.*, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, substituted benzyl, methyl, methoxymethanol, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or arylalkyl esters. In certain instances, the protecting group may also be a polymer resin, such as a Wang resin or a 2-chlorotrityl-chloride resin. Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. It will also be appreciated by those skilled in the art, although such protected derivatives of compounds described herein may not possess pharmacological activity as such, they may be administered to a subject and thereafter metabolized in the body to form compounds described herein which are pharmacologically active. Such derivatives may therefore be described as “prodrugs”. All prodrugs of compounds described herein are included within the scope of the use described herein.

[0159] As used herein, the term “prodrug” means a form of an instant compound (*e.g.*, a drug precursor) that is transformed *in vivo* to yield an active compound of Formula (I) or a form thereof. The transformation may occur by various mechanisms (*e.g.*, by metabolic and/or non-metabolic chemical processes), such as, for example, by hydrolysis and/or metabolism in

blood, liver and/or other organs and tissues. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

[0160] In one example, when a compound of Formula (I) or a form thereof contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a functional group such as alkyl and the like. In another example, when a compound of Formula (I) or a form thereof contains a hydroxyl functional group, a prodrug form can be prepared by replacing the hydrogen atom of the hydroxyl with another functional group such as alkyl, alkylcarbonyl or a phosphonate ester and the like. In another example, when a compound of Formula (I) or a form thereof contains an amine functional group, a prodrug form can be prepared by replacing one or more amine hydrogen atoms with a functional group such as alkyl or substituted carbonyl.

Pharmaceutically acceptable prodrugs of compounds of Formula (I) or a form thereof include those compounds substituted with one or more of the following groups: carboxylic acid esters, sulfonate esters, amino acid esters, phosphonate esters and mono-, di- or triphosphate esters or alkyl substituents, where appropriate. As described herein, it is understood by a person of ordinary skill in the art that one or more of such substituents may be used to provide a compound of Formula (I) or a form thereof as a prodrug.

[0161] One or more compounds described herein may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and the description herein is intended to embrace both solvated and unsolvated forms.

[0162] As used herein, the term "solvate" means a physical association of a compound described herein with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. As used herein, "solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like.

[0163] As used herein, the term "hydrate" means a solvate wherein the solvent molecule is water.

[0164] As used herein, the term "anhydrous" means a form of one or more compounds having a crystal form free of water.

[0165] The compounds of Formula (I) can form salts, which are intended to be included within the scope of this description. Reference to a compound of Formula (I) or a form thereof herein is understood to include reference to salt forms thereof, unless otherwise indicated. The term “salt(s)”, as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula (I) or a form thereof contains both a basic moiety, such as, without limitation an amine moiety, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions (“inner salts”) may be formed and are included within the term “salt(s)” as used herein.

[0166] The term “pharmaceutically acceptable salt(s)”, as used herein, means those salts of compounds described herein that are safe and effective (*i.e.*, physiologically acceptable) for use in mammals and that possess biological activity, although other salts are also useful. Salts of the compounds of the Formula (I) may be formed, for example, by reacting a compound of Formula (I) or a form thereof with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0167] Pharmaceutically acceptable salts include one or more salts of acidic or basic groups present in compounds described herein. Particular aspects of acid addition salts include, and are not limited to, acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, bitartrate, borate, bromide, butyrate, chloride, citrate, camphorate, camphorsulfonate, ethanesulfonate, formate, fumarate, gentisinate, gluconate, glucuronate, glutamate, iodide, isonicotinate, lactate, maleate, methanesulfonate, naphthalenesulfonate, nitrate, oxalate, pamoate, pantothenate, phosphate, propionate, saccharate, salicylate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate (also known as tosylate), trifluoroacetate salts and the like. Certain particular aspects of acid addition salts include chloride, bromide or dichloride.

[0168] Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33, 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

[0169] Suitable basic salts include, but are not limited to, aluminum, ammonium, calcium, lithium, magnesium, potassium, sodium and zinc salts.

[0170] All such acid salts and base salts are intended to be included within the scope of pharmaceutically acceptable salts as described herein. In addition, all such acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of this description.

[0171] Compounds of Formula (I) and forms thereof, may further exist in a tautomeric form. All such tautomeric forms are contemplated and intended to be included within the scope of the compounds of Formula (I) or a form thereof as described herein.

[0172] The compounds of Formula (I) or a form thereof may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. The present description is intended to include all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures.

[0173] The compounds described herein may include one or more chiral centers, and as such may exist as racemic mixtures (*R/S*) or as substantially pure enantiomers and diastereomers. The compounds may also exist as substantially pure (*R*) or (*S*) enantiomers (when one chiral center is present). In one particular aspect, the compounds described herein are (*S*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*S*) isomer. In another particular aspect, the compounds described herein are (*R*) isomers and may exist as enantiomerically pure compositions substantially comprising only the (*R*) isomer. As one of skill in the art will recognize, when more than one chiral center is present, the compounds described herein may also exist as a (*R,R*), (*R,S*), (*S,R*) or (*S,S*) diastereomeric isomer or mixture of isomers, as defined by *IUPAC* Nomenclature Recommendations.

[0174] As used herein, the term “substantially pure” refers to compounds consisting substantially of a single isomer in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100% of the single isomer.

[0175] In one aspect of the description, a compound of Formula (I) or a form thereof that is a substantially pure single isomer may exhibit stronger activity than the other substantially pure isomer of the compound of Formula (I) or the racemic mixture thereof.

[0176] In another aspect of the description, a compound of Formula (I) or a form thereof isolated as an enantiomeric or diastereomeric mixture, wherein the mixture thereof may or

may not be more active than a single isolated, substantially pure enantiomer or diastereomer of the compound of Formula (I).

[0177] In another aspect of the description, a compound of Formula (I) or a form thereof isolated as a diastereomeric mixture (having four possible diastereomers SS, RS, RR, SR), wherein each diastereomer in the mixture may have two chiral centers (each chiral center having two possible enantiomers: R or S). The diastereomer may be isolated by a single chiral center to provide a mixture of two diastereomers, wherein each diastereomer in the mixture may have one chiral center fixed and other chiral center may have two possible enantiomers: R or S (i.e., an enantiomeric diastereomer); and, wherein the mixture thereof may or may not be more active than a single isolated, substantially pure diastereomer of the compound of Formula (I).

[0178] In another aspect of the description, a compound of Formula (I) or a form thereof isolated as a racemic mixture having combinations of diastereomers, including four possible enantiomers or two possible diastereomers, wherein each mixture thereof may or may not be more active than a single isolated, substantially pure enantiomer or diastereomer of the compound of Formula (I).

[0179] As used herein, the term “racemate” refers to a 50/50 mixture of two compounds having asymmetric mirror images.

[0180] As used herein, the term “enantioenriched” refers to a mixture of two compounds having asymmetric mirror images that contains more than 50% of either of a pair of enantiomers.

[0181] In one aspect of the description, a compound of Formula (I) or a form thereof is a substantially pure (*S*) enantiomer form present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

[0182] In one aspect of the description, a compound of Formula (I) or a form thereof is a substantially pure (*R*) enantiomer form present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

[0183] In one aspect of the description, a compound of Formula (I) or a form thereof is a substantially pure enantiomer or diastereomer form present in an amount greater than or equal to 90%, in an amount greater than or equal to 92%, in an amount greater than or equal

to 95%, in an amount greater than or equal to 98%, in an amount greater than or equal to 99%, or in an amount equal to 100%.

[0184] In addition, the present description embraces all geometric and positional isomers. For example, if a compound of Formula (I) or a form thereof incorporates a double bond or a fused ring, both the *cis*- and *trans*-forms, as well as mixtures, are embraced within the scope of the description. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers and diastereomers can be separated by use of chiral HPLC column or other chromatographic methods known to those skilled in the art. Enantiomers can also be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (*e.g.*, substituted biaryls) and are considered as part of this description.

[0185] All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this description, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds described herein may, for example, be substantially free of other isomers, or may be present in a racemic mixture, as described *supra*.

[0186] Polymorphic crystalline and amorphous forms of the compounds of Formula (I) and of the salts, solvates, hydrates, esters and prodrugs of the compounds of Formula (I) are further intended to be included in the present description.

COMPOUND USES

[0187] An aspect of the present description relates to a method of use of a compound of Formula (I) or a form thereof for treating or ameliorating a disorder or condition by inhibiting dihydroorotate dehydrogenase (DHODH) in a subject in need thereof, comprising administering an effective amount of the compound of Formula (I), or a form thereof, to the

subject. Another aspect provided herein is a method of treating a disease or disorder amenable to dihydroorotate dehydrogenase inhibition using a compound of Formula (I), or a form thereof, or pharmaceutical composition thereof. Another aspect provided herein is a method of treating a disease or disorder amenable to dihydroorotate dehydrogenase inhibition in a subject in need thereof comprising administering to the subject an effective amount of a compound of Formula (I), or a form thereof, or pharmaceutical composition thereof.

[0188] In addition to use as a monotherapy, the instant compounds are useful in a combination therapy with current standard of agents, having additive or synergistic activity with one or more known agents. A combination therapy comprising compounds described herein in combination with one or more known drugs may be used to treat such disorders regardless of whether the disorder is responsive to the known drug.

[0189] Certain aspects of the present description include the use of a compound of Formula (I) or a form thereof in a combination therapy for treating or the disorder or condition in a subject in need thereof, comprising administering an effective amount of the compound of Formula (I) or a form thereof and an effective amount of one or more agent(s).

[0190] As used herein, the term “treating” refers to preventing a disease, disorder or condition from occurring in a subject that may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having the disease, disorder and/or condition.

[0191] As used herein, the term “ameliorating” refers to inhibiting a disease, disorder or condition, i.e., arresting the development thereof; and/or relieving a disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

[0192] As used herein, the term “subject” refers to an animal or any living organism having sensation and the power of voluntary movement, and which requires oxygen and organic food. In certain aspects, the subject is a mammal or a warm-blooded vertebrate animal. In other aspects, the subject is a human. As used herein, the term “patient” may be used interchangeably with “subject” and “human”.

[0193] As used herein, the terms “effective amount” or “therapeutically effective amount” mean an amount of compound of Formula (I) or a form, composition or medicament thereof that achieves a target plasma concentration that is effective in treating or ameliorating the disease or condition at issue as described herein and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect in a subject in need thereof. In one aspect, the effective amount may be the amount required to treat the disorder or condition in a subject or patient, more specifically, in a human.

DOSAGE AND ADMINISTRATION

[0194] One aspect provided herein is a use of a compound of Formula (I), or a form thereof, or pharmaceutical composition thereof, to treat or ameliorate a disease or disorder by inhibiting dihydroorotate dehydrogenase.

[0195] Another aspect provided herein is a use of a compound of Formula (I), or a form thereof, to treat or ameliorate a disease or disorder by inhibiting dihydroorotate dehydrogenase.

[0196] Another aspect provided herein is a use of a pharmaceutical composition comprising a compound of Formula (I), or a form thereof, and a pharmaceutically acceptable excipient to treat or ameliorate a disease or disorder by inhibiting dihydroorotate dehydrogenase.

[0197] One aspect provided herein is a method of use of a compound of Formula (I), or a form thereof, or pharmaceutical composition thereof to treat or ameliorate a disease or disorder in a subject in need thereof comprising, administering to the subject an effective amount of the compound of Formula (I), or a form thereof, or pharmaceutical composition thereof to inhibit dihydroorotate dehydrogenase.

[0198] Another aspect provided herein is a method of use of a compound of Formula (I), or a form thereof, to treat or ameliorate a disease or disorder in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I), or a form thereof, to inhibit dihydroorotate dehydrogenase.

[0199] Another aspect provided herein is a method of use of a pharmaceutical composition comprising a compound of Formula (I), or a form thereof, and a pharmaceutically acceptable excipient to treat or ameliorate a disease or disorder in a subject in need thereof comprising, administering to the subject an effective amount of the pharmaceutical composition to inhibit dihydroorotate dehydrogenase.

[0200] In one aspect, the methods of use of a compound of Formula (I), or a form thereof, to treat or ameliorate a disease or disorder in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I), or a form thereof, to inhibit dihydroorotate dehydrogenase, the compound of Formula (I), or a form or pharmaceutical composition thereof may be administered to a subject in need thereof by a variety of routes in amounts which result in a beneficial or therapeutic effect.

[0201] In one aspect, routes of administration include, but are not limited to, oral, intravenous, intradermal, intrathecal, intramuscular, subcutaneous, intranasal, inhalation, transdermal, topical, transmucosal, intracranial, epidural and intra-synovial.

[0202] In another aspect, the compound of Formula (I), or a form or pharmaceutical composition thereof may be orally administered to a subject in need thereof in an effective amount of a compound of Formula (I), or a form thereof, to inhibit dihydroorotate dehydrogenase, as provided herein.

[0203] In another aspect, the compound of Formula (I), or a form or pharmaceutical composition thereof may be administered orally, with or without food or water.

[0204] In another aspect, the compound of Formula (I), or a form or pharmaceutical composition thereof may be administered systemically (*e.g.*, parenterally) to a subject in need thereof.

[0205] In another aspect, the compound of Formula (I), or a form or pharmaceutical composition thereof may be administered via a route that permits the compound of Formula (I), or a form or pharmaceutical composition thereof to cross the blood-brain barrier (*e.g.*, orally).

[0206] In another aspect, the compound of Formula (I), or a form or pharmaceutical composition thereof may be administered in combination with one or more additional therapies that may be administered by the same route or a different route of administration.

[0207] In another aspect, the dosage and frequency of administration of the compound of Formula (I), or a form or pharmaceutical composition thereof in an effective amount to inhibit dihydroorotate dehydrogenase to treat or ameliorate a disease or disorder in a subject in need thereof can be determined by a practitioner, in light of factors related to the subject that requires treatment while minimizing any side effects.

[0208] Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy.

[0209] The dosage and frequency of administration of the compound of Formula (I), or a form or pharmaceutical composition thereof may be adjusted over time to provide an effective amount of the compound of Formula (I), or a form or pharmaceutical composition thereof to maintain a desired effect.

[0210] In one aspect, the term “effective amount” refers to that amount of the compound of Formula (I), or a form or pharmaceutical composition thereof administered as a monotherapy to a patient, which effective amount is in a range of from about 0.001 mg/Kg/day to about 500 mg/Kg/day, or about 0.01 mg/Kg/day to about 500 mg/Kg/day, or about 0.1 mg to about 500 mg/Kg/day, or about 1.0 mg/day to about 500 mg/Kg/day, in single, divided, or a

continuous dose for a patient or subject having a weight in a range of between about 40 to about 200 Kg (which dose may be adjusted for patients or subjects above or below this range, particularly children under 40 Kg). Dosing may be administered as a dose per kilogram, a dose per meter squared or a flat dose expressed in a unit of weight (e.g., milligrams, grams).

[0211] In another aspect, the effective amount is a dose administered to the subject that may be increased or decreased depending on subject response. The effective amount for the subject will also depend upon various factors, including the body weight, size and health of the subject. The typical adult subject is expected to have a median weight in a range of between about 60 to about 100 Kg. Accordingly, an effective amount for a given patient may be determined according to the skill and judgment of a practitioner skilled in the art.

[0212] In one aspect, daily monotherapy doses may be adjusted based upon the weight of the subject or patient, wherein the compound of Formula (I), or a form or pharmaceutical composition thereof may be formulated for delivery as a monotherapy at about 0.02, 0.025, 0.03, 0.05, 0.06, 0.075, 0.08, 0.09, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.75, 0.80, 0.90, 1.0, 1.10, 1.20, 1.25, 1.50, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 10, 20, 50, 75 or 100 mg/Kg/day or any range in between.

[0213] In another aspect, a daily dose may be adjusted based upon the weight of the subject or patient and administered as a single, divided, or continuous dose.

[0214] In another aspect, a daily dose of the compound of Formula (I), or a form or pharmaceutical composition thereof may be administered more than once per day, as in once, twice, three times, or more per day.

[0215] In another aspect, a dose of the compound of Formula (I), or a form or pharmaceutical composition thereof may be administered more than once per week, as in once, twice, three times, or more per week.

[0216] In another aspect, the effective amount may be a dose administered to the subject twice per week on different days, wherein the second dose in a week follows the first by three days, and wherein the first dose in a following week follows the second dose in a preceding week by four days. In another aspect, a subject may be administered one or more doses of an effective amount of the compound of Formula (I), or a form or pharmaceutical composition thereof, wherein the effective amount may not be the same for each dose.

[0217] In one aspect, an effective amount of the compound of Formula (I), or a form or pharmaceutical composition thereof may range from about 0.001 mg/Kg/day to about 500 mg/Kg/day. The terms "effective amount" or "therapeutically effective amount" of the compound of Formula (I), or a form or pharmaceutical composition thereof for use in the

manufacture of a medicament or in a method to treat or ameliorate a disease or disorder in a subject in need thereof is an amount sufficient to provide therapeutic benefit by inhibiting dihydroorotate dehydrogenase. The therapeutically effective amount of the compound of Formula (I), or a form or pharmaceutical composition thereof is intended to include an amount administered daily, weekly, biweekly selected from an amount in range of from about 0.01 ng to about 3500 mg; from about 0.1 ng to about 3500 mg; from about 0.1 µg to about 3500 mg; from about 0.1 mg to about 3500 mg; from about 1 mg to about 3500 mg; from about 1 mg to about 3000 mg; from about 0.05 mg to about 1500 mg; from about 0.5 mg to about 1500 mg; from about 1 mg to about 1500 mg; from about 5 mg to about 1500 mg; from about 10 mg to about 600 mg; from about 0.5 mg to about 2000 mg; or, from about 5.0 mg to about 1500 mg.

[0218] In one aspect, the effective amount of the compound of Formula (I), or a form or pharmaceutical composition thereof can be estimated initially by results from cell culture assays or from human or relevant animal models, such as the mouse, chimpanzee, marmoset or tamarin animal model. Relevant animal models may also be used to determine the appropriate concentration range and route of administration. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population). The dose ratio between the toxic and therapeutic effect is referred to as the therapeutic index, and can be expressed as the ratio, LD₅₀/ED₅₀. In another aspect, the effective amount is such that a large therapeutic index is achieved. In another aspect, the dose administered results in a range of plasma concentrations that include an ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0219] More specifically, the concentration-biological effect (pharmacodynamic) relationship observed with regard to the compound of Formula (I), or a form or pharmaceutical composition thereof suggests a target plasma concentration ranging from about 0.001 µg/mL to about 50 µg/mL, from about 0.01 µg/mL to about 20 µg/mL, from about 0.05 µg/mL to about 10 µg/mL, or from about 0.1 µg/mL to about 5 µg/mL. To achieve such plasma concentrations, the compound of Formula (I), or a form or pharmaceutical composition thereof may be administered at doses that vary from 0.001 µg to 100,000 mg, depending upon the route of administration in single, divided, or continuous doses for a patient weighing

between about 40 to about 100 kg (which dose may be adjusted for patients above or below this weight range, particularly for children under 40 kg).

[0220] In another aspect, a method for preventing, treating or ameliorating a disease or disorder in a subject in need thereof by inhibiting dihydroorotate dehydrogenase comprises the administration of an effective amount of the compound of Formula (I), or a form or pharmaceutical composition thereof to the subject, wherein the effective amount is a dose selected from a dose in a range of from about 50 mg to about 400 mg, from about 100 mg to about 200 mg, from about 125 mg to about 175 mg, from about 100 mg to about 300 mg, from about 100 mg to about 400 mg, from about 150 mg to about 200 mg, from about 150 mg to about 300 mg, from about 150 mg to about 400 mg, from about 200 mg to about 300 mg, from about 225 mg to about 275 mg, from about 225 mg to about 300 mg, from about 275 mg to about 300 mg, from about 200 mg to about 225 mg, from about 200 mg to about 275 mg, from about 200 mg to about 400 mg, from about 250 mg to about 300 mg, from about 250 mg to about 400 mg, from about 250 mg to about 350 mg, and the like, administered orally once, twice or three times per week.

[0221] In another aspect, a method for preventing, treating or ameliorating a disease or disorder in a subject in need thereof by inhibiting dihydroorotate dehydrogenase comprises the administration of an effective amount of the compound of Formula (I), or a form or pharmaceutical composition thereof to the subject, wherein the effective amount is administered once, twice or three times biweekly.

[0222] In another aspect, a method for preventing, treating or ameliorating a disease or disorder in a subject in need thereof by inhibiting dihydroorotate dehydrogenase comprises the administration of an effective amount of the compound of Formula (I), or a form or pharmaceutical composition thereof to the subject, wherein the effective amount is administered once, twice or three times every two weeks.

PHARMACEUTICAL COMPOSITIONS

[0223] Aspects of the present description include the use of a compound of Formula (I) or a form thereof in a pharmaceutical composition for treating or ameliorating a disorder or condition described herein in a subject in need thereof, comprising administering an effective amount of the compound of Formula (I) or a form thereof in admixture with one or more pharmaceutically acceptable excipient(s).

[0224] An aspect of the present description includes the use of a pharmaceutical composition of the compound of Formula (I) or a form thereof in the preparation of a kit comprising the

pharmaceutical composition of the compound of Formula (I) or a form thereof and instructions for administering the compound for treating or ameliorating the disease or condition in a subject in need thereof.

[0225] As used herein, the term “composition” means a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

[0226] The pharmaceutical compositions described herein may be formulated to achieve a physiologically compatible pH, ranging from about pH 3 to about pH 11. In certain aspects, the pharmaceutical composition is formulated to achieve a pH of from about pH 3 to about pH 7. In other aspects, the pharmaceutical composition is formulated to achieve a pH of from about pH 5 to about pH 8.

[0227] The term “pharmaceutically acceptable excipient” refers to an excipient for administration of a pharmaceutical agent, such as the compounds described herein. Pharmaceutically acceptable excipients may be determined in part by the particular composition being administered, as well as by the particular mode of administration and/or dosage form. Nonlimiting examples of pharmaceutically acceptable excipients include carriers, solvents, stabilizers, adjuvants, diluents, *etc.* Accordingly, there exists a wide variety of suitable formulations of pharmaceutical compositions for the instant compounds described herein (*see, e.g.,* Remington’s Pharmaceutical Sciences).

[0228] Suitable excipients may be carrier molecules that include large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive antibodies. Other exemplary excipients include antioxidants such as ascorbic acid; chelating agents such as EDTA; carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose (*e.g.,* hydroxypropylmethylcellulose, also known as HPMC), stearic acid; liquids such as oils, water, saline, glycerol and ethanol; wetting or emulsifying agents; pH buffering substances; and the like. Liposomes are also included within the definition of pharmaceutically acceptable excipients.

[0229] The pharmaceutical compositions described herein may be formulated in any form suitable for the intended use described herein. Suitable formulations for oral administration include solids, liquid solutions, emulsions and suspensions, while suitable inhalable formulations for pulmonary administration include liquids and powders. Alternative formulations include syrups, creams, ointments, tablets, and lyophilized solids which can be reconstituted with a physiologically compatible solvent prior to administration.

[0230] When intended for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, non-aqueous solutions, dispersible powders or granules (including micronized particles or nanoparticles), emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents, and preserving agents, in order to provide a palatable preparation.

[0231] Pharmaceutically acceptable excipients suitable for use in conjunction with tablets include, for example, inert diluents, such as celluloses, calcium or sodium carbonate, lactose, calcium or sodium phosphate; disintegrating agents, such as croscarmellose sodium, cross-linked povidone, maize starch, or alginic acid; binding agents, such as povidone, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid, or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0232] Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example celluloses, lactose, calcium phosphate, or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with non-aqueous or oil medium, such as glycerin, propylene glycol, polyethylene glycol, peanut oil, liquid paraffin, or olive oil.

[0233] In other aspects, pharmaceutical compositions described herein may be formulated as suspensions comprising a compound of Formula (I) or a form thereof in admixture with one or more pharmaceutically acceptable excipient(s) suitable for the manufacture of a suspension. In yet other aspects, pharmaceutical compositions described herein may be formulated as dispersible powders and granules suitable for preparation of a suspension by the addition of one or more excipient(s).

[0234] Excipients suitable for use in connection with suspensions include suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia, dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycethanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a

hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate); and thickening agents, such as carbomer, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives such as acetic acid, methyl and/or *n*-propyl *p*-hydroxy-benzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

[0235] The pharmaceutical compositions described herein may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth; naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids; hexitol anhydrides, such as sorbitan monooleate; and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

[0236] Additionally, the pharmaceutical compositions described herein may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous emulsion or oleaginous suspension. Such emulsion or suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a parenterally acceptable diluent or solvent, such as a solution in 1,2-propanediol. The sterile injectable preparation may also be prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may be employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[0237] The compounds described herein may be substantially insoluble in water and sparingly soluble in most pharmaceutically acceptable protic solvents and vegetable oils, but generally soluble in medium-chain fatty acids (*e.g.*, caprylic and capric acids) or triglycerides and in propylene glycol esters of medium-chain fatty acids. Thus, contemplated in the description are compounds which have been modified by substitutions or additions of chemical or biochemical moieties which make them more suitable for delivery (*e.g.*, increase

solubility, bioactivity, palatability, decrease adverse reactions, *etc.*), for example by esterification, glycosylation, PEGylation, *etc.*

[0238] In certain aspects, the compound described herein is formulated for oral administration in a lipid-based composition suitable for low solubility compounds. Lipid-based formulations can generally enhance the oral bioavailability of such compounds. As such, pharmaceutical compositions described herein may comprise an effective amount of a compound of Formula (I) or a form thereof, together with at least one pharmaceutically acceptable excipient selected from medium chain fatty acids or propylene glycol esters thereof (*e.g.*, propylene glycol esters of edible fatty acids such as caprylic and capric fatty acids) and pharmaceutically acceptable surfactants, such as polysorbate 20 or 80 (also referred to as Tween® 20 or Tween® 80, respectively) or polyoxyl 40 hydrogenated castor oil.

[0239] In other aspects, the bioavailability of low solubility compounds may be enhanced using particle size optimization techniques including the preparation of nanoparticles or nanosuspensions using techniques known to those skilled in the art. The compound forms present in such preparations include amorphous, partially amorphous, partially crystalline or crystalline forms.

[0240] In alternative aspects, the pharmaceutical composition may further comprise one or more aqueous solubility enhancer(s), such as a cyclodextrin. Nonlimiting examples of cyclodextrin include hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α -, β -, and γ -cyclodextrin, and hydroxypropyl- β -cyclodextrin (HPBC). In certain aspects, the pharmaceutical composition further comprises HPBC in a range of from about 0.1% to about 20%, from about 1% to about 15%, or from about 2.5% to about 10%. The amount of solubility enhancer employed may depend on the amount of the compound in the composition.

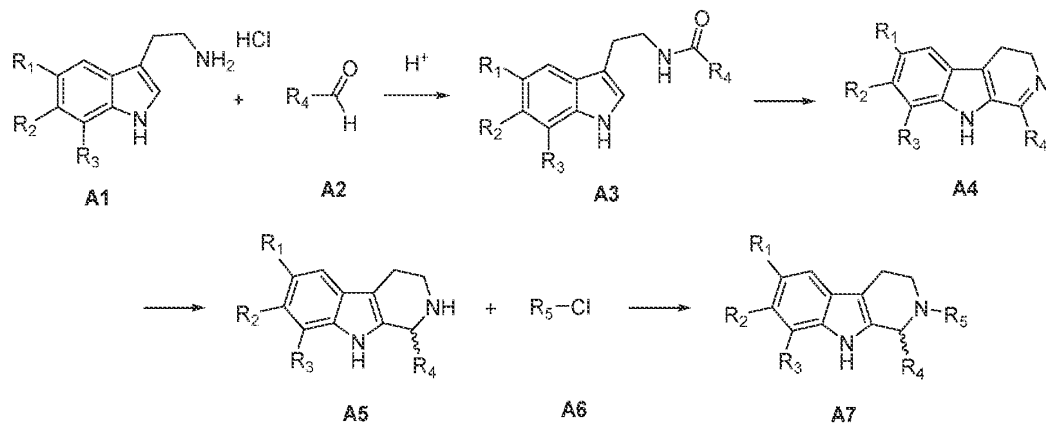
GENERAL SYNTHETIC METHODS OF PREPARING COMPOUNDS

[0241] As disclosed herein, general methods for preparing the compounds of Formula (I) or a form thereof as described herein are available via standard, well-known synthetic methodology. Many of the starting materials are commercially available or, when not available, can be prepared using the routes described below using techniques known to those skilled in the art. The synthetic schemes provided herein comprise multiple reaction steps, each of which is intended to stand on its own and can be carried out with or without any

preceding or succeeding step(s). In other words, each of the individual reaction steps of the synthetic schemes provided herein in isolation is contemplated.

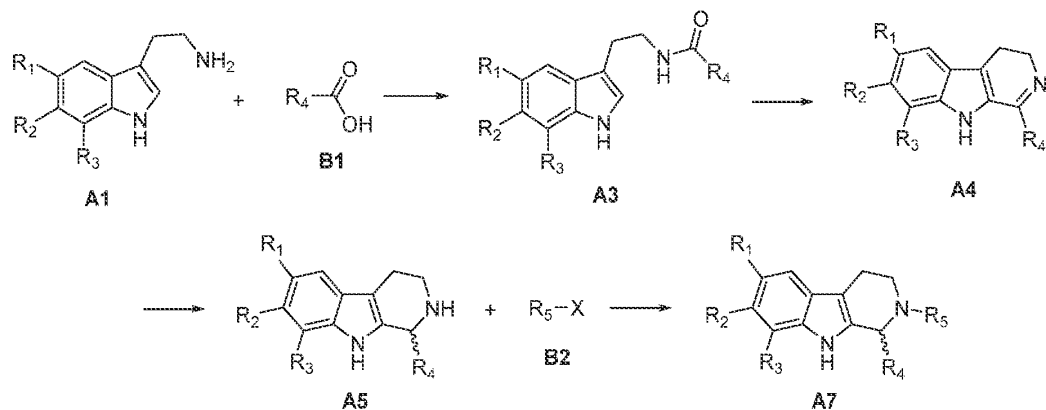
Scheme A:

[0242] Compounds of Formula (I) may be prepared as described in Scheme A below:



Scheme B:

[0243] Compounds of Formula (I) may be prepared as described in Scheme B below:



EXAMPLES

[0244] The following examples include non-limiting, representative illustrations of aspects of the compounds of Formula (I) described herein. The examples include non-limiting methods for preparing specific compounds of Formula (I).

SPECIFIC SYNTHETIC EXAMPLES

[0245] To assist in understanding the scope of the compounds of Formula (I) or a form thereof described herein, the following general and specific synthetic examples are included.

Among other things, these examples illustrate the preparation of certain representative compounds. Those of skill in the art will understand that the techniques described in these examples represent techniques, as described by those of ordinary skill in the art, that function well in synthetic practice, and as such constitute preferred modes for the practice thereof. However, it should be appreciated that those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific methods that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the present description.

[0246] Other than in the following examples, unless indicated to the contrary, all numbers expressing quantities of ingredients, reaction conditions, experimental data, and so forth used in the specification and claims are to be understood as being modified by the term “about”. Accordingly, all such numbers represent approximations that may vary depending upon the desired properties sought to be obtained by a reaction or as a result of variable experimental conditions. Therefore, within an expected range of experimental reproducibility, the term “about” in the context of the resulting data, refers to a range for data provided that may vary according to a standard deviation from the mean. As well, for experimental results provided, the resulting data may be rounded up or down to present data consistently, without loss of significant figures. While the numerical ranges and parameters setting forth the characterization of the compounds of Formula (I) or a form thereof described herein are approximations, the numerical values set forth in the working examples are reported as precisely as possible. Any numerical value, however, inherently contains a standard deviation which is a range of values necessarily resulting from experimental error.

[0247] The term “Rac,” as used in synthetic flowschemes *infra*, indicate that the starting material or final product are racemic mixtures with a relative configuration as shown. The relative configuration of compounds in the racemic mixture may or may not have been determined. 2D-NMR data for certain racemic mixtures has been obtained without assignment of a particular diastereomer to a configuration. In one example depicted herein, the racemic mixture of a compound may be depicted as a diastereomer having an (S,S) relative configuration, wherein the isolated product obtained includes the (S,S) and (R,R) diastereomer absolute configurations. In another example depicted herein, the racemic mixture of a compound may be depicted as a diastereomer having an (S,S) relative configuration, wherein the isolated product obtained includes the (S,S) and (S,R) enantiomer absolute configurations. In another example depicted herein, the racemic mixture may be depicted without designation of any relative configuration (i.e., flat-line bonds), wherein the

isolated product obtained includes the (S,S), (R,R), (S,R) and (R,S) diastereomer absolute configurations. The Structure and Name tables *supra* reflect the individual diastereomers or enantiomers expected to be found in the racemic mixtures obtained.

[0248] The relative configurations were determined based on NMR; where the NMR data clearly showed relative configuration, the relative configuration was assigned; in instances where the NMR data was ambiguous, the relative configuration was assigned based on the understanding of those skilled in the art. In some examples, the absolute configurations were determined based on biological data; wherein, based on biological activity, the most active enantiomer at C1 was known to be the (S) enantiomer while the (R) enantiomer was known to be relatively inactive. In some instances, as described herein, absolute configuration was determined based on absolute configuration of the chiral acid or catalyst used. In other instances, as described herein, absolute configuration was determined based on asymmetric synthesis of one diastereomer and use of comparative NMR to determine the absolute configuration of the other diastereomer in a racemic mixture.

[0249] The reagents and solvents were used as purchased (from a variety of vendors), except where noted. All reactions were conducted under inert atmosphere unless otherwise specified. Where applicable, the term "Celite" is used as shown in the following examples to represent the tradename CELITE® (brand of diatomaceous earth). Where applicable, chromatographic separations were performed using techniques and equipment commonly available such as, for example, by using an ISCO CombiFlash® Rf system. Where applicable, NMR spectra were obtained using techniques and equipment commonly available such as, for example, by using a Bruker Avance III⁵⁰⁰ spectrometer with deuterated solvents such as, for example, DMSO-*d*₆ or residual solvent as standard. Where applicable, melting points were determined using techniques and equipment commonly available such as, for example, by using a SRS OptiMelt® MPA100 (values as obtained without correction/calibration). Where applicable, TLC or LCMS analysis were performed using techniques and equipment commonly available such as, for example, by using Aldrich 254 nm glass-backed plates (60 Å, 250 µm), visualized using UV and I₂ stains. Where applicable, ESI mass spectra were obtained using techniques and equipment commonly available such as, for example, by using an ACQUITY UPLC® System, with values shown as [M+H]⁺ or [M-H]⁻, unless otherwise indicated. Where applicable, the structure of the product or the relative configuration was confirmed by using chiral building blocks and analyzing the relative chemical shifts of the relevant signals using NMR spectroscopy. Where applicable,

the structure of the product was established via 2D-NMR spectroscopy, including COSY, HSQC, HMBC, NOESY.

[0250] The following abbreviations are provided to ensure the terms used herein are unambiguous to one skilled in the art:

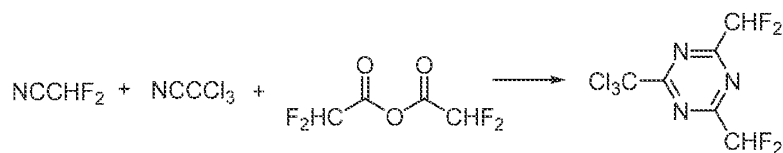
Abbreviation	Meaning
AcOH or HOAc	acetic acid
ACN or MeCN	acetonitrile
AlMe ₃	trimethylaluminum
APC	allylpalladium (II) chloride dimer
aq.	aqueous
Boc	<i>tert</i> -butoxycarbonyl
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
CsOAc	cesium acetate
CHCl ₃	chloroform or trichloromethane
18-Crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
DCM or CH ₂ Cl ₂	dichloromethane
DI	deionized
DIBAL-H	diisobutylaluminium hydride
DIPEA	N,N-diisopropylethylamine
DME	dimethoxyethane
DMF	dimethyl formamide
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
eq., or equiv.	equivalent
EtOAc	ethyl acetate
EtOH	ethanol
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
h, hr, min, s	hour (h or hr), minute (min), second (s)
iPrMgCl*LiCl	isopropylmagnesium chloride lithium chloride complex
iPrOAc	isopropyl acetate
K ₂ CO ₃	potassium carbonate
K ₃ PO ₄	potassium phosphate
KOtBu or <i>t</i> -BuOK	potassium <i>tert</i> -butoxide
LDA	lithium diisopropylamide

Abbreviation	Meaning
LC/MS, LCMS or LC-MS	liquid chromatographic mass spectroscopy
MeOH	methanol
MeCN	acetonitrile
MeNH ₂ x HCl	methylamine hydrochloride
MS	mass spectroscopy
m.p.	melting point (shown in °Centigrade)
MPS	potassium peroxymonosulfate (2KHSO ₅ ·KHSO ₄ ·K ₂ SO ₄)
NaCl	sodium chloride
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
NaHMDS	sodium hexamethyldisilazide
NaIO ₄	sodium periodate
NaOH	sodium hydroxide
NaOtAm	sodium <i>tert</i> -pentoxide
NaOMe	sodium methoxide
NaOEt	sodium ethoxide
NaOtBu	sodium <i>tert</i> -butoxide
Na ₂ SO ₄	sodium sulfate
NCS	N-chlorosuccinimide
NEt ₃	triethylamine
NH ₄ Cl	ammonium chloride
NH ₄ OH	ammonium hydroxide
NIS	N-iodosuccinimide
NMP	N-methylpyrrolidone
NMR	nuclear magnetic resonance
Oxone	potassium peroxymonosulfate
PCl ₅	phosphorus perchloride or phosphorus pentachloride
PCy ₃	tricyclohexylphosphine
[Pd]	palladium
Pd/C°	palladium on carbon
Pd ₂ (dba) ₃ or Pd ₂ dba ₃	tris(dibenzylideneacetone)dipalladium(0)
Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
PdCl ₂ (ACN)	bis(acetonitrile)dichloropalladium(II)
PdCl ₂ (allyl)	chloroallylpalladium(II) dimer
[Pd(OAc) ₂] ₃	palladium (II) acetate
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium
PE	petroleum ether
POCl ₃	phosphorus oxychloride

Abbreviation	Meaning
PPh ₃	triphenylphosphine
psi	pounds per square inch pressure
Pt/C	platinum on carbon
PTSA	p-toluenesulfonic acid
Q-Phos or QPhos	1,2,3,4,5-pentaphenyl-1'-(di- <i>tert</i> -butylphosphino)ferrocene
RT	room temperature
RBF	round bottom flask
RuPhos	dicyclohexyl-[2-[2,6-di(propan-2-yloxy)phenyl]phenyl]phosphane
RuCl[(<i>R,R</i>)-TsDPEN](mesitylene)	[N-[(1 <i>R</i> ,2 <i>R</i>)-2-(amino-κN)-1,2-diphenylethyl]-4-methylbenzenesulfonamido-κN]chloro[(1,2,3,4,5,6-η)-1,3,5-trimethylbenzene]-ruthenium
RuCl(<i>p</i> -cymene)[(<i>R,R</i>)-Ts-DPEN]	[N-[(1 <i>R</i> ,2 <i>R</i>)-2-(amino-κN)-1,2-diphenylethyl]-4-methylbenzenesulfonamido-κN]chloro[(1,2,3,4,5,6-η)-1-methyl-4-(1-methylethyl)benzene]-ruthenium
TBSO or OTBS	<i>tert</i> -butyldimethylsilyloxy
TCDI	1,1'-thiocarbonyldiimidazole
<i>t</i> -Bu	<i>tert</i> -butyl
TEA, NEt ₃ , Et ₃ N	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPEA	triisopropyl ethyl amine
Tol	<i>p</i> -toluyl
TsOH X H ₂ O	<i>p</i> -toluenesulfonic acid monohydrate
TsO	<i>p</i> -toluenesulfonyloxy
UPLC	Ultra Performance Liquid Chromatography
Xphos or XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPhos Pd G3	(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate

Example 1

Synthesis of 2,4-bis(difluoromethyl)-6-(trichloromethyl)-1,3,5-triazine



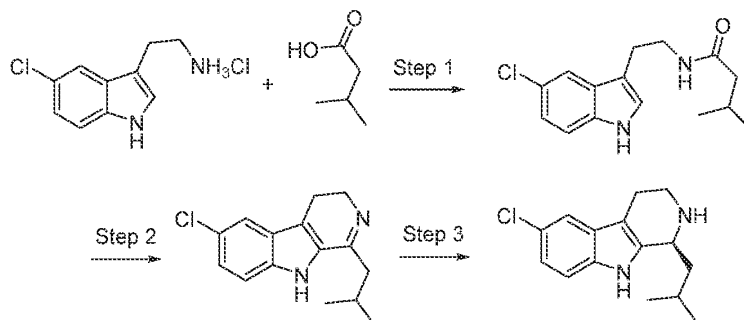
[0251] Ammonia (~50 mL) was condensed into a 3-neck 100 mL round bottom flask at -78 °C and difluoroacetonitrile (NCCHF₂) (5.71 g, 74.2 mmol) was added to the system in one

portion under an inert atmosphere. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 4 hours and was allowed to warm to room temperature overnight. The remaining ammonia was removed from the reaction mixture by rotary evaporation. The resulting solid was flushed with argon and dissolved in Dichloromethane (50 mL). Trichloroacetonitrile (NCCl_3) (7.44 mL, 74.2 mmol) was added via syringe at $0\text{ }^{\circ}\text{C}$. After stirring for 4 hours at $0\text{ }^{\circ}\text{C}$, difluoroacetic anhydride (26.6 g, 148 mmol) was added to the solution at $0\text{ }^{\circ}\text{C}$ and was allowed to warm to room temperature slowly overnight. The solvent and resulting organic acids were removed by rotary evaporation and the crude product was purified by column chromatography, eluting with 0-80% hexanes: CH_2Cl_2 to afford 2,4-bis(difluoromethyl)-6-(trichloromethyl)-1,3,5-triazine as a clear oil (11.2 g, 37.5 mmol, 51% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.23 (t, $J = 56\text{ Hz}$, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 174.0, 170.8 (t, $J = 26\text{ Hz}$), 110.5 (t, $J = 242\text{ Hz}$), 93.6; ^{19}F NMR (377 MHz, $\text{DMSO}-d_6$) δ 123.72 (d, 52.8 Hz).

[0252] The product, obtained as described in Example 1 above, was used as a building block in other examples provided herein to obtain additional compounds.

Example 2

General Procedure A for Asymmetric Carboline Synthesis

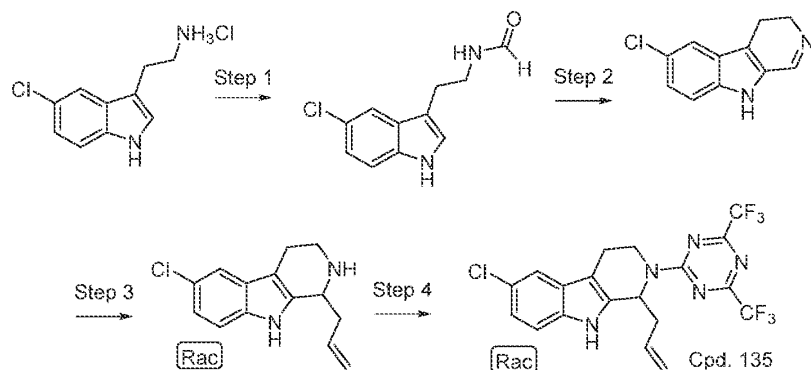


[0253] **Step 1:** A 3-neck round bottom flask was charged with 3-methylbutanoic acid (38.8 g, 380 mmol), diisopropylethylamine (89.2 g, 690 mmol) and N,N -dimethylformamide (400 mL, 5170 mmol, 14.9), a solution of HATU (170 g, 438.154 mmol) in N,N -dimethylformamide (400 mL, 5170 mmol) was added and stirred for 5 min at ambient temperature. 2-(5-chloro-1H-indol-3-yl)ethanamine hydrochloride (80 g, 346.14 mmol) was added and the mixture allowed to stir for 14 h at ambient temperature. Water (2 L) was added to the reaction mixture and the solid filtered and washed with water, dried under vacuum, to give N -[2-(5-chloro-1H-indol-3-yl)ethyl]-3-methyl-butanimide (87 g, 312.1 mmol, 90.2% yield) as an amorphous solid.

[0254] **Step 2:** A round bottom flask was charged with N-[2-(5-chloro-1H-indol-3-yl)ethyl]-3-methyl-butanamide (87 g, 312.1 mmol) and suspended in dry acetonitrile (500 mL). Phosphoryl chloride (30 mL, 323 mmol) was added in one portion and the mixture allowed to stir at 80°C for 16 h. The reaction mixture was cooled to 10 °C, quenched by addition of MeOH, the resulting solid filtered, and washed with acetonitrile. The obtained solid was then suspended between NaHCO₃ (saturated, aq), and DCM (5% MeOH). After stirring the biphasic mixture and dissolving all solids, the organic phase was separated and the aqueous phase extracted 3 times with DCM (5% MeOH). The combined organic phases were dried over Na₂SO₄, volatiles removed under reduced pressure to afford 6-chloro-1-isobutyl-4,9-dihydro-3H-pyrido[3,4-b]indole (37 g, 141.9 mmol, 45.5% yield) as an amorphous solid.

[0255] **Step 3:** A 3-neck round bottom flask equipped with an Argon inlet was charged with 6-chloro-1-isobutyl-4,9-dihydro-3H-pyrido[3,4-b]indole (4.7 g, 18 mmol) in dichloromethane (50 mL, 780.0 mmol). RuCl[(R,R)-TsDpen](Mesitylene) (250 mg, 0.361 mmol) and formic acid triethylamine complex 5:2 (16 g, 36.253 mmol) are added, the flask was put under an Argon atmosphere, the resulting mixture was stirred at 25 °C for 1 h after which volatiles were removed under reduced pressure. The residue was suspended in acetonitrile, filtered, the solid washed with K₂CO₃ (2M aq), then dried under vacuum to afford an enantiomer (1S)-6-chloro-1-isobutyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (3.7 g, 14 mmol, 78% yield) as an amorphous solid. MS m/z 263.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.86 (s, 1H), 7.36 (s, 1H), 7.27 (d, *J* = 8.38 Hz, 1H), 6.98 (d, *J* = 8.50 Hz, 1H), 3.94 (d, *J* = 9.63 Hz, 1H), 3.28-3.32 (m, 1H), 3.06-3.15 (m, 1H), 2.77-2.87 (m, 1H), 2.54-2.55 (m, 1H), 2.17 (br s, 1H), 1.88-1.99 (m, 1H), 1.62-1.70 (m, 1H), 1.45-1.54 (m, 1H), 0.98 (d, *J* = 6.38 Hz, 3H), 0.93 (d, *J* = 6.63 Hz, 3H)

[0256] The product, obtained as described in Example 2 above, was used as a building block in other examples provided herein to obtain additional compounds.

Example 3**Synthesis of Compound 135**

[0257] **Step 1:** To a single neck round bottom flask equipped with magnetic stirring was charged 5-chlorotryptamine hydrochloride (21 g, 85.6 mmol) and ethyl formate (excess, enough to fully submerge solids). The reaction mixture was flushed with nitrogen and continued under nitrogen. Triethylamine (22 mL, 158 mmol) was added, and the reaction was heated to 100 °C under reflux for 48 hours. After 48 hours, the reaction was complete as judged by LCMS analysis. The reaction mixture was concentrated to dryness yielding crude N-[2-(5-chloro-1H-indol-3-yl)ethyl]formamide as an off-white solid. 22.7 g, 119% yield, product contains triethylamine hydrochloride. The product was used directly in the next step without further purification.

[0258] **Step 2:** To a single neck round bottom flask equipped with magnetic stirring was charged N-[2-(5-chloro-1H-indol-3-yl)ethyl]formamide (17.4 g 78.1 mmol) and acetonitrile (175 mL). The reaction mixture was flushed with nitrogen and continued under nitrogen. The reaction was cooled to 0 °C in an ice bath. Phosphoryl chloride (22 mL, 237 mmol) was added dropwise to the reaction mixture. The reaction mixture was removed from the ice bath and allowed to stir overnight. After 16 hours, the reaction mixture was filtered, and the filter cake was washed with acetonitrile (2 x 50 mL). The solids were allowed to dry on the filter. The product 6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-2-ium was isolated as a white solid salt (10 g) with an unspecified counterion. The product was used directly in the next step without further purification.

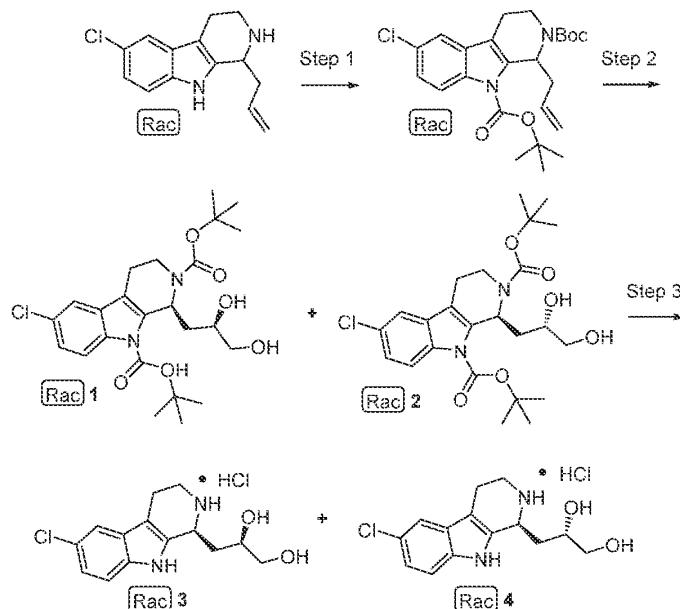
[0259] **Step 3:** To a single neck round bottom flask equipped with magnetic stirring was charged 6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-2-ium (5 g, 24.3 mmol) and THF (100 mL). The reaction was flushed with nitrogen and continued under nitrogen. Allylmagnesium bromide (1 mol/L, 98 mL, 98 mmol) in diethyl ether was added. The reaction mixture was

allowed to stir for 4 hours, at which point all starting material was consumed as judged by LCMS analysis. The reaction mixture was quenched with saturated NH_4Cl , extracted with 10% MeOH in DCM, and concentrated to give a racemic mixture of crude 1-allyl-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a tan solid. MS m/z 247.0 $[\text{M}+\text{H}]^+$. ^1H NMR ($\text{DMSO}-d_6$, 400MHz) 10.92(s, 1H), 7.37 (d, $J=1.6$ Hz, 1H), 7.27 (d, $J=8.4$ Hz, 1H), 6.99 (dd, $J=2.0, 8.4$ Hz, 1H), 5.97-5.80 (m, 1H), 5.14-5.02 (m, 2H), 4.00 (dd, $J=3.2, 8.0$ Hz, 1H), 3.16-3.10 (m, 1H), 2.85-2.78 (m, 1H), 2.67-2.61 (m, 1H), 2.59-2.51 (m, 2H), 2.44-2.36 (m, 1H). [0260] The product, obtained as described in Step 3 above, was used as a building block in other examples provided herein to obtain additional compounds.

[0261] **Step 4:** To a screw-cap vial equipped with magnetic stirring was charged 1-allyl-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (19 mg, 0.08 mmol), 4-DMAP (10 mg, 0.08 mmol), acetonitrile (0.5 mL), and 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (35 mg, 0.10 mmol). The reaction mixture turned black and went into solution upon addition of 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine. After 5 minutes the reaction was complete as judged by LCMS. The reaction mixture was concentrated down directly and purified by silica gel chromatography to give a racemic mixture of the title compound as a white solid (21 mg, 59% yield) MS m/z 460.0 $[\text{M}-\text{H}]^-$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.77-2.96 (m, 4 H) 3.55-3.68 (m, 1 H) 4.93-5.05 (m, 2 H) 5.08-5.22 (m, 1 H) 5.75-5.91 (m, 1 H) 5.92-6.02 (m, 1 H) 7.04-7.16 (m, 1 H) 7.34-7.43 (m, 1 H) 7.47-7.56 (m, 1 H) 11.16-11.28 (m, 1 H)

[0262] Using the procedure described for Example 3, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
134	MS m/z 476.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 11.28(s, 1H), 7.49 (m, 1H), 7.39-7.37(d, 1H, $J=8.4\text{Hz}$), 7.09-7.06(dd, 1H, $J=2.0\text{Hz}$, $J=8.4\text{Hz}$), 6.08-6.05(m, 1H), 4.96-4.92(dd, 1H, $J=1.2\text{Hz}$, $J=12.4\text{Hz}$), 4.71(m, 2H), 3.68-3.61(m, 1H), 2.91-2.86(m, 1H), 2.81-2.74(m, 2H), 2.71-2.67(m, 1H), 1.85(s, 3H)
280	MS m/z 446.0 $[\text{M}-\text{H}]^-$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.29(s, 1H), 7.52(d, $J=4\text{Hz}$, 1H), 7.37(d, $J=8.8\text{Hz}$, 1H), 7.09(q, $J=6.4\text{Hz}$, 1H), 6.32(d, $J=5.2\text{Hz}$, 1H), 6.18-6.09(m, 1H), 5.37(d, $J=10.4\text{Hz}$, 1H), 5.26(d, $J=17.2\text{Hz}$, 1H), 4.97(q, $J=8.4\text{Hz}$, 1H), 3.49-3.42(m, 1H), 2.90 (q, $J=12.0\text{Hz}$, 1H), 2.84-2.77(m, 1H)
281	MS m/z 247.0 $[\text{M}+\text{H}]^+$; ^1H NMR (400MHz, $\text{DMSO}-d_6$) δ 11.13 (s, 1H), 7.51-7.50 (m, 1H), 7.36-7.34 (d, 1H, $J=8.4$ Hz), 7.09-7.06 (dd, 1H, $J=2.0$ Hz, $J=8.4$ Hz), 6.58-6.56 (m, 1H), 5.83-5.68 (m, 2H), 5.00-4.95 (dd, 1H, $J=4.4$ Hz, $J=12.8$ Hz), 3.63-3.58 (m, 1H), 2.95-2.90 (m, 1H), 2.82-2.78 (m, 1H), 2.01-1.99 (m, 3H)

Example 4**General Procedure for Synthesis of Diol Diastereomers**

[0263] **Step 1:** To a single neck round bottom flask equipped with magnetic stirring was charged a racemic mixture of 1-allyl-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (0.97 g, 3.9 mmol) and 4-DMAP (180 mg, 1.5 mmol). The reaction flask was flushed with nitrogen and continued under nitrogen. To the reaction mixture was added DCM (10 mL), THF (10 mL), triethylamine (1.5 mL, 11 mmol), and Boc₂O (1.9 mL, 8.8 mmol). The reaction mixture was allowed to stir overnight. After stirring for 16 hours, the reaction was judged complete by LCMS analysis. The resulting mixture was concentrated directly and purified by silica gel chromatography to give a racemic mixture of crude di-tert-butyl 1-allyl-6-chloro-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate as a white solid. (1.7 g, 97% yield). The product was used directly in the next step without further purification.

[0264] **Step 2:** To a screw-cap vial equipped with magnetic stirring was charged a racemic mixture of di-tert-butyl 1-allyl-6-chloro-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate (105 mg, 0.23 mmol), potassium osmate(VI) dihydrate (8 mg, 0.02 mmol), and N-methylmorpholine N-oxide (40 mg, 0.34 mmol). The reaction flask was flushed with nitrogen and the reaction was continued under nitrogen. Acetone (1.5 mL) and water (1 mL) were added and the reaction mixture was stirred at room temperature for 16 hours. After 16 hours the reaction was complete as judged by LCMS analysis. The reaction was quenched with sodium sulfite solution, extracted with EtOAc, the organic layer was dried over sodium

sulfate, and concentrated to dryness. The crude product was purified by silica gel chromatography to give a racemic mixture (Rac 1) of di-tert-butyl (S)-6-chloro-1-((S)-2,3-dihydroxypropyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate and di-tert-butyl (R)-6-chloro-1-((R)-2,3-dihydroxypropyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate; and, a racemic mixture (Rac 2) of di-tert-butyl (S)-6-chloro-1-((R)-2,3-dihydroxypropyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate and di-tert-butyl (R)-6-chloro-1-((S)-2,3-dihydroxypropyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate.

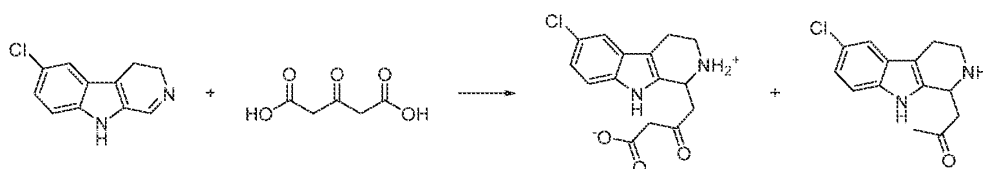
[0265] **Step 3:** To a screw-cap vial equipped with magnetic stirring was charged the racemic mixture (Rac 1) of di-tert-butyl (S)-6-chloro-1-((S)-2,3-dihydroxypropyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate and di-tert-butyl (R)-6-chloro-1-((R)-2,3-dihydroxypropyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate (225 mg, 0.47 mmol) and hydrochloric acid in dioxane (5 mL, 20 mmol, 4 mol/L). The reaction was flushed with nitrogen and allowed to stir for 24 hours at room temperature. After 24 hours, a precipitate formed and the reaction was judged complete by LCMS. The mixture was filtered and the filter cake was washed with dioxane. The solids were dried in vacuo to give a racemic mixture (Rac 3) of (S)-3-((S)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol hydrochloride salt and (R)-3-((R)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol hydrochloride salt as a white solid. (129 mg, 87% yield) MS m/z 281.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.25 (br s, 1 H) 2.05-2.19 (m, 2 H) 2.92 (br s, 2 H) 3.37-3.37 (m, 1 H) 3.39-3.48 (m, 1 H) 3.57 (s, 3 H) 3.77 (br s, 1 H) 4.83 (br s, 2 H) 5.34 (br s, 1 H) 5.76 (s, 1 H) 7.11 (br d, *J*=8.63 Hz, 1 H) 7.38 (d, *J*=8.63 Hz, 1 H) 7.54 (s, 1 H) 8.92 (br d, *J*=8.38 Hz, 1 H) 9.64 (br s, 1 H) 11.36 (s, 1 H)

[0266] **Step 4:** Using the procedure of Step 3, the racemic mixture (Rac 2) of di-tert-butyl (S)-6-chloro-1-((R)-2,3-dihydroxypropyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate and di-tert-butyl (R)-6-chloro-1-((S)-2,3-dihydroxypropyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate was used to obtain a racemic mixture (Rac 4) of (S)-3-((R)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol hydrochloride salt and (R)-3-((S)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol hydrochloride salt, MS m/z 281.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.85 (dt, *J*=14.54, 9.36 Hz, 1 H) 2.36 (br d, *J*=14.76 Hz, 1 H) 2.84-2.98 (m, 2 H) 3.28-3.50 (m, 8 H) 3.91 (br d, *J*=4.75 Hz, 1 H) 4.79 (br s, 1 H) 7.07-7.14 (m, 1 H) 7.39 (m, *J*=8.63 Hz, 1 H) 7.54 (s, 1 H) 9.10 (br s, 1 H) 9.32 (br s, 1 H) 11.35 (s, 1 H)

[0267] The products, obtained as described in Example 4 above, were used as building blocks in other examples provided herein to obtain additional compounds.

Example 5

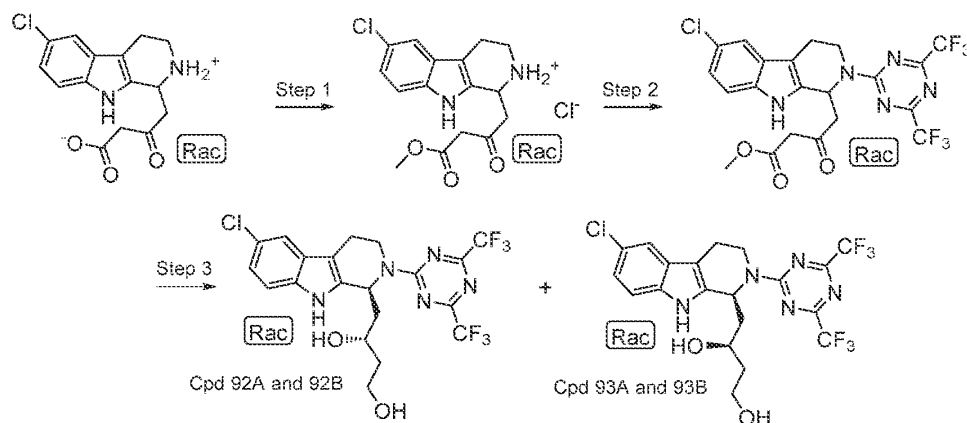
General Procedure B for Synthesis of Diol Diastereomers



[0268] 6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-2-ium chloride (3.5 g, 14.6 mmol) was placed in a flask and suspended in 180 mL of a 2:1 MeOH/water mixture. Sodium bicarbonate (15 g, 17.5 mmol) was added and the slurry was stirred at room temperature for 5 min, followed by addition of 3-oxopentanedioic acid (3.4 g, 23.3 mmol). The mixture was stirred for 2 hours at RT after which the solid was collected by filtration. The solid was washed with water followed by acetonitrile, and then dried in vacuo to afford a racemic mixture of 3.5 g (11 mmol, 79% yield) of 4-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-oxo-butanoic acid.

[0269] The water/acetonitrile filtrate was collected, basified with 2M aq. NaOH solution, and extracted 3 times with DCM. The combined organic layers were concentrated under reduced pressure to afford a racemic mixture of 1-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propan-2-one as a byproduct (150 mg, 0.6 mmol, 4% yield).

[0270] The products, obtained as described in Example 5 above, were used as building blocks in other examples provided herein to obtain additional compounds.

Example 6**Synthesis of Compound 92A and 92B and Compound 93A and 93B**

[0271] **Step 1:** A racemic mixture of 4-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-oxo-butanoic acid (6.1 g, 20 mmol) was suspended in 120 mL of MeOH and 60 mL of 3M HCl in MeOH was added. The mixture was stirred at RT for 16 hours. The suspension was concentrated under reduced pressure and the solid was washed with methanol to afford a racemic mixture 3.3 g (9.1 mmol, 46% yield) of methyl 4-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-oxo-butanoate hydrochloride which was used directly in the next step.

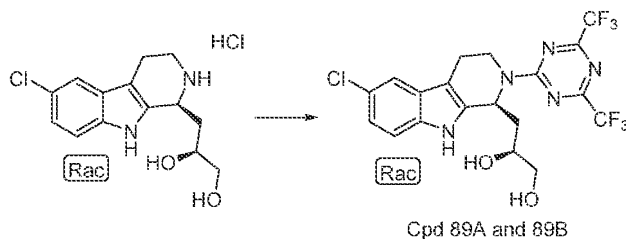
[0272] **Step 2:** The racemic mixture of methyl-4-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-oxo-butanoate hydrochloride (840 mg, 2.4 mmol) and 4-dimethylaminopyridine (1.0 g, 8.0 mmol) were suspended in 50 mL of MeCN. 2-bis(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (1.6 g 4.7 mmol) was added to the mixture at room temperature and stirred for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography to afford a racemic mixture of methyl-4-[2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]-3-oxo-butanoate (560 mg, 1.1 mmol, 44% yield). MS m/z 358.1 $[M+H]^+$.

[0273] **Step 3:** A flask was charged with the racemic mixture of methyl-4-[2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]-3-oxo-butanoate (520 mg-, 1,0 mmol) and flushed with argon. The material was dissolved in DCM (15 mL) and cooled to 0 °C. A 1M solution of DIBAL-H (1 mol/L) in hexanes (4.9 mL, 4.9 mmol) was added drop-wise then warmed to room temperature and stirred for 3 hours. The solution was cooled 0 °C and quenched with 5 mL of aqueous 2M NaOH. After

warming to room temperature and stirring for 30 min, the organic layer was partitioned and washed with water and brine. The organic layer was concentrated and the crude residue was purified by silica gel chromatography to afford a racemic mixture of Compound 92A (3R)-4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butane-1,3-diol AND Compound 92B (3S)-4-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butane-1,3-diol (110 mg, 22 % y) and a racemic mixture of Compound 93A (3S)-4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butane-1,3-diol AND Compound 93B (3R)-4-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butane-1,3-diol (92 mg, 19 % yield).

[0274] Compound 92A/B MS m/z 508.1 $[M-H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.08 (s, 1H), 7.47 (d, $J = 2.2$ Hz, 1H), 7.36 (d, $J = 8.6$ Hz, 1H), 7.07 (dd, $J = 8.6, 2.1$ Hz, 1H), 6.05 (dd, $J = 9.7, 4.9$ Hz, 1H), 4.94 (dd, $J = 13.4, 5.2$ Hz, 1H), 4.49 (d, $J = 5.5$ Hz, 1H), 4.31 (t, $J = 4.9$ Hz, 1H), 3.79 (s, 1H), 3.72-3.51 (m, 1H), 3.48 (dd, $J = 10.0, 5.4$ Hz, 2H), 2.83 (ddd, $J = 32.9, 13.7, 4.8$ Hz, 2H), 2.21-1.89 (m, 2H), 1.80-1.62 (m, 1H), 1.58-1.40 (m, 1H). The relative configuration between the diastereomers was not determined; NMR data was obtained without assignment to a particular diastereomer.

[0275] Compound 93A/B MS m/z 508.0 $[M-H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.21 (s, 1H), 7.46 (d, $J = 2.1$ Hz, 1H), 7.33 (d, $J = 8.6$ Hz, 1H), 7.05 (dd, $J = 8.6, 2.1$ Hz, 1H), 6.13 (dd, $J = 9.4, 4.0$ Hz, 1H), 4.93 (dd, $J = 13.1, 5.2$ Hz, 1H), 4.40 (d, $J = 5.4$ Hz, 1H), 4.32 (t, $J = 5.0$ Hz, 1H), 3.77-3.53 (m, 2H), 3.47 (q, $J = 6.0$ Hz, 2H), 2.83 (ddd, $J = 27.2, 13.7, 5.1$ Hz, 2H), 2.26-1.94 (m, 2H), 1.54 (q, $J = 6.4$ Hz, 2H). The relative configuration between the diastereomers was not determined; NMR data was obtained without assignment to a particular diastereomer.

Example 7**Synthesis of Compound 89A and 89B**

[0276] To a screw-cap vial equipped with magnetic stirring was charged a racemic mixture of (S)-3-((S)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol hydrochloride (20 mg, 0.06 mmol), DIPEA (1 mL), and acetonitrile (1 mL). The reaction was allowed to stir at room temperature for 1 hour at which point a solution formed. To the reaction mixture was charged 4-DMAP (9 mg, 0.07 mmol) and 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (26 mg, 0.08 mmol). After 15 minutes the reaction was judged complete by LCMS. The reaction mixture was concentrated down under nitrogen stream and purified by reverse phase prep-HPLC to give a racemic mixture of Compound 89A (S)-3-((S)-2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol and Compound 89B (R)-3-((R)-2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol as a white solid. (9 mg, 29% yield) MS m/z 494.0 $[M-H]^-$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.94-2.04 (m, 1 H) 2.13-2.22 (m, 1 H) 2.68-2.91 (m, 2 H) 3.21-3.31 (m, 3 H) 3.49 (br s, 1 H) 3.58 (td, $J=12.73, 4.31$ Hz, 1 H) 4.50-4.60 (m, 2 H) 4.94 (br dd, $J=13.01, 5.00$ Hz, 1 H) 6.12-6.18 (m, 1 H) 7.06 (d, $J=8.74$ Hz, 1 H) 7.33 (d, $J=8.63$ Hz, 1 H) 7.47 (s, 1 H) 11.20 (s, 1 H). The relative configuration was not determined; NMR data was obtained without assignment to a particular diastereomer.

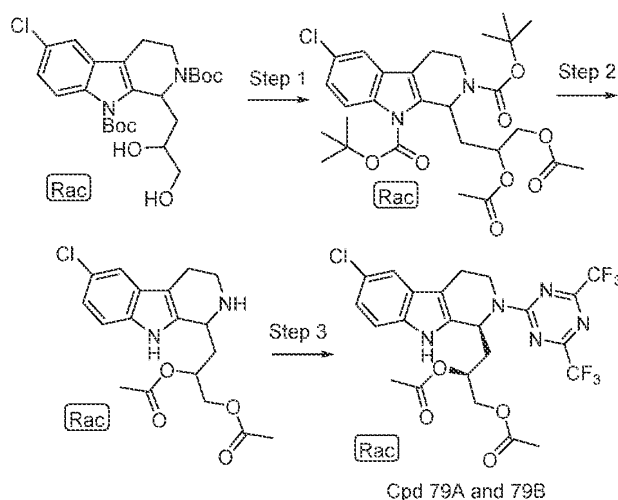
[0277] Using the procedure described for Example 7, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
90	MS m/z 494.1 $[M-H]^-$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.98 (ddd, $J=14.32, 10.07, 3.75$ Hz, 1 H) 2.18 (td, $J=11.98, 1.94$ Hz, 1 H) 2.73-2.91 (m, 2 H) 3.20-3.31 (m, 2 H) 3.44-3.53 (m, 1 H) 3.54-3.62 (m, 1 H) 4.51-4.60 (m, 2 H) 4.95 (dd, $J=13.13, 5.00$ Hz, 1 H) 6.16 (dd, $J=9.26, 3.50$ Hz, 1 H) 7.06 (dd, $J=8.57, 2.06$ Hz, 1 H) 7.33 (d, $J=8.50$ Hz, 1 H) 7.47 (d, $J=1.88$ Hz, 1 H) 11.21 (br s, 1 H)

Cpd	Data
151A and 151B	MS m/z 458.2 [M-H] ⁻ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 1.94 (ddd, <i>J</i> =14.20, 10.26, 3.44 Hz, 1 H) 2.11-2.20 (m, 1 H) 2.71-2.89 (m, 2 H) 3.22-3.30 (m, 2 H) 3.44-3.55 (m, 2 H) 4.56-4.62 (m, 2 H) 4.99 (dd, <i>J</i> =13.26, 4.50 Hz, 1 H) 6.16 (d, <i>J</i> =9.34 Hz, 1 H) 6.75 (t, <i>J</i> =53.66 Hz, 1 H) 6.81 (t, <i>J</i> =53.53 Hz, 1 H) 7.05 (dd, <i>J</i> =8.57, 2.06 Hz, 1 H) 7.32 (d, <i>J</i> =8.63 Hz, 1 H) 7.46 (d, <i>J</i> =2.13 Hz, 1 H) 11.22 (s, 1 H)

Example 82

Synthesis of Compound 79A and 79B



[0278] **Step 1:** To a screw-cap vial equipped with magnetic stirring was charged a racemic mixture of di-tert-butyl 6-chloro-1-(2,3-dihydroxypropyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate (43 mg, 0.09 mmol), DCM (0.4 mL), 4-DMAP (10 mg, 0.09 mmol), NEt₃ (0.045 mL, 0.32 mmol) and acetic anhydride (0.022 mL, 0.23 mmol). The reaction was allowed to stir for 2 hours at room temperature. After 2 hours the reaction was judged complete by LCMS analysis. The reaction mixture was put directly on silica gel column for purification, giving a single product. The product was used directly in the next step without further analysis or purification.

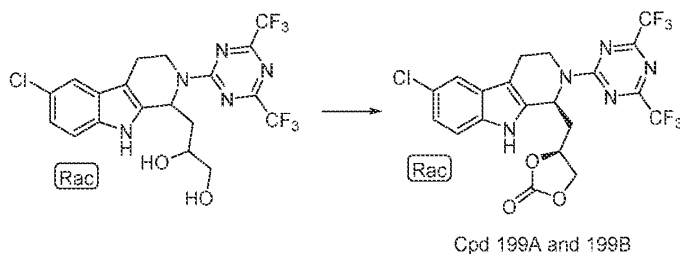
[0279] **Step 2:** To a screw-cap vial equipped with magnetic stirring was charged a racemic mixture of di-tert-butyl 6-chloro-1-(2,3-diacetoxypropyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-2,9-dicarboxylate (40 mg, 0.07 mmol), DCM (0.5 mL) and trifluoroacetic acid (0.5 mL). The reaction was allowed to stir overnight at room temperature. After 16 hours the reaction was judged complete by LCMS analysis. The reaction was quenched with triethylamine, dissolved in EtOAc, washed with saturated NaCl (3x), dried over NaSO₄, and

concentrated. The concentrate was used directly in the next step without further purification or analysis.

[0280] **Step 3:** To a screw-cap vial equipped with magnetic stirring was charged a racemic mixture of 3-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diyl diacetate (20 mg, 0.06 mmol), acetonitrile (1 mL), 4-DMAP (9 mg, 0.07 mmol) and 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (26 mg, 0.08 mmol). The reaction was allowed to stir for 15 minutes at room temperature. After 15 minutes the reaction was judged complete by LCMS. The reaction was concentrated down directly under nitrogen and purified by reverse phase prep-HPLC to give a racemic mixture of Compound 79A (2S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diyl diacetate and Compound 79B (2R)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diyl diacetate as a white solid. (9mg, 36% yield) MS m/z 578.0 [M-H]⁻. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.99 (d, $J=4.25$ Hz, 6 H) 2.33-2.41 (m, 2 H) 2.74-2.89 (m, 2 H) 3.59-3.69 (m, 1 H) 4.01 (dd, $J=12.19, 5.07$ Hz, 1 H) 4.29 (dd, $J=11.94, 2.44$ Hz, 1 H) 4.88-4.97 (m, 2 H) 6.01-6.07 (m, 1 H) 7.08 (br d, $J=8.50$ Hz, 1 H) 7.34 (d, $J=8.63$ Hz, 1 H) 7.48 (s, 1 H) 11.39 (s, 1 H)

Example 9

Synthesis of Compound 199A and 199B



[0281] To a screw-cap vial equipped with magnetic stirring was charged a racemic mixture of 3-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol (29 mg, 0.058 mmol, 1.0 equiv.), pyridine (0.2 mL) and phosgene 15% in Tol (0.041 mL, 0.4 mmol). The reaction was allowed to stir at room temperature for 15 minutes. After 15 minutes the reaction was judged complete by LCMS. The reaction mixture was concentrated directly and purified by silica gel chromatography to give a racemic mixture of Compound 199A (4S)-4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1,3-dioxolan-2-

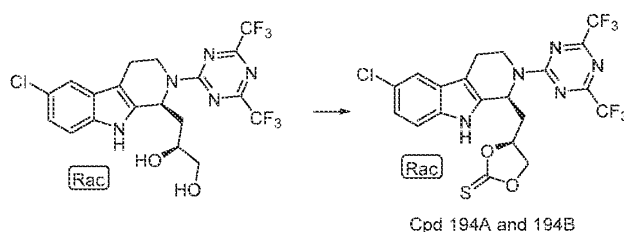
one AND Compound 199B (4R)-4-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1,3-dioxolan-2-one as a white solid. (15 mg, 49% yield) MS m/z 520.0 [M-H]⁻. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.38-2.47 (m, 1 H) 2.72-2.92 (m, 2 H) 3.28-3.33 (m, 1 H) 3.53-3.62 (m, 1 H) 4.17 (t, J =7.69 Hz, 1 H) 4.53 (t, J =8.25 Hz, 1 H) 4.88-4.98 (m, 2 H) 6.13 (br d, J =9.88 Hz, 1 H) 7.08 (br d, J =8.63 Hz, 1 H) 7.36 (d, J =8.50 Hz, 1 H) 7.50 (s, 1 H) 11.36 (s, 1 H)

[0282] Using the procedure described for Example 9, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
32	MS m/z 534.1 [M-H] ⁻ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 2.00-2.23 (m, 2 H) 2.37 (dt, J =6.75, 3.38 Hz, 1 H) 2.71-2.95 (m, 2 H) 3.54-3.72 (m, 1 H) 4.16 (dd, J =10.19, 7.57 Hz, 1 H) 4.35-4.43 (m, 1 H) 4.48 (dd, J =10.26, 7.00 Hz, 1 H) 4.66 (dd, J =10.38, 3.88 Hz, 1 H) 4.94 (br dd, J =13.26, 4.88 Hz, 1 H) 5.93 (dd, J =10.63, 2.75 Hz, 1 H) 7.09 (dd, J =8.57, 1.81 Hz, 1 H) 7.39 (d, J =8.63 Hz, 1 H) 7.50 (d, J =1.13 Hz, 1 H) 11.24 (s, 1 H)
200A and 200B	MS m/z 520.0 [M-H] ⁻ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 2.36-2.48 (m, 1 H) 2.56-2.65 (m, 1 H) 2.72-2.82 (m, 1 H) 2.85-2.93 (m, 1 H) 3.30-3.31 (m, 1 H) 3.60-3.69 (m, 1 H) 4.51-4.63 (m, 2 H) 4.91-5.02 (m, 2 H) 5.90 (br d, J =8.63 Hz, 1 H) 7.09 (dd, J =8.57, 1.81 Hz, 1 H) 7.41 (d, J =8.50 Hz, 1 H) 7.51 (s, 1 H) 11.14 (s, 1 H)

Example 10

Synthesis of Compound 194A and 194B



[0283] To a screw-cap vial equipped with magnetic stirring was charged a racemic mixture of 3-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol (430 mg, 0.9 mmol) and DCM (25 mL). The reaction was flushed with nitrogen and continued under nitrogen. To the reaction was charged 4-DMAP (100 mg, 0.8 mmol), pyridine (0.75 mL, 9.3 mmol) and thiophosgene (0.1 mL, 1 mmol). The reaction was stirred at room temperature for 30 minutes. After 30 minutes the reaction was judged complete by LCMS. The reaction was quenched with 1N HCl, extracted with DCM, dried over Na₂SO₄ and concentrated. The concentrate was purified by silica gel

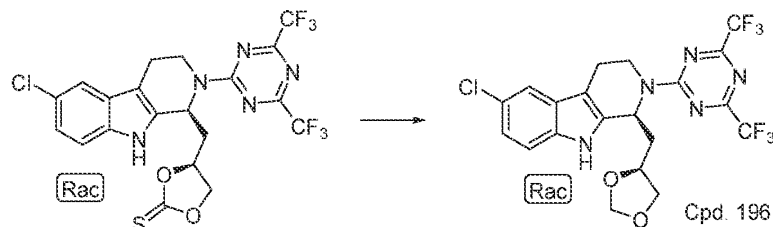
chromatography to give a racemic mixture of Compound 194A (4S)-4-(((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1,3-dioxolane-2-thione AND Compound 194B (4R)-4-(((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1,3-dioxolane-2-thione as a yellow solid. (400 mg, 86% yield) MS m/z 538.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 2.58 (s, 1 H) 2.74-2.93 (m, 2 H) 3.56-3.66 (m, 1 H) 4.43-4.53 (m, 1 H) 4.75-4.87 (m, 1 H) 4.89-5.01 (m, 1 H) 5.15-5.25 (m, 1 H) 6.13-6.22 (m, 1 H) 6.18 (s, 1 H) 7.05-7.13 (m, 1 H) 7.33-7.43 (m, 1 H) 7.46-7.55 (m, 1 H) 11.31-11.43 (m, 1 H)

[0284] Using the procedure described for Example 10, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
195A and 195B	MS m/z 536.0 $[M-H]^-$ 1H NMR (500 MHz, DMSO- d_6) δ ppm 2.42-2.48 (m, 1 H) 2.64-2.80 (m, 2 H) 2.85-2.93 (m, 1 H) 3.34 (br s, 2 H) 3.66 (br t, $J=11.67$ Hz, 1 H) 4.79-4.88 (m, 2 H) 4.97 (br d, $J=10.99$ Hz, 1 H) 5.27 (br s, 1 H) 5.90 (br d, $J=10.99$ Hz, 1 H) 7.10 (br d, $J=7.02$ Hz, 1 H) 7.42 (br d, $J=8.54$ Hz, 1 H) 7.51 (br s, 1 H) 11.12 (br s, 1 H)

Example 11

Synthesis of Compound 196



[0285] To a screw-cap vial equipped with magnetic stirring was charged a racemic mixture of (S)-4-(((S)-2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1,3-dioxolane-2-thione and (R)-4-(((R)-2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1,3-dioxolane-2-thione (350 mg, 0.7 mmol), 2,2'-azobis(2-methylpropionitrile) (9 mg, 0.06 mmol), triphenyltin hydride (460 mg, 1.3 mmol) and toluene (15 mL). The reaction mixture was flushed with nitrogen and kept under nitrogen. The reaction mixture was heated to 100 °C for 15 minutes. After 15 minutes the reaction was judged complete by LCMS analysis. The reaction mixture was put directly on silica gel and purified by silica gel

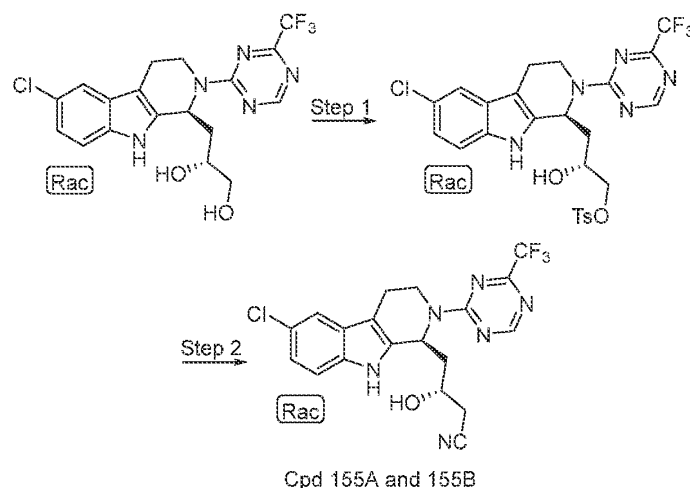
chromatography to give a racemic mixture of 2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxolan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white solid. (100 mg, 30% yield) MS m/z 508.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.98 (ddd, *J*=14.32, 10.07, 3.75 Hz, 1 H) 2.18 (td, *J*=11.98, 1.94 Hz, 1 H) 2.73-2.91 (m, 2 H) 3.20-3.31 (m, 2 H) 3.44-3.53 (m, 1 H) 3.54-3.62 (m, 1 H) 4.51-4.60 (m, 2 H) 4.95 (dd, *J*=13.13, 5.00 Hz, 1 H) 6.16 (dd, *J*=9.26, 3.50 Hz, 1 H) 7.06 (dd, *J*=8.57, 2.06 Hz, 1 H) 7.33 (d, *J*=8.50 Hz, 1 H) 7.47 (d, *J*=1.88 Hz, 1 H) 11.21 (br s, 1 H)

[0286] Using the procedure described for Example 11, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
197A and 197B	MS m/z 506.2 [M-H] ⁻ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 2.16-2.27 (m, 1 H) 2.30-2.39 (m, 1 H) 2.72-2.92 (m, 2 H) 3.63 (td, <i>J</i> =12.57, 4.00 Hz, 1 H) 3.76 (t, <i>J</i> =6.75 Hz, 1 H) 3.91-4.06 (m, 1 H) 4.17 (quin, <i>J</i> =6.47 Hz, 1 H) 4.69 (s, 1 H) 4.92 (s, 1 H) 4.93-5.02 (m, 1 H) 5.89 (br d, <i>J</i> =8.25 Hz, 1 H) 7.08 (br d, <i>J</i> =8.63 Hz, 1 H) 7.38 (d, <i>J</i> =8.50 Hz, 1 H) 7.49 (s, 1 H) 11.20 (s, 1 H)
198A and 198B	MS m/z 470.2 [M-H] ⁻ ¹ H NMR (400 MHz, ACETONITRILE- <i>d</i> ₃) δ ppm 2.16-2.34 (m, 2 H) 2.73-2.91 (m, 2 H) 3.35-3.43 (m, 1 H) 3.43-3.58 (m, 1 H) 3.83-4.00 (m, 1 H) 4.15-4.32 (m, 1 H) 4.77-4.89 (m, 1 H) 4.94-5.06 (m, 1 H) 5.06-5.20 (m, 1 H) 6.09-6.21 (m, 1 H) 6.29-6.68 (m, 2 H) 7.06-7.15 (m, 1 H) 7.28-7.42 (m, 1 H) 7.42-7.53 (m, 1 H) 9.28-9.42 (m, 1 H)

Example 12

Synthesis of Compound 155A and 155B



[0287] **Step 1:** To a screw-cap vial equipped with magnetic stirring was charged a racemic mixture of (S)-3-((S)-6-chloro-2-(4-(trifluoromethyl)-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-

1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol and (R)-3-((R)-6-chloro-2-(4-(trifluoromethyl)-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol (150 mg, 0.4 mmol), DCM (2 mL), NEt₃ (0.06 mL, 0.4 mmol) and p-toluenesulfonyl chloride (70 mg, 0.4 mmol). The reaction was stirred under nitrogen for 16 hours. After 16 hours the reaction was judged complete by LCMS. The reaction was put directly on silica gel and purified by silica gel chromatography. The title compound was isolated as a white solid (85 mg, 42% yield) and used directly in the next step.

[0288] **Step 2:** To a screw-cap vial equipped with magnetic stirring was charged sodium cyanide (35 mg, 0.71 mmol), a racemic mixture of (S)-3-((S)-6-chloro-2-(4-(trifluoromethyl)-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-hydroxypropyl 4-methylbenzenesulfonate and (R)-3-((R)-6-chloro-2-(4-(trifluoromethyl)-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-hydroxypropyl 4-methylbenzenesulfonate (87 mg, 0.13 mmol) and DMSO (1.0 mL). The reaction mixture was flushed with nitrogen and continued under nitrogen, then heated to 60 °C and allowed to stir for 20 minutes. After 20 minutes the reaction was judged complete by LCMS. The mixture was diluted with deionized water, extracted with EtOAc, dried over Na₂SO₄, and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography to give a racemic mixture of Compound 155A (3R)-4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-hydroxybutanenitrile AND Compound 155B (3S)-4-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-hydroxybutanenitrile as a white solid. (10 mg, 20% yield) MS m/z 504.3 [M-H]⁻. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.07-2.24 (m, 2 H) 2.60-2.68 (m, 1 H) 2.72-2.91 (m, 3 H) 3.50-3.63 (m, 1 H) 3.94-4.03 (m, 1 H) 4.94 (dd, *J*=13.32, 5.19 Hz, 1 H) 5.38 (d, *J*=5.63 Hz, 1 H) 5.99 (t, *J*=7.13 Hz, 1 H) 7.08 (dd, *J*=8.63, 2.13 Hz, 1 H) 7.38 (d, *J*=8.50 Hz, 1 H) 7.48 (d, *J*=1.88 Hz, 1 H) 11.11 (s, 1 H).

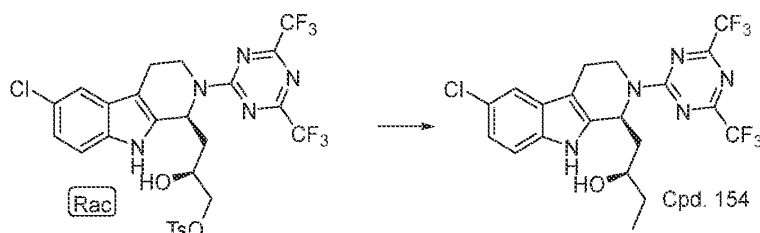
[0289] Using the procedure described for Example 12, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
76A and 76B	MS m/z 508.1 [M-H] ⁻ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 2.00-2.17 (m, 2 H) 2.74-2.92 (m, 2 H) 3.23 (s, 3 H) 3.24-3.27 (m, 2 H) 3.53- 3.61 (m, 1 H) 3.66 (br s, 1 H) 4.70 (d, <i>J</i> =5.38 Hz, 1 H) 4.94 (dd, <i>J</i> =13.32, 5.07 Hz, 1 H) 6.13 (dd, <i>J</i> =8.88, 4.00 Hz, 1 H) 7.06 (dd, <i>J</i> =8.57, 2.06 Hz, 1 H) 7.34 (d, <i>J</i> =8.63 Hz, 1 H) 7.47 (d, <i>J</i> =1.88 Hz, 1 H) 11.20 (s, 1 H)

Cpd	Data
77A and 77B	MS m/z 508.1 [M-H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 1.90-2.02 (m, 1 H) 2.12-2.32 (m, 1 H) 2.72-2.92 (m, 2 H) 3.23-3.30 (m, 5 H) 3.53-3.64 (m, 1 H) 3.82-3.89 (m, 1 H) 4.71 (d, <i>J</i> =5.38 Hz, 1 H) 4.94 (dd, <i>J</i> =13.32, 4.94 Hz, 1 H) 6.07 (dd, <i>J</i> =9.94, 4.44 Hz, 1 H) 7.07 (dd, <i>J</i> =8.57, 2.06 Hz, 1 H) 7.35 (d, <i>J</i> =8.50 Hz, 1 H) 7.47 (d, <i>J</i> =2.00 Hz, 1 H) 11.12 (s, 1 H)
156A and 156B	MS m/z 517.2 [M-H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.14 (s, 1H), 7.49 (s, 1H), 7.38 (d, <i>J</i> = 8.6 Hz, 1H), 7.08 (d, <i>J</i> = 8.4 Hz, 1H), 5.99 (dd, <i>J</i> = 9.6, 5.3 Hz, 1H), 4.95 (dd, <i>J</i> = 13.6, 5.2 Hz, 1H), 4.82 (d, <i>J</i> = 5.7 Hz, 1H), 3.59 (dd, <i>J</i> = 17.8, 7.3 Hz, 2H), 2.95-2.68 (m, 2H), 2.62-2.53 (m, 1H), 2.46-2.37 (m, 1H), 2.25-1.91 (m, 3H), 1.73-1.56 (m, 1H).
157A and 157B	MS m/z 517.2 [M-H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.22 (s, 1H), 7.48 (s, 1H), 7.35 (d, <i>J</i> = 8.6 Hz, 1H), 7.07 (d, <i>J</i> = 8.6 Hz, 1H), 6.14 (dd, <i>J</i> = 9.4, 3.9 Hz, 1H), 4.94 (dd, <i>J</i> = 13.4, 5.3 Hz, 1H), 4.73 (d, <i>J</i> = 5.6 Hz, 1H), 3.61 (dt, <i>J</i> = 12.7, 6.7 Hz, 2H), 3.07-2.70 (m, 2H), 2.28-1.95 (m, 2H), 1.68 (ddt, <i>J</i> = 28.9, 14.8, 8.1 Hz, 2H), 0.91-0.76 (m, 1H).

Example 13

Synthesis of Compound 154

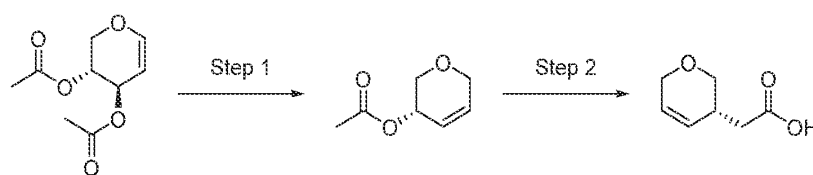


[0290] To a screw-cap vial equipped with magnetic stirring was charged cuprous iodide (200 mg, 1.0 mmol). The reaction was flushed with nitrogen and continued under nitrogen. To the reaction mixture was charged THF (1 mL). The reaction mixture was cooled to -40 °C, then methyl magnesium bromide solution in dibutyl ether (1.8 mL, 1.8 mmol) was added dropwise. The reaction mixture was allowed to stir for 15 minutes at -40 °C. To the reaction was added a racemic mixture of (S)-3-((S)-2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-hydroxypropyl 4-methylbenzenesulfonate and (R)-3-((R)-2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-hydroxypropyl 4-methylbenzenesulfonate (300 mg, 0.46 mmol) in THF (1 mL). The reaction was allowed to stir for 1 hour at -40 °C. After 1 hour the reaction was judged complete by LCMS. The reaction mixture was quenched with saturated ammonium chloride, extracted with EtOAc, dried over Na₂SO₄ and concentrated to dryness. The crude concentrate was purified by silica gel chromatography and reverse phase preparative HPLC to give (2R)-1-((1S)-2-[4,6-

bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]butan-2-ol as a white solid. (2.0 mg, 1% yield) MS m/z 494.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 0.72-0.85 (m, 3 H) 1.24-1.44 (m, 2 H) 1.88-2.11 (m, 2 H) 2.65-2.87 (m, 2 H) 3.34-3.46 (m, 1 H) 3.46-3.61 (m, 1 H) 4.28-4.42 (m, 1 H) 4.79-4.95 (m, 1 H) 5.97-6.11 (m, 1 H) 6.95-7.06 (m, 1 H) 7.18-7.35 (m, 1 H) 7.36-7.46 (m, 1 H) 11.07-11.20 (m, 1 H).

Example 14

Synthesis of (R)-2-(3,6-dihydro-2H-pyran-3-yl)acetic acid



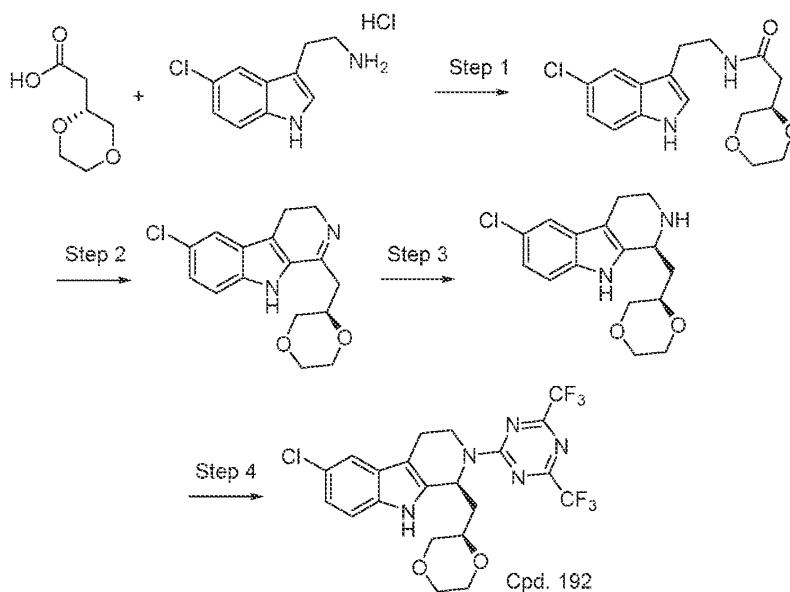
[0291] **Step 1:** To a screw-cap vial equipped with a magnetic stir bar was charged [(3R,4R)-4-acetoxy-3,4-dihydro-2H-pyran-3-yl] acetate (1.7 g, 8.5 mmol) DCM (6 mL). The reaction mixture was flushed with nitrogen and kept under nitrogen, triethylsilane (0.85 mL, 5.31 mmol) was added in one portion, followed by boron trifluoride diethyl etherate (0.62 mL, 4.9 mmol) dropwise (careful: exotherm). The reaction mixture was allowed to stir for 30 minutes then quenched with aqueous saturated bicarbonate solution. The aqueous layer was extracted with DCM (3x). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by silica gel chromatography 5-50% EtOAc in hexanes giving a clear oil which was used directly in the next step without further purification or analysis.

[0292] **Step 2:** To a flame dried scintillation vial, back filled with argon, was charged THF (30 mL), diisopropylamine (3.6 mL, 26 mmol). The reaction mixture was cooled to $-78^\circ C$, then n-butyl lithium in hexanes (2.5 mol/L, 9.3 mL, 23 mmol) was added. The resulting lithium diisopropylamide (LDA) solution was allowed to stir at $-78^\circ C$ for 10 minutes. To the LDA solution was added (3S)-3,6-dihydro-2H-pyran-3-yl] acetate (3 g, 21 mmol) in THF (15 mL) dropwise at $-78^\circ C$. The reaction mixture was allowed to stir at $-78^\circ C$ for 45 minutes. To the reaction was added tert-butyldimethylsilyl chloride (TBDMSCl) (4.26 g, 27.4 mmol) dissolved in N,N'-dimethylpropyleneurea (DMPU) (15 mL) dropwise at $-78^\circ C$. The reaction mixture was allowed to stir for 30 minutes at $-78^\circ C$, then placed in an ice bath and allowed to stir for an additional 30 minutes. The mixture was then allowed to warm to RT and stirred for 2 hours, then diluted with n-pentane and washed with DI water (3x). The water was back extracted with n-pentane. The n-pentane was passed through a drying tube and concentrated

to dryness. The resulting oil was dissolved in toluene (90 mL) and heated to 90 °C under nitrogen for 16 hours, then concentrated to dryness directly. The crude oil was dissolved in THF (35 mL) and water (15 mL) and heated to 70 °C for 3 hours, then diluted with saturated sodium bicarbonate and extracted with diethyl ether (2x). The aqueous layer was then acidified with 2N HCl until pH ~ 2. The acid aqueous layer was then extracted with dichloromethane (DCM) (3x). The organics were passed through a drying tube and concentrated to give the desired product (R)-2-(3,6-dihydro-2H-pyran-3-yl)acetic acid as a crude oil (1.5 g, 52% yield) ¹H NMR (400 MHz, CHCl₃-*d*) δ ppm 2.18-2.39 (m, 2 H) 2.41-2.54 (m, 1 H) 3.37-3.47 (m, 1 H) 3.64-3.77 (m, 1 H) 3.90-4.03 (m, 2 H) 5.54-5.73 (m, 2 H).

[0293] The product, obtained as described in Example 14 above, was used as a building block in other examples provided herein to obtain additional compounds.

Example 15 Synthesis of Compound 192



[0294] **Step 1:** To a screw-cap vial equipped with magnetic stirring was charged with 2-[(2R)-1,4-dioxan-2-yl]acetic acid (125 mg, 0.7 mmol), THF (1.5 mL), NEt₃ (0.22 mL, 1.6 mmol), HATU (315 mg, 0.8 mmol) and 2-(5-chloro-1H-indol-3-yl)ethyl ammonium chloride (168 mg, 0.7mmol). The reaction mixture was allowed to stir at room temperature for 3 hours. After 3 hours the reaction was judged complete by LCMS. The reaction was diluted with EtOAc, washed with 2N HCl, 2N NaOH, saturated bicarbonate, dried with Na₂SO₄, and

concentrated to dryness. The crude concentrate was purified by silica gel chromatography to give a white foam. (140 mg, 60% yield). The product was used directly in the next step without further purification.

[0295] **Step 2:** To a screw-cap vial equipped with magnetic stirring was charged (R)-N-(2-(5-chloro-1H-indol-3-yl)ethyl)-2-(1,4-dioxan-2-yl)acetamide (400 mg, 1.2 mmol). The reaction mixture was flushed with nitrogen and continued under nitrogen. To the reaction mixture was added acetonitrile (10 mL) and phosphoryl chloride (0.25 mL, 2.7 mmol). The reaction mixture was heated to 90 °C for 30 minutes. After 30 minutes the reaction was judged complete by LCMS. The reaction mixture was cooled to 0 °C and quenched with 20% NaOH until the pH was > 11. The product was extracted with EtOAc, dried over Na₂SO₄ and concentrated in vacuo. The product was purified using silica gel chromatography to give a solid. (318 mg, 84% yield) The resulting material was used directly in the next step without further purification.

[0296] **Step 3:** To a screw-cap vial equipped with magnetic stirring was charged (R)-1-((1,4-dioxan-2-yl)methyl)-6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indole (318 mg, 1.0 mmol). The reaction mixture was flushed with nitrogen and continued under nitrogen. To the reaction mixture was charged DCM (15 mL), formic acid triethylamine complex 5:2 (0.6 mL) and RuCl[(R,R)-TSDPEN](mesitylene) (20 mg, 0.03 mmol). The reaction mixture was allowed to stir at room temperature for 1 hour. After 1 hour a product was precipitated and the reaction was judged to be complete by LCMS. The reaction mixture was concentrated under vacuum and purified by reverse phase column to give a white solid (120 mg, 37% yield). The product was used directly in the next step without further purification.

[0297] **Step 4:** To a screw-cap vial equipped with magnetic stirring was charged (S)-1-(((R)-1,4-dioxan-2-yl)methyl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (65 mg, 0.2 mmol), acetonitrile (1 mL) and DIPEA (0.5 mL). The reaction mixture was flushed with nitrogen and continued under nitrogen. The reaction mixture was cooled to 0 °C. To the reaction mixture was charged 4-DMAP (23 mg, 0.2 mmol) and 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (70 mg, 0.21 mmol). The reaction mixture was allowed to stir for 15 minutes while warming to room temperature. After 15 minutes the reaction was judged complete by LCMS. The product was concentrated in vacuo and purified by silica gel chromatography to give (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(((2R)-1,4-dioxan-2-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white solid. (65 mg, 67% yield) MS m/z 520.1 [M-H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.03-2.11 (m, 2 H) 2.71-2.91 (m, 2 H) 3.21-3.31 (m, 2 H) 3.37-3.46 (m, 1 H) 3.47-3.63 (m, 3 H)

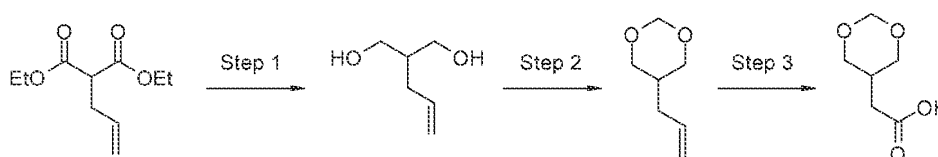
3.68-3.77 (m, 1 H) 3.84 (dd, $J=11.26, 2.13$ Hz, 1 H) 4.94 (dd, $J=13.32, 4.94$ Hz, 1 H) 6.02 (dd, $J=9.19, 4.44$ Hz, 1 H) 7.08 (dd, $J=8.63, 2.00$ Hz, 1 H) 7.37 (d, $J=8.50$ Hz, 1 H) 7.48 (d, $J=1.88$ Hz, 1 H) 11.11 (s, 1 H)

[0298] Using the procedure described for Example 15, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
191A and 191B	MS m/z 522.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 11.22 (d, $J=80.7$ Hz, 1H), 7.48 (dd, $J=6.6, 1.9$ Hz, 1H), 7.34 (dd, $J=29.1, 8.6$ Hz, 1H), 7.11–7.03 (m, 1H), 6.22–5.98 (m, 1H), 4.94 (dd, $J=13.4, 4.8$ Hz, 1H), 3.84 (dd, $J=11.3, 2.2$ Hz, 1H), 3.76–3.70 (m, 1H), 3.60 (dd, $J=15.1, 7.8$ Hz, 2H), 3.50 (d, $J=10.6$ Hz, 1H), 3.46–3.37 (m, 1H), 3.36–3.15 (m, 2H), 2.91–2.71 (m, 2H), 2.15–1.90 (m, 2H)
193	1H NMR (400 MHz, DMSO- d_6) δ ppm 1.90-2.00 (m, 1 H) 2.01-2.12 (m, 1 H) 2.68-2.90 (m, 2 H) 3.14-3.30 (m, 2 H) 3.41-3.53 (m, 3 H) 3.58-3.66 (m, 2 H) 3.68-3.75 (m, 1 H) 4.93 (br dd, $J=13.45, 4.69$ Hz, 1 H) 6.19 (br d, $J=8.38$ Hz, 1 H) 7.03-7.10 (m, 1 H) 7.30 (d, $J=8.63$ Hz, 1 H) 7.45-7.49 (m, 1 H) 11.32 (s, 1 H)
219A and 219B	MS m/z 521.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 11.20 (d, $J=57.2$ Hz, 1H), 7.51–7.44 (m, 2H), 7.33 (dd, $J=23.5, 8.6$ Hz, 1H), 7.06 (dt, $J=8.5, 3.1$ Hz, 1H), 6.21–5.94 (m, 1H), 4.92 (dd, $J=13.4, 4.7$ Hz, 1H), 3.91 (dd, $J=11.3, 2.3$ Hz, 1H), 3.67 (ddd, $J=8.9, 6.2, 2.5$ Hz, 1H), 3.59 (s, 1H), 3.46 (dd, $J=9.4, 3.5$ Hz, 2H), 3.43–3.24 (m, 3H), 2.85–2.69 (m, 2H), 2.13–1.98 (m, 2H).
314	MS m/z 516.0 $[M-H]^-$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.3 (s, 1H), 7.47 (s, 1H), 7.33 (d, $J=8.63$ Hz, 1H), 7.06 (br d, $J=8.63$ Hz, 1H), 6.19 (br d, $J=10.13$ Hz, 1H), 6.02 (br d, $J=8.25$ Hz, 1H), 5.81 (br d, $J=10.0$ Hz, 1H), 4.97-4.89 (m, 1H), 4.01 (br s, 2H), 3.75 (br dd, $J=10.88, 4.38$ Hz, 1H), 3.68-3.56 (m, 1H), 3.37 (br d, $J=5.38$ Hz, 1H), 2.91-2.73 (m, 2H), 2.31-2.22 (m, 1H), 2.13-9.14 (m, 2H)
315	MS m/z 516.0 $[M-H]^-$. 1H NMR (400 MHz, DMSO- d_6) δ 11.3 (s, 1H), 7.47 (m, 1H), 7.35-7.33 (d, $J=5.6$ Hz, 1H), 7.07-7.05 (dd, $J=8.4$ Hz, $J=2.0$ Hz, 1H), 5.94-5.90 (m, 1H), 5.77-5.67 (m, 2H), 4.94-4.90 (m, 1H), 4.04 (s, 2H), 3.91-3.87 (m, 1H), 3.83-3.79 (m, 1H), 3.65-3.62 (m, 1H), 2.89-2.77 (m, 2H), 2.22-2.47 (m, 1H), 2.09-2.02 (m, 2H)

Example 16

General Procedure for 2-(1,3-dioxan-5-yl)acetic acid Synthesis



[0299] **Step 1:** A solution of diethyl 2-allylpropanedioate (10.0 mL, 51.4 mmol) in THF (50 mL) was added dropwise to a stirred suspension of LAH (6.17 g, 154 mmol) in THF (200 mL) at 0 °C over 30 min. The ice bath was removed, and the reaction mixture was stirred at room temperature overnight at which time it was judged complete by TLC. After cooling to 0

°C, 6.0 mL of water, 6.0 mL of 15% sodium hydroxide aqueous solution, and 18 mL of water in this order were added to the reaction mixture. The reaction mixture was stirred for 15 min at room temperature, added some MgSO₄, then stirred for 15 more min. The slurry was filtered through celite, the filtrate was concentrated under reduced pressure to afford 2-allylpropane-1,3-diol as a colorless oil (5.80 g, 49.9 mmol, 97.1% yield), and the crude material was used in the next step without further purification. ¹H NMR (CDCl₃, 400 MHz) δ 5.74-5.88 (m, 1H), 5.02-5.13 (m, 2H), 3.60-3.88 (m, 4H), 2.08 (t, *J* = 6.94 Hz, 2H), 1.84-1.93 (m, 1H)

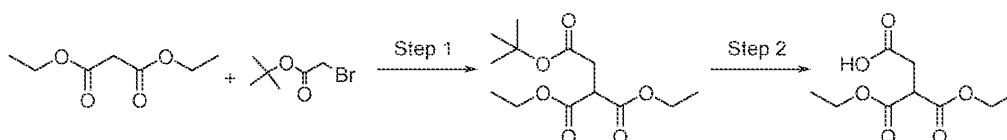
[0300] **Step 2:** Lithium bromide (2.17 g, 25.0 mmol), (1*S*)-(+)-camphor-10-sulfonic acid (3.00 g, 12.8 mmol) were added into a solution of 2-allylpropane-1,3-diol (5.80 g, 49.9 mmol) in dimethoxymethane (100 mL). The reaction mixture was stirred for 24 h at 50 °C at which time it was judged complete by TLC. Water was added to the reaction mixture, the aqueous layer was extracted with EtOAc (3 x 150 ml), the combined organic layers were dried over Na₂SO₄, and concentrated under reduced pressure. The material was purified by distillation at 18 mbar by Buchi vacuum pump and the heating block set at 160 °C. The material with boiling range 58-60 °C was collected to obtain 5-allyl-1,3-dioxane (4.20 g, 32.8 mmol, 65.6% yield) as a colorless oily material. ¹H NMR (CDCl₃, 400 MHz) δ 5.58-5.73 (m, 1H), 4.94-5.02 (m, 2H), 4.87-4.92 (m, 1H), 4.56-4.63 (m, 1H), 3.91-4.01 (m, 2H), 3.29-3.41 (m, 2H), 1.85-1.97 (m, 3H)

[0301] **Step 3:** 5-allyl-1,3-dioxane (4.20 g, 32.8 mmol) was dissolved in a mixture of ACN (82 mL) and water (82 mL) at rt. Ruthenium chloride (0.272 g, 1.31 mmol) and sodium periodate (31.5 g, 144 mmol) were added to the solution in one portion (caution: exothermic reaction!). The slurry was stirred at 0 °C for 30 min, then warmed to room temperature, and stirred for 2 h, at which time it was judged completed by TLC. The reaction mixture was quenched by saturated aqueous NaHSO₃ (150 ml) at 0 °C (caution: exotherm event!), then stirred for 1 more h. 2.0 M NaOH solution (~200 ml) to adjust pH >9 was added, then the aqueous layer was washed with DCM (2 x 150 ml). 2 M HCl solution (~100 ml) to adjust pH <2 was added to the aqueous solution at 0 °C. The aqueous layer was extracted with CHCl₃/IPA (3:1) (3 x 100 ml). The combined organic layers were dried over MgSO₄, filtered, and then concentrated under reduced pressure to afford 2-(1,3-dioxan-5-yl)acetic acid (3.40 g, 23.3 mmol, 71.0% yield) as a yellow oily material. ¹H NMR (CDCl₃, 400 MHz) δ 4.91 (d, *J* = 6.25 Hz, 1H), 4.81 (d, *J* = 6.25 Hz, 1H), 4.07 (dd, *J* = 11.38, 3.50 Hz, 2H), 3.66 (dd, *J* = 11.38, 6.50 Hz, 2H), 2.50 (d, *J* = 7.13 Hz, 2H), 2.25-2.35 (m, 1H)

[0302] The product, obtained as described in Example 16 above, was used as a building block in other examples provided herein to obtain additional compounds.

Example 17

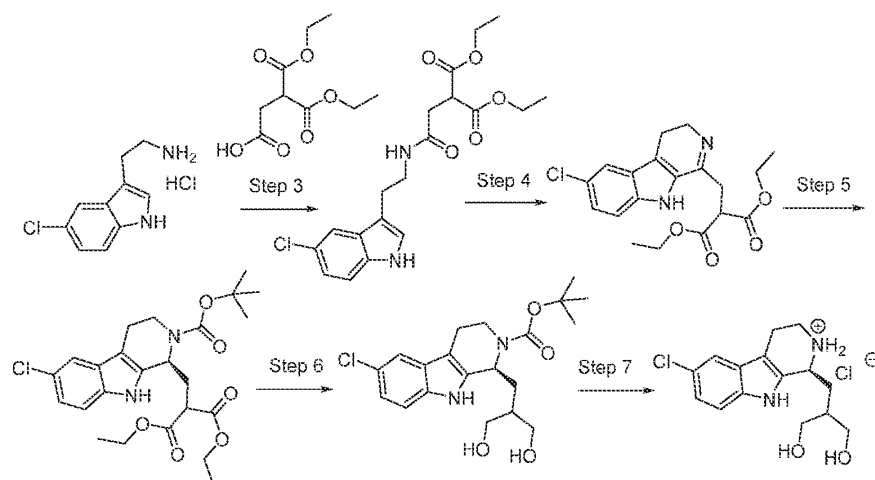
Procedure for 4-Ethoxy-3-(Ethoxycarbonyl)-4-Oxobutanoic Acid Synthesis



[0303] **Step 1:** To a suspension of sodium hydride in oil (60 mass%, 1.30 g, 32.5 mmol) in anhydrous THF (50 mL) at 0°C was added diethyl propanedioate (5 g, 31.2 mmol) dropwise. On complete addition, the reaction mixture was stirred for 1 h while warming to room temperature. The reaction mixture was then cooled to 0°C and tert-butyl bromoacetate (6.76 g, 32.9 mmol) was added dropwise to the stirring mixture, a white suspension formed, which was stirred overnight at room temperature. Saturated ammonium chloride solution (15 mL) was added, and the mixture was extracted with diethyl ether (20 mL) two times. The combined organic extract was dried over anhydrous sodium sulfate, concentrated under reduced pressure. The crude 2-(tert-butyl) 1,1-diethyl ethane-1,1,2-tricarboxylate was used in the next step without further purification.

[0304] **Step 2:** To a solution of 2-(tert-butyl) 1,1-diethyl ethane-1,1,2-tricarboxylate in dichloromethane (100 mL) was added TFA (40 g, 333.27 mmol). The mixture was stirred at ambient temperature for 3 h. Evaporated all volatiles, and the residual oil was used without further purification.

[0305] The product, obtained as described in Step 2 above, was used as a building block in other examples provided herein to obtain additional compounds.



[0306] **Step 3:** 4-Ethoxy-3-(ethoxycarbonyl)-4-oxobutanoic acid was dissolved in acetonitrile (70 mL) in a 250 mL RBF equipped with a magnetic stir bar, then the solution was immersed in an ice-water bath and stirred for 15 min. Chloro-*N,N,N',N'*-tetramethylformamidium hexafluorophosphate (TCFH) (10 g, 33.86 mmol) was added in one portion, followed by 1-methylimidazole (8.2 g, 95 mmol) in portions, maintaining internal temperature below 30°C using an ice-water bath. The resulting mixture was stirred for 15 min in the ice-water bath, allowed to cool to ~10°C, then 5-chlorotryptamine hydrochloride (8 g, 32.88 mmol) was added in one portion. The mixture was stirred for 15 h at ambient temperature. The mixture was partitioned between ethyl acetate and water, the organic phase was washed with brine, dried over MgSO_4 , then concentrated under reduced pressure. The crude material was purified with silica gel chromatography, eluting with 0-100% ethyl acetate in hexane to afford diethyl 2-[2-[2-(5-chloro-1H-indol-3-yl)ethylamino]-2-oxo-ethyl]propanedioate (7.92 g, 64.3% yield). (Trituration with DCM afforded a white solid). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 11.03 (br s, 1H), 8.11 (br t, $J=5.6$ Hz, 1H), 7.55 (d, $J=2.0$ Hz, 1H), 7.35 (d, $J=8.5$ Hz, 1H), 7.18-7.29 (m, 1H), 7.06 (dd, $J=8.5, 2.0$ Hz, 1H), 3.98-4.28 (m, 4H), 3.76 (t, $J=7.5$ Hz, 1H), 3.24-3.42 (m, 3H), 2.77 (t, $J=7.3$ Hz, 2H), 2.61-2.71 (m, 2H), 1.18 (t, $J=7.0$ Hz, 6H).

[0307] **Step 4:** A 250 mL of RBF was charged with diethyl 2-[2-[2-(5-chloro-1H-indol-3-yl)ethylamino]-2-oxo-ethyl]propanedioate (3.2 g, 8.1 mmol) and ACN (20 mL). The mixture was degassed under Argon, Phosphorus(V) oxychloride (4.0 g, 25.30 mmol) was added to it. The resulting mixture was stirred at 60°C overnight, then concentrated on rotavap to afford a light-yellow foam diethyl 2-((6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-

yl)methyl)malonate (3.95 g, ~85 mass%, 100% yield) used in the next step without further purification.

[0308] **Step 5:** Preparation of the free imine: Diethyl 2-((6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)methyl)malonate (965.0 mg, ~85% purity) was partitioned between dichloromethane and saturated NaHCO₃ (with ice). The organic phase was washed with brine, dried over MgSO₄, then concentrated on rotovap while keeping the water bath temperature less than 30°C. The free-base form of the imine is unstable and was used immediately without further purification. A RBF charged with diethyl 2-[(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)methyl]propanedioate (710.0 mg, 1.60 mmol, ~85 mass%), RuCl[(R,R)-Tsdpen](Mesitylene) (35.0 mg, 3%) and acetonitrile (5 mL), the mixture was degassed under argon. Then formic acid triethylamine complex 5:2 (0.95 mL, 2.2 mmol) was added dropwise at 0°C. After stirring for 5 min, it was warmed to room temperature and stirred for 30 min. TLC indicated complete consumption of the starting material. The mixture was cooled in ice bath, diluted with ethyl acetate (30 mL) and saturated aqueous solution of NaHCO₃ was added until pH reached ~ 8, followed by addition of tert-butoxycarbonyl tert-butyl carbonate (550.0 mg, 2.52 mmol) in ACN (0.5 mL). The resulting mixture was stirred at room temperature for 5 h. The organic phase was washed with brine, dried over MgSO₄, then concentrated under reduced pressure. The residual material was purified with silica gel chromatography, eluting with 0-60% ethyl acetate in hexane to afford the first fraction as the desired product diethyl 2-[[[(1S)-2-tert-butoxycarbonyl-6-chloro-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]methyl]propanedioate (445.0 mg, 58% yield). ¹H NMR ((400 MHz, CHCl₃-d) δ: 8.47-8.69 (m, 1H), 7.37-7.50 (m, 1H), 7.22-7.33 (m, 1H), 7.11-7.17 (m, 1H), 5.02-5.50 (m, 1H), 4.14-4.57 (m, 5H), 3.72-3.81 (m, 1H), 3.04-3.25 (m, 1H), 2.71-2.91 (m, 1H), 2.59-2.71 (m, 1H), 2.44-2.54 (m, 1H), 2.21-2.35 (m, 1H), 1.49 (s, 9H), 1.30 (s, 6H)

[0309] **Step 6:** A 100 mL RBF was charged with diethyl 2-[(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)methyl]propanedioate (445.0 mg, 0.93 mmol) and THF (2 mL), the mixture was placed in an ice bath and degassed under argon. Then lithium borohydride in THF (2.5 mL, 5.0 mmol, 2.0 mol/L) was added to it. The mixture was stirred at 60°C for 3 h. Upon completion, it was quenched with saturated aqueous solution of NH₄Cl at 0°C and stirred for 30 min, then extracted with ethyl acetate. The organic phase was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residual material was purified with silica gel chromatography, eluting with 0-10% methanol in dichloromethane to

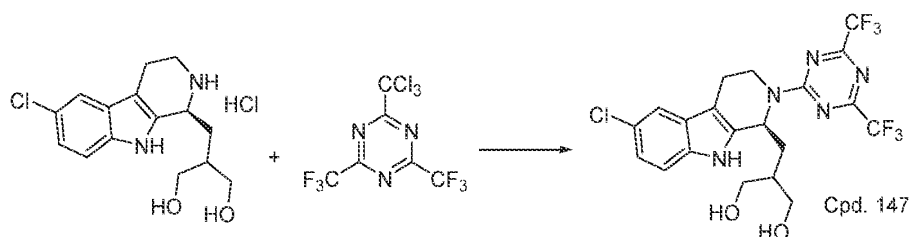
afford diethyl 2-[[[(1S)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]methyl]propanedioate (240.0 mg, 74% yield) as an off-white solid material.

[0310] **Step 7:** To tert-butyl (1S)-6-chloro-1-[3-hydroxy-2-(hydroxymethyl)propyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carboxylate (55 mg, 0.14 mmol) was added HCl in dioxane (0.5 mL, 4 mol/L). The mixture was stirred at room temperature for 4 h. After completion, the volatiles were evaporated and the remaining solid material (S)-6-chloro-1-(3-hydroxy-2-(hydroxymethyl)propyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-ium was used without further purification.

[0311] The product, obtained as described in Example 17 above, was used as a building block in other examples provided herein to obtain additional compounds.

Example 18

Synthesis of Compound 147



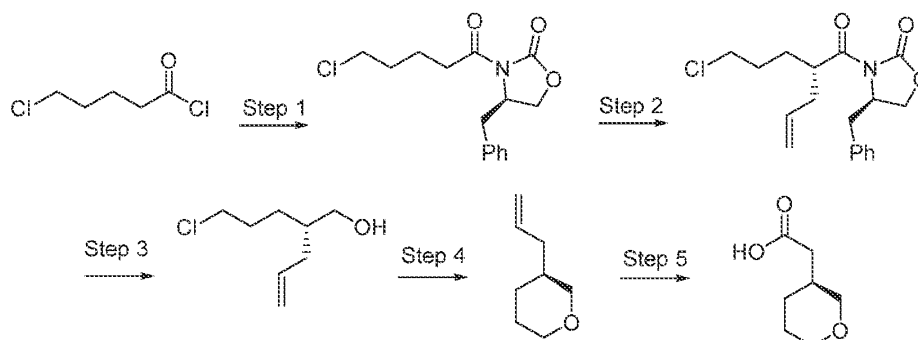
[0312] To a mixture of (S)-2-((6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)propane-1,3-diol hydrochloride (40 mg, 0.12 mmol), DMAP (35 mg, 0.28 mmol) and acetonitrile (0.8 mL) was added a solution of 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (80 mg, 0.24 mmol) in acetonitrile (0.2 mL, 99.8 mass%) at 0°C under argon. The mixture was stirred at room temperature for 90 min, then partitioned between ethyl acetate and 5% aqueous NH_4OH solution. The organic phase was washed with brine, dried over MgSO_4 , then concentrated under reduced pressure. The residual oil was purified via silica gel chromatography, eluting with 0-100% ethyl acetate and hexane to afford (S)-2-((2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)propane-1,3-diol (36 mg, 65% yield) as a white power. MS m/z 510.1 $[\text{M}+\text{H}]^+$, ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 11.07 (s, 1H), 7.40 (d, $J=1.8$ Hz, 1H), 7.29 (d, $J=8.5$ Hz, 1H), 7.00 (dd, $J=8.5, 2.0$ Hz, 1H), 5.95 (t, $J=7.3$ Hz, 1H), 4.77-4.94 (m, 1H), 4.29-4.42 (m, 1H), 4.20 (t, $J=5.4$ Hz, 1H), 3.63-3.63 (m, 1H), 3.44-3.67 (m, 2H), 3.39 (dt, $J=10.4, 5.4$ Hz, 1H), 3.13-3.29 (m, 1H), 2.62-2.91 (m, 2H), 1.91 (br t, $J=7.0$ Hz, 2H), 1.38-1.61 (m, 1H); ^{19}F NMR (400 MHz, $\text{DMSO}-d_6$) δ : -72.09 (d, $J=54.1$ Hz).

[0313] Using the procedure described for Example 18, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
119	ESI-MS m/z 478.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.23 (s, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.06 (q, J = 8.8 Hz, 1H), 5.88 (q, J = 9.2 Hz, 1H), 4.94 (q, J = 13.2 Hz, 1H), 3.52-3.59 (m, 1H), 2.80-2.85 (m, 1H), 2.72-2.76 (m, 1H), 1.98-2.08 (m, 2H), 1.22-1.47 (m, 4H), 0.86 (t, J = 6.8 Hz, 3H)
279	MS m/z 500.2 $[M-H]^-$; 1H NMR (DMSO- d_6) δ : 11.20-11.40 (m, 1H), 7.48 (s, 1H), 7.29-7.40 (m, 1H), 7.07 (br d, J = 8.8 Hz, 1H), 5.93-6.08 (m, 2H), 5.70-5.83 (m, 1H), 4.89-5.02 (m, 1H), 3.55-3.71 (m, 1H), 2.66-2.94 (m, 3H), 2.29-2.41 (m, 1H), 2.17-2.29 (m, 1H), 1.97-2.16 (m, 2H), 1.73-1.87 (m, 1H), 1.38-1.57 (m, 1H)

Example 19

Synthesis of Compound 49



[0314] **Step 1:** A solution of *n*-butyl lithium (10.0 mol/L) in hexanes (6.7 mL, 67.0 mmol) was added dropwise at -78 °C into a solution of the (4*R*)-4-benzyl-2-oxazolidin-2-one (10.0 g, 55.7 mmol) in tetrahydrofuran (230 mL). After stirring for 1 h, a solution of 5-chloropentanoyl chloride (8.5 mL, 64.0 mmol) in tetrahydrofuran (55 mL) was added dropwise. Stirring continued for 30 min at -78 °C and overnight at room temperature. Saturated aqueous NaHCO₃ (500 mL) and EtOAc (200 mL) were added, the layers were separated, and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, and concentrated under reduced pressure. After evaporation, the solid material formed, diethyl ether was added. The solid was filtered, then washed with diethyl ether to obtain the desired product (4*R*)-4-benzyl-3-(5-chloropentanoyl)oxazolidin-2-one (12.5 g, 42.4 mmol, 76.2% yield) as a white solid material. MS m/z 368.0 $[M+73, MeOH + H_2O \text{ adduction}]$, 1H NMR (CDCl₃, 400 MHz) δ 7.29-7.42 (m, 3H), 7.23 (d, J = 6.88 Hz, 2H), 4.65-4.75 (m, 1H), 4.16-4.26 (m, 2H), 3.56-

3.66 (m, 2H), 3.33 (dd, $J = 13.38, 3.38$ Hz, 1H), 2.89-3.08 (m, 2H), 2.80 (dd, $J = 13.38, 9.63$ Hz, 1H), 1.82-1.95 (m, 4H)

[0315] **Step 2:** To a stirred solution of (4*R*)-4-benzyl-3-(5-chloropentanoyl)oxazolidin-2-one (11.5 g, 38.8 mmol) in THF (100 mL) at -78 °C, sodium bis(trimethylsilyl)amide in THF (24.0 mL, 48.0 mmol, 2.00 mol/L) was added and stirring was continued at the same temperature for 1 h. Allyl iodide (7.3 mL, 77.7 mmol) was added to the reaction mixture and stirred until consumption of starting material as judged by TLC at -78 °C. After 3 h, the reaction mixture was quenched with saturated NH₄Cl solution, allowed to warm up to room temperature, then extracted with EtOAc (2 x 250 mL). The extracts were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography on ISCO with 20% EtOAc/Hex furnished the product (4*R*)-4-benzyl-3-[(2*S*)-2-(3-chloropropyl)pent-4-enoyl]oxazolidin-2-one (10.9 g, 32.7 mmol, 84.2% yield) as a colorless oily material. The diastereomeric ratio (>97/3) was measured by ¹H-NMR in acetone-*d*₆ and calculated from the ratio of integration for the signals at 2.86 ppm (minor diastereomer) and 2.80 ppm (major diastereomer) in acetone-*d*₆. MS *m/z* 336.8

[M+H]⁺, ¹H NMR (Acetone-*d*₆, 400 MHz) δ 7.14-7.27 (m, 5H), 5.66-5.82 (m, 1H), 4.93-5.06 (m, 2H), 4.66-4.73 (m, 1H), 4.24 (t, $J = 8.51$ Hz, 1H), 4.10-4.15 (m, 1H), 3.78 (dt, $J = 13.01, 6.63$ Hz, 1H), 3.47 (t, $J = 6.44$ Hz, 2H), 3.09 (dd, $J = 13.38, 3.13$ Hz, 1H), 2.80 (dd, $J = 13.45, 8.82$ Hz, 1H), 2.33-2.46 (m, 1H), 2.15-2.27 (m, 1H), 1.60-1.78 (m, 3H), 1.50-1.60 (m, 1H)

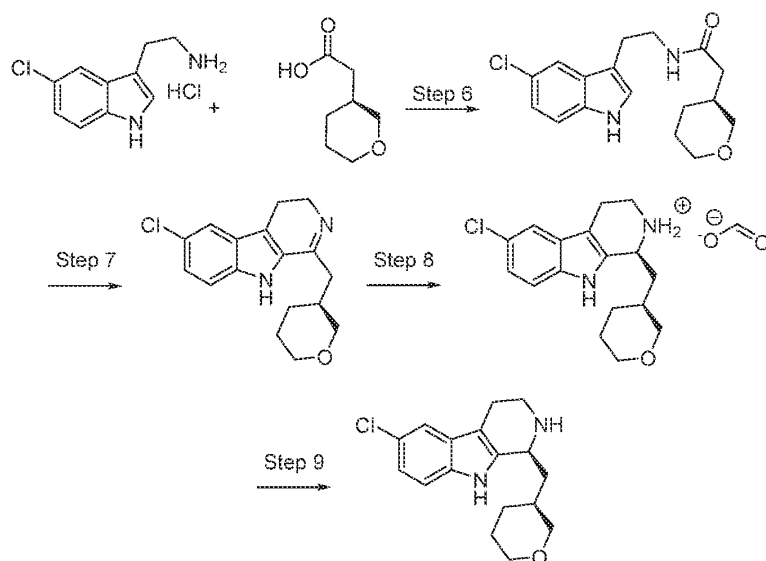
[0316] **Step 3:** (4*R*)-4-benzyl-3-[(2*S*)-2-(3-chloropropyl)pent-4-enoyl]oxazolidin-2-one (11.82 g, 35.2 mmol) was dissolved in Et₂O (80 mL) and water (0.63 mL, 35.2 mmol) was added. The mixture was cooled to 0 °C, lithium borohydride in THF (8.8 mL, 35.2 mmol, 4 mol/L) was added portionwise over 10 min and the reaction was stirred at the same temperature for another 2 h. The reaction mixture was quenched by the addition of aqueous HCl (125 mL, 1.0 M). The aqueous layer was extracted with Et₂O (3 x 150 mL) and the combined organic layers were washed with aqueous HCl (100 mL, 1.0 M), brine (100 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was dissolved in 1:3 EtOAc/Hex, the solution was loaded onto a cartridge containing 250 g of silica gel, and eluted with ~200 mL of 1:3 EtOAc/Hex. The filtrate was evaporated to afford the desired product (2*S*)-2-(3-chloropropyl)pent-4-en-1-ol (4.47 g, 27.5 mmol, 78.1% yield) as a colorless oil. ¹H NMR (CDCl₃, 400 MHz) δ 5.77-5.89 (m, 1H), 5.04-5.13 (m, 2H), 3.54-3.61 (m, 4H), 2.16 (t, $J = 6.88$ Hz, 2H), 1.81-1.89 (m, 2H), 1.61-1.70 (m, 1H), 1.47-1.58 (m, 2H)

[0317] **Step 4:** Sodium hydride in oil (60 mass%, 2.2 g, 55.0 mmol) and THF (14 mL) were added to a round bottom flask equipped with a mechanical stirrer. The suspension was cooled

to 5-10 °C in an ice bath and stirred for 5 min. A solution of (2*S*)-2-(3-chloropropyl)pent-4-en-1-ol (4.47 g, 27.5 mmol) in THF (14 mL) was added from an addition funnel over 25 min. The resulting creamy suspension was stirred for 30 min at the same temperature. The reaction mixture was warmed to room temperature and stirred overnight, at which time it was judged complete by TLC. The reaction mixture was cooled to 0 °C and quenched by addition of H₂O (100 mL) and HCl (1*N*, 100 mL). The phases were separated, and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic layers were washed with water, brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to furnish the crude product as a yellow oily material, which was purified by distillation at 25 mbar and the heating block setting at 90-100 °C, the material that distilled at 56-58 °C was collected to obtain (3*S*)-3-allyltetrahydropyran (1.92 g, 15.2 mmol, 55.4% yield) as a colorless oily material. Note: the crude material was unstable and quickly decomposed. If necessary, the material can be briefly stored under inert atmosphere in a refrigerator. ¹H NMR (DCM-*d*₂, 400 MHz) δ 5.59-5.70 (m, 1H), 4.83-4.91 (m, 2H), 3.65-3.71 (m, 2H), 3.13-3.25 (m, 1H), 2.90 (t, *J* = 10.57 Hz, 1H), 1.68-1.84 (m, 3H), 1.40-1.53 (m, 3H), 0.95-1.09 (m, 1H)

[0318] **Step 5:** (3*S*)-3-allyltetrahydropyran (1.90 g, 15.1 mmol) was dissolved in a mixture of ACN (38 mL) and water (38 mL) at rt. Ruthenium chloride (0.125 g, 0.60 mmol) and sodium periodate (14.5 g, 66.4 mmol) were added to the solution in one portion (caution: exothermic reaction). The slurry was stirred at 0 °C for 30 min, then warmed to room temperature, then stirred for 2 h, at which time it was judged completed by TLC. The reaction mixture was quenched by saturated aqueous solution of NaHSO₃ (150 mL) at 0 °C (caution: exothermic reaction) and stirred for 1 h. 2.0 *M* NaOH solution (~100 mL) to adjust pH >9 was added, then the aqueous layer was washed with DCM (2 x 150 mL). Conc. HCl solution (~100 mL) to adjust pH <2 was added to the aqueous solution at 0 °C. The aqueous layer was extracted with CHCl₃/IPA (3:1) (3 x 100 mL). The combined organic layers were dried over MgSO₄, filtered, and then concentrated under reduced pressure to afford 2-[(3*S*)-tetrahydropyran-3-yl]acetic acid (1.87 g, 13.0 mmol, 86.2% yield) as a yellow oily material, pure according to ¹H NMR spectrum. ¹H NMR (CDCl₃, 400 MHz) δ 3.83-3.95 (m, 2H), 3.39-3.48 (m, 1H), 3.13-3.26 (m, 1H), 2.18-2.33 (m, 2H), 2.09-2.18 (m, 1H), 1.88-1.99 (m, 1H), 1.60-1.70 (m, 2H), 1.24-1.35 (m, 1H).

[0319] The product, obtained as described in Step 5 above, was used as a building block in other examples provided herein to obtain additional compounds.



[0320] **Step 6:** To a 500-mL three-necked round-bottom flask was added a solution of 2-(5-chloro-1H-indol-3-yl)ethan-1-amine hydrochloride (9.62 g, 41.6 mmol) in DMF (200 mL) at room temperature. 2-[(3S)-tetrahydropyran-3-yl]acetic acid (6.00 g, 41.6 mmol), DIPEA (22.0 mL, 126 mmol) and HATU (24.2 g, 62.4 mmol) were then added in sequence. The mixture was stirred at room temperature for 1 h, at which time the reaction was deemed complete by UPLC analysis. The reaction mixture was quenched with water (500 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 200 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was dissolved in EtOAc, washed with 2 M NaOH, 2 M HCl, water, sat. NaHCO₃, brine, dried over Na₂SO₄, filtered, and then concentrated under reduced pressure to afford N-[2-(5-chloro-1H-indol-3-yl)ethyl]-2-[(3S)-tetrahydropyran-3-yl]acetamide (12.91 g, 40.24 mmol, 96.7% yield) as a white solid. MS *m/z* 321.0 [M+H]⁺, ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.08-1.17 (m, 1H), 1.40-1.56 (m, 2H), 1.65-1.73 (m, 1H), 1.85-1.98 (m, 3H), 2.73-2.83 (m, 2H), 2.91-3.05 (m, 1H), 3.22-3.34 (m, 3H), 3.64-3.76 (m, 2H), 7.06 (dd, *J* = 8.57, 1.69 Hz, 1H), 7.19-7.25 (m, 1H), 7.35 (d, *J* = 8.63 Hz, 1H), 7.54-7.59 (m, 1H), 7.92 (br t, *J* = 5.44 Hz, 1H), 11.03 (br s, 1H)

[0321] **Step 7:** To a 250-mL round-bottom flask was charged N-[2-(5-chloro-1H-indol-3-yl)ethyl]-2-[(3S)-tetrahydropyran-3-yl]acetamide (12.91 g, 40.24 mmol). The reaction vessel was flushed with nitrogen and then held under a nitrogen atmosphere. To the flask was charged MeCN (80 mL), and POCl₃ (9.4 mL, 100 mmol). The reaction mixture was heated to 50 °C for 1 h, whereupon LCMS analysis indicated complete consumption of starting

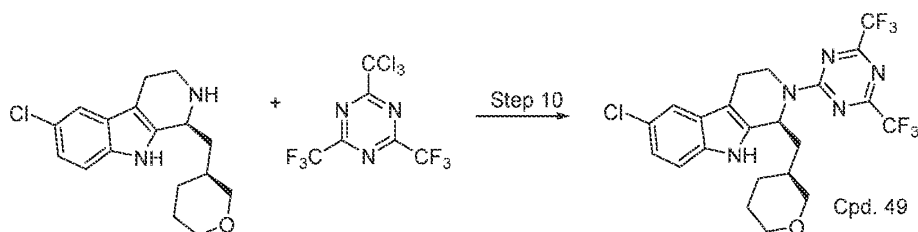
material. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was diluted with EtOAc and cooled to 0 °C. Saturated aqueous NaHCO₃ was added, the layers were shaken vigorously and separated, and the aqueous layer was extracted with EtOAc (3 x 250 ml). Combined organic layers were dried over Na₂SO₄, filtered, concentrated, and dried in a vacuum oven (50 °C, 30 mbar) overnight to afford 6-chloro-1-[[[(3S)-tetrahydropyran-3-yl]methyl]-4,9-dihydro-3H-pyrido[3,4-b]indole as a chlorophosphate or phosphate of unknown composition (14.56 g) as a yellow solid material. MS m/z 303.1 [M+H], ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.26-1.36 (m, 1H), 1.38-1.51 (m, 1H), 1.55-1.64 (m, 1H), 1.72-1.80 (m, 1H), 2.01-2.11 (m, 1H), 2.79-2.91 (m, 1H), 2.93-3.05 (m, 1H), 3.12-3.21 (m, 1H), 3.21-3.28 (m, 2H), 3.28-3.36 (m, 1H), 3.69-3.78 (m, 1H), 3.78-3.85 (m, 1H), 3.91-3.99 (m, 2H), 7.47 (br d, *J* = 8.88 Hz, 1H), 7.61 (d, *J* = 8.88 Hz, 1H), 7.95 (s, 1H), 12.43 (br s, 1H), 12.67 (s, 1H).

[0322] **Step 8:** The product 6-chloro-1-[[[(3S)-tetrahydropyran-3-yl]methyl]-4,9-dihydro-3H-pyrido[3,4-b]indole from Step 7 (14.56 g) was adjusted pH to ~9 by the slow addition of ~300 ml of 2 M aqueous Na₂CO₃. The heterogeneous mixture was then stirred for 30-60 min until all material dissolved. The resulting homogenous solution was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to give 12.51 g of the free imine as a pale-yellow solid material. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.21-1.28 (m, 1H), 1.41-1.50 (m, 1H), 1.52-1.60 (m, 1H), 1.77-1.86 (m, 1H), 2.00-2.07 (m, 1H), 2.42-2.50 (m, 1H), 2.69-2.78 (m, 3H), 3.08 (t, *J* = 10.32 Hz, 1H), 3.23-3.39 (m, 2H), 3.69-3.76 (m, 3H), 3.82 (br dd, *J* = 10.88, 3.25 Hz, 1H), 7.16-7.21 (d, *J* = 8.63 Hz, 1H), 7.43 (d, *J* = 8.63 Hz, 1H), 7.62 (s, 1H), 11.51 (s, 1H). To a 3-neck round-bottom flask under nitrogen atmosphere was added imine (12.51 g), RuCl[(R,R)-TsDPEN](mesitylene) (0.482 g, 0.727 mmol), and MeCN (58 mL) at room temperature. Formic acid triethylamine complex 5:2 (47 mL, 110 mmol) was then added, and the reaction mixture was stirred at rt for 40-60 min. The homogenous solution became a suspension within 5 min. Once full consumption of imine starting material had been confirmed by TLC and/or UPLC, 200 ml of diethyl ether was added to the reaction mixture. The resulting solid was collected by vacuum filtration through a fine glass frit, and the filter cake was washed with diethyl ether (2 x 50 mL). The filtrate was evaporated and then diluted with DCM (20 mL) and diethyl ether (200 mL). The resulting solid was again collected by vacuum filtration through a fine glass frit and washed with minimal diethyl ether. The combined solids were dried in a vacuum oven (50 °C, 30 mbar) overnight to afford (1S)-6-chloro-1-[[[(3S)-tetrahydropyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-ium formate (9.50

g, 27.1 mmol, 74.5% yield) as a pale-yellow solid. MS m/z 305.1 [M+H, free base], ^1H NMR (400 MHz, DMSO- d_6) δ 1.15-1.26 (m, 1H), 1.41-1.64 (m, 3H), 1.69-1.80 (m, 1H), 1.83-1.95 (m, 1H), 2.00 (br d, J = 11.51 Hz, 1H), 2.58-2.69 (m, 2H), 2.88-3.04 (m, 2H), 3.16-3.26 (m, 1H), 3.26-3.37 (m, 1H), 3.68-3.83 (m, 2H), 4.15 (br d, J = 9.51 Hz, 1H), 7.02 (br d, J = 8.63 Hz, 1H), 7.30 (d, J = 8.50 Hz, 1H), 7.41 (s, 1H), 8.25 (s, 1H), 11.01 (s, 1H).

[0323] **Step 9:** (1S)-6-chloro-1-[[[(3S)-tetrahydropyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-ium formate (5.91 g, 16.8 mmol) was adjusted pH to ~9 by the addition of ~200 ml of Na_2CO_3 aqueous solution and the heterogeneous solution was stirred for 30-60 min until all material dissolved. The resulting homogenous solution was extracted with EtOAc (3 X 150 mL), and the combined organic layers were dried over Na_2SO_4 , filtered, and concentrated in vacuo to give (1S)-6-chloro-1-[[[(3S)-tetrahydropyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (4.83 g, 15.8 mmol, 94.1% yield) as a yellow solid. MS m/z 305.1 [M+H], ^1H NMR (400 MHz, DMSO- d_6) δ 1.15-1.25 (m, 1H), 1.31-1.41 (m, 1H), 1.46-1.70 (m, 3H), 1.82-1.93 (m, 1H), 1.93-2.02 (m, 1H), 2.13-2.29 (m, 1H), 2.52-2.58 (m, 2H), 2.75-2.86 (m, 1H), 2.95-3.03 (m, 1H), 3.04-3.13 (m, 1H), 3.26-3.32 (m, 1H), 3.69-3.78 (m, 2H), 3.96 (br d, J = 9.51 Hz, 1H), 6.98 (br d, J = 8.50 Hz, 1H), 7.27 (d, J = 8.50 Hz, 1H), 7.36 (s, 1H), 10.88 (s, 1H).

[0324] The product, obtained as described in Step 9 above, was used as a building block in other examples provided herein to obtain additional compounds.



[0325] **Step 10:** To a mixture of (S)-6-chloro-1-(((S)-tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (500 mg, 1.64 mmol), DMAP (223 mg, 1.80 mmol) and acetonitrile (7 mL) was added drop-wise 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (539 mg, 1.81 mmol) at RT. The mixture was stirred at RT for 60 min. Upon completion the solution was diluted in ethyl acetate and the organic layer was washed with a saturated NH_4Cl solution and a 5% NH_4OH aqueous solution. The organic phase was washed again with Brine, dried over MgSO_4 , then condensed under reduced pressure. The residual oil was purified with silica gel chromatography, eluting with 0-100% ethyl acetate and hexane to afford (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-

chloro-1-([(3S)-oxan-3-yl]methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (853 mg, 65% yield) as a white power. ESI-MS m/z 518.1 [M-H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.28 (s, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 8.6, 2.1 Hz, 1H), 5.95 (dd, J = 10.7, 3.1 Hz, 1H), 4.91 (dd, J = 13.3, 5.0 Hz, 1H), 3.80-3.63 (m, 2H), 3.65-3.47 (m, 1H), 3.29 (d, J = 2.4 Hz, 1H), 3.00 (dd, J = 11.1, 9.7 Hz, 1H), 2.90-2.69 (m, 2H), 2.33 (d, J = 11.8 Hz, 1H), 1.88 (ddd, J = 14.0, 10.8, 3.1 Hz, 1H), 1.80-1.67 (m, 1H), 1.58 (td, J = 11.9, 3.7 Hz, 2H), 1.48-1.27 (m, 2H).

[0326] Using the procedure described for Example 19, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

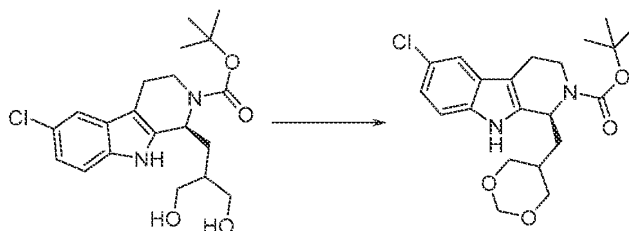
Cpd	Data
22	MS m/z 452.0 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 10.47 (s, 1H), 8.76-8.89 (m, 1H), 7.39 (s, 1H), 7.28 (d, J =8.5 Hz, 1H), 6.99 (dd, J =8.6, 1.9 Hz, 1H), 5.70-5.98 (m, 1H), 4.86-4.99 (m, 1H), 4.68-4.85 (m, 1H), 4.50-4.66 (m, 1H), 4.17 (br s, 1H), 3.73-3.95 (m, 1H), 3.54-3.66 (m, 1H), 3.31-3.50 (m, 2H), 2.59-2.81 (m, 2H), 1.64-2.00 (m, 3H)
23	MS m/z 498.0 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 11.26 (br s, 1H), 8.87-8.95 (m, 1H), 7.58-7.64 (m, 1H), 7.28-7.36 (m, 1H), 7.12-7.25 (m, 1H), 5.80-6.05 (m, 1H), 4.93-5.08 (m, 1H), 4.79-4.87 (m, 1H), 4.66 (d, J =6.0 Hz, 1H), 4.15-4.33 (m, 1H), 3.90 (br d, J =10.3 Hz, 1H), 3.60-3.78 (m, 1H), 3.30-3.56 (m, 2H), 2.66-2.93 (m, 2H), 1.71-2.06 (m, 3H)
24	MS m/z 484.2 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 11.21 (s, 1H), 7.38-7.42 (m, 1H), 7.28 (d, J =8.5 Hz, 1H), 7.00 (dd, J =8.8, 2.0 Hz, 1H), 6.56-6.90 (m, 2H), 5.87 (dd, J =10.6, 3.1 Hz, 1H), 4.85-4.95 (m, 1H), 4.75 (d, J =6.3 Hz, 1H), 4.59 (d, J =6.3 Hz, 1H), 4.17 (br dd, J =10.9, 3.4 Hz, 1H), 3.77-3.89 (m, 1H), 3.59-3.70 (m, 1H), 3.41-3.54 (m, 1H), 3.31-3.40 (m, 1H), 2.59-2.83 (m, 2H), 1.88-1.99 (m, 1H), 1.67-1.86 (m, 2H)
25	MS m/z 530.0 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 11.29 (s, 1H), 7.58-7.68 (m, 1H), 7.29-7.36 (m, 1H), 7.15-7.22 (m, 1H), 6.60-6.98 (m, 2H), 5.87-6.12 (m, 1H), 4.96 (br dd, J =13.5, 4.8 Hz, 1H), 4.82 (d, J =6.0 Hz, 1H), 4.63-4.71 (m, 1H), 4.18-4.29 (m, 1H), 3.85-3.95 (m, 1H), 3.67-3.77 (m, 1H), 3.48-3.61 (m, 1H), 3.38-3.47 (m, 1H), 2.65-2.90 (m, 2H), 1.73-2.08 (m, 3H)
28	MS m/z 520.1 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 11.28 (s, 1H), 7.43-7.54 (m, 1H), 7.37 (d, J =8.5 Hz, 1H), 7.08 (dd, J =8.8, 2.0 Hz, 1H), 5.82-5.96 (m, 1H), 4.92 (br dd, J =13.6, 4.9 Hz, 1H), 4.84 (d, J =6.3 Hz, 1H), 4.68 (d, J =6.0 Hz, 1H), 4.23 (br dd, J =11.0, 3.0 Hz, 1H), 3.90 (br dd, J =11.0, 3.3 Hz, 1H), 3.72 (dd, J =11.1, 7.4 Hz, 1H), 3.61 (td, J =12.6, 4.4 Hz, 1H), 3.38-3.50 (m, 1H), 2.72-2.93 (m, 2H), 1.97-2.11 (m, 1H), 1.91 (br t, J =11.1 Hz, 2H)
29	MS m/z 565.9 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 11.30 (s, 1H), 7.63 (s, 1H), 7.33 (d, J =8.5 Hz, 1H), 7.19 (d, J =8.5 Hz, 1H), 5.81-5.98 (m, 1H), 4.86-5.01 (m, 1H), 4.83 (d, J =5.8 Hz, 1H), 4.67 (d, J =6.3 Hz, 1H), 4.15-4.27 (m, 1H), 3.85-3.96 (m, 1H), 3.67-3.78 (m, 1H), 3.53-3.66 (m, 1H), 3.38-3.49 (m, 1H), 2.70-2.92 (m, 2H), 1.97-2.11 (m, 1H), 1.83-1.96 (m, 2H)

Cpd	Data
46	ESI-MS m/z 518.1 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.28 (s, 1H), 7.45 (d, J =2.0 Hz, 1H), 7.36 (d, J =8.8 Hz, 1H), 7.07 (dd, J =8.4, 2.0 Hz, 1H), 4.94-4.90 (m, 1H), 3.86-3.76 (m, 2H), 3.64-3.57 (m, 1H), 3.28-3.19 (m, 2H), 2.89-2.73 (m, 2H), 2.17 (d, J =12.8 Hz, 1H), 2.06-1.99 (m, 1H), 1.86-1.80 (m, 1H), 1.60-1.48 (m, 2H), 1.36-1.16 (m, 2H).
48	ESI-MS m/z 519.9 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24 (s, 1H), 7.47 (d, J =2.0 Hz, 1H), 7.35 (d, J =8.8 Hz, 1H), 7.05-7.08 (m, 1H), 5.87-5.91 (m, 1H), 4.88-4.92 (m, 1H), 4.05-4.08 (m, 1H), 3.59-3.70 (m, 2H), 3.21-3.29 (m, 2H), 2.83-2.87 (m, 2H), 1.86-1.95 (m, 2H), 1.64-1.76 (m, 2H), 1.47-1.52 (m, 2H), 1.18-1.27 (m, 1H).
51	ESI-MS m/z 464.1 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.17 (s, 1H), 7.32 (q, 1H, J =4.4 Hz), 7.18 (q, 1H, J =7.2 Hz), 6.92-6.87 (m, 1H), 5.93 (t, 1H, J =2.1 Hz), 4.90 (q, 1H, J =8 Hz), 3.74-3.66 (m, 2H), 3.62-3.56 (m, 1H), 3.29-3.26 (m, 1H), 2.99 (t, 1H, J =10.4 Hz), 2.84-2.75 (m, 2H), 2.33-2.32 (m, 1H), 1.87-1.84 (m, 1H), 1.77-1.71 (m, 1H), 1.61-1.55 (m, 2H), 1.44-1.30 (m, 2H).
52	ESI-MS m/z 502.0 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.12 (s, 1H), 7.32 (q, 1H, J =4 Hz), 7.17 (q, 1H, J =8.8 Hz), 6.92-6.87 (m, 1H), 5.89 (q, 1H, J =5.6 Hz), 4.90 (q, 1H, J =9.6 Hz), 4.07 (q, 1H, J =8 Hz), 3.70-3.59 (m, 2H), 3.31-3.20 (m, 2H), 2.81-2.76 (m, 2H), 1.93-1.86 (m, 2H), 1.76-1.61 (m, 1H), 1.51-1.45 (m, 2H), 1.24-1.19 (m, 2H).
56	ESI-MS m/z 452.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.29-11.09 (m, 1H), 8.88-8.85 (m, 1H), 7.46-7.44 (m, 1H), 7.37-7.33 (m, 0.7H), 7.29-7.27 (m, 0.3H), 7.07-7.03 (m, 1H), 6.21-5.96 (m, 1H), 5.02-4.87 (m, 1H), 3.91-3.86 (m, 0.3H), 3.61-3.58 (m, 0.7H), 3.50-3.43 (m, 1H), 3.18-3.01 (m, 1H), 2.88-2.79 (m, 1H), 2.79-2.50 (m, 1H), 2.16-2.00 (m, 2H), 2.00-1.71 (m, 2H), 1.50-1.38 (m, 4H), 1.25-1.20 (m, 1H).
122	MS m/z 490 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23 (s, 1H), 7.48 (t, J =1.6 Hz, 1H), 7.35 (d, J =8.6 Hz, 1H), 7.07 (dd, J =8.6, 2.1 Hz, 1H), 5.99-5.84 (m, 1H), 4.94 (dd, J =13.3, 4.7 Hz, 1H), 3.56 (td, J =12.8, 4.3 Hz, 1H), 2.97-2.67 (m, 2H), 2.03-2.01 (m, 2H), 1.41-1.23 (m, 6H), 0.85 (t, J =7.1 Hz, 3H).
150	MS m/z 472.1 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.06-11.29 (m, 1H), 7.47 (d, J =2.0 Hz, 1H), 7.32-7.40 (m, 1H), 7.03-7.11 (m, 1H), 6.58-6.96 (m, 2H), 6.01-6.12 (m, 1H), 4.98 (br dd, J =13.4, 5.1 Hz, 1H), 4.41 (t, J =5.1 Hz, 1H), 4.31 (t, J =5.4 Hz, 1H), 3.40-3.71 (m, 4H), 3.25-3.36 (m, 1H), 2.67-2.91 (m, 2H), 1.90-2.02 (m, 2H), 1.45-1.58 (m, 1H).
169	MS m/z 476.1 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.94 (s, 1H), 7.49 (s, 1H), 7.41 (d, J =8.6 Hz, 1H), 7.08 (dd, J =8.6, 2.1 Hz, 1H), 6.25 (dd, J =7.6, 5.3 Hz, 1H), 4.95 (dd, J =13.4, 5.2 Hz, 1H), 3.59 (td, J =12.6, 4.4 Hz, 1H), 3.31-3.23 (m, 1H), 3.13 (dd, J =16.1, 7.7 Hz, 1H), 2.95-2.70 (m, 2H), 2.20 (s, 3H).
185	MS m/z 442.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.98-11.11 (m, 1H), 8.79 (d, J =13.8 Hz, 1H), 7.34-7.45 (m, 1H), 7.28 (d, J =8.5 Hz, 1H), 6.99 (dd, J =8.6, 1.9 Hz, 1H), 5.85-6.08 (m, 1H), 4.72-5.03 (m, 1H), 4.14-4.45 (m, 2H), 3.33-3.61 (m, 4H), 3.19-3.28 (m, 1H), 2.57-2.81 (m, 2H), 1.81-1.94 (m, 2H), 1.39-1.57 (m, 1H).

Cpd	Data
278	MS m/z 592.1 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 11.22-11.39 (m, 1H), 7.50 (d, J =2.0 Hz, 1H), 7.38 (d, J =8.5 Hz, 1H), 7.09 (dd, J =8.6, 2.1 Hz, 1H), 6.06 (dd, J =10.9, 2.4 Hz, 1H), 4.81-4.97 (m, 1H), 3.84-4.40 (m, 5H), 3.65-3.78 (m, 1H), 3.44-3.61 (m, 1H), 2.82-2.95 (m, 1H), 2.63-2.82 (m, 2H), 1.19 (t, J =7.1 Hz, 3H), 1.07 (t, J =7.1 Hz, 3H)

Example 20

Procedure for tert-butyl (S)-1-((1,3-dioxan-5-yl)methyl)-6-chloro-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate synthesis



[0327] An 8 mL vial equipped with a stir bar was charged with tert-butyl (1S)-6-chloro-1-[3-hydroxy-2-(hydroxymethyl)propyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carboxylate (75.0 mg, 0.18 mmol), (1S)-(+)-camphor-10-sulfonic acid (50.0 mg, 0.21 mmol), and lithium bromide (25.0 mg, 0.29 mmol), then degassed under argon. Dimethoxymethane (1mL) was added and the mixture was stirred at room temperature for 3 days. The mixture was partitioned between ethyl acetate and water, the organic phase was washed with brine, dried over MgSO₄, then concentrated. The residual oil was purified by silica gel chromatography, eluting with 0-100% ethyl acetate in hexane to afford tert-butyl (1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carboxylate (38.0 mg, 51.8% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ : 11.02-11.26 (m, 1H), 7.43 (s, 1H), 7.32 (d, J =8.5 Hz, 1H), 7.01-7.09 (m, 1H), 5.04-5.28 (m, 1H), 4.83-4.96 (m, 1H), 4.58-4.71 (m, 1H), 4.05-4.34 (m, 2H), 3.89-4.01 (m, 1H), 3.51-3.62 (m, 1H), 3.36-3.46 (m, 1H), 3.01-3.21 (m, 1H), 2.56-2.70 (m, 2H), 1.82-2.05 (m, 1H), 1.53-1.80 (m, 2H), 1.38-1.50 (m, 9H)

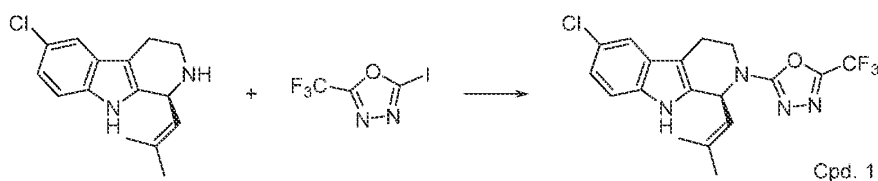
[0328] The product, obtained as described in Example 20 above, was used as a building block in other examples provided herein to obtain additional compounds such as those selected from:

Cpd	Data
30A and 30B	MS m/z 522.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 11.22 (s, 1H), 7.49 (d, J =2.1 Hz, 1H), 7.38 (d, J =8.6 Hz, 1H), 7.08 (dd, J =8.6, 2.1 Hz, 1H), 5.96 (d, J =8.0 Hz, 1H), 4.94 (dd, J =13.1, 5.0 Hz, 1H), 4.80 (d, J =6.2 Hz, 1H), 4.49 (d, J =6.2 Hz, 1H), 4.02 (dd, J =11.2, 4.6 Hz, 1H), 3.79 (d, J =9.2 Hz, 1H), 3.61 (t, J =12.2 Hz, 2H), 3.06-2.82 (m, 1H), 2.81-2.68 (m, 1H), 2.31-2.07 (m, 2H), 1.88 (d, J =13.0 Hz, 1H), 1.81-1.61 (m, 1H).

Cpd	Data
31A and 31B	MS m/z 522.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.35 (s, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.30 (d, <i>J</i> = 8.6 Hz, 1H), 7.06 (dd, <i>J</i> = 8.5, 2.0 Hz, 1H), 6.33-5.99 (m, 1H), 4.93 (q, <i>J</i> = 6.2, 4.6 Hz, 2H), 4.56 (d, <i>J</i> = 6.3 Hz, 1H), 3.95 (dd, <i>J</i> = 11.2, 4.6 Hz, 1H), 3.77-3.51 (m, 3H), 2.93-2.70 (m, 2H), 2.31-2.00 (m, 2H), 1.63 (dd, <i>J</i> = 12.1, 4.8 Hz, 1H), 1.42 (d, <i>J</i> = 13.0 Hz, 1H).
244	MS m/z 453.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.21 (s, 1H), 8.75 (d, <i>J</i> = 4.8 Hz, 1H), 7.43 (d, <i>J</i> = 2.0 Hz, 1H), 7.32 (d, <i>J</i> = 8.4 Hz, 1H), 7.07 (d, <i>J</i> = 4.8 Hz, 1H), 7.04 (dd, <i>J</i> = 6.8 Hz, 1H), 5.95-5.85 (m, 1H), 4.98-4.89 (m, 1H), 4.83 (d, <i>J</i> = 6.4 Hz, 1H), 4.62 (d, <i>J</i> = 6.0 Hz, 1H), 4.25 (d, <i>J</i> = 10.0 Hz, 1H), 3.90 (d, <i>J</i> = 11.2 Hz, 1H), 3.67-3.62 (m, 1H), 3.43-3.38 (m, 2H), 2.73-2.69 (m, 2H), 1.90-1.80 (m, 3H).
247	MS m/z 518.9 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23 (s, 1H), 7.51 (s, 1H), 7.45 (d, <i>J</i> = 2.0 Hz, 1H), 7.34 (d, <i>J</i> = 8.8 Hz, 1H), 7.05 (dd, <i>J</i> = 8.4 Hz, <i>J</i> = 2.0 Hz, 1H), 5.87 (dd, <i>J</i> = 10.8 Hz, <i>J</i> = 3.2 Hz, 1H), 4.88 (dd, <i>J</i> = 13.2 Hz, <i>J</i> = 4.4 Hz, 1H), 4.83 (d, <i>J</i> = 6.4 Hz, 1H), 4.64 (d, <i>J</i> = 6.4 Hz, 1H), 4.24 (dd, <i>J</i> = 11.2 Hz, <i>J</i> = 3.6 Hz, 1H), 3.91 (dd, <i>J</i> = 11.0 Hz, <i>J</i> = 3.6 Hz, 1H), 3.70-3.66 (m, 1H), 3.55-3.48 (m, 1H), 3.45-3.40 (m, 1H), 2.82-2.69 (m, 2H), 2.00-1.93 (m, 1H), 1.89-1.82 (m, 2H).

Example 21

Synthesis of Compound 1

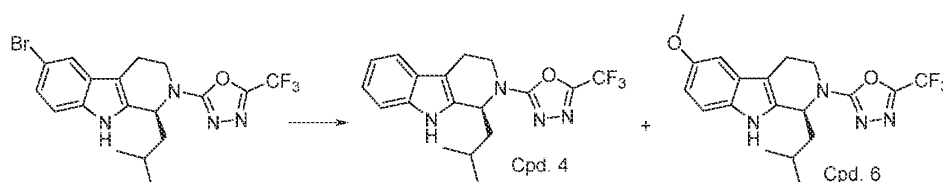


[0329] A 40 mL vial equipped with a stir bar was charged with (1S)-6-chloro-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (200 mg, 0.767 mmol), acetonitrile (4 mL), 2-iodo-5-(trifluoromethyl)-1,3,4-oxadiazole (230 mg, 0.87 mmol) and N,N-diisopropylethylamine (0.33 mL, 1.9 mmol). The vial was closed and the mixture allowed to stir at ambient temperature for 14 h. The reaction mixture was concentrated under reduced pressure and the resulting residue subjected to silica gel purification (hexanes EtOAc eluent) to provide (1S)-6-chloro-1-(2-methylprop-1-en-1-yl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (156 mg, 0.393 mmol, 45% yield) isolated as an off-white amorphous solid. MS m/z 395.1 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.04 (s, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.08 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.84 (d, *J* = 9.8 Hz, 1H), 5.45 (dt, *J* = 9.9, 1.5 Hz, 1H), 4.22 (dt, *J* = 13.2, 3.7 Hz, 1H), 3.64 (dt, *J* = 13.4, 8.0 Hz, 1H), 2.86 (dd, *J* = 7.9, 3.6 Hz, 2H), 1.97 (d, *J* = 1.3 Hz, 3H), 1.74 (d, *J* = 1.3 Hz, 3H); ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ 64.59.

[0330] Using the procedure described for Example 21, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
5	MS m/z 423.0 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24 (s, 1H), 7.61 (d, <i>J</i> = 1.9 Hz, 1H), 7.31 (d, <i>J</i> = 8.5 Hz, 1H), 7.17 (dd, <i>J</i> = 8.6, 1.9 Hz, 1H), 5.28-5.19 (m, 1H), 4.16 (dd, <i>J</i> = 13.9, 5.3 Hz, 1H), 3.67-3.55 (m, 1H), 2.93-2.81 (m, 1H), 2.76 (dd, <i>J</i> = 15.6, 4.2 Hz, 1H), 1.95 (t, <i>J</i> = 10.7 Hz, 1H), 1.80-1.65 (m, 2H), 1.07 (d, <i>J</i> = 6.0 Hz, 3H), 0.94 (d, <i>J</i> = 6.3 Hz, 3H); ¹⁹ F NMR (376 MHz, DMSO- <i>d</i> ₆) δ -64.57.
7	MS m/z 439.1 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24 (s, 1H), 7.47 (d, <i>J</i> = 2.1 Hz, 1H), 7.36 (d, <i>J</i> = 8.6 Hz, 1H), 7.07 (dd, <i>J</i> = 8.5, 2.1 Hz, 1H), 5.27 (dd, <i>J</i> = 10.7, 3.3 Hz, 1H), 4.16 (dd, <i>J</i> = 13.9, 5.2 Hz, 1H), 3.80-3.55 (m, 3H), 3.35 (d, <i>J</i> = 2.6 Hz, 1H), 3.04 (dd, <i>J</i> = 11.1, 9.1 Hz, 1H), 2.95-2.70 (m, 2H), 2.20-2.06 (m, 1H), 1.91-1.58 (m, 4H), 1.55-1.26 (m, 2H).
8	MS m/z 439.0 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.19 (s, 1H), 7.47 (d, <i>J</i> = 2.1 Hz, 1H), 7.36 (d, <i>J</i> = 8.6 Hz, 1H), 7.07 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 5.22 (t, <i>J</i> = 7.2 Hz, 1H), 4.16 (dd, <i>J</i> = 14.0, 5.2 Hz, 1H), 4.02 (d, <i>J</i> = 9.9 Hz, 1H), 3.74 (d, <i>J</i> = 11.2 Hz, 1H), 3.68-3.56 (m, 1H), 3.31-3.27 (m, 1H), 3.19 (dd, <i>J</i> = 11.1, 9.0 Hz, 1H), 3.07-2.69 (m, 2H), 1.96-1.69 (m, 3H), 1.52 (ddq, <i>J</i> = 14.2, 10.2, 4.4, 4.0 Hz, 2H), 1.33-1.12 (m, 2H).
11A and 11B	MS m/z 483.2 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.26 (s, 1H), 7.67 (d, <i>J</i> = 1.9 Hz, 1H), 7.38 (d, <i>J</i> = 8.6 Hz, 1H), 7.24 (dd, <i>J</i> = 8.6, 2.0 Hz, 1H), 5.33-5.23 (m, 1H), 4.21 (dd, <i>J</i> = 14.1, 5.3 Hz, 1H), 4.08-4.04 (m, 1H), 3.80 (d, <i>J</i> = 11.2 Hz, 1H), 3.74-3.60 (m, 1H), 3.24 (dd, <i>J</i> = 11.1, 9.0 Hz, 1H), 3.02-2.88 (m, 1H), 2.83 (dd, <i>J</i> = 15.5, 4.2 Hz, 1H), 1.96-1.67 (m, 4H), 1.65-1.45 (m, 1H), 1.38-1.16 (m, 4H).
12	MS m/z 430.2 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.31 (s, 1H), 8.04 (s, overlapping 2H), 8.03 (s, overlapping 1H), 7.78 (dd, <i>J</i> = 8.8, 2.1 Hz, 1H), 7.49 (d, <i>J</i> = 8.8 Hz, 1H), 5.28 (d, <i>J</i> = 10.4 Hz, 1H), 4.19 (dd, <i>J</i> = 13.7, 5.3 Hz, 1H), 3.72-3.59 (m, 1H), 3.03-2.91 (m, 1H), 2.85 (dd, <i>J</i> = 15.5, 4.1 Hz, 1H), 1.98 (t, <i>J</i> = 10.6 Hz, 1H), 1.75 (d, <i>J</i> = 11.7 Hz, 2H), 1.09 (d, <i>J</i> = 5.8 Hz, 3H), 0.95 (dd, <i>J</i> = 6.4, 4.9 Hz, 3H); ¹⁹ F NMR (376 MHz, DMSO- <i>d</i> ₆) δ -64.54.
332	MS m/z 457.3 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.26 (s, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.36 (d, <i>J</i> = 8.6 Hz, 1H), 7.07 (dd, <i>J</i> = 8.5, 2.1 Hz, 1H), 5.58 (dd, <i>J</i> = 10.3, 3.7 Hz, 1H), 3.93 (dd, <i>J</i> = 12.8, 5.1 Hz, 2H), 3.75-3.53 (m, 2H), 3.31-3.28 (m, 1H), 3.06 (dd, <i>J</i> = 11.1, 9.3 Hz, 1H), 2.94 (ddd, <i>J</i> = 16.8, 10.8, 6.3 Hz, 1H), 2.78 (dd, <i>J</i> = 15.1, 3.6 Hz, 1H), 2.12 (d, <i>J</i> = 12.1 Hz, 1H), 1.93-1.75 (m, 2H), 1.71-1.60 (m, 2H), 1.51-1.28 (m, 2H).
333	MS m/z 457.1 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.14 (s, 1H), 7.40 (d, <i>J</i> = 2.0 Hz, 1H), 7.29 (d, <i>J</i> = 8.6 Hz, 1H), 7.00 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 5.47 (t, <i>J</i> = 7.1 Hz, 1H), 4.08-3.93 (m, 1H), 3.87 (dt, <i>J</i> = 10.7, 3.0 Hz, 2H), 3.67 (dt, <i>J</i> = 11.3, 3.9 Hz, 1H), 3.25-3.18 (m, 1H), 3.12 (dd, <i>J</i> = 11.1, 9.3 Hz, 1H), 2.87 (ddd, <i>J</i> = 16.7, 10.4, 7.1 Hz, 1H), 2.72 (dt, <i>J</i> = 15.8, 3.1 Hz, 1H), 1.86-1.57 (m, 4H), 1.44 (qt, <i>J</i> = 9.8, 4.3 Hz, 2H), 1.17 (dtd, <i>J</i> = 14.7, 10.2, 5.4 Hz, 1H).
334	MS m/z 455.1 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.17 (s, 1H), 7.42 (d, <i>J</i> = 2.0 Hz, 1H), 7.30 (d, <i>J</i> = 8.6 Hz, 1H), 7.01 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 5.44 (s, 1H), 3.83 (s, 2H), 3.72-3.49 (m, 2H), 3.25-3.16 (m, 1H), 2.96 (t, <i>J</i> = 10.3 Hz, 1H), 2.79 (ddd, <i>J</i> = 18.3, 13.1, 9.5 Hz, 2H), 2.16 (d, <i>J</i> = 12.0 Hz, 1H), 1.87-1.63 (m, 2H), 1.59-1.43 (m, 2H), 1.40-1.04 (m, 2H).

Cpd	Data
335	MS m/z 455.1 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.18 (s, 1H), 7.49 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.08 (dd, J = 8.6, 2.1 Hz, 1H), 5.43 (s, 1H), 4.06 (d, J = 11.0 Hz, 1H), 3.91 (s, 2H), 3.72 (d, J = 11.1 Hz, 1H), 3.31-3.26 (m, 1H), 3.19 (dd, J = 11.0, 9.3 Hz, 1H), 3.01-2.72 (m, 2H), 1.88 (dt, J = 9.5, 4.7 Hz, 2H), 1.79 (d, J = 12.1 Hz, 1H), 1.67 (d, J = 10.0 Hz, 1H), 1.61-1.37 (m, 2H), 1.31-1.15 (m, 1H).
336	MS m/z 414.1 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.22 (s, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.08 (dd, J = 8.6, 2.1 Hz, 1H), 5.47 (s, 1H), 3.87 (d, J = 24.2 Hz, 2H), 3.04-2.69 (m, 2H), 2.08-1.85 (m, 1H), 1.84-1.47 (m, 2H), 1.02 (dd, J = 59.8, 6.2 Hz, 6H).

Example 22**Synthesis of Compound 4 and Compound 6**

[0331] An 8 mL vial equipped with septum cap and a stir bar was charged with 2-[(1S)-6-bromo-1-isobutyl-1,3,4,9-tetrahydropyrido[3,4-b]indol-2-yl]-5-(trifluoromethyl)-1,3,4-oxadiazole (65 mg, 0.147 mmol), [(2-di-tert-butylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (14 mg, 0.016 mmol), and cesium fluoride (82 mg, 0.540 mmol), then capped and sparged with argon. Toluene (1.6 mL) was added and the reaction placed into a stirring block preheated to 70 °C. After being allowed to stir for 10 minutes, methanol (0.05 mL, 1 mmol) was added by syringe and the reaction allowed to stir at 70 °C for 3 h. The dark suspension was allowed to cool to ambient temperature, diluted with DCM, filtered, concentrated, taken up in DMSO, then filtered and subjected to prep HPLC purification eluted with water and acetonitrile.

[0332] Both products were separated then lyophilized. Compound 4 (1S)-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (15 mg, 0.041 mmol, 28% yield) was isolated as an amorphous white solid. MS m/z 363.2 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.99 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 5.23 (d, J = 10.8 Hz, 1H), 4.16 (d, J = 15.7 Hz, 1H), 3.62 (t, J = 13.1 Hz, 1H), 2.89 (t, J = 11.3 Hz, 1H), 2.75 (d, J = 15.5 Hz, 2H), 1.94 (t, J = 10.4 Hz, 1H), 1.74 (s, 2H), 1.14-1.02 (m, 3H), 0.94 (d, J = 5.4 Hz, 3H); ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -64.57.

[0333] Compound 6 (1S)-6-methoxy-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (25 mg, 0.063 mmol, 43% yield) was isolated as an amorphous white solid. MS m/z 393.2 [M-H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.82 (s, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 6.90 (d, *J* = 2.5 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.21 (d, *J* = 9.4 Hz, 1H), 4.16 (dd, *J* = 13.9, 5.4 Hz, 1H), 3.73 (s, 3H), 3.68-3.55 (m, 1H), 2.93-2.80 (m, 1H), 2.73 (dd, *J* = 15.5, 4.0 Hz, 1H), 1.93 (t, *J* = 10.5 Hz, 1H), 1.82-1.63 (m, 2H), 1.07 (d, *J* = 5.8 Hz, 3H), 0.94 (d, *J* = 6.0 Hz, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -64.57.

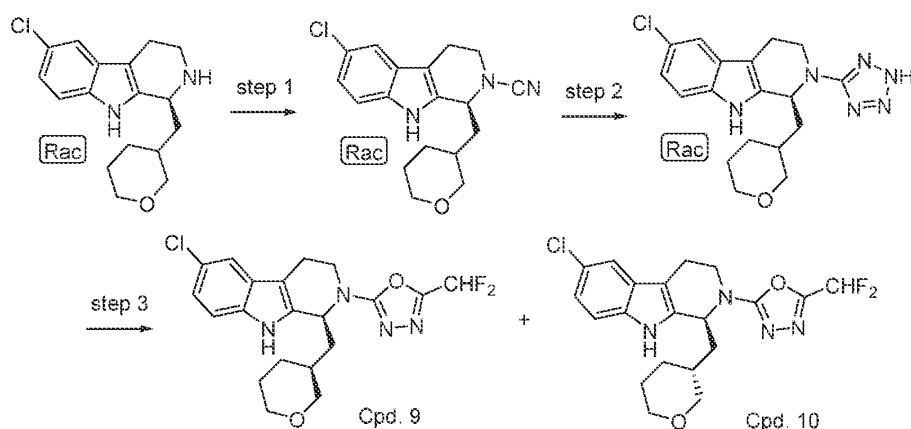
[0334] Using the procedure described for Example 22, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
33	MS m/z 486.3 [M-H] ⁺ ; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.06 (s, 1H), 7.41 (d, <i>J</i> = 7.8 Hz, 1H), 7.34 (d, <i>J</i> = 8.1 Hz, 1H), 7.07 (t, <i>J</i> = 7.6 Hz, 1H), 6.98 (t, <i>J</i> = 7.4 Hz, 1H), 5.87 (dd, <i>J</i> = 10.6, 3.3 Hz, 1H), 4.92 (dd, <i>J</i> = 13.4, 5.0 Hz, 1H), 4.83 (d, <i>J</i> = 6.1 Hz, 1H), 4.66 (d, <i>J</i> = 6.1 Hz, 1H), 4.23 (dd, <i>J</i> = 11.2, 3.5 Hz, 1H), 3.89 (dd, <i>J</i> = 11.0, 3.7 Hz, 1H), 3.70 (dd, <i>J</i> = 11.1, 7.6 Hz, 1H), 3.61 (td, <i>J</i> = 12.6, 4.7 Hz, 1H), 3.48-3.38 (m, 1H), 2.90-2.75 (m, 2H), 2.09-1.99 (m, 1H), 1.94-1.85 (m, 2H).
34	MS m/z 450.0 [M-H] ⁺ ; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.06 (s, 1H), 7.40 (d, <i>J</i> = 7.8 Hz, 1H), 7.33 (d, <i>J</i> = 8.1 Hz, 1H), 7.07 (t, <i>J</i> = 7.6 Hz, 1H), 6.98 (t, <i>J</i> = 7.5 Hz, 1H), 6.93-6.66 (apparent dt, 2H), 5.93 (d, <i>J</i> = 10.7 Hz, 1H), 4.96 (d, <i>J</i> = 13.3 Hz, 1H), 4.82 (d, <i>J</i> = 6.1 Hz, 1H), 4.65 (d, <i>J</i> = 6.1 Hz, 1H), 4.25 (d, <i>J</i> = 11.2 Hz, 1H), 3.89 (d, <i>J</i> = 11.3 Hz, 1H), 3.75-3.63 (m, 1H), 3.54 (t, <i>J</i> = 11.8 Hz, 1H), 3.43 (m, 1H), 2.87-2.71 (m, 2H), 1.99 (d, <i>J</i> = 12.0 Hz, 1H), 1.92-1.72 (m, 2H).
35	MS m/z 480.1 [M-H] ⁺ ; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.88 (s, 1H), 7.22 (d, <i>J</i> = 8.7 Hz, 1H), 6.90 (overlapping s, 1H), 6.94-6.67 (overlapping apparent dt, 2H), 6.73-6.67 (overlapping m, 1H), 5.93-5.88 (m, 1H), 4.95 (dd, <i>J</i> = 13.1, 5.0 Hz, 1H), 4.82 (d, <i>J</i> = 6.1 Hz, 1H), 4.65 (d, <i>J</i> = 6.1 Hz, 1H), 4.24 (dd, <i>J</i> = 11.0, 3.7 Hz, 1H), 3.89 (dd, <i>J</i> = 11.0, 3.9 Hz, 1H), 3.73 (s, 3H), 3.68 (dd, <i>J</i> = 11.2, 8.1 Hz, 1H), 3.52 (dt, <i>J</i> = 12.7, 7.4 Hz, 1H), 3.41 (q, <i>J</i> = 7.7 Hz, 1H), 2.84-2.68 (m, 2H), 1.98 (t, <i>J</i> = 12.0 Hz, 1H), 1.91-1.74 (m, 2H).
36	MS m/z 516.3 [M-H] ⁺ ; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.88 (s, 1H), 7.22 (d, <i>J</i> = 8.7 Hz, 1H), 6.91 (d, <i>J</i> = 2.4 Hz, 1H), 6.71 (dt, <i>J</i> = 8.8, 1.9 Hz, 1H), 5.85 (dd, <i>J</i> = 10.4, 3.3 Hz, 1H), 4.90 (dd, <i>J</i> = 13.4, 5.0 Hz, 1H), 4.83 (d, <i>J</i> = 6.1 Hz, 1H), 4.66 (d, <i>J</i> = 6.2 Hz, 1H), 4.22 (dd, <i>J</i> = 11.2, 3.5 Hz, 1H), 3.91-3.86 (m, 1H), 3.73 (d, <i>J</i> = 1.6 Hz, 3H), 3.69 (dd, <i>J</i> = 11.0, 7.6 Hz, 1H), 3.59 (td, <i>J</i> = 12.6, 4.6 Hz, 1H), 3.46-3.38 (m, 1H), 2.86-2.71 (m, 2H), 2.00 (dd, <i>J</i> = 14.4, 10.5 Hz, 1H), 1.93-1.83 (m, 2H).
164	MS m/z 442.2 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.07 (s, 1H), 7.43 (d, <i>J</i> = 7.8 Hz, 1H), 7.35 (d, <i>J</i> = 8.1 Hz, 1H), 7.09 (t, <i>J</i> = 7.5 Hz, 1H), 7.00 (t, <i>J</i> = 7.4 Hz, 1H), 5.99 (dd, <i>J</i> = 10.4, 3.4 Hz, 1H), 4.95 (dd, <i>J</i> = 13.3, 4.6 Hz, 1H), 3.69-3.58 (m, 1H), 2.93-2.77 (m, 2H), 2.02 (ddd, <i>J</i> = 14.0, 10.5, 3.5 Hz, 1H), 1.87-1.75 (m, 1H), 1.68 (d, <i>J</i> = 6.1 Hz, 0H), 1.13 (d, <i>J</i> = 6.3 Hz, 3H), 0.95 (d, <i>J</i> = 6.6 Hz, 3H); ¹⁹ F NMR (376 MHz, DMSO- <i>d</i> ₆) δ -72.04, -72.18.

Cpd	Data
168	MS m/z 404.2 [M-H] ⁺ ; Two rotamers visible ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.83 (s, 0.6 H), 10.81 (s, 0.4H), 8.86 (d, J = 8.1 Hz, 1H), 7.20 (dd, J = 8.7, 1.8 Hz, 1H), 6.89 (t, J = 2.4 Hz, 1H), 6.69 (dd, J = 8.7, 2.4 Hz, 1H), 6.01 (d, J = 8.0 Hz, 0.4 H), 5.92 (d, J = 7.7 Hz, 0.6 H), 4.98 (d, J = 12.4 Hz, 0.6 H), 4.88 (s, 0.4 H), 3.56-3.44 (m, 1H), 2.76 (s, 1H), 2.00-1.89 (m, 1H), 1.74 (ddd, J = 13.9, 9.9, 3.7 Hz, 1H), 1.60 (s, 1H), 1.09 (dd, J = 6.4, 3.9 Hz, 3H), 0.92 (dd, J = 6.6, 1.4 Hz, 3H); ¹⁹ F NMR (376 MHz, DMSO- <i>d</i> ₆) δ -72.10, -72.27.
190	MS m/z 478.2 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.87 (s, 1H), 7.21 (d, J = 8.7 Hz, 1H), 6.90 (overlapping s, 1H), 6.80 (overlapping t, J = 53.1 Hz, 1H), 6.78 (overlapping t, J = 53.1 Hz, 1H), 6.70 (overlapping dd, J = 8.7, 2.3 Hz, 1H), 5.99 (dd, J = 10.6, 3.3 Hz, 1H), 4.96 (dd, J = 13.5, 4.8 Hz, 1H), 3.74 (overlapping s, 3H), 3.67 (overlapping dd, J = 10.7, 3.8 Hz, 2H), 3.51 (td, J = 12.6, 4.9 Hz, 1H), 3.30-3.21 (m, 1H), 2.99 (t, J = 10.4 Hz, 1H), 2.85-2.63 (m, 2H), 2.33 (d, J = 11.6 Hz, 1H), 1.88-1.67 (m, 2H), 1.60 (d, J = 13.2 Hz, 1H), 1.55-1.21 (m, 3H).

Example 23

Synthesis of Compound 9 and Compound 10



[0335] **Step 1:** Placed (1S)-6-chloro-1-(tetrahydropyran-3-ylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (500 mg, 1.64 mmol) in a vial and suspended in 15 mL of MeCN, then N,N-diisopropylethylamine (0.86 mL, 4.92 mmol) was added followed by cyanogen bromide (170 mg, 1.61 mmol). The reaction mixture was stirred at room temperature for three hours then solvent volume was reduced under vacuum. 20 mL of water was added, resulting in precipitation of a solid. The solid was collected by vacuum filtration thus affording (1S)-6-chloro-1-(tetrahydropyran-3-ylmethyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carbonitrile (520 mg, 1.58 mmol, 96 % yield). MS m/z 328.1 [M-H]⁺.

[0336] **Step 2:** Sodium azide (240 mg 3.70 mmol) was added to a vial containing triethyl amine hydrochloride (507 mg, 3.68 mmol) and (1S)-6-chloro-1-(tetrahydropyran-3-ylmethyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carbonitrile (405 mg, 1.3 mmol) in 15mL

of toluene under nitrogen. The resulting suspension was stirred at 80 °C for 2 hours then cooled to 0 °C. The resulting suspension was filtered and the solid was washed with Et₂O followed water to afford (1S)-6-chloro-1-(tetrahydropyran-3-ylmethyl)-2-(1H-tetrazol-5-yl)-1,3,4,9-tetrahydropyrido[3,4-b]indole (446 mg, 1.20 mmol, 97% yield) as a white solid MS m/z 370.2 [M-H]⁺.

[0337] **Step 3:** (1S)-6-chloro-1-(tetrahydropyran-3-ylmethyl)-2-(1H-tetrazol-5-yl)-1,3,4,9-tetrahydropyrido[3,4-b]indole (98 mg, 0.26 mmol) was placed in a vial, backfilled with N₂ and dissolved in 5 mL of DCM. N,N-diisopropyl amine (0.14 mL, 0.79 mmol) was added to the vial and the solution was cooled to 0 °C. (2,2-difluoroacetyl) 2,2-difluoroacetate (90 mg, 0.53 mmol) was added to the mixture. The ice bath was removed and the mixture was heated to 50 °C and stirred for 4 hours. The mixture was cooled to room temperature, the organic layer was washed with saturated sodium bicarbonate solution, dried and concentrated and the crude mixture was purified by HPLC to afford the individual diastereomers of the title compounds as white powders. Absolute configuration of individual diastereomers was determined based on asymmetric synthesis of one diastereomer followed by comparative NMR to determine the absolute configuration of the other diastereomer in the racemic mixture.

[0338] Compound 9: MS m/z 423.1 [M-H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.23 (s, 1H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.43-7.15 (m, 2H), 7.07 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.24 (dd, *J* = 10.7, 3.4 Hz, 1H), 4.15 (dd, *J* = 13.8, 5.0 Hz, 1H), 3.79-3.68 (m, 2H), 3.60 (ddd, *J* = 13.8, 11.3, 4.8 Hz, 1H), 3.31 (d, *J* = 9.0 Hz, 1H), 3.04 (dd, *J* = 11.1, 9.3 Hz, 1H), 2.91-2.67 (m, 2H), 2.16-2.05 (m, 1H), 1.88-1.59 (m, 4H), 1.54-1.28 (m, 2H).

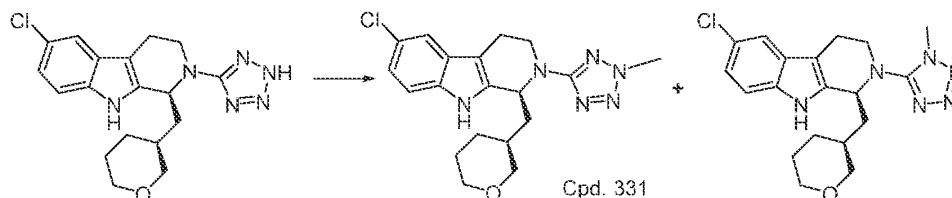
[0339] Compound 10: MS m/z 423.1 [M-H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.19 (s, 1H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.44-7.15 (m, 2H), 7.07 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.37-5.01 (m, 1H), 4.14 (dd, *J* = 13.9, 5.0 Hz, 1H), 4.08-3.93 (m, 1H), 3.74 (dt, *J* = 11.2, 3.8 Hz, 1H), 3.62 (ddd, *J* = 14.0, 11.3, 4.9 Hz, 1H), 3.33-3.26 (m, 1H), 3.18 (dd, *J* = 11.1, 9.1 Hz, 1H), 2.86-2.70 (m, 2H), 1.93-1.64 (m, 5H), 1.52 (qt, *J* = 9.8, 4.3 Hz, 2H).

[0340] Using the procedure described for Example 23, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
2	MS m/z 397.2 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23 (s, 1H), 7.47 (d, <i>J</i> = 2.1 Hz, 1H), 7.35 (d, <i>J</i> = 8.6 Hz, 1H), 7.07 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 5.50-5.13 (m, 1H), 4.16 (dd, <i>J</i> = 14.0, 5.2 Hz, 1H), 3.62 (ddd, <i>J</i> = 13.9, 11.7, 4.5 Hz, 1H), 2.95-2.65 (m, 2H), 1.95 (t, <i>J</i> = 10.6 Hz, 1H), 1.82-1.55 (m, 2H), 1.07 (d, <i>J</i> = 6.16798 Hz, 2H), 0.94 (d, <i>J</i> = 6.2 Hz, 2H).
3	MS m/z 379.1 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.22 (s, 1H), 7.45 (d, <i>J</i> = 2.1 Hz, 1H), 7.42-7.13 (m, 2H), 7.06 (dd, <i>J</i> = 8.5, 2.1 Hz, 1H), 5.35-4.93 (m, 1H), 4.14 (dd, <i>J</i> = 14.0, 5.1 Hz, 1H), 3.59 (ddd, <i>J</i> = 13.9, 11.5, 4.7 Hz, 1H), 2.91-2.63 (m, 2H), 1.93 (t, <i>J</i> = 10.5 Hz, 1H), 1.71 (td, <i>J</i> = 9.7, 9.1, 3.3 Hz, 2H), 1.06 (d, <i>J</i> = 6.0 Hz, 3H), 0.94 (d, <i>J</i> = 6.2 Hz, 3H).

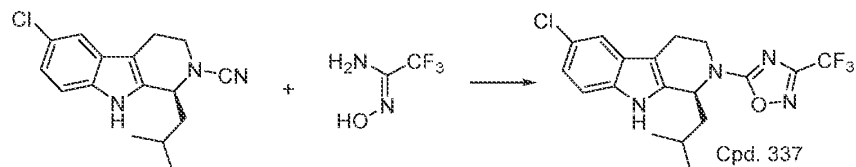
Example 24

Synthesis of Compound 331

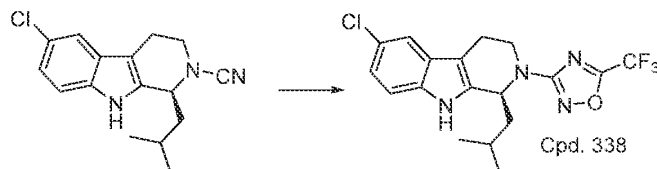


[0341] (S)-6-chloro-1-(((S)-tetrahydro-2H-pyran-3-yl)methyl)-2-(2H-tetrazol-5-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (60 mg, 0.16 mmol) and sodium carbonate (18.8 mg, 0.18 mmol) were placed in a vial with a stir bar. The solids were dissolved in 0.3 mL of DMA and to the vial was added dimethyl sulfate (22.3 mg, 0.18 mmol) at room temperature.

[0342] The mixture was stirred at room temperature for 1 hour after which 1 mL of water was added, resulting in precipitate formation. The solid was collected by filtration and purified by silica gel chromatography to afford (S)-6-chloro-2-(1-methyl-1H-tetrazol-5-yl)-1-(((S)-tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (impure product, structure established by 2D-NOESY NMR) and Compound 331 (S)-6-chloro-2-(2-methyl-2H-tetrazol-5-yl)-1-(((S)-tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white solid (41 mg, 62% y). MS m/z 385.2 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.08 (s, 1H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 6.95 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.18 (d, *J* = 10.7 Hz, 1H), 4.07 (s, 3H), 4.04 (d, *J* = 5.4 Hz, 1H), 3.67 (d, *J* = 11.1 Hz, 2H), 3.48-3.34 (m, 1H), 3.22 (s, 1H), 3.08-2.92 (m, 1H), 2.77-2.64 (m, 1H), 2.53 (dd, *J* = 15.7, 4.1 Hz, 1H), 2.00 (d, *J* = 12.5 Hz, 1H), 1.75-1.53 (m, 4H), 1.46-1.20 (m, 2H).

Example 25**Synthesis of Compound 337**

[0343] (1S)-6-chloro-1-isobutyl-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carbonitrile (190 mg, 0.66 mmol) and 2,2,2-trifluoro-N'-hydroxyacetamidine (13 mg, 0.88 mmol) were placed in a vial and dissolved in a 8 mL of 1:1 mixture of EtOAc and THF. A 1.0 M solution of zinc chloride in diethyl ether (1.3 mL, 1.32 mmol) was added to the vial and the mixture was stirred at room temperature for 15 hours. The solvent was removed under reduced pressure and the residue was redissolved in minimal methanol and solids were precipitated out of solution by addition of diethyl ether and collected by vacuum filtration. The organic solid was placed in a flask and dissolved in 10 mL of ethanol. 2 mL of concentrated Aq. HCl was then added to the mixture. Upon complete addition the reaction mixture was heated to 100 °C and stirred for 15 hours. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography using EtOAc/Hexanes as eluent to afford (1S)-6-chloro-1-(2-methylpropyl)-2-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white solid (92 mg, 35% y). MS m/z 397.2 [M-H]⁺; ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.27 (s, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.08 (dt, J = 8.7, 1.5 Hz, 1H), 5.47-5.13 (m, 1H), 4.29 (dd, J = 13.8, 5.0 Hz, 1H), 3.68 (ddd, J = 13.6, 11.1, 5.1 Hz, 1H), 2.99-2.73 (m, 2H), 1.97 (ddd, J = 13.9, 10.6, 3.4 Hz, 1H), 1.82-1.56 (m, 2H), 1.08 (d, J = 6.0 Hz, 3H), 0.94 (d, J = 6.2 Hz, 3H).

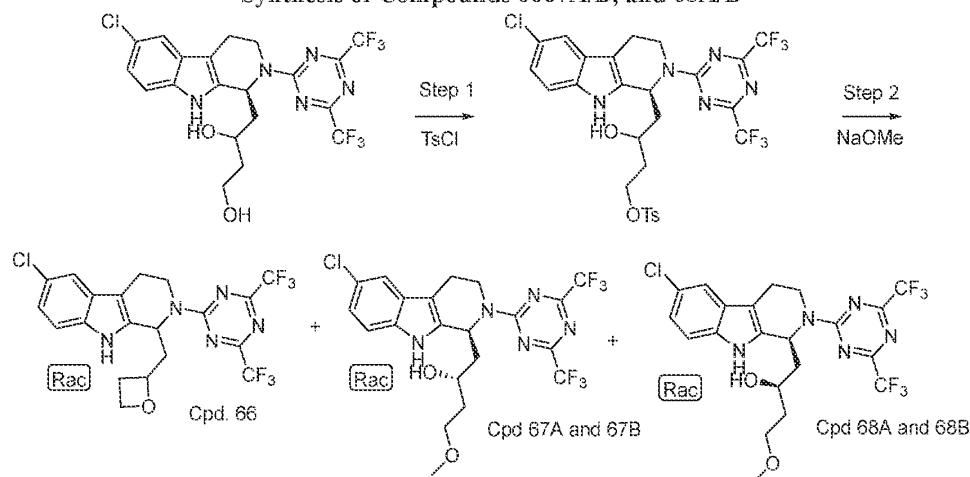
Example 26**Synthesis of Compound 338**

[0344] Hydroxylamine hydrochloride (72 mg, 1.04 mmol) (1S)-6-chloro-1-isobutyl-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carbonitrile (150 mg, 0.52 mmol) and sodium carbonate (60 mg, 0.57 mmol) were placed in a vial and suspended in 1.5 mL of DMF. The resulting

mixture was stirred at 80 °C for 30 minutes. The reaction was then cooled to 25 °C and toluene (3 mL) was added, followed by pyridine (0.18 mL, 2.2 mmol,) and trifluoroacetic anhydride (0.29 mL, 2.1 mmol). The reaction was stirred at room temperature for 18 hours after which it was concentrated under reduced pressure to a volume of approximately 2 mL. Water was then added causing material to precipitate out of the solution. The solid residue was collected by filtration and further purified by silica gel chromatography with DCM as eluent. (1S)-6-chloro-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (103 mg, 50% yield) was obtained as white solid material. MS m/z 397.3 [M-H]⁺; ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.20 (s, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.05 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.16 (dd, *J* = 10.9, 3.4 Hz, 1H), 4.12 (dd, *J* = 13.9, 5.4 Hz, 1H), 3.55 (td, *J* = 12.9, 4.4 Hz, 1H), 2.99-2.58 (m, 2H), 1.94 (ddd, *J* = 14.2, 10.8, 3.7 Hz, 1H), 1.72 (dddd, *J* = 43.8, 13.4, 8.1, 3.4 Hz, 2H), 1.07 (d, *J* = 6.3 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H).

[0345] Using the procedure described for Example 26, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
339	MS m/z 379.1 [M-H] ⁺ ; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.19 (s, 1H), 7.44 (d, <i>J</i> = 2.1 Hz, 1H), 7.42-7.18 (m, 2H), 7.05 (dt, <i>J</i> = 8.6, 1.7 Hz, 1H), 5.17 (dd, <i>J</i> = 11.0, 3.5 Hz, 1H), 4.11 (dd, <i>J</i> = 13.9, 5.4 Hz, 1H), 3.52 (td, <i>J</i> = 12.9, 4.4 Hz, 1H), 2.80 (ddd, <i>J</i> = 16.9, 11.7, 5.6 Hz, 1H), 2.68 (dd, <i>J</i> = 15.7, 4.2 Hz, 1H), 1.93 (ddd, <i>J</i> = 14.3, 10.8, 3.8 Hz, 1H), 1.76 (ddt, <i>J</i> = 10.5, 6.7, 3.5 Hz, 1H), 1.66 (ddd, <i>J</i> = 13.4, 9.5, 3.6 Hz, 1H), 1.07 (d, <i>J</i> = 6.4 Hz, 3H), 0.95 (d, <i>J</i> = 6.5 Hz, 3H).

Example 27**Synthesis of Compounds 6667A/B, and 68A/B**

[0346] **Step 1:** 4-Toluenesulfonyl chloride (270 mg, 1.4 mmol) and 4-[2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]butane-1,3-diol (640 mg, 1.3 mmol) were placed in a round bottom flask and dissolved in 15 mL of DCM. The mixture was cooled to 0 °C and to it was added N,N-diisopropylethylamine (243 mg, 1.9 mmol) and 4-dimethylaminopyridine (15 mg, 0.12 mmol) the mixture was allowed to slowly warm to room temperature and stirred for 18 hours. The solution was concentrated under reduced pressure and the crude material was purified by silica gel chromatography (eluent EtOAc/hexanes) to afford [4-[2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]-3-hydroxy-butyl] 4-methylbenzenesulfonate (408 mg, 0.6 mmol, 49% yield) as white solid.

[0347] **Step 2:** [4-[2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]-3-hydroxy-butyl] 4-methylbenzenesulfonate (81 mg, 0.13 mmol) and dissolved in 4 mL of methanol. A solution of 30% sodium methoxide in methanol (1.4 mL, 6.2 mmol) was added to the mixture which was then stirred at room temperature for 16 hours.

[0348] The reaction mixture was quenched by addition of 10% aq. acetic acid solution until pH ~5-6, followed by a wash with saturated NaHCO₃ (aq). The aqueous layer was extracted three times with DCM and the combined organic portions were dried, concentrated, and submitted to silica gel chromatography for purification, allowing for isolation of three individual reaction products.

[0349] **Compound 66:** By-product isolated as a mixture of diastereomers (ratio 0.4:0.6) 2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(oxetan-2-ylmethyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole (7 mg, 0.014 mmol, 12% yield). MS m/z 490.1 [M-H]⁻; ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 9.36 (app d, J = 11.7 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.02 (dd, J = 8.6, 2.1 Hz, 1H), 5.99 (t, J = 6.9 Hz, 0.6H, major diastereomer), 5.80 (t, J = 6.0 Hz, 0.4 H, minor diastereomer), 5.09-4.84 (m, 2H), 4.61-4.34 (m, 2H), 3.59-3.36 (m, 1H), 2.88-2.41 (m, 4H), 2.32 (t, J = 6.6 Hz, 1H), 2.29-2.11 (m, 1H), 2.01 (d, J = 1.9 Hz, 1H).

[0350] **Compound 67A/B:** Isolated as a racemic mixture Compound 67A (2S)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-methoxybutan-2-ol and Compound 67B (2R)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-methoxybutan-2-ol (16 mg, 0.031 mmol, 25 % yield) MS m/z 522.1 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.12 (s, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.08 (dd, J = 8.5, 2.1 Hz, 1H), 6.04 (dd, J = 9.7, 4.8 Hz, 1H), 4.95 (dd, J = 13.2, 5.3 Hz, 1H), 4.53 (d, J = 5.7 Hz, 1H), 3.72 (s, 1H), 3.60 (td, J = 12.6, 4.5 Hz, 1H), 3.39 (td, J = 6.9, 6.4, 3.7 Hz, 2H), 3.18 (s, 2H), 2.99-2.70 (m, 2H), 2.25-1.99 (m, 2H), 1.96-1.78 (m, 1H), 1.58 (dq, J = 13.9, 6.4 Hz, 1H).

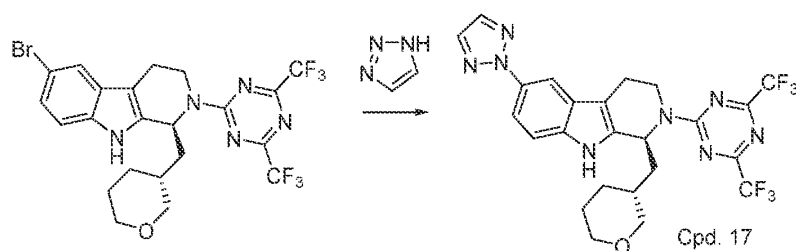
[0351] **Compound 68A/B:** Isolated as a racemic mixture Compound 68A (2S)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-methoxybutan-2-ol and Compound 68B (2R)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-methoxybutan-2-ol (28 mg, 0.055 mmol 44% yield) MS m/z 522.0 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.13 (s, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 6.99 (dd, J = 8.6, 2.1 Hz, 1H), 6.06 (dd, J = 9.2, 4.0 Hz, 1H), 4.87 (dd, J = 13.2, 5.2 Hz, 1H), 4.41 (d, J = 5.5 Hz, 1H), 3.72-3.40 (m, 2H), 3.39-3.26 (m, 2H), 3.10 (s, 3H), 2.92-2.60 (m, 2H), 2.03 (dddd, J = 39.8, 14.2, 9.2, 3.6 Hz, 2H), 1.54 (p, J = 7.0 Hz, 2H).

[0352] Using the procedure described for Example 27, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
80A and 80B	MS m/z 492.2 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.20 (s, 1H), 7.49 (d, <i>J</i> = 2.1 Hz, 1H), 7.37 (d, <i>J</i> = 8.6 Hz, 1H), 7.08 (dd, <i>J</i> = 8.6, 2.0 Hz, 1H), 5.99 (dd, <i>J</i> = 11.0, 3.2 Hz, 1H), 4.94 (dd, <i>J</i> = 13.4, 5.3 Hz, 1H), 3.68-3.55 (m, 1H), 3.49 (q, <i>J</i> = 6.2 Hz, 1H), 3.04 (s, 3H), 2.83 (ddd, <i>J</i> = 30.9, 13.7, 4.7 Hz, 2H), 2.29 (ddd, <i>J</i> = 20.7, 11.2, 5.9 Hz, 1H), 2.01 (ddd, <i>J</i> = 14.8, 6.7, 3.3 Hz, 1H), 1.24 (d, <i>J</i> = 5.8 Hz, 3H).
81A and 81B	MS m/z 492.0 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.38 (s, 1H), 7.53 (d, <i>J</i> = 2.0 Hz, 1H), 7.36 (d, <i>J</i> = 8.6 Hz, 1H), 7.12 (dd, <i>J</i> = 8.5, 2.0 Hz, 1H), 6.27 (d, <i>J</i> = 10.1 Hz, 1H), 4.98 (dd, <i>J</i> = 13.4, 5.0 Hz, 1H), 3.91-3.58 (m, 1H), 3.33-3.30 (m, 1H), 3.25 (s, 3H), 3.00-2.75 (m, 2H), 2.16 (dt, <i>J</i> = 55.8, 13.5 Hz, 2H), 1.17 (d, <i>J</i> = 6.0 Hz, 3H).
82A and 82B	MS m/z 456.1 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.20 (s, 1H), 7.47 (s, 1H), 7.36 (d, <i>J</i> = 8.6 Hz, 1H), 7.22-7.01 (m, 1H), 6.81 (td, <i>J</i> = 53.5, 5.5 Hz, 2H), 6.29-5.53 (m, 1H), 4.99 (dd, <i>J</i> = 13.4, 5.2 Hz, 1H), 3.62-3.38 (m, 2H), 3.01 (s, 3H), 2.99-2.64 (m, 2H), 2.33-2.19 (m, 1H), 1.99 (dd, <i>J</i> = 14.5, 5.8 Hz, 1H), 1.24 (d, <i>J</i> = 5.8 Hz, 3H).
83A and 83B	MS m/z 456.1 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.30 (s, 1H), 7.46 (s, 1H), 7.31 (d, <i>J</i> = 8.6 Hz, 1H), 7.06 (d, <i>J</i> = 8.6 Hz, 1H), 6.79 (td, <i>J</i> = 53.5, 20.8 Hz, 2H), 6.25 (d, <i>J</i> = 9.9 Hz, 1H), 4.97 (dd, <i>J</i> = 13.7, 5.1 Hz, 1H), 3.71-3.47 (m, 1H), 3.27 (d, <i>J</i> = 6.3 Hz, 1H), 3.19 (s, 3H), 2.87-2.70 (m, 2H), 2.22-1.95 (m, 2H), 1.11 (d, <i>J</i> = 6.0 Hz, 3H).

Example 28

Synthesis of Compound 17



[0353] A 20 mL vial was charged with cesium fluoride (86 mg, 0.566 mmol), tris (dibenzylideneacetone) dipalladium(0) (18 mg, 0.019 mmol), 2-di-tert-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (20 mg, 0.039 mmol), (1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-[(3R)-tetrahydropyran-3-yl]methyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole (100 mg, 0.189 mmol). The vial was capped, put under argon atmosphere and toluene added (1.9 mL) and the suspension allowed to stir at 100 °C for 5 minutes, then 1H-triazole (26 mg, 0.376 mmol) in 1,4-dioxane (0.4 mL) was added and the reaction allowed to stir for 14 h at 100 °C. After being allowed to cool to ambient temperature volatiles were removed, the resulting residue taken up in DMSO, filtered and subjected to purification by prep HPLC. After lyophilization the desired compound (1S)-2-

[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[[[(3R)-oxan-3-yl]methyl]-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (35 mg, 0.063 mmol, 35% yield) was isolated as an off-white powder. MS m/z 551.1 [M-H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.32 (s, 1H), 8.04 (s, 3H), 7.79 (dd, J = 8.5, 2.1 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 5.93 (d, J = 6.1 Hz, 1H), 4.95 (dd, J = 13.3, 5.2 Hz, 1H), 4.09 (d, J = 11.2 Hz, 1H), 3.74-3.56 (m, 2H), 3.34-3.17 (m, 2H), 2.95 (d, J = 11.9 Hz, 1H), 2.91-2.78 (m, 1H), 1.95 (t, J = 14.5 Hz, 2H), 1.77 (d, J = 12.8 Hz, 1H), 1.65 (s, 1H), 1.50 (d, J = 16.8 Hz, 2H), 1.23 (s, 1H).

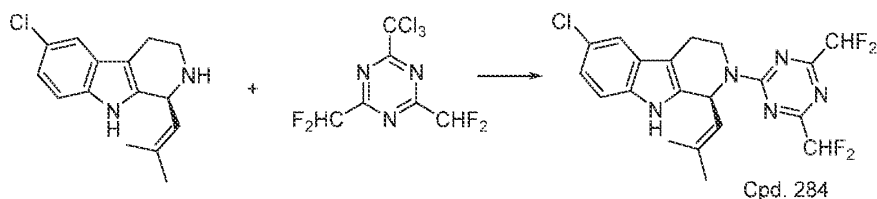
[0354] Using the procedure described for Example 28, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
13	MS m/z 443.2 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.28-11.38 (m, 1H), 8.85-8.91 (m, 1H), 8.04 (s, 3H), 7.78 (d, J=9.0 Hz, 1H), 7.49 (d, J=8.8 Hz, 1H), 5.90-6.16 (m, 1H), 4.81-5.22 (m, 1H), 3.45-3.78 (m, 1H), 2.69-3.01 (m, 2H), 1.93-2.16 (m, 1H), 1.71-1.84 (m, 1H), 1.61 (br d, J=6.3 Hz, 1H), 1.08-1.19 (m, 3H), 0.86-0.97 (m, 3H)
14	MS m/z 457.2 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.25-11.34 (m, 1H), 8.85-8.92 (m, 1H), 7.97 (s, 1H), 7.79 (s, 1H), 7.73 (d, J=8.8 Hz, 1H), 7.45 (d, J=8.5 Hz, 1H), 5.92-6.12 (m, 1H), 4.84-5.09 (m, 1H), 3.48-3.63 (m, 1H), 2.75-2.94 (m, 2H), 2.30-2.43 (m, 3H), 1.92-2.11 (m, 1H), 1.72-1.87 (m, 1H), 1.54-1.69 (m, 1H), 1.07-1.17 (m, 3H), 0.90-0.98 (m, 3H)
15	MS m/z 525.2 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.37 (s, 1H), 8.05 (s, 3H), 7.74-7.85 (m, 1H), 7.50 (d, J=8.8 Hz, 1H), 5.91-6.12 (m, 1H), 4.88-5.07 (m, 1H), 3.58-3.78 (m, 1H), 2.78-3.09 (m, 2H), 1.98-2.13 (m, 1H), 1.75-1.90 (m, 1H), 1.60-1.73 (m, 1H), 1.07-1.20 (m, 3H), 0.83-0.98 (m, 3H)
16	MS m/z 509.2 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.37 (s, 1H), 8.05 (s, 3H), 7.74-7.85 (m, 1H), 7.50 (d, J=8.8 Hz, 1H), 5.91-6.12 (m, 1H), 4.88-5.07 (m, 1H), 3.58-3.78 (m, 1H), 2.78-3.09 (m, 2H), 1.98-2.13 (m, 1H), 1.75-1.90 (m, 1H), 1.60-1.73 (m, 1H), 1.07-1.20 (m, 3H), 0.83-0.98 (m, 3H)
18	MS m/z 515.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.38 (s, 1H), 8.04 (q, J = 1.7 Hz, 3H), 7.78 (dd, J = 8.8, 2.3 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.05-6.55 (m, 2H), 6.05 (d, J = 10.4 Hz, 1H), 5.00 (dd, J = 13.9, 4.9 Hz, 1H), 3.70 (t, J = 14.5 Hz, 2H), 3.61-3.51 (m, 1H), 3.01 (t, J = 10.5 Hz, 1H), 2.92 (d, J = 14.8 Hz, 1H), 2.81 (t, J = 13.9 Hz, 1H), 2.36 (d, J = 11.8 Hz, 1H), 1.93-1.70 (m, 2H), 1.61 (d, J = 12.9 Hz, 1H), 1.57-1.08 (m, 4H).
20	MS m/z 555.1 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.30 (s, 1H), 7.98 (s, 3H), 7.73 (br d, J=8.8 Hz, 1H), 7.44 (d, J=8.8 Hz, 1H), 5.76-5.97 (m, 1H), 4.88 (br dd, J=13.3, 5.0 Hz, 1H), 4.73-4.82 (m, 1H), 4.62 (d, J=6.0 Hz, 1H), 4.17 (br d, J=9.3 Hz, 1H), 3.84 (br d, J=8.0 Hz, 1H), 3.49-3.74 (m, 2H), 3.38 (br dd, J=10.4, 7.9 Hz, 1H), 2.71-2.96 (m, 2H), 1.74-2.10 (m, 3H)
301	MS m/z 510.3 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.17-11.42 (m, 1H), 8.04 (s, 3H), 7.77 (br d, J=8.5 Hz, 1H), 7.44-7.52 (m, 2H), 6.01 (br d, J=10.5 Hz, 1H), 4.84-5.01 (m, 1H), 3.45-3.66 (m, 1H), 2.73-3.03 (m, 2H), 1.95-2.08 (m, 1H), 1.71-1.84 (m, 1H), 1.59-1.71 (m, 1H), 1.12 (br d, J=6.3 Hz, 3H), 0.94 (br d, J=6.5 Hz, 3H)

Cpd	Data
302	MS m/z 524.3 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.28 (s, 1H), 7.97 (s, 1H), 7.78 (s, 1H), 7.72 (br d, J=8.8 Hz, 1H), 7.39-7.49 (m, 2H), 5.95-6.08 (m, 1H), 4.86-4.98 (m, 1H), 3.48-3.63 (m, 1H), 2.73-2.92 (m, 2H), 2.32-2.40 (s, 3H), 1.94-2.07 (m, 1H), 1.71-1.84 (m, 1H), 1.57-1.71 (m, 1H), 1.07-1.18 (m, 3H), 0.89-0.99 (m, 3H)
303	MS m/z 442.2 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.28 (br s, 1H), 8.73 (br s, 1H), 7.99-8.06 (m, 3H), 7.76 (d, J=8.8 Hz, 1H), 7.46 (d, J=8.8 Hz, 1H), 7.04 (d, J=5.0 Hz, 1H), 5.88-6.22 (m, 1H), 4.74-5.22 (m, 1H), 3.42-3.56 (m, 1H), 2.73-2.88 (m, 2H), 1.89-2.05 (m, 1H), 1.59-1.84 (m, 2H), 1.08-1.16 (m, 3H), 0.91-0.99 (m, 3H)
306	MS m/z 443.2 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.35-11.43 (m, 1H), 8.83-8.95 (m, 1H), 8.67-8.79 (m, 1H), 7.82-8.02 (m, 2H), 7.42-7.66 (m, 2H), 5.93-6.24 (m, 1H), 4.79-5.12 (m, 1H), 3.44-3.67 (m, 1H), 2.73-2.97 (m, 2H), 1.93-2.09 (m, 1H), 1.76-1.90 (m, 1H), 1.56-1.72 (m, 1H), 1.05-1.17 (m, 3H), 0.94 (d, J=6.5 Hz, 3H)
307	MS m/z 507.3 [M-H] ⁻ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.19 (s, 1H), 7.99-8.16 (m, 3H), 7.81 (d, J=8.8 Hz, 1H), 7.50 (d, J=8.5 Hz, 1H), 6.44-6.63 (m, 1H), 5.55 (br d, J=9.8 Hz, 1H), 5.01 (br dd, J=12.9, 4.6 Hz, 1H), 3.60-3.74 (m, 1H), 2.97-3.10 (m, 1H), 2.79-2.95 (m, 1H), 2.06 (s, 3H), 1.71-1.82 (m, 3H)
308	MS m/z 521.3 [M-H] ⁻ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.15 (s, 1H), 8.01 (s, 1H), 7.80 (s, 1H), 7.73-7.78 (m, 1H), 7.46 (d, J=8.8 Hz, 1H), 6.52 (d, J=9.5 Hz, 1H), 5.54 (br d, J=10.0 Hz, 1H), 4.96-5.04 (m, 1H), 3.60-3.71 (m, 2H), 2.96-3.05 (m, 1H), 2.80-2.92 (m, 1H), 2.36 (s, 3H), 2.03-2.07 (m, 3H), 1.74-1.79 (m, 3H)

Example 29

Synthesis of Compound 284



[0355] A 40 mL vial equipped with a stir bar, septum cap and a nitrogen inlet was charged with (1S)-6-chloro-1-(2-methylprop-1-enyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (200 mg, 0.767 mmol), 4-dimethylaminopyridine (130 mg, 1.06 mmol), acetonitrile (7.7 mL) followed by addition of 2,4-bis(difluoromethyl)-6-(trichloromethyl)-1,3,5-triazine (300 mg, 1.00 mmol). The vial was closed, flushed with Nitrogen and allowed to stir at ambient temperature. After stirring over night the reaction mixture was concentrated under reduced pressure, the dark residue absorbed on silica gel and subjected to ISCO purification (hexanes EtOAc). (1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylprop-1-enyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (324 mg, 0.737 mmol, 96% yield) was isolated as an off white amorphous solid. MS m/z 437.7 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.07 (s, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 8.6, 2.1 Hz, 1H), 6.95-6.59 (m, 2H), 6.53 (d, J = 9.7 Hz, 1H), 5.47 (dt, J = 9.6, 1.5 Hz, 1H),

5.01 (dd, J = 13.2, 5.1 Hz, 1H), 3.60-3.44 (m, 1H), 2.89 (dd, J = 15.7, 3.6 Hz, 1H), 2.82-2.69 (m, 1H), 2.04 (d, J = 1.3 Hz, 3H), 1.73 (d, J = 1.4 Hz, 3H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -123.24--123.78 (m).

[0356] Using the procedure described for Example 29, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
19	MS m/z 519.3 [M+H] $^{+}$; ^1H NMR (400 MHz, DMSO- d_6) δ : 11.29-11.49 (m, 1H), 8.04 (s, 3H), 7.79 (br d, J=8.8 Hz, 1H), 7.50 (d, J=8.8 Hz, 1H), 6.59-7.05 (m, 2H), 5.98 (br d, J=9.3 Hz, 1H), 4.92-5.10 (m, 1H), 4.83 (br d, J=6.3 Hz, 1H), 4.67 (br d, J=6.0 Hz, 1H), 4.20-4.32 (m, 1H), 3.86-3.97 (m, 1H), 3.69-3.78 (m, 1H), 3.53-3.64 (m, 1H), 3.41-3.49 (m, 1H), 2.75-3.00 (m, 2H), 1.97-2.14 (m, 1H), 1.73-1.97 (m, 2H)
21	MS m/z 487.3 [M+H] $^{+}$; ^1H NMR (400 MHz, DMSO- d_6) δ : 11.28-11.43 (m, 1H), 8.84-9.01 (m, 1H), 7.96-8.16 (m, 3H), 7.73-7.87 (m, 1H), 7.44-7.58 (m, 1H), 5.89 (br d, J=9.0 Hz, 1H), 5.02 (br dd, J=12.9, 4.4 Hz, 1H), 4.84 (br d, J=6.0 Hz, 1H), 4.62-4.71 (m, 1H), 4.21-4.34 (m, 1H), 3.87-3.99 (m, 1H), 3.63-3.78 (m, 1H), 3.49-3.63 (m, 1H), 3.38-3.49 (m, 1H), 2.74-2.98 (m, 2H), 1.95-2.08 (m, 1H), 1.78-1.95 (m, 2H)
40	MS m/z 412.0 [M+H] $^{+}$; ^1H NMR (DMSO- d_6 , 400MHz) δ 11.20 (s, 1H), 7.42 (d, J=1.6 Hz, 1H), 7.33 (d, J=8.4 Hz, 1H), 7.04 (q, J=6.4 Hz, 1H), 6.04 (q, J=4.0 Hz, 1H), 4.98 (q, J=8.8 Hz, 1H), 3.90 (d, J=9.2 Hz, 1H), 3.78 (d, J=8.0 Hz, 1H), 3.33-3.15 (m, 3H), 2.74-2.63 (m, 2H), 2.34 (s, 3H), 2.29 (s, 3H), 2.23 (d, J=20.4 Hz, 1H), 1.95-1.88 (m, 1H), 1.80-1.74 (m, 1H), 1.47 (d, J=10.8 Hz, 2H), 1.36-1.29 (m, 1H), 1.27-1.17 (m, 1H)
44	MS m/z 526.1 [M-H] $^{-}$; ^1H NMR (400 MHz, DMSO- d_6) δ 11.30 (s, 1H), 7.61 (d, J = 1.9 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.18 (dd, J = 8.5, 2.0 Hz, 1H), 6.81 (ti, J = 54.6 Hz, 1H), 6.78 (t, J = 54.6 Hz, 1H), 6.02 (dd, J = 10.7, 3.3 Hz, 1H), 4.97 (dd, J = 13.4, 5.1 Hz, 1H), 3.77-3.61 (m, 2H), 3.52 (td, J = 12.5, 4.3 Hz, 1H), 3.28 (dd, J = 11.1, 2.6 Hz, 1H), 3.00 (t, J = 10.4 Hz, 1H), 2.91-2.65 (m, 2H), 2.35 (d, J = 11.5 Hz, 1H), 1.86 (td, J = 12.4, 3.3 Hz, 1H), 1.80-1.69 (m, 1H), 1.61 (d, J = 13.4 Hz, 1H), 1.54-1.22 (m, 3H).
50	MS m/z 562.2 [M-H] $^{-}$; ^1H NMR (400 MHz, DMSO- d_6) δ 11.25 (s, 1H), 7.62 (d, J = 1.9 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.19 (dd, J = 8.6, 2.0 Hz, 1H), 5.91 (dd, J = 10.0, 4.2 Hz, 1H), 4.92 (dd, J = 13.4, 5.1 Hz, 1H), 4.08 (d, J = 9.3 Hz, 1H), 3.75-3.66 (m, 1H), 3.61 (td, J = 12.6, 4.5 Hz, 1H), 3.33 (td, J = 10.5, 3.1 Hz, 1H), 3.25 (dd, J = 11.0, 8.8 Hz, 1H), 2.94-2.70 (m, 2H), 2.00-1.82 (m, 2H), 1.76 (d, J = 12.9 Hz, 1H), 1.63 (td, J = 8.6, 4.2 Hz, 1H), 1.58-1.38 (m, 1H), 1.29-1.19 (m, 2H).
53	MS m/z 520.1 [M+H] $^{+}$; ^1H NMR (400 MHz, DMSO- d_6) δ 11.23 (d, J= 56.0 Hz, 1H), 7.47 (t, J= 3.6 Hz, 1H), 7.33 (dd, J= 27.9, 8.6 Hz, 1H), 7.11 -7.03 (m, 1H), 6.22 (d, J= 7.9 Hz, 1H), 4.93 (dd, J= 13.1, 4.6 Hz, 1H), 3.86 (d, J= 11.3 Hz, 1H), 3.58 (td, J= 13.1, 4.3 Hz, 1H), 3.23 (t, J= 10.2 Hz, 2H), 2.82 (ddd, J= 16.2, 13.3, 4.1 Hz, 2H), 2.07 (ddd, J= 21.7, 19.0, 12.6 Hz, 2H), 1.73 (s, 1H), 1.53 -1.21 (m, 5H)

Cpd	Data
60	MS m/z 470.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.28 (s, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.35 (d, <i>J</i> = 8.6 Hz, 1H), 7.07 (dd, <i>J</i> = 8.6, 2.0 Hz, 1H), 6.80 (td, <i>J</i> = 53.5, 7.2 Hz, 2H), 5.90 (dd, <i>J</i> = 10.4, 3.7 Hz, 1H), 4.99 (dd, <i>J</i> = 13.2, 5.2 Hz, 1H), 3.88 (t, <i>J</i> = 7.7 Hz, 1H), 3.79-3.69 (m, 1H), 3.69-3.43 (m, 3H), 2.99-2.64 (m, 2H), 2.32-1.89 (m, 4H), 1.46 (dq, <i>J</i> = 13.8, 7.2 Hz, 1H).
61	MS m/z 470.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.28 (s, 1H), 7.47 (s, 1H), 7.36 (d, <i>J</i> = 8.6 Hz, 1H), 7.07 (d, <i>J</i> = 8.6 Hz, 1H), 6.80 (td, <i>J</i> = 53.5, 8.8 Hz, 2H), 6.26-5.83 (m, 1H), 4.98 (dd, <i>J</i> = 13.4, 5.1 Hz, 1H), 3.88-3.66 (m, 2H), 3.65-3.44 (m, 2H), 3.22 (t, <i>J</i> = 7.1 Hz, 1H), 2.84 (dd, <i>J</i> = 15.9, 4.0 Hz, 1H), 2.80-2.67 (m, 1H), 2.33-1.92 (m, 4H), 1.87-1.68 (m, 1H).
62A and 62B	MS m/z 506.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.29 (d, <i>J</i> = 4.4 Hz, 1H), 7.47 (s, 1H), 7.36 (dd, <i>J</i> = 8.5, 4.0 Hz, 1H), 7.06 (d, <i>J</i> = 8.5 Hz, 1H), 6.00-5.79 (m, 1H), 4.95 (d, <i>J</i> = 13.0 Hz, 1H), 3.82 (dt, <i>J</i> = 13.3, 8.0 Hz, 1H), 3.73 (dd, <i>J</i> = 14.2, 6.6 Hz, 1H), 3.68-3.57 (m, 2H), 3.23 (s, 1H), 2.90-2.72 (m, 2H), 2.28 (s, 1H), 2.19-1.91 (m, 3H), 1.47 (td, <i>J</i> = 13.7, 7.1 Hz, 1H).
63	MS m/z 506.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.28 (s, 1H), 7.49 (d, <i>J</i> = 2.0 Hz, 1H), 7.36 (d, <i>J</i> = 8.6 Hz, 1H), 7.08 (dd, <i>J</i> = 8.5, 2.0 Hz, 1H), 5.84 (dd, <i>J</i> = 10.4, 3.7 Hz, 1H), 4.95 (dd, <i>J</i> = 13.3, 5.1 Hz, 1H), 3.84 (t, <i>J</i> = 7.7 Hz, 1H), 3.77-3.72 (m, 1H), 3.68-3.56 (m, 3H), 2.94-2.72 (m, 2H), 2.29 (s, 1H), 2.21-1.92 (m, 3H), 1.48 (dq, <i>J</i> = 13.7, 7.0 Hz, 1H).
64	MS m/z 506.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.29 (s, 1H), 7.48 (d, <i>J</i> = 2.1 Hz, 1H), 7.37 (d, <i>J</i> = 8.6 Hz, 1H), 7.08 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 5.93 (dd, <i>J</i> = 10.6, 3.2 Hz, 1H), 4.94 (dd, <i>J</i> = 13.3, 5.1 Hz, 1H), 3.88-3.70 (m, 2H), 3.67-3.51 (m, 2H), 3.30 (s, 1H), 3.23 (t, <i>J</i> = 7.5 Hz, 1H), 2.91-2.70 (m, 2H), 2.27 (q, <i>J</i> = 5.5 Hz, 1H), 2.19-2.08 (m, 1H), 2.05-1.97 (m, 1H), 1.80 (dq, <i>J</i> = 14.0, 7.3 Hz, 1H).
69	MS m/z 534.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.19 (s, 1H), 7.48 (d, <i>J</i> = 2.1 Hz, 1H), 7.38 (d, <i>J</i> = 8.6 Hz, 1H), 7.08 (dd, <i>J</i> = 8.5, 2.0 Hz, 1H), 6.03-5.88 (m, 1H), 4.94 (dd, <i>J</i> = 13.4, 5.2 Hz, 1H), 3.65-3.58 (m, 1H), 3.55 (s, 3H), 2.98-2.73 (m, 3H), 2.15 (dd, <i>J</i> = 15.7, 8.8 Hz, 1H), 1.98 (dt, <i>J</i> = 27.5, 10.0 Hz, 3H), 0.94 (d, <i>J</i> = 5.4 Hz, 3H).
73	MS m/z 507.1 [M+H] ⁺ ; ¹ H NMR (400MHz, DMSO- <i>d</i> ₆) 11.26(s, 1H), 7.49(d, <i>J</i> =1.2Hz, 1H), 7.36(d, <i>J</i> =8.0Hz, 1H), 7.08(dd, <i>J</i> =8.4, 1.6Hz, 1H), 7.49(d, <i>J</i> =7.2Hz, 1H), 4.92(dd, <i>J</i> =13.6, 4.8Hz, 1H), 3.55-3.43(m, 5H), 2.78-2.61(m, 3H), 2.48-2.19(m, 2H)
108	MS m/z 486.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.27 (d, <i>J</i> = 3.6 Hz, 1H), 7.46 (s, 1H), 7.34 (d, <i>J</i> = 8.8 Hz, 1H), 7.06 (q, <i>J</i> = 4.2 Hz, 1H), 6.67-6.96 (m, 1H), 5.95 (q, <i>J</i> = 24.0 Hz, 1H), 4.91-5.00 (m, 1H), 3.55 (t, <i>J</i> = 11.2 Hz, 1H), 2.71-2.87 (m, 2H), 1.84-2.10 (m, 4H), 1.59-1.70 (m, 3H), 1.36-1.48 (m, 3H), 1.10-1.15 (m, 1H).
109	MS m/z 504.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.27 (s, 1H), 7.47 (d, <i>J</i> = 2.0 Hz, 1H), 7.35 (d, <i>J</i> = 8.8 Hz, 1H), 7.07 (q, <i>J</i> = 12.0 Hz, 1H), 5.92 (q, <i>J</i> = 8.0 Hz, 1H), 4.93 (q, <i>J</i> = 12.0 Hz, 1H), 3.55-3.62 (m, 1H), 2.72-2.88 (m, 2H), 2.08 (t, <i>J</i> = 8.0 Hz, 1H), 1.89-1.99 (m, 3H), 1.59-1.72 (m, 3H), 1.39-1.49 (m, 3H), 1.10-1.18 (m, 1H).
110	MS m/z 436.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24 (d, <i>J</i> = 4.4 Hz, 1H), 8.86 (d, <i>J</i> = 7.2 Hz, 1H), 7.45 (d, <i>J</i> = 2.0 Hz, 1H), 7.34 (q, <i>J</i> = 8.0 Hz, 1H), 7.06 (q, <i>J</i> = 8.0 Hz, 1H), 5.88-6.00 (m, 1H), 4.87-5.02 (m, 1H), 3.49 (t, <i>J</i> = 2.2 Hz, 1H), 2.76-2.80 (m, 2H), 1.87-1.99 (m, 4H), 1.57-1.62 (m, 3H), 1.43-1.49 (m, 3H), 1.08-1.14 (m, 1H).

Cpd	Data
113	MS m/z 410.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.28-11.23 (m, 1H), 8.93-8.85 (m, 1H), 7.50-7.43 (m, 1H), 7.33 (dd, J = 8.8, 1.6 Hz, 1H), 7.05 (dd, J = 8.8, 2.0 Hz, 1H), 6.05-5.92 (m, 1H), 5.00-4.85 (m, 1H), 3.54-3.46 (m, 1H), 2.88-2.67 (m, 2H), 2.00-1.91 (m, 1H), 1.80-1.57 (m, 2H), 1.09 (dd, J = 8.8, 3.6 Hz, 3H), 7.05 (d, J = 6.4 Hz, 3H).
114	MS m/z 442.1 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.26 (s, 1H), 7.46 (s, 1H), 7.34 (d, J=8.5 Hz, 1H), 7.06 (dd, J=8.6, 1.9 Hz, 1H), 6.57-6.97 (m, 2H), 6.03 (br d, J=8.0 Hz, 1H), 4.96 (br dd, J=13.4, 5.1 Hz, 1H), 3.53 (td, J=12.5, 4.0 Hz, 1H), 2.68-2.92 (m, 2H), 1.90-2.02 (m, 1H), 1.70-1.84 (m, 1H), 1.54-1.68 (m, 1H), 1.04-1.17 (m, 3H), 0.92 (d, J=6.5 Hz, 3H)
115	MS m/z 476.0 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.29 (s, 1H), 7.48 (d, J=2 Hz, 1H), 7.35 (d, J=8.4 Hz, 1H), 7.07 (q, J= 6.4 Hz, 1H), 5.97 (q, J = 7.2 Hz, 1H), 4.91 (q, J = 8.8 Hz, 1H), 3.64-3.56 (m, 1H), 2.88-2.77 (m, 2H), 2.04-1.97 (m, 1H), 1.80-1.74 (m, 1H), 1.67-1.63 (m, 1H), 1.11 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.4 Hz, 3H).
116	MS m/z 457.9 [M-H] ⁻ ; ¹ H NMR (400 MHz, CDCl ₃) δ 10.86 (s, 1H), 7.35-7.35 (d, J = 2.0 Hz, 1 H), 7.27-7.25 (d, J = 8.8 Hz, 1H), 6.99-6.96 (dd, J = 2.0 Hz, 8.8 Hz, 1H), 3.95-3.93 (d, J = 9.2 Hz, 1H), 3.12-3.07 (m, 1H), 2.84-2.78 (m, 1H), 2.58-2.53 (m, 2H), 1.98-1.89 (m, 1H), 1.69-1.62 (m, 1H), 1.52-1.46 (m, 1H), 0.97-0.96 (d, J = 6.4 Hz, 3H), 0.93-0.91 (d, J = 6.4 Hz, 3H).
123	MS m/z 533.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.26 (s, 1H), 7.47 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.06 (dd, J = 8.6, 2.0 Hz, 1H), 5.96 (d, J = 9.0 Hz, 1H), 4.91 (dd, J = 13.1, 4.7 Hz, 1H), 3.58 (dd, J = 16.7, 8.1 Hz, 1H), 2.88-2.67 (m, 4H), 2.22 (d, J = 8.5 Hz, 1H), 2.12 (s, 3H), 2.06-1.96 (m, 1H), 1.80 (d, J = 13.6 Hz, 3H), 1.53 (d, J = 10.3 Hz, 1H), 1.23 (t, J = 14.2 Hz, 3H).
128	1:1.2 diastereomeric mixture. MS m/z 582.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.27 (app d, J = 17.6 Hz, 1H), 7.47 (s, 1H), 7.35 (dd, J = 8.6, 2.0 Hz, 1H), 7.07 (dd, J = 8.6, 2.1 Hz, 1H), 6.01 (d, J = 11.8 Hz, 1H), 5.28-4.78 (m, 1H), 3.61 (q, J = 10.8, 9.9 Hz, 1H), 3.35 (t, J = 3.6 Hz, 1H), 2.83 (q, J = 13.5, 11.6 Hz, 2H), 2.09 (t, J = 12.8 Hz, 1H), 1.92 (t, J = 12.3 Hz, 1H), 1.80-1.58 (m, 3H), 1.59-1.48 (m, 6H), 1.45-1.15 (m, 3H), 1.03 (app dd, J = 73.4, 6.4 Hz, 3H).
130	MS m/z 490.0 [M+H] ⁺ ; (DMSO- <i>d</i> ₆ , 400 MHz), d : 11.26 (d, J = 13.2 Hz, 1 H), 7.47 (dd, J = 1.6 Hz, 4.0 Hz, 1 H), 7.35 (dd, J = 7.2 Hz, 8.4 Hz, 1 H), 7.07 (dt, J = 2.0 Hz, 8.4 Hz, 1 H), 6.02-5.74 (m, 2 H), 5.07-4.8 (m, 3H), 3.64-3.57 (m, 1 H), 2.87-2.77 (m, 2 H), 2.31-2.88 (m, 1 H), 2.15-2.05 (m, 1 H), 2.00-1.89 (m, 1 H), 1.10 (dd, J=6.4 Hz, 14.0 Hz, 3 H)
131	MS m/z 474.1 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.22 (s, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 8.5, 2.1 Hz, 1H), 5.98-5.79 (m, 2H), 5.03 (d, J = 17.3 Hz, 1H), 4.99-4.90 (m, 2H), 3.59 (t, J = 10.7 Hz, 1H), 2.87 (d, J = 12.5 Hz, 1H), 2.82-2.70 (m, 1H), 2.25-2.03 (m, 4H).
133	1:1.3 diastereomeric mixture. MS m/z 546.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.26 (app d, J = 21.8 Hz, 1H), 7.47 (s, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 8.4, 2.3 Hz, 1H), 6.00 (t, J = 6.9 Hz, 1H), 5.09-4.75 (m, 2H), 3.61 (tt, J = 12.7, 6.1 Hz, 1H), 3.00-2.59 (m, 2H), 2.08 (q, J = 12.9 Hz, 1H), 1.98-1.67 (m, 4H), 1.58 (app d, J = 6.5 Hz, 3H), 1.51 (app d, J = 9.0 Hz, 3H), 1.45-1.14 (m, 3H), 1.02 (app dd, J = 72.3, 6.4 Hz, 3H).

Cpd	Data
167	MS m/z 436.2 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.85 (s, 1H), 7.20 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 2.3 Hz, 1H), 6.73-6.66 (m, 1H), 6.04-5.96 (m, 1H), 4.96 (dd, J = 13.3, 4.8 Hz, 1H), 3.73 (s, 3H), 3.52 (dt, J = 12.3, 6.8 Hz, 1H), 2.85-2.62 (m, 2H), 2.03-1.86 (m, 1H), 1.75 (t, J = 11.2 Hz, 1H), 1.58 (s, 1H), 1.10 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H).
174	MS m/z 504.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 1.29 (s, 1H), 7.53 (d, J = 1.9 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.11 (dd, J = 8.6, 2.1 Hz, 1H), 6.33 (d, J = 9.1 Hz, 1H), 4.95 (dd, J = 13.4, 4.9 Hz, 1H), 3.74 (td, J = 13.3, 4.5 Hz, 1H), 3.37 (dd, J = 18.9, 8.1 Hz, 1H), 2.99 (dd, J = 23.6, 11.8 Hz, 1H), 2.92-2.75 (m, 2H).
176	MS m/z 518.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.2 (s, 1H), 7.47-7.46 (m, 1H), 7.35-7.33 (d, J = 8.4 Hz, 1H), 7.07-7.04 (m, 1H), 5.99-5.97 (m, 1H), 4.93-4.89 (m, 1H), 3.59-3.58 (m, 1H), 2.84-2.76 (m, 2H), 2.30-2.27 (m, 1H), 1.94-1.93 (m, 1H), 1.80-1.79 (m, 1H), 1.58-1.68 (m, 4H), 1.19-0.81 (m, 6H).
177	MS m/z 498.0 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.26 (s, 1H), 7.46 (s, 1H), 7.35-7.33 (d, J = 8.4 Hz, 1H), 7.07-7.04 (m, 1H), 6.96-6.64 (m, 1H), 6.06-5.67 (m, 1H), 4.99-4.94 (m, 1H), 3.58-3.33 (m, 1H), 2.86-2.75 (m, 2H), 2.30-2.27 (m, 1H), 1.96-1.93 (m, 1H), 1.82-1.76 (m, 1H), 1.69-1.59 (m, 4H), 1.39-0.80 (m, 6H).
178	MS m/z 450.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24-11.23 (m, 1H), 8.88-8.85 (m, 1H), 7.45-7.44 (m, 1H), 7.34-7.32 (m, 1H), 7.06-7.04 (m, 1H), 6.06-5.94 (m, 1H), 5.00-4.84 (m, 1H), 3.52-3.45 (m, 1H), 2.83-2.73 (m, 2H), 2.30-2.13 (m, 1H), 1.91-1.88 (m, 1H), 1.81-1.76 (m, 1H), 1.69-1.57 (m, 4H), 1.23-0.95 (m, 6H).
180	MS m/z 410.4 [M+H] ⁺ ; ¹ H NMR (400 MHz, CDCl ₃) δ 7.80 (s, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.10 (dd, J = 8.6, 2.0 Hz, 1H), 6.16 (dd, J = 10.4, 3.8 Hz, 1H), 5.15 (dd, J = 13.4, 5.3 Hz, 1H), 3.42-3.23 (m, 1H), 2.89-2.77 (m, 1H), 2.71 (dd, J = 15.5, 3.7 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 3H), 1.87 (ddd, J = 14.2, 10.3, 3.9 Hz, 1H), 1.68 (s, 1H), 1.31-0.95 (m, 1H).
181	MS m/z 370.0 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz) δ 11.19 (s, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.04 (q, J = 6.4 Hz, 1H), 6.06 (q, J = 4.0 Hz, 1H), 4.96 (q, J = 9.2 Hz, 1H), 3.29 (d, J = 5.2 Hz, 1H), 2.74-2.61 (m, 2H), 2.33 (s, 3H), 2.29 (s, 3H), 1.92-1.86 (m, 1H), 1.73-1.66 (m, 1H), 1.61-1.56 (m, 1H), 1.11 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H).
182	MS m/z 382.0 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz) δ 11.17 (s, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.04 (q, J = 6.8 Hz, 1H), 5.92 (q, J = 4.8 Hz, 1H), 4.99 (q, J = 8.8 Hz, 1H), 3.31-3.24 (m, 1H), 2.74-2.59 (m, 2H), 2.33 (s, 3H), 2.29 (s, 3H), 2.12-1.77 (m, 8H), 1.64-1.55 (m, 1H).
183	MS m/z 396.0 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz) δ 11.18 (s, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.04 (q, J = 6.4 Hz, 1H), 6.00 (t, J = 7.6 Hz, 1H), 4.99 (q, J = 9.2 Hz, 1H), 3.30 (q, J = 8.4 Hz, 1H), 2.74-2.61 (m, 2H), 2.34 (s, 3H), 2.29 (s, 3H), 2.01-1.95 (m, 2H), 1.89-1.78 (m, 2H), 1.71-1.53 (m, 3H), 1.51-1.33 (m, 3H), 1.15-1.08 (m, 1H).
205	MS m/z 438.9 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.18 (d, J = 6.4 Hz, 1H), 8.73 (d, J = 4.4 Hz, 1H), 7.43 (d, J = 2.0 Hz, 1H), 7.32 (dd, J = 8.6, 2.4 Hz, 1H), 7.05-7.03 (m, 2H), 5.89 (br, 1H), 4.96 (br, 1H), 3.43-3.34 (m, 1H), 3.32-3.28 (m, 1H), 3.18 (d, J = 14.0 Hz, 3H), 2.76-2.66 (m, 2H), 2.12-1.88 (m, 2H), 1.64-1.42 (m, 2H), 1.06-1.03 (m, 3H).

Cpd	Data
206	MS m/z 438.9 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.21 (s, 1H), 8.72 (d, J=4.0 Hz, 1H), 7.44 (d, J=2.0 Hz, 1H), 7.33 (d, J=8.8 Hz, 1H), 7.04-7.06 (m, 2H), 5.95 (s, 1H), 4.91 (s, 1H), 3.50 (s, 3H), 2.68-2.73 (m, 2H), 2.46-2.49 (m, 2H), 2.30-2.44 (m, 2H), 2.12-2.22 (m, 1H).
212	MS m/z 519.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24 (s, 1H), 7.48 (s, 1H), 7.45 (d, J=2.0 Hz, 1H), 7.34 (d, J=8.4 Hz, 1H), 7.05 (dd, J=8.6, 2.0 Hz, 1H), 5.98-5.98 (m, 1H), 4.90-4.86 (m, 1H), 3.87-3.76 (m, 2H), 3.53-3.50 (m, 1H), 3.26-3.13 (m, 2H), 2.82-2.71 (m, 2H), 2.19-2.16 (m, 1H), 2.03-1.96 (m, 1H), 1.84-1.77 (m, 1H), 1.56-1.49 (m, 2H), 1.37-1.18 (m, 2H).
217A and 217B	MS m/z 505.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24 (d, J=4.6 Hz, 1H), 7.50-7.44 (m, 2H), 7.34 (dd, J=8.6, 3.7 Hz, 1H), 7.06 (d, J=9.2 Hz, 1H), 5.88 (ddd, J=13.9, 10.2, 3.3 Hz, 1H), 4.98-4.81 (m, 1H), 3.88-3.76 (m, 1H), 3.75-3.68 (m, 1H), 3.67-3.53 (m, 2H), 3.27-3.20 (m, 1H), 2.85-2.69 (m, 2H), 2.23 (s, 1H), 2.18-1.95 (m, 3H), 1.64 (ddd, J=122.0, 11.9, 7.1 Hz, 1H).
221	MS m/z 409.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.20 (s, 1H), 8.73 (s, 1H), 7.42 (d, J=2.0 Hz, 1H), 7.31 (d, J=8.8 Hz, 1H), 7.04 (q, J=5.2 Hz, 2H), 6.05-5.97 (m, 1H), 4.94 (q, J=41.6 Hz, 1H), 3.46-3.38 (m, 1H), 2.73-2.67 (m, 2H), 1.98-1.91 (m, 1H), 1.74-1.62 (m, 2H), 1.10 (d, J=6.0 Hz, 3H), 0.92 (d, J=6.8 Hz, 3H).
223	MS m/z 477.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24 (s, 1H), 7.47 (s, 1H), 7.45 (d, J=2.0 Hz, 1H), 7.33 (d, J=8.4 Hz, 1H), 7.05 (q, J=6.4 Hz, 1H), 5.97 (q, J=7.2 Hz, 1H), 4.88 (q, J=9.2 Hz, 1H), 3.55-3.49 (m, 1H), 2.82-2.68 (m, 2H), 2.00-1.94 (m, 1H), 1.77-1.71 (m, 1H), 1.66-1.61 (m, 1H), 1.10 (d, J=6.4 Hz, 3H), 0.93 (d, J=6.4 Hz, 3H).
224	MS m/z 475.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, CDCl ₃) δ 10.86 (s, 1H), 7.35-7.35 (d, J=2.0 Hz, 1H), 7.27-7.25 (d, J=8.8 Hz, 1H), 6.99-6.96 (dd, J=2.0, 8.8 Hz, 1H), 3.95-3.93 (d, J=9.2 Hz, 1H), 3.12-3.07 (m, 1H), 2.84-2.78 (m, 1H), 2.58-2.53 (m, 2H), 1.98-1.89 (m, 1H), 1.69-1.62 (m, 1H), 1.52-1.46 (m, 1H), 0.97-0.96 (d, J=6.4 Hz, 3H), 0.93-0.91 (d, J=6.4 Hz, 3H).
226	MS m/z 463.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.20 (s, 1H), 7.46-7.45 (m, 2H), 7.32 (d, J=8.4 Hz, 1H), 7.04 (dd, J=8.6 Hz, 2.4 Hz, 1H), 5.90 (t, J=7.0 Hz, 1H), 4.91 (dd, J=13.4 Hz, 4.4 Hz, 1H), 3.51-3.44 (m, 1H), 2.82-2.72 (m, 2H), 1.97 (dd, J=14.6 Hz, 7.2 Hz, 2H), 1.44-1.35 (m, 2H), 0.96 (t, J=7.4 Hz, 3H).
228	MS m/z 475.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.15 (s, 1H), 7.45 (d, J=2.8 Hz, 2H), 7.33 (d, J=8.4 Hz, 1H), 7.04 (q, J=8.4 Hz, 1H), 5.97-6.00 (m, 1H), 4.97 (q, J=12.0 Hz, 1H), 3.48-3.51 (m, 1H), 2.72-2.84 (m, 2H), 1.90-1.98 (m, 1H), 1.80-1.87 (m, 1H), 0.69-0.75 (m, 1H), 0.28-0.38 (m, 2H), 0.04-0.15 (m, 2H).
231	MS m/z 435.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.18 (s, 1H), 8.72 (d, J=4.1 Hz, 1H), 7.42 (d, J=2.0 Hz, 1H), 7.32 (d, J=8.6 Hz, 1H), 7.09-6.96 (m, 2H), 5.96 (d, J=25.9 Hz, 1H), 4.91 (d, J=36.4 Hz, 1H), 3.48-3.34 (m, 1H), 2.71 (dd, J=9.3, 3.7 Hz, 2H), 2.09-1.77 (m, 4H), 1.74-1.51 (m, 3H), 1.51-1.27 (m, 3H), 1.19-1.02 (m, 1H).
234	MS m/z 433.2 [M+H] ⁺ ; (DMSO- <i>d</i> ₆ , 400 MHz) δ 11.19 (d, J=8.8 Hz, 1H), 8.87 (d, J=4 Hz, 1H), 7.42 (d, J=2 Hz, 1H), 7.32-7.29 (m, 1H), 7.04-7.01 (m, 2H), 6.09-5.57 (m, 3H), 5.00-4.84 (m, 1H), 3.47-3.36 (m, 1H), 2.76-2.63 (m, 3H), 2.45-2.07 (m, 3H), 2.02-1.92 (m, 2H), 1.79-1.68 (m, 1H).

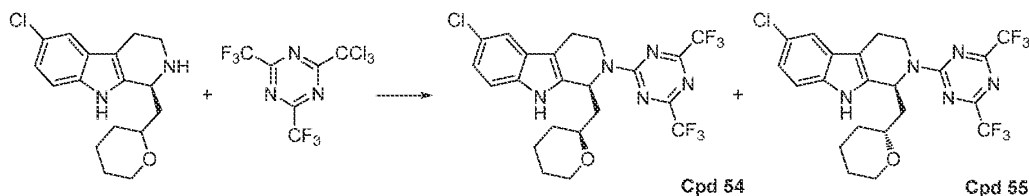
Cpd	Data
237	MS m/z 449.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.18 (s, 1H), 8.72 (s, 1H), 7.41 (s, 1H), 7.32-7.30 (d, J = 8.8, 2H), 7.03-7.02 (m, 2H), 6.00-5.97 (m, 1H), 4.97-4.93 (m, 1H), 3.44-3.40 (m, 1H), 2.71-2.70 (m, 2H), 2.29-2.27 (m, 1H), 1.90-1.85 (m, 1H), 1.75-1.71 (m, 1H), 1.68-1.59 (m, 4H), 1.31-0.93 (m, 6H).
238	MS m/z 510.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23 (s, 1H), 7.47 (s, 1H), 7.44 (d, J = 2 Hz, 1H), 7.33-7.31 (dd, J = 8.4 Hz, 1H), 7.05-7.03 (m, 1H), 6.00-5.96 (m, 1H), 4.89-4.84 (m, 1H), 3.50-3.47 (m, 1H), 2.77-2.72 (m, 2H), 2.29-2.26 (m, 1H), 1.91-1.88 (m, 1H), 1.79-1.77 (m, 1H), 1.69-1.59 (m, 4H), 1.28-0.83 (m, 6H).
240	MS m/z 453.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.30 (s, 1H), 8.71 (s, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.33 (d, J = 10.0 Hz, 1H), 7.03 (d, J = 5.2 Hz, 1H), 6.05-5.81 (m, 1H), 5.03-4.77 (m, 1H), 3.45-3.38 (m, 1H), 2.75-2.64 (m, 2H), 2.06-1.86 (m, 4H), 1.76-1.32 (m, 6H), 1.17-1.04 (m, 1H).
241	MS m/z 425.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23 (s, 1H), 8.72 (d, J = 4.2 Hz, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.35 (d, J = 10.2 Hz, 1H), 7.02 (d, J = 4.8 Hz, 1H), 5.98 (s, 1H), 5.13-4.88 (m, 1H), 3.47-3.37 (m, 1H), 2.82-2.60 (m, 2H), 1.97-1.70 (m, 2H), 0.78-0.65 (m, 1H), 0.45-0.20 (m, 2H), 0.18-0.01 (m, 2H).
253	MS m/z 411.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.11 (s, 1H), 7.39 (s, 1H), 7.30 (d, J = 8.5 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.39 (s, 1H), 6.08 (d, J = 10.4 Hz, 1H), 4.95 (d, J = 13.2 Hz, 1H), 3.89 (d, J = 9.2 Hz, 1H), 3.78 (d, J = 8.8 Hz, 1H), 3.28-3.07 (m, 3H), 2.63 (s, 2H), 2.22 (s, 6H), 2.07 (d, J = 2.3 Hz, 1H), 1.86 (d, J = 11.1 Hz, 1H), 1.72 (d, J = 13.5 Hz, 1H), 1.49 (d, J = 12.9 Hz, 2H), 1.26 (dd, J = 32.9, 11.9 Hz, 2H).
258	MS m/z 435.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.28 (s, 1H), 8.35 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 4.0 Hz, 1H), 6.00-5.87 (m, 1H), 4.88-4.78 (m, 1H), 3.88 (d, J = 8.0 Hz, 1H), 3.78 (dd, J = 12.0, 4.0 Hz, 1H), 3.43-3.36 (m, 1H), 3.26-3.16 (m, 2H), 2.70-2.69 (m, 2H), 1.97-1.88 (m, 1H), 1.81-1.78 (m, 1H), 1.55-2.69 (m, 2H), 1.41-1.17 (m, 3H).
262	MS m/z 359.0 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz), δ 11.24 (s, 1H), 8.37 (d, J = 4.5 Hz, 2H), 7.51 (d, J = 7.3 Hz, 1H), 7.30 (d, J = 10.2 Hz, 1H), 6.61 (t, J = 4.6 Hz, 1H), 6.03 (d, J = 10.2 Hz, 1H), 5.00-4.76 (m, 1H), 3.33-3.24 (m, 1H), 2.71-2.61 (m, 2H), 1.96-1.81 (m, 1H), 1.74-1.62 (m, 2H), 1.07 (d, J = 5.5 Hz, 3H), 0.91 (d, J = 5.7 Hz, 3H).
263	MS m/z 369.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.10 (s, 1H), 7.38 (s, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.01 (d, J = 7.4 Hz, 1H), 6.39 (s, 1H), 6.10 (d, J = 9.5 Hz, 1H), 4.94 (d, J = 9.3 Hz, 1H), 3.23 (d, J = 7.7 Hz, 1H), 2.63 (s, 2H), 2.23 (s, 6H), 1.85 (d, J = 10.1 Hz, 1H), 1.65 (d, J = 6.0 Hz, 2H), 1.11 (d, J = 5.3 Hz, 3H), 0.91 (d, J = 5.5 Hz, 3H).
264	MS m/z 367.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.03 (s, 1H), 7.46-7.20 (m, 2H), 7.02 (d, J = 8.6 Hz, 1H), 6.38 (s, 1H), 6.05 (s, 1H), 5.05 (s, 1H), 3.40 (s, 1H), 2.66 (s, 2H), 2.22 (d, J = 12.5 Hz, 6H), 1.80 (d, J = 45.4 Hz, 2H), 0.72 (s, 1H), 0.36 (s, 2H), 0.07 (s, 2H).
265	MS m/z 381.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.12 (s, 1H), 7.40 (d, J = 1.8 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.02 (dd, J = 8.6, 2.0 Hz, 1H), 6.43 (s, 1H), 6.10-5.85 (m, 1H), 4.96 (d, J = 13.1 Hz, 1H), 3.25 (dd, J = 13.1, 7.9 Hz, 1H), 2.65 (d, J = 4.8 Hz, 2H), 2.37 (dd, J = 15.4, 8.1 Hz, 1H), 2.26 (s, 6H), 2.09 (s, 1H), 2.00 (t, J = 8.3 Hz, 2H), 1.90 (s, 1H), 1.78 (dd, J = 8.6, 5.4 Hz, 2H), 1.64-1.53 (m, 1H), 1.24 (s, 1H).

Cpd	Data
266	MS m/z 395.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.10 (s, 1H), 7.38 (d, J=2.0 Hz, 1H), 7.29 (d, J=8.5 Hz, 1H), 7.01 (dd, J=8.5, 2.1 Hz, 1H), 6.38 (s, 1H), 6.05 (dd, J=10.1, 3.1 Hz, 1H), 5.09–4.81 (m, 1H), 3.31–3.11 (m, 1H), 2.65 (d, J=8.7 Hz, 2H), 2.23 (s, 6H), 2.02–1.75 (m, 4H), 1.73–1.52 (m, 3H), 1.55–1.29 (m, 3H), 1.12 (dd, J=11.9, 7.9 Hz, 1H)
267	MS m/z 409.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.10 (s, 1H), 7.52–7.20 (m, 2H), 7.01 (d, J=8.3 Hz, 1H), 6.38 (s, 1H), 6.10 (d, J=9.0 Hz, 1H), 4.96 (d, J=11.6 Hz, 1H), 3.26–3.12 (m, 1H), 2.63 (s, 2H), 2.34 (d, J=10.0 Hz, 1H), 2.23 (s, 6H), 1.87–1.42 (m, 6H), 1.34–0.86 (m, 6H)
276	MS m/z 647.4 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.21 (s, 1H), 7.53 (d, J=1.9 Hz, 1H), 7.48 (t, J=1.3 Hz, 1H), 6.05 (t, J=7.2 Hz, 1H), 4.89 (dd, J=13.5, 5.1 Hz, 1H), 3.72 (d, J=10.9 Hz, 1H), 3.61 (dt, J=17.0, 7.0 Hz, 2H), 3.29 (m, 1H), 3.01 (t, J=10.4 Hz, 1H), 2.91–2.69 (m, 2H), 2.36 (s, 1H), 1.90–1.77 (m, 2H), 1.58 (s, 1H), 1.50 (s, 1H), 1.44–1.30 (m, 1H), 1.24 (s, 1H)
282	MS m/z 474.0 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.11 (s, 1H), 7.50 (d, J=1.6 Hz, 1H), 7.35 (d, J=2.4 Hz, 1H), 7.08 (m, 1H), 6.49 (d, J=9.6 Hz, 1H), 5.51 (d, J=8.4 Hz, 1H), 4.97 (q, J=8.4 Hz, 1H), 3.65–3.57 (m, 1H), 2.92 (q, J=12.4 Hz, 1H), 2.82–2.74 (m, 1H), 2.03 (s, 3H), 1.75 (s, 3H)
283	MS m/z 458.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.10 (d, J=4.8 Hz, 1H), 7.50 (s, 1H), 7.34 (d, J=8.8 Hz, 1H), 7.08 (q, J=6.4 Hz, 1H), 6.83 (t, J=53.2 Hz, 1H), 6.51 (q, J=13.6 Hz, 1H), 5.49 (d, J=9.6 Hz, 1H), 5.05–4.94 (m, 1H), 3.61–3.54 (m, 1H), 2.91 (d, J=15.6 Hz, 1H), 2.78 (q, J=11.6 Hz, 1H), 2.04 (d, J=6.4 Hz, 3H), 1.75 (s, 3H)
285	MS m/z 408.2 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.07 (d, J=5.6 Hz, 1H), 8.87 (d, J=1.6 Hz, 1H), 7.48 (d, J=2.0 Hz, 1H), 7.34 (q, J=7.2 Hz, 1H), 7.07 (q, J=11.2 Hz, 1H), 6.50 (q, J=26.4 Hz, 1H), 5.48 (q, J=8.4 Hz, 1H), 5.06–4.91 (m, 1H), 3.55–3.47 (m, 1H), 2.87 (q, J=12 Hz, 1H), 2.79–2.71 (m, 1H), 2.03 (d, J=3.6 Hz, 3H), 1.74 (s, 3H)
291	MS m/z 518.0 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> , 400 MHz) δ 11.28 (s, 1H), 7.49 (d, J=2.0 Hz, 1H), 7.37 (d, J=8.4 Hz, 1H), 7.07 (q, J=6.4 Hz, 1H), 6.01 (q, J=6.4 Hz, 1H), 5.50 (s, 1H), 4.94 (q, J=8.1 Hz, 1H), 3.89 (d, J=16.4 Hz, 1H), 3.72–3.61 (m, 3H), 3.39 (t, J=4.8 Hz, 1H), 2.88 (q, J=12.4 Hz, 1H), 2.81–2.65 (m, 3H), 2.34 (d, J=17.6 Hz, 1H), 2.02 (d, J=16.8 Hz, 1H)
294	MS m/z 368.2 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> , 400 MHz) δ 11.00 (s, 1H), 7.45 (d, J=2 Hz, 1H), 7.32 (d, J=8.4 Hz, 1H), 7.05 (q, J=6.4 Hz, 1H), 6.54 (d, J=9.6 Hz, 1H), 5.42 (d, J=9.2 Hz, 1H), 5.02 (q, J=8.4 Hz, 1H), 3.33–3.29 (m, 1H), 2.79 (q, J=12 Hz, 1H), 2.71–2.63 (m, 1H), 2.31 (d, J=4.4 Hz, 6H), 2.05 (s, 3H), 1.72 (s, 3H)
295	MS m/z 368.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.00 (s, 1H), 7.45 (d, J=2 Hz, 1H), 7.32 (d, J=8.4 Hz, 1H), 7.05 (q, J=6.4 Hz, 1H), 6.54 (d, J=9.6 Hz, 1H), 5.42 (d, J=9.2 Hz, 1H), 5.02 (q, J=8.4 Hz, 1H), 3.33–3.29 (m, 1H), 2.79 (q, J=12 Hz, 1H), 2.71–2.63 (m, 1H), 2.31 (d, J=4.4 Hz, 6H), 2.05 (s, 3H), 1.72 (s, 3H)
296	MS m/z 367.2 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 10.91 (s, 1H), 7.42 (d, J=1.8 Hz, 1H), 7.30 (d, J=8.6 Hz, 1H), 7.02 (dd, J=8.5, 2.0 Hz, 1H), 6.57 (d, J=9.4 Hz, 1H), 6.39 (s, 1H), 5.41 (d, J=9.4 Hz, 1H), 5.02 (dd, J=13.3, 4.2 Hz, 1H), 3.26 (dd, J=11.3, 8.6 Hz, 1H), 2.70 (d, J=3.7 Hz, 2H), 2.24 (s, 6H), 2.06 (s, 3H), 1.70 (s, 3H)
297	MS m/z 367.2 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 10.91 (s, 1H), 7.42 (d, J=1.8 Hz, 1H), 7.30 (d, J=8.6 Hz, 1H), 7.02 (dd, J=8.5, 2.0 Hz, 1H), 6.57 (d, J=9.4 Hz, 1H), 6.39 (s, 1H), 5.41 (d, J=9.4 Hz, 1H), 5.02 (dd, J=13.3, 4.2 Hz, 1H), 3.26 (dd, J=11.3, 8.6 Hz, 1H), 2.70 (d, J=3.7 Hz, 2H), 2.24 (s, 6H), 2.06 (s, 3H), 1.70 (s, 3H)

Cpd	Data
299	MS m/z 435.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24(s, 1H), 7.49 (s, 1H), 7.48(d, J=2.4Hz, 1H), 7.34(d, J=8.8Hz, 1H), 7.06(dd, J=8.4, 2.0 Hz, 1H), 5.81-5.76(m, 1H), 4.97(d, J=13.2, 4.4Hz, 1H), 3.48-3.42(m, 1H), 2.87-2.83(m, 1H), 2.76-2.68 (m, 1H), 1.56(d, J=6.4 Hz, 3H).
300	MS m/z 449.7 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.17(s, 1H), 7.46-7.45(m, 2H), 7.33(d, J=8.8Hz, 1H), 7.05(dd, J= 8.4 Hz, 2.0 Hz, 1H), 5.82(dd, J= 9.4Hz, 4.0 Hz, 1H), 4.93 (dd, J= 13.4 Hz, 4.8 Hz, 1H), 3.50-3.46(m, 1H), 2.83-2.69(m, 2H), 2.13-2.07(m, 1H), 1.99-1.91(m, 1H), 0.96(t, J= 7.6Hz, 3H).
313	MS m/z 480.1 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 1.24 (br s, 1 H) 2.00-2.10 (m, 2 H) 2.19 (br s, 1 H) 2.71-2.86 (m, 2 H) 3.37-3.42 (m, 1 H) 3.55 (br s, 1 H) 3.75 (br s, 1 H) 4.00 (br s, 2 H) 4.96 (br d, J=11.13 Hz, 1 H) 5.79 (br d, J=10.88 Hz, 1 H) 6.07 (br d, J=7.25 Hz, 1 H) 6.18-6.24 (m, 1 H) 6.64-6.95 (m, 2 H) 7.06 (br d, J=8.63 Hz, 1 H) 7.33 (br d, J=7.75 Hz, 1 H) 7.46 (br s, 1 H) 11.29 (br s, 1 H)
321	MS m/z 419.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.28 (s, 1H), 8.10 (d, J=6.4Hz, 1H), 7.57 (d, J=7.2Hz, 1H), 7.34 (d, J=10.0Hz, 1H), 7.11-6.99 (m, 1H), 6.06-5.88 (m, 1H), 4.37-4.17 (m, 1H), 3.61-3.41 (m, 1 H), 2.75-2.66 (m, 2H), 2.07-1.99 (m, 2H), 1.84-1.83(m, 2H), 1.58-1.29 (m, 6H), 1.12-1.04 (m, 1H)
340	MS m/z 409.9 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24 (s, 1H), 9.17 (s, 1H), 7.45 (d, J=1.6 Hz, 1H), 7.33 (d, J=8.8 Hz, 1H), 7.02 (dd, J=8.6, 2.0 Hz, 1H), 6.34-5.75 (m, 1H), 5.25- 4.69 (m, 1H), 3.57 (s, 1H), 2.82-2.73 (m, 2H), 2.05-1.98 (m, 1H), 1.76-1.62 (m, 2H), 1.09 (d, J=6.4 Hz, 3H), 0.93(d, J=6.4Hz, 3H)
341	MS m/z 357.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.04 (s, 1H), 8.39 (d, J= 4.7Hz, 2H), 7.56 (d, J= 7.4Hz, 1H), 7.28 (d, J= 10.2Hz, 1H), 6.62 (t, J=4.7Hz, 1H), 6.54 (d, J=9.2Hz, 1H), 5.44 (d, J=9.2Hz, 1H), 4.96 (dd, J=13.2, 3.8Hz, 1H), 3.34-3.26 (m, 1H), 2.79-2.63 (m, 2H), 2.00 (s, 3H), 1.72 (s, 3H)

Example 30

Synthesis of Compound 54 and 55



[0357] A 20 mL vial was charged subsequently with (1S)-6-chloro-1-(tetrahydropyran-2-ylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (100 mg, 0.328 mmol), 4-dimethylaminopyridine (81 mg, 0.656 mmol), acetonitrile (3.3 mL) and 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (220 mg, 0.658 mmol), closed and allowed to stir at ambient temperature for 3 h after which volatiles were removed under reduced pressure. The dark residue obtained was subjected to purification by silica gel chromatography (hexanes:EtOAc) to isolate each diastereomer Compound 54 and Compound 55 as

amorphous white solids. The relative configuration was not determined; NMR data was obtained without assignment to a particular diastereomer.

[0358] **Compound 54**: MS m/z 518.2 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.31 (s, 1H), 7.46 (d, J = 2.1 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.05 (dd, J = 8.6, 2.1 Hz, 1H), 6.22 (d, J = 9.7 Hz, 1H), 4.92 (dd, J = 13.3, 5.1 Hz, 1H), 3.85 (d, J = 11.3 Hz, 1H), 3.58 (td, J = 12.5, 4.4 Hz, 1H), 3.28-3.15 (m, 2H), 2.92-2.70 (m, 2H), 2.19-2.07 (m, 1H), 2.07-1.96 (m, 1H), 1.72 (s, 1H), 1.45 (q, J = 13.7 Hz, 4H), 1.32-1.12 (m, 1H).

[0359] **Compound 55** MS m/z 518.2 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.16 (s, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 8.7, 2.1 Hz, 1H), 6.02 (d, J = 10.1 Hz, 1H), 4.94 (dd, J = 13.7, 5.2 Hz, 1H), 3.57 (d, J = 11.2 Hz, 2H), 3.44 (s, 1H), 3.13-2.95 (m, 1H), 2.86 (d, J = 13.9 Hz, 1H), 2.82-2.69 (m, 1H), 2.23-1.94 (m, 2H), 1.83 (d, J = 12.6 Hz, 1H), 1.75 (s, 1H), 1.39 (d, J = 5.7 Hz, 3H), 1.32-1.14 (m, 1H).

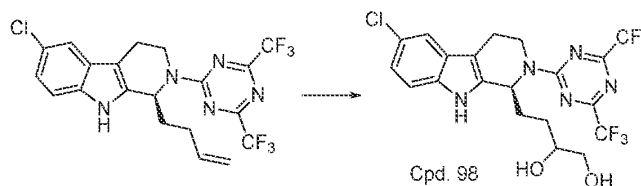
[0360] Using the procedure described for Example 30, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
42	MS m/z 482.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.21 (s, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.28 (d, J = 8.6 Hz, 1H), 6.99 (dd, J = 8.6, 2.1 Hz, 1H), 6.72 (td, J = 53.5, 12.8 Hz, 2H), 5.95 (dd, J = 10.6, 3.3 Hz, 1H), 4.90 (dd, J = 13.4, 5.1 Hz, 1H), 3.86-3.52 (m, 2H), 3.45 (ddd, J = 13.2, 11.6, 4.5 Hz, 1H), 3.21 (dd, J = 11.2, 2.9 Hz, 1H), 2.93 (dd, J = 11.0, 9.7 Hz, 1H), 2.84-2.57 (m, 2H), 2.27 (dd, J = 12.2, 4.1 Hz, 1H), 1.73 (dddd, J = 40.7, 14.0, 10.1, 3.4 Hz, 2H), 1.53 (dt, J = 12.6, 3.4 Hz, 1H), 1.45-1.16 (m, 3H).
43	MS m/z 482.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.16 (s, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 8.6 Hz, 1H), 6.99 (dd, J = 8.6, 2.1 Hz, 1H), 6.72 (td, J = 53.5, 16.5 Hz, 2H), 5.89 (dd, J = 10.4, 4.1 Hz, 1H), 4.89 (dd, J = 13.2, 5.1 Hz, 1H), 4.03 (ddd, J = 11.0, 4.2, 1.5 Hz, 1H), 3.62 (dt, J = 11.1, 4.0 Hz, 1H), 3.46 (ddd, J = 13.2, 11.6, 4.6 Hz, 1H), 3.25-3.21 (m, 1H), 3.15 (dd, J = 11.1, 8.9 Hz, 1H), 2.84-2.58 (m, 2H), 1.97-1.73 (m, 2H), 1.68 (dd, J = 12.9, 4.2 Hz, 1H), 1.58-1.28 (m, 3H), 1.23-1.05 (m, 1H).
47A and 47B	MS m/z 520.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.26 (d, J = 22.6 Hz, 1H), 7.47 (s, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 8.6, 1.8 Hz, 1H), 5.93 (dd, J = 23.8, 7.0 Hz, 1H), 4.92 (dd, J = 13.2, 4.8 Hz, 1H), 4.13-3.55 (m, 3H), 3.36-2.97 (m, 2H), 2.89-2.73 (m, 2H), 2.01 (ddd, J = 93.0, 31.9, 11.0 Hz, 2H), 1.74 (t, J = 10.6 Hz, 1H), 1.69-1.40 (m, 3H), 1.37-1.17 (m, 1H).
58	MS m/z 450.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.26 (s, 1H), 8.87 (d, 1H, J = 10Hz), 7.45 (d, 1H, J = 2.4Hz), 7.34 (d, 1H, J = 8.4Hz), 7.05 (q, 1H, J = 6.8Hz), 6.04-5.90 (m, 1H), 5.00-4.84 (m, 1H), 3.73-3.66 (m, 2H), 3.52-3.45 (m, 1H), 3.32-3.25 (m, 1H), 3.03-2.97 (m, 1H), 2.83-2.72 (m, 2H), 1.87-1.68 (m, 2H), 1.62-1.58 (m, 1H), 1.46-1.23 (m, 4H).

Cpd	Data
59	MS m/z 450.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.21 (s, 1H), 8.87 (d, 1H, <i>J</i> = 8.8 Hz), 7.45 (d, 1H, <i>J</i> = 2.0 Hz), 7.34 (q, 1H, <i>J</i> = 6.4 Hz), 7.05 (q, 1H, <i>J</i> = 6.8 Hz), 5.98-5.85 (m, 1H), 4.99-4.84 (m, 1H), 4.12-4.06 (m, 1H), 3.70-3.67 (m, 1H), 3.54-3.46 (m, 1H), 3.30-3.26 (m, 1H), 3.20 (q, 1H, <i>J</i> = 9.6 Hz), 2.83-2.66 (m, 2H), 1.92-1.80 (m, 2H), 1.75-1.72 (m, 1H), 1.60-1.40 (m, 3H), 1.25-1.15 (m, 1H).
100	MS m/z 562.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.28 (s, 1H), 7.47 (d, <i>J</i> = 2.1 Hz, 1H), 7.35 (d, <i>J</i> = 8.6 Hz, 1H), 7.07 (dd, <i>J</i> = 8.5, 2.1 Hz, 1H), 6.29-5.80 (m, 1H), 4.92 (dd, <i>J</i> = 13.4, 5.0 Hz, 1H), 4.04 (q, <i>J</i> = 7.1 Hz, 1H), 3.59 (td, <i>J</i> = 12.4, 4.6 Hz, 1H), 2.97-2.70 (m, 2H), 2.08 (t, <i>J</i> = 12.7 Hz, 1H), 1.84-1.64 (m, 1H), 1.48 (s, 1H), 1.23 (tt, <i>J</i> = 13.4, 6.5 Hz, 5H), 1.11 (d, <i>J</i> = 6.4 Hz, 3H), 1.02 (br s, 6zH).
101	MS m/z 562.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.24 (s, 1H), 7.47 (d, <i>J</i> = 2.1 Hz, 1H), 7.35 (d, <i>J</i> = 8.6 Hz, 1H), 7.07 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 6.13-5.89 (m, 1H), 4.92 (dd, <i>J</i> = 13.6, 4.9 Hz, 1H), 4.16-3.99 (m, 1H), 3.75-3.48 (m, 1H), 2.89-2.76 (m, 2H), 1.91 (q, <i>J</i> = 5.9 Hz, 2H), 1.73 (d, <i>J</i> = 13.1 Hz, 1H), 1.55 (s, 1H), 1.44-1.07 (m, 5H), 1.07-1.00 (m, 7H), 0.93 (d, <i>J</i> = 6.5 Hz, 3H).
213A and 213B	MS m/z 519.3 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.22 (d, <i>J</i> = 20.1 Hz, 1H), 7.47 (dd, <i>J</i> = 14.5, 1.8 Hz, 2H), 7.33 (d, <i>J</i> = 8.5 Hz, 1H), 7.05 (dd, <i>J</i> = 8.6, 2.0 Hz, 1H), 5.99-5.87 (m, 1H), 4.87 (d, <i>J</i> = 11.6 Hz, 1H), 4.13-3.65 (m, 2H), 3.50 (td, <i>J</i> = 11.4, 5.3 Hz, 1H), 3.15 (ddd, <i>J</i> = 84.0, 16.6, 7.0 Hz, 2H), 2.83-2.71 (m, 2H), 2.33 (s, 1H), 1.92-1.71 (m, 2H), 1.42 (ddd, <i>J</i> = 37.2, 36.5, 24.3 Hz, 4H).

Example 31

Synthesis of Compound 98



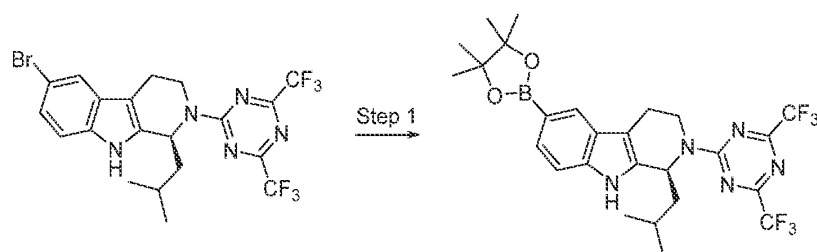
[0361] A 20 mL vial was charged with (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-but-3-enyl-6-chloro-1,3,4,9-tetrahydropyrido[3,4-b]indole (90 mg, 0.189 mmol), potassium osmate (VI) dihydrate (4 mg, 0.011 mmol), 4-methylmorpholine N-oxide (30 mg, 0.248 mmol), suspended in acetone (5 mL), water (1 mL) and allowed to stir at ambient temp for 14 h. Volatiles were removed under reduced pressure and the obtained residue taken up in DMSO and subjected to prep HPLC purification (water acetonitrile). After lyophilization 4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butane-1,2-diol (35 mg, 0.069 mmol, 36% yield) was obtained as a white amorphous solid. MS m/z 508.1 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.22 (s, 1H), 7.48 (d, *J* = 2.1 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.07 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.98-5.79 (m, 2H), 5.03 (d, *J* = 17.3 Hz, 1H), 4.99-4.90 (m, 2H), 3.59 (t, *J* = 10.7 Hz, 1H), 2.87 (d, *J* = 12.5 Hz, 1H), 2.82-2.70 (m, 1H), 2.25-2.03 (m, 4H).

[0362] Using the procedure described for Example 31, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

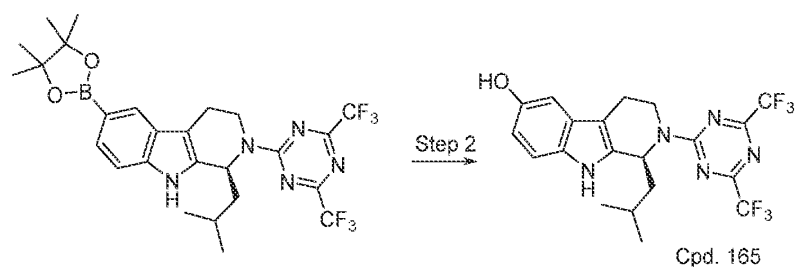
Cpd	Data
102	MS m/z 578.1 [M-H] ⁺ ; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.62-11.03 (m, 1H), 7.50 (d, <i>J</i> = 2.4 Hz, 1H), 7.37 (d, <i>J</i> = 8.3 Hz, 1H), 7.09 (dd, <i>J</i> = 8.6, 2.1 Hz, 1H), 6.13-5.78 (m, 1H), 4.93 (dd, <i>J</i> = 13.8, 5.7 Hz, 1H), 4.31-4.11 (m, 1H), 4.09-3.82 (m, 1H), 3.62 (q, <i>J</i> = 13.5 Hz, 1H), 3.35 (app s, 1H), 3.20-2.92 (m, 1H), 2.94-2.73 (m, 2H), 2.26-1.98 (m, 1H), 1.98-1.79 (m, 1H), 1.72 (p, <i>J</i> = 11.1, 10.1 Hz, 1H), 1.61-1.39 (m, 1H), 1.26 (app s, 1H), 1.14 (dd, <i>J</i> = 9.2, 6.0 Hz, 2H), 1.06-0.92 (m, 8H).

Example 32

Synthesis of Compound 165



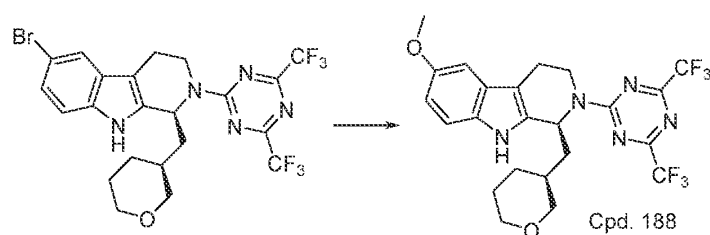
[0363] **Step 1:** A 20 mL was charged with bis(pinacolato)diboron (117 mg, 0.461 mmol), potassium acetate (56 mg, 0.571 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (63 mg, 0.076 mmol), (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-isobutyl-1,3,4,9-tetrahydro pyrido [3,4-b]indole (200 mg, 0.383 mmol), closed and put under argon atmosphere. The solids were suspended in dioxane and allowed to stir at 100 °C overnight. After being allowed to cool to ambient temperature, volatiles were removed under reduced pressure and the residue obtained subjected to purification by silica gel chromatography (hexanes EtOAc). (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-isobutyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,4,9-tetrahydropyrido[3,4-b]indole (130 mg, 0.228 mmol, 59% yield) was isolated as an amorphous off white solid. MS m/z 568.1 [M-H]⁺; ¹H NMR (400 MHz, DMSO) δ 11.19 (s, 1H), 7.80 (s, 1H), 7.41 (s, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 5.97 (d, *J* = 10.3 Hz, 1H), 4.94 (dd, *J* = 13.1, 5.1 Hz, 1H), 3.58 (d, *J* = 13.9 Hz, 1H), 2.97-2.73 (m, 2H), 1.99 (t, *J* = 12.3 Hz, 1H), 1.78 (t, *J* = 12.0 Hz, 1H), 1.66 (s, 1H), 1.29 (s, 12H), 1.11 (d, *J* = 6.2 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H).



[0364] **Step 2:** An 8 mL vial was charged with (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-isobutyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,4,9-tetrahydropyrido[3,4-b]indole (130 mg, 0.228 mmol), tetrahydrofuran (1 mL), water (1 mL) followed by addition of sodium perborate (100 mg, 1.16 mmol). The reaction mixture was allowed to stir for 14 h at ambient temperature. The reaction mixture was then filtered, the aqueous phase was washed with DCM, the combined organic phases were dried over Na_2SO_4 , volatiles removed, and the residue subjected to silica gel chromatography (hexanes EtOAc). The product (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-6-ol (81 mg, 0.176 mmol, 77% yield) was isolated as an off white solid. MS m/z 458.2 $[\text{M}-\text{H}]^-$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.69 (s, 1H), 8.61 (s, 1H), 7.10 (d, $J = 8.6$ Hz, 1H), 6.70 (s, 1H), 6.57 (dd, $J = 8.4, 2.2$ Hz, 1H), 5.91 (d, $J = 10.3$ Hz, 1H), 4.89 (d, $J = 13.1$ Hz, 1H), 3.58 (dt, $J = 14.6, 8.1$ Hz, 1H), 2.74 (d, $J = 7.9$ Hz, 2H), 2.04-1.90 (m, 1H), 1.75 (t, $J = 12.5$ Hz, 1H), 1.64 (s, 1H), 1.09 (d, $J = 6.3$ Hz, 3H), 0.92 (d, $J = 6.5$ Hz, 3H).

Example 33

Synthesis of Compound 188



[0365] To a scintillation vial was charged (1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-bromo-1-[[[(3S)-tetrahydropyran-3-yl]methyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole (120 mg, 0.21 mmol), [(2-Di-tert-butylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (20 mg, 0.02 mmol), cesium fluoride (100 mg, 0.66 mmol), and toluene (1 mL). The reaction vial was flushed with argon

and sealed, then the mixture was heated to 50 °C for 15 minutes, and methanol (0.035 mL, 0.87 mmol) was added. The reaction vial was again flushed with argon and sealed, then the mixture was allowed to stir at 50 °C for 16 hours. The mixture was concentrated directly and purified by silica gel chromatography to give the desired compound (29 mg, 26% yield).

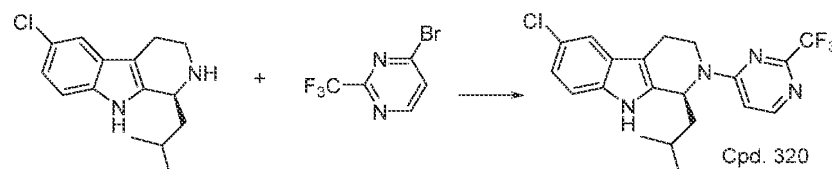
[0366] Compound 188: ESI-MS m/z 514 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 10.88(s, 1H), 7.21(d, 1H, $J=4.8$ Hz), 6.90(d, 1H, $J=2.4$ Hz), 6.70 (q, 1H, $J=6.4$ Hz), 5.92(q, 1H, $J=8$ Hz), 4.96(q, 1H, $J=9.2$ Hz), 3.83(s, 3H), 3.71-3.55(m, 3H), 3.29(t, 1H, $J=2.4$ Hz), 2.99(t, 1H, $J=10.4$ Hz), 2.80-2.75(m, 2H), 2.33-2.30(m, 1H), 1.86-1.73(m, 2H), 1.61-1.32(m, 4H).

[0367] Using the procedure described for Example 33, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
189	ESI-MS m/z 514 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 10.83 (s, 1H), 7.21 (d, 1H, $J=8.8$ Hz), 6.90(d, 1H, $J=2.4$ Hz), 6.70 (q, 1H, $J=6.4$ Hz), 5.86 (q, 1H, $J=6$ Hz), 4.90(q, 1H, $J=9.2$ Hz), 4.06(q, 1H, $J=8.4$ Hz), 3.73(s, 3H), 3.71-3.67(m, 1H), 3.60-3.57(m, 1H), 3.28 (d, 1H, $J=2.8$ Hz), 3.24-3.19(m, 1H), 2.81-2.76(m, 2H), 1.92-1.85(m, 2H), 1.76-1.73(m, 1H), 1.64-1.60 (m, 1H), 1.51-1.44 (m, 2H)
218	ESI-MS m/z 513.1 $[M-H]^-$; 1H NMR (500 MHz, DMSO- d_6) δ 10.86 (s, 1H), 7.49 (s, 1H), 7.21 (d, $J=8.7$ Hz, 1H), 6.90 (d, $J=2.4$ Hz, 1H), 6.70 (dd, $J=8.7, 2.4$ Hz, 1H), 5.93 (dd, $J=10.9, 3.2$ Hz, 1H), 5.04-4.79 (m, 1H), 3.74-3.68 (m, 5H), 3.60-3.47 (m, 1H), 3.29 (td, $J=11.5, 2.3$ Hz, 1H), 3.01 (t, $J=10.5$ Hz, 1H), 2.81-2.72 (m, 2H), 2.32 (d, $J=11.4$ Hz, 1H), 1.89-1.79 (m, 1H), 1.72 (ddd, $J=13.9, 10.0, 3.2$ Hz, 1H), 1.60 (d, $J=12.8$ Hz, 1H), 1.52 (d, $J=7.2$ Hz, 1H), 1.36 (dq, $J=20.7, 11.5$ Hz, 2H)

Example 34

Synthesis of Compound 320

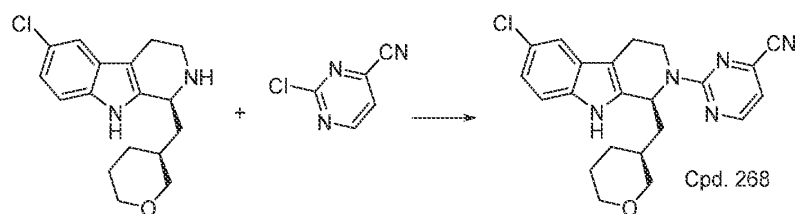


[0368] An 8 mL vial was charged with (1S)-6-chloro-1-isobutyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (100 mg, 0.380 mmol), cesium fluoride (170 mg, 1.119 mmol), (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (33 mg, 0.038 mmol), closed and put under argon atmosphere. 4-bromo-2-(trifluoromethyl) pyrimidine (100 mg, 0.427 mmol) in toluene (4 mL) was added and the reaction mixture allowed to stir at 100C for 8 h. After being allowed to cool to ambient temperature volatiles were removed under reduced pressure and the

residue absorbed on silica gel and subjected to silica gel chromatography (hexanes EtOAc). (1S)-6-chloro-1-(2-methylpropyl)-2-[2-(trifluoromethyl)pyrimidin-4-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (79 mg, 0.193 mmol, 51% yield) was isolated as an off-white solid. MS m/z 407.0 $[M-H]^-$; 1H NMR (500 MHz, DMSO- d_6) δ 11.25 (s, 1H), 8.37 (t, $J = 4.4$ Hz, 1H), 7.44 (s, 1H), 7.31 (d, $J = 9.0$ Hz, 2H), 7.04 (d, $J = 8.5$ Hz, 1H), 6.16 (d, $J = 10.7$ Hz, 1H), 4.34 (d, $J = 14.4$ Hz, 1H), 4.02 (d, $J = 7.4$ Hz, 1H), 3.60 (s, 1H), 2.74 (d, $J = 6.8$ Hz, 2H), 1.68 (d, $J = 13.3$ Hz, 1H), 1.59 (s, 1H), 1.11 (s, 3H), 0.91 (s, 3H).

Example 35

Synthesis of Compound 268



[0369] An 8 mL vial equipped with stir bar and septum cap was charged with (1S)-6-chloro-1-[(3S)-tetrahydropyran-3-yl]methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole; formic acid (100 mg, 0.285 mmol), 2-chloropyrimidine-4-carbonitrile (61 mg, 0.428 mmol), suspended in 1-butanol (1 mL). N,N-Diisopropylethylamine (0.15 mL, 0.86 mmol) was added and the vial placed into a heating block pre-heated to 100 °C and the reaction mixture allowed to stir for 6h at ambient temperature. Reaction mixture was concentrated and subjected to isco purification (hexanes EtOAc 0-100%). The product 2-[(1S)-6-chloro-1-[(3S)-oxan-3-yl]methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl]pyrimidine-4-carbonitrile (72 mg, 0.176 mmol, 62% yield) was isolated as an off white solid. MS m/z 406.3 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.18 (s, 1H), 8.69 (s, 1H), 7.42 (d, $J = 2.0$ Hz, 1H), 7.32 (d, $J = 8.6$ Hz, 1H), 7.18 (d, $J = 4.7$ Hz, 1H), 7.07-6.97 (m, 1H), 6.09-5.75 (m, 1H), 4.97-4.67 (m, 1H), 3.70 (t, $J = 12.8$ Hz, 2H), 3.39 (dt, $J = 14.8, 8.7$ Hz, 1H), 3.28 (d, $J = 11.4$ Hz, 1H), 3.02 (t, $J = 10.3$ Hz, 1H), 2.71 (br s, 2H), 2.32-2.05 (m, 1H), 1.88-1.67 (m, 2H), 1.67-1.47 (m, 2H), 1.48-1.21 (m, 2H).

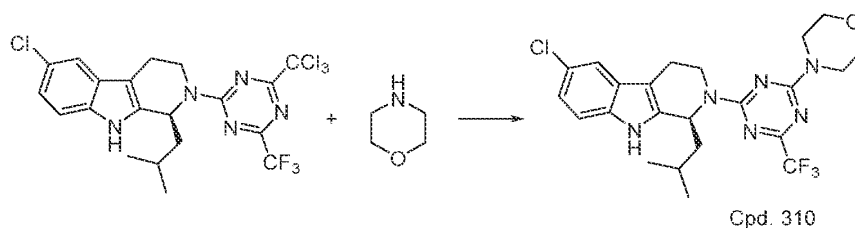
[0370] Using the procedure described for Example 35, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
39	ESI-MS m/z 412.20 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 11.05-11.26 (m, 1H), 7.36 (s, 1H), 7.23-7.30 (m, 1H), 6.94-7.02 (m, 1H), 5.81-5.95 (m, 1H), 4.85-4.97 (m, 1H), 4.72-4.81 (m, 1H), 4.47-4.63 (m, 1H), 4.16-4.36 (m, 1H), 3.73-3.89 (m, 1H), 3.53-3.66 (m, 1H), 3.29-3.41 (m, 1H), 3.18-3.29 (m, 2H), 2.52-2.76 (m, 2H), 2.28 (s, 3H), 2.23 (s, 3H), 1.71 (br d, J=10.5 Hz, 2H)
41	MS m/z 410.2 [M-H] ⁻ ; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ: 11.21 (s, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.32 (dd, J = 8.6, 2.1 Hz, 1H), 7.03 (dt, J = 8.8, 2.1 Hz, 1H), 6.03 (dd, J = 10.7, 3.4 Hz, 1H), 5.00-4.93 (m, 1H), 3.71 (d, J = 11.3 Hz, 1H), 3.65 (dt, J = 11.1, 2.6 Hz, 1H), 3.29 (tt, J = 9.1, 5.3 Hz, 2H), 2.99 (t, J = 10.4 Hz, 1H), 2.79-2.59 (m, 2H), 2.34 (overlapping s, 3H), 2.33-2.31 (overlapping m, 1H), 2.30 (overlapping s, 3H), 1.80-1.56 (m, 3H), 1.51-1.41 (m, 1H), 1.42-1.20 (m, 2H).
207A or 207B	ESI-MS m/z 450.9 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 11.21 (s, 1H), 8.73 (s, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.02-7.05 (m, 2H), 5.95-6.03 (m, 1H), 4.81-4.96 (m, 1H), 3.66-3.72 (m, 2H), 3.27 (t, J = 10.0 Hz, 1H), 3.00 (t, J = 11.0 Hz, 1H), 2.68-2.72 (m, 2H), 2.31-2.32 (m, 1H), 1.77-1.81 (m, 1H), 1.61-1.75 (m, 1H), 1.44-1.71 (m, 3H), 1.11-1.37 (m, 2H). The characteristic NMR signals for each compound overlapped to provide a single NMR spectrum without assignment to a particular diastereomer
208A or 208B	ESI-MS m/z 451.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 11.17 (s, 1H), 8.73 (s, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.02-7.05 (m, 2H), 5.90-5.99 (m, 1H), 4.81-4.95 (m, 1H), 4.12 (d, J = 9.2 Hz, 1H), 3.69 (d, J = 10.8 Hz, 1H), 3.41-3.45 (m, 1H), 3.16-3.28 (m, 2H), 2.67-2.72 (m, 2H), 1.73-1.84 (m, 3H), 1.41-1.60 (m, 3H), 1.19-1.25 (m, 1H). The relative configuration was not determined; NMR data was obtained without assignment to a particular diastereomer
209A or 209B	ESI-MS m/z 433 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 11.19 (s, 1H), 8.61 (d, J = 4.4 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.02 (q, J = 6.8 Hz, 1H), 6.85 (d, J = 4.8 Hz, 1H), 6.74 (t, J = 54.4 Hz, 1H), 6.01 (s, 1H), 4.90 (s, 1H), 3.72-2.66 (m, 2H), 3.40-2.36 (m, 1H), 3.33-3.25 (m, 1H), 3.00 (t, J = 10.4 Hz, 1H), 2.32-2.28 (m, 1H), 2.68 (t, J = 3.5 Hz, 2H), 1.79-1.72 (m, 2 H), 1.61-1.57 (m, 2 H), 1.39-1.28 (m, 2H). The relative configuration was not determined; NMR data was obtained without assignment to a particular diastereomer
210A or 210B	ESI-MS m/z 433 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 11.15 (s, 1H), 8.61 (d, J = 4.4 Hz, 1H), 7.40 (d, J = 1.6 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.02 (q, J = 6.8 Hz, 1H), 6.85 (d, J = 5.2 Hz, 1H), 6.74 (t, J = 53.6 Hz, 1H), 5.95 (s, 1H), 4.90 (s, 1H), 4.11 (q, J = 8.0 Hz, 1H), 3.69 (d, J = 11.2 Hz, 1H), 3.41-3.59 (m, 1 H), 3.28-3.25 (q, J = 8.4 Hz, 1H), 3.18 (t, J = 9.2 Hz, 1H), 2.68 (t, J = 2.4 Hz, 2H), 1.82-1.78 (m, 2H), 1.76-1.72 (m, 1H), 1.61-1.59 (m, 1H), 1.52-1.42 (m, 2H), 1.25-1.16 (m, 1H). The relative configuration was not determined; NMR data was obtained without assignment to a particular diastereomer
211	MS m/z 465.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 11.23 (s, 1H), 7.44 (d, J = 1.9 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.06 (dd, J = 8.6, 2.1 Hz, 1H), 7.00 (s, 1H), 6.14-5.89 (m, 1H), 5.09-4.78 (m, 1H), 3.72 (t, J = 14.3 Hz, 2H), 3.35-3.25 (m, 2H), 3.02 (s, 1H), 2.78-2.67 (m, 2H), 2.45 (d, J = 19.0 Hz, 3H), 2.34 (d, J = 10.1 Hz, 1H), 1.77 (dt, J = 24.8, 9.5 Hz, 2H), 1.56 (d, J = 25.5 Hz, 2H), 1.35 (s, 2H).

Cpd	Data
214	ESI-MS m/z 519.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.20 (s, 1H), 7.49 (s, 1H), 7.45 (d, J = 1.9 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.05 (dd, J = 8.6, 2.0 Hz, 1H), 5.89 (dd, J = 9.8, 4.4 Hz, 1H), 4.87 (dd, J = 13.4, 4.0 Hz, 1H), 4.10 (d, J = 8.5 Hz, 1H), 3.69 (d, J = 11.2 Hz, 1H), 3.56–3.47 (m, 1H), 3.31–3.28 (m, 1H), 3.25–3.17 (m, 1H), 2.79–2.71 (m, 2H), 1.92–1.82 (m, 2H), 1.78–1.71 (m, 1H), 1.64–1.55 (m, 1H), 1.53–1.40 (m, 2H), 1.24–1.18 (m, 1H).
215	MS m/z 519.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.25 (s, 1H), 7.48 (s, 1H), 7.45 (d, J = 1.9 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.05 (dd, J = 8.6, 2.1 Hz, 1H), 5.95 (d, J = 8.0 Hz, 1H), 4.87 (dd, J = 13.5, 3.8 Hz, 1H), 3.70 (t, J = 12.5 Hz, 2H), 3.57–3.43 (m, 1H), 3.31–3.25 (m, 1H), 3.00 (t, J = 10.4 Hz, 1H), 2.73 (dd, J = 15.7, 10.9 Hz, 2H), 2.33 (s, 1H), 1.83 (dd, J = 17.8, 6.9 Hz, 1H), 1.72 (dd, J = 12.1, 8.8 Hz, 1H), 1.57 (t, J = 21.8 Hz, 2H), 1.34 (dd, J = 22.2, 12.4 Hz, 2H).
216	MS m/z 519.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.26 (s, 1H), 7.48–7.41 (m, 2H), 7.28 (d, J = 8.6 Hz, 1H), 7.04 (dd, J = 8.6, 2.0 Hz, 1H), 6.21 (dd, J = 9.4, 3.0 Hz, 1H), 4.89 (dd, J = 13.3, 4.2 Hz, 1H), 3.87 (d, J = 11.4 Hz, 1H), 3.49 (td, J = 13.3, 4.7 Hz, 1H), 3.19 (dt, J = 16.9, 8.5 Hz, 2H), 2.82–2.68 (m, 2H), 2.12–1.98 (m, 2H), 1.72 (s, 1H), 1.51–1.35 (m, 4H), 1.24 (d, J = 6.1 Hz, 1H).
220	ESI-MS m/z 509.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.12 (s, 1H), 7.60–7.22 (m, 3H), 7.05 (m, J = 8.6, 2.1 Hz, 1H), 6.20–5.76 (m, 1H), 4.89 (m, J = 13.3, 4.3 Hz, 1H), 4.36 (m, J = 49.6, 5.3 Hz, 2H), 3.62 (t, J = 5.0 Hz, 2H), 3.49 (m, J = 16.2, 11.3, 5.2 Hz, 2H), 3.31 (dd, J = 11.0, 5.2 Hz, 1H), 2.86–2.65 (m, 2H), 1.94 (m, J = 14.3, 7.7 Hz, 2H), 1.61–1.50 (m, 1H).
222	ESI-MS m/z 391.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.17 (s, 1H), 8.60 (d, J = 4.4 Hz, 1H), 7.40 (d, J = 1.6 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.02 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.84 (d, J = 4.8 Hz, 1H), 6.74 (t, J = 5.4 Hz, 1H), 6.03 (d, J = 8.0 Hz, 1H), 4.94–4.85 (m, 1H), 2.74–2.67 (m, 3H), 1.95–1.88 (m, 1H), 1.73–1.61 (m, 2H), 1.09–1.08 (m, 3H), 0.92–0.90 (m, 3H).
225	MS m/z 523.2 $[M+H]^+$; 1H NMR (DMSO- d_6) δ : 11.24 (s, 1H), 7.59 (s, 1H), 7.46 (s, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 5.97 (br d, J = 8.0 Hz, 1H), 4.88 (br dd, J = 13.4, 3.6 Hz, 1H), 3.37–3.64 (m, 2H), 2.66–2.94 (m, 1H), 1.90–2.09 (m, 1H), 1.52–1.85 (m, 2H), 1.10 (d, J = 6.3 Hz, 3H), 0.92 (br d, J = 6.5 Hz, 3H).
230	MS m/z 500.9 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.23 (s, 1H), 7.45 (t, J = 2.8 Hz, 2H), 7.33 (d, J = 8.4 Hz, 1H), 7.05 (q, J = 8.0 Hz, 1H), 5.91 (d, J = 8.0 Hz, 1H), 4.90 (q, J = 4.0 Hz, 1H), 3.47–3.53 (m, 1H), 2.74–2.77 (m, 2H), 1.87–2.09 (m, 4H), 1.62–1.68 (m, 3H), 1.43–1.46 (m, 3H), 1.12–1.14 (m, 1H).
239	MS m/z 467.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.30 (s, 1H), 8.73 (s, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.33 (d, J = 10.0 Hz, 1H), 7.03 (d, J = 4.8 Hz, 1H), 6.11–5.91 (m, 1H), 5.01–4.75 (m, 1H), 3.46–3.38 (m, 1H), 2.76–2.61 (m, 2H), 2.35–2.06 (m, 1H), 1.89–1.84 (m, 1H), 1.78–1.52 (m, 5H), 1.32–0.91 (m, 6H).
242	MS m/z 437.0 $[M-H]^-$; 1H NMR (400 MHz, CDCl ₃) δ 8.51 (s, 1H), 7.82 (s, 1H), 7.43 (d, J = 4.0 Hz, 1H), 7.11 (d, J = 12.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.92 (s, 1H), 5.10 (dd, J = 16.0, 8.0 Hz, 1H), 3.40–3.33 (m, 1H), 2.88–2.79 (m, 1H), 2.70 (dd, J = 16.0, 4.0 Hz, 1H), 2.53–2.45 (m, 1H), 2.18 (s, 1H), 2.20–1.93 (m, 3H), 1.90–1.82 (m, 2H), 1.77–1.67 (m, 2H).
243	MS m/z 467.0 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.30 (s, 1H), 8.73 (s, 1H), 7.55 (d, J = 3.6 Hz, 1H), 7.34 (d, J = 10.0 Hz, 1H), 7.04 (d, J = 4.8 Hz, 1H), 6.04–5.94 (m, 1H), 4.96–4.83 (m, 1H), 3.87–3.84 (m, 1H), 3.80–3.76 (m, 1H), 3.46–3.38 (m, 1H), 3.25–3.08 (m, 2H), 2.74–2.65 (m, 2H), 2.18–2.06 (m, 1H), 1.99–1.91 (m, 1H), 1.81–1.76 (m, 1H), 1.51–1.49 (m, 2H), 1.36–1.18 (m, 2H).

Cpd	Data
245	ESI-MS m/z 435.2. [M+H] ⁺ , ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.09-11.30 (m, 1H), 8.63 (d, J=4.6 Hz, 1H), 7.39-7.46 (m, 1H), 7.28-7.36 (m, 1H), 6.99-7.09 (m, 1H), 6.60-6.83 (m, 1H), 6.58-6.96 (m, 1H), 5.95 (br d, J=9.8 Hz, 1H), 4.91 (br d, J=12.1 Hz, 1H), 4.83 (br d, J=5.9 Hz, 1H), 4.63 (d, J=6.0 Hz, 1H), 4.19-4.30 (m, 1H), 3.85-3.98 (m, 1H), 3.57-3.72 (m, 1H), 3.29-3.48 (m, 2H), 2.70 (br d, J=5.5 Hz, 2H), 1.74-1.97 (m, 3H)
248	ESI-MS m/z 413.2. [M+H] ⁺ , ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.05-11.23 (m, 1H), 7.40 (s, 1H), 7.23-7.36 (m, 1H), 7.02 (br d, J=8.5 Hz, 1H), 6.44 (s, 1H), 5.95-6.04 (m, 1H), 4.88-5.02 (m, 2H), 4.81-4.88 (m, 1H), 4.56-4.68 (m, 2H), 4.29-4.40 (m, 1H), 3.84-3.95 (m, 1H), 3.60-3.71 (m, 1H), 3.40 (br s, 1H), 3.19-3.33 (m, 1H), 2.60-2.73 (m, 2H), 2.25 (s, 4H), 1.65-1.95 (m, 3H)
249	ESI-MS m/z 399.0 [M+H] ⁺ , ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ: 11.13 (s, 1H), 8.26 (d, J=4.8 Hz, 1H), 7.40 (s, 1H), 7.26-7.36 (m, 1H), 7.03 (br d, J=8.5 Hz, 1H), 6.55 (d, J=5.0 Hz, 1H), 5.98 (br d, J=10.3 Hz, 1H), 4.87-5.01 (m, 1H), 4.81-4.86 (m, 1H), 4.58-4.67 (m, 1H), 4.24-4.36 (m, 1H), 3.84-3.96 (m, 1H), 3.63 (br t, J=9.8 Hz, 1H), 3.40 (br t, J=9.8 Hz, 1H), 3.23-3.35 (m, 1H), 2.62-2.72 (m, 2H), 2.30 (s, 3H), 1.69-1.98 (m, 3H)
252	MS m/z 395.1 [M-H] ⁻ ; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.16 (s, 1H), 8.24 (d, J = 4.9 Hz, 1H), 7.39 (d, J = 2.3 Hz, 1H), 7.30 (dd, J = 8.7, 2.0 Hz, 1H), 7.01 (dd, J = 8.6, 2.1 Hz, 1H), 6.52 (dd, J = 4.9, 1.9 Hz, 1H), 6.08-6.02 (m, 1H), 4.94-4.88 (m, 1H), 3.70 (t, J = 12.3 Hz, 2H), 3.38 (d, J = 2.7 Hz, 1H), 3.32-3.22 (m, 2H), 3.01 (t, J = 10.4 Hz, 1H), 2.65 (h, J = 11.9 Hz, 2H), 2.28 (s, 3H), 1.84-1.47 (m, 4H), 1.46-1.25 (m, 2H).
254	MS m/z 409.2 [M-H] ⁻ ; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.15 (s, 1H), 7.39 (d, J = 2.5 Hz, 1H), 7.30 (dd, J = 8.5, 2.0 Hz, 1H), 7.01 (dd, J = 8.5, 2.1 Hz, 1H), 6.41 (s, 1H), 6.07 (dd, J = 10.8, 3.4 Hz, 1H), 4.98-4.91 (m, 1H), 3.74-3.64 (m, 2H), 3.33-3.19 (m, 2H), 3.00 (t, J = 10.4 Hz, 1H), 2.64 (dd, J = 10.7, 4.8 Hz, 2H), 2.33 (t, J = 14.5 Hz, 1H), 2.23 (s, 6H), 1.79-1.46 (m, 4H), 1.43-1.26 (m, 2H).
255	MS m/z 429.3 [M+H] ⁺ ; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ ppm 1.26-1.43 (m, 2 H) 1.55-1.76 (m, 4 H) 2.26-2.29 (m, 6 H) 2.46-2.48 (m, 1 H) 2.59-2.69 (m, 2 H) 3.01 (br t, J=10.30 Hz, 1 H) 3.20-3.30 (m, 2 H) 3.65-3.73 (m, 2 H) 4.82 (br d, J=12.21 Hz, 1 H) 5.95 (br d, J=10.68 Hz, 1 H) 7.01 (br d, J=8.54 Hz, 1 H) 7.30 (br d, J=8.70 Hz, 1 H) 7.39 (s, 1 H) 11.14 (s, 1 H)
256	MS m/z 415.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 1.22-1.48 (m, 2 H) 1.60 (br s, 2 H) 1.64-1.81 (m, 2 H) 2.21 (br d, J=6.00 Hz, 1 H) 2.31-2.33 (m, 3 H) 2.59-2.72 (m, 2 H) 3.02 (t, J=10.32 Hz, 1 H) 3.26-3.30 (m, 2 H) 3.66-3.74 (m, 2 H) 4.76-4.82 (m, 1 H) 5.94 (br d, J=7.50 Hz, 1 H) 7.01 (br d, J=8.63 Hz, 1 H) 7.30 (d, J=8.50 Hz, 1 H) 7.39 (s, 1 H) 8.31 (s, 1 H) 11.13 (s, 1 H)
257	MS m/z 399.2 [M-H] ⁻ ; ¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 11.16 (s, 1H), 8.48 (d, J = 2.0 Hz, 2H), 7.39 (d, J = 2.0 Hz, 1H), 7.30 (dd, J = 8.5, 2.0 Hz, 1H), 7.01 (dt, J = 8.7, 2.0 Hz, 1H), 5.94 (dd, J = 10.6, 3.6 Hz, 1H), 4.77 (dd, J = 13.6, 4.9 Hz, 1H), 3.76-3.63 (m, 2H), 3.32-3.23 (m, 2H), 3.01 (t, J = 10.0 Hz, 1H), 2.75-2.57 (m, 2H), 2.17-2.10 (m, 1H), 1.83-1.66 (m, 2H), 1.60 (d, J = 12.4 Hz, 2H), 1.40 (q, J = 12.0 Hz, 1H), 1.35-1.24 (m, 1H).

Cpd	Data
269	MS m/z 424.2 [M-H] ⁻ ; ¹ H NMR (500 MHz, Acetone) δ 10.34 (s, 1H), 8.74 (s, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.34 (dd, J = 8.6, 2.2 Hz, 1H), 7.05 (dt, J = 8.6, 2.2 Hz, 1H), 6.02 (s, 1H), 4.90 (s, 1H), 3.77-3.71 (m, 2H), 3.56-3.45 (m, 1H), 3.30 (t, J = 11.0 Hz, 1H), 3.09-2.95 (m, 1H), 2.80-2.72 (m, 1H), 2.29 (s, 1H), 1.91 (ddd, J = 14.7, 10.6, 4.6 Hz, 1H), 1.86-1.73 (m, 1H), 1.74-1.56 (m, 2H), 1.49 (d, J = 12.0 Hz, 1H), 1.39-1.22 (m, 2H).
298	MS m/z 475.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.03 (s, 1H), 7.48 (t, J = 3.6 Hz, 2H), 7.34 (d, J = 8.4 Hz, 1H), 7.06 (q, J = 6.4 Hz, 1H), 6.45 (d, J = 9.6 Hz, 1H), 5.47 (d, J = 9.6 Hz, 1H), 4.96 (q, J = 8.8 Hz, 1H), 3.55-3.48 (m, 1H), 2.87 (q, J = 12.4 Hz, 1H), 2.79-2.68 (m, 1H), 2.02 (d, J = 0.8 Hz, 3H), 1.73 (d, J = 0.8 Hz, 3H).
304	MS m/z 440.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 11.08 (s, 1H), 8.74 (d, J=4.50 Hz, 1H), 8.04 (s, 3H), 7.78 (br d, J=8.75 Hz, 1H), 7.47 (d, J=8.76 Hz, 1H), 7.04 (d, J=4.50 Hz, 1H), 6.42-6.66 (m, 1H), 5.36-5.63 (m, 1H), 4.90-5.16 (m, 1H), 3.40-3.55 (m, 1H), 2.88 (br s, 2H), 2.04 (s, 3H), 1.74 (s, 3H).
305	MS m/z 440.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 11.13 (s, 1H), 8.70-8.78 (m, 2H), 7.92 (d, J=7.75 Hz, 2H), 7.53-7.60 (m, 2H), 7.05 (d, J=4.50 Hz, 1H), 6.52 (br d, J=9.01 Hz, 1H), 5.49 (br d, J=8.50 Hz, 1H), 5.03 (br s, 1H), 3.38-3.56 (m, 1H), 2.75-3.00 (m, 2H), 2.04 (s, 3H), 1.74 (s, 3H).

Example 36**Synthesis of Compound 310**

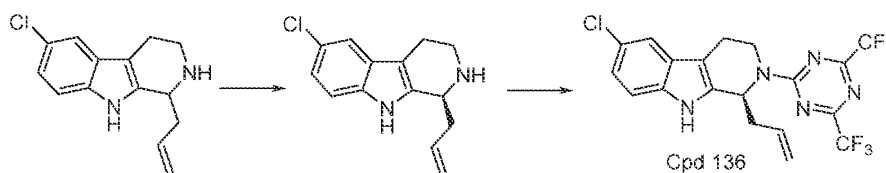
[0371] A 20 mL vial equipped with a stir bar was charged with (1S)-6-chloro-1-isobutyl-2-[4-(trichloromethyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1,3,4,9-tetrahydropyrido[3,4-b]indole (50 mg, 0.095 mmol), morpholine (12 mg, 0.138 mmol), N,N-dimethylformamide (3 mL), N,N-diisopropylethylamine (393 mg, 3.041 mmol), 4-dimethylaminopyridine (24 mg, 0.194 mmol), the vial closed and the reaction mixture allowed to stir at 70 °C for 14 h. After being allowed to cool to ambient temperature, the reaction was stopped by addition of water (30 mL), extracted with EtOAc (2 x 30 mL), the combined organic phases were washed with brine (20 mL), then dried over Na₂SO₄, and volatiles evaporated in vacuum. The resulting residue was purified by prep-HPLC (water-acetonitrile). After lyophilization (1S)-6-chloro-1-(2-methylpropyl)-2-[4-(morpholin-4-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (34 mg, 0.069 mmol, 72% yield) as an amorphous yellow solid. MS m/z 493.0 [M-H]⁻; ¹H NMR (400 MHz, CDCl₃) δ 7.82 (s, 1H), 7.41-7.40 (d, J = 2.0

Hz 1H), 7.21-7.20 (d, J = 3.6 Hz, 1H), 7.09-7.08 (t, J = 2.0 Hz, 1H), 5.99-5.95 (dd, J = 4.8, 9.6 Hz, 1H), 5.01-4.96 (dd, J = 4.8, 9.6 Hz, 1H), 3.88-3.75 (m, 8H), 3.35-3.27 (m, 1H), 2.87-2.81 (m, 1H), 2.72-2.67 (dd, J = 4.8, 14.8 Hz, 1H), 1.93-1.86 (m, 1H), 1.77-1.59 (m, 1H), 1.12-1.07 (d, J = 6.4 Hz, 3H), 1.00-0.95 (d, J = 6.4 Hz, 3H).

[0372] Using the procedure described for Example 36, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
111	MS m/z 534.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.16 (d, J = 18.8 Hz, 1H), 7.43 (t, J = 2.0 Hz, 1H), 7.31 (q, J = 4.4 Hz, 1H), 7.04 (q, J = 8.8 Hz, 1H), 5.92 (q, J = 2.8 Hz, 1H), 4.90 (t, J = 24.0 Hz, 1H), 3.74-3.84 (m, 4H), 2.51-2.72 (m, 2H), 2.34-2.40 (m, 4H), 2.20 (d, J = 8.0 Hz, 3H), 1.82-2.02 (m, 4H), 1.48-1.67 (m, 6H), 1.06-1.08 (m, 1H).
112	MS m/z 506.0 [M-H] ⁻ ; ¹ H NMR (400 MHz, CDCl ₃) δ 7.82 (s, 1H), 7.42-7.42 (d, J = 2.0 Hz, 1H), 7.20-7.20 (d, J = 2.4 Hz, 1H), 7.09-7.08 (t, J = 2.0 Hz, 1H), 6.07-6.03 (dd, J = 4.0, 13.2 Hz, 1H), 5.14-5.09 (dd, J = 5.2, 13.6 Hz, 1H), 3.89-3.84 (m, 4H), 3.34-3.26 (m, 1H), 2.87-2.80 (m, 1H), 2.71-2.70 (d, J = 4.0 Hz, 1H), 2.47-2.42 (m, 4H), 2.35 (s, 3H), 1.93-1.86 (m, 1H), 1.77-1.65 (m, 1H), 1.58-1.55 (m, 1H), 1.12-1.00 (d, J = 6.4 Hz, 3H), 0.97-0.95 (d, J = 6.4 Hz, 3H).
179	MS m/z 548.0 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.18-11.14 (s, 1H), 7.43-7.41 (m, 1H), 7.32-7.29 (m, 1H), 7.04-7.02 (m, 1H), 5.98-5.92 (m, 1H), 4.92-4.89 (m, 1H), 3.87-3.67 (m, 5H), 2.71-2.67 (m, 2H), 2.44-2.27 (m, 5H), 2.22-2.19 (m, 3H), 1.85-1.80 (m, 1H), 1.74-1.68 (m, 1H), 1.66-1.50 (m, 4H), 1.23-0.94 (m, 6H).
286	MS m/z 454.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (mixture of rotamers) 11.01 (apparent d, J = 37.6 Hz, 1H), 7.48 (q, J = 2.8 Hz, 1H), 7.34 (q, J = 2.8 Hz, 1H), 7.07 (q, J = 16.5 Hz, 1H), 6.50 (q, J = 52.4 Hz, 1H), 5.48 (q, J = 1.2 Hz, 1H), 5.08-4.90 (m, 1H), 3.53-3.45 (m, 1H), 2.90-2.73 (m, 2H), 2.56 (d, J = 6 Hz, 3H), 2.02 (q, J = 8.4 Hz, 3H), 1.74 (d, J = 4 Hz, 3H).
287	MS m/z 506.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.95 (d, J = 39.2, 1H), 7.46 (q, J = 2.8 Hz, 1H), 7.33 (q, J = 6.8 Hz, 1H), 7.05 (q, J = 6.8 Hz, 1H), 6.51 (q, J = 28.8 Hz, 1H), 5.45 (t, J = 13.6 Hz, 1H), 4.99-4.91 (m, 1H), 3.79 (q, J = 26.8 Hz, 4H), 3.37 (q, J = 12.8 Hz, 1H), 2.82-2.67 (m, 2H), 2.36 (t, J = 5.6 Hz, 4H), 2.22 (d, J = 4.0 Hz, 3H), 1.99 (d, J = 6.0 Hz, 3H), 1.73 (d, J = 6.4 Hz, 3H).
309	MS m/z 493.2 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.46 (d, J = 35.6 Hz, 1H), 7.46 (q, J = 2.8 Hz, 1H), 7.30 (q, J = 2 Hz, 1H), 7.05 (q, J = 6.8 Hz, 1H), 6.51 (q, J = 28.4 Hz, 1H), 5.46 (t, J = 9.6 Hz, 1H), 4.99-4.92 (m, 1H), 3.87-3.76 (m, 4H), 3.67-3.61 (m, 4H), 3.42 (s, 1H), 2.83-2.67 (m, 2H), 2.00 (s, 3H), 1.74 (t, J = 5.6 Hz, 3H).
311	MS m/z 521.3 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.16 (d, J = 23.2 Hz, 1H), 7.43 (t, J = 2.4 Hz, 1H), 7.32 (q, J = 4.0 Hz, 1H), 7.04 (q, J = 2.0 Hz, 1H), 5.90 (q, J = 5.2 Hz, 1H), 4.91 (t, J = 17.2 Hz, 1H), 3.75-3.80 (m, 4H), 3.65-3.69 (m, 4H), 3.33-3.35 (m, 1H), 2.61-2.72 (m, 2H), 1.71-2.10 (m, 4H), 1.46-1.60 (m, 3H), 1.37-1.44 (m, 3H), 1.04-1.13 (m, 1H).

Cpd	Data
312	MS m/z 535.0 [M-H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.18-11.13 (dd, 1H), 7.43-7.42 (m, 1H), 7.33-7.30 (m, 1H), 7.05-7.02 (m, 1H), 6.00-5.93 (m, 1H), 4.94-4.83 (m, 1H), 3.83-3.64 (m, 9H), 2.73-2.67 (m, 2H), 2.34-2.15 (m, 1H), 1.87-1.81 (m, 1H), 1.70-1.67 (m, 1H), 1.65-1.55 (m, 4H), 1.23-0.94 (m, 6H).

Example 37**Synthesis of Compound 136**

[0373] **Step 1:** A 250 mL round bottom flask was charged with 1-allyl-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (1 g, 4.05 mmol), (2S)-3-phenyl-2-(p-tolylsulfonylamino)propanoic acid (1 g, 3.131 mmol) suspended in methanol (25 mL) and heated to reflux. Methanol (70 mL) was continuously added under reflux. After being allowed to stir at reflux for 1 h the reaction was allowed to cool to ambient temperature and the white solid was filtered off. The solid was suspended between EtOAc (100 mL) and NH₄OH aq. (100 mL) and mixed until all solids dissolved. The organic phase was separated and concentrated under reduced pressure yielding: (1S)-1-allyl-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (295 mg, 1.20 mmol, 100 mass%) enantioenriched (>98:2 er).

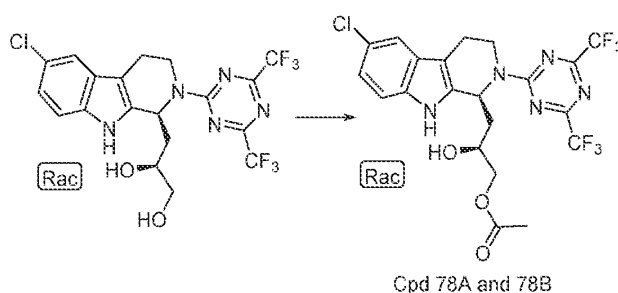
[0374] **Step 2:** A 20 mL vial was charged with (1S)-1-allyl-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (135 mg, 0.547 mmol), 4-dimethylaminopyridine (100 mg, 0.810 mmol), acetonitrile (5.5 mL), 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (275 mg, 0.822 mmol), and the mixture allowed to stir at ambient temperature for 14 h. The reaction mixture was concentrated under reduced pressure, absorbed on celite and subjected to ISCO purification silica gel chromatography (hexanes EtOAc 0-100%). (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(prop-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (240 mg, 0.520 mmol, 95% yield) was isolated as an amorphous off-white solid. MS m/z 460.2 [M-H]⁺; ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.23 (s, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.08 (dd, J = 8.7, 2.1 Hz, 1H), 5.95 (dd, J = 8.9, 4.4 Hz, 1H), 5.81 (ddt, J = 17.2, 10.1, 7.2 Hz, 1H), 5.13 (dd, J = 17.0, 2.1 Hz, 1H), 5.00 (d, J = 10.3 Hz, 1H), 4.97 (dd, J = 13.1, 5.1 Hz, 1H), 3.58 (td, J = 12.7, 4.2 Hz, 1H), 2.93-2.84 (m, 2H), 2.84-2.70 (m, 2H).

[0375] Using the procedure described for Example 37, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
117	MS m/z 522.2 [M-H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ: 11.29 (s, 1H), 7.62 (s, 1H), 7.32 (d, J=8.5 Hz, 1H), 7.13-7.24 (m, 1H), 5.97 (br d, J=7.8 Hz, 1H), 4.92 (br dd, J=13.1, 4.6 Hz, 1H), 3.60 (td, J=12.4, 4.3 Hz, 1H), 2.71-2.94 (m, 2H), 1.92-2.10 (m, 1H), 1.73-1.86 (m, 1H), 1.59-1.71 (m, 1H), 1.06-1.15 (m, 3H), 0.88-0.98 (m, 3H)

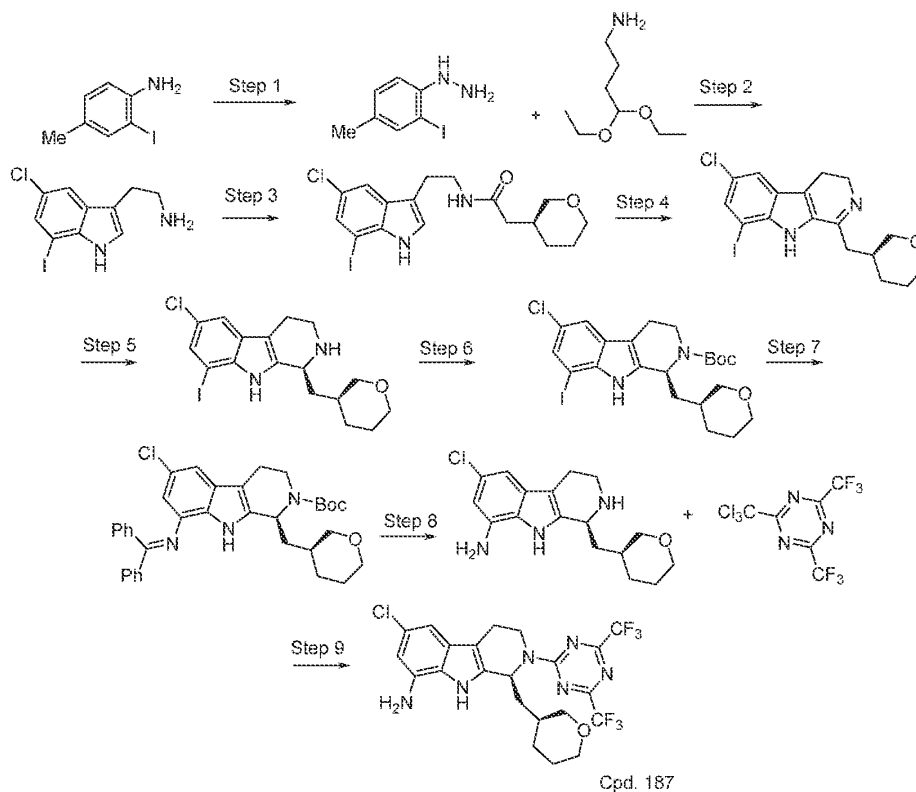
Example 38

Synthesis of Compound 78A and 78B



[0376] An 8 mL vial equipped with a stir bar was charged with a racemic mixture of (2S)-3-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]propane-1,2-diol and (2R)-3-[(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl]propane-1,2-diol (210 mg, 0.424 mmol), tetrahydrofuran (4 mL), triethylamine (0.09 mL, 0.6 mmol), acetic anhydride (0.048 mL, 0.51 mmol). The mixture was allowed to stir at ambient temperature for 14 h.

Afterwards, the reaction mixture was concentrated under reduced pressure and the residue obtained was absorbed on silica gel and purified by silica gel chromatography (0 to 40% hexanes/EtOAc) to provide a racemic mixture of Compound 78A (2S)-3-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-2-hydroxypropyl acetate and Compound 78B (2R)-3-[(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-2-hydroxypropyl acetate (98 mg, 0.182 mmol, 43.% yield) isolated as an amorphous colorless solid. MS m/z 536.15 [M-H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.23 (s, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 8.6, 2.1 Hz, 1H), 6.17 (dd, J = 9.6, 4.0 Hz, 1H), 4.98-4.89 (m, 2H), 4.00-3.82 (m, 2H), 3.74 (s, 1H), 3.66-3.54 (m, 1H), 2.92-2.72 (m, 2H), 2.23-2.02 (m, 2H), 2.00 (s, 3H).

Example 39**Synthesis of Compound 187**

[0377] **Step 1:** 2-iodo-4-methyl-aniline (3.0 g, 12.9 mmol, 100 mass%) was suspended in an ice-cold aqueous solution of concentrated hydrochloric acid (10 mL, 121.8 mmol). A solution of sodium nitrite (0.850 g, 12.3 mmol) in 5 mL water was added drop-wise. After 45 min stirring at 0 °C, a solution of tin chloride (5.3 g, 27.7 mmol) in 6 mL of concentrated HCl was added to the mixture. The reaction mixture was allowed to warm to room temp over 3 hours. Stirred at room temperature for 12 hours. After that, the suspension was diluted with water and the aqueous layer was washed with DCM twice. The aqueous layer was basified with 6 M NaOH solution until pH > 10. The suspension was extracted twice with DCM and 1x with EtOAc, dried over MgSO₄ and filtered. The crude material was purified by silica gel chromatography, (2-iodo-4-methyl-phenyl)hydrazine was isolated as a yellow solid (2.1 g 68% yield).

[0378] **Step 2:** A round bottom flask was charged with a solution of 4,4-diethoxybutan-1-amine (7.2 g, 45 mmol) in water (80 mL), followed by sequential addition of (4-chloro-2-iodo-phenyl)hydrazine (13.0 g, 48.4 mmol) and sulfuric acid (2.28 M, 8 mL, 18.2 mmol). The

reaction mixture was allowed to stir at 100 °C for 8h, then allowed to cool to ambient temperature. The suspension was filtered and the solid washed with water. 2-(5-chloro-7-iodo-1H-indol-3-yl)ethanamine (6.0 g, 19 mmol, 39% yield) was isolated as a brown solid material.

[0379] **Step 3:** A 40 mL vial was charged with 2-[(3S)-tetrahydropyran-3-yl]acetic acid (450 mg, 3.12 mmol), suspended in tetrahydrofuran (14 mL), triethylamine (1.8 mL, 13 mmol) was added followed by HATU (1.6 g, 4.1 mmol). The mixture was allowed to stir at ambient temperature for 15 minutes, then 2-(5-chloro-7-iodo-1H-indol-3-yl)ethanamine (1 g, 3.12 mmol) was added in one portion and stirring allowed to continue at ambient temperature for 14h. The reaction mixture was then diluted with EtOAc (50 mL) and the organic phase was washed subsequently with NaOH (2M, 50 mL), hydrochloric acid (aq, 2M, 50 mL), water (50 mL), NaHCO₃ (aq saturated, 50 mL) and brine (50 mL). The organic phase was dried over Na₂SO₄, filtered and volatiles removed under reduced pressure. The product N-[2-(5-chloro-7-iodo-1H-indol-3-yl)ethyl]-2-[(3S)-tetrahydropyran-3-yl]acetamide (1.85 g, 4.14 mmol, 97% yield) was isolated as a tan solid material.

[0380] **Step 4:** A 100 mL round bottom flask was charged with N-[2-(5-chloro-7-iodo-1H-indol-3-yl)ethyl]-2-[(3S)-tetrahydropyran-3-yl]acetamide (1.9 g, 4.3 mmol), acetonitrile (10 mL), phosphoryl chloride (2.4 mL, 26 mmol) and allowed to stir at ambient temp for 16h. Volatiles were removed under reduced pressure, the residue taken up in EtOAc (200 mL) and washed with NH₄OH (100 mL). The organic phase was concentrated and the residue absorbed on silica gel and subjected to silica gel chromatography (methanol in DCM 0-20% gradient). The product 6-chloro-8-iodo-1-[[[(3S)-tetrahydropyran-3-yl]methyl]-4,9-dihydro-3H-pyrido[3,4-b]indole (1.74 g, 4.06 mmol, 95% yield) isolated as a brown amorphous solid material.

[0381] **Step 5:** A 40 mL vial was charged with 6-chloro-8-iodo-1-[[[(3S)-tetrahydropyran-3-yl]methyl]-4,9-dihydro-3H-pyrido[3,4-b]indole (1.74 g, 4.06 mmol), RuCl[(R,R)-TsDpen](mesitylene) (140 mg, 0.202 mmol), acetonitrile (14 mL), formic acid triethylamine complex 5:2 (3.4 mL, 8.1 mmol) and allowed to stir at ambient while continuously being purged with argon. After stirring for 16 h the reaction mixture was diluted with EtOAc (100 mL) and washed with NaOH (1M, 100 mL). The organic phase was dried over Na₂SO₄, filtered, volatiles removed under reduced pressure and the residue absorbed on silica gel and subjected to silica gel chromatography (methanol in DCM 0-20% gradient). The product (1S)-6-chloro-8-iodo-1-[[[(3S)-tetrahydropyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-

pyrido[3,4-b]indole (1.684 g, 3.91 mmol, 96% yield) was isolated as a isolated as amorphous dark solid material.

[0382] **Step 6:** A 20 mL vial was charged with (1S)-6-chloro-8-iodo-1-[[(3S)-tetrahydropyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (1.1 g, 2.6 mmol), dichloromethane (10 mL), di-tert-butyl dicarbonate (0.2 mL, 0.9 mmol), triethylamine (0.6 mL, 4 mmol) and allowed to stir at ambient temperature for 12 h. Then volatiles were removed under reduced pressure, the residue absorbed on a silica gel and subjected to silica gel chromatography (EtOAc in hexanes 0-100% gradient). The product tert-butyl-(1S)-6-chloro-8-iodo-1-[[(3S)-tetrahydropyran-3-yl]methyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carboxylate (860 mg, 1.62 mmol, 63% yield) was isolated as an amorphous off-white solid material.

[0383] **Step 7:** A 40 mL vial was charged with tert-butyl (1S)-6-chloro-8-iodo-1-[[(3S)-tetrahydropyran-3-yl]methyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carboxylate (290 mg, 0.546 mmol), (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate (142 mg, 0.164 mmol), sodium tert-butoxide (200 mg, 2.08 mmol). The vial was put under a nitrogen atmosphere and solids suspended in toluene (4 mL, 38 mmol). Benzophenone imine (0.20 mL, 1.2 mmol) was added and the reaction allowed to stir at 100 C for 14h. After being allowed to cool to ambient temperature, volatiles were removed under reduced pressure and the residue absorbed on silica gel and subjected to silica gel chromatography (EtOAc in hexanes 0-100% gradient). Tert-butyl-(1S)-8-(benzhydrylideneamino)-6-chloro-1-[[(3S)-tetrahydropyran-3-yl]methyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carboxylate (70 mg, 0.120 mmol, 22% yield) was isolated as an off-white amorphous solid.

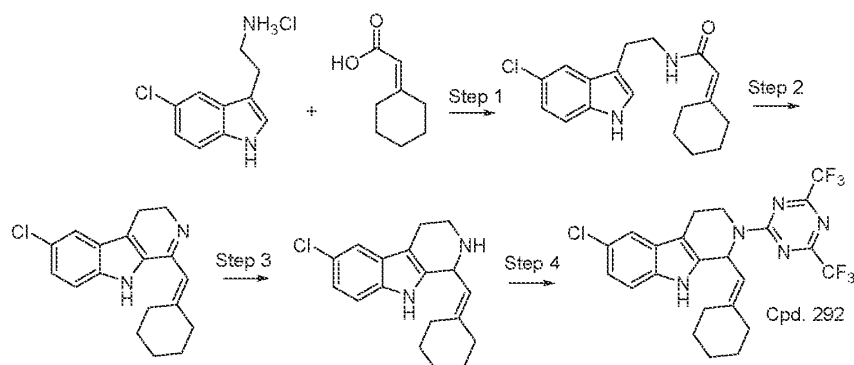
[0384] **Step 8:** A 20 mL vial was charged with tert-butyl-(1S)-8-(benzhydrylideneamino)-6-chloro-1-[[(3S)-tetrahydropyran-3-yl]methyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carboxylate (70 mg, 0.120 mmol), dichloromethane (5 mL) followed by addition of trifluoroacetic acid (0.5 mL, 7 mmol). The reaction mixture was allowed to stir for 1h at ambient temperature, after which volatiles were removed under reduced pressure and the residue taken up and co-evaporated with acetonitrile (3 x 10 mL). The product 1,1-diphenyl-N-[(1S)-6-chloro-1-[[(3S)-tetrahydropyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-8-yl]methanimine was used in the next step without further purification.

[0385] **Step 9:** A vial containing 1,1-diphenyl-N-[(1S)-6-chloro-1-[[(3S)-tetrahydropyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-8-yl]methanimine (60 mg, 0.120 mmol) was charged with N,N-dimethylpyridin-4-amine (46 mg, 0.376 mmol) followed by a solution

of 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (80 mg, 0.239 mmol) in acetonitrile (1.3 mL). The reaction mixture was allowed to stir at ambient temp for 1h, then concentrated under reduced pressure. The dark residue was then suspended in tetrahydrofuran (4 mL) and water (0.4 mL). Sodium acetate (30 mg, 0.366 mmol) was added followed by addition of hydroxylamine; hydrochloride (87 mg, 1.252 mmol). The reaction mixture was sonicated for 2 minutes till a homogenous solution formed, which was then allowed to stir for 1 h at ambient temperature. The reaction mixture was concentrated taken up in DMSO and subjected to prep HPLC purification (acetonitrile in water 5-100% gradient). After lyophilization, the product (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-8-amine (9 mg, 0.017 mmol, 13% yield) was isolated as an amorphous white solid. MS m/z 533.0 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.72 (s, 1H), 6.67 (s, 1H), 6.34 (d, *J* = 1.9 Hz, 1H), 5.98-5.84 (m, 1H), 5.23 (s, 2H), 4.89 (d, *J* = 12.3 Hz, 1H), 3.72 (t, *J* = 14.3 Hz, 2H), 3.61-3.50 (m, 1H), 3.01 (t, *J* = 10.3 Hz, 1H), 2.87-2.61 (m, 2H), 2.34 (d, *J* = 13.2 Hz, 1H), 1.89 (t, *J* = 12.4 Hz, 1H), 1.69 (t, *J* = 12.1 Hz, 1H), 1.59 (br s, 2H), 1.45 (m, 1H), 1.38-1.18 (m, 1H).

Example 40

Synthesis of Compound 292



[0386] **Step 1:** To a round bottom flask equipped with magnetic stirring was charged 2-cyclohexylideneacetic acid (3 g, 21.4 mmol), DMF (24 mL) and DIPEA (11.4 mL). The reaction was allowed to stir at room temperature for 5 minutes. To the reaction was charged 2-(5-chloro-1H-indol-3-yl)ethanamine hydrochloride (5.0 g, 21.7 mmol). The reaction was allowed to stir for 2 hours at room temperature. After 2 hours the reaction was judged complete by LCMS analysis. The reaction mixture was concentrated in vacuo and purified by silica gel chromatography to provide a solid residue. (5g, 75% yield). The product was used directly in the next step without further purification or analysis.

[0387] **Step 2:** To a round bottom flask equipped with magnetic stirring was charged N-[2-(5-chloro-1H-indol-3-yl)ethyl]-2-cyclohexylidene-acetamide (500 mg, 1.6 mmol). The reaction mixture was flushed with nitrogen and continued under nitrogen. To the reaction mixture was added acetonitrile (5 mL) and phosphoryl chloride (0.75 mL 8.2 mmol). The reaction mixture was heated to 90 °C for 4 hours. After 4 hours the reaction was judged complete by LCMS analysis. The reaction mixture was cooled to room temperature and concentrated in vacuo. To the concentrate was added saturated sodium bicarbonate solution, extracted with EtOAc, washed with brine, dried over Na₂SO₄, and concentrated to give a yellow oily material (350 mg, 73% yield). The product was used directly in the next step without further purification or analysis.

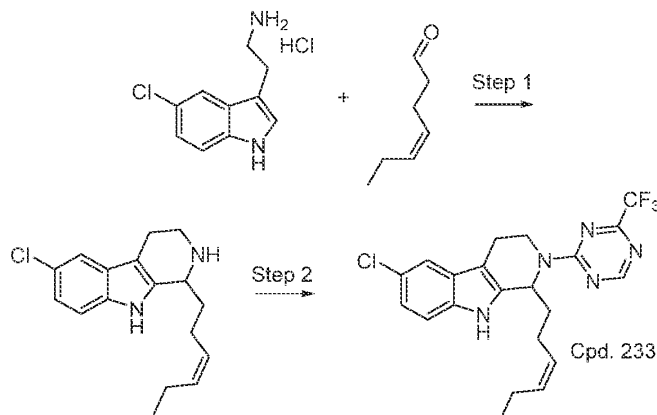
[0388] **Step 3:** To round bottom flask equipped with magnetic stirring was charged imine 6-chloro-1-(cyclohexylidenemethyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (750 mg, 2.5 mmol) as a solution in methanol (30 mL). The reaction mixture was flushed with nitrogen and kept under nitrogen. To the reaction mixture was added sodium borohydride (405 mg, 10.7 mmol) in one portion. The reaction mixture was allowed to stir at room temperature for 2 hours. After 2 hours the reaction was judged complete by LCMS analysis. The reaction mixture was cooled to 0 °C and quenched with 1% acetic acid solution. The solution was adjusted to pH ~ 9 with 10% NaOH. The mixture was extracted with EtOAc, dried over Na₂SO₄, and concentrated in vacuo. (405 mg, 54% yield) The concentrate was used directly in the next step without further analysis or purification.

[0389] **Step 4:** To a round bottom flask equipped with a magnetic stir bar was added 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (356 mg, 1.1 mmol) as a solution in THF (5.0 mL). The reaction mixture was flushed with nitrogen and kept under nitrogen. To the reaction mixture was added 6-chloro-1-(cyclohexylidenemethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (80 mg, 0.3 mmol,) and DIPEA (138 mg, 1.1 mmol). The mixture was allowed to stir at room temperature for 17 hours. After 17 hours the reaction was judged complete by LCMS analysis. The reaction mixture was concentrated in vacuo. The crude concentrate was purified by silica gel chromatography to give 2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(cyclohexylidenemethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (8 mg, 0.01551 mmol, 5.8% yield) as a white solid material. MS m/z 516.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.30 (s, 1H), 7.49 (d, J= 1.7 Hz, 1H), 7.37 (d, J= 8.6 Hz, 1H), 7.08 (dd, J= 8.6, 1.9 Hz, 1H), 6.01 (dd, J= 10.0, 3.7 Hz, 1H), 5.41 (s, 1H), 4.94 (dd, J= 13.3, 4.9 Hz, 1H), 3.63 (td, J= 12.9, 4.3 Hz, 1H), 2.89 (dd, J= 15.4, 3.5 Hz, 1H), 2.82–2.72

(m, 1H), 2.70–2.57 (m, 2H), 2.33 (d, J= 16.9 Hz, 1H), 1.95–1.81 (m, 2H), 1.64 (d, J= 16.6 Hz, 1H), 1.53 (d, J= 9.2 Hz, 1H), 1.34 (t, J= 14.0 Hz, 3H).

[0390] Using the procedure described for Example 40, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
65	MS m/z 506.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.21 (d, J= 21.1 Hz, 1H), 7.48 (d, J= 2.0 Hz, 1H), 7.36 (dd, J= 13.6, 8.6 Hz, 1H), 7.07 (dt, J= 8.6, 1.9 Hz, 1H), 6.01 (ddd, J= 13.7, 9.1, 4.1 Hz, 1H), 4.95 (dd, J= 13.3, 4.4 Hz, 1H), 3.94–3.79 (m, 1H), 3.74 (td, J= 7.9, 5.9 Hz, 1H), 3.56 (ddt, J= 22.5, 14.7, 8.6 Hz, 2H), 2.87 (dd, J= 15.2, 3.7 Hz, 1H), 2.82–2.66 (m, 1H), 2.34–2.07 (m, 3H), 1.76 (dddd, J= 41.6, 20.9, 13.1, 7.2 Hz, 3H).
118	MS m/z 472.0 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23(s, 1H), 7.48(d, J=2.0Hz, 1H), 7.36(d, J=8.8Hz, 1H), 7.07(q, J=6.4Hz, 1H), 5.97(q, J=7.2 Hz, 1H), 4.94(q, J=8.8 Hz, 1H), 3.61-3.53(m, 1H), 2.86 (q, J=12.4 Hz, 1H), 2.80-2.72(m, 2H), 2.35-2.16(m, 4H).
158A and 158B	MS m/z 494.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.95 (s, 1H), 7.47 (d, J= 1.9 Hz, 1H), 7.38 (d, J= 8.6 Hz, 1H), 7.05 (dd, J= 8.6, 2.0 Hz, 1H), 5.74 (d, J= 7.8 Hz, 1H), 5.37 (d, J= 6.6 Hz, 1H), 4.94 (dd, J= 13.2, 4.6 Hz, 1H), 3.72 (ddd, J= 16.7, 9.9, 4.2 Hz, 2H), 2.92–2.79 (m, 2H), 1.86–1.78 (m, 1H), 0.99 (t, J= 6.7 Hz, 6H).
159A and 159B	MS m/z 494.0 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.25 (s, 1H), 7.47 (d, J= 1.9 Hz, 1H), 7.36 (d, J= 8.6 Hz, 1H), 7.07 (dd, J= 8.6, 2.0 Hz, 1H), 5.93 (d, J= 3.4 Hz, 1H), 5.22 (d, J= 6.1 Hz, 1H), 4.96 (dd, J= 12.9, 5.1 Hz, 1H), 4.05 (dd, J= 12.7, 7.9 Hz, 1H), 3.80 (dd, J= 10.4, 6.4 Hz, 1H), 2.80 (dd, J= 29.9, 7.5 Hz, 2H), 1.83 (dd, J= 13.3, 6.7 Hz, 1H), 1.01 (dd, J= 43.1, 6.6 Hz, 6H).
160	MS m/z 473.0 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.30(s, 1H), 7.49(d, J= 2Hz, 1H), 7.37(d, J= 8.4Hz, 1H), 7.08(q, J= 6.4Hz, 1H), 5.97 (q, J= 5.2Hz, 1H), 4.93 (q, J= 8.4Hz, 1H), 3.61-3.54(m, 1H), 2.86(q, J= 12.0Hz, 1H), 2.80-2.73(m, 1H), 2.67-2.59(m, 2H), 2.39-2.33 (m, 2H).

Example 41**Synthesis of Compound 233**

[0391] **Step 1:** To a round-bottom flask equipped with magnetic stirring was charged 2-(5-chloro-1H-indol-3-yl)ethanamine;hydrochloride (200 mg, 0.9), 1,2-DCE (3 mL), (Z)-hept-4-enal (145 mg, 1.3 mmol) and TFA (0.2 mL, 2.6 mmol). The reaction mixture was flushed with nitrogen and kept under nitrogen. The reaction mixture was heated to 90 °C for 2 hours. After 2 hours the reaction was judged complete by LCMS analysis. The reaction mixture was concentrated in vacuo. The concentrate was triturated with petroleum ether/EtOAc 20:1 and filtered. The filter cake was dried in vacuo to give 6-chloro-1-[(Z)-hex-3-enyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole;2,2,2-trifluoroacetaldehyde as pale brown solid material. (300 mg, 90% yield). Product was used directly in the next step without further purification.

[0392] **Step 2:** To a round-bottom flask equipped with magnetic stir bar was charged 6-chloro-1-[(Z)-hex-3-enyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole;2,2,2-trifluoroacetaldehyde (150 mg, 0.4 mmol), 1-butanol (3 mL), 2-chloro-4-(trifluoromethyl)pyrimidine (142 mg, 0.8) and DIPEA (0.3 mL, 2 mmol). The reaction mixture was flushed with nitrogen and kept under nitrogen. The mixture was heated to 120 °C and allowed to stir for 16 hours. After 16 hours the reaction was judged complete by LCMS analysis. The reaction mixture was diluted with EtOAc, washed with DI water, saturated NaCl, dried over Na₂SO₄, and concentrated in vacuo. The concentrate was purified by silica gel chromatography to give 6-chloro-1-[(3Z)-hex-3-en-1-yl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a pale yellow solid. (87 mg, 52% yield) MS m/z 435.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.17 (s, 1H), 8.73 (d, J = 4.4 Hz, 1H), 7.43 (d, J=2.0 Hz, 1H), 7.32 (d, J =8.4 Hz, 1H), 7.052-7.048

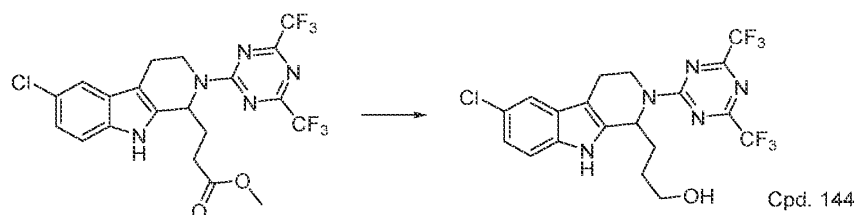
(m, 1H), 7.04-7.03 (m, 1H), 5.95 (s, 1H), 5.41-5.29 (m, 2H), 4.96 (s, 1H), 3.44-3.35 (m, 1H), 2.73-2.69 (m, 2H), 2.19-1.98 (m, 4H), 1.96-1.90 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H).

[0393] Using the procedure described for Example 41, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
129	MS m/z 467.7 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23(s, 1H), 7.48(d, J=1.6Hz, 1H), 7.36(d, J=8.4Hz, 1H), 7.07(dd, J=8.8Hz, 2.0Hz, 1H), 5.94-5.83(m, 2H), 5.03(d, J=17.2 Hz, 1H), 4.95(dd, J=13Hz, 4.4Hz, 2H), 3.62 -3.55 (m, 1H), 2.87(dd, J=15.6 Hz, 3.6Hz, 1H), 2.81-2.73(m, 1H), 2.20-2.12(m, 4H).
132	MS m/z 503.7 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23 (s, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.36 (d, J=8.4 Hz, 1H), 7.07 (dd, J =8.6 Hz, 1.6Hz, 1H), 5.95-5.94 (m, 1H), 5.45-5.30 (m, 2H), 4.95 (dd, J =5.6 Hz, 4.8Hz, 1H), 3.62 -3.55 (m, 1H), 2.90 -2.85 (m, 1H), 2.81-2.73 (m, 1H), 2.18-2.09 (m, 4H), 1.98-1.91 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H).
232	MS m/z 407.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.18 (s, 1H), 8.73 (d, J = 4.8 Hz, 1H), 7.44 (d, J=2.0 Hz, 1H), 7.33 (d, J =8.4 Hz, 1H), 7.06-7.03 (m, 2H), 5.94-5.84 (m, 2H), 5.04-4.94 (m, 3H), 3.45-3.38 (m, 1H), 2.78-2.66 (m, 2H), 2.23-1.99 (m, 4H).

Example 42

Synthesis of Compound 144

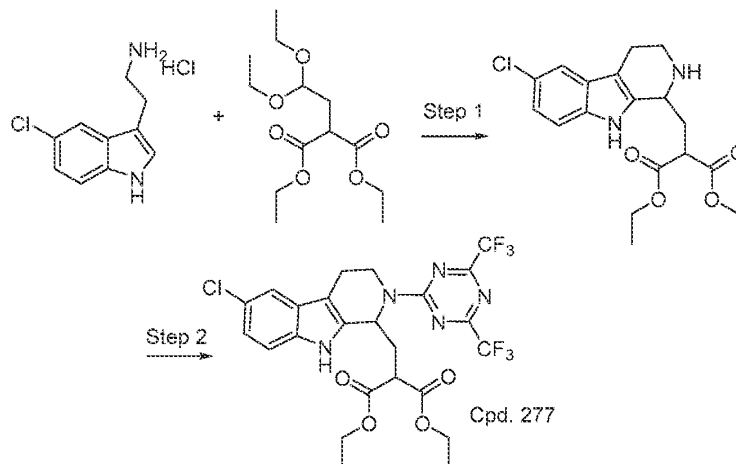


[0394] To a round-bottom flask equipped with magnetic stir bar was charged 3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1,3,4,9-tetrahydropyrido[3,4-b]indol-1-yl}propanoate (100 mg, 0.2 mmol) and DCM (10 mL). The reaction mixture was flushed with nitrogen and kept under nitrogen. The mixture was cooled to 0 °C. To the mixture was added DIBAL-H in hexanes (2 mL, 2 mmol). The reaction mixture was removed from the ice bath and allowed to stir at rt for 4 hours. After 4 hours the reaction was judged complete by LCMS analysis. The reaction was quenched with saturated ammonium chloride solution and extracted with DCM, dried over Na₂SO₄ and concentrated in vacuo. The concentrate was purified by prep-HPLC to give 3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propan-1-ol as a white solid material. (18 mg, 0.04 mmol, 19.0% yield) was white solid. MS m/z 505.9 [M+H]⁺; (DMSO-*d*₆, 400MHz) 11.26(s, 1H), 7.49(d, J=1.2Hz, 1H), 7.36(d, J=8.0Hz, 1H), 7.08(dd, J=8.4,

1.6Hz, 1H), 7.49(d, $J=7.2$ Hz, 1H), 4.92(dd, $J=13.6, 4.8$ Hz, 1H), 3.55-3.43(m, 5H), 2.78-2.61(m, 3H), 2.48-2.19(m, 2H).

[0395] Using the procedure described for Example 42, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
86A and 86B	MS m/z 478.1 [M-H] ⁻ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.16 (s, 1H), 7.47 (d, $J=2.1$ Hz, 1H), 7.36 (d, $J=8.6$ Hz, 1H), 7.07 (dd, $J=8.6, 2.1$ Hz, 1H), 5.98 (dd, $J=10.0, 4.3$ Hz, 1H), 4.93 (dd, $J=13.4, 5.3$ Hz, 1H), 4.52 (d, $J=4.5$ Hz, 1H), 3.78 (s, 1H), 3.57 (dd, $J=12.4, 4.3$ Hz, 1H), 2.82 (ddd, $J=32.7, 13.6, 4.7$ Hz, 2H), 2.15-1.84 (m, 2H), 1.22 (d, $J=6.1$ Hz, 3H).
87A and 87B	MS m/z 478.1 [M-H] ⁻ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.19 (s, 1H), 7.47 (d, $J=2.1$ Hz, 1H), 7.34 (d, $J=8.6$ Hz, 1H), 7.06 (dd, $J=8.5, 2.1$ Hz, 1H), 6.06 (dd, $J=8.8, 4.3$ Hz, 1H), 4.93 (dd, $J=13.5, 5.2$ Hz, 1H), 4.47 (d, $J=4.6$ Hz, 1H), 3.75 (s, 1H), 3.58 (dd, $J=12.7, 4.5$ Hz, 1H), 3.07-2.69 (m, 2H), 2.15-1.84 (m, 2H), 1.11 (d, $J=6.1$ Hz, 3H).
96	MS m/z 520.2 [M-H] ⁻ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.25 (s, 1H), 7.47 (d, $J=2.1$ Hz, 1H), 7.35 (d, $J=8.6$ Hz, 1H), 7.07 (dd, $J=8.6, 2.1$ Hz, 1H), 5.98 (t, $J=7.0$ Hz, 1H), 4.91 (dd, $J=13.2, 5.1$ Hz, 1H), 4.32 (t, $J=5.0$ Hz, 1H), 3.78-3.51 (m, 1H), 3z.44-3.33 (m, 2H), 3.02-2.68 (m, 2H), 1.91 (t, $J=6.8$ Hz, 2H), 1.79-1.39 (m, 3H), 1.40-1.09 (m, 2H), 0.93 (d, $J=6.5$ Hz, 3H).
97	MS m/z 520.2 [M-H] ⁻ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.29 (s, 1H), 7.47 (d, $J=2.1$ Hz, 1H), 7.35 (d, $J=8.6$ Hz, 1H), 7.07 (dd, $J=8.6, 2.1$ Hz, 1H), 6.01 (dd, $J=11.2, 3.0$ Hz, 1H), 4.91 (dd, $J=13.2, 5.0$ Hz, 1H), 4.32 (t, $J=5.1$ Hz, 1H), 3.78-3.52 (m, 1H), 3.37-3.33 (m, 2H), 3.12-2.72 (m, 2H), 2.08 (t, $J=12.8$ Hz, 1H), 1.90-1.64 (m, 1H), 1.42 (tq, $J=9.7, 6.2$ Hz, 3H), 1.36-1.12 (m, 2H), 1.11 (d, $J=6.4$ Hz, 3H).
99	MS m/z 508.1 [M+H] ⁺ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23 (s, 1H), 7.48 (d, $J=2.1$ Hz, 1H), 7.36 (d, $J=8.6$ Hz, 1H), 7.07 (dd, $J=8.6, 2.0$ Hz, 1H), 6.00 (dd, $J=9.5, 4.9$ Hz, 1H), 4.93 (dd, $J=13.3, 5.2$ Hz, 1H), 4.21 (t, $J=4.8$ Hz, 1H), 3.63 (dd, $J=12.7, 4.6$ Hz, 1H), 3.43 (dq, $J=11.7, 5.5$ Hz, 2H), 2.83 (dtd, $J=21.9, 15.6, 7.3$ Hz, 2H), 1.92 (ddd, $J=22.2, 11.0, 7.2$ Hz, 3H), 1.68 (s, 1H), 1.29 (td, $J=14.1, 7.0$ Hz, 1H), 0.95 (d, $J=6.6$ Hz, 3H).
152A and 152B	MS m/z 442.1 [M-H] ⁻ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.16 (s, 1H), 7.46 (d, $J=2.1$ Hz, 1H), 7.36 (d, $J=8.6$ Hz, 1H), 7.07 (dd, $J=8.6, 2.1$ Hz, 1H), 6.78 (td, $J=53.5, 13.2$ Hz, 2H), 6.02 (dd, $J=10.1, 4.3$ Hz, 1H), 4.99 (dd, $J=13.3, 5.2$ Hz, 1H), 4.51 (d, $J=4.8$ Hz, 1H), 3.73 (p, $J=6.0$ Hz, 1H), 3.53 (td, $J=12.7, 4.4$ Hz, 1H), 2.95-2.61 (m, 2H), 2.22-1.88 (m, 2H), 1.25 (d, $J=6.0$ Hz, 3H).
153A and 153B	MS m/z 442.2 [M-H] ⁻ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.13 (s, 1H), 7.39 (d, $J=2.0$ Hz, 1H), 7.26 (d, $J=8.6$ Hz, 1H), 6.99 (dd, $J=8.6, 2.1$ Hz, 1H), 6.72 (td, $J=53.5, 15.6$ Hz, 2H), 5.99 (dd, $J=8.9, 4.3$ Hz, 1H), 4.91 (dd, $J=13.3, 5.2$ Hz, 1H), 4.44 (d, $J=4.4$ Hz, 1H), 3.67 (dt, $J=10.3, 5.0$ Hz, 1H), 3.45 (td, $J=12.6, 4.4$ Hz, 1H), 2.98-2.57 (m, 2H), 1.97 (pt, $J=8.3, 4.0$ Hz, 2H), 1.04 (d, $J=6.1$ Hz, 3H).
288	MS m/z 490.0 [M-H] ⁻ . ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.10 (s, 1H), 7.51 (d, $J=2.0$ Hz, 1H), 7.34 (d, $J=8.8$ Hz, 1H), 7.07 (q, $J=6.8$ Hz, 1H), 6.55 (d, $J=9.6$ Hz, 1H), 5.69 (q, $J=8.8$ Hz, 1H), 4.98 (q, $J=8.8$ Hz, 1H), 4.92 (s, 1H), 3.85 (t, $J=14.8$ Hz, 2H), 3.64-3.56 (m, 1H), 2.94 (q, $J=12.4$ Hz, 1H), 2.83-2.75 (m, 1H), 1.96 (s, 3H).

Example 43**Synthesis of Compound 277**

[0396] **Step 1:** To a round-bottom flask was charged 2-(5-chloro-1H-indol-3-yl)ethanamine; hydrochloride (506 mg, 2.1893 mmol, 1.1 equiv.), diethyl 2-(2,2-diethoxyethyl)propanedioate (550 mg, 1.991 mmol, 1.0 equiv.), 1,2-DCE (8 mL), and TFA (0.3 mL, 4 mmol, 2.0 equiv.). The reaction mixture was heated to 90 °C and stirred for 2 hours. The reaction mixture was analyzed by LCMS and all starting material was consumed. The reaction was quenched by addition of DI water, extracted with DCM (2x), dried over Na₂SO₄, concentrated and purified by silica gel chromatography to give diethyl 2-[(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl]propanedioate. (480 mg, 64% yield). The product was used directly in the next step without further purification or analysis.

[0397] **Step 2:** To a round-bottom flask equipped with magnetic stirring was charged diethyl 2-[(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl]propanedioate (100 mg, 0.26 mmol, 1.0 equiv.), 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (106 mg, 0.32 mmol, 1.2 equiv.), DMF (5 mL), DIPEA (0.2 mL, 1 mmol, 4.0 equiv.), and 4-DMAP (1 mg, 0.01 mmol, 0.03 equiv.). The reaction was allowed to stir for 16 hours at room temperature. The reaction was analyzed by LCMS that indicated that all starting material had been consumed. The reaction was quenched by addition of DI water, extracted with EtOAc (2x), dried over Na₂SO₄, concentrated, and purified by reverse phase prep-HPLC to give diethyl 2-[(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl]propanedioate as a yellow solid. (8 mg, 5.1% yield) MS m/z 594.0 [M+H]⁺; (CDCl₃, 400MHz), d : 8.93 (s, 1 H), 7.44-7.44 (d, J = 1.6 Hz, 1 H), 7.29-7.28 (m, 2 H), 7.16-7.14 (dd, J = 8.4 Hz, 1.6 Hz, 1 H), 5.96-5.93 (dd, J = 1.6 Hz, 8.0 Hz, 1 H),

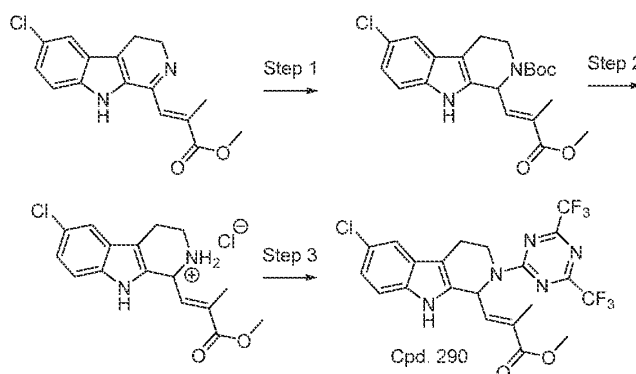
5.21-5.16 (m, 1H), 4.37-4.17 (m, 4 H), 3.73-3.69 (dd, J = 6.4 Hz, 8.8 Hz, 1 H), 3.54-3.46 (m, 1 H), 2.92-2.88 (m, 1 H), 2.69-2.62 (m, 1 H), 2.44-2.36 (m, 1 H), 1.32 –1.29 (t, J=7.2Hz, 3 H), 1.27–1.24(t, J=7.2Hz, 3 H).

[0398] Using the procedure described for Example 43, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
85	MS m/z 508.0 [M+H] ⁺ ; (DMSO- <i>d</i> ₆ , 400MHz) 11.19(s, 1H), 7.50(d, J=2.0Hz, 1H), 7.37(d, J=8.4Hz, 1H), 7.07(q, J=6.4Hz, 1H), 6.23(t, J=7.2 Hz, 1H), 4.97 (q, J=8.4 Hz, 1H), 4.00-3.92(m, 2H), 3.70-3.63(m, 1H), 3.08 (d, J=6.8 Hz, 2H), 2.90(q, J=12.4Hz, 1H), 2.82-2.74(m, 1H), 2.05(t, J=7.2 Hz, 3H).

Example 44

Synthesis of Compound 290



[0399] **Step 1:** To a round-bottom flask equipped with magnetic stir bar was charged methyl (E)-3-(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-2-methyl-prop-2-enoate (3.0 g, 10.0 mmol), methanol (30 mL) and Boc₂O (3.00 g, 13.3 mmol). The reaction was cooled to 0 °C. To the reaction was added sodium borohydride (1.00 g, 26.4 mmol). The mixture was allowed to stir for 1 hour. After 1 hour at 0 °C the reaction was judged complete by LCMS analysis. The mixture was diluted with EtOAc, washed with DI water, brine, dried over Na₂SO₄ and concentrated in vacuo. The material was purified by silica gel chromatography to give tert-butyl 6-chloro-1-[(E)-3-methoxy-2-methyl-3-oxo-prop-1-enyl]-1,3,4,9-tetrahydropyrido[3,4-b]indole-2-carboxylates as a solid. (2.00 g, 50% % yield) The product was used directly in the next step without further purification or analysis.

[0400] **Step 2:** To a round bottom flask equipped with magnetic stir bar was charged tert-butyl 4-[[6-[(3-chloro-4-pyridyl)amino]pyridine-3-carbonyl]amino]piperidine-1-carboxylate (2.00 g, 4.9 mmol), hydrochloric acid in dioxane (10 mL, 40 mmol) and DCM (10 mL). The

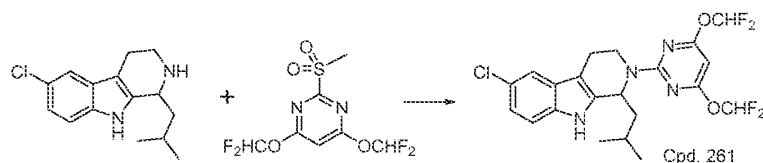
reaction was allowed to stir for 1 hour. The reaction precipitated and after 1 hour the reaction was judged complete by LCMS. The reaction was filtered and dried in vacuo to afford (E)-6-chloro-1-(3-methoxy-2-methyl-3-oxoprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-ium chloride as a solid. (1.40 g, 93% yield) The product was used directly in the next step without further purification or analysis.

[0401] **Step 3:** To a round-bottom flask equipped with magnetic stirring was charged (E)-6-chloro-1-(3-methoxy-2-methyl-3-oxoprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-ium chloride (1.5 g, 2.9 mmol), 4-DMAP (0.58 g, 4.7 mmol) and acetonitrile (10 mL). The reaction was flushed with nitrogen and continued under nitrogen. The reaction was cooled to 0 °C. To the reaction was charged 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (1.60 g, 4.8 mmol) and the reaction as stirred for 2 hours. After 2 hours the reaction was judged complete by LCMS. The reaction was concentrated in vacuo and purified by silica gel chromatography to give methyl (2E)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylprop-2-enoate a white solid. (1.50 g, 63% yield). MS m/z 518.0 [M-H]⁺; (DMSO-*d*₆, 400MHz)

11.15(s,1H), 7.55(d, J=2.0Hz, 1H), 7.36(d, J=8.8 Hz, 1H), 7.10(q, J=6.8Hz, 1H), 6.73(q, J=9.2 Hz, 1H), 6.55 (d, J=10.0Hz, 1H), 5.01(q, J=9.2 Hz, 1H), 3.70 (q, J=9.2 Hz, 1H), 3.66(s, 3H), 2.98(q, J=12.4Hz, 1H), 2.85-2.77(m, 1H), 2.24(d, J=1.2 Hz, 3H).

Example 45

Synthesis of Compound 261

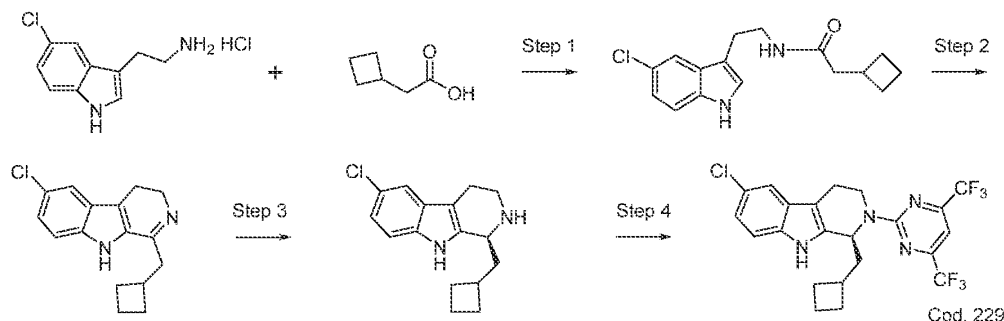


[0402] A mixture of 6-chloro-1-isobutyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (0.5576 g, 2.12 mmol), 4,6-bis(difluoromethoxy)-2-(methylsulfonyl)pyrimidine (0.4607 g, 1.59 mmol), and K₂CO₃ (0.7010 g, 5.02 mmol) in DMF (8 mL) was heated at 70 °C under Argon for 20 h. The reaction mixture was then cooled to room temperature and quenched with water and brine, extracted twice with ethyl acetate. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel (40 g column) eluted with 0 to 40% ethyl acetate/hexane over 20 min and then by reversed phase HPLC (30x150mm prep) eluted with 15 to 90% ACN/H₂O over 20 min to afford 0.1277 g (17%) of 2-[4,6-

bis(difluoromethoxy)pyrimidin-2-yl]-6-chloro-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole. ESI-MS m/z 473.3 $[M+H]^+$, 471.3 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.06 (s, 1H), 8.01-7.46 (m, 2H), 7.36 (s, 1H), 7.26 (d, $J = 8.5$ Hz, 1H), 6.97 (br d, $J = 8.5$ Hz, 1H), 5.90 (s, 1H), 5.79 (br d, $J = 8.9$ Hz, 1H), 4.76 (br d, $J = 11.9$ Hz, 1H), 3.37-3.19 (m, 1H), 2.68-2.59 (m, 2H), 1.89-1.72 (m, 1H), 1.70-1.57 (m, 2H), 1.00 (br d, $J = 5.4$ Hz, 3H), 0.87 (br d, $J = 5.5$ Hz, 3H).

[0403] Using the procedure described for Example 45, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents, and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
259	ESI-MS m/z 443.3 $[M+H]^+$, 441.4 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.09 (s, 1H), 7.34 (s, 1H), 7.24 (d, $J = 8.5$ Hz, 1H), 6.96 (br d, $J = 8.5$ Hz, 1H), 5.90 (br d, $J = 7.8$ Hz, 1H), 5.36 (s, 1H), 4.79 (br dd, $J = 4.5, 13.3$ Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.65 (br d, $J = 10.3$ Hz, 2H), 3.25-3.18 (m, 2H), 2.97 (br t, $J = 10.0$ Hz, 1H), 2.72-2.54 (m, 2H), 2.16 (br d, $J = 11.8$ Hz, 1H), 1.74-1.52 (m, 4H), 1.41-1.22 (m, 2H).
260	ESI-MS m/z 515.2 $[M+H]^+$, 513.2 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.16 (s, 1H), 8.09-7.55 (m, 2H), 7.44 (s, 1H), 7.34 (d, $J = 8.5$ Hz, 1H), 7.05 (br d, $J = 8.5$ Hz, 1H), 6.00 (s, 1H), 5.97-5.79 (m, 1H), 4.83 (br d, $J = 12.1$ Hz, 1H), 3.76-3.63 (m, 2H), 3.04 (br t, $J = 10.3$ Hz, 1H), 2.72 (br s, 2H), 2.15 (br d, $J = 10.5$ Hz, 1H), 1.86-1.66 (m, 2H), 1.66-1.53 (m, 2H), 1.47-1.21 (m, 4H).
274	ESI-MS m/z 402.3 $[M+H]^+$, 400.3 $[M-H]^-$; 1H NMR (500 MHz, CDCl ₃) δ 7.89 (br s, 1H), 7.34 (s, 1H), 7.16 (br d, $J = 8.4$ Hz, 1H), 7.02 (br d, $J = 8.4$ Hz, 1H), 5.97 (br d, $J = 9.0$ Hz, 1H), 5.01-4.89 (m, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.28 (br t, $J = 12.4$ Hz, 1H), 2.90-2.73 (m, 1H), 2.64 (br d, $J = 15.3$ Hz, 1H), 1.87-1.77 (m, 1H), 1.75-1.66 (m, 1H), 1.66-1.52 (m, 1H), 1.03 (br d, $J = 6.1$ Hz, 3H), 0.92 (br d, $J = 6.3$ Hz, 3H).
275	ESI-MS m/z 444.3 $[M+H]^+$, 442.3 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.14 (s, 1H), 7.36 (s, 1H), 7.26 (d, $J = 8.5$ Hz, 1H), 6.97 (br d, $J = 8.5$ Hz, 1H), 5.88 (br d, $J = 6.5$ Hz, 1H), 4.82 (br d, $J = 12.0$ Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.63 (br t, $J = 11.5$ Hz, 2H), 3.31-3.18 (m, 2H), 2.96 (br t, $J = 10.3$ Hz, 1H), 2.74-2.54 (m, 2H), 2.14 (br d, $J = 11.8$ Hz, 1H), 1.76-1.62 (m, 2H), 1.54 (br s, 2H), 1.40-1.21 (m, 2H).

Example 46**Synthesis of Compound 229**

[0404] **Step 1:** A mixture of 2-(5-chloro-1H-indol-3-yl)ethan-1-amine hydrochloride (500 mg, 2.16 mmol), 2-cyclobutylacetic acid (360 mg, 3.15 mmol), HATU (1.5 g, 3.9 mmol), and DIPEA (2.2 mL, 13 mmol) in DMF (10 mL) was stirred at room temperature for 2 h. The reaction mixture was then quenched with water, extracted three times with ethyl acetate. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by Prep HPLC to afford 450 mg (71.5%) of N-(2-(5-chloro-1H-indol-3-yl)ethyl)-2-cyclobutylacetamide as a white solid. ESI-MS *m/z* 290.0 (M+H)⁺.

[0405] **Step 2:** To a solution of N-(2-(5-chloro-1H-indol-3-yl)ethyl)-2-cyclobutylacetamide (400 mg, 1.37 mmol) in acetonitrile (10 mL) was added phosphoryl chloride (0.6 mL, 6 mmol). The reaction mixture was stirred at 50 °C for 3 h and then adjusted to pH 8 with aqueous solution of NaHCO₃. The mixture was extracted twice with ethyl acetate. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the crude product (300 mg, 80%) was obtained as a yellow solid, which was directly used in the next step without further purification. ESI-MS *m/z* 273.1 (M+H)⁺.

[0406] **Step 3:** A mixture of 6-chloro-1-(cyclobutylmethyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (100 mg, 0.37 mmol), formic acid-triethylamine complex 5:2 (0.3 mL, 0.7 mmol), and RuCl[(*R,R*)-TsDPEN](mesitylene) (3 mg, 0.0043 mmol) in DMF (8 mL) was stirred at room temperature for 2 h. The reaction mixture was then quenched with aqueous solution of Na₂CO₃ and extracted three times with ethyl acetate. The combined organic phase was washed with brine and dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography on silica gel eluted with 0 to 10% MeOH/DCM to afford 80 mg (79%) of (S)-6-chloro-1-(cyclobutylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a brown solid. ESI-MS *m/z* 275.1 [M+H]⁺.

[0407] **Step 4:** To a solution of (S)-6-chloro-1-(cyclobutylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (80 mg, 0.29 mmol) and 2-chloro-4,6-bis(trifluoromethyl)pyrimidine (90 mg, 0.36 mmol) in acetonitrile (5 mL) was added DIPEA (0.15 mL, 0.86 mmol). The reaction mixture was stirred at room temperature for 16 h. After the solvent was evaporated under the reduced pressure, the residue was purified by Prep HPLC to afford 80 mg (56%) of (1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(cyclobutylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white solid. ESI-MS m/z 486.9 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.21 (s, 1H), 7.43 (t, $J = 2.4$ Hz, 2H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.04 (q, $J = 8.8$ Hz, 1H), 5.82 (t, $J = 7.0$ Hz, 1H), 4.88 (q, $J = 12.0$ Hz, 1H), 3.45-3.48 (m, 1H), 2.70-2.80 (m, 2H), 2.33-2.37 (m, 1H), 2.06-2.09 (m, 3H), 1.77-1.90 (m, 4H), 1.55-1.65 (m, 1H).

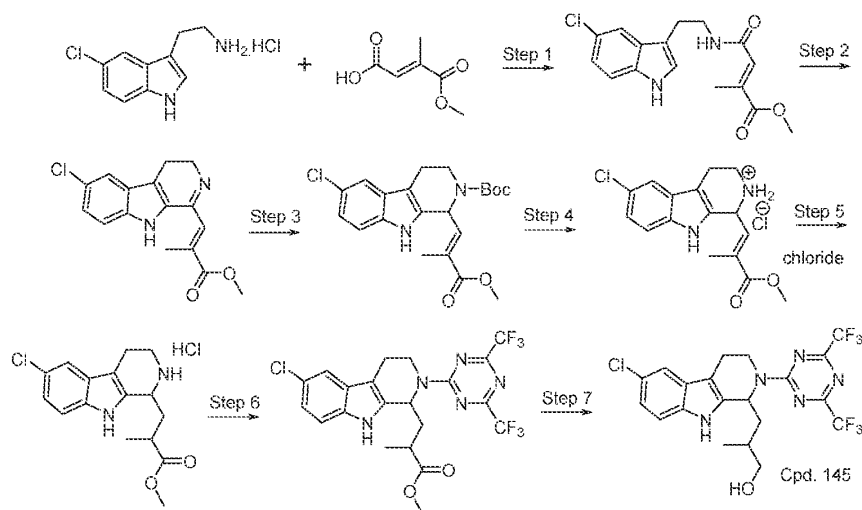
[0408] Using the procedure described for Example 46, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
57	ESI-MS m/z 450 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.25 (d, $J = 4$ Hz, 1H), 8.86 (d, $J = 17.6$ Hz, 1H), 7.45 (t, $J = 2.4$ Hz, 1H), 7.34 (d, $J = 8.8$ Hz, 1H), 7.34 (q, $J = 6.8$ Hz, 1H), 6.05-5.92 (m, 1H), 5.00-4.85 (m, 1H), 3.87-3.75 (m, 2H), 3.54-3.47 (m, 1H), 3.30-3.13 (m, 2H), 2.83-2.66 (m, 2H), 2.19-2.0 (m, 1H), 2.08-1.77 (m, 2H), 1.56-1.44 (m, 2H), 1.35-1.17 (m, 2H)
71	ESI-MS m/z 536.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.23 (s, 1H), 7.48 (d, $J = 2.0$ Hz, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.07 (dd, $J = 8.8, 2.0$ Hz, 1H), 5.90 (t, $J = 7.0$ Hz, 1H), 4.94 (dd, $J = 6.2, 4.8$ Hz, 1H), 3.58-3.52 (m, 4H), 2.86 (dd, $J = 15.4, 4.4$ Hz, 1H), 2.80-2.71 (m, 1H), 2.33-2.45 (m, 2H), 2.06-1.99 (m, 2H), 1.75-1.66 (m, 1H), 1.61-1.53 (m, 1H), 1.41-1.35 (m, 2H)
72	ESI-MS m/z 550.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.21 (s, 1H), 7.47 (d, $J = 2.0$ Hz, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.06 (q, $J = 8.2$ Hz, 1H), 5.86-5.90 (m, 1H), 4.91-4.96 (m, 1H), 3.52-3.58 (m, 4H), 2.84 (d, $J = 3.6$ Hz, 1H), 2.71-2.75 (m, 1H), 2.27 (t, $J = 7.2$ Hz, 2H), 1.98-2.03 (m, 2H), 1.49-1.52 (m, 2H), 1.31-1.40 (m, 4H)
120	ESI-MS m/z 492.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.28 (d, $J = 13.8$ Hz, 1H), 7.47 (s, 1H), 7.35 (dd, $J = 8.6, 1.6$ Hz, 1H), 7.07 (dd, $J = 8.6, 1.7$ Hz, 1H), 5.99 (t, $J = 10.0$ Hz, 1H), 4.91 (d, $J = 13.3$ Hz, 1H), 3.60 (dd, $J = 20.5, 8.4$ Hz, 1H), 2.89-2.73 (m, 2H), 1.84 (ddd, $J = 55.4, 25.8, 7.5$ Hz, 2H), 1.43 (s, 1H), 1.33-1.14 (m, 2H), 1.00 (dd, $J = 79.0, 6.5$ Hz, 3H), 0.84 (dd, $J = 16.2, 7.4$ Hz, 3H).
121	ESI-MS m/z 489.9 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.25 (s, 1H), 7.47 (d, $J = 2.0$ Hz, 1H), 7.34 (d, $J = 8.8$ Hz, 1H), 7.06 (dd, $J = 8.8, 2.0$ Hz, 1H), 5.97 (dd, $J = 8.8, 5.6$ Hz, 1H), 4.91 (dd, $J = 13.2, 4.8$ Hz, 1H), 3.63-3.56 (m, 1H), 2.88-2.72 (m, 2H), 1.91-1.78 (m, 3H), 1.48-1.42 (m, 1H), 1.22-1.12 (m, 1H), 0.90 (d, $J = 4.0$ Hz, 3H), 0.84 (t, $J = 7.2$ Hz, 3H).

Cpd	Data
166	ESI-MS m/z 472.0 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 10.88 (s, 1H), 7.21 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 6.70 (q, J = 6.4 Hz, 1H), 5.94 (q, J = 7.6 Hz, 1H), 4.91 (q, J = 10.4 Hz, 1H), 3.73 (s, 3H), 3.62-3.55 (m, 1H), 2.83-2.73 (m, 2H), 2.01-1.94 (m, 1H), 1.80-1.73 (m, 1H), 1.67-1.61 (m, 1H), 1.09 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H)
172	ESI-MS m/z 530.0 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.3 (m, 1H), 7.50 (m, 1H), 7.39-7.36 (m, 1H), 7.10-7.07 (m, 1H), 6.02-5.99 (m, 1H), 4.95-4.91 (m, 1H), 3.64-3.55 (m, 1H), 2.95-2.70 (m, 3H), 2.41-2.22 (m, 1H), 2.06-1.99 (m, 1H), 1.37-1.35 (m, 1.5H), 1.15-1.13 (m, 1.5H). (1:1) mixture of two isomers.
184	ESI-MS m/z 408.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.17 (d, J = 7.2 Hz, 1H), 8.86 (d, J = 10.8 Hz, 1H), 7.46 (s, 1H), 7.33-7.36 (m, 1H), 7.05 (d, J = 8.8 Hz, 1H), 5.96-6.05 (m, 1H), 4.95-5.09 (m, 1H), 3.46-3.52 (m, 1H), 2.67-2.85 (m, 2H), 1.87-1.92 (m, 2H), 0.68-0.74 (m, 1H), 0.29-0.42 (m, 2H), 0.03-0.16 (m, 2H).
227	ESI-MS m/z 477.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.91 (s, 1H), 7.44 (t, J = 2.6 Hz, 2H), 7.32 (d, J = 8.4 Hz, 1H), 7.04 (q, J = 8.4 Hz, 1H), 5.86-5.89 (m, 1H), 4.90 (q, J = 13.4 Hz, 1H), 3.43-3.50 (m, 1H), 2.67-2.81 (m, 2H), 1.94-2.03 (m, 2H), 1.30-1.45 (m, 4H), 0.84 (t, J = 7.0 Hz, 3H)
293	ESI-MS m/z 514 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.29 (s, 1H), 7.48 (d, J = 2 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.07 (q, J = 6.8 Hz, 1H), 6.01 (q, J = 6.8 Hz, 1H), 5.40 (s, 1H), 4.93 (q, J = 8.4 Hz, 1H), 3.66-3.59 (m, 1H), 2.89 (m, 1H), 2.80-2.72 (m, 1H), 2.67-2.57 (m, 2H), 2.32 (m, 1H), 1.87 (t, J = 16.4 Hz, 2H), 1.65-1.49 (m, 2H), 1.37-1.23 (m, 3H)

Example 47

Synthesis of Compound 145



[0409] **Step 1:** A mixture of 2-(5-chloro-1H-indol-3-yl)ethan-1-amine hydrochloride (4.65 g, 20.1 mmol), (E)-4-methoxy-3-methyl-4-oxobut-2-enoic acid (2.90 g, 20.1 mmol), HATU (9.37 g, 24.1 mmol), and DIPEA (7 mL, 40 mmol) in THF (20 mL) was stirred at room

temperature for 16 h. The reaction mixture was then quenched with water, extracted three times with ethyl acetate. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel eluted with 0 to 80% ethyl acetate/hexane to afford 5.5 g (85%) of methyl (E)-4-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-2-methyl-4-oxobut-2-enoate as a yellow solid. ESI-MS m/z 321.2 (M+H)⁺.

[0410] **Step 2:** To a solution of methyl (E)-4-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-2-methyl-4-oxobut-2-enoate (4.00 g, 12.5 mmol) in acetonitrile (50 mL) was added phosphoryl chloride (3.5 mL, 38 mmol). The reaction mixture was stirred at 90 °C for 0.5 h. After the solvent was evaporated under the reduced pressure, the crude product (3.50 g, 92.7%) was directly used in the next step without further purification. ESI-MS m/z 303.2 (M+H)⁺.

[0411] **Step 3:** To a solution of methyl (E)-3-(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-2-methylacrylate (3.00 g, 9.91 mmol) and di-*tert*-butyl decarbonate (3.00 g, 13.3 mmol) in MeOH (30 mL) was added in portion NaBH₄ (1.00 g, 26.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then quenched with water and brine, extracted twice with ethyl acetate. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel eluted with 0 to 100% ethyl acetate/hexane to afford 2.00 g (49.9%) of *tert*-butyl (E)-6-chloro-1-(3-methoxy-2-methyl-3-oxoprop-1-en-1-yl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate. ESI-MS m/z 405.3 [M+H]⁺.

[0412] **Step 4:** To a solution of *tert*-butyl (E)-6-chloro-1-(3-methoxy-2-methyl-3-oxoprop-1-en-1-yl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (2.00 g, 4.94 mmol) in DCM (10 mL) was added hydrogen chloride solution (4.0 M in dioxane, 10 mL, 40 mmol). The reaction mixture was stirred at room temperature for 1 h. The solid (1.40 g, 93%) of methyl (E)-3-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylacrylate HCl salt was collected by filtration. ESI-MS m/z 305.2 [M+H]⁺.

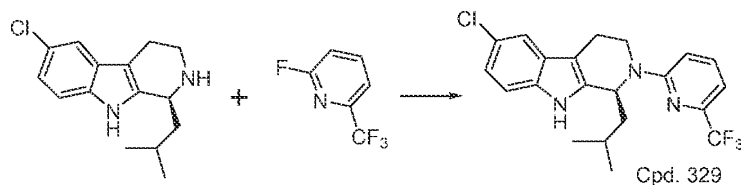
[0413] **Step 5:** A mixture of (E)-6-chloro-1-(3-methoxy-2-methyl-3-oxoprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-ium chloride (300 mg, 0.98 mmol) and Pd Lindlar catalyst (5 wt%, 240 mg, 0.11 mmol) in THF (5 mL) was stirred at room temperature under hydrogen for 16 h. The reaction mixture was then filtrated. After the filtrate was evaporated under the reduced pressure, the crude product methyl 3-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropanoate HCl salt (300 mg, 94%) was obtained as a yellow solid. ESI-MS m/z 307 [M+H]⁺.

[0414] **Step 6:** To a mixture of methyl 3-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropanoate HCl salt (0.30 g, 0.93 mmol) and DMAP (2 Equivalents) in acetonitrile (2 mL) was added dropwise 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (0.34 g, 1.0 mmol) at 0 °C under N₂. The reaction mixture was stirred at room temperature for 2 h. After the solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography on silica gel eluted with 0 to 20% ethyl acetate/hexanes to afford 0.30 g (62%) of methyl 3-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropanoate as a white solid. ESI-MS m/z 520 [M-H]⁻.

[0415] **Step 7:** To a solution of methyl 3-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropanoate (100 mg, 0.19 mmol) in DCM (2 mL) was added dropwise DIBAL-H (1.0 M in hexanes, 0.25 mL, 0.25 mmol) at -78 °C under N₂. The reaction mixture was stirred at -78 °C for 2 h. After work-up, the residue was purified by prep HPLC to afford 3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropan-1-ol as a white solid. ESI-MS m/z 492 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.31 (s, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.06 (q, *J* = 6.4 Hz, 1H), 6.01 (q, *J* = 9.2 Hz, 1H), 4.91 (q, *J* = 8.4 Hz, 1H), 4.96 (t, *J* = 5.2 Hz, 1H), 3.59-3.51 (m, 1H), 3.25-3.17 (m, 2H), 2.86 (q, *J* = 11.6 Hz, 1H), 2.81-2.73 (m, 1H), 2.19 (t, *J* = 12.0 Hz, 1H), 1.71-1.64 (m, 1H), 1.56-1.47 (m, 1H), 1.07 (d, *J* = 6.4 Hz, 3H).

[0416] Using the procedure described for Example 47, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
74	MS m/z 520.0 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) 11.31(d, <i>J</i> =29.2 Hz, 1H), 7.47(d, <i>J</i> =2.0Hz, 1H), 7.36(q, <i>J</i> =3.6Hz, 1H), 7.07(q, <i>J</i> =6.8Hz, 1H), 5.99(t, <i>J</i> =9.2 Hz, 1H), 4.88 (q, <i>J</i> =8.4Hz, 1H), 3.58-3.45(m, 4H), 2.86 (q, <i>J</i> =12.0Hz, 1H), 2.79-2.71(m, 1H), 2.61(q, <i>J</i> =6.4Hz, 1H), 2.44-2.36(m, 1H), 2.12-2.06(m, 1H), 1.29-1.17 (m, 3H).

Example 48**Synthesis of Compound 329**

[0417] A mixture of (S)-6-chloro-1-isobutyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (200 mg, 0.76 mmol), 2-fluoro-6-(trifluoromethyl)pyridine (188 mg, 1.14 mmol), and DIPEA (0.4 mL, 2 mmol) in NMP (2 mL) was heated at 160 °C for 4 h under microwave. The reaction mixture was then quenched with water, extracted three times with ethyl acetate. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by Prep HPLC to afford 95 mg (30.6%) of the partially epimerized (1S)-6-chloro-1-(2-methylpropyl)-2-[6-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white solid. ESI-MS *m/z* 408.2 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.17 (s, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.28 (dd, *J* = 8.6, 2.4 Hz, 2H), 7.02-6.97 (m, 2H), 6.05 (d, *J* = 9.6 Hz, 1H), 4.32 (dd, *J* = 14.2, 4.0 Hz, 1H), 3.55-3.47 (m, 1H), 2.79-2.71 (m, 1H), 2.65 (dd, *J* = 15.6, 3.2 Hz, 1H), 1.92 (t, *J* = 10.6 Hz, 1H), 1.70-1.62 (m, 2H), 1.09 (d, *J* = 5.6 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H).

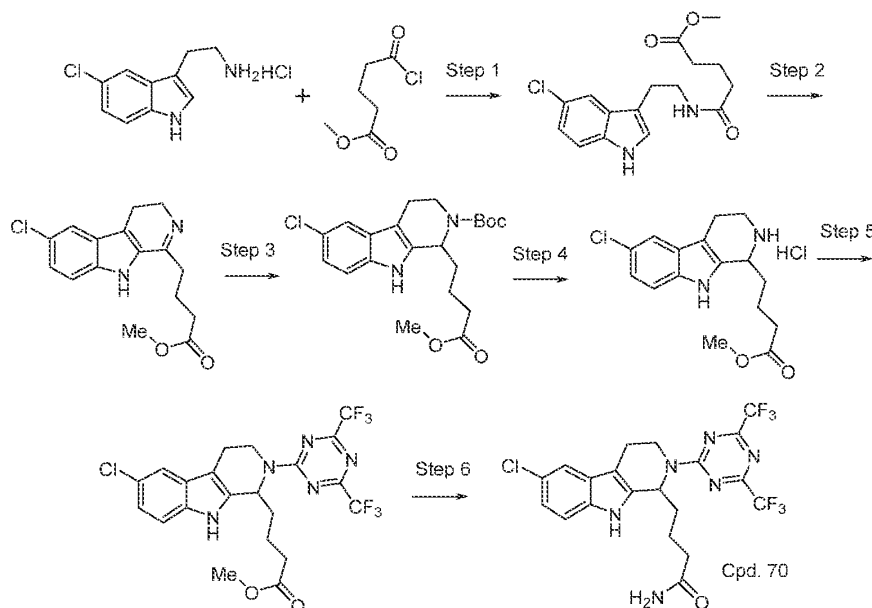
[0418] Using the procedure described for Example 48, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
325	ESI-MS <i>m/z</i> 447.9 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.11 (s, 1H), 8.30 (d, <i>J</i> = 5.1 Hz, 1H), 7.40 (d, <i>J</i> = 1.9 Hz, 1H), 7.31 (d, <i>J</i> = 8.6 Hz, 1H), 7.24 (s, 1H), 7.02 (dd, <i>J</i> = 8.6, 2.0 Hz, 1H), 6.84 (d, <i>J</i> = 5.1 Hz, 1H), 6.12 (d, <i>J</i> = 8.5 Hz, 1H), 4.43 (d, <i>J</i> = 10.2 Hz, 1H), 3.86 (d, <i>J</i> = 9.7 Hz, 1H), 3.79 (d, <i>J</i> = 9.2 Hz, 1H), 3.60-3.46 (m, 1H), 3.30-3.11 (m, 2H), 2.82-2.69 (m, 1H), 2.69-2.58 (m, 1H), 2.04-1.87 (m, 2H), 1.83-1.72 (m, 1H), 1.64 (s, 1H), 1.56 (d, <i>J</i> = 13.2 Hz, 1H), 1.36-1.19 (m, 2H).
326	ESI-MS <i>m/z</i> 448 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.19 (s, 1H), 8.31 (d, <i>J</i> = 5.6 Hz, 1H), 7.39 (d, <i>J</i> = 2 Hz, 1H), 7.30 (d, <i>J</i> = 8.4 Hz, 1H), 7.24 (s, 1H), 7.01 (q, <i>J</i> = 6.4 Hz, 1H), 6.84 (d, <i>J</i> = 4.8 Hz, 1H), 6.07 (d, <i>J</i> = 8.8 Hz, 1H), 4.43 (q, <i>J</i> = 10 Hz, 1H), 3.72-2.67 (m, 2H), 3.52-3.45 (m, 1H), 2.28-3.25 (m, 1H), 3.03 (t, <i>J</i> = 9.6 Hz, 1H), 2.73-2.69 (m, 1H), 2.67-2.64 (m, 1H), 2.12-2.09 (d, <i>J</i> = 8.8 Hz, 1H), 1.82-1.59 (m, 3 H), 1.37-1.23 (m, 3H). The relative configuration was not determined; NMR data was obtained without assignment to a particular diastereomer

Cpd	Data
327	ESI-MS m/z 448 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.08 (s, 1H), 8.30 (d, J = 5.2 Hz, 1H), 7.39 (d, J = 2 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.24 (s, 1H), 7.01 (q, J = 6.4 Hz, 1H), 6.84 (d, J = 5.2 Hz, 1H), 6.05-6.02 (m, 1H), 4.42 (q, J = 10.4 Hz, 1H), 4.07 (q, J = 8.8 Hz, 1H), 3.74-3.65 (m, 1H), 3.54-3.47 (m, 1H), 3.27-3.24 (m, 1H), 3.16 (t, J = 10.4 Hz, 1H), 2.78-2.70 (m, 1H), 2.66-2.61 (m, 1H), 1.82-1.77 (m, 3H), 1.66 (s, 1H), 1.50-1.42 (m, 2H), 1.25-1.18 (m, 1H). The relative configuration was not determined; NMR data was obtained without assignment to a particular diastereomer
328	ESI-MS m/z 448.0 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.18 (s, 1H), 7.79-7.71 (m, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.29 (dd, J = 8.7, 6.1 Hz, 2H), 7.05-6.97 (m, 2H), 6.06 (d, J = 9.5 Hz, 1H), 4.31 (dd, J = 14.2, 4.2 Hz, 1H), 3.90-3.75 (m, 2H), 3.61-3.48 (m, 1H), 3.27-3.09 (m, 2H), 2.80-2.71 (m, 1H), 2.66 (dd, J = 15.4, 3.4 Hz, 1H), 2.19 (s, 1H), 1.99-1.88 (m, 1H), 1.80-1.68 (m, 1H), 1.59 (d, J = 8.1 Hz, 1H), 1.52 (d, J = 13.1 Hz, 1H), 1.37-1.17 (m, 2H)
330	ESI-MS m/z 408.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.10 (s, 1H), 8.30 (d, J = 5.2 Hz, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.22 (s, 1H), 7.01 (dd, J = 8.8, 2.0 Hz, 1H), 6.83 (d, J = 4.8 Hz, 1H), 6.07 (d, J = 9.2 Hz, 1H), 4.44 (dd, J = 14.6, 3.6 Hz, 1H), 3.53-3.46 (m, 1H), 2.78-2.70 (m, 1H), 2.66-2.61 (m, 1H), 1.98-1.89 (m, 1H), 1.72-1.65 (m, 2H), 1.06 (d, J = 5.6 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H)

Example 49

Synthesis of Compound 70



[0419] **Step 1:** To a solution of 2-(5-chloro-1H-indol-3-yl)ethan-1-amine hydrochloride (1.2 g, 5.2 mmol) and TEA (2.2 mL, 16 mmol) in DCM (15 mL) was added methyl 5-chloro-5-oxopentanoate (1.0 g, 6.07 mmol) at 0 °C. The reaction mixture was slowly allowed to room

temperature overnight. After work-up, the residue was purified by chromatography on silica gel to afford 900 mg (54%) of methyl 5-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-5-oxopentanoate as a white solid. ESI-MS m/z 323.1 $[M+H]^+$.

[0420] **Step 2:** To a solution of methyl 5-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-5-oxopentanoate (1.8 g, 5.6 mmol) in acetonitrile (10 mL) was added phosphoryl chloride (2.6 mL, 28 mmol). The reaction mixture was stirred at 90 °C for 16 h. After the solvent was evaporated under the reduced pressure, the crude product (1.4 g, 82%) was directly used in the next step without further purification. ESI-MS m/z 305.1 $(M+H)^+$.

[0421] **Step 3:** To a solution of methyl 4-(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)butanoate (200 mg, 0.656 mmol) and di-*tert*-butyl decarbonate (220 mg, 0.978 mmol) in MeOH (3 mL) was added NaBH₄ (40 mg, 1.06 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel eluted with 0 to 25% ethyl acetate/hexane to afford 180 mg (67.4%) of *tert*-butyl 6-chloro-1-(4-methoxy-4-oxobutyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate as a white solid. ESI-MS m/z 407.2 $[M+H]^+$.

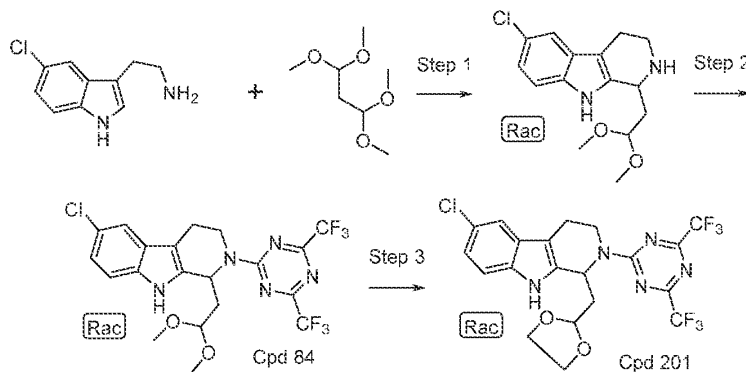
[0422] **Step 4:** To a solution of *tert*-butyl 6-chloro-1-(4-methoxy-4-oxobutyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (180 mg, 0.44 mmol) in DCM (4 mL) was added hydrogen chloride solution (4.0 M in dioxane, 1 mL, 4 mmol). The reaction mixture was stirred at room temperature for 2 h. After the solvent was evaporated under the reduced pressure, 130 mg (85.6%) of methyl 4-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butanoate hydrochloride was obtained as a yellow solid. ESI-MS m/z 307.1 $[M+H]^+$.

[0423] **Step 5:** To a mixture of methyl 4-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butanoate hydrochloride (130 mg, 0.38 mmol) and DMAP (100 mg, 0.81 mmol) in acetonitrile (2 mL) was added dropwise 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (130 mg, 0.39 mmol) at 0 °C under N₂. The reaction mixture was stirred at room temperature for 0.5 h. After the solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography on silica gel and then by prep HPLC to afford 130 mg (65.7%) of methyl 4-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butanoate as a white solid. ESI-MS m/z 522.1 $[M+H]^+$; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.21 (s, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.06 (dd, J = 13.2, 2.4 Hz, 1H), 5.90-5.87 (m, 1H), 4.94 (dd, J = 13.4, 4.4 Hz, 1H), 3.57 (s, 3H), 3.56-3.51 (m, 1H), 2.89-2.85 (m, 1H), 2.80-2.72 (m, 1H), 2.46-2.34 (m, 2H), 2.08-1.99 (m, 2H), 1.67-1.60 (m, 2H).

[0424] **Step 6:** A mixture of methyl 4-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butanoate (150 mg, 0.287 mmol) and ammonia solution (2.0 M in methanol, 3 mL, 6 mmol) was stirred at 75 °C for 48 h in a sealed tube. After the solvent was evaporated under the reduced pressure, the residue was purified by Prep HPLC to afford 90 mg (61.7%) of methyl 4-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}butanoate as a white solid. ESI-MS m/z 508.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.22 (s, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.21 (s, 1H), 7.07 (dd, J = 8.4, 2.0 Hz, 1H), 6.72 (s, 1H), 5.90-5.87 (m, 1H), 4.95 (dd, J = 13.2, 4.8 Hz, 1H), 3.58-3.51 (m, 1H), 2.89-2.85 (m, 1H), 2.80-2.72 (m, 1H), 2.15-2.04 (m, 3H), 1.99-1.91 (m, 1H), 1.68-1.55 (m, 2H).

[0425] Using the procedure described for Example 49, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
94	ESI-MS m/z 494.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.22 (s, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.06 (dd, J = 7.8, 2.0 Hz, 1H), 5.91-5.87 (m, 1H), 4.95 (dd, J = 13.4, 4.4 Hz, 1H), 4.55 (s, 1H), 3.60-3.51 (m, 2H), 2.89-2.84 (m, 1H), 2.80-2.73 (m, 1H), 2.07-1.98 (m, 2H), 1.58-1.51 (m, 1H), 1.48-1.39 (m, 3H), 0.86 (t, J = 8.0 Hz, 1H)
95	ESI-MS m/z 508.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.22 (s, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.06 (dd, J = 8.4, 2.0 Hz, 1H), 5.88 (dd, J = 9.2, 4.0 Hz, 1H), 4.94 (dd, J = 13.2, 4.8 Hz, 1H), 3.59-3.52 (m, 1H), 3.35 (t, J = 5.6 Hz, 2H), 2.89-2.84 (m, 1H), 2.80-2.72 (m, 1H), 2.07-1.96 (m, 2H), 1.40-1.29 (m, 6H)
103	ESI-MS m/z 535.9 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.23 (s, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.06 (q, J = 8.8 Hz, 1H), 5.88 (q, J = 9.0 Hz, 1H), 4.93 (q, J = 13.2 Hz, 1H), 3.53-3.59 (m, 1H), 2.84-2.88 (m, 1H), 2.71-2.78 (m, 1H), 2.17 (t, J = 7.2 Hz, 2H), 2.00-2.03 (m, 2H), 1.24-1.29 (m, 6H)
104	ESI-MS m/z 519.9 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.22 (s, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.06 (q, J = 8.8 Hz, 1H), 5.87-5.90 (m, 1H), 4.92-4.96 (m, 1H), 4.31-4.34 (m, 1H), 3.52-3.58 (m, 1H), 3.36-3.37 (m, 2H), 2.84-2.88 (m, 1H), 2.76-2.80 (m, 1H), 1.98-2.05 (m, 2H), 1.22-1.42 (m, 8H)
126	ESI-MS m/z 518.9 $[M-H]^-$; 1H NMR (DMSO- d_6) δ 11.33 (s, 1H), 7.47 (s, 1H), 7.40-7.17 (m, 2H), 7.12-6.95 (m, 1H), 6.76 (s, 1H), 6.01 (d, J = 10.7 Hz, 1H), 5.00-4.68 (m, 1H), 3.85-3.45 (m, 1H), 2.81 (d, J = 20.7 Hz, 2H), 2.18-1.64 (m, 5H), 1.38-0.98 (m, 4H)

Example 50**Synthesis of Compound 201**

[0426] **Step 1:** To a solution of 2-(5-chloro-1H-indol-3-yl)ethan-1-amine (1.0 g, 5.1 mmol) in MeOH (5 mL) and CHCl_3 (5 mL) was added 40 mg of hydrochloric acid to adjust pH to 2. 1,1,3,3-tetramethoxypropane (1.80 g, 11.0 mmol) was then added to the mixture. The reaction mixture was stirred at 75 °C for 16 h. After the solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography on silica gel eluted with 0 to 10% MeOH/DCM to afford a racemic mixture (0.70 g, 46%) of 6-chloro-1-(2,2-dimethoxyethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a yellow solid. ESI-MS m/z 295 $[\text{M}+\text{H}]^+$.

[0427] **Step 2:** To a mixture of 6-chloro-1-(2,2-dimethoxyethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (0.50 g, 1.7 mmol) and DMAP (0.24 g, 1.9 mmol) in acetonitrile (5 mL) was added dropwise 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (0.60 g, 1.8 mmol) at 0 °C under N_2 . The reaction mixture was stirred at room temperature for 2 h. After the solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography on silica gel eluted with 0 to 20% ethyl acetate/hexane to afford a racemic mixture (0.30 g, 35%) of Compound 84 2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-1-(2,2-dimethoxyethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole. ESI-MS m/z 508.2 $[\text{M}-\text{H}]^-$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.26 (s, 1H), 7.49 (s, 1H), 7.35 (d, $J = 8.6$ Hz, 1H), 7.08 (d, $J = 8.7$ Hz, 1H), 6.07 (dd, $J = 9.7, 3.7$ Hz, 1H), 4.95 (dd, $J = 13.3, 5.1$ Hz, 1H), 4.53 (t, $J = 5.5$ Hz, 1H), 3.63 (dt, $J = 12.7, 7.3$ Hz, 1H), 3.28 (s, 3H), 3.13 (s, 3H), 2.95-2.72 (m, 2H), 2.29 (ddd, $J = 19.8, 12.9, 7.4$ Hz, 2H).

[0428] **Step 3:** A mixture of 2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-1-(2,2-dimethoxyethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (100 mg, 0.196 mmol), *p*-toluenesulfonic acid (10 mg, 0.057 mmol), trimethyl orthoformate (10 mg, 0.094 mmol), and

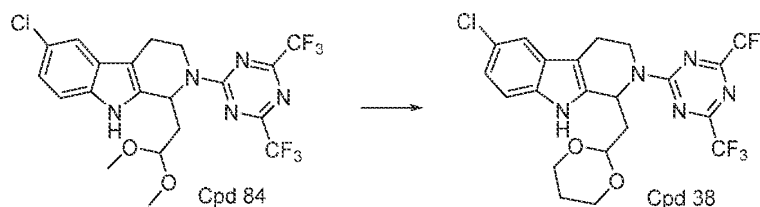
ethylene glycol (40 mg, 0.64 mmol) in toluene (3 mL) was stirred at 80 °C for 3 h. After the solvent was evaporated under the reduced pressure, the residue was purified by prep HPLC to afford a racemic mixture (70 mg, 70%) of 2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxolan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white solid. ESI-MS m/z 506 [M-H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.23 (s, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.07 (q, J = 6.4 Hz, 1H), 6.11 (q, J = 5.6 Hz, 1H), 4.98-4.93 (m, 2H), 3.86-3.80 (m, 2H), 3.75-3.58 (m, 3H), 2.87 (q, J = 12.0 Hz, 1H), 2.80-2.72 (m, 1H), 2.43-2.30 (m, 2H).

[0429] Using the procedure described for Example 50, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
202	ESI-MS m/z 439.2 [M+H] ⁺ , 437.4 [M-H] ⁻ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ : 11.16 (br s, 1H), 8.72 (br d, J =4.3 Hz, 1H), 7.44 (s, 1H), 7.33 (d, J =8.5 Hz, 1H), 6.99-7.09 (m, 2H), 6.11 (br s, 1H), 4.81-5.09 (m, 2H), 3.86 (br s, 2H), 3.62-3.78 (m, 2H), 3.37-3.52 (m, 1H), 2.65-2.79 (m, 2H), 2.25-2.36 (m, 2H)
203	ESI-MS m/z 439.4 [M-H] ⁻ ; ¹ H NMR (DMSO- <i>d</i> ₆) δ : 11.18 (s, 1H), 8.74 (br d, J =4.3 Hz, 1H), 7.43 (s, 1H), 7.32 (d, J =8.5 Hz, 1H), 7.01-7.09 (m, 2H), 6.07 (br s, 1H), 4.83-5.04 (m, 1H), 4.48 (t, J =5.3 Hz, 1H), 3.39-3.49 (m, 1H), 3.26-3.29 (m, 3H), 3.13 (s, 3H), 2.66-2.78 (m, 2H), 2.23 (br t, J =6.0 Hz, 2H)
204	ESI-MS m/z 425.2 [M+H] ⁺ , 423.4 [M-H] ⁻ ; ¹ H NMR (DMSO- <i>d</i> ₆) Complex mixture of diastereomers. Characteristic signals are provided, δ : 11.03-11.31 (m, 1H), 8.73 (br s, 1H), 7.43 (br d, J =9.2 Hz, 1H), 7.25-7.37 (m, 1H), 6.95-7.14 (m, 2H), 5.88-6.31 (m, 1H), 4.77-5.03 (m, 1H), 3.15-3.23 (m, 2H), 3.09 (br s, 2H), 2.65-2.79 (m, 2H), 2.18-2.36 (m, 1H), 2.03 (br d, J =5.2 Hz, 1H), 1.93 (br s, 1H), 1.29 (br s, 2H), 1.10 (br d, J =5.8 Hz, 2H)
236	ESI-MS m/z 464.2 [M+H] ⁺ ; ¹ H NMR (DMSO- <i>d</i> ₆) Complex mixture of diastereomers. Only characteristic signals are provided, δ : 11.19 (br s), 8.74 (br s), 7.44 (br s), 7.34 (br t, J =7.9 Hz), 7.04 (br d, J =7.0 Hz), 6.06 (br s), 5.94 (br d, J =10.1 Hz), 4.97 (br s), 4.87 (br s).

Example 51

Synthesis of Compound 38

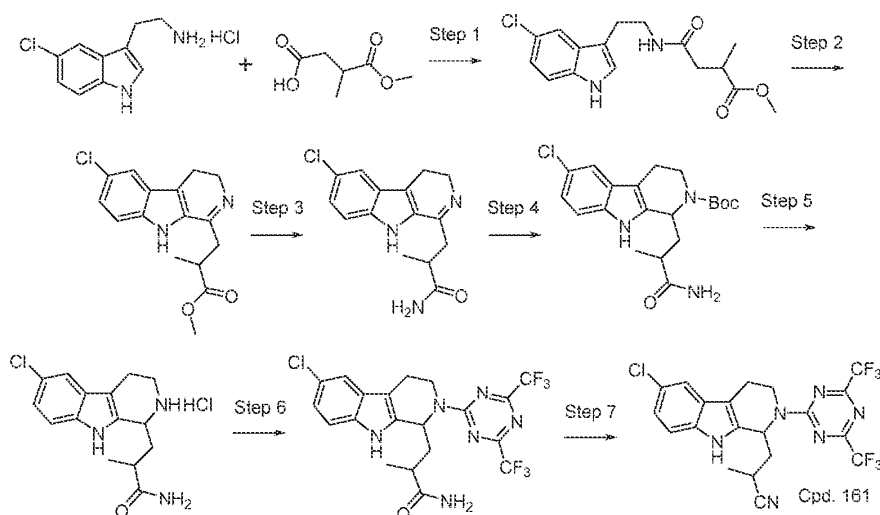


[0430] A mixture of Compound 84 2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-1-(2,2-dimethoxyethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (120 mg, 0.235 mmol), *p*-

toluenesulfonic acid (10 mg, 0.057 mmol), trimethyl orthoformate (12 mg, 0.113 mmol), and propane-1,3-diol (55 mg, 0.72 mmol) in toluene (3 mL) was stirred at 80 °C for 3 h. After the solvent was evaporated under the reduced pressure, the residue was purified by prep HPLC to afford 90 mg (73%) of Compound 38, 2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white solid. ESI-MS m/z 520 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.28 (s, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 7.06 (q, J = 6.8 Hz, 1H), 6.11 (q, J = 7.2 Hz, 1H), 4.92 (q, J = 8.4 Hz, 1H), 4.65 (q, J = 2.0 Hz, 1H), 3.98 (q, J = 6.8 Hz, 1H), 3.84 (q, J = 6.4 Hz, 1H), 3.69-3.52 (m, 3H), 2.85 (q, J = 12.0 Hz, 1H), 2.79-2.71 (m, 1H), 2.31-2.17 (m, 2H), 1.87-1.77 (m, 1H), 1.31 (d, J = 13.2 Hz, 1H).

Example 52

Synthesis of Compound 161



[0431] **Step 1:** A mixture of 2-(5-chloro-1H-indol-3-yl)ethan-1-amine hydrochloride (1.5 g, 6.5 mmol), 4-methoxy-3-methyl-4-oxobutanoic acid (1.1 g, 7.5 mmol), HATU (3.8 g, 9.8 mmol), and DIPEA (3.4 mL, 19 mmol) in DMF (20 mL) was stirred at room temperature for 3 h. The reaction mixture was then quenched with water, extracted three times with ethyl acetate. The combined organic phase was dried over Na_2SO_4 . After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel to afford 1.4 g (67%) of methyl 4-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-2-methyl-4-oxobutanoate as a brown oily material. ESI-MS m/z 323.1 $(M+H)^+$.

[0432] **Step 2:** To a solution of methyl 4-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-2-methyl-4-oxobutanoate (1.3 g, 4.0 mmol) in acetonitrile (15 mL) was added phosphoryl chloride (2.0

mL, 22 mmol). The reaction mixture was stirred at room temperature for 5 h. After the solvent was evaporated under the reduced pressure, the crude product (0.9 g, 70%) was directly used in the next step without further purification. ESI-MS m/z 305.1 $[M+H]^+$.

[0433] **Step 3:** A mixture of methyl 3-(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-2-methylpropanoate (0.9 g, 3 mmol) and ammonia solution (2.0 M in methanol, 10 mL, 20 mmol) was stirred at room temperature overnight in a sealed tube. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel to afford 0.7 g (80%) of 3-(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-2-methylpropanamide as a yellow solid. ESI-MS m/z 290.1 $[M+H]^+$.

[0434] **Step 4:** To a solution of 3-(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-2-methylpropanamide (80 mg, 0.276 mmol) and di-*tert*-butyl decarbonate (0.1 mL, 0.5 mmol) in MeOH (2 mL) was added NaBH₄ (50 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for 8 h and then quenched with water and brine, extracted twice with ethyl acetate. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel eluted with 0 to 100% ethyl acetate/hexane to afford 65 mg (60%) of *tert*-butyl 1-(3-amino-2-methyl-3-oxopropyl)-6-chloro-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate. ESI-MS m/z 292.2 $[M-100+H]^+$.

[0435] **Step 5:** To a solution of *tert*-butyl 1-(3-amino-2-methyl-3-oxopropyl)-6-chloro-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (65 mg, 0.166 mmol) in DCM (2 mL) was added hydrogen chloride solution (4.0 M in dioxane, 0.5 mL, 2 mmol). The reaction mixture was stirred at room temperature for 2 h. After the solvent was evaporated under the reduced pressure, The crude product (50 mg, 92%) was obtained as a yellow solid. ESI-MS m/z 292.2 $[M+H]^+$.

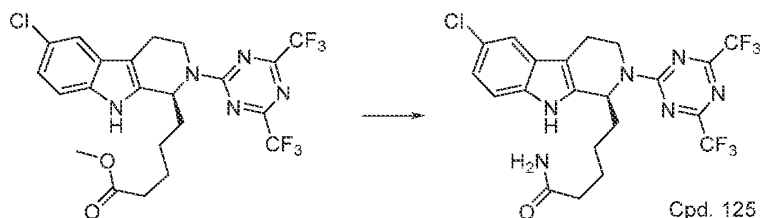
[0436] **Step 6:** To a mixture of 3-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropanamide hydrochloride (50 mg, 0.152 mmol) and DMAP (40 mg, 0.324 mmol) in acetonitrile (2 mL) was added dropwise 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (50 mg, 0.15 mmol) at 0 °C under N₂. The reaction mixture was stirred at room temperature for 2 h. After the solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography on silica gel to afford 50 mg (64.7%) of 3-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropanamide as a brown solid. ESI-MS m/z 507 $[M+H]^+$.

[0437] **Step 7:** To a solution of 3-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropanamide (50 mg, 0.098 mmol)

and DIPEA (0.04 mL, 0.2 mmol) in THF (2 mL) was added trifluoroacetic anhydride (0.02 mL, 0.1 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h. After the solvent was evaporated under the reduced pressure, the residue was purified by prep HPLC to afford 3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanenitrile. ESI-MS m/z 486.9 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.47 (s, 0.7 H), 11.25 (s, 0.3 H), 7.50-7.47 (m, 1H), 7.39 (d, J = 8.8 Hz, 0.3H), 7.36 (d, J = 8.8 Hz, 0.7H), 7.10-7.07 (m, 1H), 6.11-6.08 (m, 0.7H), 5.99-5.95 (m, 0.3 H), 4.95-4.91 (m, 1H), 3.65-3.56 (m, 1H), 3.03-2.98 (m, 1H), 2.89-2.77 (m, 2H), 2.67-2.66 (m, 0.3H), 2.33-2.28 (m, 1.7 H), 1.44 (d, J = 6.8 Hz, 1H), 1.29 (d, J = 7.2 Hz, 2H).

[0438] Using the procedure described for Example 52, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

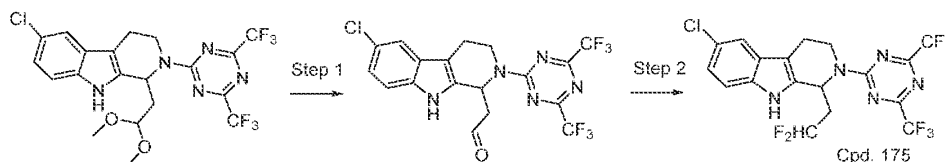
Cpd	Data
138A or 138B	ESI-MS m/z 507.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.28 (s, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.10-7.06 (m, 2H), 6.66 (s, 1H), 5.99-5.96 (m, 1H), 4.87 (dd, J = 13.2, 4.8 Hz, 1H), 3.60-3.52 (m, 1H), 2.87-2.82 (m, 1H), 2.79-2.74 (m, 1H), 2.32-2.23 (m, 2H), 2.02-1.96 (m, 1H), 1.21 (d, J = 6.8 Hz, 3H). The relative configuration was not determined; NMR data was obtained without assignment to a particular diastereomer
162A or 162B	ESI-MS m/z 486.9 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.25 (s, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.09 (dd, J = 8.6, 2.0 Hz, 1H), 5.97 (dd, J = 10.4, 2.0 Hz, 1H), 4.93 (dd, J = 13.2, 4.8 Hz, 1H), 3.69-3.62 (m, 1H), 3.02-2.97 (m, 1H), 2.89-2.85 (m, 1H), 2.80-2.72 (m, 1H), 2.54-2.47 (m, 1H), 2.24-2.18 (m, 1H), 1.44 (d, J = 7.2 Hz, 3H). The relative configuration was not determined; NMR data was obtained without assignment to a particular diastereomer
163A or 163B	ESI-MS m/z 486.9 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.46 (s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.08 (dd, J = 8.4, 2.0 Hz, 1H), 6.11-6.08 (m, 1H), 4.93 (dd, J = 13.4, 4.8 Hz, 1H), 3.64-3.57 (m, 1H), 3.03-2.98 (m, 1H), 2.89-2.84 (m, 1H), 2.82-2.73 (m, 1H), 2.54-2.47 (m, 1H), 2.32-2.28 (m, 1H), 1.29 (d, J = 6.8 Hz, 3H). The relative configuration was not determined; NMR data was obtained without assignment to a particular diastereomer

Example 53**Synthesis of Compound 125**

[0439] A mixture of methyl (S)-5-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)pentanoate (200 mg, 0.373 mmol) and ammonia solution (2.0 M in methanol, 5 mL, 10 mmol) was stirred at 75 °C for 5 days in a sealed tube. After the solvent was evaporated under the reduced pressure, the residue was purified by prep HPLC to afford 94 mg (48.3%) of 5-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)pentanamide as a white solid material. ESI-MS m/z 521.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.23 (s, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.18 (s, 1H), 7.07 (dd, J = 8.6, 2.4 Hz, 1H), 6.68 (s, 1H), 5.89 (dd, J = 8.4, 4.8 Hz, 1H), 4.94 (dd, J = 13.2, 4.8 Hz, 1H), 3.59-3.52 (m, 1H), 2.87 (dd, J = 15.0, 3.2 Hz, 1H), 2.80-2.73 (m, 1H), 2.06-1.99 (m, 4H), 1.63-1.51 (m, 2H), 1.42-1.31 (m, 2H).

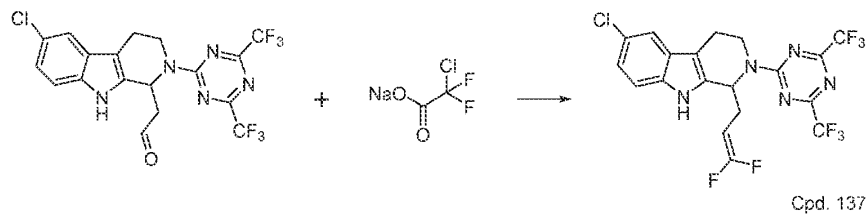
[0440] Using the procedure described for Example 53, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
124	ESI-MS m/z 507.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.22 (s, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.21 (s, 1H), 7.07 (dd, J = 8.4, 2.0 Hz, 1H), 6.72 (s, 1H), 5.90-5.87 (m, 1H), 4.95 (dd, J = 13.2, 4.8 Hz, 1H), 3.58-3.51 (m, 1H), 2.89-2.85 (m, 1H), 2.80-2.72 (m, 1H), 2.15-2.04 (m, 3H), 1.99-1.91 (m, 1H), 1.68-1.55 (m, 2H)
127	ESI-MS m/z 535.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.23 (s, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.19 (s, 1H), 7.06 (q, J = 8.6 Hz, 1H), 6.67 (s, 1H), 5.86-5.89 (m, 1H), 4.92-4.96 (m, 1H), 3.52-3.59 (m, 1H), 2.84-2.88 (m, 1H), 2.75-2.79 (m, 1H), 2.00 (t, J = 7.2 Hz, 4H), 1.22-1.47 (m, 6H).

Example 54**Synthesis of Compound 175**

[0441] **Step 1:** A mixture of Compound 84 2-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-1-(2,2-dimethoxyethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (0.40 g, 0.78 mmol) and TFA (0.11 mL, 1.5 mmol) in DCM (2 mL) and water (0.1 mL) was stirred at room temperature for 16 h. NaHCO_3 was added to the mixture to adjust pH to 7. After aqueous work-up, the residue was purified by flash chromatography on silica gel eluted with 0 to 20% ethyl acetate/hexanes to afford 0.30 g (82%) of 2-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetaldehyde. ESI-MS m/z 462 $[\text{M}-\text{H}]^-$.

[0442] **Step 2:** To a solution of 2-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetaldehyde (100 mg, 0.216 mmol) in DCM (2 mL) was added dropwise Bis(2-methoxyethyl)aminosulfur trifluoride (50wt% in THF, 150 mg, 0.339 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After the solvent was evaporated under the reduced pressure, the residue was purified by Prep HPLC to afford 68 mg (64.9%) of 2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2,2-difluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a yellow solid. ESI-MS m/z 483.9 $[\text{M}-\text{H}]^-$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.33 (s, 1H), 7.51 (d, $J = 1.6$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.09 (q, $J = 6.4$ Hz, 1H), 6.35-6.07 (m, 2H), 4.95 (q, $J = 8.8$ Hz, 1H), 3.69-3.62 (m, 1H), 2.88 (q, $J = 12.0$ Hz, 1H), 2.81-2.66 (m, 2H), 2.60-2.54 (m, 1H).

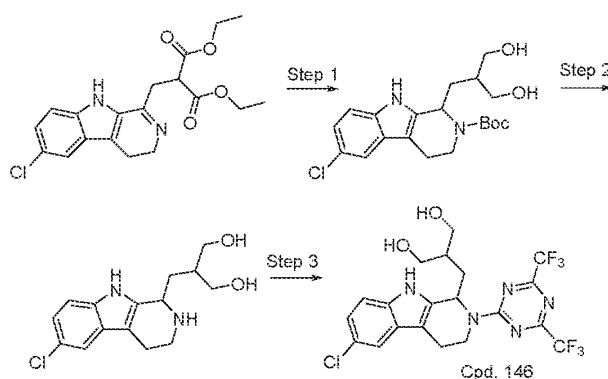
Example 55**Synthesis of Compound 137**

[0443] A mixture of 2-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetaldehyde (80 mg, 0.17 mmol), triphenylphosphine

(140 mg, 0.53 mmol), and sodium 2-chloro-2,2-difluoroacetate (80 mg, 0.52 mmol) in DMF (2 mL) was stirred at 100 °C for 2 h. After the solvent was evaporated under the reduced pressure, the residue was purified by Prep HPLC to afford 10 mg (12%) of 2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(3,3-difluoroprop-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a yellow solid. ESI-MS m/z 495.9 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 9.70 (s, 1H), 8.06 (s, 1H), 7.69 (d, $J = 2.0$ Hz, 1H), 7.41 (q, $J = 6.4$ Hz, 1H), 6.44 (d, $J = 8.0$ Hz, 1H), 4.95 (q, $J = 7.6$ Hz, 1H), 4.63 (t, $J = 25.6$ Hz, 1H), 3.70-3.62 (m, 1H), 2.96 (q, $J = 12.4$ Hz, 1H), 2.88-2.66 (m, 3H).

Example 56

Synthesis of Compound 146



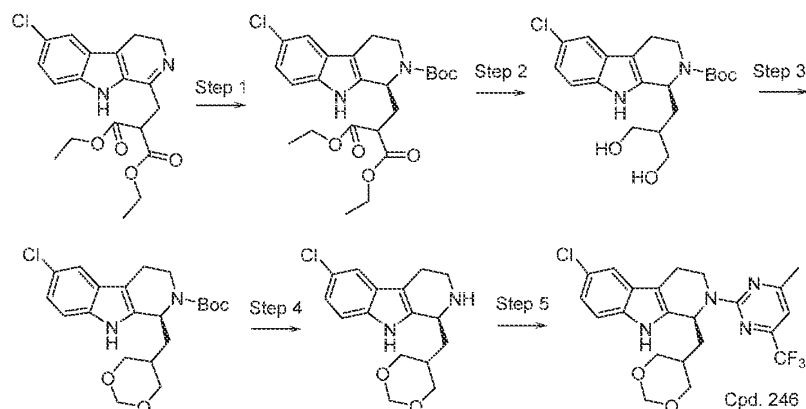
[0444] **Step 1:** To a solution of diethyl 2-((6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)methyl)malonate (1.00 g, 2.65 mmol), and di-*tert*-butyl decarbonate (3 mL, 14 mmol) in MeOH (20 mL) was added $NaBH_4$ (0.51 g, 13 mmol). The reaction mixture was stirred at room temperature for 12 h and then quenched with water and brine, extracted twice with ethyl acetate. The combined organic phase was dried over Na_2SO_4 . After the solvent was evaporated under the reduced pressure, the residue was dissolved in MeOH (20 mL) and then $NaBH_4$ (0.45 g, 12 mmol) was added. The reaction mixture was stirred at room temperature for 3 h and then quenched with water and brine, extracted twice with ethyl acetate. The combined organic phase was dried over Na_2SO_4 . After the solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography on silica gel eluted with 0 to 10% MeOH/DCM to afford 300 mg (32%) of *tert*-butyl 6-chloro-1-(3-hydroxy-2-(hydroxymethyl)propyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate as a yellow solid. ESI-MS m/z 296 $[M-100+H]^+$.

[0445] **Step 2:** A mixture of tert-butyl 6-chloro-1-(3-hydroxy-2-(hydroxymethyl)propyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole-2-carboxylate (300 mg, 0.76 mmol) and TFA (60 μ L, 0.80 mmol) in DCM (10 mL) was stirred at room temperature for 3 h. The reaction mixture was then quenched with ammonia solution (7 N in MeOH). After the solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography on silica gel eluted with 0 to 10% MeOH/DCM to afford 180 mg (80%) of 2-((6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)propane-1,3-diol as a yellow oily material used as is for the next step. ESI-MS m/z 296 $[M+H]^+$.

[0446] **Step 3:** To a mixture of 2-((6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)propane-1,3-diol (140 mg, 0.475 mmol) and DMAP (70 mg, 0.573 mmol) in acetonitrile (10 mL) was added dropwise 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (175 mg, 0.523 mmol) at 0 $^{\circ}$ C under N_2 . The reaction mixture was stirred at room temperature for 3 h. After the solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography on silica gel eluted with 0 to 10% MeOH/DCM and then by prep HPLC to afford 90 mg (37%) of 2-((2-([4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)propane-1,3-diol as a white solid. ESI-MS m/z 510.0 $[M+H]^+$; 1H NMR (400 MHz, $DMSO-d_6$) δ 11.15 (s, 1H), 7.46 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.02-6.05 (m, 1H), 4.92-4.96 (m, 1H), 4.29-4.44 (m, 2H), 3.58-3.63 (m, 3H), 3.46-3.48 (m, 1H), 3.32-3.35 (m, 1H), 2.79-2.88 (m, 2H), 1.99-2.00 (m, 2H), 1.57 (br. s, 1H).

Example 57

Synthesis of Compound 246



[0447] **Step 1:** To a round bottom flask was charged diethyl 2-[(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)methyl]propanedioate (A, 7.0 g, 19 mmol), acetonitrile (100 mL),

and $\text{RuCl}[(R,R)\text{-TsDPEN}](\text{mesitylene})$ (350 mg, 0.5560 mmol, 99 mass%, 0.030). The reaction was cooled to 0 °C. Formic acid triethylamine complex 5:2 (9.5 mL). The reaction was allowed to warm to room temperature for 30 minutes. TLC analysis showed the reaction had reached completion. The reaction was diluted with EtOAc and saturated aqueous sodium bicarbonate was added until the pH ~ 8. After reaching pH ~8 Boc_2O (5.5g, 25 mmol) was added in a solution of acetonitrile (30 mL). The reaction was allowed to stir at room temperature for 5 hours. At which point the reaction was judged complete by LCMS. The mixture was extracted with EtOAc and concentrated. The crude was purified by silica gel chromatography (PET ether: EtOAc 19:1) to give a yellow oil (350 mg, 3% yield) which was used directly in the next step without further analysis or purification.

[0448] **Step 2:** To a 100 mL single neck round-bottomed flask was charged diethyl 2-[[$(1S)$ -2-*tert*-butoxycarbonyl-6-chloro-1,3,4,9-tetrahydropyrido[3,4-*b*]indol-1-yl]methyl]propanedioate (10.0 g, 20.9 mmol), THF (100 mL), then lithium borohydride (2 mol/L) in THF (63.0 mL, 126 mmol). The reaction mixture was stirred and heated to 60 °C for 3 hours. After 3 hours the reaction was judged complete by LCMS. The reaction was quenched with saturated ammonium chloride aqueous solution and extracted with ethyl acetate (3x). The organic phase was concentrated to give a residue which was purified by silica gel chromatography to obtain the desired product (6.5 g, 79% yield) as off-yellow solid. The material was used directly in the next step without further purification or analysis.

[0449] **Step 3:** To a 250 mL single neck round-bottomed flask was charged *tert*-butyl $(1S)$ -6-chloro-1-[3-hydroxy-2-(hydroxymethyl)propyl]-1,3,4,9-tetrahydropyrido[3,4-*b*]indole-2-carboxylate (2.0 g, 5.1 mmol), lithium bromide (650 mg, 7.4846 mmol), PTSA (1.3 g, 7.5 mmol), THF (100 mL) and dimethoxymethane (2.0 mL). The the mixture was stirred at room temperature for 12 hours and the reaction was judged complete by LCMS. The reaction was quenched with saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate (3x). The organic phase was concentrated to give the crude product (1.5 g) which was used directly in the next step without further purification of analysis.

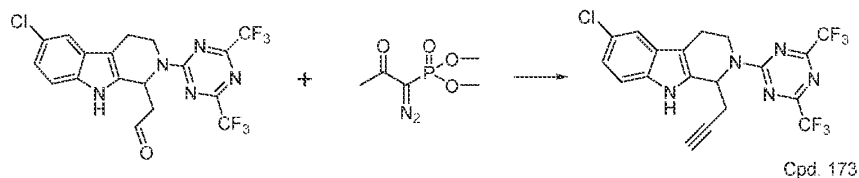
[0450] **Step 4:** To a 100 mL single neck round-bottomed flask was charged *tert*-butyl $(1S)$ -6-chloro-1-(1,3-dioxan-5-ylmethyl)-1,3,4,9-tetrahydropyrido[3,4-*b*]indole-2-carboxylate (1.5 g, 3.7 mmol), DCM (30.0 mL) and TFA (3.0 mL). The reaction was stirred at room temperature for 3 hours and was judged to be complete by LCMS. Then the mixture was concentrated directly and dissolved in ammonia in methanol. The solution was then concentrated to dryness. The residue was purified by silica gel chromatography to give the desired product

(900 mg, 80% yield) as off-yellow solid which was used in the next step without further purification.

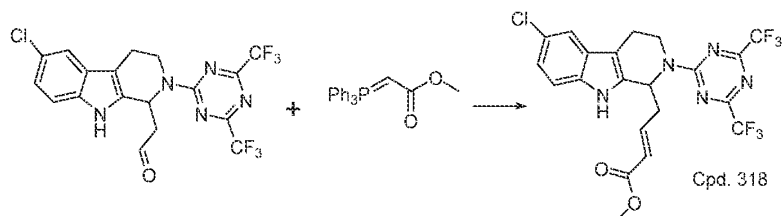
[0451] **Step 5:** To a scintillation vial was charged (1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (60 mg, 0.2 mmol), 1-butanol (5 mL), then 2-chloro-4-methyl-6-(trifluoromethyl)pyrimidine (46 mg, 0.23 mmol) and DIPEA (102 mg, 0.79 mmol). The reaction was topped with nitrogen and sealed. Heated to 120 °C for 16 hours. The reaction was then poured into EtOAc and extracted with DI water (2x) brine (2x). The organics were dried over sodium sulfate and concentrated. Purified by prep-HPLC to give the title compound (1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (59 mg, 65.0 % yield) as white solid. ESI-MS m/z 467.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.18 (s, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.00 (s, 1H), 5.92 (d, J = 36.0 Hz, 1H), 5.00-4.82 (m, 2H), 4.62 (d, J = 5.6 Hz, 1H), 4.28 (s, 1H), 3.89 (d, J = 11.2 Hz, 1H), 3.65 (t, J = 8.8 Hz, 1H), 3.43-3.33 (m, 2H), 2.71-2.70 (m, 2H), 2.45 (s, 3H), 1.90-1.75 (m, 3H).

[0452] Using the procedure described for Example 57, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
37	ESI-MS m/z 504.1 $[M-H]^-$; 1H NMR (DMSO- d_6) δ : 11.18 (s, 1H), 7.34 (dd, J = 8.9, 4.4 Hz, 1H), 7.19 (dd, J = 9.8, 2.3 Hz, 1H), 6.84-6.96 (m, 1H), 5.80-5.93 (m, 1H), 4.87-4.96 (m, 1H), 4.84 (d, J = 6.0 Hz, 1H), 4.67 (d, J = 6.0 Hz, 1H), 4.14-4.29 (m, 1H), 3.84-3.95 (m, 1H), 3.67-3.77 (m, 1H), 3.53-3.66 (m, 1H), 3.40-3.48 (m, 1H), 2.82 (br d, J = 4.3 Hz, 2H), 1.96-2.12 (m, 1H), 1.84-1.96 (m, 2H)
250	ESI-MS m/z 413.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.14 (s, 1H), 8.28 (d, 1H, J = 4.8 Hz), 7.39 (d, 1H, J = 1.6 Hz), 7.30 (d, 1H, J = 8.4 Hz), 7.02 (q, 1H, J = 6.8 Hz), 6.54 (d, 1H, J = 5.2 Hz), 5.98 (d, 1H, J = 7.2 Hz), 4.92 (d, 1H, J = 2 Hz), 4.89 (d, 1H, J = 4 Hz), 4.61 (d, 1H, J = 6 Hz), 4.31 (t, 1H, J = 2.8 Hz), 3.39 (q, 1H, J = 7.2 Hz), 3.62 (t, 1H, J = 4 Hz), 3.42-3.37 (m, 1H), 3.32-3.30 (m, 1H), 2.68 (d, 2H, J = 10.4 Hz), 2.59-2.54 (m, 2H), 1.93-1.75 (m, 3H), 1.19 (t, 3H, J = 7.6 Hz).

Example 58**Synthesis of Compound 173**

[0453] A mixture of 2-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetaldehyde (100 mg, 0.216 mmol), dimethyl (1-diazo-2-oxopropyl)phosphonate (100 mg, 0.500 mmol), and K_2CO_3 (60 mg, 0.434 mmol) in MeOH (2 mL) was stirred at room temperature for 2 h. After work-up, the residue was purified by prep HPLC to afford 45 mg (45%) of 2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(prop-2-yn-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white solid material. ESI-MS m/z 457.9 $[M-H]^-$; 1H NMR (400 MHz, $DMSO-d_6$) δ 11.17 (s, 1H), 7.52 (d, $J = 2.0$ Hz, 1H), 7.39 (d, $J = 8.8$ Hz, 1H), 7.10 (q, $J = 6.4$ Hz, 1H), 6.01 (t, $J = 6.0$ Hz, 1H), 5.03 (q, $J = 8.4$ Hz, 1H), 3.82-3.75 (m, 1H), 3.07-3.00 (m, 2H), 2.93 (q, $J = 12.8$ Hz, 1H), 2.85 (t, $J = 2.4$ Hz, 1H), 2.80-2.72 (m, 1H).

Example 59**Synthesis of Compound 318**

[0454] A mixture of 2-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetaldehyde (100 mg, 0.216 mmol) and methyl (triphenylphosphoranylidene)acetate (90 mg, 0.269 mmol) in acetonitrile (2 mL) was stirred at 90 °C for 16 h. After the solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography on silica gel eluted with 0 to 20% ethyl acetate/hexanes and then by prep HPLC to afford 16 mg of methyl (2E)-4-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}but-2-enoate as a white solid. ESI-MS m/z 517.9 $[M-H]^-$; 1H NMR (400 MHz, $DMSO-d_6$) δ 11.26 (s, 1H), 7.50 (d, $J = 2.0$ Hz, 1H), 7.39 (d, $J = 8.8$ Hz, 1H), 7.09 (q, $J = 6.4$ Hz, 1H),

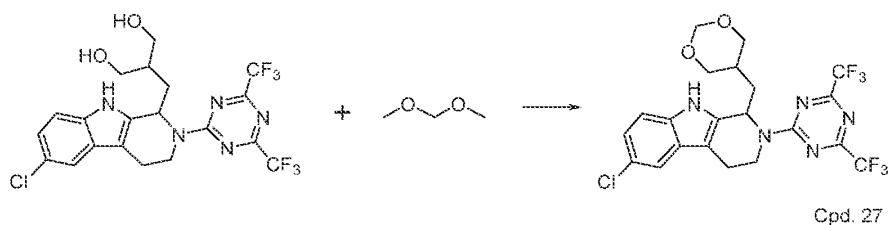
6.88-6.80 (m, 1H), 6.01-5.94 (m, 2H), 4.98 (q, $J = 8.8$ Hz, 1H), 3.56 (s, 3H), 3.51 (q, $J = 8.8$ Hz, 1H), 3.05-2.95 (m, 2H), 2.91 (q, $J = 12.0$ Hz, 1H), 2.79-2.71 (m, 1H).

[0455] Using the procedure described for Example 59, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

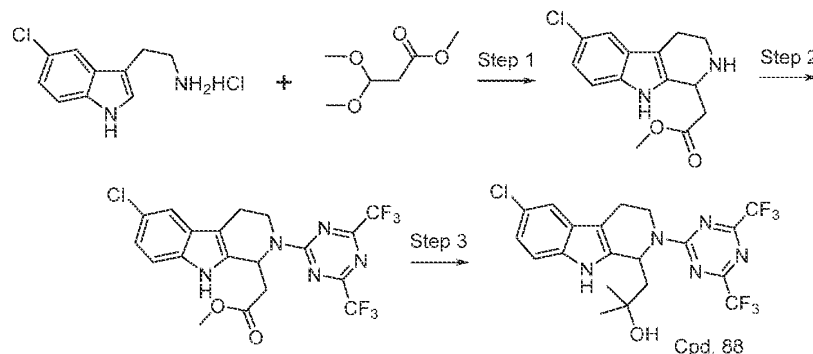
Cpd	Data
319	ESI-MS m/z 517.8 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.26 (s, 1H), 7.50 (d, $J = 2.0$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 7.09 (q, $J = 6.4$ Hz, 1H), 6.41-6.34 (m, 1H), 6.07 (q, $J = 3.6$ Hz, 1H), 5.85 (d, $J = 11.2$ Hz, 1H), 4.94 (q, $J = 8.8$ Hz, 1H), 3.58 (s, 3H), 3.53 (q, $J = 8.8$ Hz, 1H), 3.43-3.39 (m, 2H), 2.90 (q, $J = 12.0$ Hz, 1H), 2.80-2.72 (m, 1H).

Example 60

Synthesis of Compound 27



[0456] A mixture of 2-((2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)propane-1,3-diol (60.0 mg, 0.118 mmol), LiBr (12.3 mg, 0.142 mmol), dimethoxymethane (13.5 mg, 0.177 mmol), and p-TsOH (31.0 mg, 0.178 mmol) in DCM (10 mL) was stirred at room temperature for 3 h. The reaction mixture was quenched with aqueous $NaHCO_3$ solution and extracted three times with DCM. The combined organic phase was dried over Na_2SO_4 . After the solvent was evaporated under the reduced pressure, the residue was purified by Prep HPLC to afford 14 mg (23%) of 2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white solid. ESI-MS m/z 552.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.28 (s, 1H), 7.47 (d, $J = 2.0$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.07 (d, $J = 6.8$ Hz, 1H), 5.88 (d, $J = 7.2$ Hz, 1H), 4.88-4.93 (m, 1H), 4.82 (d, $J = 6.0$ Hz, 1H), 4.66 (d, $J = 6.0$ Hz, 1H), 4.22 (d, $J = 8.0$ Hz, 1H), 3.89 (d, $J = 11.2$ Hz, 1H), 3.70-3.73 (m, 1H), 3.56-3.63 (m, 1H), 3.42-3.45 (m, 1H), 2.74-2.87 (m, 2H), 1.99-2.03 (m, 1H), 1.86-1.92 (m, 2H).

Example 61**Synthesis of Compound 88**

[0457] **Step 1:** A mixture of 2-(5-chloro-1H-indol-3-yl)ethan-1-amine hydrochloride (2.3 g, 10 mmol), methyl 3,3-dimethoxypropanoate (4.4 g, 30 mmol), and TFA (3.4 g, 30 mmol) in 1,2-dichloroethane (30 mL) was stirred at 80 °C overnight. The reaction mixture was cooled to room temperature and filtered to afford 2.0 g (72%) of methyl 2-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetate as a white solid. ESI-MS m/z 279 ($M+H$)⁺.

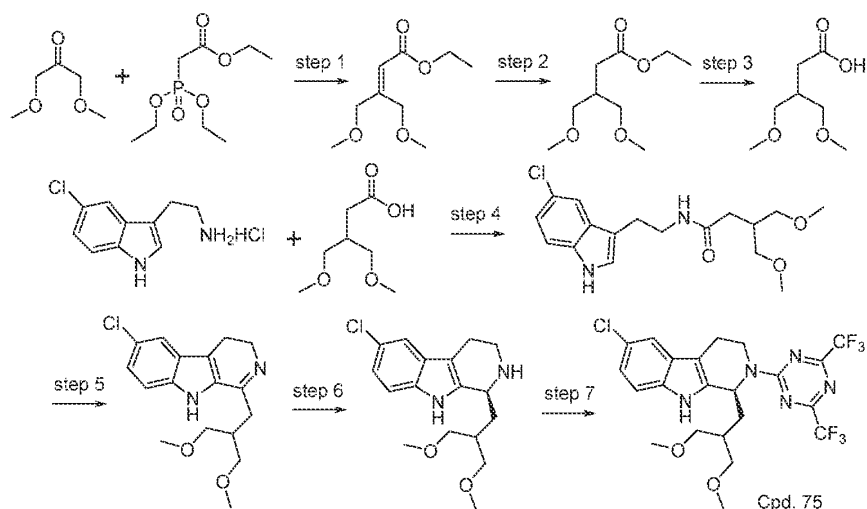
[0458] **Step 2:** To a mixture of methyl 2-(6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetate (200 mg, 0.72 mmol) and DMAP (110 mg, 0.90 mmol) in acetonitrile (6 mL) was added dropwise 2-(trichloromethyl)-4,6-bis(trifluoromethyl)-1,3,5-triazine (300 mg, 0.90 mmol) at 0 °C under N₂. The reaction mixture was stirred at room temperature for 16 h. After the solvent was evaporated under the reduced pressure, the residue was purified by flash chromatography on silica gel to afford 190 mg (53.6%) of methyl 2-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetate as a solid material. ESI-MS m/z 494 ($M+H$)⁺.

[0459] **Step 3:** To a solution of methyl 2-(2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetate (200 mg, 0.405 mmol) in THF (10 mL) was added methylmagnesium chloride solution (3.0 M in THF, 1 mL, 3.0 mmol) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature overnight and then quenched with aqueous NH₄Cl, extracted twice with DCM. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by prep HPLC to afford 32 mg (16%) of 1-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropan-2-ol as a solid. ESI-MS m/z 494 [$M+H$]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.13 (s, 1H), 7.46 (m, 1H), 7.37-7.35 (d, J = 8.8 Hz, 1H), 7.07-7.05 (dd, J = 8.4, 2.4

Hz, 1H), 6.15-6.12 (m, 1H), 4.93-4.88 (m, 1H), 4.37 (s, 1H), 3.66-3.59 (m, 1H), 2.88-2.77 (m, 2H), 2.21-2.15 (m, 1H), 2.02-1.98 (m, 1H), 1.28 (s, 3H), 1.22 (s, 3H).

Example 62

Synthesis of Compound 75



[0460] **Step 1:** To a suspension of sodium hydride (60% in mineral oil, 400 mg, 10 mmol) in THF (20 mL) was added ethyl 2-(diethoxyphosphoryl)acetate (3.0 g, 13.4 mmol) at 0 °C. After the mixture was stirred at 0 °C for 2 h, 1,3-dimethoxypropan-2-one (1.0 g, 8.5 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 2 h and then quenched with brine, extracted twice with DCM. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel eluted with 0 to 20% ethyl acetate/hexane to afford 1.1 g (69%) of ethyl 4-methoxy-3-(methoxymethyl)but-2-enoate as a colorless oily material. ESI-MS *m/z* 189 [M+H]⁺.

[0461] **Step 2:** A mixture of ethyl 4-methoxy-3-(methoxymethyl)but-2-enoate (400 mg, 2.12 mmol) and Pd/C (10 wt%, 100 mg, 0.094 mmol) in ethyl acetate (6 mL) was stirred at room temperature under hydrogen for 16 h. The reaction mixture was then filtrated. After the filtrate was evaporated under the reduced pressure, 310 mg (76.7%) of ethyl 4-methoxy-3-(methoxymethyl)butanoate was obtained as a colorless oil, which was used in the next step without further purification.

[0462] **Step 3:** To a solution of ethyl 4-methoxy-3-(methoxymethyl)butanoate (310 mg, 1.6 mmol) in MeOH (5 mL) and water (1 mL) was added LiOH (100 mg, 4 mmol). The mixture

was stirred at room temperature for 16 h and then acidified with 2 N HCl, extracted twice with ethyl acetate. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the crude product (250 mg) was used in the next step without further purification.

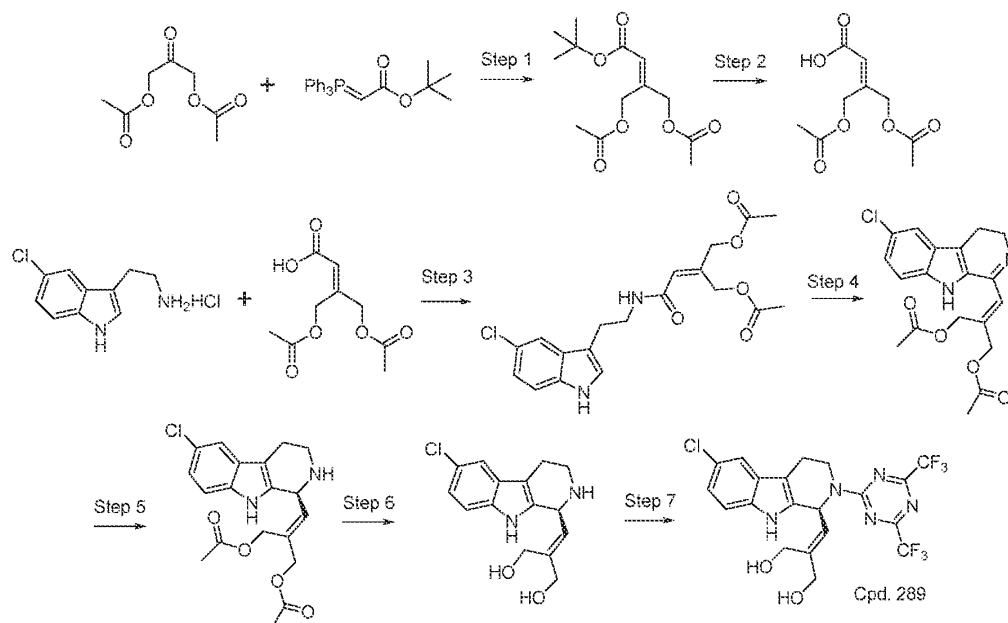
[0463] **Step 4:** The crude product was carried according to step 1 for the procedure of Example 46 to provide N-(2-(5-chloro-1H-indol-3-yl)ethyl)-4-methoxy-3-(methoxymethyl)butanamide.

[0464] **Step 5:** N-(2-(5-chloro-1H-indol-3-yl)ethyl)-4-methoxy-3-(methoxymethyl)butanamide was carried according to step 2 for the procedure of Example 46 to provide 6-chloro-1-(3-methoxy-2-(methoxymethyl)propyl)-4,9-dihydro-3H-pyrido[3,4-b]indole.

[0465] **Step 6:** 6-chloro-1-(3-methoxy-2-(methoxymethyl)propyl)-4,9-dihydro-3H-pyrido[3,4-b]indole was carried according to step 3 for the procedure of Example 46 to provide (S)-6-chloro-1-(3-methoxy-2-(methoxymethyl)propyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.

[0466] **Step 7:** (S)-6-chloro-1-(3-methoxy-2-(methoxymethyl)propyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole was carried according to step 4 for the procedure of Example 46 to provide Compound 75 2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[3-methoxy-2-(methoxymethyl)propyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole. ESI-MS *m/z* 535.8 [M-H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.19 (s, 1H), 7.47 (d, *J* = 1.6 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.06 (dd, *J* = 7.6, 2.0 Hz, 1H), 5.97 (t, *J* = 5.2 Hz, 1H), 4.90 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.59-3.53 (m, 1H), 3.51-3.43 (m, 2H), 3.25 (s, 3H), 3.18 (s, 3H), 2.88-2.73 (m, 3H), 2.01 (t, *J* = 7.2 Hz, 3H), 1.94-1.90 (m, 1H).

Example 63
Synthesis of 289



[0467] **Step 1:** A mixture of 3-acetoxy-2-oxopropyl acetate (10.0 g, 57.4 mmol) and tert-butyl 2-(triphenylphosphanylidene)acetate (21.6 g, 57.4 mmol) in THF (150 mL) was stirred at 70 °C for 2 h. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel to afford 11.5 g (73.6%) of tert-butyl 4-acetoxy-3-(acetoxymethyl)but-2-enoate. ESI-MS m/z 272 $[M+H]^+$.

[0468] **Step 2:** A mixture of tert-butyl 4-acetoxy-3-(acetoxymethyl)but-2-enoate (11.5 g, 42.2 mmol) and TFA (34.5 mL) in DCM (70 mL) was stirred at room temperature for 4 h. After the mixture was evaporated under the reduced pressure, the residue was diluted with DCM, washed with brine. The combined organic phase was dried over Na_2SO_4 . After the solvent was evaporated under the reduced pressure, 7.0 g (77%) of 4-acetoxy-3-(acetoxymethyl)but-2-enoic acid was obtained as an oil, which was used in the next step without further purification. ESI-MS m/z 217 $[M+H]^+$.

[0469] **Step 3:** 4-acetoxy-3-(acetoxymethyl)but-2-enoic acid was carried according to step 1 for the procedure of Example 46 to provide 2-(2-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-2-oxoethylidene)propane-1,3-diyl diacetate.

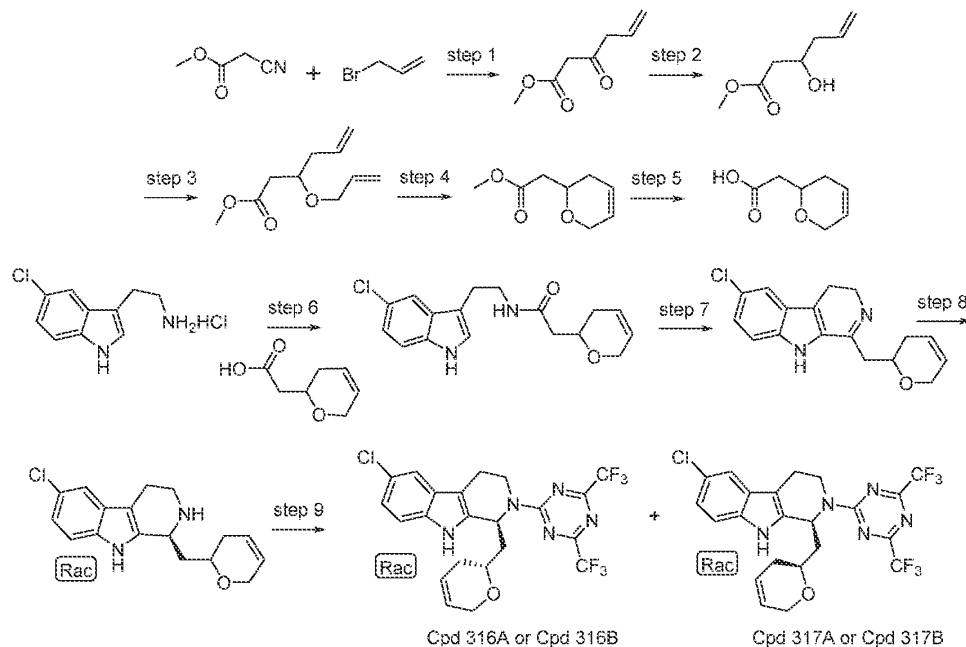
[0470] **Step 4:** 2-(2-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-2-oxoethylidene)propane-1,3-diyl diacetate was carried forward according to step 2 for the procedure of Example 46 to

provide 2-((6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)methylene)propane-1,3-diyl diacetate.

[0471] **Step 5:** 2-((6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)methylene)propane-1,3-diyl diacetate was carried according to step 3 for the procedure of Example 46 to provide (S)-2-((6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methylene)propane-1,3-diyl diacetate.

[0472] **Step 6:** To a solution of (S)-2-((6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methylene)propane-1,3-diyl diacetate (700 mg, 1.86 mmol) in MeOH (60 mL) was added 2 mL of 4.0 M HCl in 1,4-dioxane. The reaction mixture was stirred at 70 °C for 16 h. After the solvent was evaporated under the reduced pressure, the residue was purified by prep HPLC to afford 30 mg (5.5 %) of (S)-2-((6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methylene)propane-1,3-diol as a solid. ESI-MS m/z 293 $[M+H]^+$.

[0473] **Step 7:** (S)-2-((6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methylene)propane-1,3-diol was carried according to step 4 for the procedure of Example 46 to provide 2-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methylidene)propane-1,3-diol. ESI-MS m/z 506 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 10.75 (s, 1H), 7.52-7.51 (m, 1H), 7.40-7.38 (d, $J = 8.8$ Hz, 1H), 7.10-7.06 (dd, $J = 8.4, 1.6$ Hz, 1H), 6.70-6.68 (d, $J = 10$ Hz, 1H), 5.75-5.72 (m, 1H), 5.03-4.98 (m, 1H), 4.97-4.95 (m, 1H), 4.88-4.85 (m, 1H), 4.59-4.54 (dd, $J = 12.8, 1.2$ Hz, 1H), 4.18-4.14 (m, 1H), 4.04-4.01 (m, 2H), 3.66-3.58 (m, 1H), 2.98-2.93 (m, 1H), 2.84-2.80 (m, 1H).

Example 64**Synthesis of 316A or 316B or 317A or 317B**

[0474] **Step 1:** To a mixture of methyl 2-cyanoacetate (500 mg, 5.05 mmol) and allyl bromide (800 mg, 6.6 mmol) in THF (10 mL) were added zinc (1.16 g, 17.7 mmol) and aluminum chloride (0.3 g, 2 mmol) at 0 °C under nitrogen. The reaction mixture was allowed to slowly warm to room temperature overnight. The mixture was then quenched with 1 N HCl, extracted twice with ethyl acetate. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel eluted with 0 to 10% ethyl acetate/hexane to afford 400 mg (55.8%) of methyl 3-oxohex-5-enoate as a light yellow oil. ESI-MS *m/z* 143.1 [M+H]⁺.

[0475] **Step 2:** To a solution of methyl 3-oxohex-5-enoate (1.0 g, 7.03 mmol) in THF (10 mL) was added sodium borohydride (266 mg, 7.03 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then quenched with aqueous NH₄Cl, extracted twice with DCM. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel eluted with 0 to 75% ethyl acetate/hexane to afford 650 mg (64%) of methyl 3-hydroxyhex-5-enoate as a light yellow oil.

[0476] **Step 3:** A mixture of methyl 3-hydroxyhex-5-enoate (500 mg, 3.47 mmol), allyl bromide (1.5 mL, 17 mmol) and silver oxide (4.0 g, 17 mmol) in ethyl acetate (15 mL) was

stirred at room temperature for 90 h. The mixture was filtered. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel eluted with 0 to 5% ethyl acetate/hexane to afford 450 mg (70.4%) of methyl 3-(allyloxy)hex-5-enoate as a colorless oil.

[0477] **Step 4:** To a solution of methyl 3-(allyloxy)hex-5-enoate (500 mg, 2.7 mmol) in DCM (10 mL) was added Grubbs catalyst 2nd generation (70 mg, 0.08 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 20 h. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel eluted with 0 to 10% ethyl acetate/hexane to afford 350 mg (82.6%) of methyl 2-(3,6-dihydro-2H-pyran-2-yl)acetate as a light yellow oil.

[0478] **Step 5:** To a solution of methyl 2-(3,6-dihydro-2H-pyran-2-yl)acetate (300 mg, 1.92 mmol) in MeOH (3 mL) was added lithium hydroxide monohydrate (650 mg, 15.5 mmol) and water (1 mL). The mixture was stirred at room temperature for 4 h and then acidified with 1 N HCl, extracted three times with DCM. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the crude product was used in the next step without further purification.

[0479] **Step 6:** The crude product was carried according to step 1 for the procedure of Example 46 to provide N-(2-(5-chloro-1H-indol-3-yl)ethyl)-2-(3,6-dihydro-2H-pyran-2-yl)acetamide.

[0480] **Step 7:** was carried according to step 2 for the procedure of Example 46 to provide

[0481] **Step 8:** was carried according to step 3 for the procedure of Example 46 to provide (1S)-6-chloro-1-((3,6-dihydro-2H-pyran-2-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.

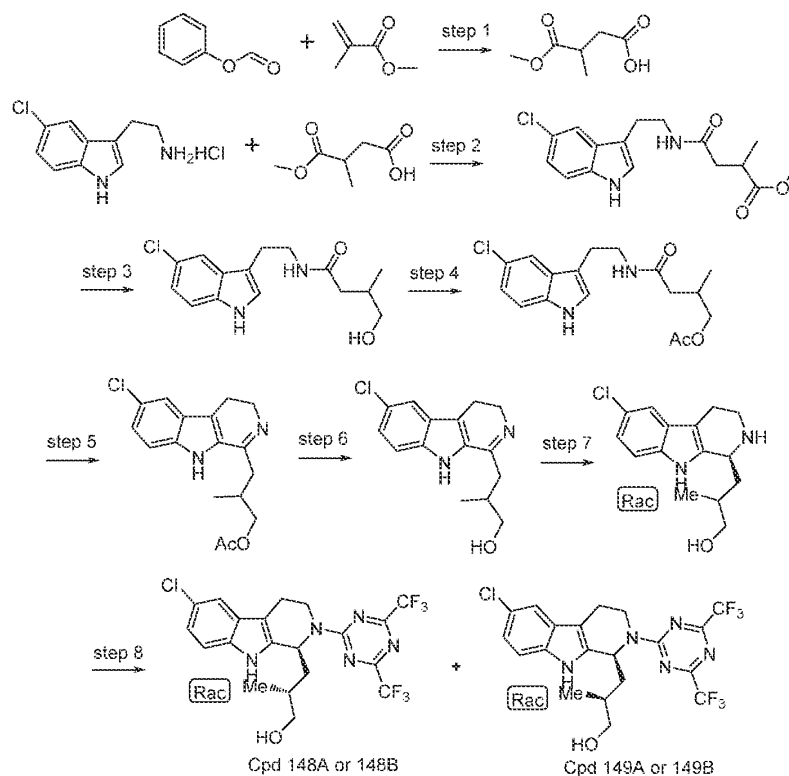
[0482] **Step 9:** (1S)-6-chloro-1-((3,6-dihydro-2H-pyran-2-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole was carried according to step 4 for the procedure of Example 46 and further separated by chiral HPLC to provide a racemic mixture of Compound 316A (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{[(2R)-3,6-dihydro-2H-pyran-2-yl]methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole or Compound 316B (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{[(2S)-3,6-dihydro-2H-pyran-2-yl]methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole and a racemic mixture of Compound 317A (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{[(2S)-3,6-dihydro-2H-pyran-2-yl]methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole or Compound 317B (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{[(2R)-3,6-dihydro-2H-pyran-2-yl]methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.

[0483] Compound 316A/B: ESI-MS m/z 515.9 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.35 (s, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 8.8, 2.0 Hz, 1H), 6.29-6.26 (m, 1H), 5.78-5.72 (m, 2H), 4.95-4.90 (m, 1H), 4.11-3.96 (m, 2H), 3.66-3.56 (m, 1H), 3.50-3.44 (m, 1H), 2.88-2.83 (m, 2H), 2.26-2.19 (m, 1H), 2.11-2.04 (m, 1H), 1.96-1.89 (m, 2H).

[0484] Compound 317A/B: ESI-MS m/z 515.9 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.18 (s, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.08 (dd, J = 8.4, 2.0 Hz, 1H), 6.07-6.04 (m, 1H), 5.79-5.75 (m, 1H), 5.69-5.66 (m, 1H), 4.97-4.92 (m, 1H), 3.91-3.87 (m, 1H), 3.72-3.69 (m, 2H), 3.64-3.57 (m, 1H), 2.90-2.85 (m, 1H), 2.80-2.75 (m, 1H), 2.25-2.21 (m, 2H), 2.17-2.12 (m, 1H), 2.05-1.94 (m, 1H).

Example 65

Synthesis of Compound 148A or 148B or Compound 149A or 149B



[0485] **Step 1:** A mixture of methyl methacrylate (1.5 g, 15 mmol), phenyl formate (2.2 g, 18 mmol), formic acid (1.1 mL, 29 mmol), DPPF (830 mg, 1.5 mmol), and palladium acetate (170 mg, 0.76 mmol) in toluene (15 mL) was stirred at 90 °C under nitrogen for 20 h. The

reaction mixture was then quenched with saturated NaHCO_3 (100 mL), washed twice with DCM. The aqueous layer was acidified with 2 N HCl (60 mL), extracted three times with DCM. The combined organic phase was dried over Na_2SO_4 . After the solvent was evaporated under the reduced pressure, 700 mg (32%) of 4-methoxy-3-methyl-4-oxobutanoic acid was obtained as a brown oil, which was used in the next step without further purification.

[0486] **Step 2:** 4-methoxy-3-methyl-4-oxobutanoic acid was carried according to Step 1 for the procedure of Example 46 to provide methyl 4-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-2-methyl-4-oxobutanoate.

[0487] **Step 3:** To a solution of methyl 4-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-2-methyl-4-oxobutanoate (1.0 g, 3.1 mmol) in THF (8 mL) and MeOH (2 mL) was added sodium borohydride (590 mg, 15.6 mmol). The reaction mixture was stirred at room temperature for 4 d. The mixture was then quenched with water, extracted three times with ethyl acetate. The combined organic phase was dried over Na_2SO_4 . After the solvent was evaporated under the reduced pressure, 900 mg (99%) of N-(2-(5-chloro-1H-indol-3-yl)ethyl)-4-hydroxy-3-methylbutanamide was obtained, which was used in the next step without further purification.

[0488] **Step 4:** To a solution of N-(2-(5-chloro-1H-indol-3-yl)ethyl)-4-hydroxy-3-methylbutanamide (900 mg, 3.05 mmol), DMAP (50 mg, 0.4 mmol) and DIPEA (1.1 mL, 6.3 mmol) in THF (10 mL) was added acetic anhydride (620 mg, 6.07 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was then quenched with water, extracted three times with DCM. The combined organic phase was dried over Na_2SO_4 . After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel eluted with 0 to 10% MeOH/DCM to afford 620 mg (60.2%) of 4-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-2-methyl-4-oxobutyl acetate as a colorless oil. ESI-MS m/z 337.1 $[\text{M}+\text{H}]^+$.

[0489] **Step 5:** 4-((2-(5-chloro-1H-indol-3-yl)ethyl)amino)-2-methyl-4-oxobutyl acetate was carried according to step 2 for the procedure of Example 46 to provide 3-(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-2-methylpropyl acetate.

[0490] **Step 6:** A mixture of 3-(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-2-methylpropyl acetate (500 mg, 1.57 mmol) and NaOH (190 mg, 4.75 mmol) in THF (10 mL) and water (2 mL) was stirred at room temperature for 2 h. The mixture was then quenched with water, extracted three times with ethyl acetate. The combined organic phase was dried over Na_2SO_4 . After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel eluted with 0 to 10% MeOH/DCM to afford 400 mg

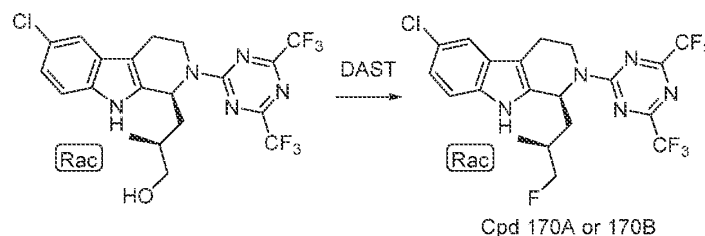
(92%) of 3-(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol as a yellow solid. ESI-MS m/z 277.1 $[M+H]^+$.

[0491] **Step 7:** 3-(6-chloro-4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol was carried according to step 3 for the procedure of Example 46 to provide 3-((*S*)-6-chloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2-methylpropan-1-ol.

[0492] **Step 8:** 3-((*S*)-6-chloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2-methylpropan-1-ol was carried according to step 4 for the procedure of Example 46 and further separated by chiral HPLC to provide a racemic mixture of Compound 148A (2*R*)-3-((1*S*)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2-methylpropan-1-ol or Compound 148B (2*S*)-3-((1*S*)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2-methylpropan-1-ol and Compound 149A (2*S*)-3-((1*S*)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2-methylpropan-1-ol or Compound 149B (2*R*)-3-((1*S*)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-2-methylpropan-1-ol.

[0493] Compound 148A/B: ESI-MS m/z 494.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.29 (s, 1H), 7.47 (d, $J = 1.6$ Hz, 1H), 7.34 (d, $J = 8.8$ Hz, 1H), 7.06 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.01 (d, $J = 8.8$ Hz, 1H), 4.91 (dd, $J = 13.2, 4.4$ Hz, 1H), 4.59-4.32 (m, 1H), 3.58-3.47 (m, 1H), 3.28-3.16 (m, 2H), 2.86 (dd, $J = 16.0, 4.4$ Hz, 1H), 2.81-2.74 (m, 1H), 2.18 (t, $J = 12.0$ Hz, 1H), 1.69-1.43 (m, 1H), 1.55-1.48 (m, 1H), 1.07 (d, $J = 6.4$ Hz, 3H).

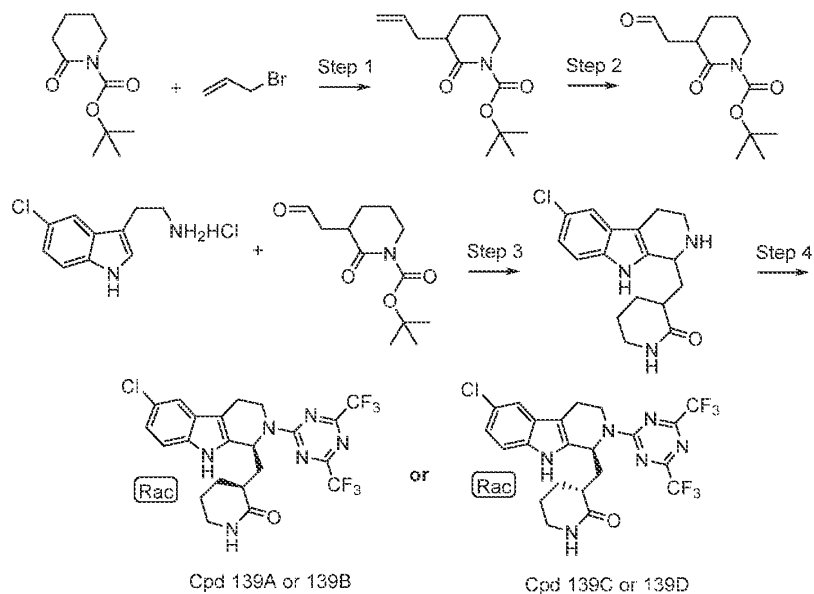
[0494] Compound 149A/B: ESI-MS m/z 494.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.15 (s, 1H), 7.47 (d, $J = 2.0$ Hz, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.06 (dd, $J = 8.4, 2.0$ Hz, 1H), 5.96-5.93 (m, 1H), 4.94-4.89 (m, 1H), 4.39-4.36 (m, 1H), 3.64-3.57 (m, 1H), 3.45-3.39 (m, 2H), 2.89-2.85 (m, 1H), 2.82-2.75 (m, 1H), 2.10-2.07 (m, 1H), 1.77-1.69 (m, 2H), 0.93 (d, $J = 6.4$ Hz, 3H).

Example 66**Synthesis of 170A or 170B**

[0495] In a 50 mL single neck round-bottomed flask a racemic mixture of (S)-3-((S)-2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol or (R)-3-((S)-2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol (50 mg, 0.10 mmol) was dissolved in 5 mL of dichloromethane. The solution was cooled to 0 °C, then DAST (diethylaminosulfur trifluoride) (0.04 mL, 0.3 mmol) was added into the solution. The reaction mixture was stirred at room-temperature for 3 hours, after which the solvent was removed in vacuo and the crude residue was purified by Prep-HPLC to provide a racemic mixture of Compound 170A (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-3-fluoro-2-methylpropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole or Compound 170B (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-3-fluoro-2-methylpropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (30 mg, 0.06 mmol, 60% yield) as a white solid. ESI-MS m/z 496.1 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.25 (s, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 8.5, 2.1 Hz, 1H), 5.93 (dd, J = 10.1, 4.0 Hz, 1H), 4.92 (dd, J = 13.2, 5.1 Hz, 1H), 4.51 (ddd, J = 48.1, 4.6, 2.5 Hz, 2H), 3.78-3.44 (m, 1H), 3.02-2.67 (m, 2H), 2.19-1.79 (m, 2H), 1.47 (dd, J = 37.9, 21.7 Hz, 1H), 0.99 (d, J = 6.3 Hz, 3H). The relative configuration was not determined; NMR data was obtained without assignment to a particular diastereomer.

[0496] Using the procedure described for Example 66, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
171A or 171B	ESI-MS m/z 496.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.32 (s, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 8.6, 2.1 Hz, 1H), 6.01 (dd, J = 11.5, 2.7 Hz, 1H), 4.92 (dd, J = 13.2, 5.1 Hz, 1H), 4.28 (ddd, J = 47.6, 5.4, 2.4 Hz, 2H), 3.74-3.49 (m, 1H), 2.81 (dtd, J = 21.0, 15.5, 4.8 Hz, 2H), 2.16 (t, J = 12.3 Hz, 1H), 2.02-1.63 (m, 2H), 1.17 (d, J = 6.2 Hz, 3H).

Example 67**Synthesis of Compound 139A, 139B, 139C, or 139D**

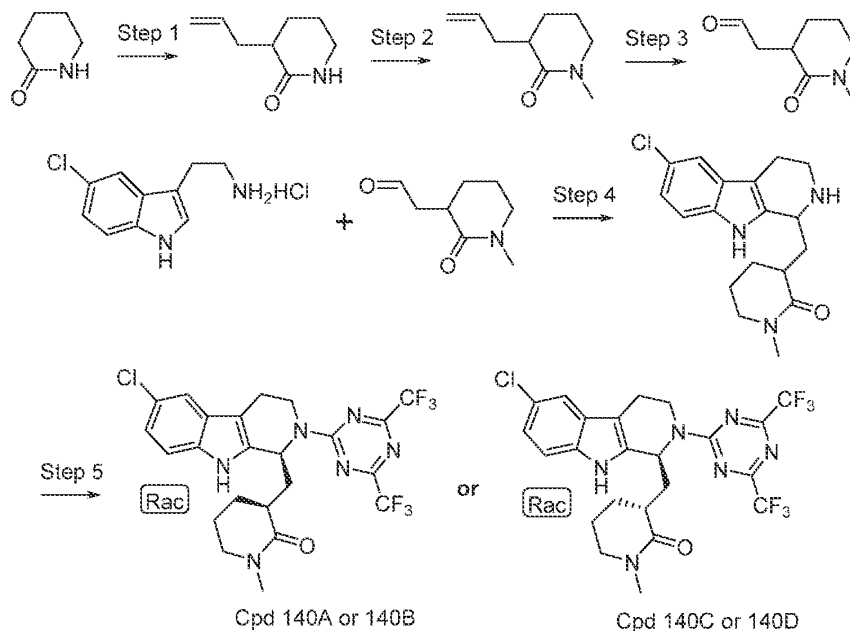
[0497] **Step 1:** To a solution of tert-butyl 2-oxopiperidine-1-carboxylate (1.6 g, 8.0 mmol) in THF (16 mL) was added LDA solution (8.8 mmol) under nitrogen at -78 °C. After 1 h, a solution of allyl bromide (0.7 g, 6 mmol) in THF (10 mL) was added dropwise at -50 °C. After 0.5 h, the reaction mixture was allowed to warm to -20 °C. The mixture was then quenched with saturated NH₄Cl, extracted three times with DCM. The combined organic phase was dried over MgSO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by chromatography on silica gel to afford 0.40 g (30%) of tert-butyl 3-allyl-2-oxopiperidine-1-carboxylate. ESI-MS *m/z* 240 [M+H]⁺.

[0498] **Step 2:** To a solution of tert-butyl 3-allyl-2-oxopiperidine-1-carboxylate (1.0 g, 4.2 mmol) in diethyl ether (20 mL) water (20 mL) were added potassium osmate(VI) dihydrate (46 mg, 0.14 mmol) and sodium periodate (2.7 g, 13 mmol). The reaction mixture was vigorously stirred at room temperature for 4 h. The mixture was then quenched with water, extracted three times with ethyl acetate. The combined organic phase was dried over MgSO₄. After the solvent was evaporated under the reduced pressure, 1.0 g (99%) of tert-butyl 2-oxo-3-(2-oxoethyl)piperidine-1-carboxylate was obtained, which was directly used in the next step without further purification. ESI-MS *m/z* 242 [M+H]⁺.

[0499] **Step 3:** A mixture of 2-(5-chloro-1H-indol-3-yl)ethan-1-amine hydrochloride (230 mg, 1.0 mmol), tert-butyl 2-oxo-3-(2-oxoethyl)piperidine-1-carboxylate (482 mg, 2.0 mmol),

and TFA (342 mg, 3.0 mmol) in 1,2-dichloroethane (3 mL) was stirred at 80 °C for 2 h. After the mixture was cooled to room temperature and concentrated under the reduced pressure, the residue was treated with acetonitrile (5 mL) and filtered to afford 180 mg (56.9%) of 3-((6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)piperidin-2-one TFA salt as a white solid. ESI-MS m/z 318 $[M+H]^+$.

[0500] **Step 4:** 3-((2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)piperidin-2-one was prepared as described in the synthesis of Compound 119 to afford a racemic mixture of Compound 139A (3S)-3-(((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)piperidin-2-one; Compound 139B (3R)-3-(((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)piperidin-2-one; Compound 139C, (3R)-3-(((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)piperidin-2-one and Compound 139D (3S)-3-(((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)piperidin-2-one. ESI-MS m/z 531.0 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.27 (s, 1H), 7.48-7.47 (m, 2H), 7.37 (d, J = 8.4 Hz, 1H), 7.08 (dd, J = 8.4, 2.0 Hz, 1H), 5.97 (d, J = 9.6 Hz, 1H), 4.95 (dd, J = 13.2, 4.8 Hz, 1H), 3.56-3.51 (m, 1H), 3.12 (m, 2H), 2.91-2.86 (m, 1H), 2.82-2.77 (m, 1H), 2.69-2.62 (m, 1H), 2.37-2.33 (m, 1H), 2.21-2.19 (m, 1H), 1.90-1.84 (m, 1H), 1.80-1.77 (m, 1H), 1.64-1.60 (m, 2H).

Example 68**Synthesis of Compound 140A, 140B, 140C, and 140D**

[0501] **Step 1:** To a solution of piperidin-2-one (4 g, 40 mmol) in THF (60 mL) was added dropwise *n*-BuLi (2.5 M, 36 mL, 90 mmol) at 0 °C. After 1 h, the reaction mixture was cooled to -78 °C and a solution of allyl bromide (5.85 g, 48.4 mmol) in THF (10 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature over 1 h. The mixture was quenched with saturated brine, extracted three times with DCM. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, 4 g (71%) of 3-allylpiperidin-2-one was obtained, which was directly used in the next step without further purification. ESI-MS *m/z* 140 [M+H]⁺.

[0502] **Step 2:** To a mixture of sodium hydride (60 wt% in mineral oil, 432 mg, 10.8 mmol) in THF (20 mL) was added a solution of 3-allylpiperidin-2-one (1 g, 7.18 mmol) in THF (30 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 2 h and iodomethane (1.22 g, 8.60 mmol) was added. After an additional hour at room temperature, the mixture was quenched with saturated brine, extracted three times with ethyl acetate. The combined organic phase was dried over MgSO₄. After the solvent was evaporated under the reduced pressure, 1 g (90.8%) of 3-allyl-1-methylpiperidin-2-one was obtained, which was directly used in the next step without further purification. ESI-MS *m/z* 154 [M+H]⁺.

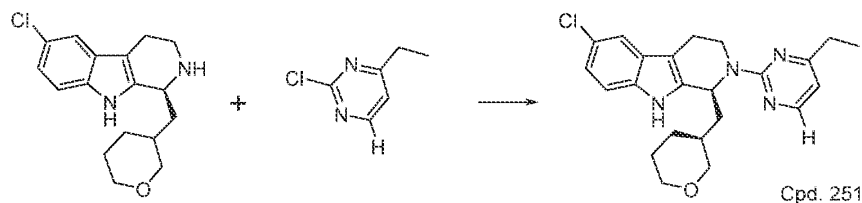
[0503] **Step 3:** 3-allyl-1-methylpiperidin-2-one was carried according to step 2 for the procedure of Example 67 to provide 2-(1-methyl-2-oxopiperidin-3-yl)acetaldehyde, which was directly used in the next step without further purification.

[0504] **Step 4:** 2-(1-methyl-2-oxopiperidin-3-yl)acetaldehyde was carried according to step 3 for the procedure of Example 67 to provide 3-((6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1-methylpiperidin-2-one.

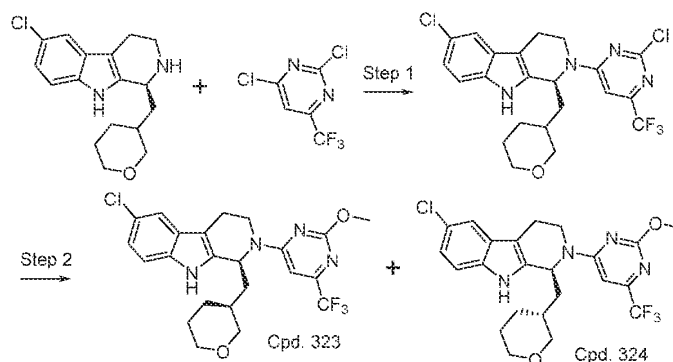
[0505] **Step 5:** 3-((6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1-methylpiperidin-2-one was carried according to step 4 of Example 67 to afford a diastereomeric mixture of Compound 140A (3S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1-methylpiperidin-2-one; Compound 140B (3R)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1-methylpiperidin-2-one; Compound 140C (3R)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1-methylpiperidin-2-one; and Compound 140D, (3S)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1-methylpiperidin-2-one. ESI-MS m/z 547.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.26 (s, 1H), 7.48 (d, $J = 1.9$ Hz, 1H), 7.37 (d, $J = 8.6$ Hz, 1H), 7.07 (dd, $J = 8.6, 2.0$ Hz, 1H), 5.94 (d, $J = 9.3$ Hz, 1H), 4.95 (dd, $J = 13.2, 4.9$ Hz, 1H), 3.58–3.49 (m, 1H), 3.31–3.22 (m, 2H), 2.92–2.86 (m, 1H), 2.83–2.76 (m, 4H), 2.73–2.63 (m, 1H), 2.36–2.22 (m, 2H), 1.93–1.82 (m, 2H), 1.74–1.63 (m, 2H).

[0506] Using the procedure described for Example 68, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
141	ESI-MS m/z 533.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.28 (d, $J = 3.2$ Hz, 1H), 7.49 (d, $J = 1.6$ Hz, 1H), 7.39-7.35 (m, 1H), 7.09-7.06 (m, 1H), 6.03-5.94 (m, 1H), 4.98-4.88 (m, 1H), 3.66-3.51 (m, 1H), 3.38-3.35 (m, 1H), 3.26-3.14 (m, 1H), 2.91-2.86 (m, 1H), 2.81-2.77 (m, 1H), 2.72 (s, 2H), 2.63 (s, 1H), 2.46-2.38 (m, 2H), 2.13-2.02 (m, 1H), 1.94-1.77 (m, 2H).

Example 69**Synthesis of Compound 251**

[0507] To a solution of (1S)-6-chloro-1-((tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (60 mg, 0.2 mmol) in 1-butanol (1 mL) were added DIPEA (80 mg, 0.6 mmol) and 2-chloro-4-ethylpyrimidine (42 mg, 0.3 mmol). The reaction mixture was stirred at 120 °C for 16 h. After the solvent was evaporated under the reduced pressure, the residue was purified by Prep HPLC to afford (1S)-6-chloro-2-(4-ethylpyrimidin-2-yl)-1-((3S)-oxan-3-yl)methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as the first product. ESI-MS m/z 411.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.15 (s, 1H), 8.26 (d, $J = 4.9$ Hz, 1H), 7.39 (d, $J = 2.0$ Hz, 1H), 7.30 (d, $J = 8.6$ Hz, 1H), 7.01 (m, 1H), 6.53 (d, $J = 5.0$ Hz, 1H), 6.07 (d, $J = 8.2$ Hz, 1H), 4.91 (d, $J = 12.9$ Hz, 1H), 3.71 (t, $J = 8.1$ Hz, 2H), 3.27 (d, $J = 8.6$ Hz, 2H), 3.06–2.99 (m, 1H), 2.63 (m, 5H), 1.70 (m, 4H), 1.35 (dd, $J = 23.4$, 14.8 Hz, 2H), 1.19 (t, $J = 7.6$ Hz, 3H).

Example 70**Synthesis of Compound 323 and Compound 324**

[0508] **Step 1:** To a mixture of (1S)-6-chloro-1-((tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (200 mg, 0.65 mmol), 2,4-dichloro-6-(trifluoromethyl)pyrimidine (170 mg, 0.78 mmol) in 1-butanol (3 mL) were added DIPEA (0.4 mL, 2.0 mmol). The reaction mixture was stirred at 120 °C overnight. The mixture was then quenched with water, extracted three times with ethyl acetate. The combined organic

phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by Prep TLC to afford 380 mg of (1S)-6-chloro-2-(2-chloro-6-(trifluoromethyl)pyrimidin-4-yl)-1-((tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a yellow oil. ESI-MS m/z 485.0 [M+H]⁺.

[0509] **Step 2:** To a solution of (1S)-6-chloro-2-(2-chloro-6-(trifluoromethyl)pyrimidin-4-yl)-1-((tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (180 mg, 0.37 mmol) in methanol (4 mL) was added sodium methoxide (100 mg, 1.8 mmol). The reaction mixture was stirred at 70 °C for 1 h. The mixture was then quenched with water, extracted three times with ethyl acetate. The combined organic phase was dried over Na₂SO₄. After the solvent was evaporated under the reduced pressure, the residue was purified by Prep HPLC to afford Compound 323 (S)-6-chloro-2-(2-methoxy-6-(trifluoromethyl)pyrimidin-4-yl)-1-(((S)-tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (45 mg, 25%) and Compound 324 (S)-6-chloro-2-(2-methoxy-6-(trifluoromethyl)pyrimidin-4-yl)-1-(((R)-tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (45 mg, 25%).

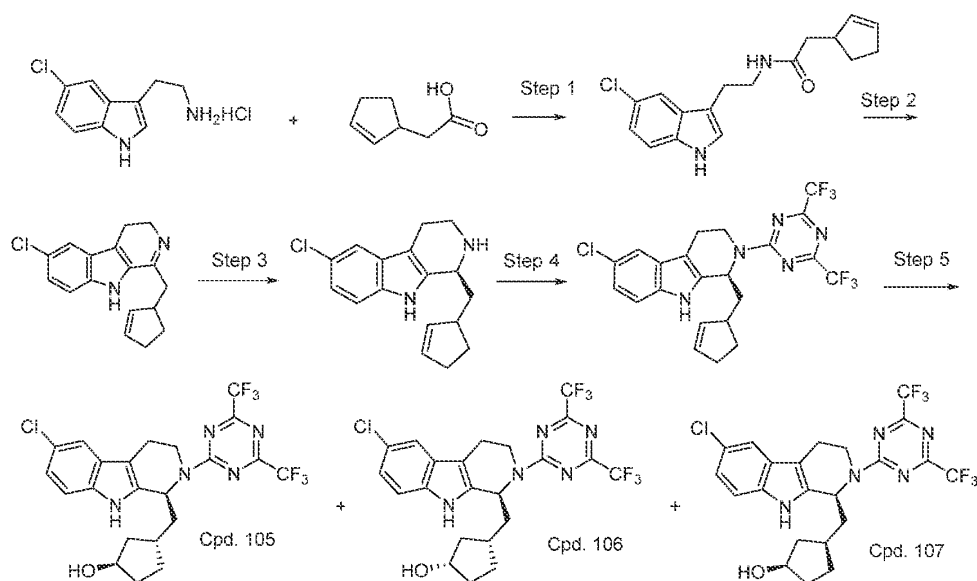
[0510] Compound 323: ESI-MS m/z 481.0 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.21 (s, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.16 (s, 1H), 7.04 (dd, J = 8.6, 1.6 Hz, 1H), 6.19-6.17 (m, 1H), 4.42 (d, J = 12.8 Hz, 1H), 3.88-3.86 (m, 3H), 3.72-3.69 (m, 2H), 3.62-3.54 (m, 1H), 3.30-3.27 (m, 1H), 3.03 (t, J = 10.2 Hz, 1H), 2.73-2.72 (m, 2H), 2.18-2.15 (m, 1H), 1.86-1.72 (m, 2H), 1.63-1.51 (m, 2H), 1.43-1.28 (m, 2H).

[0511] Compound 324: ESI-MS m/z 480.9 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.17 (s, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.33-7.31 (m, 1H), 7.16 (s, 1H), 7.04 (dd, J = 8.6, 1.6 Hz, 1H), 6.13 (t, J = 7.2 Hz, 1H), 4.42 (d, J = 13.6 Hz, 1H), 4.15 (d, J = 10.4 Hz, 1H), 3.86 (s, 3H), 3.73-3.70 (m, 1H), 3.63-3.55 (m, 1H), 3.29-3.26 (m, 1H), 3.18 (t, J = 10.2 Hz, 1H), 2.75-2.72 (m, 2H), 1.84-1.74 (m, 3H), 1.62-1.58 (m, 1H), 1.53-1.44 (m, 2H), 1.24-1.15 (m, 1H).

[0512] Using the procedure described for Example 70, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
270	ESI-MS m/z 481.1 [M+H] ⁺ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.19 (d, J = 5.6 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.50 (d, J = 4.8 Hz, 1H), 5.97 (d, J = 9.2 Hz, 1H), 4.94-4.83 (m, 1H), 4.97 (d, J = 18.0 Hz, 3H), 3.73-3.66 (m, 2H), 3.42-3.38 (m, 0.5H), 3.28-3.24 (m, 0.5H), 3.08-2.97 (m, 1H), 2.75-2.66 (m, 2H), 2.36-2.33 (m, 1H), 1.81-1.25 (m, 7H)

Cpd	Data
322	ESI-MS m/z 439.0 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.16 (d, J = 46.1 Hz, 1H), 7.44 (s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.16 (s, 1H), 7.05 (d, J = 8.5 Hz, 1H), 6.22 (d, J = 7.7 Hz, 1H), 4.43 (d, J = 14.3 Hz, 1H), 3.87 (s, 3H), 3.64–3.54 (m, 1H), 2.73 (s, 2H), 1.94 (t, J = 10.3 Hz, 1H), 1.80–1.59 (m, 2H), 1.10 (d, J = 6.0 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H)

Example 71**Synthesis of Compound 105, 106, and 107**

[0513] **Step 1:** 2-(5-chloro-1H-indol-3-yl)ethan-1-amine hydrochloride was carried forward according to step 4 of Example 62 to provide N-(2-(5-chloro-1H-indol-3-yl)ethyl)-2-(cyclopent-2-en-1-yl)acetamide.

[0514] **Step 2:** N-(2-(5-chloro-1H-indol-3-yl)ethyl)-2-(cyclopent-2-en-1-yl)acetamide was carried according to step 5 of Example 62 to provide 6-chloro-1-(cyclopent-2-en-1-ylmethyl)-4,9-dihydro-3H-pyrido[3,4-b]indole.

[0515] **Step 3:** 6-chloro-1-(cyclopent-2-en-1-ylmethyl)-4,9-dihydro-3H-pyrido[3,4-b]indole was carried according to step 6 of Example 62 to provide (1S)-6-chloro-1-(cyclopent-2-en-1-ylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole.

[0516] **Step 4:** (1S)-6-chloro-1-(cyclopent-2-en-1-ylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole was carried according to step 7 of Example 62 to provide (1S)-2-(4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl)-6-chloro-1-(cyclopent-2-en-1-ylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white solid. ESI-MS m/z 500.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.20–11.40 (m, 1H), 7.48 (s, 1H), 7.29–7.40 (m, 1H), 7.07 (br d, J = 8.8

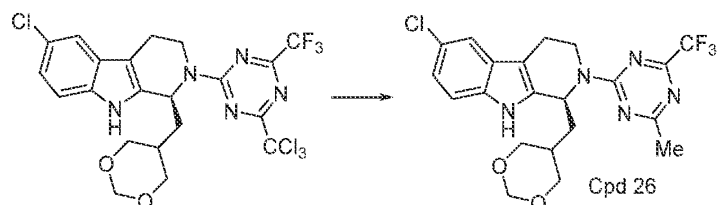
Hz, 1H), 5.93-6.08 (m, 2H), 5.70-5.83 (m, 1H), 4.89-5.02 (m, 1H), 3.55-3.71 (m, 1H), 2.66-2.94 (m, 3H), 2.29-2.41 (m, 1H), 2.17-2.29 (m, 1H), 1.97-2.16 (m, 2H), 1.73-1.87 (m, 1H), 1.38-1.57 (m, 1H).

[0517] **Step 5:** An 8 mL vial equipped with a stir bar was charged with (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(cyclopent-2-en-1-ylmethyl)-1,3,4,9-tetrahydropyrido[3,4-b]indole (300 mg, 0.6 mmol) and THF (2 mL), capped and was sparged with N₂. 9-Borabicyclo[3.3.1]nonane (9-BBN) (2.6 mL, 1 mmol) was added and the mixture was stirred at room temperature for overnight. Water (3 mL) and sodium perborate (600 mg, 7.2 mmol) were added to it under N₂. The mixture was stirred at room temperature for 5h, partitioned between ethyl acetate and water, the organic phase was washed with Brine, then dried over MgSO₄, and condensed under reduced pressure. The residual oil was purified with silica gel chromatography, eluting with 0-70% ethyl acetate in hexane to afford Compound 105 (1R,3S)-3-(((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)cyclopentan-1-ol; Compound 106 (1S,3S)-3-(((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)cyclopentan-1-ol; and, Compound 107 (1R,3R)-3-(((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)cyclopentan-1-ol. The structure for Compound 106 was established via 2D-NMR; The structures for Compounds 105 and 107 could not be unambiguously established due to signal overlap in 2D-NMR spectra.

[0518] Compound 105: ESI-MS m/z 518.2 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.08-11.27 (m, 1H), 7.43-7.56 (m, 1H), 7.36 (d, J=8.5 Hz, 1H), 7.08 (br d, J=8.8 Hz, 1H), 5.84-6.03 (m, 1H), 4.85-5.08 (m, 1H), 4.62-4.65 (m, 1H), 3.69-3.81 (m, 1H), 3.53-3.67 (m, 1H), 2.72-2.97 (m, 2H), 2.17-2.32 (m, 1H), 1.70-1.92 (m, 4H), 1.57-1.68 (m, 1H), 1.38-1.56 (m, 2H), 1.14-1.30 (m, 1H).

[0519] Compound 106: ESI-MS m/z 518.2 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.17-11.39 (m, 1H), 7.45-7.51 (m, 1H), 7.31-7.40 (m, 1H), 7.02-7.12 (m, 1H), 5.85-5.98 (m, 1H), 4.85-5.01 (m, 1H), 4.28-4.51 (m, 1H), 3.99-4.23 (m, 1H), 3.53-3.67 (m, 1H), 2.72-2.95 (m, 2H), 1.73-2.35 (m, 5H), 1.03-1.71 (m, 4H).

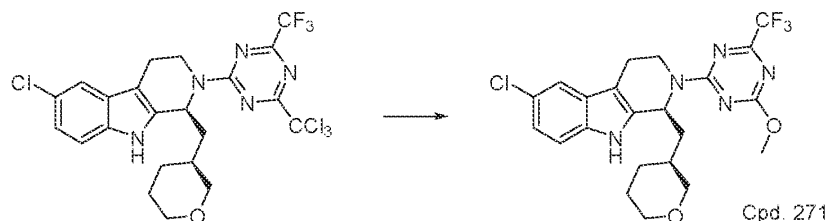
[0520] Compound 107: ESI-MS m/z 518.2 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.31 (s, 1H), 7.48 (s, 1H), 7.33-7.38 (m, J=8.5 Hz, 1H), 7.05-7.10 (m, J=8.5 Hz, 1H), 5.92 (br d, J=9.3 Hz, 1H), 4.93 (br dd, J=13.1, 4.4 Hz, 1H), 4.46 (d, J=3.5 Hz, 1H), 4.03 (br d, J=4.8 Hz, 1H), 3.52-3.65 (m, 1H), 2.72-2.90 (m, 2H), 2.08-2.18 (m, 1H), 1.85-2.06 (m, 4H), 1.47-1.71 (m, 3H), 1.01-1.15 (m, 1H).

Example 72**Synthesis of Compound 26**

[0521] To a mixture of (S)-1-((1,3-dioxan-5-yl)methyl)-6-chloro-2-(4-(trichloromethyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (100 mg, 0.18 mmol), ethanol (3 mL) and water (1 mL) was added ammonium chloride (100 mg, 1.9 mmol) and Zinc (230 mg, 3.5 mmol). The resulting mixture was stirred at 85°C for 1h. After cooling, the solid material was filtered off and the filtrate was concentrated under reduced pressure. The residual material was purified by prep-HPLC to afford (1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-methyl-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (40 mg, 48.9% yield) as a white solid material. ESI-MS m/z 466.0 [M-H]⁻; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.24 (d, $J=4.0$ Hz, 1H), 7.45 (s, 1H), 7.34 (q, $J=7.2$ Hz, 1H), 7.05 (q, $J=6.4$ Hz, 1H), 5.98-5.84(m, 1H), 5.04-4.86 (m, 1H), 4.83 (t, $J=6.4$ Hz, 1H), 4.65 (q, $J=6.4$ Hz, 1H), 4.31-4.23 (m, 1H), 3.87 (q, $J=5.6$ Hz, 1H), 3.72-3.64 (m, 1H), 3.50-3.38 (m, 2H), 3.33 (s, 3H), 2.80 (q, $J=11.6$ Hz, 1H), 2.76-2.69 (m, 1H), 2.46 (s, 1H), 1.99-1.93 (m, 1H), 1.85-1.77 (m, 1H).

[0522] Using the procedure described for Example 72, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
45A or 45B	ESI-MS m/z 464.1 [M-H] ⁻ ; ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.25 (s, 1H), 7.44 (d, 1H, $J=1.6$ Hz), 7.33(q, 1 H, $J=6.8$ Hz), 7.05 (q, 1H, $J=6.4$ Hz), 6.06-5.92 (m, 1H), 5.04-4.85 (m, 1H), 3.73-3.63 (m, 2H), 3.48-3.41 (m, 1H), 3.27-3.25 (m, 1H), 3.00 (q, 1H, $J=10.4$ Hz), 2.82-2.65 (m, 2H), 2.44 (s, 1H), 2.33-2.31 (m, 1H), 1.85-1.66 (m, 3H), 1.50-1.20 (m, 5H)

Example 73**Synthesis of Compound 271**

[0523] To a round bottom flask was charged (S)-6-chloro-1-((S)-tetrahydro-2H-pyran-3-yl)methyl)-2-(4-(trichloromethyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (100 mg, 0.18 mmol), methanol (2 mL), and sodium methoxide (100 mg, 0.46 mmol). The reaction mixture was stirred for an hour at room temperature. The mixture was poured into diethyl ether and water, extracted with diethyl ether (3x). The organics were concentrated and purified by prep-HPLC to give the desired compound as a white solid material. (8 mg, 9.5% yield). ESI-MS m/z 480.0 $[M-H]^-$; 1H NMR (400 MHz, DMSO- d_6) δ 11.24 (d, 1H, $J=4.4$ Hz), 7.45 (t, 1H, $J=3.6$ Hz), 7.34 (q, 1H, $J=5.2$ Hz), 7.05 (q, 1H, $J=6.8$ Hz), 5.99-5.92 (m, 1H), 4.96-4.87 (m, 1H), 3.99 (s, 1H), 3.96 (s, 1H), 3.73-3.64 (m, 2H), 3.50-3.38 (m, 1H), 3.28-3.26 (m, 1H), 3.06-2.96 (m, 1H), 2.78-2.66 (m, 2H), 2.54 (s, 1H), 2.35-2.22 (m, 1H), 1.84-1.56 (m, 3H), 1.50-1.23 (m, 3H).

[0524] Using the procedure described for Example 73, above, additional compounds described herein may be prepared by substituting the appropriate starting materials, suitable reagents and reaction conditions, obtaining compounds such as those selected from:

Cpd	Data
272	ESI-MS m/z 482 $[M-H]^-$; 1H NMR (DMSO- d_6 , 400MHz) 11.23 (d, $J=3.2$ Hz, 1H), 7.45 (t, $J=2.4$ Hz, 1H), 7.35 (q, $J=6.8$ Hz, 1H), 7.05 (q, $J=6.8$ Hz, 1H), 5.92-5.84 (m, 1H), 4.96-4.87 (m, 1H), 4.83 (t, $J=6.8$ Hz, 1H), 4.65 (q, $J=6.0$ Hz, 1H), 4.25 (t, $J=9.2$ Hz, 1H), 3.98 (d, $J=10.4$ Hz, 3H), 3.93-3.87 (m, 1H), 3.70-3.64 (m, 1H), 3.51-3.39 (m, 2H), 2.82-2.75 (m, 2H), 1.95-1.77 (m, 3H).
273	ESI-MS m/z 440 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 11.22(d, 1H, $J=10$ Hz), 7.44(t, 1H, $J=3.2$ Hz), 7.33 (q, 1H, $J=4.4$ Hz), 7.05(q, 1H, $J=6.8$ Hz), 6.00-5.93(m, 1H), 4.95-4.87(m, 1H), 3.97(d, 3H, $J=10.4$ Hz), 3.50-3.43(m, 1H), 2.74-2.66(m, 2H), 1.98-1.89(m, 1H), 1.79-1.52(m, 2H), 1.10(t, 3H, $J=6$ Hz), 0.92(q, 3H, $J=4.8$ Hz).

BIOLOGICAL EXAMPLES

[0525] The following *in vitro* biological examples demonstrate the usefulness of the compounds of the present description as DHODH inhibitors.

[0526] To describe in more detail and assist in understanding the present description, the following biological examples are not to be construed as limiting the scope of the present description but are offered to illustrate the scope thereof. Such variations of the present description that may be now known or later developed, which would be within the purview of one skilled in the art to ascertain, are considered to fall within the scope of the present description and as hereinafter claimed.

Example 74

MOLM-13 Cell Proliferation Assay

[0527] The following assay was conducted to measure proliferation of MOLM-13 cells in the presence of each compound studied. This assay was included as an indicator of DHODH inhibition, as growth of MOLM-13 cells is known to depend on synthesis of pyrimidines using the *de novo* pathway, which can be blocked by inhibition of DHODH.

[0528] 1. MOLM-13 cells were cultured in RPMI1640 medium + 10% Fetal Bovine Serum (FBS). Only low passage cells (< 20) were used for the compound tests

[0529] 2. On day 1, Log-phase growing Molm-13 Cells were counted and diluted to 105 cells/mL in RPMI 1640 medium + 10% FBS

[0530] 3. 100 mL of diluted MOLM-13 cells in 96 well white plates were seeded, for a final density of 104 cells/well.

[0531] 4. 0.5 mL of pre-diluted 200x compounds or DMSO control was added to each well. The final DMSO concentration was 0.5%.

[0532] 5. After 72Hours of culture at 37°C, 5% CO₂, the plates were taken out and cooled to RT, then 50 mL CellTiter-Glo® (Promega) was added, and the composition was mixed at RT for 10 minutes.

[0533] 6. The plates were then read by ViewLux (Speed-fast, Gain-High, Bining-1X, 5 seconds).

[0534] As shown in Table 1, the IC₅₀ (nM) for inhibition of proliferation was calculated for each compound (Cpd).

Table 1

Cpd	IC ₅₀
1	1.32
2	1.75
3	5.18
4	39.72
5	1.11
6	8.39

Cpd	IC ₅₀
114	0.53
115	0.39
116	0.57
117	0.36
118	4.22
119	1.55

Cpd	IC ₅₀
229	2.36
230	1.23
231	3.61
232	30.35
233	18.91
234	1.19

Cpd	IC ₅₀
7	0.69
8	2.98
9	3.47
10	9.86
11	3.47
12	9.59
13	3.16
14	23.27
15	4.19
16	0.72
17	0.47
18	1.30
19	3.45
20	0.64
21	7.69
22	1.73
23	2.45
24	0.98
25	0.91
26	0.79
27	0.52
28	0.34
29	0.20
30	4.29
31	2.26
32	3.49
33	4.50
34	42.09
35	7.40
36	0.67
37	2.55
38	4.13
39	6.87
40	32.23
41	1.35
42	0.15
43	2.00
44	0.12
45	0.65
46	0.83
47	0.12
48	0.46
49	0.08
50	0.48
51	0.58
52	8.48
53	0.80
54	1.13

Cpd	IC ₅₀
120	1.32
121	1.20
122	2.04
123	17.84
124	41.51
125	18.63
126	3.70
127	7.25
128	4.14
129	2.52
130	0.91
131	2.11
132	3.11
133	5.04
134	22.99
135	12.60
136	10.66
137	14.63
138A/B	31.54
139A/B/C/D	3.01
140A/B/C/D	2.15
141	3.04
144	12.05
145	1.73
146	9.58
147	5.38
148A/B	1.36
149A/B	4.96
150	34.65
151A/B	49.80
152A/B	37.79
153A/B	32.11
154	5.69
155A/B	45.34
156A/B	38.97
157A/B	11.80
158A/B	17.08
159A/B	16.63
160	10.75
161	2.21
162A/B	1.81
163A/B	2.49
164	11.51
165	37.68
166	1.06
167	3.22
168	5.19
169	13.50

Cpd	IC ₅₀
236	20.27
237	2.81
238	2.45
239	3.09
240	2.40
241	34.87
242	10.91
243	8.36
244	2.85
245	4.18
246	1.73
247	0.35
248	3.13
249	5.65
250	8.38
251	2.72
252	2.49
253	12.04
254	0.81
255	0.99
256	1.10
257	3.42
258	13.90
259	6.18
260	3.78
261	37.13
262	26.37
263	3.22
264	22.44
265	12.99
266	4.81
267	2.80
268	1.87
269	1.94
270	1.08
271	0.58
272	1.05
273	2.05
274	30.26
275	3.10
276	42.11
277	1.91
278	2.37
279	0.25
280	5.98
281	2.96
282	0.19
283	0.38

Cpd	IC ₅₀
55	2.28
56	7.03
57	4.76
58	0.72
59	3.36
60	4.10
61	5.20
62	0.97
63	0.81
64	0.72
65	1.62
66	5.01
67	11.85
68	2.10
69	1.22
70	4.17
71	1.35
72	0.95
73	5.92
74	4.53
75	8.76
76	10.46
77	10.45
78	30.89
79	32.20
80	6.71
81	12.21
82	29.57
83	17.42
84	3.37
85	17.13
86	9.64
87	3.98
88	22.43
89	19.50
90	10.32
92	28.60
93	27.74
94	9.23
95	2.43
96	8.54
97	4.42
98	26.92
99	5.60
100	4.19
101	2.37
102	6.32
103	14.85

Cpd	IC ₅₀
170A/B	0.67
171A/B	0.55
172	1.66
173	30.85
174	5.07
175	3.25
176	0.34
177	0.56
178	1.49
179	11.24
180	3.95
181	11.34
182	19.89
183	7.13
184	16.67
185	41.61
187	0.80
188	0.26
189	1.50
190	1.36
191A/B	0.79
192	1.17
193	0.78
194A/B	35.08
195A/B	20.43
196	6.24
197A/B	1.98
198A/B	18.23
199A/B	16.98
200A/B	14.90
201	2.58
202	19.91
203	14.81
204	23.69
205	37.45
206	42.97
207A/B	0.73
208A/B	4.08
209A/B	2.27
210A/B	6.12
211	0.67
212	1.75
213A/B	0.27
214	1.06
215	0.25
216	3.21
217A/B	2.64
218	0.96

Cpd	IC ₅₀
284	0.79
285	1.84
286	1.07
287	4.16
288	2.49
289	33.46
290	1.23
291	27.97
292	20.09
293	12.28
294	7.65
295	3.23
296	2.18
297	44.69
298	0.52
299	10.05
300	12.70
301	1.47
302	16.85
303	4.64
304	3.77
305	39.83
306	19.46
307	0.35
308	1.84
309	2.51
310	4.29
311	4.56
312	5.48
313	0.89
314	0.27
315	0.16
316A/B	3.53
317A/B	3.21
318	9.04
319	3.16
320	29.55
321	42.58
322	3.67
323	1.00
324	4.35
325	8.78
326	2.00
327	8.93
328	28.35
329	14.63
330	4.02
331	17.34

Cpd	IC ₅₀
104	0.83
105	4.26
106	4.74
107	2.45
108	0.52
109	0.40
110	1.64
111	6.49
112	6.50
113	1.38

Cpd	IC ₅₀
219A/B	1.90
220	10.74
221	3.40
222	4.35
223	1.00
224	1.80
225	1.17
226	2.58
227	3.20
228	4.42

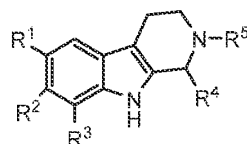
Cpd	IC ₅₀
332	3.77
333	10.92
334	1.28
335	6.75
336	19.63
337	2.66
338	4.43
339	6.56
340	1.14
341	30.73

[0535] Although certain aspects have been described in detail above, those having ordinary skill in the art will clearly understand that many modifications are possible without departing from the teachings thereof and are intended to be encompassed within the claims as described herein.

CLAIMS

We claim:

1. A compound of Formula (I):



(I)

or a form thereof, wherein:

R^1 is hydrogen, halo, hydroxy, C_{1-8} alkoxy, amino, or heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; and, wherein heteroaryl is optionally substituted with one, two, or three R^{1A} substituents;

R^{1A} is C_{1-8} alkyl;

R^2 is hydrogen, halo, hydroxy, C_{1-8} alkyl, C_{1-8} alkoxy, or amino;

R^3 is hydrogen, hydroxy, or amino;

R^4 is halo, hydroxy, cyano, C_{1-8} alkyl, C_{1-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, C_{1-8} alkylthio, or thiocarbonyl; wherein C_{1-8} alkyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo, C_{1-8} alkoxy, C_{1-8} alkoxycarbonyl, aminocarbonyl, C_{1-8} alkylcarbonyloxy, carboxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, heteroaryl, or heterocyclyl; wherein C_{1-8} alkenyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, C_{1-8} alkoxycarbonyl, C_{3-8} cycloalkyl, or heterocyclyl; wherein C_{1-8} alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, heteroaryl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents;

R^{4A} is halo, hydroxy, cyano, oxo, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} alkylthio, or thiocarbonyl; wherein C_{1-8} alkyl is optionally substituted with one, two, or three substituents

independently selected from halo; and, wherein C₁₋₈alkoxy is optionally substituted with one, two, or three substituents independently selected from halo;

R⁵ is heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; and, wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents;

R^{5A} is halo, cyano, C₁₋₈alkyl, C₁₋₈alkylthio, C₁₋₈alkoxy, or heterocyclyl; wherein C₁₋₈alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C₁₋₈alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and wherein heterocyclyl is optionally substituted with one or two R^{5B} substituents;

R^{5B} is halo, hydroxy, cyano, oxo, C₁₋₈alkyl, C₁₋₈alkyl, C₁₋₈alkylthio, C₁₋₈alkoxy, or thiocarbonyl; wherein C₁₋₈alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C₁₋₈alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; and, wherein the form of the compound is selected from the group consisting of a free acid, free base, salt, hydrate, solvate, anhydrous, racemate, enantiomer, diastereomer, stereoisomer, and tautomer thereof.

2. The compound of claim 1, wherein R¹ is hydrogen, halo, hydroxy, C₁₋₈alkoxy, or heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 or 6 ring members or a bicyclic ring having 9 or 10 ring members; wherein heteroaryl is optionally substituted with one R^{1A} substituent; and, wherein R^{1A} is C₁₋₈alkyl.
3. The compound of claim 1, wherein R² is hydrogen or halo and R³ is hydrogen, or amino.
4. The compound of claim 1, wherein R⁴ is hydroxy, C₁₋₈alkyl, C₁₋₈alkenyl, C₂₋₈alkynyl, or thiocarbonyl; wherein C₁₋₈alkyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, cyano, oxo, C₁₋₈alkoxy, C₁₋₈alkoxycarbonyl, aminocarbonyl, C₁₋₈alkylcarbonyloxy, carboxy, C₃₋₈cycloalkyl, C₃₋₈scycloalkenyl, or heterocyclyl; wherein C₁₋₈alkenyl is optionally substituted with one, two, or three substituents independently selected from halo, hydroxy, C₁₋₈alkoxycarbonyl, C₃₋₈scycloalkyl, or heterocyclyl; wherein heterocyclyl is selected from a monocyclic ring

having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7 or 8 ring members or a polycyclic ring having 13-16 ring members; and, wherein C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, and heterocyclyl are optionally substituted with one, two, or three R^{4A} substituents; and, wherein R^{4A} is oxo, C₁₋₈alkyl, thiocarbonyl, or hydroxy.

5. The compound of claim 1, wherein R⁵ is heteroaryl, wherein heteroaryl is selected from a monocyclic ring having 5 to 6 ring members or a bicyclic ring having from 9 to 10 ring members; wherein heteroaryl is optionally substituted with one, two, or three R^{5A} substituents; wherein, R^{5A} is halo, cyano, C₁₋₈alkyl, C₁₋₈alkylthio, C₁₋₈alkoxy, or heterocyclyl; wherein C₁₋₈alkyl is optionally substituted with one, two, or three substituents independently selected from halo; wherein C₁₋₈alkoxy is optionally substituted with one, two, or three substituents independently selected from halo; wherein heterocyclyl is selected from a monocyclic ring having 3-7 ring members, a bicyclic ring having 6-10 ring members, a bicyclic ring having 7-8 ring members or a polycyclic ring having 13-16 ring members; wherein heterocyclyl is optionally substituted with one or two R^{5B} substituents; wherein R^{5B} is C₁₋₈alkyl; wherein C₁₋₈alkyl is optionally substituted with one, two, or three substituents independently selected from halo.

6. A compound selected from the group consisting of:

(1S)-6-chloro-1-(2-methylprop-1-en-1-yl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-bromo-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-methoxy-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-1-[[{(3S)-oxan-3-yl]methyl}]-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-1-[[{(3R)-oxan-3-yl]methyl}]-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1-[[{(3S)-oxan-3-yl]methyl}]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

(1S)-6-chloro-2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-1-[[3(R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-bromo-1-[[3(R)-oxan-3-yl]methyl]-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-6-bromo-1-[[3(S)-oxan-3-yl]methyl]-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-1-(2-methylpropyl)-6-(2H-1,2,3-triazol-2-yl)-2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-1-(2-methylpropyl)-6-(2H-1,2,3-triazol-2-yl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-1-(2-methylpropyl)-6-(4-methyl-2H-1,2,3-triazol-2-yl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-6-(4-methyl-2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[[3(R)-oxan-3-yl]methyl]-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-1-[[3(S)-oxan-3-yl]methyl]-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-1-[(1,3-dioxan-5-yl)methyl]-6-(2H-1,2,3-triazol-2-yl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-bromo-1-[(1,3-dioxan-5-yl)methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-methyl-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[4(S)-1,3-dioxan-4-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[4(R)-1,3-dioxan-4-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[[(4S)-1,3-dioxan-4-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[[(4R)-1,3-dioxan-4-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
5-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1,3-dioxan-2-one,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-6-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-6-fluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-[(oxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-[[[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[[(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-[[[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-methyl-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[[[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-6-chloro-2-[4-methyl-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[[[(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[[(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-[[[(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-fluoro-1-[[{(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-fluoro-1-[[{(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(2S)-oxan-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(2R)-oxan-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(oxan-2-yl)methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(oxan-4-yl)methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[[{(3S)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[[{(3R)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(3S)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(3R)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(3S)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(3R)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(3S)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(3R)-oxolan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxolan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxetan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(2S)-1-[(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-4-methoxybutan-2-ol AND (2R)-1-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-4-methoxybutan-2-ol,
(2S)-1-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-4-methoxybutan-2-ol AND (2R)-1-[(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-4-methoxybutan-2-ol,
methyl 4-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-3-methylbutanoate,
methyl 4-[2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]butanoate,

methyl 5-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} pentanoate,
methyl 6-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} hexanoate,
methyl 3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} propanoate,
methyl 3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanoate,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[3-methoxy-2-(methoxymethyl)propyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(2S)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-methoxypropan-2-ol AND (2R)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-methoxypropan-2-ol,
(2R)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-methoxypropan-2-ol AND (2S)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-methoxypropan-2-ol,
(2S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-hydroxypropyl acetate AND (2R)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-hydroxypropyl acetate,
(2S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} propane-1,2-diyl diacetate AND (2R)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} propane-1,2-diyl diacetate,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-2-methoxypropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2,2-dimethoxyethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
ethyl {2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} acetate,

(2S)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propan-2-ol AND (2R)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propan-2-ol,
(2R)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propan-2-ol AND (2S)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propan-2-ol,
1-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl-2-methylpropan-2-ol,
(2S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol AND (2R)-3-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol,
(2S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)propane-1,2-diol,
(3R)-4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butane-1,3-diol AND (3S)-4-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butane-1,3-diol,
(3S)-4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butane-1,3-diol AND (3R)-4-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butane-1,3-diol,
4-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl butan-1-ol,
5-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)pentan-1-ol,
(4S)-5-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-methylpentan-1-ol,
(4R)-5-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-methylpentan-1-ol,
4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)butane-1,2-diol,
(3R)-4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-methylbutan-1-ol,
(6R)-7-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2,6-dimethylheptan-2-ol,
(6S)-7-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2,6-dimethylheptan-2-ol,
7-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2,6-dimethylheptane-2,3-diol,
6-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)hexanoic acid,
6-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)hexan-1-ol,
(1R,3S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methylcyclopentan-1-ol,
(1S,3S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methylcyclopentan-1-ol,

(1R,3R)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)cyclopentan-1-ol,
(1S)-6-chloro-1-(cyclopentylmethyl)-2-[4-(difluoromethyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(cyclopentylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(cyclopentylmethyl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(cyclopentylmethyl)-2-[4-(4-methylpiperazin-1-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-(4-methylpiperazin-1-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(2-methylpropyl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-(difluoromethyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-bromo-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(but-3-yn-1-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-butyl-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-2-methylbutyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylbutyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-pentyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1-methylpiperidin-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
4-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}butanamide,
5-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]pentanamide,
(3S)-4-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]-3-methylbutanamide,
6-[(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl]hexanamide,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(6-chloro-2,6-dimethylheptyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(but-3-en-1-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylbut-3-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(but-3-en-1-yl)-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(3Z)-hex-3-en-1-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2,6-dimethylhept-5-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylprop-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(prop-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(prop-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(3,3-difluoroprop-2-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(2S)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanamide OR (2R)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanamide,
(3S)-3-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)piperidin-2-one OR (3R)-3-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)piperidin-2-one OR (3R)-3-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)piperidin-2-one OR (3S)-3-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)piperidin-2-one,
(3S)-3-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)-1-methylpiperidin-2-one OR (3R)-3-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)-1-methylpiperidin-2-one OR (3R)-3-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)-1-methylpiperidin-2-one OR (3S)-3-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)-1-methylpiperidin-2-one,
3-({2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)-1-methylpyrrolidin-2-one,
3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} propan-1-ol,
3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropan-1-ol,
2-({2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)propane-1,3-diol,
2-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)propane-1,3-diol,

(2R)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol OR (2S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol,
(2S)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol OR (2R)-3-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol,
2-((1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl) methyl)propane-1,3-diol,
(2S)-3-((1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl) propane-1,2-diol AND (2R)-3-((1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl) propane-1,2-diol,
(2R)-1-((1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl) propan-2-ol AND (2S)-1-((1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl) propan-2-ol,
(2S)-1-((1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl) propan-2-ol AND (2R)-1-((1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl) propan-2-ol,
(2R)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl) butan-2-ol,
(3R)-4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-hydroxybutanenitrile AND (3S)-4-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-3-hydroxybutanenitrile,
(4S)-5-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-hydroxypentanenitrile AND (4R)-5-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-hydroxypentanenitrile,
(4R)-5-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-hydroxypentanenitrile AND (4S)-5-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-4-hydroxypentanenitrile,
(1S)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol AND (1R)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol,
(1R)-1-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol AND (1S)-1-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-methylpropan-1-ol,
3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} propanenitrile,
3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanenitrile,

(2S)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanenitrile OR (2R)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanenitrile,
(2R)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanenitrile OR (2S)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylpropanenitrile,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-6-ol,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-methoxy-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-methoxy-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-methoxy-1-(2-methylpropyl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
1-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}propan-2-one,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-3-fluoro-2-methylpropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-3-fluoro-2-methylpropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2R)-3-fluoro-2-methylpropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(2S)-3-fluoro-2-methylpropyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(3,3,3-trifluoro-2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(prop-2-yn-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2,2,2-trifluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2,2-difluoroethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(cyclohexylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(cyclohexylmethyl)-2-[4-(difluoromethyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(cyclohexylmethyl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(cyclohexylmethyl)-2-[4-(4-methylpiperazin-1-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(cyclohexylmethyl)-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(cyclobutylmethyl)-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(cyclopentylmethyl)-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(cyclopropylmethyl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-({(1S)-6-chloro-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)propane-1,3-diol,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(3S)-oxan-3-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-8-amine,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-methoxy-1-{{(3S)-oxan-3-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-methoxy-1-{{(3R)-oxan-3-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-methoxy-1-{{(3S)-oxan-3-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,4-dioxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,4-dioxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(2R)-1,4-dioxan-2-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(2S)-1,4-dioxan-2-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(4S)-4-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)-1,3-dioxolane-2-thione AND (4R)-4-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)-1,3-dioxolane-2-thione,
(4R)-4-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)-1,3-dioxolane-2-thione AND (4S)-4-({(1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methyl)-1,3-dioxolane-2-thione,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxolan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(4R)-1,3-dioxolan-4-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(4S)-1,3-dioxolan-4-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(4S)-1,3-dioxolan-4-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-{{(4R)-1,3-dioxolan-4-yl}methyl}-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

(4S)-4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1,3-dioxolan-2-one AND (4R)-4-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1,3-dioxolan-2-one,
(4R)-4-((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1,3-dioxolan-2-one AND (4S)-4-((1R)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)-1,3-dioxolan-2-one,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1,3-dioxolan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-[(1,3-dioxolan-2-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(2,2-dimethoxyethyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(2-methoxypropyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(3-methoxybutyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
methyl 3-[6-chloro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl] propanoate,
(1S)-6-chloro-1-[[{(3R)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-6-chloro-1-[[{(3S)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[[{(3S)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-6-chloro-1-[[{(3R)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-[[{(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-[[{(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-[[{(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-[[{(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]-1-[[{(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(oxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(S)-2-(4,6-bis(trifluoromethyl)pyrimidin-2-yl)-6-chloro-1-(((R)-tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (S)-2-(4,6-bis(trifluoromethyl)pyrimidin-2-yl)-6-chloro-1-(((S)-tetrahydro-2H-pyran-3-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[[{(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[[{(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(oxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(oxolan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(oxolan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-methoxy-1-[(3S)-oxan-3-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(1,4-dioxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole AND (1R)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(1,4-dioxan-2-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl]propane-1,3-diol,
(1S)-6-chloro-1-(2-methylpropyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-bromo-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-propyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-1-butyl-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(cyclopropylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(cyclobutylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(cyclopentylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(cyclopentylmethyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
1-(but-3-en-1-yl)-6-chloro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-[(3Z)-hex-3-en-1-yl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(cyclopent-2-en-1-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
3-[(6-chloro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl]piperidin-2-one,
(1S)-6-chloro-1-(cyclohexylmethyl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(cyclohexylmethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(cyclohexylmethyl)-7-fluoro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

6-chloro-1-(cyclopentylmethyl)-7-fluoro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(cyclopropylmethyl)-7-fluoro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(cyclobutylmethyl)-7-fluoro-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-7-fluoro-1-[(oxan-4-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-(difluoromethyl)pyrimidin-2-yl]-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-methyl-6-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-[(1,3-dioxan-5-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-(4-methylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-(4-ethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(4-ethylpyrimidin-2-yl)-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(4-methylpyrimidin-2-yl)-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-[(oxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(5-fluoro-4,6-dimethylpyrimidin-2-yl)-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(5-fluoro-4-methylpyrimidin-2-yl)-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(5-fluoropyrimidin-2-yl)-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-2-(4-chloropyrimidin-2-yl)-7-fluoro-1-[(oxan-4-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(4,6-dimethoxypyrimidin-2-yl)-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethoxy)pyrimidin-2-yl]-6-chloro-1-[(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(difluoromethoxy)pyrimidin-2-yl]-6-chloro-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-7-fluoro-1-(2-methylpropyl)-2-(pyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(cyclopropylmethyl)-2-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(cyclobutylmethyl)-2-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(cyclopentylmethyl)-2-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-1-(cyclohexylmethyl)-2-(4,6-dimethylpyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[(1S)-6-chloro-1-[[[(3S)-oxan-3-yl]methyl]]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl]pyrimidine-4-carbonitrile,
2-[(1S)-6-chloro-1-[[[(3S)-oxan-3-yl]methyl]]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl]-5-fluoropyrimidine-4-carbonitrile,
(1S)-6-chloro-2-[4-methoxy-6-(trifluoromethyl)pyrimidin-2-yl]-1-[[[(3S)-oxan-3-yl]methyl]]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-[[[(3S)-oxan-3-yl]methyl]]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(1,3-dioxan-5-yl)methyl]-2-[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-methoxy-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-2-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(4,6-dimethoxy-1,3,5-triazin-2-yl)-1-[[[(3S)-oxan-3-yl]methyl]]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-8-iodo-1-[[[(3S)-oxan-3-yl]methyl]]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
diethyl ((2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)propanedioate,
diethyl ((1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)methyl)propanedioate,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(cyclopent-2-en-1-yl)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-ethenyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(1E)-prop-1-en-1-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-(difluoromethyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(2-methylprop-1-en-1-yl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

(1S)-6-chloro-1-(2-methylprop-1-en-1-yl)-2-[4-(methylsulfanyl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[4-(4-methylpiperazin-1-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(2E)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylprop-2-en-1-ol,
2-({(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl} methylidene)propane-1,3-diol,
methyl (2E)-3-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}-2-methylprop-2-enoate,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[(oxan-4-ylidene)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(cyclohexylidenemethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-(cyclohexylidenemethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(4,6-dimethyl-1,3,5-triazin-2-yl)-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1R)-6-chloro-2-(4,6-dimethylpyrimidin-2-yl)-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-(2-methylprop-1-en-1-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-6-chloro-1-ethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-1-(2-methylpropyl)-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)pyrimidin-2-yl]-1-(2-methylpropyl)-6-(4-methyl-2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-1-(2-methylpropyl)-6-(2H-1,2,3-triazol-2-yl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-1-(2-methylprop-1-en-1-yl)-6-(2H-1,2,3-triazol-2-yl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-1-(2-methylprop-1-en-1-yl)-6-(1H-1,2,3-triazol-1-yl)-2-[4-(trifluoromethyl)pyrimidin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-1-(2-methylpropyl)-6-(1H-1,2,3-triazol-1-yl)-2-[4-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylprop-1-en-1-yl)-6-(2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-1-(2-methylprop-1-en-1-yl)-6-(4-methyl-2H-1,2,3-triazol-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

(1S)-6-chloro-1-(2-methylprop-1-en-1-yl)-2-[4-(morpholin-4-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(2-methylpropyl)-2-[4-(morpholin-4-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(cyclopentylmethyl)-2-[4-(morpholin-4-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(cyclohexylmethyl)-2-[4-(morpholin-4-yl)-6-(trifluoromethyl)-1,3,5-triazin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(difluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(3R)-3,6-dihydro-2H-pyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(3R)-3,6-dihydro-2H-pyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(3S)-3,6-dihydro-2H-pyran-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(2R)-3,6-dihydro-2H-pyran-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(2S)-3,6-dihydro-2H-pyran-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(2S)-3,6-dihydro-2H-pyran-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole OR (1S)-2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-1-[[{(2R)-3,6-dihydro-2H-pyran-2-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
methyl (2E)-4-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}but-2-enoate,
methyl (2Z)-4-{2-[4,6-bis(trifluoromethyl)-1,3,5-triazin-2-yl]-6-chloro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl}but-2-enoate,
(1S)-6-chloro-1-(2-methylpropyl)-2-[2-(trifluoromethyl)pyrimidin-4-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
6-chloro-2-(2-chloropyrimidin-4-yl)-1-(cyclopentylmethyl)-7-fluoro-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[2-methoxy-6-(trifluoromethyl)pyrimidin-4-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[2-methoxy-6-(trifluoromethyl)pyrimidin-4-yl]-1-[[{(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-2-[2-methoxy-6-(trifluoromethyl)pyrimidin-4-yl]-1-[[{(3R)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(oxan-4-yl)methyl]-2-[4-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[[{(3S)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[[{(3R)-oxan-3-yl]methyl]-2-[4-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-[(oxan-4-yl)methyl]-2-[6-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
(1S)-6-chloro-1-(2-methylpropyl)-2-[6-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

(1S)-6-chloro-1-(2-methylpropyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-2-(2-methyl-2H-tetrazol-5-yl)-1-[[3-(3S)-oxan-3-yl]methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-1-[[3-(3S)-oxan-3-yl]methyl]-2-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-1-[[3-(3R)-oxan-3-yl]methyl]-2-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-1-[[3-(3S)-oxan-3-yl]methyl]-2-[3-(trifluoromethyl)-1,2,4-thiadiazol-5-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-1-[[3-(3R)-oxan-3-yl]methyl]-2-[3-(trifluoromethyl)-1,2,4-thiadiazol-5-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-1-(2-methylpropyl)-2-[3-(trifluoromethyl)-1,2,4-thiadiazol-5-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-1-(2-methylpropyl)-2-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 (1S)-6-chloro-2-[5-(difluoromethyl)-1,2,4-oxadiazol-3-yl]-1-(2-methylpropyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,
 6-chloro-1-(2-methylpropyl)-2-[5-(trifluoromethyl)-1,2,4-triazin-3-yl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole, and
 6-chloro-7-fluoro-1-(2-methylprop-1-en-1-yl)-2-(pyrimidin-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

or a form thereof selected from the group consisting of a free acid, free base, salt, hydrate, solvate, anhydrous, racemate, enantiomer, diastereomer, stereoisomer, and tautomer thereof.

7. A method of use of a compound of Formula (I), or a form thereof, selected from either claim 1 or 6 to treat or ameliorate a disease or disorder in a subject in need thereof comprising, administering to the subject an effective amount of a compound of Formula (I), or a form thereof, to inhibit dihydroorotate dehydrogenase.
8. A pharmaceutical composition comprising a compound of Formula (I), or a form thereof, selected from either claim 1 or 6 and a pharmaceutically acceptable excipient to treat or ameliorate a disease or disorder by inhibiting dihydroorotate dehydrogenase.