AMINO QUINOLINE COMPOUNDS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of United States Provisional Patent Application No. 63/618,189 filed January 5, 2024, which is hereby incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] Aspects of the invention generally relate to amino quinoline compounds, pharmaceutical compositions, kits comprising the same, their use as biomolecular condensate modifying drugs (c-mods), and their use in the treatment of a disease or condition.

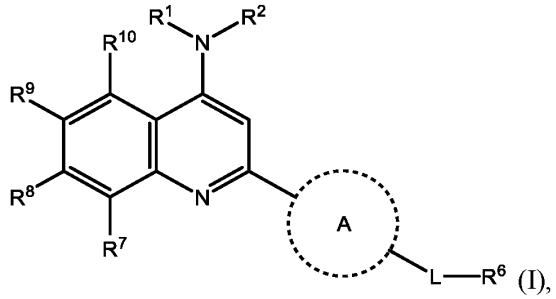
BACKGROUND OF THE INVENTION

[0003] TAR DNA-binding protein 43 (TDP-43) is a highly conserved and ubiquitously-expressed RNA/DNA-binding protein involved in RNA processing. Cytoplasmic aggregates of TDP-43 occur in >97% of amyotrophic lateral sclerosis (ALS) cases. Stress-induced formation of cytoplasmic TDP-43 biological condensates represent an intermediate, reversible, pre-pathological state in neurons. Over time, TDP-43-containing condensates lose their fluid-like properties and potentially convert into irreversible, toxic aggregates [Ling, *et al.*, *Neuron* 79, 416–438 (2013); Markmiller, *et al. Cell Reports* 36, 109685 (2021); and Lu *et al. Nat Cell Biol* 1–16 (2022)].

[0004] The role of condensate dysfunction in ALS pathogenesis is supported by the discovery of condensate genes as genetic modifiers of ALS (*e.g.,* TAF15, EWSR1, TIA1, HNRNPA1, HNRNPA2B1), as well as co-localization of C9ORF72 ALS G_4C_2 expansion-derived dipeptide repeats (DPRs) and stress granule proteins with TDP-43 inclusions in preclinical models. Nuclear depletion of TDP-43 into cytoplasmic condensates leads to toxic loss of splicing function in motor neurons. Small molecule condensate modifying drugs (c-mods) that directly modulate TDP-43 condensates can treat diverse forms of ALS. [Chew, J. *et al.*, *Mol. Neurodegener.* 14, 9 (2019); and Taylor, J. P., *et al.*, *Nature* 539, 197–206 (2016)].

BRIEF SUMMARY OF THE INVENTION

[0005] In one aspect, provided herein is a compound of formula (I)



(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein

R^1 and R^2 are each independently C_{1-6}alkyl, C_{2-6}alkenyl, $-C(=O)R^{14}$, $-C(=O)OR^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl wherein

the C_{1-6}alkyl of R^1 or R^2 is optionally substituted with one or more R^{1a},

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^1 or R^2 is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C_{1-6}alkyl, C_{2-6}alkenyl, $-C(=O)R^{14}$, $-C(=O)OR^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or C_{3-8}cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1b};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl, wherein

the 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of R^1 and R^2 is optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, oxo, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, -

$N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with one or more R^{3a}, and

optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b};

Ring A is 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 12-membered unsaturated heterocyclyl or 5- to 10-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^4 is optionally substituted by one or more R^{4a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^4 is optionally substituted with one or more R^{4b}, and

the 3- to 8-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

L is a bond, C_{1-6}alkyl, $-O-(C_{1-6}$alkyl$)-$, $-S-(C_{1-6}$alkyl$)-$, or $-N(R^5)(C_{1-6}$alkyl$)-$, wherein

the C_{1-6}alkyl, $-O-(C_{1-6}$alkyl$)-$, $-S-(C_{1-6}$alkyl$)-$, or $-N(R^5)(C_{1-6}$alkyl$)-$ is optionally substituted by one or more R^L;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, -

$OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a C_{3-8}cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-C(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, or $-S(=O)_2N(R^{13})(R^{14})$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, -O-(3- to 12-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^6 is optionally substituted by one or more R^{6a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -O-(3- to 12-membered N-containing heterocyclyl), or -O-(5- to 6-membered N-containing heteroaryl) of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 8-membered heterocyclyl of R^6 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^6 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{6b};

R^7, R^8, R^9, and R^{10} are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -OR^{11}, -OR^{12}, -SR^{12}, -SF_5, -$N(R^x)(R^y)$, -NO_2, -CN, -$N(R^{13})C(=O)R^{14}$, -$N(R^{13})C(=O)N(R^{13})R^{14}$, -$N(R^{13})C(=O)OR^{14}$, -$OC(=O)R^{14}$, -$OC(=O)N(R^{13})R^{14}$, -$OC(=O)OR^{14}$, -$C(=O)R^{14}$, -$C(=O)N(R^{13})(R^{14})$, -$C(=O)OR^{14}$, -$C(=NR^{15})R^{14}$, -$C(=NOR^{14})R^{14}$, -$C(=NR^{15})N(R^{13})R^{14}$, -$C(=NR^{15})OR^{14}$, -$N(R^{13})S(=O)_2R^{14}$, -$S(=O)R^{14}$, -$S(=O)N(R^{13})R^{14}$, -$S(=O)OR^{14}$, -$S(=NR^{15})R^{14}$, -$S(=NR^{15})N(R^{13})R^{14}$, -$S(=NR^{15})OR^{14}$, -$S(=O)_2R^{14}$, -$S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^7, R^8, R^9, or R^{10} is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^7, R^8, R^9, or R^{10} is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^7, R^8, R^9, or R^{10} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^7, R^8, R^9, or R^{10} are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, -$N(R^x)(R^y)$, -OR^{12}, -SR^{12}, -SF_5, -NO_2, -CN, -$N(R^{13})C(=O)R^{14}$, -$N(R^{13})C(=O)N(R^{13})R^{14}$, -$N(R^{13})C(=O)OR^{14}$, -$OC(=O)R^{14}$, -$OC(=O)N(R^{13})R^{14}$, -$OC(=O)OR^{14}$, -$C(=O)R^{14}$, -$C(=O)N(R^{13})(R^{14})$, -$C(=O)OR^{14}$, -$C(=NR^{15})R^{14}$, -$C(=NOR^{14})R^{14}$, -$C(=NR^{15})N(R^{13})R^{14}$, -$C(=NR^{15})OR^{14}$, -$N(R^{13})S(=O)_2R^{14}$, -$S(=O)R^{14}$, -$S(=O)_2R^{14}$, -$S(=O)N(R^{13})R^{14}$, -$S(=O)OR^{14}$, -$S(=NR^{15})R^{14}$, -$S(=NR^{15})N(R^{13})R^{14}$, -$S(=NR^{15})OR^{14}$, -$S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, -OR^{11}, -$N(R^x)(R^y)$, oxo, -CN, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;

each R^{11} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^{11} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, or $-N(R^x)(R^y)$, and

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{11} is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl of R^{12} is optionally substituted with one or more halo, deuterium, C_{1-6}alkoxy, $-N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, $-O(C_{1-6}$alkyl), -SH, $-S(C_{1-6}$alkyl), $-(C=O)NH_2$, -(C=O)OH, $-O(C=O)C_{1-8}$alkyl), $-NH(C=NH)NH_2$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the 6- to 10-membered aryl is optionally substituted by -OH, and

the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, -OH, or $-N(R^x)(R^y)$;

each R^{15} is independently H or C_{1-6}alkyl; and

each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, $-C(=O)(C_{1-6}$alkyl), or $-C(=O)O(C_{1-6}$alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with halo, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, $-NH_2$, $NH(C_{1-6}$alkyl), or $-N(C_{1-6}$alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of $-C(=O)(C_{1-6}$alkyl) or $-C(=O)O(C_{1-6}$alkyl) is optionally substituted with $-O(C=O)C_{1-8}$alkyl).

[0006] In some embodiments, the compound of formula (I) is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0007] Any embodiments provided herein of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, apply where applicable to any other formula detailed herein, the same as if each and every embodiment were specifically and individually listed. Thus, it is understood and described that each embodiment provided herein of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, such as embodiments related to R^1, R^2, R^3, Ring A, R^4, L, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{1a}, R^{3a}, R^{6a}, R^{7a}, R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, R^{7b}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^x, and R^y, apply to formula (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the same as if each and every embodiment were specifically and individually listed. It is also understood and described that all such embodiments may be used in any of the pharmaceutical compositions, methods, kits, uses, or other aspects detailed herein.

[0008] In one aspect, provided is a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another variation, provided is a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0009] In one aspect, provided is a method for treating a disease or condition mediated by TDP-43, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a

pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another variation, provided is a method for treating a disease or condition mediated by TDP-43, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0010] In one aspect, provided herein is a method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another variation, provided herein is a method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0011] In one aspect, provided herein is a method of modulating TDP-43 target gene expression levels, comprising contacting a cell with an effective amount of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. This aspect in some embodiments may employ a

compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another variation, provided herein is a method of modulating TDP-43 target gene expression levels, comprising contacting a cell with an effective amount of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0012] In one aspect, provided herein is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients, for use in the treatment of a disease or condition mediated by TDP-43. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another variation, provided herein is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients, for use in the treatment of a disease or condition mediated by TDP-43. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0013] In one aspect, provided herein is the use of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients, in the manufacture a medicament for the treatment of

a disease or condition mediated by TDP-43. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another variation, provided herein is the use of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients, in the manufacture a medicament for the treatment of a disease or condition mediated by TDP-43. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0014] In one aspect, provided herein is a kit, comprising (i) a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and (ii) instructions for use in treating a TDP-43 mediated disease or condition in an individual in need thereof. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another variation, provided herein is a kit, comprising (i) a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) instructions for use in treating a TDP-43 mediated disease or condition in an individual in need thereof. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0015] All pharmaceutical compositions, methods, kits, uses, or other aspects described herein with reference to formula (I), or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, are also hereby described and embraced for any one of the other formulas detailed herein such as formula (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), the same as if each and every embodiment were specifically and individually listed.

DETAILED DESCRIPTION OF THE INVENTION

[0016] "Individual" refers to mammals and includes humans and non-human mammals. Examples of individuals include, but are not limited to, mice, rats, hamsters, guinea pigs, pigs, rabbits, cats, dogs, goats, sheep, cows, and humans. In some embodiments, individual refers to a human.

[0017] As used herein, "about" a parameter or value includes and describes that parameter or value per se. For example, "about X" includes and describes X per se.

[0018] "Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired results may include one or more of the following: decreasing one or more symptom resulting from the disease or condition; diminishing the extent of the disease or condition; slowing or arresting the development of one or more symptom associated with the disease or condition (*e.g.*, stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition); and relieving the disease, such as by causing the regression of clinical symptoms (*e.g.*, ameliorating the disease state, enhancing the effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival).

[0019] As used herein, "delaying" development of a disease or condition means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease or condition. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease or condition.

[0020] As used herein, the term "therapeutically effective amount" or "effective amount" intends such amount of a compound of the disclosure or a pharmaceutically salt thereof sufficient to effect treatment when administered to an individual. As is understood in the art, an effective amount may be in one or more doses, *e.g.*, a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved.

[0021] As used herein, "unit dosage form" refers to physically discrete units, suitable as unit dosages, each unit containing a predetermined quantity of active ingredient, or compound, which may be in a pharmaceutically acceptable carrier.

[0022] As used herein, by "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a pharmaceutical composition administered to an individual without causing significant undesirable biological effects.

[0023] The term "alkyl", as used herein, refers to an unbranched or branched saturated univalent hydrocarbon chain. As used herein, alkyl has 1-20 carbons (*i.e.*, C_{1-20}alkyl), 1-16 carbons (*i.e.*, C_{1-16}alkyl), 1-12 carbons (*i.e.*, C_{1-12}alkyl), 1-10 carbons (*i.e.*, C_{1-10}alkyl), 1-8 carbons (*i.e.*, C_{1-8}alkyl), 1-6 carbons (*i.e.*, C_{1-6}alkyl), 1-4 carbons (*i.e.*, C_{1-4}alkyl), or 1-3 carbons (*i.e.*, C_{1-3}alkyl). Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, pentyl, 2-pentyl, *iso*-pentyl, *neo*-pentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or molecular formula, all positional isomers having that number of carbon atoms may be encompassed—for example, "butyl" includes *n*-butyl, *sec*-butyl, *iso*-butyl, and *tert*-butyl; and "propyl" includes *n*-propyl and *iso*-propyl. Certain commonly used alternative names may be used and will be understood by those of ordinary skill in the art. For instance, a divalent group, such as a divalent "alkyl" group, may be referred to as an "alkylene".

[0024] The term "alkenyl", as used herein, refers to a branched or unbranched univalent hydrocarbon chain comprising at least one carbon-carbon double bond. As used herein, alkenyl has 2-20 carbons (*i.e.*, C_{2-20}alkenyl), 2-16 carbons (*i.e.*, C_{2-16}alkenyl), 2-12 carbons (*i.e.*, C_{2-12}alkenyl), 2-10 carbons (*i.e.*, C_{2-10}alkenyl), 2-8 carbons (*i.e.*, C_{2-8}alkenyl), 2-6 carbons (*i.e.*, C_{2-6}alkenyl), 2-4 carbons (*i.e.*, C_{2-4}alkenyl), or 2-3 carbons (*i.e.*, C_{2-3}alkenyl). Examples of alkenyl include, but are not limited to, ethenyl, prop-1-enyl, prop-2-enyl 1,2-butadienyl, and 1,3-butadienyl. When an alkenyl residue having a specific number of carbons is named by chemical name or molecular formula, all positional isomers having that number of carbon atoms may be encompassed—for example, "propenyl" includes prop-1-enyl and prop-2-enyl. Certain commonly used alternative names may be used and will be understood by those of ordinary skill in the art. For instance, a divalent group, such as a divalent "alkenyl" group, may be referred to as an "alkenylene".

[0025] The term "alkynyl", as used herein, refers to a branched or unbranched univalent hydrocarbon chain comprising at least one carbon-carbon triple bond. As used herein, alkynyl has 2-20 carbons (*i.e.*, C_{2-20}alkynyl), 2-16 carbons (*i.e.*, C_{2-16}alkynyl), 2-12 carbons (*i.e.*, C_{2-12}alkynyl), 2-10 carbons (*i.e.*, C_{2-10}alkynyl), 2-8 carbons (*i.e.*, C_{2-8}alkynyl), 2-6 carbons (*i.e.*, C_{2-6}alkynyl), 2-4 carbons (*i.e.*, C_{2-4}alkynyl), or 2-3 carbons (*i.e.*, C_{2-3}alkynyl).

Examples of alkynyl include, but are not limited to, ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, and but-3-ynyl. When an alkynyl residue having a specific number of carbons is named by chemical name or molecular formula, all positional isomers having that number of carbon atoms may be encompassed—for example, "propynyl" includes prop-1-ynyl and prop-2-ynyl. Certain commonly used alternative names may be used and will be understood by those of ordinary skill in the art. For instance, a divalent group, such as a divalent "alkynyl" group, may be referred to as an "alkynylene".

[0026] The term "alkoxy", as used herein, refers to an -O-alkyl moiety. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, and 1,2-dimethylbutoxy.

[0027] The term "aryl", as used herein, refers to a fully unsaturated carbocyclic ring moiety. The term "aryl" encompasses monocyclic and polycyclic fused-ring moieties. As used herein, aryl encompasses ring moieties comprising, for example, 6 to 20 annular carbon atoms (*i.e.*, 6- to 20-membered aryl), 6 to 16 annular carbon atoms (*i.e.*, 6- to 16-membered aryl), 6 to 12 annular carbon atoms (*i.e.*, 6- to 12-membered aryl), or 6 to 10 annular carbon atoms (*i.e.*, 6- to 10-membered aryl). Examples of aryl moieties include, but are not limited to, phenyl, naphthyl, fluorenyl, and anthryl.

[0028] The term "cycloalkyl", as used herein, refers to a saturated or partially unsaturated carbocyclic ring moiety. The term "cycloalkyl" encompasses monocyclic and polycyclic ring moieties, wherein the polycyclic moieties may be fused, branched, or spiro. Cycloalkyl includes cycloalkenyl groups, wherein the ring moiety comprises at least one annular double bond. Cycloalkyl includes any polycyclic carbocyclic ring moiety comprising at least one non-aromatic ring, regardless of the point of attachment to the remainder of the molecule. As used herein, cycloalkyl includes rings comprising, for example, 3 to 20 annular carbon atoms (*i.e.*, a C_{3-20}cycloalkyl), 3 to 16 annular carbon atoms (*i.e.*, a C_{3-16}cycloalkyl), 3 to 12 annular carbon atoms (*i.e.*, a C_{3-12}cycloalkyl), 3 to 10 annular carbon atoms (*i.e.*, a C_{3-10}cycloalkyl), 3 to 8 annular carbon atoms (*i.e.*, a C_{3-8}cycloalkyl), 3 to 6 annular carbon atoms (*i.e.*, a C_{3-6}cycloalkyl), or 3 to 5 annular carbon atoms (*i.e.*, a C_{3-5}cycloalkyl). Monocyclic cycloalkyl ring moieties include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic groups include, for example, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantyl, norbonyl, decalinyl, 7,7-dimethyl -bicyclo [2.2.1]heptanyl, and the like. Still further, cycloalkyl also includes spiro cycloalkyl ring moieties, for example, spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro [5.5]undecanyl.

[0029] The term "halo", as used herein, refers to atoms occupying groups VIIA of The Periodic Table and includes fluorine (fluoro), chlorine (chloro), bromine (bromo), and iodine (iodo). Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "$C_{1\text{-}4}$haloalkyl" is mean to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, difluoromethyl, and the like.

[0030] The term "heteroaryl", as used herein, refers to an aromatic (fully unsaturated) ring moiety that comprises one or more annular heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The term "heteroaryl" includes both monocyclic and polycyclic fused-ring moieties. As used herein, a heteroaryl comprises, for example, 5 to 20 annular atoms (*i.e.*, a 5- to 20-membered heteroaryl), 5 to 16 annular atoms (*i.e.*, a 5- to 16-membered heteroaryl), 5 to 12 annular atoms (*i.e.*, a 5- to 12-membered heteroaryl), 5 to 10 annular atoms (*i.e.*, a 5- to 10-membered heteroaryl), 5 to 8 annular atoms (*i.e.*, a 5- to 8-membered heteroaryl), or 5 to 6 annular atoms (*i.e.*, a 5- to 6-membered heteroaryl). Any monocyclic or polycyclic aromatic ring moiety comprising one or more annular heteroatoms is considered a heteroaryl, regardless of the point of attachment to the remainder of the molecule (*i.e.*, the heteroaryl moiety may be attached to the remainder of the molecule through any annular carbon or any annular heteroatom of the heteroaryl moiety). Examples of heteroaryl groups include, but are not limited to, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, and pyridazinyl.

[0031] The term "heterocyclyl", as used herein, refers to a saturated or partially unsaturated cyclic moiety that encompasses one or more annular heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The term "heterocyclyl" includes both monocyclic and polycyclic ring moieties, wherein the polycyclic ring moieties may be fused, bridged, or spiro. Any non-aromatic monocyclic or polycyclic ring moiety comprising at least one annular heteroatom is considered a heterocyclyl, regardless of the point of attachment to the remainder of the molecule (*i.e.*, the heterocyclyl moiety may be attached to the remainder of the molecule through any annular carbon or any annular heteroatom of the heterocyclyl moiety). Further, the term heterocyclyl is intended to encompass any polycyclic ring moiety comprising at least one annular heteroatom wherein the polycyclic ring moiety comprises at least one non-aromatic ring, regardless of the point of attachment to the remainder of the molecule. As used herein, a heterocyclyl comprises, for example, 3 to 20 annular atoms (*i.e.*, a 3- to 20-membered heterocyclyl), 3 to 16 annular atoms (*i.e.*, a 3- to 16-membered heterocyclyl), 3 to 12 annular atoms (*i.e.*, a 3- to 12-membered heterocyclyl), 3 to 10 annular atoms (*i.e.*, a 3- to 10-membered heterocyclyl), 3 to 8 annular atoms (*i.e.*, a 3- to

8-membered heterocyclyl), 3 to 6 annular atoms (*i.e.*, a 3-6 membered heterocyclyl), 3 to 5 annular atoms (*i.e.*, a 3- to 5-membered heterocyclyl), 5 to 8 annular atoms (*i.e.*, a 5- to 8-membered heterocyclyl), or 5 to 6 annular atoms (*i.e.*, a 5- to 6-membered heterocyclyl). Examples of heterocyclyl groups include, *e.g.*, azetidinyl, piperidinyl, piperazinyl, pyrrolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrofuryl, or tetrahydropyranyl. Examples of spiro heterocyclyl rings include, but are not limited to, bicyclic and tricyclic ring systems, such as 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.4]octanyl, and 6-oxa-1-azaspiro[3.3]heptanyl. Examples of fused heterocyclyl rings include, but are not limited to, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidinyl, 6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidinyl, 5,7-dihydrofuro[3,4-d]pyrimidinyl, and 5,7-dihydrothieno[3,4-d]pyrimidinyl, where the heterocyclyl can be bound via either ring of the fused system.

[0032] The term "oxo", as used herein, refers to a =O moiety.

[0033] The terms "spiro", "spirocycle" and "spirocyclic", as used herein, refer to a polycyclic moiety in which two of the rings share one atom in common. The terms "spiro", "spirocycle" and "spirocyclic" may refer to a saturated or partially unsaturated carbocycle, or a saturated or partially unsaturated heterocycle.

[0034] The term "fused", as used herein, refers to a polycyclic moiety in which two of the rings share two adjacent atoms in common. The term "fused" may refer to a saturated or partially unsaturated carbocycle, or a saturated or partially unsaturated heterocycle.

[0035] The term "bridged", as used herein, refers to a polycyclic moiety in which two of the rings share three or more atoms in common, and the bridgehead atoms are separated by at least one atoms. The term "bridged" may refer to a saturated or partially unsaturated carbocycle, or a saturated or partially unsaturated heterocycle.

[0036] The terms "optional" and "optionally", as used herein, mean that the subsequently described event or circumstance may or may not occur and that the description includes instances where the event or circumstance occurs and instances where it does not. Accordingly, the term "optionally substituted" infers that any one or more (*e.g.*, 1, 2, 1 to 5, 1 to 3, 1 to 2, etc.) hydrogen atoms on the designated atom or moiety or group may be replaced or not replaced by an atom or moiety or group other than hydrogen. By way of illustration and not limitation, the phrase "methyl optionally substituted with one or more chloro" encompasses $-CH_3$, $-CH_2Cl$, $-CHCl_2$, and $-CCl_3$ moieties.

[0037] It is understood that aspects and embodiments described herein as "comprising" include "consisting of" and "consisting essentially of" embodiments.

[0038] The term "pharmaceutically acceptable salt", as used herein, of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" include, for example, salts with inorganic acids, and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. *See, e.g., Handbook of Pharmaceutical Salts Properties, Selection, and Use*, International Union of Pure and Applied Chemistry, John Wiley & Sons (2008), which is incorporated herein by reference in its entirety. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic or organic acids. Salts derived from inorganic acids include, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include, *e.g.*, acetic acid, propionic acid, gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, trifluoroacetic acid, and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic or organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(*iso*-propyl) amine, tri(*n*-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0039] Isotopically labeled forms of the compounds depicted herein may be prepared. Isotopically labeled compounds have structures depicted herein, except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. In some

embodiments, a compound of formula (I) is provided wherein one or more hydrogen is replaced by deuterium or tritium.

[0040] Some of the compounds provided herein may exist as tautomers. Tautomers are in equilibrium with one another. By way of illustration, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown and regardless of the nature of the equilibrium among tautomers, the compounds of this disclosure are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, for example, amide-containing compounds are understood to include their imidic acid tautomers. Likewise, imidic-acid containing compounds are understood to include their amide tautomers.

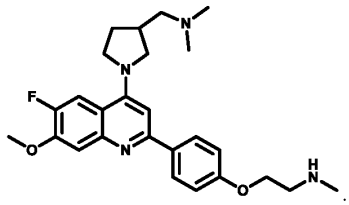
[0041] Also provided herein are prodrugs of the compounds depicted herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In some embodiments, provided herein are prodrugs of the compounds depicted herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof. Prodrugs are compounds that may be administered to an individual and release, *in vivo*, a compound depicted herein as the parent drug compound. It is understood that prodrugs may be prepared by modifying a functional group on a parent drug compound in such a way that the modification is cleaved *in vitro* or *in vivo* to release the parent drug compound. *See*, *e.g.*, Rautio, J., Kumpulainen, H., Heimbach, T. *et al.* Prodrugs: design and clinical applications. *Nat Rev Drug Discov* 7, 255–270 (2008), which is incorporated herein by reference in its entirety.

[0042] The compounds of the present disclosure, or their pharmaceutically acceptable salts, hydrates, or solvates may include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- (or as (D)- or (L)- for amino acids). The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms and mixtures thereof in any ratio. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or may be resolved using conventional techniques, for example, chromatography and/or fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or the resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC), and chiral supercritical fluid chromatography (SFC). When the compounds described herein contain olefinic double bonds or other centers

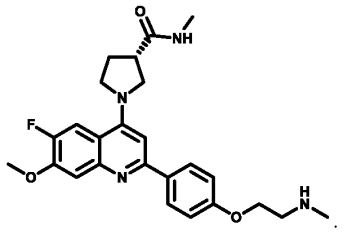
of geometric asymmetry, unless specified otherwise, it is intended that the present disclosure includes both E and Z geometric isomers. Likewise, cis- and trans- are used in their conventional sense to describe relative spatial relationships.

[0043] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds, but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers, or mixtures thereof, and includes "enantiomers," which refers to two stereoisomers whose structures are non-superimposable mirror images of one another. "Diastereomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror images of each other.

[0044] Where enantiomeric and/or diastereomeric forms exist of a given structure, flat bonds indicate a mixture of stereoisomeric forms of the depicted structure may be present, *e.g.*,

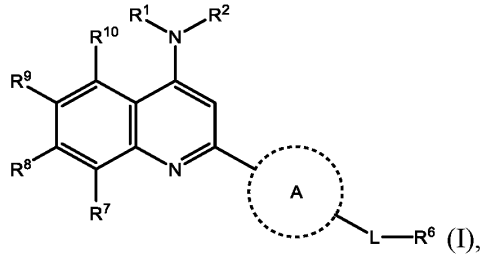


. Where the composition is made up of at least 90%, by weight, dashes or wedges with or without the presence of an "(S)" or "(R)" designation indicate a single enantiomer or diastereomer with known relative or absolute stereochemistry, *e.g.*,



COMPOUNDS

[0045] In one aspect, provided herein is a compound of formula (I)



(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein

R^1 and R^2 are each independently C_{1-6}alkyl, C_{2-6}alkenyl, -C(=O)R^{14}, -C(=O)OR^{14}, -C(=O)N(R^{13})(R^{14}), -S(=O)$_2R^{14}$, -S(=O)$_2$N(R^{13})(R^{14}), C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl wherein

the C_{1-6}alkyl of R^1 or R^2 is optionally substituted with one or more R^{1a},

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^1 or R^2 is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C_{1-6}alkyl, C_{2-6}alkenyl, -C(=O)R^{14}, -C(=O)OR^{14}, -C(=O)N(R^{13})(R^{14}), -S(=O)$_2R^{14}$, -S(=O)$_2$N(R^{13})(R^{14}), or C_{3-8}cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1b};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein

the 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of R^1 and R^2 is optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, oxo, -OR^{12}, -SR^{12}, -SF_5, -N(R^x)(R^y), -NO_2, -CN, -N(R^{13})C(=O)R^{14}, -N(R^{13})C(=O)N(R^{13})R^{14}, -N(R^{13})C(=O)OR^{14}, -OC(=O)R^{14}, -OC(=O)N(R^{13})R^{14}, -OC(=O)OR^{14}, -C(=O)R^{14}, -C(=O)N(R^{13})(R^{14}), -C(=O)OR^{14}, -C(=NR^{15})R^{14}, -C(=NOR^{14})R^{14}, -C(=NR^{15})N(R^{13})R^{14}, -C(=NR^{15})OR^{14}, -N(R^{13})S(=O)$_2R^{14}$, -S(=O)R^{14}, -S(=O)N(R^{13})R^{14}, -S(=O)OR^{14}, -S(=NR^{15})R^{14}, -S(=NR^{15})N(R^{13})R^{14}, -S(=NR^{15})OR^{14}, -S(=O)$_2R^{14}$, -S(=O)$_2$N(R^{13})(R^{14}), C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with one or more R^{3a}, and

optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b};

Ring A is 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 12-membered unsaturated heterocyclyl or 5- to 10-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^4 is optionally substituted by one or more R^{4a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^4 is optionally substituted with one or more R^{4b}, and

the 3- to 8-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

L is a bond, C_{1-6}alkyl, $-O-(C_{1-6}$alkyl$)-$, $-S-(C_{1-6}$alkyl$)-$, or $-N(R^5)(C_{1-6}$alkyl$)-$, wherein

the C_{1-6}alkyl, $-O-(C_{1-6}$alkyl$)-$, $-S-(C_{1-6}$alkyl$)-$, or $-N(R^5)(C_{1-6}$alkyl$)-$ is optionally substituted by one or more R^L;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a C_{3-8}cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-C(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, -

$N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, or $-S(=O)_2N(R^{13})(R^{14})$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, -O-(3- to 12-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^6 is optionally substituted by one or more R^{6a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -O-(3- to 12-membered N-containing heterocyclyl), or -O-(5- to 6-membered N-containing heteroaryl) of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 8-membered heterocyclyl of R^6 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^6 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{6b};

R^7, R^8, R^9, and R^{10} are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{11}$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^7, R^8, R^9, or R^{10} is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^7, R^8, R^9, or R^{10} is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^7, R^8, R^9, or R^{10} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^7, R^8, R^9, or R^{10} are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;

each R^{11} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^{11} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, or $-N(R^x)(R^y)$, and

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{11} is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, -$N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl of R^{12} is optionally substituted with one or more halo, deuterium, C_{1-6}alkoxy, -$N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, -O(C_{1-6}alkyl), -SH, -S(C_{1-6}alkyl), -(C=O)NH_2, -(C=O)OH, -O(C=O)C_{1-8}alkyl), -NH(C=NH)NH_2, -$N(R^x)(R^y)$, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the 6- to 10-membered aryl is optionally substituted by -OH, and

the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, -OH, or -$N(R^x)(R^y)$;

each R^{15} is independently H or C_{1-6}alkyl; and

each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -C(=O)(C_{1-6}alkyl), or -C(=O)O(C_{1-6}alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with halo, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -NH_2, NH(C_{1-6}alkyl), or -N(C_{1-6}alkyl)(C_{1-6}alkyl), and the C_{1-6}alkyl of -C(=O)(C_{1-6}alkyl) or -C(=O)O(C_{1-6}alkyl) is optionally substituted with -O(C=O)C_{1-8}alkyl). In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0046] In some embodiments of formula (I),

R^1 and R^2 are each independently C_{1-6}alkyl, C_{2-6}alkenyl, -C(=O)R^{14}, -C(=O)OR^{14}, -C(=O)N(R^{13})(R^{14}), -S(=O)$_2R^{14}$, -S(=O)$_2$N(R^{13})(R^{14}), C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl wherein

the C_{1-6}alkyl of R^1 or R^2 is optionally substituted with one or more R^{1a},

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^1 or R^2 is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C_{1-6}alkyl, C_{2-6}alkenyl, $-C(=O)R^{14}$, $-C(=O)OR^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or C_{3-8}cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1b};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein

the 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of R^1 and R^2 is optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, oxo, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with one or more R^{3a}, and

optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b};

Ring A is 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 12-membered unsaturated heterocyclyl or 5- to 10-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^4 is optionally substituted by one or more R^{4a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^4 is optionally substituted with one or more R^{4b}, and

the 3- to 8-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

L is a bond, C_{1-6}alkyl, -O-(C_{1-6}alkyl)-, -S-(C_{1-6}alkyl)-, or $-N(R^5)(C_{1-6}$alkyl)-, wherein

the C_{1-6}alkyl, -O-(C_{1-6}alkyl)-, -S-(C_{1-6}alkyl)-, or $-N(R^5)(C_{1-6}$alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a C_{3-8}cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-C(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, or $-S(=O)_2N(R^{13})(R^{14})$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, -O-(3- to 12-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), $-SR^{12}$, $-SF_5$, -

$N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^6 is optionally substituted by one or more R^{6a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -O-(3- to 12-membered N-containing heterocyclyl), or -O-(5- to 6-membered N-containing heteroaryl) of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 8-membered heterocyclyl of R^6 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^6 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{6b};

R^7, R^8, R^9, and R^{10} are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{11}$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^7, R^8, R^9, or R^{10} is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^7, R^8, R^9, or R^{10} is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^7, R^8, R^9, or R^{10} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^7, R^8, R^9, or R^{10} are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, $-N(R^x)(R^y)$, oxo, -CN, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;

each R^{11} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^{11} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, or $-N(R^x)(R^y)$, and

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{11} is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl of R^{12} is optionally substituted with one or more halo, deuterium, C_{1-6}alkoxy, -N(R^x)(R^y), or 3- to 8-membered heterocyclyl;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, -O(C_{1-6}alkyl), -SH, -S(C_{1-6}alkyl), -(C=O)NH_2, -(C=O)OH, -O(C=O)C_{1-8}alkyl), -NH(C=NH)NH_2, -N(R^x)(R^y), C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the 6- to 10-membered aryl is optionally substituted by -OH, and

the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, -OH, or -N(R^x)(R^y);

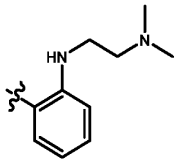
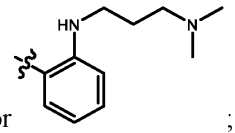
each R^{15} is independently H or C_{1-6}alkyl; and

each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -C(=O)(C_{1-6}alkyl), or -C(=O)O(C_{1-6}alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with halo, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -NH_2, NH(C_{1-6}alkyl), or -N(C_{1-6}alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of -C(=O)(C_{1-6}alkyl) or -C(=O)O(C_{1-6}alkyl) is optionally substituted with -O(C=O)C_{1-8}alkyl) , wherein

(i) when Ring A is phenyl and R^6 is selected from the group consisting of -NH_2, -$NHCH_3$, and -$N(CH_3)_3$, R^1 and R^2 are not both C_{1-2}alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of -NH_2, -$NHC(O)CH_3$, and -$NHC(O)O\text{-}C(CH_3)_3$; and

(iv) when Ring A is pyridin-4yl substituted with -$NHC(CH_3)$phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl.

[0047] In some embodiments of formula (I),

R^1 and R^2 are each independently C_{1-6}alkyl, C_{2-6}alkenyl, -C(=O)R^{14}, -C(=O)OR^{14}, -C(=O)N(R^{13})(R^{14}), -S(=O)$_2R^{14}$, -S(=O)$_2$N(R^{13})(R^{14}), C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl wherein

the C_{1-6}alkyl of R^1 or R^2 is optionally substituted with one or more R^{1a},

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^1 or R^2 is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C_{1-6}alkyl, C_{2-6}alkenyl, -C(=O)R^{14}, -C(=O)OR^{14}, -C(=O)N(R^{13})(R^{14}), -S(=O)$_2R^{14}$, -S(=O)$_2$N(R^{13})(R^{14}), or C_{3-8}cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1b};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein

the 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of R^1 and R^2 is optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, oxo, -OR^{12}, -SR^{12}, -SF_5, -N(R^x)(R^y), -NO_2, -CN, -N(R^{13})C(=O)R^{14}, -N(R^{13})C(=O)N(R^{13})R^{14}, -N(R^{13})C(=O)OR^{14}, -OC(=O)R^{14}, -OC(=O)N(R^{13})R^{14}, -OC(=O)OR^{14}, -C(=O)R^{14}, -C(=O)N(R^{13})(R^{14}), -C(=O)OR^{14}, -C(=NR^{15})R^{14}, -C(=NOR^{14})R^{14}, -C(=NR^{15})N(R^{13})R^{14}, -C(=NR^{15})OR^{14}, -N(R^{13})S(=O)$_2R^{14}$, -S(=O)R^{14}, -S(=O)N(R^{13})R^{14}, -S(=O)OR^{14}, -S(=NR^{15})R^{14}, -S(=NR^{15})N(R^{13})R^{14}, -S(=NR^{15})OR^{14}, -S(=O)$_2R^{14}$, -S(=O)$_2$N(R^{13})(R^{14}), C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with one or more R^{3a}, and

optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b};

Ring A is 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 12-membered unsaturated heterocyclyl or 5- to 10-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^4 is optionally substituted by one or more R^{4a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^4 is optionally substituted with one or more R^{4b}, and

the 3- to 8-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

L is a bond, C_{1-6}alkyl, $-O-(C_{1-6}$alkyl$)-$, $-S-(C_{1-6}$alkyl$)-$, or $-N(R^5)(C_{1-6}$alkyl$)-$, wherein

the C_{1-6}alkyl, $-O-(C_{1-6}$alkyl$)-$, $-S-(C_{1-6}$alkyl$)-$, or $-N(R^5)(C_{1-6}$alkyl$)-$ is optionally substituted by one or more R^L;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a C_{3-8}cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-C(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, -

$N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, or $-S(=O)_2N(R^{13})(R^{14})$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^6 is optionally substituted by one or more R^{6a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 8-membered heterocyclyl of R^6 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^6 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{6b};

R^7, R^8, R^9, and R^{10} are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{11}$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^7, R^8, R^9, or R^{10} is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^7, R^8, R^9, or R^{10} is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^7, R^8, R^9, or R^{10} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^7, R^8, R^9, or R^{10} are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, $-N(R^x)(R^y)$, oxo, -CN, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;

each R^{11} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^{11} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, or $-N(R^x)(R^y)$, and

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{11} is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, C_{1-6}alkoxy, -N(R^x)(R^y), or 3- to 8-membered heterocyclyl;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, -O(C_{1-6}alkyl), -SH, -S(C_{1-6}alkyl), -(C=O)NH_2, -(C=O)OH, -O(C=O)C_{1-8}alkyl), -NH(C=NH)NH_2, -N(R^x)(R^y), C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the 6- to 10-membered aryl is optionally substituted by -OH, and

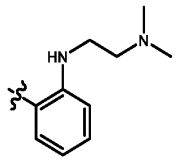
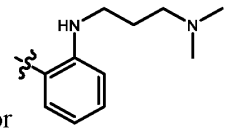
the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, -OH, or -N(R^x)(R^y);

each R^{15} is independently H or C_{1-6}alkyl; and

each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -C(=O)(C_{1-6}alkyl), or -C(=O)O(C_{1-6}alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with halo, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -NH_2, NH(C_{1-6}alkyl), or -N(C_{1-6}alkyl)(C_{1-6}alkyl), and the C_{1-6}alkyl of -C(=O)(C_{1-6}alkyl) or -C(=O)O(C_{1-6}alkyl) is optionally substituted with -O(C=O)C_{1-8}alkyl), wherein

(i) when Ring A is phenyl and R^6 is selected from the group consisting of -NH_2, -$NHCH_3$, and -$N(CH_3)_3$, R^1 and R^2 are not both C_{1-2}alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of -NH_2, -$NHC(O)CH_3$, and -$NHC(O)O\text{-}C(CH_3)_3$; and

(iv) when Ring A is pyridin-4yl substituted with -NHC(CH_3)phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl.

[0048] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or salt of any of the foregoing,

R^1 and R^2 are each independently C_{1-6}alkyl, C_{2-6}alkenyl, -C(=O)R^{14}, -C(=O)OR^{14}, -C(=O)N(R^{13})(R^{14}), or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^1 or R^2 is optionally substituted with one or more R^{1a},

the C_{3-8}cycloalkyl of R^1 or R^2 is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C_{1-6}alkyl, C_{2-6}alkenyl, -C(=O)R^{14}, -C(=O)OR^{14}, -C(=O)N(R^{13})(R^{14}), or C_{3-8}cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1b};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, oxo, -OR^{12}, -SR^{12}, -SF_5, -N(R^x)(R^y), -NO_2, -CN, -N(R^{13})C(=O)R^{14}, -N(R^{13})C(=O)N(R^{13})R^{14}, -N(R^{13})C(=O)OR^{14}, -OC(=O)R^{14}, -OC(=O)N(R^{13})R^{14}, -OC(=O)OR^{14}, -C(=O)R^{14}, -C(=O)N(R^{13})(R^{14}), -C(=O)OR^{14}, -C(=NR^{15})R^{14}, -C(=NOR^{14})R^{14}, -C(=NR^{15})N(R^{13})R^{14}, -C(=NR^{15})OR^{14}, -N(R^{13})S(=O)$_2R^{14}$, -S(=O)R^{14}, -S(=O)N(R^{13})R^{14}, -S(=O)OR^{14}, -S(=O)$_2R^{14}$, -S(=O)$_2$N(R^{13})(R^{14}), C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with one or more R^{3a}, and

optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b};

Ring A is 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 8-membered unsaturated monocyclic heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^4 is optionally substituted by one or more R^{4a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^4 is optionally substituted with one or more R^{4b}, and

the 3- to 8-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

L is a bond, C_{1-6}alkyl, $-O-(C_{1-6}$alkyl$)-$, $-S-(C_{1-6}$alkyl$)-$, or $-N(R^5)(C_{1-6}$alkyl$)-$, wherein

the C_{1-6}alkyl, $-O-(C_{1-6}$alkyl$)-$, $-S-(C_{1-6}$alkyl$)-$, or $-N(R^5)(C_{1-6}$alkyl$)-$ is optionally substituted by one or more R^L;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a C_{3-8}cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-C(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, -

$C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, or $-S(=O)_2N(R^{13})(R^{14})$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-C(=O)N(R^{13})(R^{14})$, $-C(=NR^{15})N(R^{13})R^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or 3- to 12-membered N-containing heterocyclyl, wherein

the 3- to 12-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$,and

the 3- to 12-membered N-containing heterocyclyl of R^6 further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7, R^8, R^9, and R^{10} are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{11}$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^7, R^8, R^9, or R^{10} is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^7, R^8, R^9, or R^{10} is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^7, R^8, R^9, or R^{10} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^7, R^8, R^9, or R^{10} are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, -

$S(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, $-N(R^x)(R^y)$, oxo, -CN, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;

each R^{11} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^{11} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, or $-N(R^x)(R^y)$, and

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{11} is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, C_{1-6}alkoxy, $-N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by halo, -OH, $-O(C_{1-6}$alkyl), $-O(C=O)C_{1-8}$alkyl), $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, or -$N(R^x)(R^y)$;

each R^{15} is independently H or C_{1-6}alkyl; and

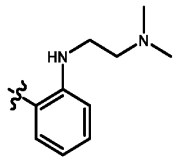
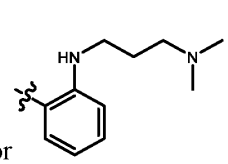
each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -C(=O)(C_{1-6}alkyl), or -C(=O)O(C_{1-6}alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -NH_2, NH(C_{1-6}alkyl), or -N(C_{1-6}alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of -C(=O)(C_{1-6}alkyl) or -C(=O)O(C_{1-6}alkyl) is optionally substituted with -O(C=O)C_{1-8}alkyl);

wherein

(i) when Ring A is phenyl and R^6 is selected from the group consisting of -NH_2, -$NHCH_3$, and -$N(CH_3)_3$, R^1 and R^2 are not both C_{1-2}alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of -NH_2, -NHC(O)CH_3, and -NHC(O)O-$C(CH_3)_3$; and

(iv) when Ring A is pyridin-4yl substituted with -NHC(CH_3)phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0049] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or salt of any of the foregoing,

R^1 and R^2 are each independently C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^1 or R^2 is optionally substituted with one or more R^{1a},

the C_{3-8}cycloalkyl of R^1 or R^2 is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-8}cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-}

$_{8}$cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1b};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, oxo, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with one or more R^{3a}, and

optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b};

Ring A is 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 12-membered unsaturated heterocyclyl or 5- to 10-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, -

$S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^4 is optionally substituted by one or more R^{4a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^4 is optionally substituted with one or more R^{4b}, and

the 3- to 8-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

L is a bond, C_{1-6}alkyl, -O-(C_{1-6}alkyl)-, -S-(C_{1-6}alkyl)-, or -N(R^5)(C_{1-6}alkyl)-, wherein

the C_{1-6}alkyl, -O-(C_{1-6}alkyl)-, -S-(C_{1-6}alkyl)-, or -N(R^5)(C_{1-6}alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a C_{3-8}cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, or $-S(=O)_2N(R^{13})(R^{14})$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-C(=O)N(R^{13})(R^{14})$, $-C(=NR^{15})N(R^{13})R^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or 3- to 12-membered N-containing heterocyclyl, wherein

the 3- to 12-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 12-membered N-containing heterocyclyl of R^6 further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7, R^8, R^9, and R^{10} are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{11}$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, -

$N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^7, R^8, R^9, or R^{10} is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^7, R^8, R^9, or R^{10} is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^7, R^8, R^9, or R^{10} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^7, R^8, R^9, or R^{10} are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b};

each R^{1a}, R^{3a}, R^{6a}, or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a}, R^{3a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{3a}, R^{6a}, or R^{7a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C_{1-6}alkyl of R^{11} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl wherein

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, or $-N(R^x)(R^y)$, and

the phenyl or 5- to 6-membered heteroaryl of R^{11} is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, $-N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl;

each R^{12} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, C_{1-6}alkoxy, $-N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by halo, -OH, $-O(C_{1-6}alkyl)$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, or $-N(R^x)(R^y)$;

each R^{15} is independently H or C_{1-6}alkyl; and

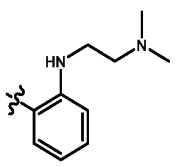
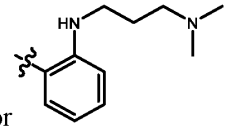
each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, $-C(=O)(C_{1-6}alkyl)$, or $-C(=O)O(C_{1-6}alkyl)$, wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, $-NH_2$, $NH(C_{1-6}alkyl)$, or $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$, and

the C_{1-6}alkyl of $-C(=O)(C_{1-6}alkyl)$ or $-C(=O)O(C_{1-6}alkyl)$ is optionally substituted with $-O(C=O)C_{1-8}$alkyl);

wherein

(i) when Ring A is phenyl and R^6 is selected from the group consisting of $-NH_2$, $-NHCH_3$, and $-N(CH_3)_3$, R^1 and R^2 are not both C_{1-2}alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of $-NH_2$, $-NHC(O)CH_3$, and $-NHC(O)O-C(CH_3)_3$; and

(iv) when Ring A is pyridin-4yl substituted with $-NHC(CH_3)$phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0050] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or salt of any of the foregoing,

R^1 and R^2 are each independently C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^1 or R^2 is optionally substituted with one or more R^{1a},

the C_{3-8}cycloalkyl of R^1 or R^2 is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-8}cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1b};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, oxo, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with one or more R^{3a}, and

optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b};

Ring A is 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 8-membered unsaturated monocyclic heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^4 is optionally substituted by one or more R^{4a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^4 is optionally substituted with one or more R^{4b}, and

the 3- to 8-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

L is a bond, C_{1-6}alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^5)(C_{1-6}alkyl)-$, wherein

the C_{1-6}alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^5)(C_{1-6}alkyl)-$ is optionally substituted by one or more R^L;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a C_{3-8}cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, or $-S(=O)_2N(R^{13})(R^{14})$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)(C_{1-6}\text{alkyl})N(R^x)(R^y)$, $-C(=O)N(R^{13})(R^{14})$, $-C(=NR^{15})N(R^{13})R^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or 3- to 12-membered N-containing heterocyclyl, wherein

the 3- to 12-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 12-membered N-containing heterocyclyl of R^6 further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7, R^8, R^9, and R^{10} are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{11}$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^7, R^8, R^9, or R^{10} is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^7, R^8, R^9, or R^{10} is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^7, R^8, R^9, or R^{10} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^7, R^8, R^9, or R^{10} are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b};

each R^{1a}, R^{3a}, R^{6a}, or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a}, R^{3a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{3a}, R^{6a}, or R^{7a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, $-N(R^x)(R^y)$, oxo, -CN, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C_{1-6}alkyl of R^{11} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl wherein

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, or $-N(R^x)(R^y)$, and

the phenyl or 5- to 6-membered heteroaryl of R^{11} is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, $-N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl;

each R^{12} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, C_{1-6}alkoxy, $-N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by halo, -OH, $-O(C_{1-6}$alkyl), $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, or -$N(R^x)(R^y)$;

each R^{15} is independently H or C_{1-6}alkyl; and

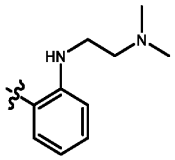
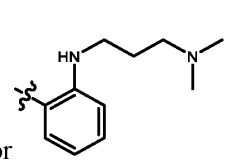
each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -C(=O)(C_{1-6}alkyl), or -C(=O)O(C_{1-6}alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -NH_2, NH(C_{1-6}alkyl), or -N(C_{1-6}alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of -C(=O)(C_{1-6}alkyl) or -C(=O)O(C_{1-6}alkyl) is optionally substituted with -O(C=O)C_{1-8}alkyl);

wherein

(i) when Ring A is phenyl and R^6 is selected from the group consisting of -NH_2, -$NHCH_3$, and -$N(CH_3)_3$, R^1 and R^2 are not both C_{1-2}alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of -NH_2, -NHC(O)CH_3, and -NHC(O)O-$C(CH_3)_3$; and

(iv) when Ring A is pyridin-4yl substituted with -$NHC(CH_3)$phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0051] In some embodiments of formula (I),

R^1 and R^2 are each independently C_{1-6}alkyl, C_{2-6}alkenyl, -C(=O)R^{14}, -C(=O)OR^{14}, -C(=O)$N(R^{13})(R^{14})$, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^1 or R^2 is optionally substituted with one or more R^{1a},

the C_{3-8}cycloalkyl of R^1 or R^2 is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C_{1-6}alkyl, C_{2-6}alkenyl, -C(=O)R^{14}, -C(=O)OR^{14}, -C(=O)$N(R^{13})(R^{14})$, or C_{3-8}cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1b};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, oxo, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with one or more R^{3a}, and

optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b};

Ring A is 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 8-membered unsaturated monocyclic heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^4 is optionally substituted by one or more R^{4a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^4 is optionally substituted with one or more R^{4b}, and

the 3- to 8-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

L is a bond, C_{1-6}alkyl, -O-(C_{1-6}alkyl)-, -S-(C_{1-6}alkyl)-, or -N(R^5)(C_{1-6}alkyl)-, wherein

the C_{1-6}alkyl, -O-(C_{1-6}alkyl)-, -S-(C_{1-6}alkyl)-, or -N(R^5)(C_{1-6}alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR^{12}, -SR^{12}, -SF_5, -NO_2, -CN, -N(R^{13})C(=O)R^{14}, -N(R^{13})C(=O)N(R^{13})R^{14}, -N(R^{13})C(=O)OR^{14}, -OC(=O)R^{14}, -OC(=O)N(R^{13})R^{14}, -OC(=O)OR^{14}, -C(=O)R^{14}, -C(=O)N(R^{13})(R^{14}), -C(=O)OR^{14}, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a C_{3-8}cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -C(=O)R^{14}, -S(=O)$_2R^{14}$, -S(=O)$_2$N(R^{13})(R^{14}), or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, -N(R^x)(R^y), -OR^{12}, -SR^{12}, -SF_5, -N(R^{13})C(=O)R^{14}, -N(R^{13})C(=O)N(R^{13})R^{14}, -N(R^{13})C(=O)OR^{14}, -OC(=O)R^{14}, -OC(=O)N(R^{13})R^{14}, -OC(=O)OR^{14}, -C(=O)R^{14}, -C(=O)N(R^{13})(R^{14}), -C(=O)OR^{14}, -C(=NR^{15})R^{14}, -C(=NOR^{14})R^{14}, -C(=NR^{15})N(R^{13})R^{14}, -C(=NR^{15})OR^{14}, -N(R^{13})S(=O)$_2R^{14}$, -S(=O)R^{14}, -S(=O)N(R^{13})R^{14}, -S(=O)OR^{14}, -S(=NR^{15})R^{14}, -S(=NR^{15})N(R^{13})R^{14}, -S(=NR^{15})OR^{14}, -S(=O)$_2R^{14}$, or -S(=O)$_2$N(R^{13})(R^{14}), and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is -OR^{12}, -O-(3- to 12-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), -N(R^x)(R^y), -N(R^{13})C(=O)R^{14}, -N(R^{13})C(=O)N(R^{13})R^{14}, -N(R^{13})C(=O)OR^{14}, -OC(=O)N(R^{13})R^{14}, -C(=O)(C_{1-6}alkyl)N(R^x)(R^y), -C(=O)N(R^{13})(R^{14}), -C(=NR^{15})N(R^{13})R^{14}, -N(R^{13})S(=O)$_2R^{14}$, -S(=O)N(R^{13})R^{14}, -S(=O)$_2$N(R^{13})(R^{14}), or 3- to 12-membered N-containing heterocyclyl, wherein

the 3- to 12-membered N-containing heterocyclyl, -O-(3- to 12-membered N-containing heterocyclyl), or -O-(5- to 6-membered N-containing heteroaryl) of R^6 is optionally substituted with one or more R^{6b}, -C(=O)R^{14}, -C(=O)N(R^{13})(R^{14}), or -C(=O)OR^{14}, and

the 3- to 12-membered N-containing heterocyclyl of R^6 optionally further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7, R^8, R^9, and R^{10} are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, -OR^{11}, -OR^{12}, -SR^{12}, -SF_5, -$N(R^x)(R^y)$, -NO_2, -CN, -$N(R^{13})C(=O)R^{14}$, -$N(R^{13})C(=O)N(R^{13})R^{14}$, -$N(R^{13})C(=O)OR^{14}$, -$OC(=O)R^{14}$, -$OC(=O)N(R^{13})R^{14}$, -$OC(=O)OR^{14}$, -$C(=O)R^{14}$, -$C(=O)N(R^{13})(R^{14})$, -$C(=O)OR^{14}$, -$C(=NR^{15})R^{14}$, -$C(=NOR^{14})R^{14}$, -$C(=NR^{15})N(R^{13})R^{14}$, -$C(=NR^{15})OR^{14}$, -$N(R^{13})S(=O)_2R^{14}$, -$S(=O)R^{14}$, -$S(=O)N(R^{13})R^{14}$, -$S(=O)OR^{14}$, -$S(=NR^{15})R^{14}$, -$S(=NR^{15})N(R^{13})R^{14}$, -$S(=NR^{15})OR^{14}$, -$S(=O)_2R^{14}$, -$S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^7, R^8, R^9, or R^{10} is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^7, R^8, R^9, or R^{10} is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^7, R^8, R^9, or R^{10} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^7, R^8, R^9, or R^{10} are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, -$N(R^x)(R^y)$, -OR^{12}, -SR^{12}, -SF_5, -NO_2, -CN, -$N(R^{13})C(=O)R^{14}$, -$N(R^{13})C(=O)N(R^{13})R^{14}$, -$N(R^{13})C(=O)OR^{14}$, -$OC(=O)R^{14}$, -$OC(=O)N(R^{13})R^{14}$, -$OC(=O)OR^{14}$, -$C(=O)R^{14}$, -$C(=O)N(R^{13})(R^{14})$, -$C(=O)OR^{14}$, -$C(=NR^{15})R^{14}$, -$C(=NOR^{14})R^{14}$, -$C(=NR^{15})N(R^{13})R^{14}$, -$C(=NR^{15})OR^{14}$, -$N(R^{13})S(=O)_2R^{14}$, -$S(=O)R^{14}$, -$S(=O)_2R^{14}$, -$S(=O)N(R^{13})R^{14}$, -$S(=O)OR^{14}$, -$S(=NR^{15})R^{14}$, -$S(=NR^{15})N(R^{13})R^{14}$, -$S(=NR^{15})OR^{14}$, -$S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, -OR^{11}, -$N(R^x)(R^y)$, oxo, -CN, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;

each R^{11} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^{11} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, or $-N(R^x)(R^y)$, and

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{11} is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl of R^{12} is optionally substituted with one or more halo, deuterium, C_{1-6}alkoxy, $-N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, $-O(C_{1-6}$alkyl), -SH, $-S(C_{1-6}$alkyl), $-(C=O)NH_2$, -(C=O)OH, $-O(C=O)C_{1-8}$alkyl), $-NH(C=NH)NH_2$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the 6- to 10-membered aryl is optionally substituted by -OH, and

the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, -OH, or $-N(R^x)(R^y)$;

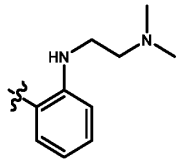
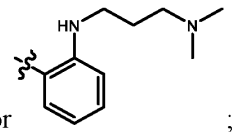
each R^{15} is independently H or C_{1-6}alkyl; and

each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, $-C(=O)(C_{1-6}$alkyl), or $-C(=O)O(C_{1-6}$alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with halo, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, $-NH_2$, $NH(C_{1-6}$alkyl), or $-N(C_{1-6}$alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of $-C(=O)(C_{1-6}$alkyl) or $-C(=O)O(C_{1-6}$alkyl) is optionally substituted with $-O(C=O)C_{1-8}$alkyl) , wherein

(i) when Ring A is phenyl and R^6 is selected from the group consisting of $-NH_2$, $-NHCH_3$, and $-N(CH_3)_3$, R^1 and R^2 are not both C_{1-2}alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of $-NH_2$, $-NHC(O)CH_3$, and $-NHC(O)O-C(CH_3)_3$; and

(iv) when Ring A is pyridin-4yl substituted with $-NHC(CH_3)$phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl.

[0052] In some embodiments of formula (I),

R^1 and R^2 are each independently C_{1-6}alkyl optionally substituted with one or more R^{1a};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, oxo, $-OR^{12}$, $-N(R^x)(R^y)$, -CN, or $-C(=O)N(R^{13})(R^{14})$, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a};

Ring A is 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 12-membered unsaturated heterocyclyl or 5- to 10-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, or $-OR^{12}$;

L is a bond, C_{1-6}alkyl, $-O-(C_{1-6}$alkyl$)-$, $-S-(C_{1-6}$alkyl$)-$, or $-N(R^5)(C_{1-6}$alkyl$)-$, wherein

the C_{1-6}alkyl, $-O-(C_{1-6}$alkyl$)-$, $-S-(C_{1-6}$alkyl$)-$, or $-N(R^5)(C_{1-6}$alkyl$)-$ is optionally substituted by one or more R^L;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, -

$OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a C_{3-8}cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, or $-OR^{12}$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is $-OR^{12}$, -O-(3- to 12-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $C(=O)N(R^{13})(R^{14})$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, $-(C_{3-8}cycloalkyl)N(R^x)(R^y)$, or 3- to 12-membered N-containing heterocyclyl, wherein

the 3- to 12-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 12-membered N-containing heterocyclyl of R^6 further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7 is H;

R^8 and R^9 are each independently H, halo, C_{1-6}alkyl, $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(O)R^{14}$, $-N(R^{13})C(O)OR^{14}$, $-N(R^{13})C(O)N(R^{13})R^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{14}$, $-OC(O)N(R^{13})R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{13})(R^{14})$, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^8 or R^9 is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl of R^8 is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^8 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

R^{10} is H;

each R^{1a}, R^{3a}, R^{6a}, or R^{7a} is independently $-OR^{12}$ or $-N(R^x)(R^y)$;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, or $-N(R^x)(R^y)$, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H or C_{1-6}alkyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkynyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^{12} is optionally substituted with one or more halo, deuterium, or -$N(R^x)(R^y)$;

each R^{13} is independently H or C_{1-6}alkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by halo, -OH, -O(C_{1-6}alkyl), -O(C=O)C_{1-8}alkyl), -$N(R^x)(R^y)$, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, or -$N(R^x)(R^y)$;

each R^{15} is independently H or C_{1-6}alkyl; and

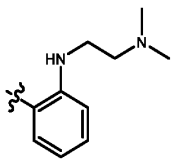
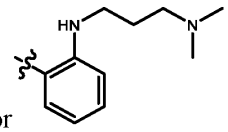
each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -C(=O)(C_{1-6}alkyl), or -C(=O)O(C_{1-6}alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with halo, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -NH_2, NH(C_{1-6}alkyl), or -N(C_{1-6}alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of -C(=O)(C_{1-6}alkyl) or -C(=O)O(C_{1-6}alkyl) is optionally substituted with -O(C=O)C_{1-8}alkyl);

wherein

(i) when Ring A is phenyl and R^6 is selected from the group consisting of -NH_2, -$NHCH_3$, and -$N(CH_3)_3$, R^1 and R^2 are not both C_{1-2}alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of -NH_2, -$NHC(O)CH_3$, and -$NHC(O)O\text{-}C(CH_3)_3$; and

(iv) when Ring A is pyridin-4yl substituted with -$NHC(CH_3)$phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl.

[0053] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing,

R^1 and R^2 are each independently C_{1-6}alkyl optionally substituted with one or more R^{1a};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, oxo, $-OR^{12}$, or $-N(R^x)(R^y)$ wherein

the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a};

Ring A is 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 12-membered unsaturated heterocyclyl or 5- to 10-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, or $-OR^{12}$;

L is a bond, C_{1-6}alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^5)(C_{1-6}alkyl)-$, wherein

the C_{1-6}alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^5)(C_{1-6}alkyl)-$ is optionally substituted by one or more R^L;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a C_{3-8}cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, or $-OR^{12}$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $C(=O)N(R^{13})(R^{14})$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or 3- to 12-membered N-containing heterocyclyl, wherein

the 3- to 12-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, -C(=O)R^{14}, -C(=O)N(R^{13})(R^{14}), or -C(=O)OR^{14}, and

the 3- to 12-membered N-containing heterocyclyl of R^6 further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7 is H;

R^8 and R^9 are each independently H, halo, C_{1-6}alkyl, -OR^{12}, -N(R^x)(R^y), -N(R^{13})C(O)R^{14}, -N(R^{13})C(O)OR^{14}, -N(R^{13})C(O)N(R^{13})R^{14}, -OC(O)R^{14}, -OC(O)OR^{14}, -OC(O)N(R^{13})R^{14}, -C(O)R^{14}, -C(O)OR^{14}, or -C(O)N(R^{13})(R^{14}) , wherein

the C_{1-6}alkyl of R^8 or R^9 is optionally substituted by one or more R^{7a};

R^{10} is H;

each R^{1a}, R^{3a}, R^{6a}, or R^{7a} is independently -OR^{12} or -N(R^x)(R^y);

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, -OR^{11}, or -N(R^x)(R^y), wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by -OR^{12}, -N(R^x)(R^y), C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H or C_{1-6}alkyl;

each R^{12} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, or -N(R^x)(R^y);

each R^{13} is independently H or C_{1-6}alkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by halo, -OH, -O(C_{1-6}alkyl), -O(C=O)C_{1-8}alkyl), -N(R^x)(R^y), C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, or -N(R^x)(R^y);

each R^{15} is independently H or C_{1-6}alkyl; and

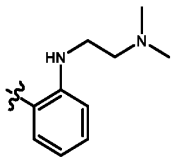
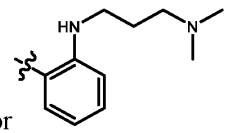
each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -C(=O)(C_{1-6}alkyl), or -C(=O)O(C_{1-6}alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -NH_2, NH(C_{1-6}alkyl), or -N(C_{1-6}alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of -C(=O)(C_{1-6}alkyl) or -C(=O)O(C_{1-6}alkyl) is optionally substituted with -O(C=O)C_{1-8}alkyl);

wherein

(i) when Ring A is phenyl and R^6 is selected from the group consisting of -NH_2, -$NHCH_3$, and -$N(CH_3)_3$, R^1 and R^2 are not both C_{1-2}alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of -NH_2, -$NHC(O)CH_3$, and -$NHC(O)O\text{-}C(CH_3)_3$; and

(iv) when Ring A is pyridin-4yl substituted with -$NHC(CH_3)$phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0054] In some embodiments of formula (I),

R^1 and R^2 are taken together with the N to which they are attached to form a saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 10-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl, wherein

the saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 9-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl is optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, oxo, -OR^{12}, -$N(R^x)(R^y)$, -CN, or -$C(=O)N(R^{13})(R^{14})$, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a};

Ring A is 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 8-membered unsaturated heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, or $-OR^{12}$;

L is a bond, C_{1-6}alkyl, -O-(C_{1-6}alkyl)-, -S-(C_{1-6}alkyl)-, or $-N(R^5)(C_{1-6}alkyl)-$;

R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, or $-OR^{12}$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is $-OR^{12}$, -O-(3- to 12-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-C(=O)N(R^{13})(R^{14})$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, -($C_{3-8}$cycloalkyl)$N(R^x)(R^y)$, or 3- to 8-membered N-containing heterocyclyl, wherein

the -O-(3- to 8-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), or 3- to 8-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 8-membered N-containing heterocyclyl of R^6 optionally further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7 is H or halo;

R^8 and R^9 are each independently H, halo, C_{1-6}alkyl, $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(O)R^{14}$, $-N(R^{13})C(O)OR^{14}$, $-N(R^{13})C(O)N(R^{13})R^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{14}$, $-OC(O)N(R^{13})R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^8 or R^9 is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl of R^8 is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^8 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

R^{10} is H;

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently $-OR^{12}$ or $-N(R^x)(R^y)$;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, or $-N(R^x)(R^y)$, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H or C_{1-6}alkyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, $-O(C_{1-6}$alkyl), or $-N(R^x)(R^y)$;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, $-O(C_{1-6}$alkyl), -SH, $-S(C_{1-6}$alkyl), $-(C=O)NH_2$, -(C=O)OH, $-O(C=O)C_{1-8}$alkyl), $-NH(C=NH)NH_2$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the 6- to 10-membered aryl of R^{14} is optionally substituted by -OH, and

the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, -OH, or $-N(R^x)(R^y)$;

each R^{15} is independently H or C_{1-6}alkyl; and

each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, $-C(=O)(C_{1-6}$alkyl), or $-C(=O)O(C_{1-6}$alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with halo, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, $-NH_2$, $NH(C_{1-6}$alkyl), or $-N(C_{1-6}$alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of $-C(=O)(C_{1-6}$alkyl) or $-C(=O)O(C_{1-6}$alkyl) is optionally substituted with $-O(C=O)C_{1-8}$alkyl), wherein

when Ring A is phenyl, then $-L-R^6$ is not $-NH_2$ or $-OCH_3$. In some embodiments of the foregoing, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0055] In some embodiments of formula (I),

R^1 and R^2 are taken together with the N to which they are attached to form a saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 10-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl, wherein

the saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 9-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl is optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, oxo, $-OR^{12}$, $-N(R^x)(R^y)$, -CN, or $-C(=O)N(R^{13})(R^{14})$, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a};

Ring A is 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 8-membered unsaturated heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, or $-OR^{12}$;

L is a bond, C_{1-6}alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^5)(C_{1-6}alkyl)-$;

R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, or $-OR^{12}$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is $-OR^{12}$, -O-(3- to 12-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-C(=O)N(R^{13})(R^{14})$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, $-(C_{3-8}cycloalkyl)N(R^x)(R^y)$, or 3- to 8-membered N-containing heterocyclyl, wherein

the -O-(3- to 8-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), or 3- to 8-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 8-membered N-containing heterocyclyl of R^6 optionally further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7 is H or halo;

R^8 and R^9 are each independently H, halo, C_{1-6}alkyl, $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(O)R^{14}$, $-N(R^{13})C(O)OR^{14}$, $-N(R^{13})C(O)N(R^{13})R^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{14}$, $-OC(O)N(R^{13})R^{14}$, -

$C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^8 or R^9 is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl of R^8 is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^8 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

R^{10} is H;

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently $-OR^{12}$ or $-N(R^x)(R^y)$;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, or $-N(R^x)(R^y)$, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H or C_{1-6}alkyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, $-O(C_{1-6}$alkyl), or $-N(R^x)(R^y)$;

each R^{13} is independently H or C_{1-6}alkyl,

each R^{14} is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, $-O(C_{1-6}$alkyl), $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, or $-N(R^x)(R^y)$;

each R^{15} is independently H or C_{1-6}alkyl; and

each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, $-C(=O)(C_{1-6}$alkyl), or $-C(=O)O(C_{1-6}$alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with halo, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, $-NH_2$, $NH(C_{1-6}$alkyl), or $-N(C_{1-6}$alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of $-C(=O)(C_{1-6}$alkyl) or $-C(=O)O(C_{1-6}$alkyl) is optionally substituted with $-O(C=O)C_{1-8}$alkyl), wherein

when Ring A is phenyl, then -L-R^6 is not -NH_2 or -OCH_3.

[0056] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing:

R^1 and R^2 are each independently C_{1-6}alkyl optionally substituted with one or more R^{1a};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, oxo, -OR^{12}, or -$N(R^x)(R^y)$ wherein

the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a};

Ring A is 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 8-membered unsaturated monocyclic heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, or -OR^{12};

L is a bond, C_{1-6}alkyl, -O-(C_{1-6}alkyl)-, -S-(C_{1-6}alkyl)-, or -$N(R^5)$(C_{1-6}alkyl)-;

R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, -$N(R^x)(R^y)$, or -OR^{12}, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is (i) -$N(R^x)(R^y)$, -$N(R^{13})C(=O)R^{14}$, -$N(R^{13})C(=O)N(R^{13})R^{14}$, -$N(R^{13})C(=O)OR^{14}$, -$OC(=O)N(R^{13})R^{14}$, -$C(=O)N(R^{13})(R^{14})$, -$N(R^{13})S(=O)_2R^{14}$, -$S(=O)N(R^{13})R^{14}$, -$S(=O)_2N(R^{13})(R^{14})$, or 3- to 12-membered N-containing heterocyclyl, wherein

the 3- to 12-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, -$C(=O)R^{14}$, -$C(=O)N(R^{13})(R^{14})$, or -$C(=O)OR^{14}$, and

the 3- to 12-membered N-containing heterocyclyl of R^6 further comprises 1 or 2 atoms selected from the group consisting of N, O, and S; or

(ii) -OC(=O)(C_{1-6}alkyl)$N(R^x)(R^y)$, -OC(=O)O(C_{1-6}alkyl)$N(R^x)(R^y)$, -C(=O)(C_{1-6}alkyl)$N(R^x)(R^y)$, -C(=O)O(C_{1-6}alkyl)$N(R^x)(R^y)$, -S(=O)(C_{1-6}alkyl)$N(R^x)(R^y)$, -

$S(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-S(=O)O(C_{1-6}alkyl)N(R^x)(R^y)$, or $-S(=O)_2(C_{1-6}alkyl)N(R^x)(R^y)$, wherein

the $-OC(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-OC(=O)O(C_{1-6}alkyl)N(R^x)(R^y)$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-C(=O)O(C_{1-6}alkyl)N(R^x)(R^y)$, $-S(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-S(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-S(=O)O(C_{1-6}alkyl)N(R^x)(R^y)$, or $-S(=O)_2(C_{1-6}alkyl)N(R^x)(R^y)$ of R^6 is optionally substituted with one or more halo, -OH, $-O(C_{1-6}alkyl)$, -SH, $-S(C_{1-6}alkyl)$, $-(C=O)NH_2$, -(C=O)OH, $-O(C=O)C_{1-8}alkyl$), $-NH(C=NH)NH_2$, $-N(R^x)(R^y)$, $C_{3-8}cycloalkyl$, phenyl, phenol, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl;

R^7 is H;

R^8 and R^9 are each independently H, halo, $C_{1-6}alkyl$, $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(O)R^{14}$, $-N(R^{13})C(O)OR^{14}$, $-N(R^{13})C(O)N(R^{13})R^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{14}$, $-OC(O)N(R^{13})R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, or $-C(O)N(R^{13})(R^{14})$, wherein

the $C_{1-6}alkyl$ of R^8 or R^9 is optionally substituted by one or more R^{7a};

R^{10} is H;

each R^{1a}, R^{3a}, R^{6a}, or R^{7a} is independently $-OR^{12}$ or $-N(R^x)(R^y)$;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, $C_{1-6}alkyl$, $-OR^{11}$, or $-N(R^x)(R^y)$, wherein

the $C_{1-6}alkyl$ of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, $C_{3-8}cycloalkyl$, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H or $C_{1-6}alkyl$;

each R^{12} is independently H, $C_{1-6}alkyl$, or $C_{3-8}cycloalkyl$,

wherein the $C_{1-6}alkyl$ is optionally substituted with one or more halo, deuterium, or $-N(R^x)(R^y)$;

each R^{13} is independently H or $C_{1-6}alkyl$;

each R^{14} is independently H, $C_{1-6}alkyl$, $C_{3-8}cycloalkyl$, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the $C_{1-6}alkyl$ of R^{14} is optionally substituted by halo, -OH, $-O(C_{1-6}alkyl)$, $-N(R^x)(R^y)$, $C_{3-8}cycloalkyl$, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the $C_{3-8}cycloalkyl$, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, $C_{1-6}alkyl$, or $-N(R^x)(R^y)$

each R^{15} is independently H or $C_{1-6}alkyl$; and

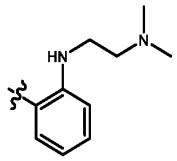
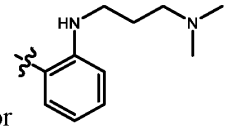
each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -C(=O)(C_{1-6}alkyl), or -C(=O)O(C_{1-6}alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, $-NH_2$, NH(C_{1-6}alkyl), or -N(C_{1-6}alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of -C(=O)(C_{1-6}alkyl) or -C(=O)O(C_{1-6}alkyl) is optionally substituted with -O(C=O)C_{1-8}alkyl);

wherein

(i) when Ring A is phenyl and R^6 is selected from the group consisting of $-NH_2$, $-NHCH_3$, and $-N(CH_3)_3$, R^1 and R^2 are not both C_{1-2}alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of $-NH_2$, $-NHC(O)CH_3$, and $-NHC(O)O-C(CH_3)_3$; and

(iv) when Ring A is pyridin-4yl substituted with $-NHC(CH_3)$phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0057] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing,

R^1 and R^2 are each independently C_{1-6}alkyl optionally substituted with one or more R^{1a};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, oxo, $-OR^{12}$, or $-N(R^x)(R^y)$ wherein

the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a};

Ring A is 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 8-membered unsaturated monocyclic heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, or $-OR^{12}$;

L is a bond, C_{1-6}alkyl, -O-(C_{1-6}alkyl)-, -S-(C_{1-6}alkyl)-, or -N(R^5)(C_{1-6}alkyl)-;

R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, -N(R^x)(R^y), or -OR^{12}, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is -N(R^x)(R^y), -N(R^{13})C(=O)R^{14}, -N(R^{13})C(=O)N(R^{13})R^{14}, -N(R^{13})C(=O)OR^{14}, -OC(=O)N(R^{13})R^{14}, -C(=O)(C_{1-6}alkyl)N(R^x)(R^y), -C(=O)N(R^{13})(R^{14}), -N(R^{13})S(=O)$_2R^{14}$, -S(=O)N(R^{13})R^{14}, -S(=O)$_2$N(R^{13})(R^{14}), or 3- to 12-membered N-containing heterocyclyl, wherein

the 3- to 12-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, -C(=O)R^{14}, -C(=O)N(R^{13})(R^{14}), or -C(=O)OR^{14}, and

the 3- to 12-membered N-containing heterocyclyl of R^6 further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7 is H;

R^8 and R^9 are each independently H, halo, C_{1-6}alkyl, $-OR^{12}$, -N(R^x)(R^y), -N(R^{13})C(O)R^{14}, -N(R^{13})C(O)OR^{14}, -N(R^{13})C(O)N(R^{13})R^{14}, -OC(O)R^{14}, -OC(O)OR^{14}, -OC(O)N(R^{13})R^{14}, -C(O)R^{14}, -C(O)OR^{14}, or -C(O)N(R^{13})(R^{14}) , wherein

the C_{1-6}alkyl of R^8 or R^9 is optionally substituted by one or more R^{7a};

R^{10} is H;

each R^{1a}, R^{3a}, R^{6a}, or R^{7a} is independently $-OR^{12}$ or -N(R^x)(R^y);

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, or -N(R^x)(R^y), wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, -N(R^x)(R^y), C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H or C_{1-6}alkyl;

each R^{12} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, or -$N(R^x)(R^y)$;

each R^{13} is independently H or C_{1-6}alkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by halo, -OH, -O(C_{1-6}alkyl), -$N(R^x)(R^y)$, C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, or -$N(R^x)(R^y)$

each R^{15} is independently H or C_{1-6}alkyl; and

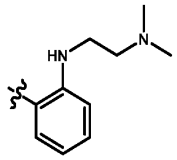
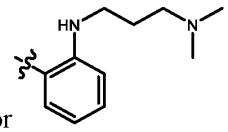
each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -C(=O)(C_{1-6}alkyl), or -C(=O)O(C_{1-6}alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -NH_2, NH(C_{1-6}alkyl), or -N(C_{1-6}alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of -C(=O)(C_{1-6}alkyl) or -C(=O)O(C_{1-6}alkyl) is optionally substituted with -O(C=O)C_{1-8}alkyl);

wherein

(i) when Ring A is phenyl and R^6 is selected from the group consisting of -NH_2, -$NHCH_3$, and -$N(CH_3)_3$, R^1 and R^2 are not both C_{1-2}alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of -NH_2, -$NHC(O)CH_3$, and -$NHC(O)O\text{-}C(CH_3)_3$; and

(iv) when Ring A is pyridin-4yl substituted with -$NHC(CH_3)$phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0058] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing,

R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

R^8 is H, halo, C_{1-6}alkyl, $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(O)R^{14}$, $-N(R^{13})C(O)OR^{14}$, $-N(R^{13})C(O)N(R^{13})R^{14}$, $-C(O)N(R^{13})(R^{14})$, or C_{3-6}cycloalkyl, wherein

the C_{1-6}alkyl of R^8 is optionally substituted by one or more R^{7a}; and

R^9 is H, halo, C_{1-6}alkyl, $-OR^{12}$, -CN, or C_{3-6}cycloalkyl, wherein

the C_{1-6}alkyl of R^9 is optionally substituted by one or more R^{7a}. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0059] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing,

R^1 and R^2 are taken together with the N to which they are attached to form a 4- to 12-membered heterocyclyl optionally substituted with one or more R^3;

Ring A is pyridinyl; and

L is a bond or $-O-(C_{1-6}alkyl)-$. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0060] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing,

R^1 and R^2 are taken together with the N to which they are attached to form a 4- to 12-membered heterocyclyl optionally substituted with one or more R^3;

Ring A is pyridinyl;

L is a bond; and

R^6 is piperazinyl optionally substituted with one or more R^{6b}. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

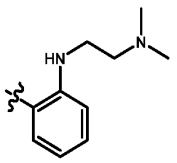
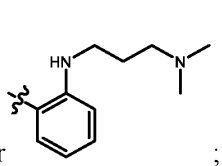
[0061] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing,

R^1 and R^2 are taken together with the N to which they are attached to form a 4- to 12-membered heterocyclyl optionally substituted with one or more R^3; and

R^8 and R^9 are each independently H, F, -N(CH_3)(CH_3), -OCH_3 or -OCD_3. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0062] In some embodiments,

(i) when Ring A is phenyl and R^6 is selected from the group consisting of -NH_2, -$NHCH_3$, and -N(CH_3)$_3$, R^1 and R^2 are not both $C_{1\text{-}2}$alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of -NH_2, -NHC(O)CH_3, and -NHC(O)O-C(CH_3)$_3$; and

(iv) when Ring A is pyridin-4yl substituted with -NHC(CH_3)phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl.

[0063] In some embodiments, when Ring A is phenyl, then -L-R^6 is not -NH_2 or -OCH_3.

[0064] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, Ring A is phenyl or 5- to 6-membered heteroaryl. In some embodiments, Ring A is selected from the group consisting of phenyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, furan, thiophene, oxazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyrazinyl, and triazinyl. In some embodiments, Ring A is phenyl, thiazolyl, or pyridinyl.

[0065] In some embodiments, Ring A is 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein the 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4; and the 4- to 8-membered unsaturated heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S. In some embodiments, Ring

A is phenyl or 5- to 6-membered heteroaryl, wherein the phenyl or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4; and the 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S. In some embodiments, Ring A is phenyl or 5- to 6-membered heteroaryl, wherein the phenyl or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4.

[0066] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^1 and R^2 are each independently C_{1-6}alkyl optionally substituted with one or more R^{1a}. In some embodiments, R^1 and R^2 are each independently C_{1-4}alkyl optionally substituted with one or more R^{1a}.

[0067] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, each R^{1a} is independently -OH, $-NH_2$, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)(C_{1-6}alkyl), -NH(C_{3-6}cycloalkyl), or -N(C_{1-6}alkyl)(C_{3-6}cycloalkyl). In some embodiments, each R^{1a} is independently -OH, $-NH_2$, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)(C_{1-4}alkyl), -NH(C_{3-6}cycloalkyl), or -N(C_{1-4}alkyl)(C_{3-6}cycloalkyl). In some embodiments, each R^{1a} is independently -OH, $-NH_2$, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)(C_{1-4}alkyl), -NH(C_{3-6}cycloalkyl), or -N(C_{1-4}alkyl)(C_{3-6}cycloalkyl). In some embodiments, each R^{1a} is independently -OH, $-NH_2$, -NH(CH_3), -N(CH_3)(CH_3), -NH(CH_2CH_3), -N(CH_3)(CH_2CH_3), or -N(CH_2CH_3)(CH_2CH_3).

[0068] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3, wherein the 3- to 12-membered heterocyclyl comprises a 3- to 8-membered monocyclic heterocyclyl, a 5- to 12-membered fused heterocyclyl, or a 6- to 12-membered spirocyclic heterocyclyl. In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a 4- to 12-membered heterocyclyl optionally substituted with one or more R^3. In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a 4- to 7-membered monocyclic heterocyclyl optionally substituted with one or more R^3. In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form an azetidinyl, pyrrolidinyl, or diazepanyl optionally substituted with one or more R^3. In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a pyrrolidinyl or diazepanyl optionally substituted with one or more R^3. In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to

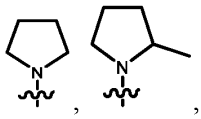
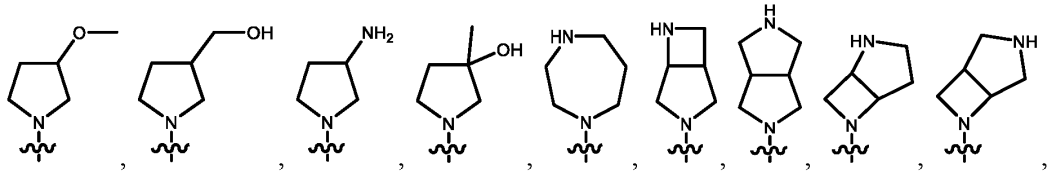
form a 6- to 12-membered fused heterocyclyl optionally substituted with one or more R^3. In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a 6- to 12-membered spirocyclic heterocyclyl optionally substituted with one or more R^3.

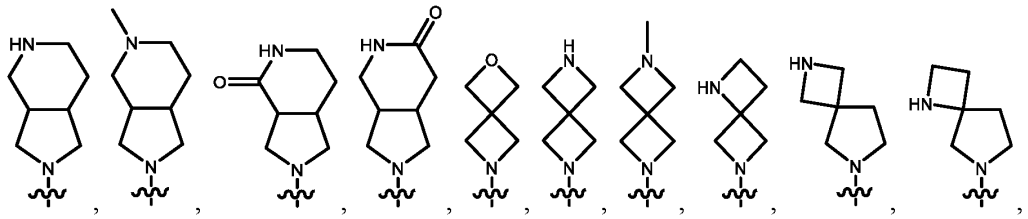
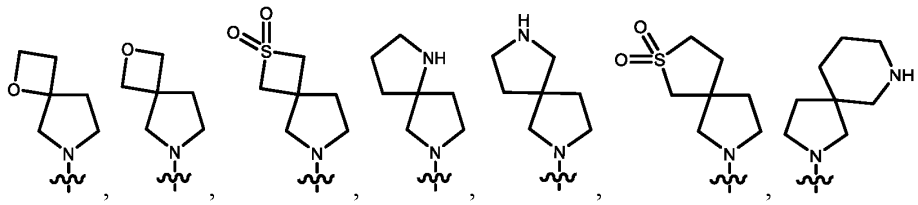
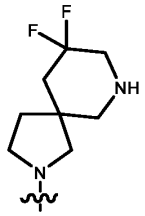
[0069] In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 9-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl, wherein the saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 9-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl is optionally substituted with one or more R^3. In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a saturated 4- to 5-membered monocyclic heterocyclyl optionally substituted with one or more R^3. In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a saturated 7- to 10-membered fused heterocyclyl optionally substituted with one or more R^3. In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a saturated 7- to 9-membered fused heterocyclyl optionally substituted with one or more R^3. In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a saturated 7- to 10-membered spirocyclic heterocyclyl optionally substituted with one or more R^3.

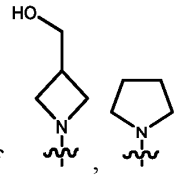
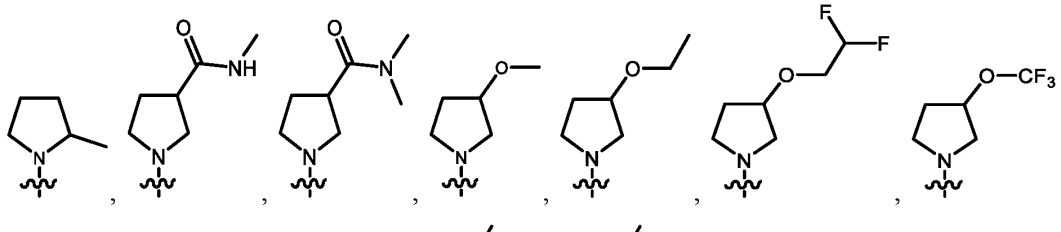
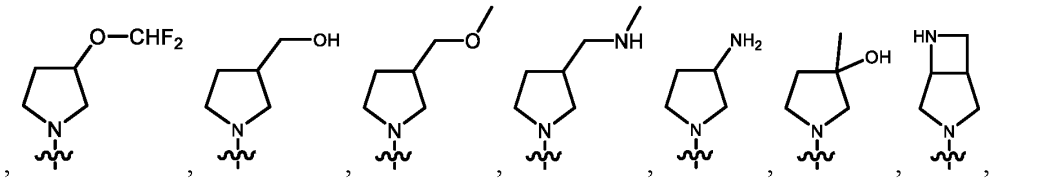
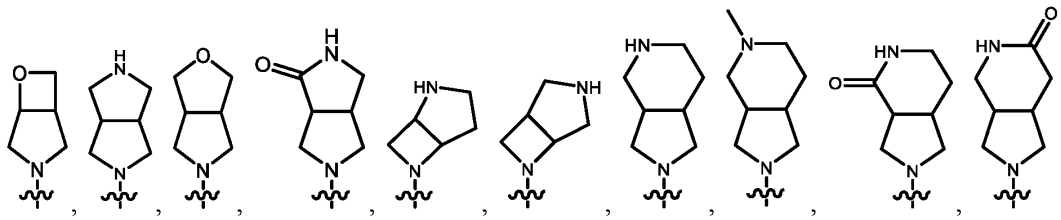
[0070] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, each R^3 is independently halo, $C_{2\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, oxo, $-OR^{12}$, $-SR^{12}$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-SC(=O)R^{14}$, $-SC(=O)N(R^{13})R^{14}$, $-SC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, $C_{3\text{-}8}$cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein the $C_{2\text{-}6}$alkyl of R^3 is optionally substituted with one or more R^{3a}, and optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a $C_{3\text{-}8}$cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein the $C_{3\text{-}8}$cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b}.

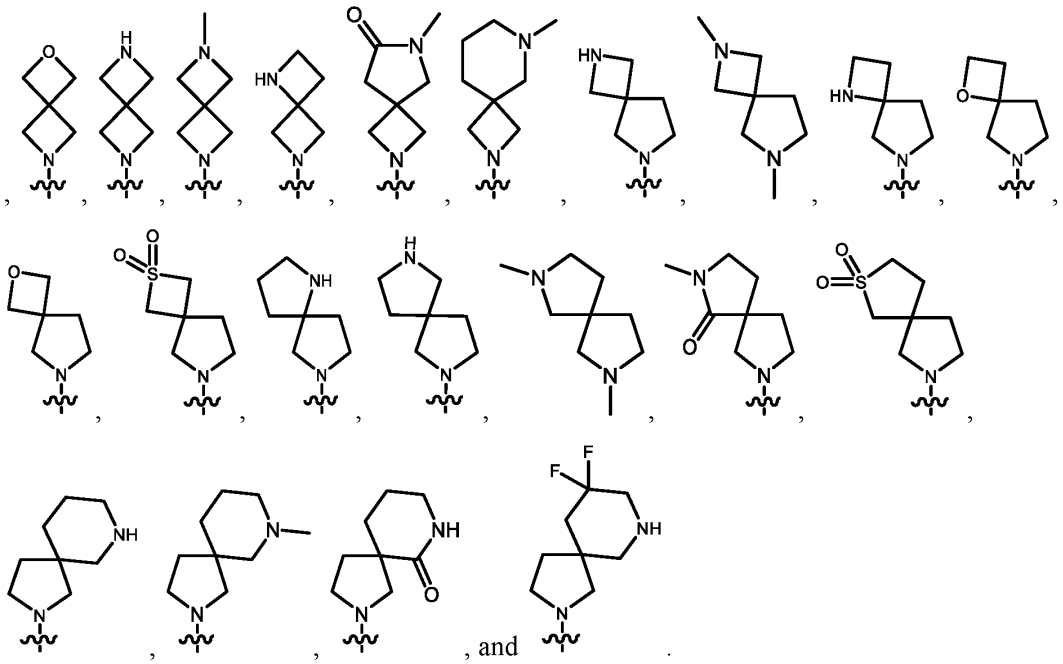
[0071] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, each R^3 is independently halo, C_{2-6}alkyl, oxo, $-OR^{12}$, or $-N(R^x)(R^y)$ wherein the C_{2-6}alkyl of R^3 is optionally substituted with R^{3a}. In some embodiments, each R^3 is independently halo, -OH, C_{1-6}alkyl, C_{1-6}alkoxy, oxo, or $-N(R^x)(R^y)$ wherein the C_{1-6}alkyl of the R^3 is optionally substituted with R^{3a}. In some embodiments, each R^3 is independently halo, -OH, C_{1-4}alkyl, C_{1-4}alkoxy, oxo, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-NH(C_{3-6}cycloalkyl)$, or $-N(C_{1-4}alkyl)(C_{3-6}cycloalkyl)$, wherein the C_{1-4}alkyl of the R^3 is optionally substituted with R^{3a}. In some embodiments, each R^3 is independently F, -OH, $-CH_3$, $-CH_2OH$, $-OCH_3$, oxo, or $-NH_2$. In some embodiments, each R^3 is independently -OH, C_{1-6}alkyl, C_{1-6}alkoxy, or $-N(R^x)(R^y)$ wherein the C_{1-6}alkyl of the R^3 is optionally substituted with R^{3a}. In some embodiments, each R^3 is independently -OH, C_{1-4}alkyl, C_{1-4}alkoxy, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-NH(C_{3-6}cycloalkyl)$, or $-N(C_{1-4}alkyl)(C_{3-6}cycloalkyl)$, wherein the C_{1-4}alkyl of the R^3 is optionally substituted with R^{3a}. In some embodiments, each R^3 is independently -OH, $-CH_3$, $-CH_2OH$, $-OCH_3$, or $-NH_2$. In some embodiments, R^3 is independently C_{1-6}alkyl or oxo. In some embodiments, each R^3 is independently $-CH_3$ or oxo. In some embodiments, each R^3 is halo. In some embodiments, R^3 is F.

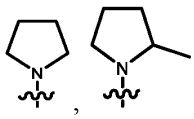
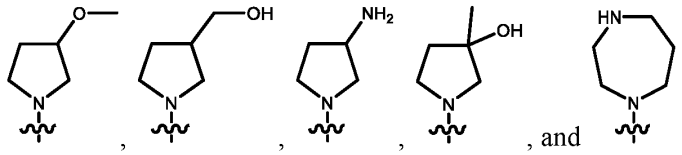
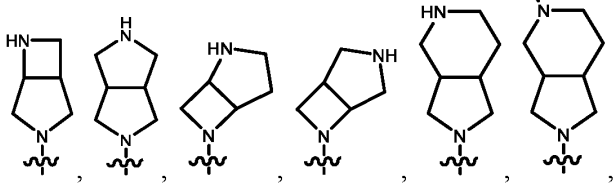
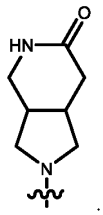
[0072] In some embodiments, each R^3 is independently halo, C_{1-6}alkyl, oxo, $-OR^{12}$, $-N(R^x)(R^y)$, -CN, or $-C(=O)N(R^{13})(R^{14})$, wherein the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a}. In some embodiments, each R^3 is independently halo, C_{2-6}alkyl, oxo, $-OR^{12}$, $-N(R^x)(R^y)$, -CN, or $-C(=O)N(R^{13})(R^{14})$, wherein the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a}.

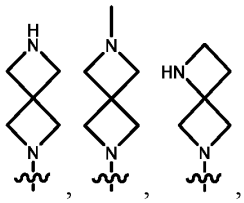
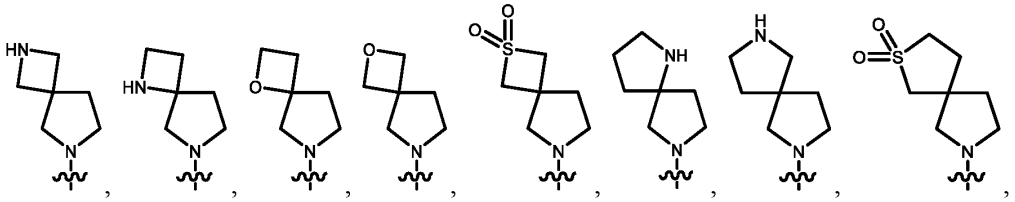
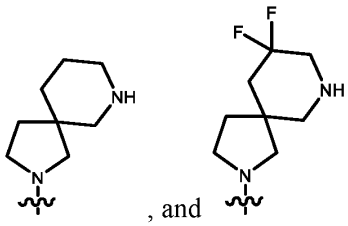
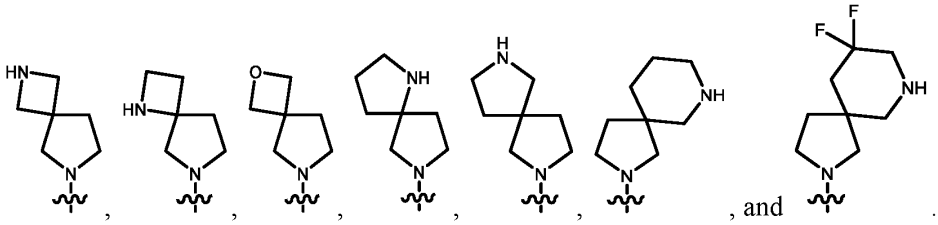
[0073] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of  ,  ,

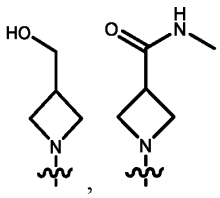
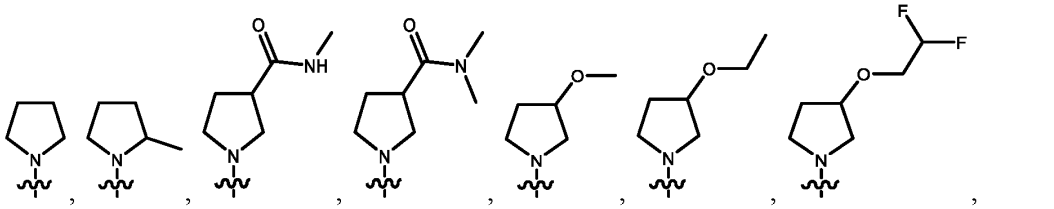
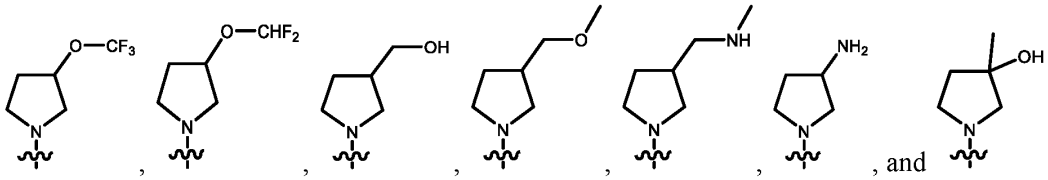



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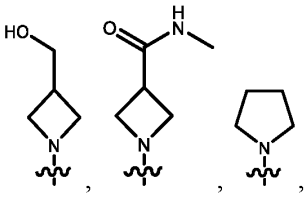
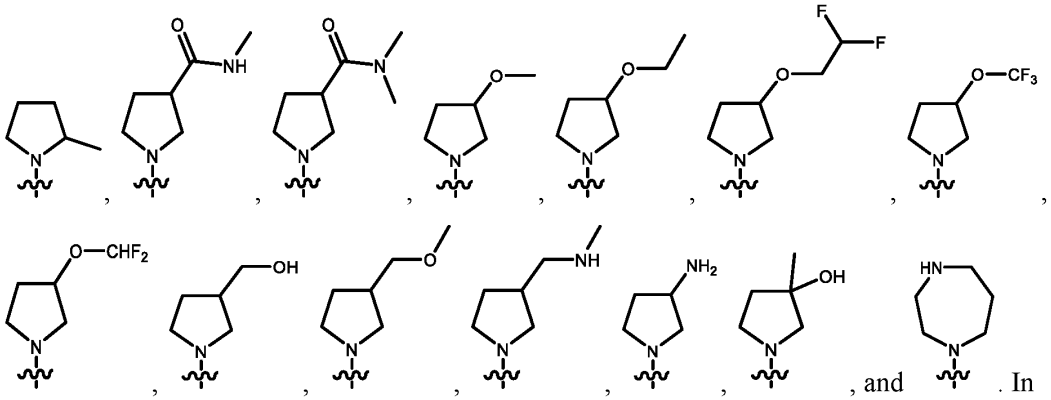
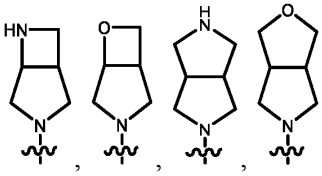
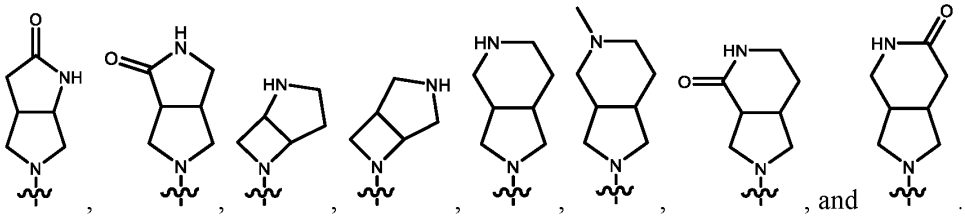
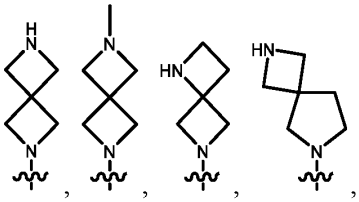
[0074] In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of 




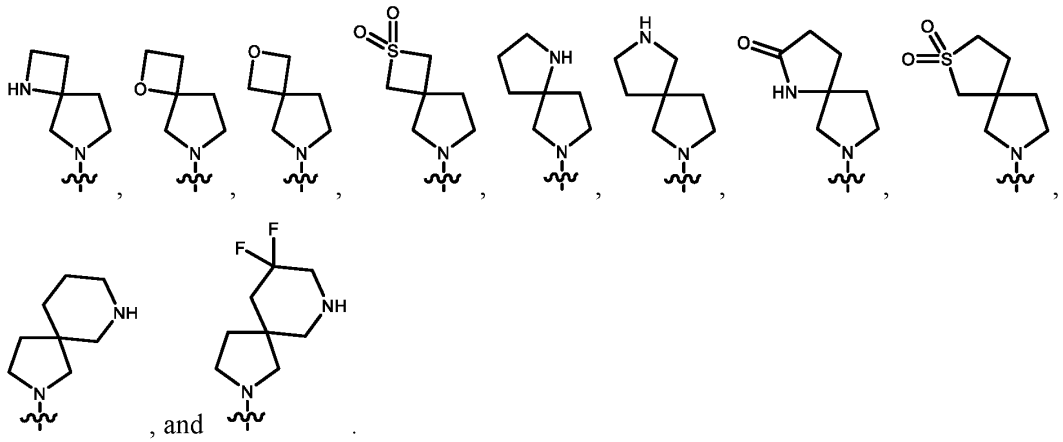


[0075] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of  ,  , and . In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of  , and  . In some embodiments, R^1 and R^2 are taken together with the N to which they are

attached to form a heterocyclyl selected from the group consisting of  ,  ,  , and . In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of  , and .

[0076] In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of  ,  ,  , and .

In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of  ,  , and . In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of  ,  , and . In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of  , .



, and .

[0077] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, each R^4 is independently halo or -O-(C_{1-6}alkyl). In some embodiments, each R^4 is independently halo or -OCH_3. In some embodiments, each R^4 is independently F, Cl, or -OCH_3.

[0078] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, -$N(R^x)(R^y)$, -OR^{12}; and the C_{3-8}cycloalkyl of R^5 is optionally substituted with one or more R^{5b}. In some embodiments, R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl. In some embodiments, R^5 is H or C_{1-6}alkyl. In some embodiments, R^5 is H.

[0079] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, L is a bond or -O-(C_{1-6}alkyl)-. In some embodiments, L is a bond or -O-(CH_2CH_2)-.

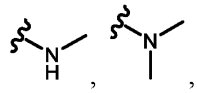
[0080] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^6 is -$N(R^x)(R^y)$, -$N(R^{13})C(=O)R^{14}$, -$N(R^{13})C(=O)OR^{14}$, -$N(R^{13})C(=O)N(R^{13})R^{14}$, -$C(=O)N(R^{13})(R^{14})$, -$C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, or 3- to 12-membered N-containing heterocyclyl optionally substituted with one or more R^{6b}. In some embodiments, R^6 is -$N(R^x)(R^y)$, -$N(R^{13})C(=O)R^{14}$, -$C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, or 3- to 12-membered N-containing heterocyclyl optionally substituted with one or more R^{6b}. In some embodiments, R^6 is -$N(R^x)(R^y)$, -$N(R^{13})C(=O)R^{14}$, -$C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, azetidinyl, or piperazinyl, wherein the azetidinyl or piperazinyl of R^6 is optionally substituted with one or

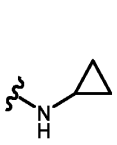
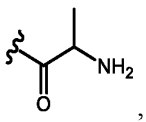
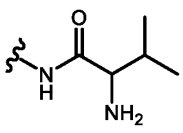
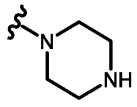
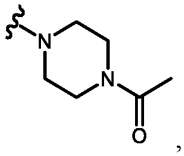
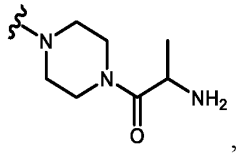
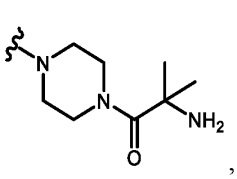
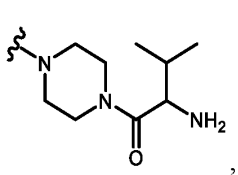
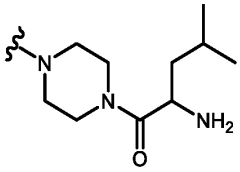
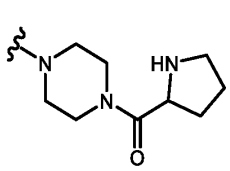
more R^{6b}. In some embodiments, R^6 is $-N(R^x)(R^y)$. In some embodiments, R^6 is $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$. In some embodiments, R^6 is $-N(R^{13})C(=O)R^{14}$ or $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$. In some embodiments, R^6 is 3- to 12-membered N-containing heterocyclyl optionally substituted with one or more R^{6b}. In some embodiments, R^6 is azetidinyl, pyrrolidinyl, or piperazinyl, wherein the azetidinyl, pyrrolidinyl, or piperazinyl is optionally substituted with one or more R^{6b}. In some embodiments, R^6 is azetidinyl or piperazinyl, wherein the azetidinyl or piperazinyl is optionally substituted with one or more R^{6b}.

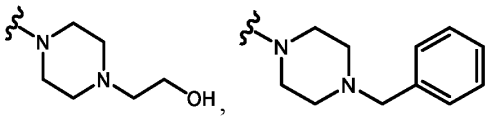
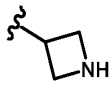
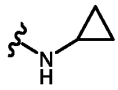
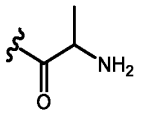
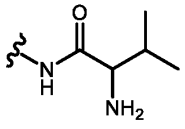
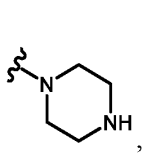
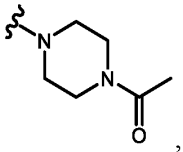
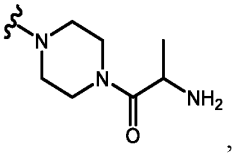
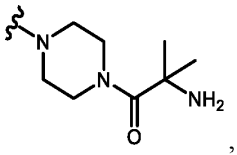
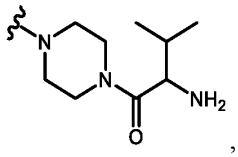
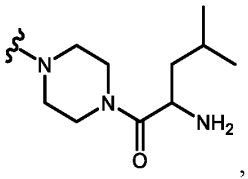
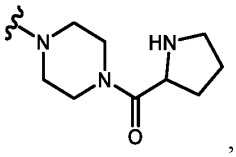
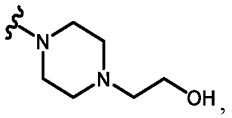
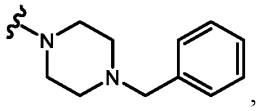
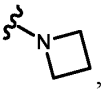
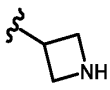
[0081] In some embodiments, R^6 is $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, or 3- to 12-membered N-containing heterocyclyl optionally substituted with one or more R^{6b}. In some embodiments, R^6 is $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, or 3- to 8-membered N-containing heterocyclyl optionally substituted with one or more R^{6b}.

[0082] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, L is a bond and R^6 is 3- to 12-membered N-containing heterocyclyl optionally substituted with one or more R^{6b}. In some embodiments, L is a bond and R^6 is azetidinyl or piperazinyl, wherein the azetidinyl or piperazinyl is optionally substituted with one or more R^{6b}.

[0083] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^6 is selected from the group consisting of



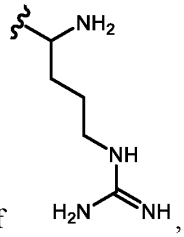
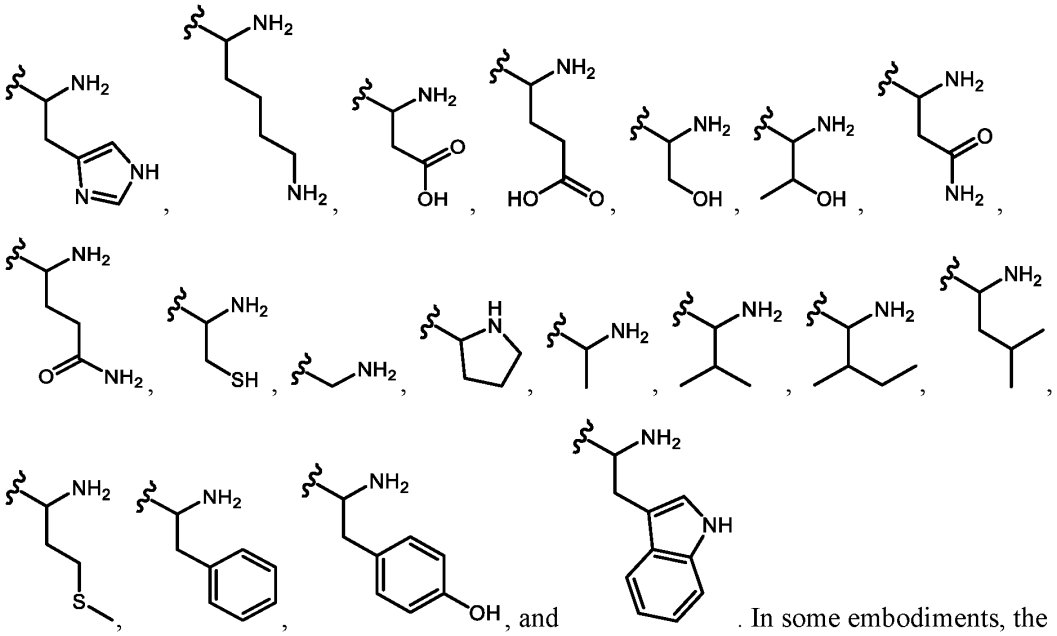











 , ,  , and  . In some embodiments, R^6 is selected from the group consisting of  ,  , and  . In some embodiments, R^6 is  or  . In some embodiments, R^6 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

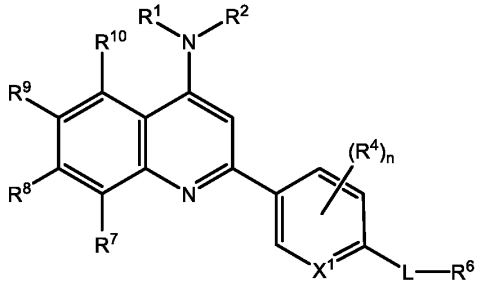
[0084] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^8 and R^9 are each independently H, halo, $-N(R^x)(R^y)$, $-OR^{11}$, $-N(R^{13})C(O)R^{14}$, or $-N(R^{13})C(O)OR^{14}$. In some embodiments, R^8 and R^9 are each independently H, halo, $-NH_2$, $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$, $-O(C_{1-6}alkyl)$, -NHC(O)(5- to 6-membered aryl), or $-NHC(O)O(C_{1-6}alkyl)$, wherein the 5- to 6-membered aryl of -NHC(O)(5- to 6-membered aryl) is optionally substituted with $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$. In some embodiments, R^8 and R^9 are each independently H, F, Cl, $-NH_2$, $-N(CH_3)(CH_3)$, $-OCH_3$, -NHC(O)(phenyl), or $-NHC(O)O(CH_2CH_3)$, wherein the phenyl of -NHC(O)(phenyl) is substituted with $-N(CH_3)(CH_3)$. In some embodiments, R^8 and R^9 are each H.

[0085] In some embodiments, each R^{12} is independently H, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{3-8}cycloalkyl$, or 5- to 10-membered heteroaryl, wherein the $C_{1-6}alkyl$ is optionally substituted with one or more halo, deuterium, $-O(C_{1-6}alkyl)$, or $-N(R^x)(R^y)$. In some embodiments, each R^{12} is independently H, $C_{1-6}alkyl$, $C_{3-8}cycloalkyl$, or 5- to 10-membered heteroaryl, wherein the $C_{1-6}alkyl$ is optionally substituted with one or more halo, deuterium,

or -N(R^x)(R^y). In some embodiments, each R^{12} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, or -N(R^x)(R^y).

[0086] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^{14} is selected from the group consisting of  ,  , and . In some embodiments, the aforementioned R^{14} groups have the (R)- configuration. In some embodiments, the aforementioned R^{14} groups have the (S)- configuration.

[0087] In some embodiments of a compound of formula (I), the compound is a compound of formula (II):

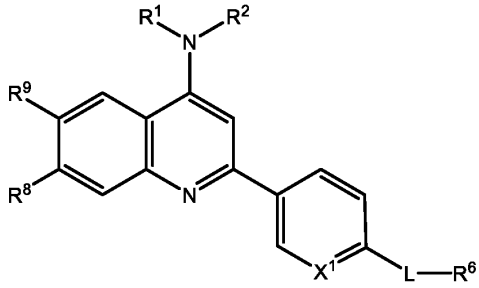


(II), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^1 is N or CH, and n is 0, 1, 2, or 3, and R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined elsewhere herein. In another variation, X^1 is N or CH, and n is 0, 1, 2, or 3, and R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0088] In some embodiments of formula (II), X^1 is N. In some embodiments, X^1 is CH.

[0089] In some embodiments of formula (II), n is 0, 1, or 2. In some embodiments In some embodiments, n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

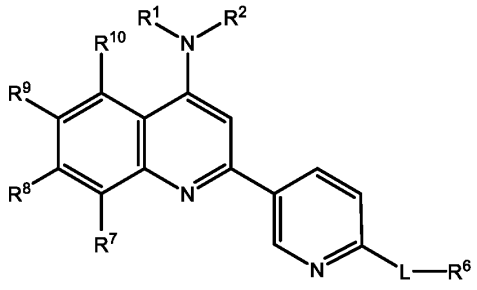
[0090] In some embodiments of a compound of formula (I), the compound is a compound of formula (II-A):



(II-A), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^1 is N or CH, and R^1, R^2, R^6, R^8, R^9, and L are as defined elsewhere herein. In another variation, X^1 is N or CH, and R^1, R^2, R^6, R^8, R^9, and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a

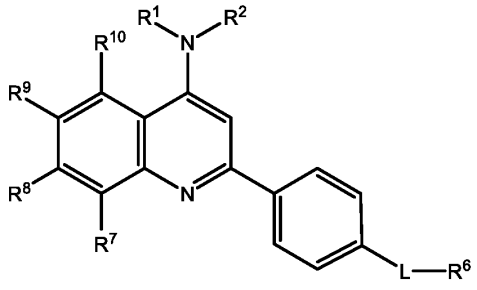
pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some of the foregoing embodiments, provided herein is a compound of formula (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0091] In some embodiments of a compound of formula (I), the compound is a compound of formula (II-B):



(II-B), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined elsewhere herein. In another variation, R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (II-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (II-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

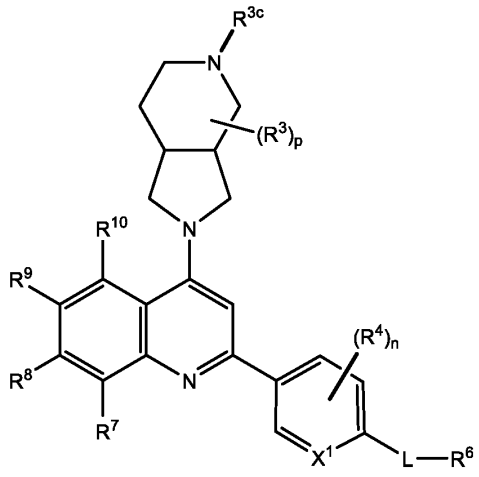
[0092] In some embodiments of a compound of formula (I), the compound is a compound of formula (II-C):



(II-C), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined elsewhere herein. In another variation, R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically

acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (II-C), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (II-C), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0093] In some embodiments of a compound of formula (I), the compound is a compound of formula (II-D)



(II-D), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^1 is N or CH; n is 0, 1, 2, or 3; R^{3c} is H or C_{1-4}alkyl; p is 0, 1, 2, 3, 4, 5, or 6; and R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined elsewhere herein. In another variation, X^1 is N or CH; n is 0, 1, 2, or 3; R^{3c} is H or C_{1-4}alkyl; p is 0, 1, 2, 3, 4, 5, or 6; and R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (II-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (II-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

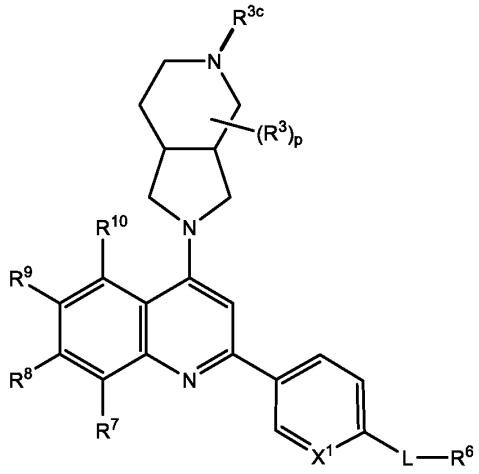
[0094] In some embodiments of formula (II-D), X^1 is N. In some embodiments, X^1 is CH.

[0095] In some embodiments of formula (II-D), n is 0, 1, or 2. In some embodiments, n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

[0096] In some embodiments of formula (II-D), R^{3c} is H or methyl. In some embodiments, R^{3c} is H. In some embodiments, R^{3c} is C_{1-4}alkyl. In some embodiments, R^{3c} is methyl.

[0097] In some embodiments of formula (II-D), p is 0, 1, 2, 3, or 4. In some embodiments, p is 0, 1, or 2. In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2.

[0098] In some embodiments of a compound of formula (I), the compound is a compound of formula (II-D-1)

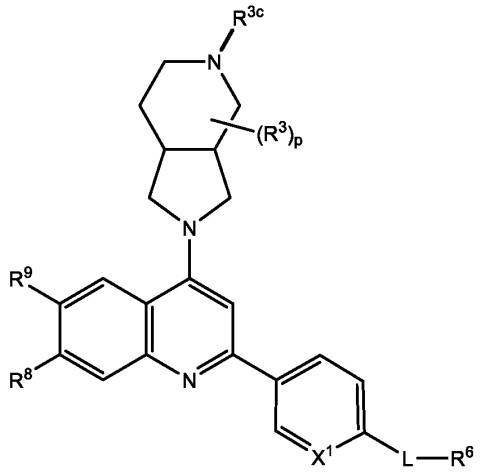


(II-D-1), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^1 is N or CH; R^{3c} is H or C_{1-4}alkyl; p is 0, 1, 2, 3, 4, 5, or 6; and R^3, R^7, R^8, R^9, R^{10}, and L are as defined elsewhere herein. In another variation, X^1 is N or CH; p is 0, 1, 2, 3, 4, 5, or 6; and R^3, R^7, R^8, R^9, R^{10}, and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (II-D-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (II-D-1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0099] In some embodiments of formula (II-D-1), R^{3c} is H or methyl. In some embodiments, R^{3c} is H. In some embodiments, R^{3c} is C_{1-4}alkyl. In some embodiments, R^{3c} is methyl.

[0100] In some embodiments of formula (II-D-1), p is 0, 1, 2, 3, or 4. In some embodiments, p is 0, 1, or 2. In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2.

[0101] In some embodiments of a compound of formula (I), the compound is a compound of formula (II-D-2)

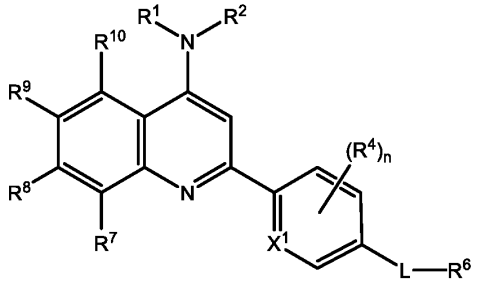


(II-D-2), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^1 is N or CH; R^{3c} is H or C_{1-4}alkyl; p is 0, 1, 2, 3, 4, 5, or 6; and R^3, R^8, R^9, and L are as defined elsewhere herein. In another variation, X^1 is N or CH; p is 0, 1, 2, 3, 4, 5, or 6; and R^3, R^8, R^9, and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (II-D-2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (II-D-2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0102] In some embodiments of formula (II-D-2), R^{3c} is H or methyl. In some embodiments, R^{3c} is H. In some embodiments, R^{3c} is C_{1-4}alkyl. In some embodiments, R^{3c} is methyl.

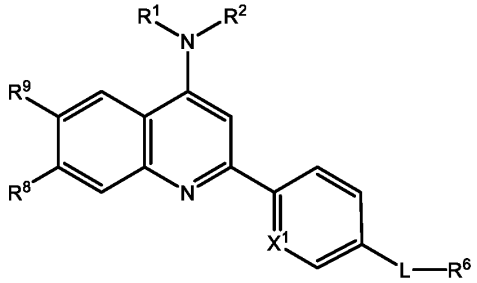
[0103] In some embodiments of formula (II-D-2), p is 0, 1, 2, 3, or 4. In some embodiments, p is 0, 1, or 2. In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2.

[0104] In some embodiments of a compound of formula (I), the compound is a compound of formula (III):



(III), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^1 is N or CH; n is 0, 1, 2, or 3; and R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined elsewhere herein. In another variation, X^1 is N or CH; n is 0, 1, 2, or 3; and R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

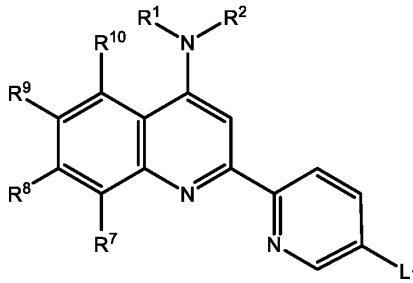
[0105] In some embodiments of a compound of formula (I), the compound is a compound of formula (III-A):



(III-A), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^1 is N or CH; and R^1, R^2, R^6, R^8, R^9, and L are as defined elsewhere herein. In another variation, X^1 is N or CH; and R^1, R^2, R^6, R^8, R^9, and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (III-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the

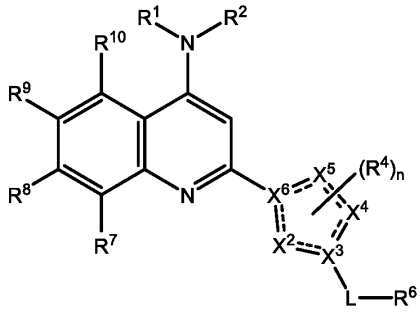
foregoing, the compound is a compound of formula (III-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0106] In some embodiments of a compound of formula (I), the compound is a compound of formula (III-B):



(III-B), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined elsewhere herein. In another variation, R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (III-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (III-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

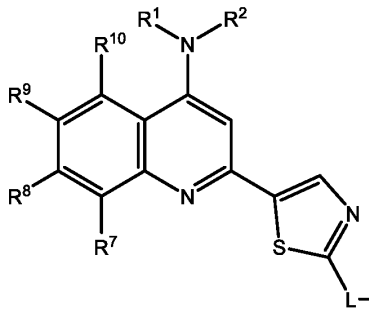
[0107] In some embodiments of a compound of formula (I), the compound is a compound of formula (IV):



(IV), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^2, X^4 and X^5 are each independently C, N, O or S; X^3 and X^6 are each independently C or N; n is 0, 1, 2, or 3, and R^1, R^2, R^4, R^6, R^7, R^8, R^9, R^{10} and L are as defined elsewhere herein. In another variation, X^2, X^4 and X^5 are each independently C, N, O or S; X^3 and X^6 are each independently C or N; n is 0, 1, 2, or 3, and R^1, R^2, R^4, R^6, R^7, R^8,

R^9, R^{10} and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0108] In some embodiments of a compound of formula (I), the compound is a compound of formula (IV-A):



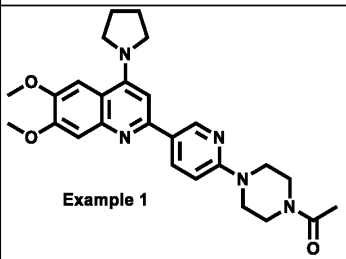
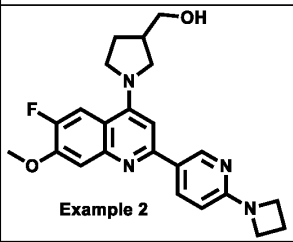
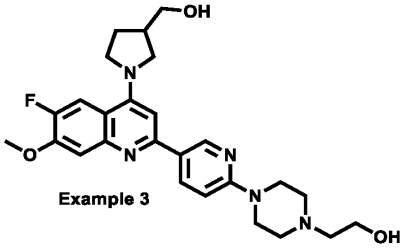
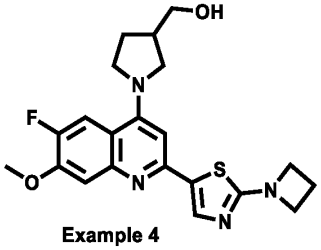
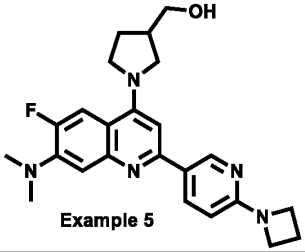
(IV-A), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1, R^2, R^6, R^7, R^8, R^9, R^{10} and L are as defined elsewhere herein. In another variation, R^1, R^2, R^6, R^7, R^8, R^9, R^{10} and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

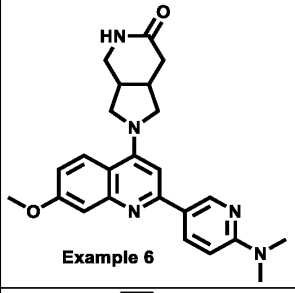
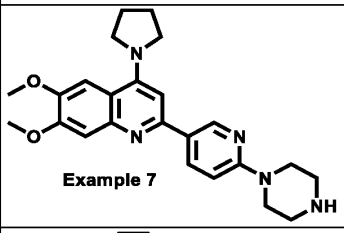
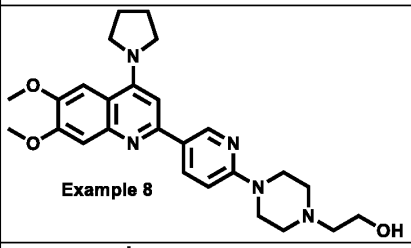
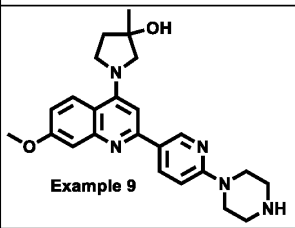
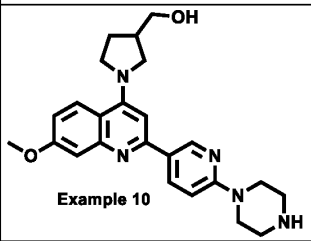
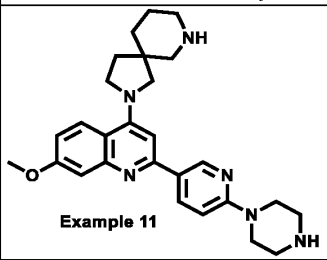
[0109] In some embodiments, the compounds of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, selectively modulate TDP-43. In some embodiments, the compounds of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, reduce TDP-43 cytoplasmic inclusions, improve nuclear TDP-43 function, or reduce neurodegeneration. In some embodiments, the compounds of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, reduce TDP-43 cytoplasmic inclusions. In some embodiments, the compounds of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or

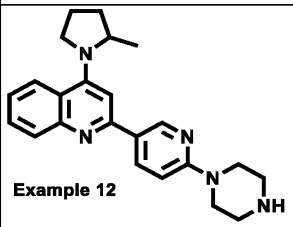
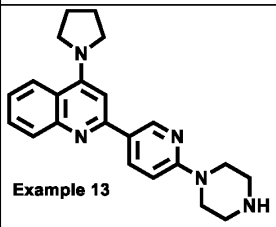
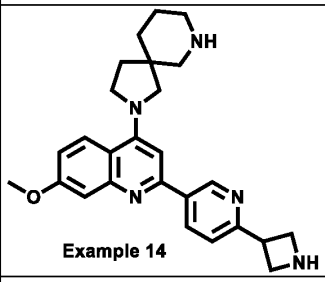
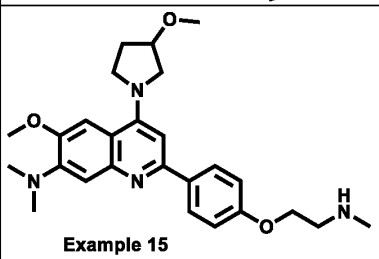
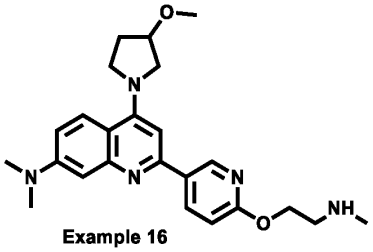
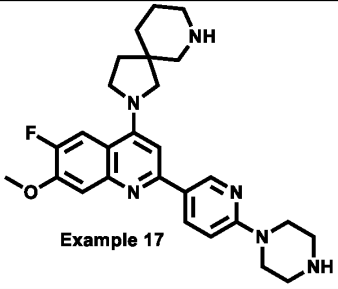
a pharmaceutically acceptable salt of any of the foregoing, improve nuclear TDP-43 function. In some embodiments, the compounds of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, reduce neurodegeneration. In some embodiments, the compounds of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, mitigate TDP-43 cytoplasmic condensates in motor neurons. In some embodiments, the motor neurons are iPSC-derived motor neurons. In some embodiments, *STMN2* and *POLDIP3* splicing in iPSC-derived motor neurons is restored.

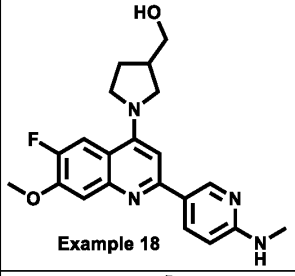
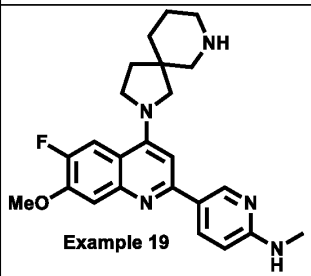
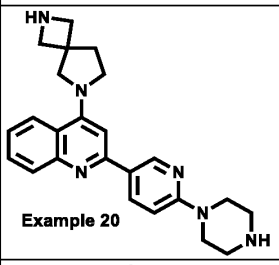
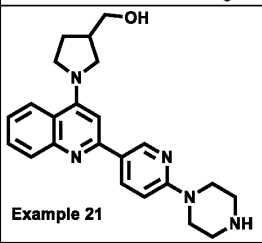
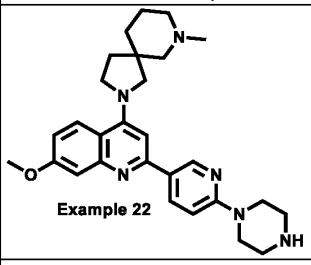
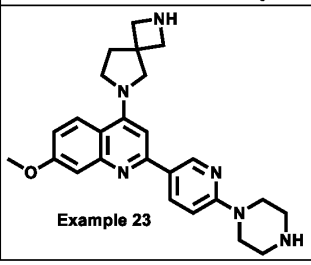
[0110] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is selected from Table 1. In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is selected from examples 1-68 of Table 1. In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is selected from Table 1, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is selected from compounds 1-68 of Table 1, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is selected from compounds 1-43, or 45-68 of Table 1, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is selected from compounds 1-43, 45-361, 363-367, 370-399, and 404-405 of Table 1, or a pharmaceutically acceptable salt of any of the foregoing.

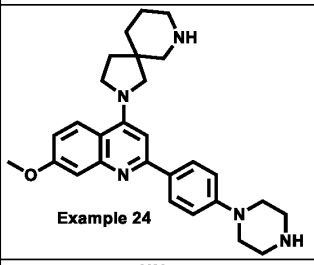
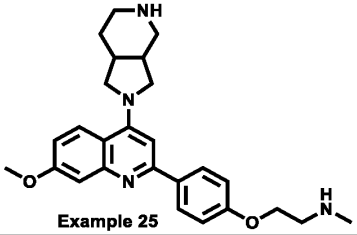
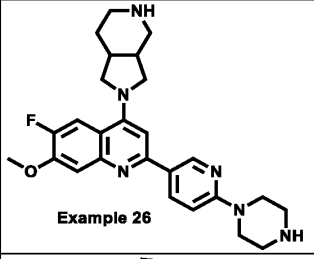
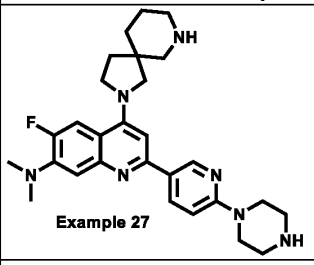
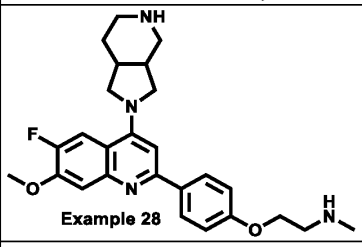
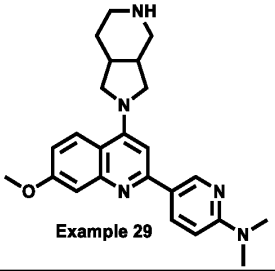
Table 1

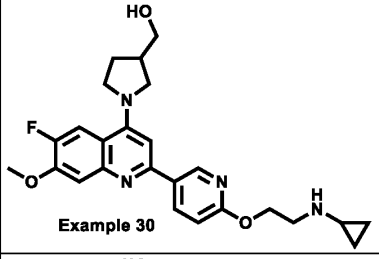
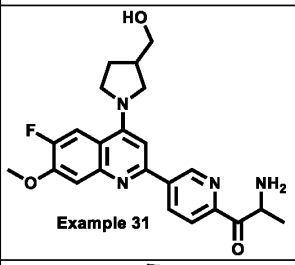
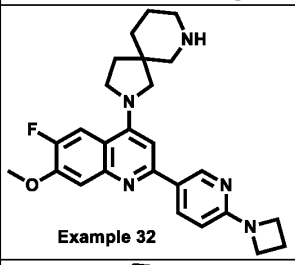
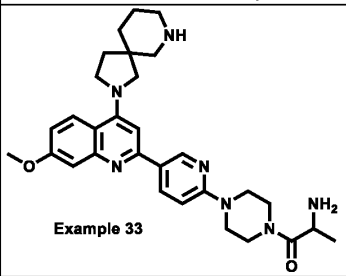
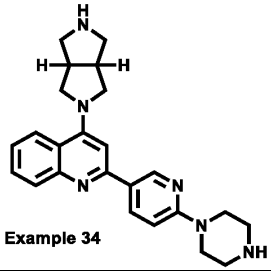
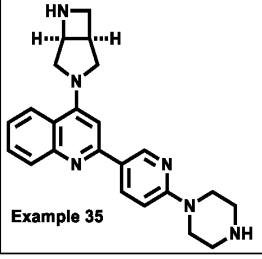
Ex. No.	Structure	Name
1	 Example 1	1-(4-(5-(6,7-dimethoxy-4-(pyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-one
2	 Example 2	(1-(2-(6-(azetidin-1-yl) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol
3	 Example 3	2-(4-(5-(6-fluoro-4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-ol
4	 Example 4	(1-(2-(2-(azetidin-1-yl) thiazol-5-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol
5	 Example 5	(1-(2-(6-(azetidin-1-yl) pyridin-3-yl)-7-(dimethylamino)-6-fluoroquinolin-4-yl) pyrrolidin-3-yl) methanol

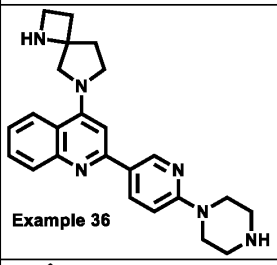
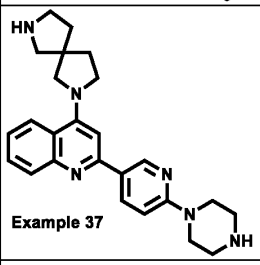
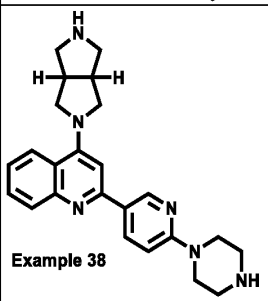
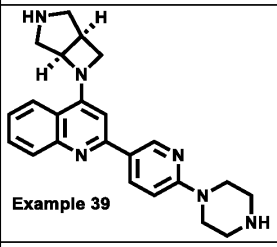
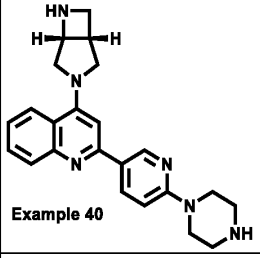
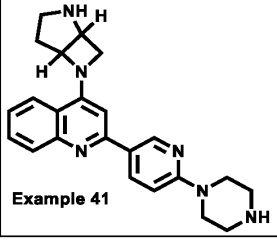
Ex. No.	Structure	Name
6	 Example 6	(cis)-2-(2-(6-(dimethylamino) pyridin-3-yl)-7-methoxyquinolin-4-yl) octahydro-6H-pyrrolo[3,4-c] pyridin-6-one
7	 Example 7	6,7-dimethoxy-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(pyrrolidin-1-yl) quinoline
8	 Example 8	2-(4-(5-(6,7-dimethoxy-4-(pyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-ol
9	 Example 9	1-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-3-methylpyrrolidin-3-ol
10	 Example 10	(1-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol
11	 Example 11	2-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane

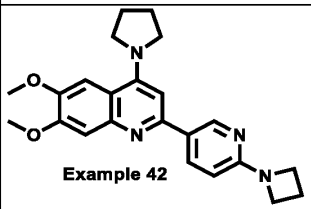
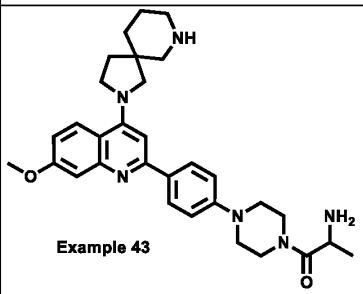
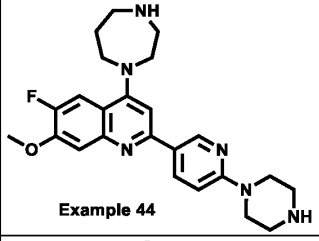
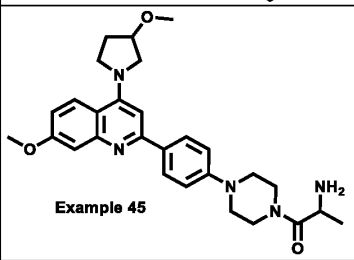
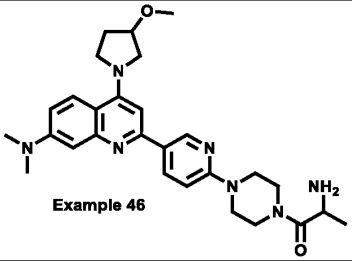
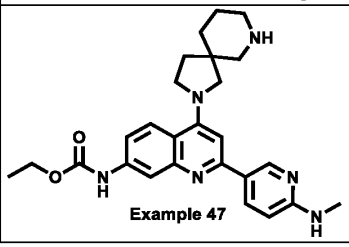
Ex. No.	Structure	Name
12	 Example 12	4-(2-methylpyrrolidin-1-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline
13	 Example 13	2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(pyrrolidin-1-yl) quinoline
14	 Example 14	2-(2-(6-(azetidin-3-yl) pyridin-3-yl)-7-methoxyquinolin-4-yl)-2,7-diazaspiro [4.5] decane
15	 Example 15	6-methoxy-4-(3-methoxypyrrolidin-1-yl)-*N*, *N*-dimethyl-2-(4-(2-(methylamino) ethoxy) phenyl) quinolin-7-amine
16	 Example 16	4-(3-methoxypyrrolidin-1-yl)-*N*, *N*-dimethyl-2-(6-(2-(methylamino) ethoxy) pyridin-3-yl) quinolin-7-amine
17	 Example 17	2-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane

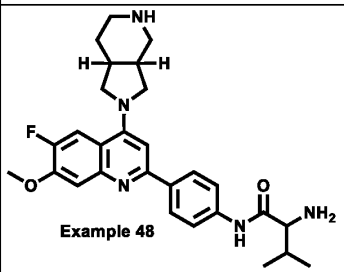
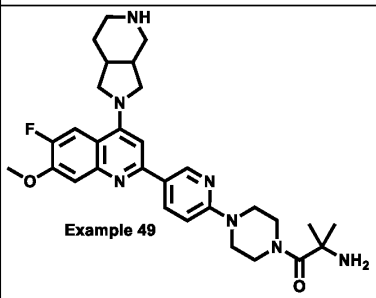
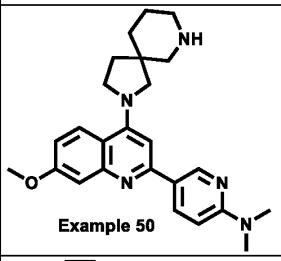
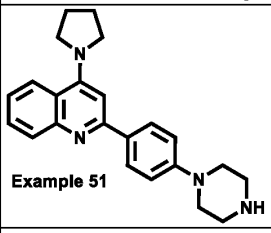
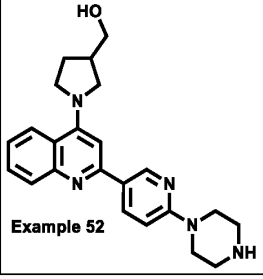
Ex. No.	Structure	Name
18	 Example 18	(1-(6-fluoro-7-methoxy-2-(6-(methylamino) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol
19	 Example 19	5-(6-fluoro-7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl)-*N*-methylpyridin-2-amine
20	 Example 20	2-(6-(piperazin-1-yl)pyridin-3-yl)-4-(2,6-diazaspiro[3.4]octan-6-yl)quinoline
21	 Example 21	(1-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol
22	 Example 22	2-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-7-methyl-2,7-diazaspiro [4.5] decane
23	 Example 23	7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,6-diazaspiro [3.4] octan-6-yl) quinoline

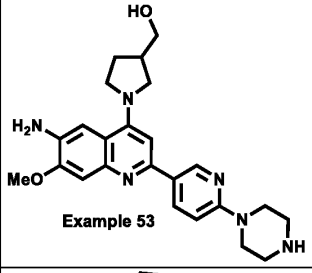
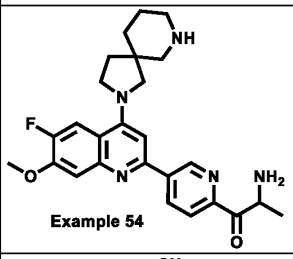
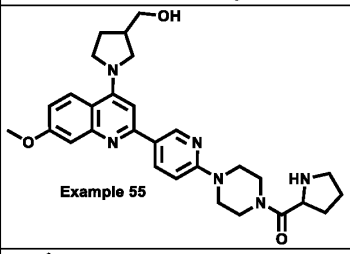
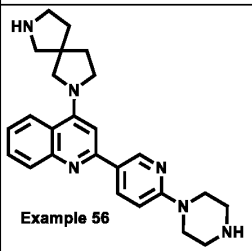
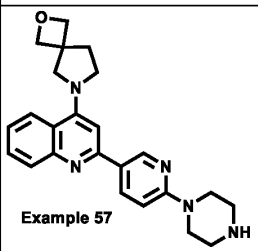
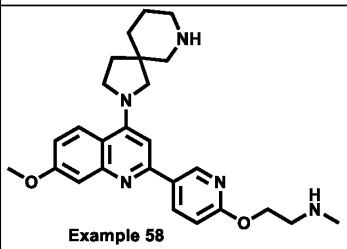
Ex. No.	Structure	Name
24	 Example 24	2-(7-methoxy-2-(4-(piperazin-1-yl) phenyl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane
25	 Example 25	(cis)-2-(4-(7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenoxy)-*N*-methylethan-1-amine
26	 Example 26	(cis)-6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline
27	 Example 27	6-fluoro-*N*, *N*-dimethyl-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-7-amine
28	 Example 28	(cis)-2-(4-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenoxy)-*N*-methylethan-1-amine
29	 Example 29	(cis)-5-(7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl)-*N*, *N*-dimethylpyridin-2-amine

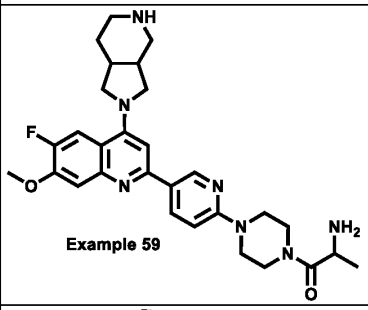
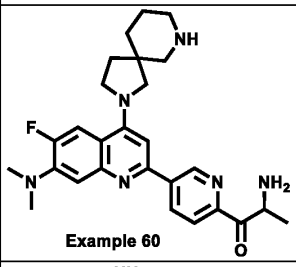
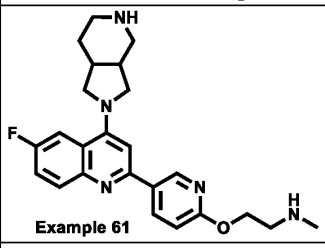
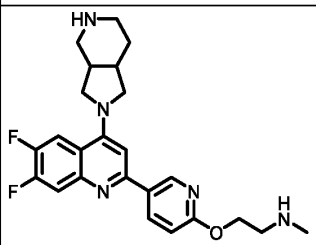
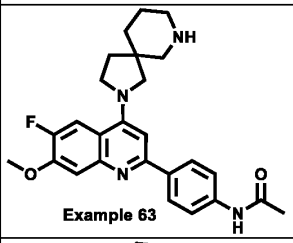
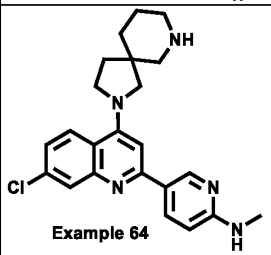
Ex. No.	Structure	Name
30	 Example 30	(1-(2-(6-(2-(cyclopropylamino) ethoxy) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol
31	 Example 31	2-amino-1-(5-(6-fluoro-4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) propan-1-one
32	 Example 32	2-(2-(6-(azetidin-1-yl) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl)-2,7-diazaspiro [4.5] decane
33	 Example 33	2-amino-1-(4-(5-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) propan-1-one
34	 Example 34	4-(cis)-hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline
35	 Example 35	1-(4-(5-(4-((1S,5S)-3,6-diazabicyclo [3.2.0] heptan-3-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-2-aminopropan-1-one

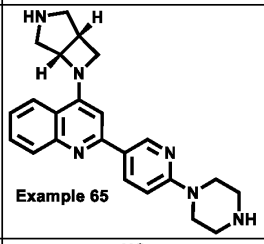
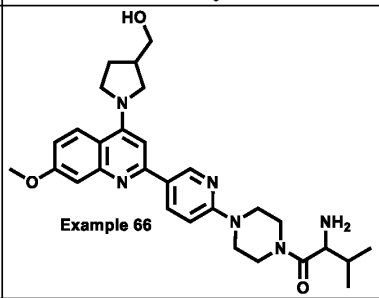
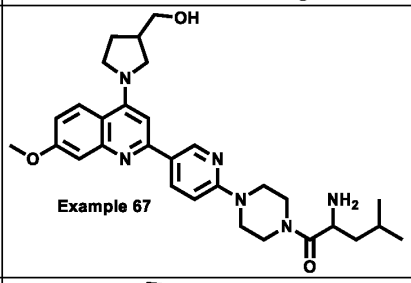
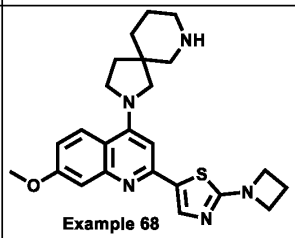
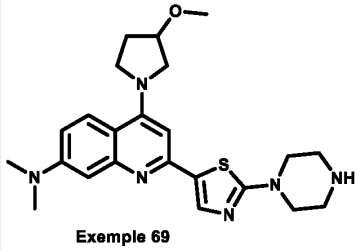
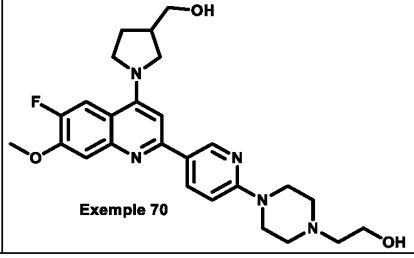
Ex. No.	Structure	Name
36	 Example 36	2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(1,6-diazaspiro [3.4] octan-6-yl) quinoline
37	 Example 37	2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.4] nonan-2-yl) quinoline
38	 Example 38	4-((trans)-hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline
39	 Example 39	4-((1S,5R)-3,6-diazabicyclo [3.2.0] heptan-6-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline
40	 Example 40	4-((1R,5R)-3,6-diazabicyclo [3.2.0] heptan-3-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline
41	 Example 41	4-((cis)-3,6-diazabicyclo [3.2.0] heptan-6-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline

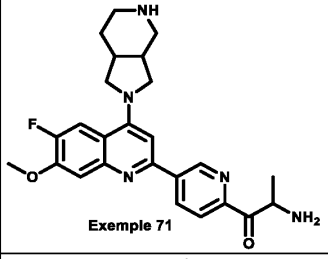
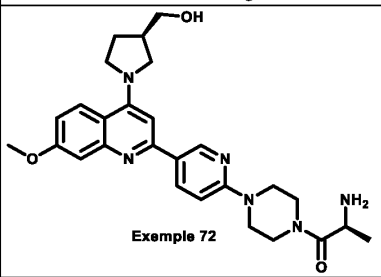
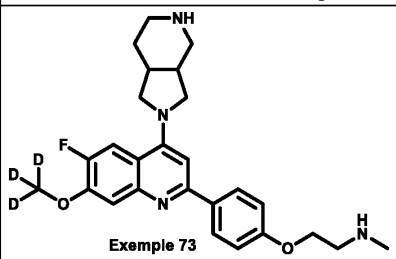
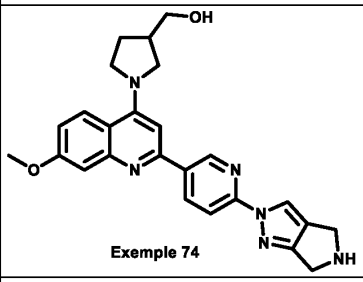
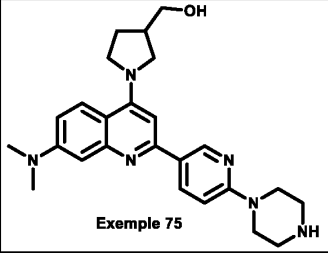
Ex. No.	Structure	Name
42	 Example 42	2-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane
43	 Example 43	2-amino-1-(4-(4-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) phenyl) piperazin-1-yl) propan-1-one
44	 Example 44	4-(1,4-diazepan-1-yl)-6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline
45	 Example 45	2-amino-1-(4-(4-(7-methoxy-4-(3-methoxypyrrolidin-1-yl) quinolin-2-yl) phenyl) piperazin-1-yl) propan-1-one
46	 Example 46	2-amino-1-(4-(5-(7-(dimethylamino)-4-(3-methoxypyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) propan-1-one
47	 Example 47	ethyl (2-(6-(methylamino) pyridin-3-yl)-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-7-yl) carbamate

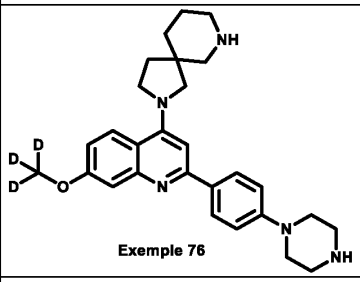
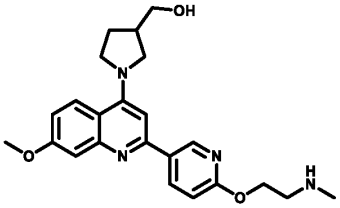
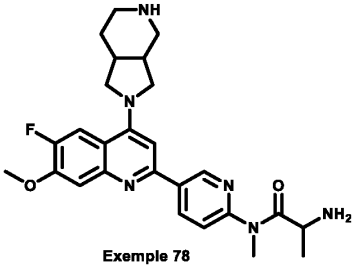
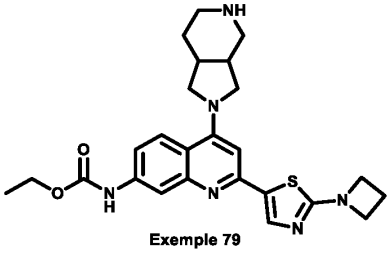
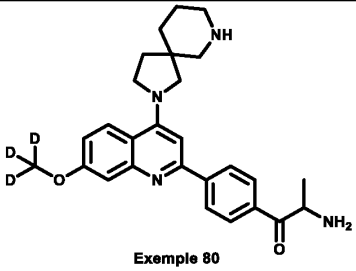
Ex. No.	Structure	Name
48	 Example 48	2-amino-*N*-(4-(6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenyl)-3-methylbutanamide
49	 Example 49	2-amino-1-(4-(5-(6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-2-methylpropan-1-one
50	 Example 50	5-[4-(2, 9-diazaspiro[4.5]decan-2-yl) -7-methoxy-2-quinolyl]-*N*, *N*-dimethyl-pyridin-2-amine
51	 Example 51	2-(4-(piperazin-1-yl) phenyl)-4-(pyrrolidin-1-yl) quinoline
52	 Example 52	(1-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol

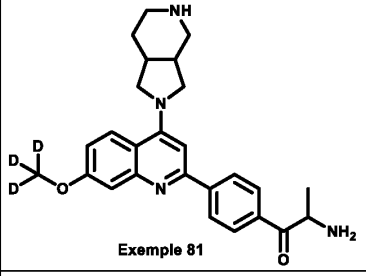
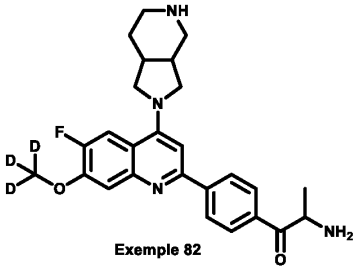
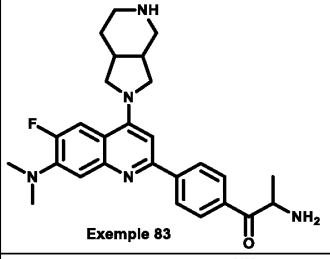
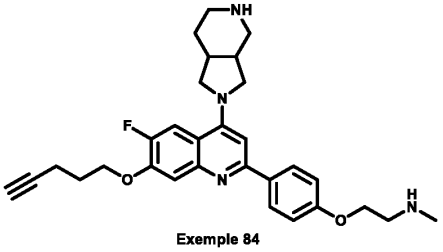
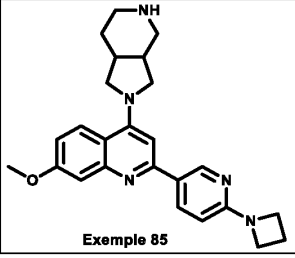
Ex. No.	Structure	Name
53	 Example 53	(1-(6-amino-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol
54	 Example 54	2-amino-1-(5-(6-fluoro-7-methoxy-4-(2,7-diazaspiro[4.5]decan-2-yl)quinolin-2-yl)pyridin-2-yl)propan-1-one
55	 Example 55	[4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazin-1-yl]-pyrrolidin-2-yl-methanone
56	 Example 56	2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.4] nonan-2-yl) quinoline
57	 Example 57	6-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2-oxa-6-azaspiro [3.4] octane
58	 Example 58	2-((5-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) pyridin-2-yl) oxy)-N-methylethan-1-amine

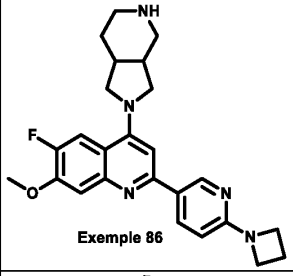
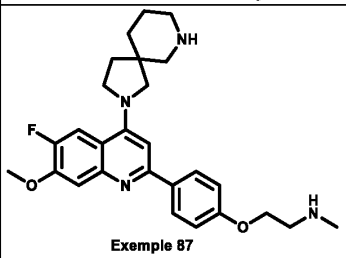
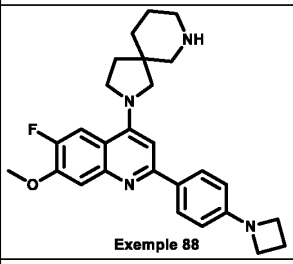
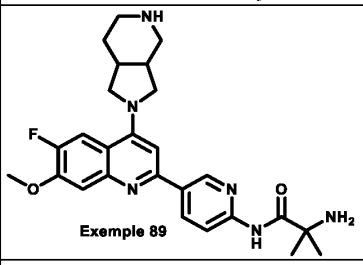
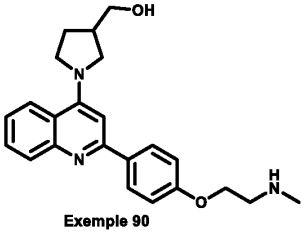
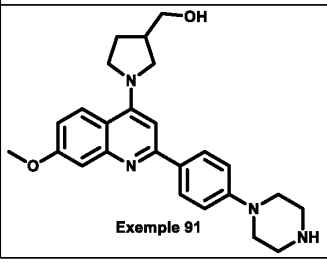
Ex. No.	Structure	Name
59	 Example 59	2-amino-1-(4-(5-(6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)piperazin-1-yl)propan-1-one
60	 Example 60	2-amino-1-[5-[4-(2,9-diazaspiro [4.5]decan-2-yl)-7-(dimethylamino)-6-fluoro-2-quinolyl]-2-pyridyl]propan-1-one
61	 Example 61	2-((5-(6-fluoro-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)-*N*-methylethan-1-amine
62	 Example 62	2-((5-(6,7-difluoro-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)-N-methylethan-1-amine
63	 Example 63	*N*-[4-[4-(2, 9-diazaspiro[4.5]decan-2-yl) -6-fluoro-7-methoxy-2-quinolyl]phenyl]acetamide
64	 Example 64	5-[7-chloro-4-(2, 9-diazaspiro[4.5]decan-2-yl)-2-quinolyl]-*N*-methyl-pyridin-2-amine

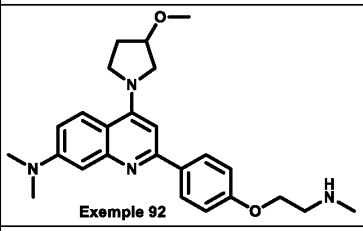
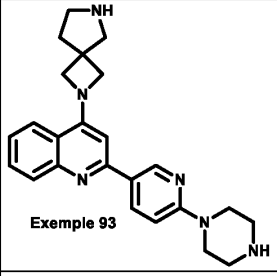
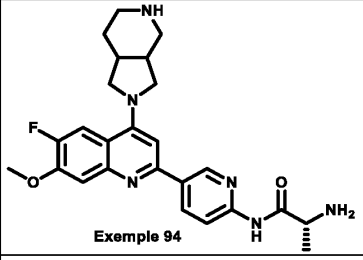
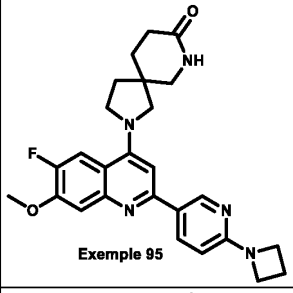
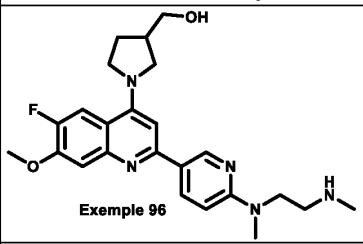
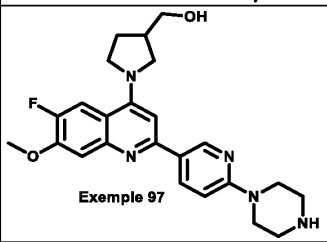
Ex. No.	Structure	Name
65	 Example 65	2-(6-piperazin-1-yl-3-pyridyl)-4-[(1R,5S)-3,6-diazabicyclo [3.2.0] heptan-6-yl] quinoline
66	 Example 66	2-amino-1-(4-(5-(4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-3-methylbutan-1-one
67	 Example 67	2-amino-1-[4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazin-1-yl]-4-methyl-pentan-1-one
68	 Example 68	2-(azetidin-1-yl)-5-[4-(2,9-diazaspiro [4.5]decan-2-yl)-7-methoxy-2-quinolyl]thiazole
69	 Exemple 69	4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(2-(piperazin-1-yl)thiazol-5-yl)quinolin-7-amine
70	 Exemple 70	2-(4-(5-(6-fluoro-4-(3-(hydroxymethyl)pyrrolidin-1-yl)-7-methoxyquinolin-2-yl)pyridin-2-yl)piperazin-1-yl)ethan-1-ol

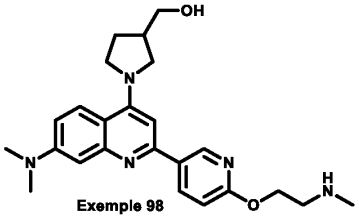
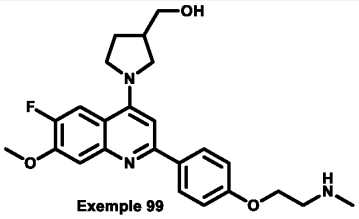
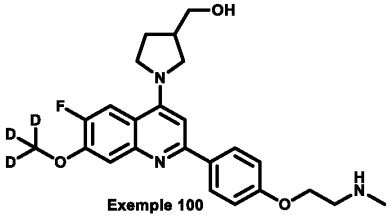
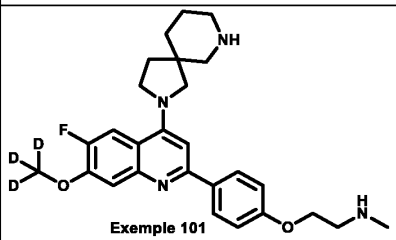
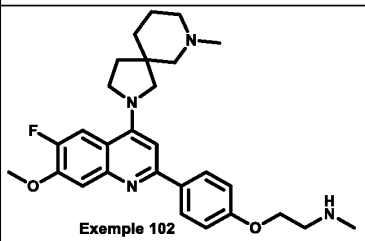
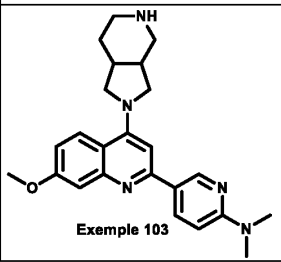
Ex. No.	Structure	Name
71	 Exemple 71	2-amino-1-(5-(6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)propan-1-one
72	 Exemple 72	(S)-2-amino-1-(4-(5-(4-((R)-3-(hydroxymethyl)pyrrolidin-1-yl)-7-methoxyquinolin-2-yl)pyridin-2-yl)piperazin-1-yl)propan-1-one
73	 Exemple 73	2-(4-(6-fluoro-7-(methoxy-d3)-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)-N-methylethan-1-amine
74	 Exemple 74	(1-(2-(6-(5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)pyridin-3-yl)-7-methoxyquinolin-4-yl)pyrrolidin-3-yl)methanol
75	 Exemple 75	(1-(7-(dimethylamino)-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol

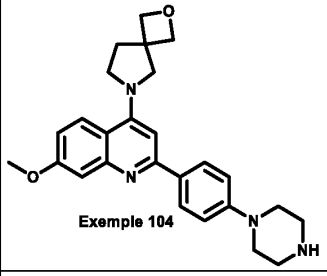
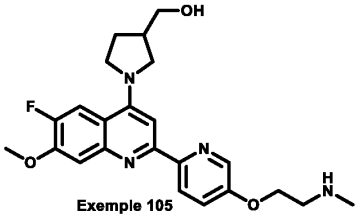
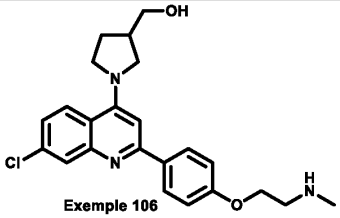
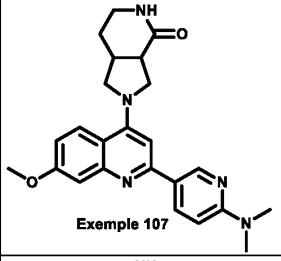
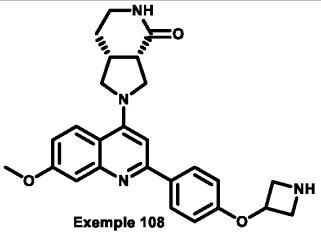
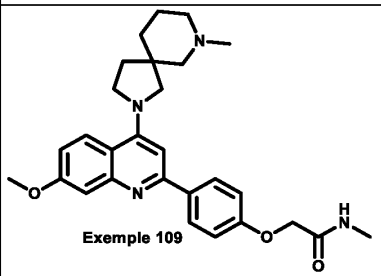
Ex. No.	Structure	Name
76	 Exemple 76	2-(7-(methoxy-d3)-2-(4-(piperazin-1-yl)phenyl)quinolin-4-yl)-2,7-diazaspiro[4.5]decane
77	 Exemple 77	(1-(7-methoxy-2-(6-(2-(methylamino)ethoxy)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol
78	 Exemple 78	2-amino-N-(5-(6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)-N-methylpropanamide
79	 Exemple 79	ethyl (2-(2-(azetidin-1-yl)thiazol-5-yl)-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-7-yl)carbamate
80	 Exemple 80	2-amino-1-(4-(7-(methoxy-d3)-4-(2,7-diazaspiro[4.5]decan-2-yl)quinolin-2-yl)phenyl)propan-1-one

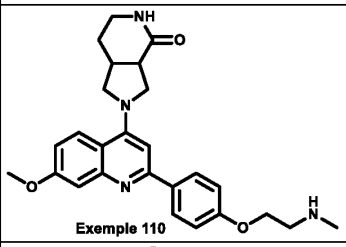
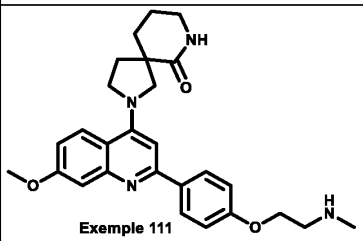
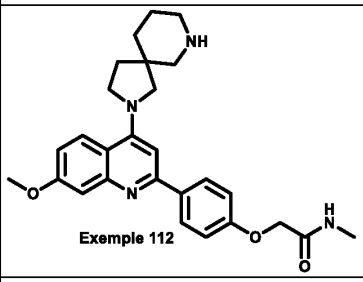
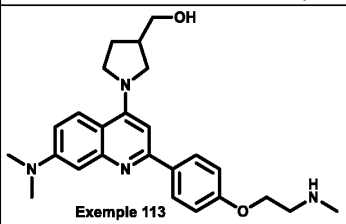
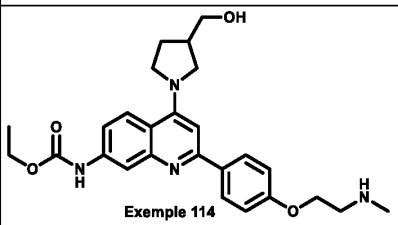
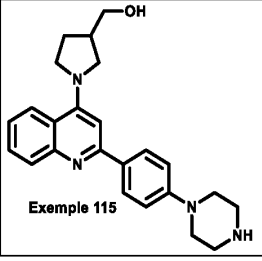
Ex. No.	Structure	Name
81	 Exemple 81	2-amino-1-(4-(7-(methoxy-d3)-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)propan-1-one
82	 Exemple 82	2-amino-1-(4-(6-fluoro-7-(methoxy-d3)-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)propan-1-one
83	 Exemple 83	2-amino-1-(4-(7-(dimethylamino)-6-fluoro-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)propan-1-one
84	 Exemple 84	2-(4-(6-fluoro-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-7-(pent-4-yn-1-yloxy)quinolin-2-yl)phenoxy)-N-methylethan-1-amine
85	 Exemple 85	2-(6-(azetidin-1-yl)pyridin-3-yl)-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinoline

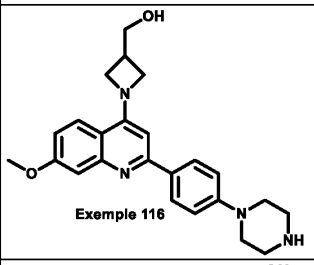
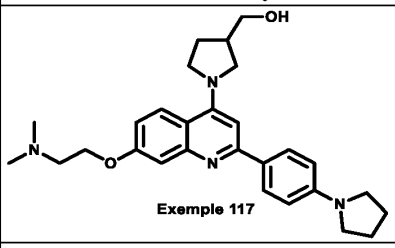
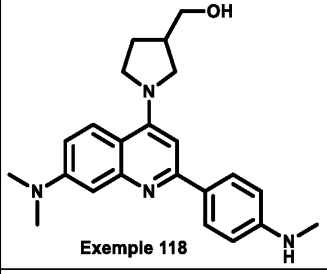
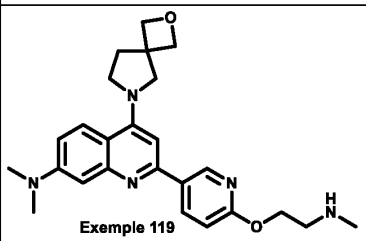
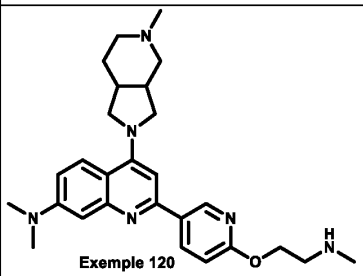
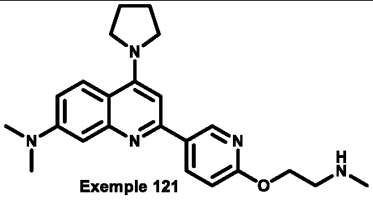
Ex. No.	Structure	Name
86	 Exemple 86	2-(6-(azetidin-1-yl)pyridin-3-yl)-6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinoline
87	 Exemple 87	2-(4-(6-fluoro-7-methoxy-4-(2,7-diazaspiro[4.5]decan-2-yl)quinolin-2-yl)phenoxy)-N-methylethan-1-amine
88	 Exemple 88	2-(2-(4-(azetidin-1-yl)phenyl)-6-fluoro-7-methoxyquinolin-4-yl)-2,7-diazaspiro[4.5]decane
89	 Exemple 89	2-amino-N-(5-(6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)-2-methylpropanamide
90	 Exemple 90	(1-(2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)methanol
91	 Exemple 91	(1-(7-methoxy-2-(4-(piperazin-1-yl)phenyl)quinolin-4-yl)pyrrolidin-3-yl)methanol

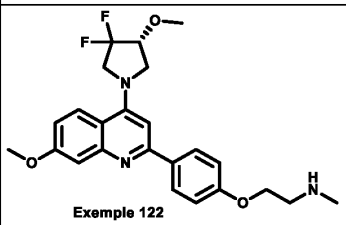
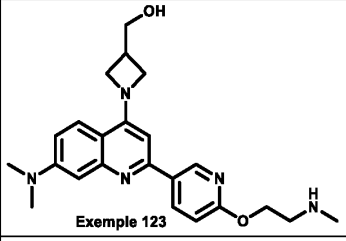
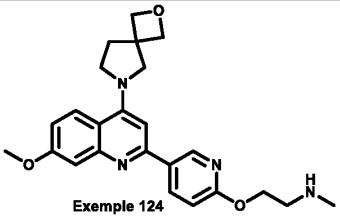
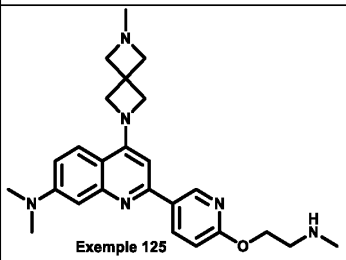
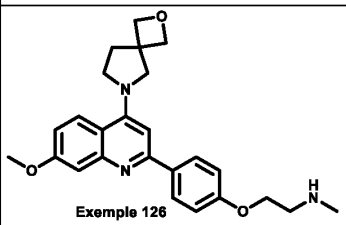
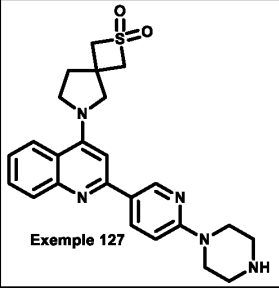
Ex. No.	Structure	Name
92	 Exemple 92	4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-7-amine
93	 Exemple 93	2-(6-(piperazin-1-yl)pyridin-3-yl)-4-(2,6-diazaspiro[3.4]octan-2-yl)quinoline
94	 Exemple 94	(2R)-2-amino-N-(5-(6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)propanamide
95	 Exemple 95	2-(2-(6-(azetidin-1-yl)pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl)-2,7-diazaspiro[4.5]decan-8-one
96	 Exemple 96	(1-(6-fluoro-7-methoxy-2-(6-(methyl(2-(methylamino)ethyl)amino)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol
97	 Exemple 97	(1-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol

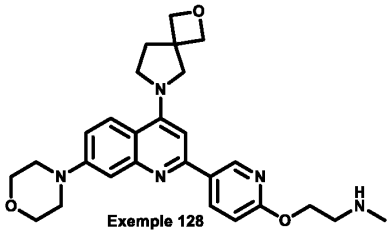
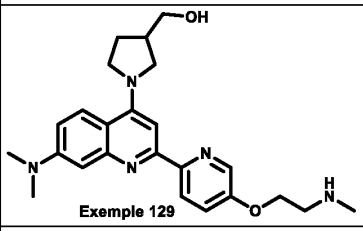
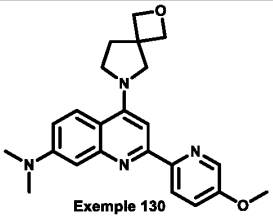
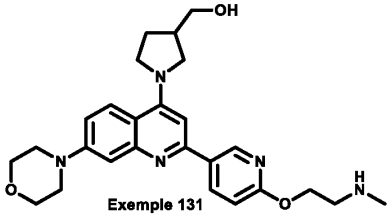
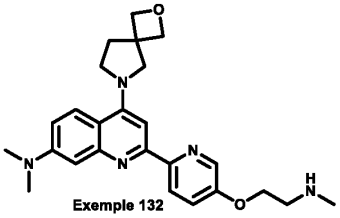
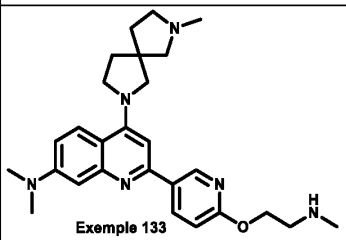
Ex. No.	Structure	Name
98	 Exemple 98	[1-[7-(dimethylamino)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol
99	 Exemple 99	[1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol
100	 Exemple 100	[1-[6-fluoro-2-[4-[2-(methylamino)ethoxy]phenyl]-7-(trideuteriomethoxy)-4-quinolyl]pyrrolidin-3-yl]methanol
101	 Exemple 101	2-[4-[4-(2,9-diazaspiro[4.5]decan-2-yl)-6-fluoro-7-(trideuteriomethoxy)-2-quinolyl]phenoxy]-N-methyl-ethanamine
102	 Exemple 102	2-[4-[6-fluoro-7-methoxy-4-(9-methyl-2,9-diazaspiro[4.5]decan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine
103	 Exemple 103	(cis)-5-[7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-N,N-dimethyl-pyridin-2-amine

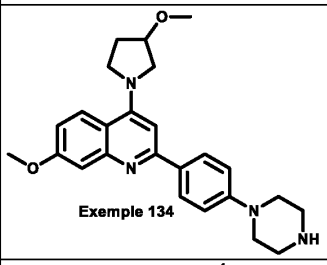
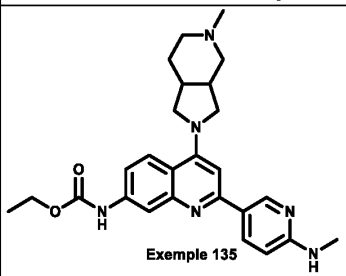
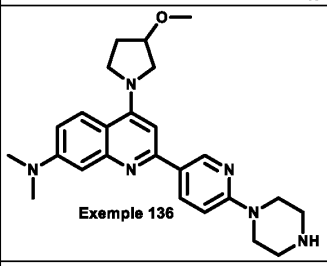
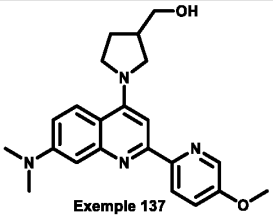
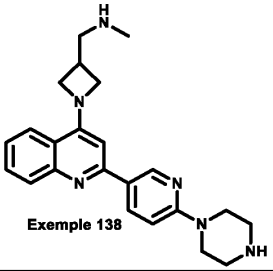
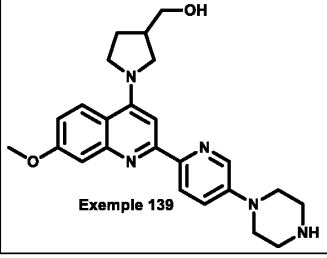
Ex. No.	Structure	Name
104	 Exemple 104	7-[7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]-2-oxa-7-azaspiro[3.4]octane
105	 Exemple 105	[1-[6-fluoro-7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol
106	 Exemple 106	[1-[7-chloro-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol
107	 Exemple 107	(cis)-2-[2-[6-(dimethylamino)-3-pyridyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
108	 Exemple 108	(3aS,7aR)-2-(2-(4-(azetidin-3-yloxy)phenyl)-7-methoxyquinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one
109	 Exemple 109	2-[4-[7-methoxy-4-(9-methyl-2,9-diazaspiro[4.5]decan-2-yl)-2-quinolyl]phenoxy]-N-methyl-acetamide

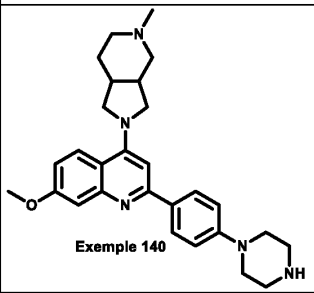
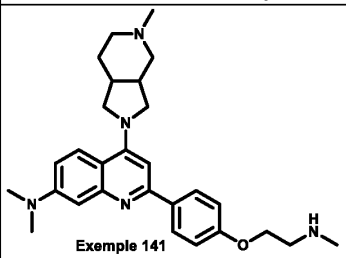
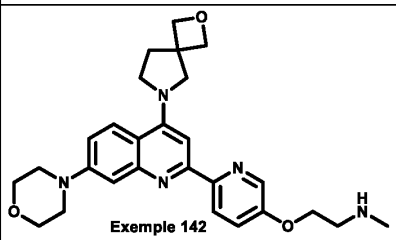
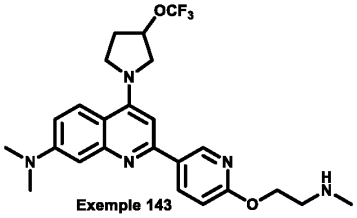
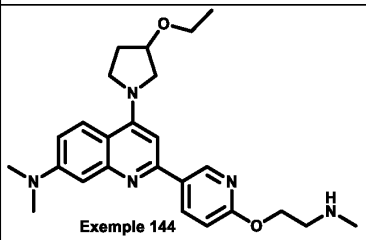
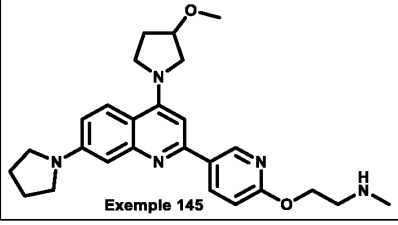
Ex. No.	Structure	Name
110	 Exemple 110	(cis)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
111	 Exemple 111	2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.5]decan-6-one
112	 Exemple 112	2-[4-[4-(2,9-diazaspiro[4.5]decan-2-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-acetamide
113	 Exemple 113	[1-[7-(dimethylamino)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol
114	 Exemple 114	ethyl N-[4-[3-(hydroxymethyl)pyrrolidin-1-yl]-2-[4-[2-(methylamino)ethoxy]phenyl]-7-quinolyl]carbamate
115	 Exemple 115	[1-[2-(4-piperazin-1-ylphenyl)-4-quinolyl]pyrrolidin-3-yl]methanol

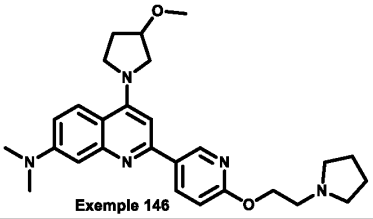
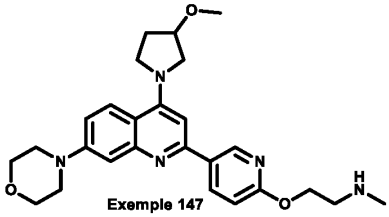
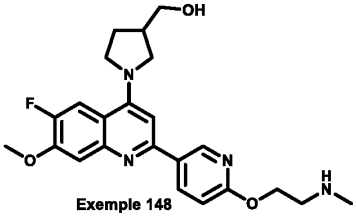
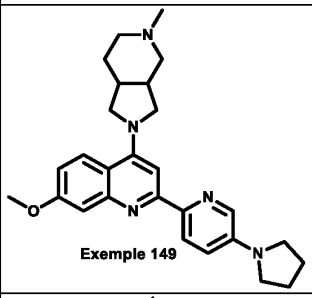
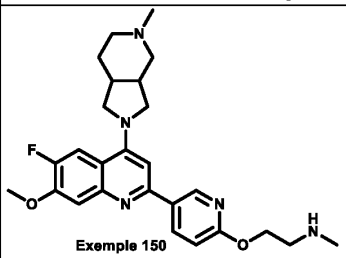
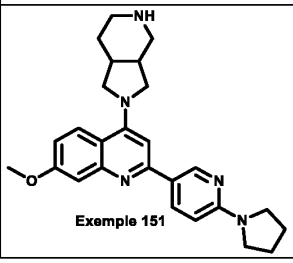
Ex. No.	Structure	Name
116	 Exemple 116	[1-[7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]azetidin-3-yl]methanol
117	 Exemple 117	[1-[7-[2-(dimethylamino)ethoxy]-2-(4-pyrrolidin-1-ylphenyl)-4-quinolyl]pyrrolidin-3-yl]methanol
118	 Exemple 118	[1-[7-(dimethylamino)-2-[4-(methylamino)phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol
119	 Exemple 119	N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine
120	 Exemple 120	(cis)-N,N-dimethyl-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]quinolin-7-amine
121	 Exemple 121	N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-pyrrolidin-1-yl-quinolin-7-amine

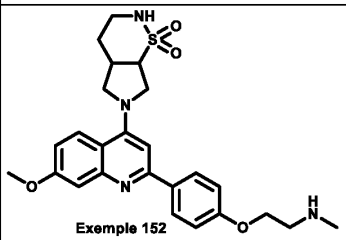
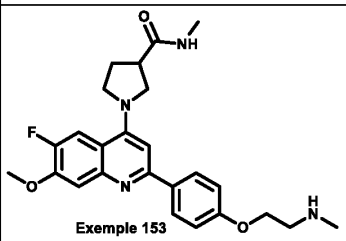
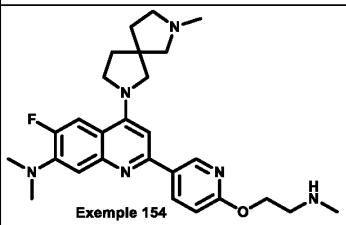
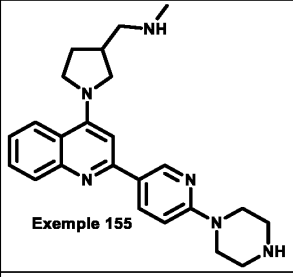
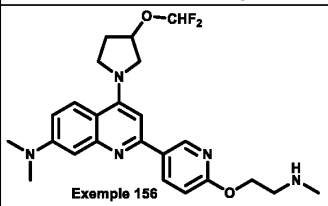
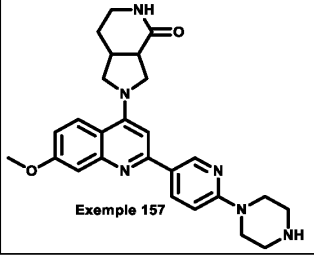
Ex. No.	Structure	Name
122	 Exemple 122	(R)-2-(4-(4-(3,3-difluoro-4-methoxypyrrolidin-1-yl)-7-methoxyquinolin-2-yl)phenoxy)-N-methylethan-1-amine
123	 Exemple 123	[1-[7-(dimethylamino)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]azetidin-3-yl]methanol
124	 Exemple 124	2-[[5-[7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine
125	 Exemple 125	N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)quinolin-7-amine
126	 Exemple 126	2-[4-[7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine
127	 Exemple 127	7-[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide

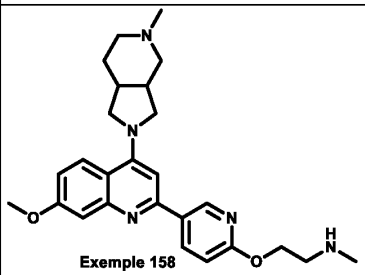
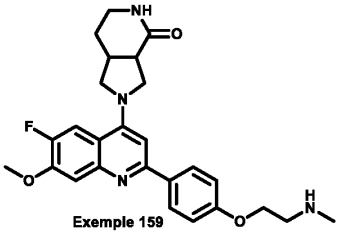
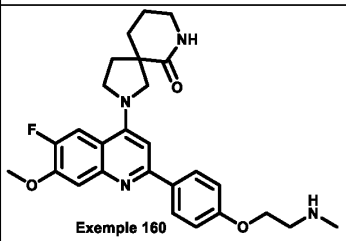
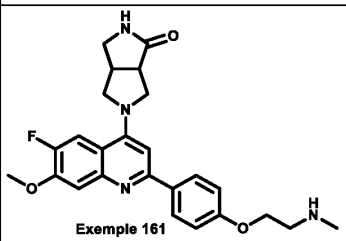
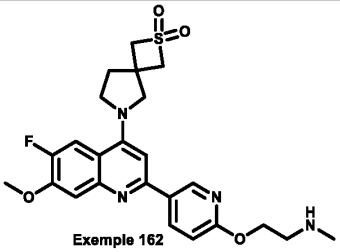
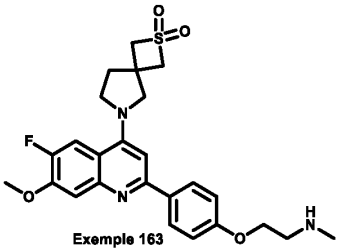
Ex. No.	Structure	Name
128	 Exemple 128	N-methyl-2-[[5-[7-morpholino-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-2-pyridyl]oxy]ethanamine
129	 Exemple 129	[1-[7-(dimethylamino)-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol
130	 Exemple 130	2-(5-methoxy-2-pyridyl)-N,N-dimethyl-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine
131	 Exemple 131	[1-[2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-7-morpholino-4-quinolyl]pyrrolidin-3-yl]methanol
132	 Exemple 132	N,N-dimethyl-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine
133	 Exemple 133	N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinolin-7-amine

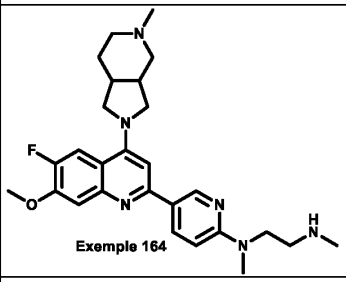
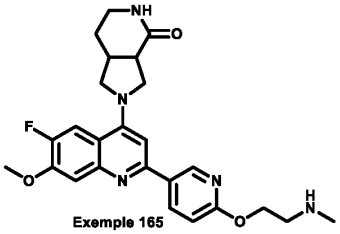
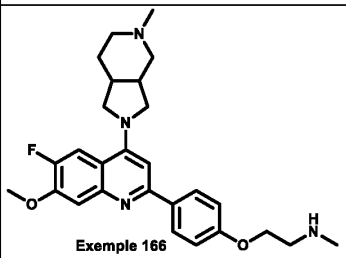
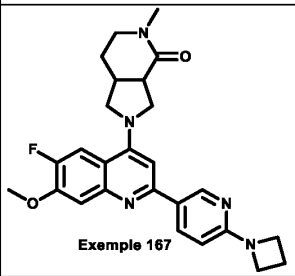
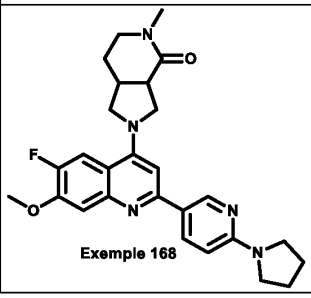
Ex. No.	Structure	Name
134	 Exemple 134	7-methoxy-4-(3-methoxypyrrolidin-1-yl)-2-(4-piperazin-1-ylphenyl)quinoline
135	 Exemple 135	(cis)-ethyl N-[4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[6-(methylamino)-3-pyridyl]-7-quinolyl]carbamate
136	 Exemple 136	4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(6-piperazin-1-yl-3-pyridyl)quinolin-7-amine
137	 Exemple 137	[1-[7-(dimethylamino)-2-(5-methoxy-2-pyridyl)-4-quinolyl]pyrrolidin-3-yl]methanol
138	 Exemple 138	N-methyl-1-[1-[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]azetidin-3-yl]methanamine
139	 Exemple 139	[1-[7-methoxy-2-(5-piperazin-1-yl-2-pyridyl)-4-quinolyl]pyrrolidin-3-yl]methanol

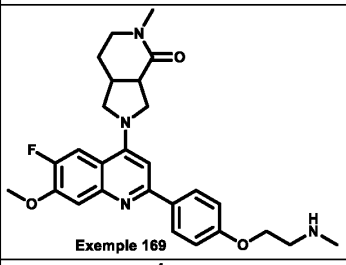
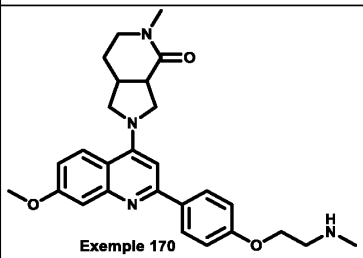
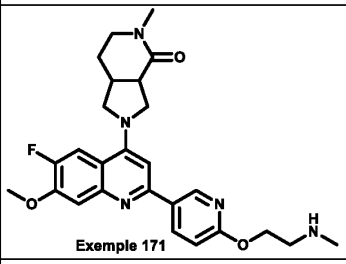
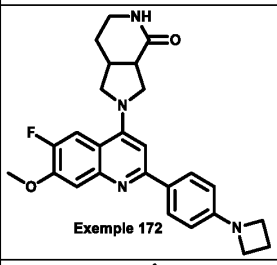
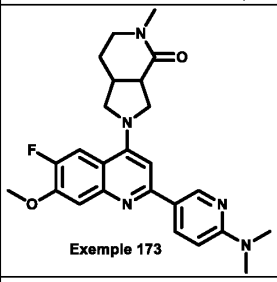
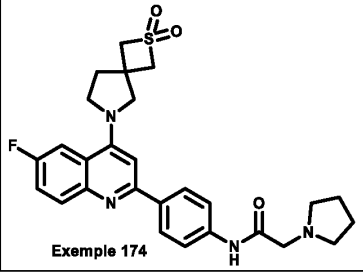
Ex. No.	Structure	Name
140	 Exemple 140	(cis)-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(4-piperazin-1-ylphenyl)quinoline
141	 Exemple 141	(cis)-N,N-dimethyl-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[4-[2-(methylamino)ethoxy]phenyl]quinolin-7-amine
142	 Exemple 142	N-methyl-2-[[6-[7-morpholino-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-3-pyridyl]oxy]ethanamine
143	 Exemple 143	N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-[3-(trifluoromethoxy)pyrrolidin-1-yl]quinolin-7-amine
144	 Exemple 144	4-(3-ethoxypyrrolidin-1-yl)-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]quinolin-7-amine
145	 Exemple 145	2-[[5-[4-(3-methoxypyrrolidin-1-yl)-7-pyrrolidin-1-yl-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine

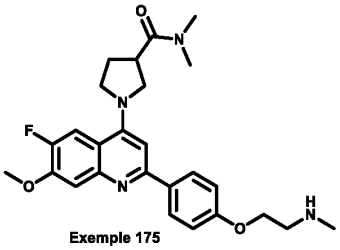
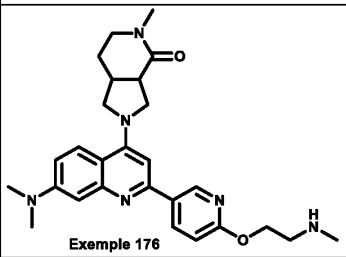
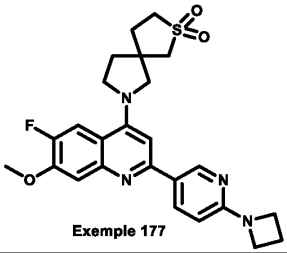
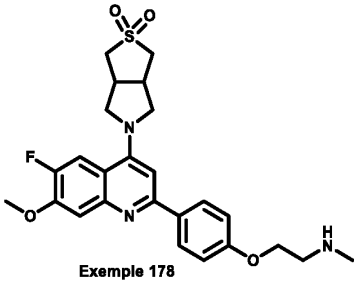
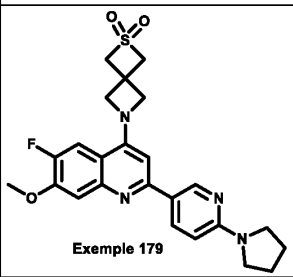
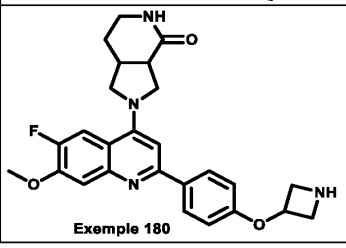
Ex. No.	Structure	Name
146	 Exemple 146	4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-[6-(2-pyrrolidin-1-ylethoxy)-3-pyridyl]quinolin-7-amine
147	 Exemple 147	2-[[5-[4-(3-methoxypyrrolidin-1-yl)-7-morpholino-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine
148	 Exemple 148	[1-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol
149	 Exemple 149	(cis)-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(5-pyrrolidin-1-yl-2-pyridyl)quinoline
150	 Exemple 150	(cis)-2-[[5-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine
151	 Exemple 151	(cis)-4-(1,3,3a,4,5,6,7,7a-octahydropyrrolo[3,4-c]pyridin-2-yl)-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)quinoline

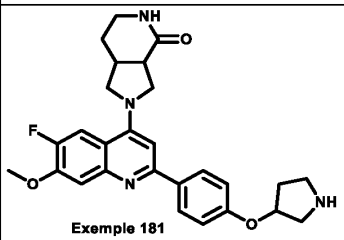
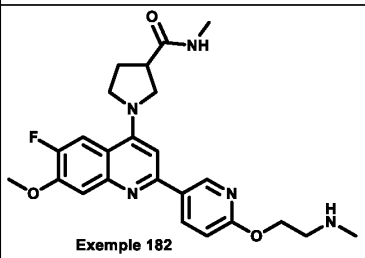
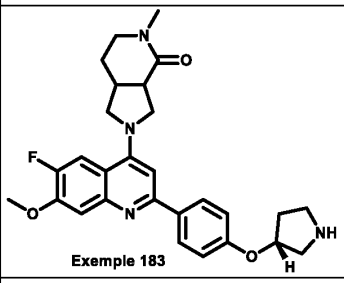
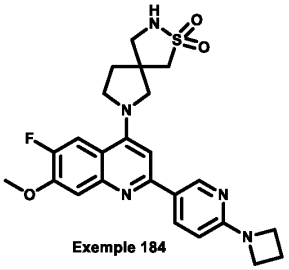
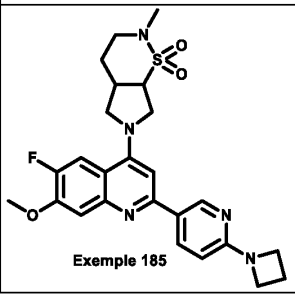
Ex. No.	Structure	Name
152	 Exemple 152	(cis)-6-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)octahydropyrrolo[3,4-e][1,2]thiazine 1,1-dioxide
153	 Exemple 153	1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
154	 Exemple 154	6-fluoro-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinolin-7-amine
155	 Exemple 155	N-methyl-1-[1-[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]pyrrolidin-3-yl]methanamine
156	 Exemple 156	4-[3-(difluoromethoxy)pyrrolidin-1-yl]-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]quinolin-7-amine
157	 Exemple 157	(cis)-2-[7-methoxy-2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one

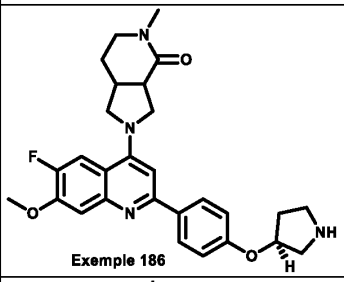
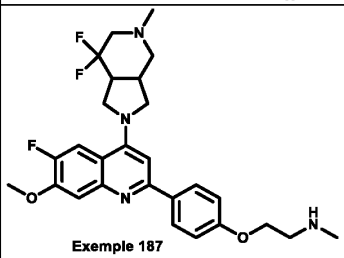
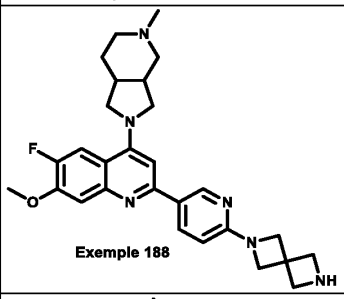
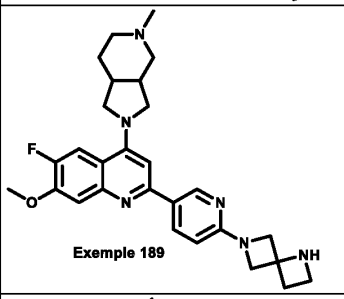
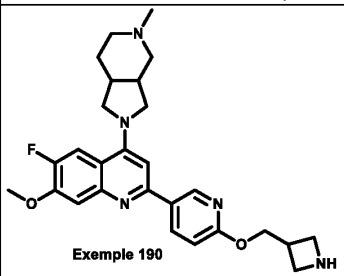
Ex. No.	Structure	Name
158	 Exemple 158	(cis)-2-[[5-[7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine
159	 Exemple 159	(cis)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
160	 Exemple 160	2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.5]decan-6-one
161	 Exemple 161	(cis)-5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one
162	 Exemple 162	2-[[5-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine
163	 Exemple 163	2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine

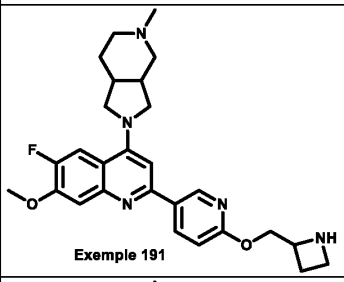
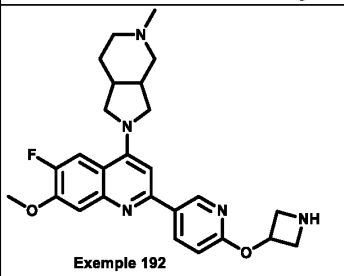
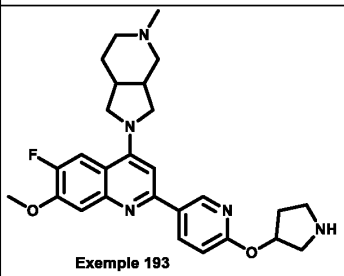
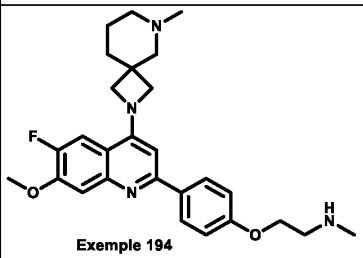
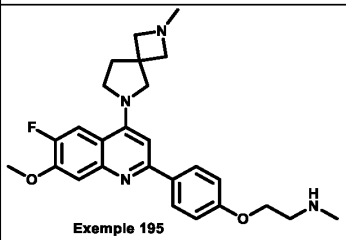
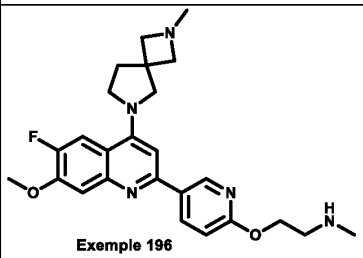
Ex. No.	Structure	Name
164	 Exemple 164	(cis)-N'-[5-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]-N,N'-dimethyl-ethane-1,2-diamine
165	 Exemple 165	(cis)-2-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
166	 Exemple 166	(cis)-2-[4-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine
167	 Exemple 167	(cis)-2-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
168	 Exemple 168	(cis)-2-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one

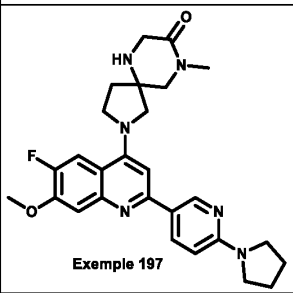
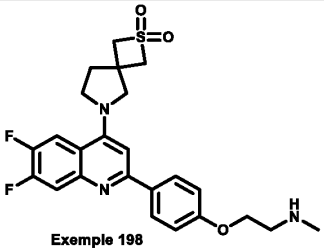
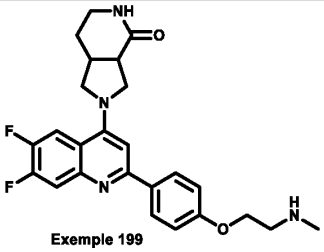
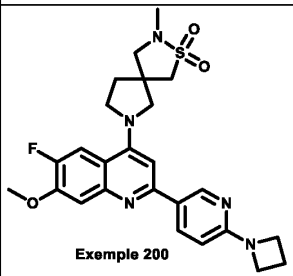
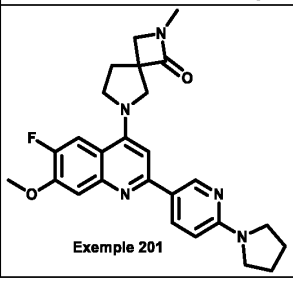
Ex. No.	Structure	Name
169	 Exemple 169	(cis)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-70methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
170	 Exemple 170	(cis)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
171	 Exemple 171	(cis)-2-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
172	 Exemple 172	(cis)-2-[2-[4-(azetidin-1-yl)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
173	 Exemple 173	(cis)-2-[2-[6-(dimethylamino)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
174	 Exemple 174	N-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-2-quinolyl]phenyl]-2-pyrrolidin-1-yl-acetamide

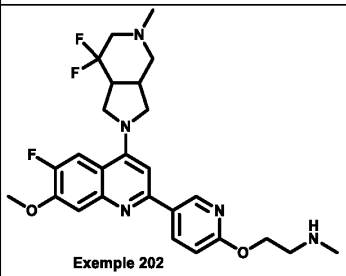
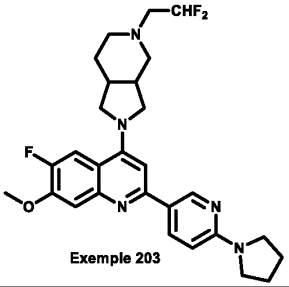
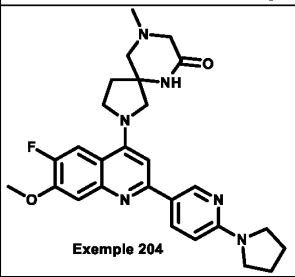
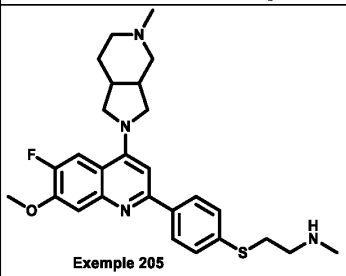
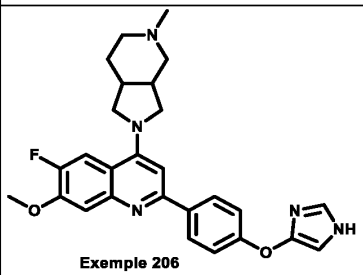
Ex. No.	Structure	Name
175	 Exemple 175	1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N,N-dimethyl-pyrrolidine-3-carboxamide
176	 Exemple 176	(cis)-2-[7-(dimethylamino)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
177	 Exemple 177	7-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2λ6-thia-7-azaspiro[4.4]nonane 2,2-dioxide
178	 Exemple 178	2-[4-[4-(2,2-dioxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine
179	 Exemple 179	6-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-2λ6-thia-6-azaspiro[3.3]heptane 2,2-dioxide
180	 Exemple 180	(cis)-2-[2-[4-(azetidin-3-yloxy)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one

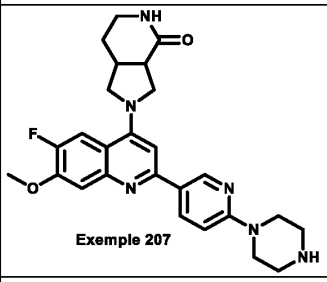
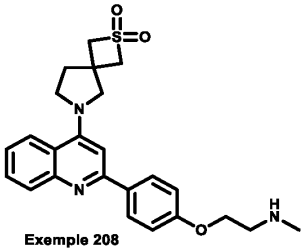
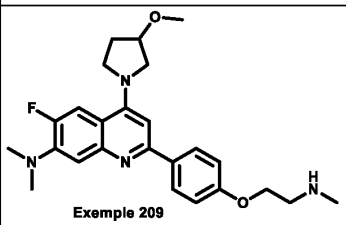
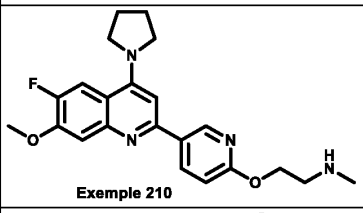
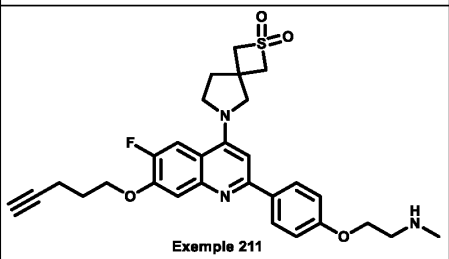
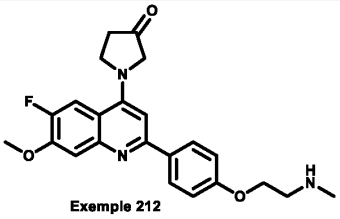
Ex. No.	Structure	Name
181	 Exemple 181	(cis)-2-[6-fluoro-7-methoxy-2-(4-pyrrolidin-3-yloxyphenyl)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
182	 Exemple 182	1-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
183	 Exemple 183	(cis)-2-[6-fluoro-7-methoxy-2-[4-[(3R)-pyrrolidin-3-yl]oxyphenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
184	 Exemple 184	7-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2λ6-thia-3,7-diazaspiro[4.4]nonane 2,2-dioxide
185	 Exemple 185	(cis)-6-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2-methyl-3,4,4a,5,7,7a-hexahydropyrrolo[3,4-e]thiazine 1,1-dioxide

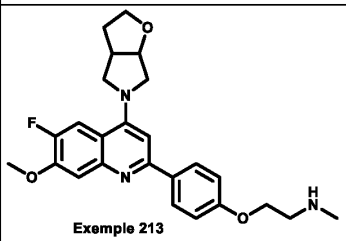
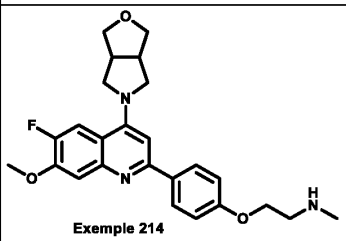
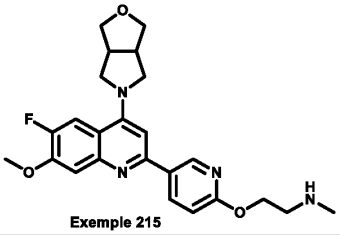
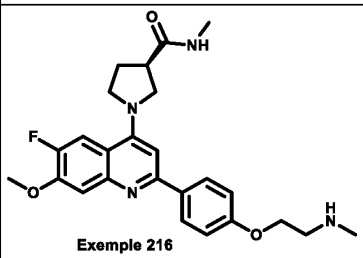
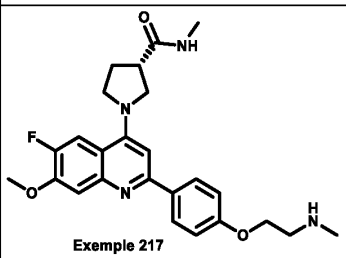
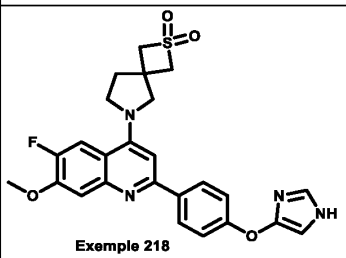
Ex. No.	Structure	Name
186	 Exemple 186	(cis)-2-[6-fluoro-7-methoxy-2-[4-[(3S)-pyrrolidin-3-yl]oxyphenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
187	 Exemple 187	(cis)-2-[4-[4-(7,7-difluoro-5-methyl-1,3,3a,4,6,7a-hexahydropyrrolo[3,4-c]pyridin-2-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine
188	 Exemple 188	(cis)-2-[6-(2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline
189	 Exemple 189	(cis)-2-[6-(1,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline
190	 Exemple 190	(cis)-2-[6-(azetidin-3-ylmethoxy)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline

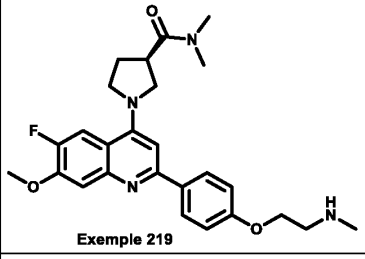
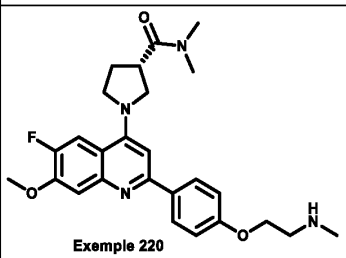
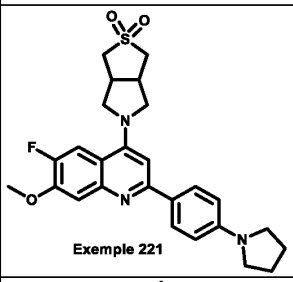
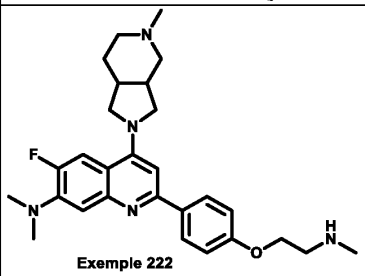
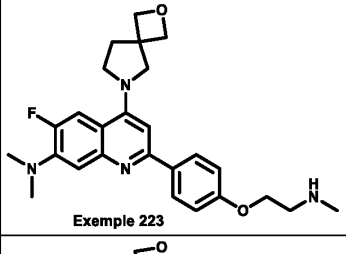
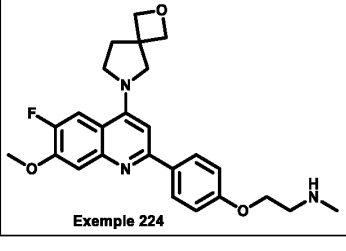
Ex. No.	Structure	Name
191	 Exemple 191	(cis)-2-[6-(azetidin-2-ylmethoxy)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline
192	 Exemple 192	(cis)-2-[4-(azetidin-3-yloxy)phenyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline
193	 Exemple 193	(cis)-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(4-pyrrolidin-3-yloxyphenyl)quinoline
194	 Exemple 194	2-[4-[6-fluoro-7-methoxy-4-(8-methyl-2,8-diazaspiro[3.5]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine
195	 Exemple 195	2-[4-[6-fluoro-7-methoxy-4-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine
196	 Exemple 196	2-[[5-[6-fluoro-7-methoxy-4-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine

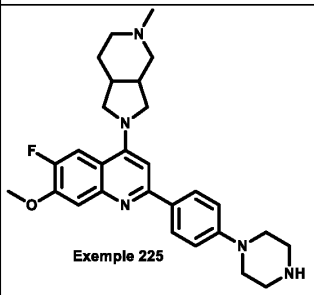
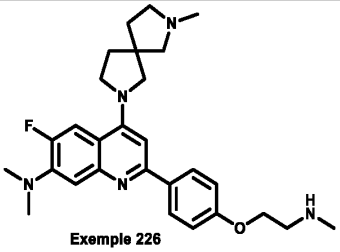
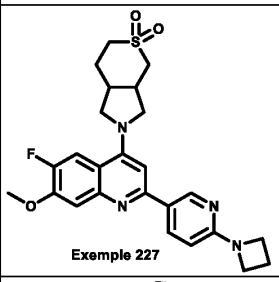
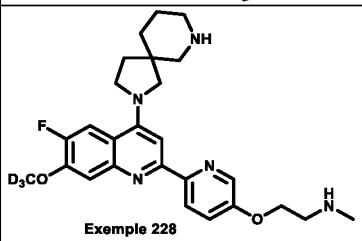
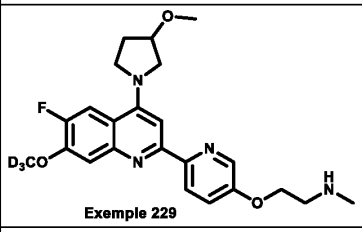
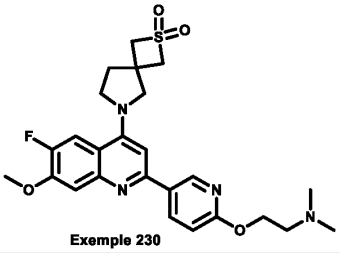
Ex. No.	Structure	Name
197	 Exemple 197	2-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-9-methyl-2,6,9-triazaspiro[4.5]decan-8-one
198	 Exemple 198	2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6,7-difluoro-2-quinolyl]phenoxy]-N-methyl-ethanamine
199	 Exemple 199	(cis)-2-[6,7-difluoro-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
200	 Exemple 200	7-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-3-methyl-2λ6-thia-3,7-diazaspiro[4.4]nonane 2,2-dioxide
201	 Exemple 201	6-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-2-methyl-2,6-diazaspiro[3.4]octan-3-one

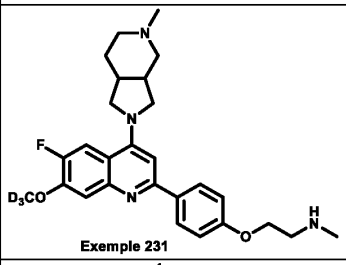
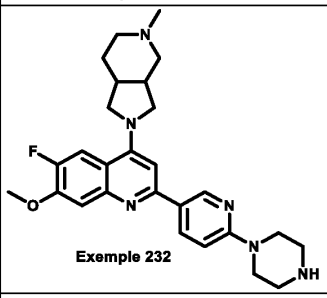
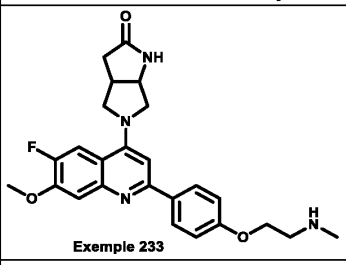
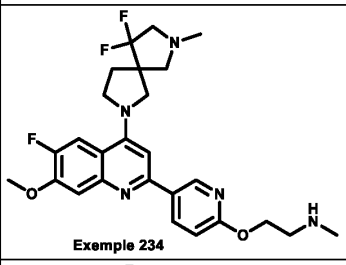
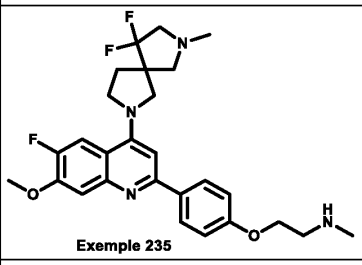
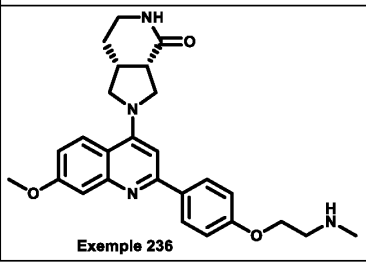
Ex. No.	Structure	Name
202	 Exemple 202	(cis)-2-[[5-[4-(7,7-difluoro-5-methyl-1,3,3a,4,6,7a-hexahydropyrrolo[3,4-c]pyridin-2-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine
203	 Exemple 203	(cis)-4-[5-(2,2-difluoroethyl)-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl]-6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)quinoline
204	 Exemple 204	2-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-9-methyl-2,6,9-triazaspiro[4.5]decan-7-one
205	 Exemple 205	(cis)-2-[4-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenyl]sulfanyl-N-methyl-ethanamine
206	 Exemple 206	(cis)-6-fluoro-2-[4-(1H-imidazol-4-yloxy)phenyl]-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline

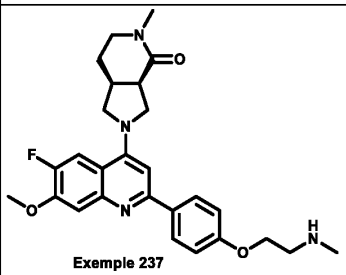
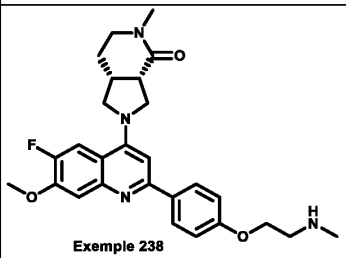
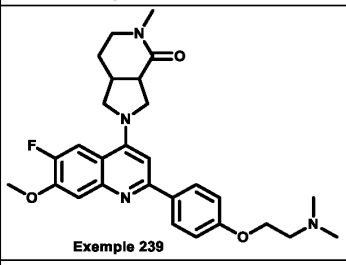
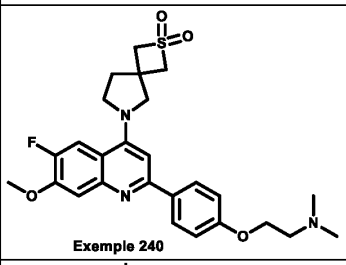
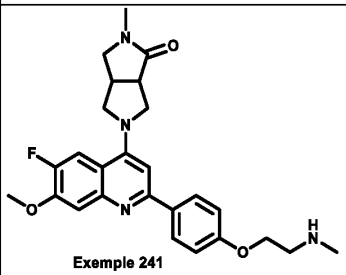
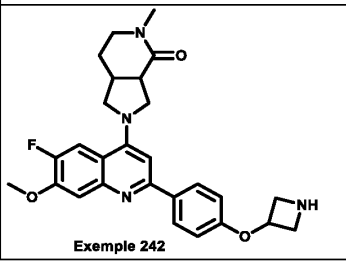
Ex. No.	Structure	Name
207	 Exemple 207	(cis)-2-[6-fluoro-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
208	 Exemple 208	2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine
209	 Exemple 209	6-fluoro-4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-[4-[2-(methylamino)ethoxy]phenyl]quinolin-7-amine
210	 Exemple 210	2-[[5-(6-fluoro-7-methoxy-4-pyrrolidin-1-yl-2-quinolyl)-2-pyridyl]oxy]-N-methyl-ethanamine
211	 Exemple 211	2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-pent-4-ynoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine
212	 Exemple 212	1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-one

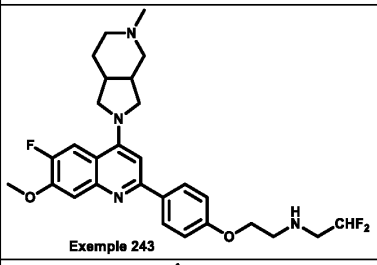
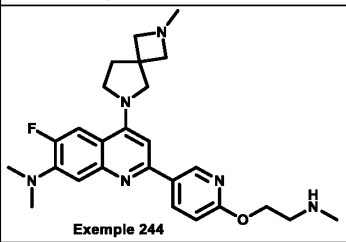
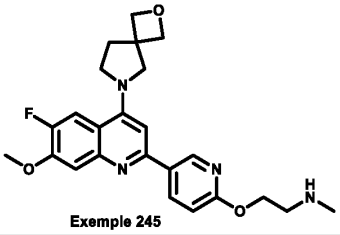
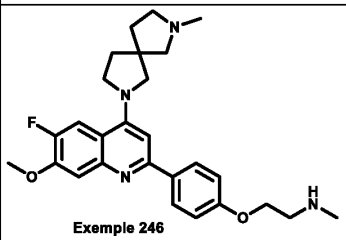
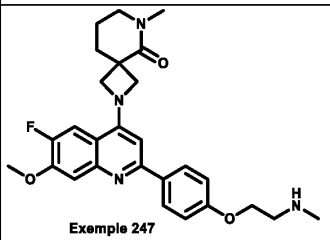
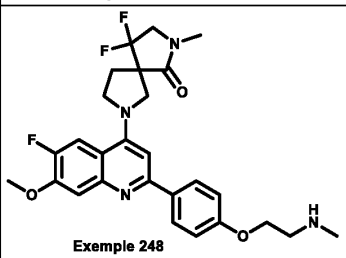
Ex. No.	Structure	Name
213	 Exemple 213	(cis)-2-[4-[4-(2,3,3a,4,6,6a-hexahydrofuro[2,3-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine
214	 Exemple 214	(cis)-2-[4-[4-(1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine
215	 Exemple 215	(cis)-2-[[5-[4-(1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine
216	 Exemple 216	(3R)-1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
217	 Exemple 217	(3S)-1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
218	 Exemple 218	7-[6-fluoro-2-[4-(1H-imidazol-4-yloxy)phenyl]-7-methoxy-4-quinolyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide

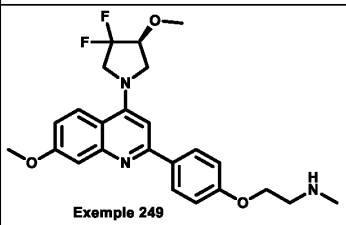
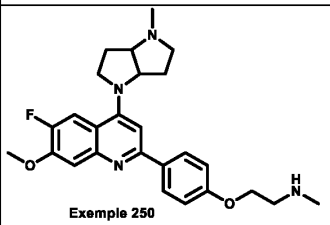
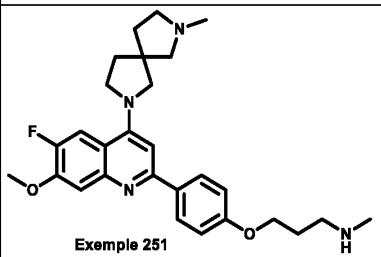
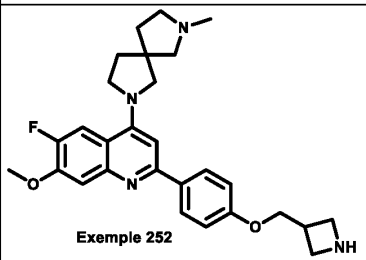
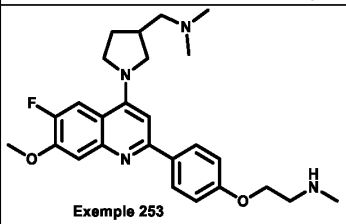
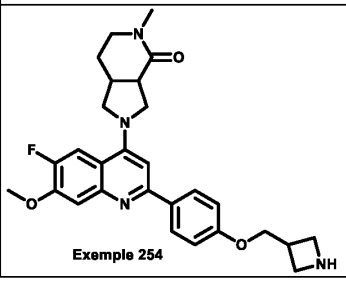
Ex. No.	Structure	Name
219	 Exemple 219	(3R)-1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N,N-dimethyl-pyrrolidine-3-carboxamide
220	 Exemple 220	(3S)-1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N,N-dimethyl-pyrrolidine-3-carboxamide
221	 Exemple 221	(cis)-5-[6-fluoro-7-methoxy-2-(4-pyrrolidin-1-ylphenyl)-4-quinolyl]-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrole 2,2-dioxide
222	 Exemple 222	(cis)-6-fluoro-N,N-dimethyl-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[4-[2-(methylamino)ethoxy]phenyl]quinolin-7-amine
223	 Exemple 223	6-fluoro-N,N-dimethyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine
224	 Exemple 224	2-[4-[6-fluoro-7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine

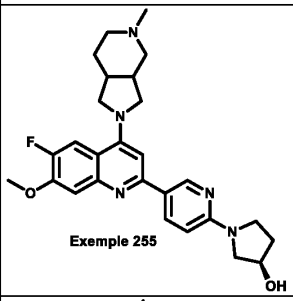
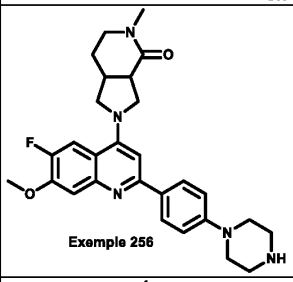
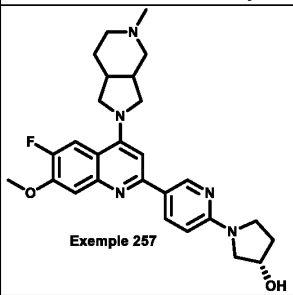
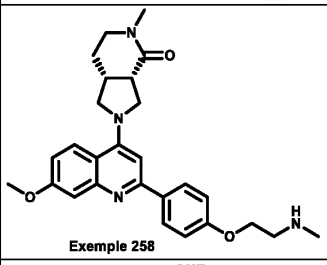
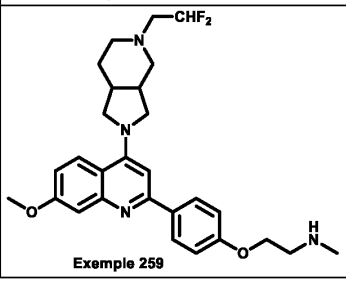
Ex. No.	Structure	Name
225	 Exemple 225	(cis)-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(4-piperazin-1-ylphenyl)quinoline
226	 Exemple 226	6-fluoro-N,N-dimethyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinolin-7-amine
227	 Exemple 227	(cis)-2-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-thiopyrano[3,4-c]pyrrole 5,5-dioxide
228	 Exemple 228	2-[[6-[4-(2,9-diazaspiro[4.5]decan-2-yl)-6-fluoro-7-(trideuteriomethoxy)-2-quinolyl]-3-pyridyl]oxy]-N-methyl-ethanamine
229	 Exemple 229	[1-[6-fluoro-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-7-(trideuteriomethoxy)-4-quinolyl]pyrrolidin-3-yl]methanol
230	 Exemple 230	2-[[5-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N,N-dimethyl-ethanamine

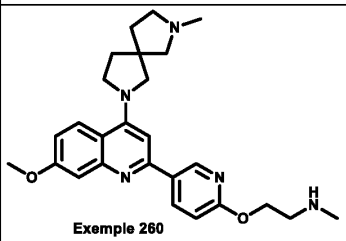
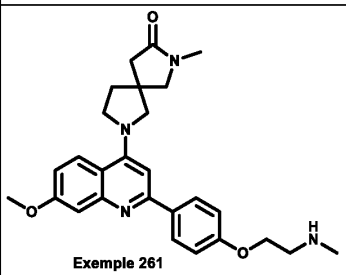
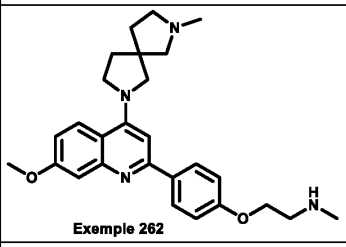
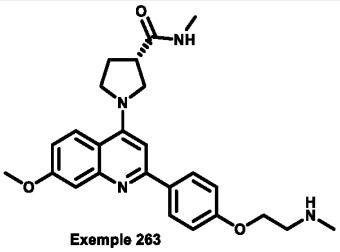
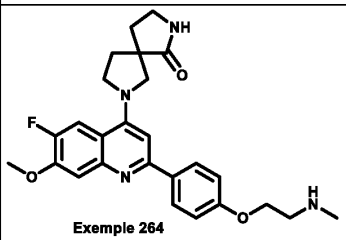
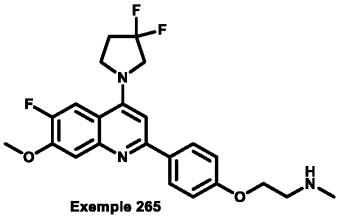
Ex. No.	Structure	Name
231	 Exemple 231	(cis)-2-[4-[6-fluoro-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-7-(trideuteriomethoxy)-2-quinolyl]phenoxy]-N-methyl-ethanamine
232	 Exemple 232	(cis)-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(6-piperazin-1-yl-3-pyridyl)quinoline
233	 Exemple 233	(cis)-5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-2-one
234	 Exemple 234	2-[[5-[4-(9,9-difluoro-7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine
235	 Exemple 235	2-[4-[4-(9,9-difluoro-7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine
236	 Exemple 236	(3aS,7aR)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one

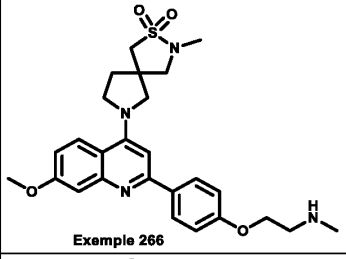
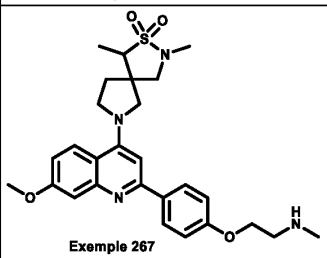
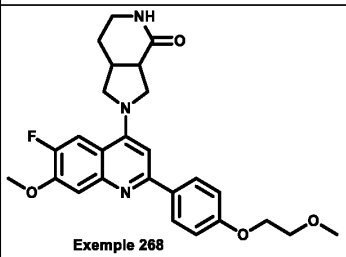
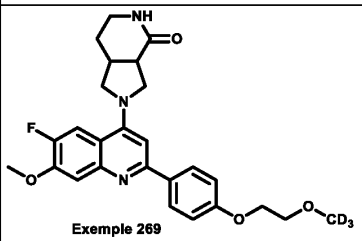
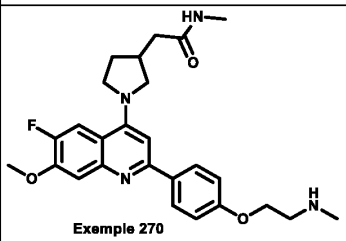
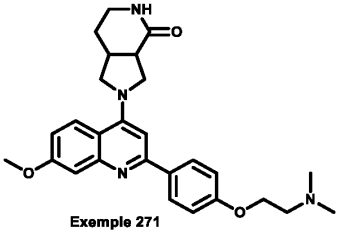
Ex. No.	Structure	Name
237	 Exemple 237	(3aR,7aS)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
238	 Exemple 238	(3aS,7aR)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
239	 Exemple 239	(cis)-2-[2-[4-[2-(dimethylamino)ethoxy]phenyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
240	 Exemple 240	2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N,N-dimethyl-ethanamine
241	 Exemple 241	(cis)-5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2-methyl-3a,4,6,6a-tetrahydro-1H-pyrrolo[3,4-c]pyrrol-3-one
242	 Exemple 242	(cis)-2-[2-[4-(azetidin-3-yloxy)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one

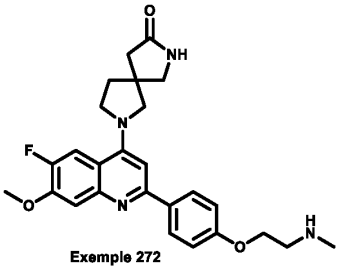
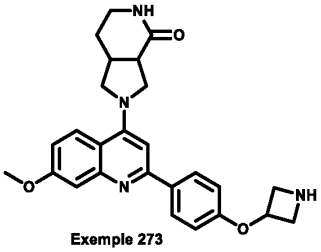
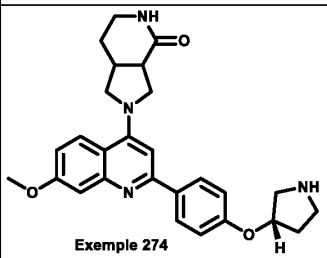
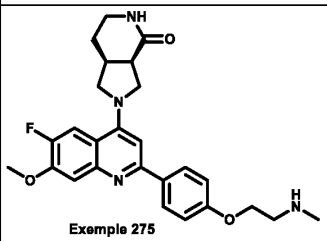
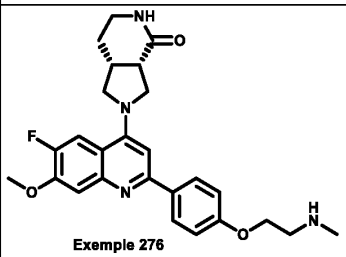
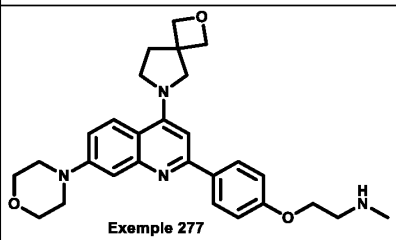
Ex. No.	Structure	Name
243	 Exemple 243	(cis)-2,2-difluoro-N-[2-[4-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenoxy]ethyl]ethanamine
244	 Exemple 244	6-fluoro-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)quinolin-7-amine
245	 Exemple 245	2-[[5-[6-fluoro-7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine
246	 Exemple 246	2-[4-[6-fluoro-7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine
247	 Exemple 247	2-[6-fluoro-7-methoxy-2-[4-[2-24(methylamino)ethoxy]phenyl]-4-quinolyl]-6-methyl-2,6-diazaspiro[3.5]nonan-5-one
248	 Exemple 248	4,4-difluoro-7-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2-methyl-2,7-diazaspiro[4.4]nonan-1-one

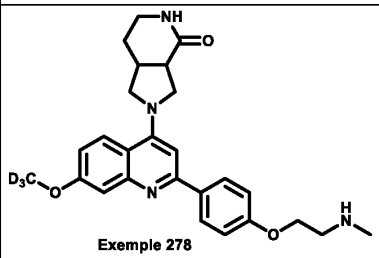
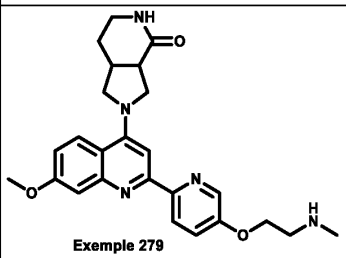
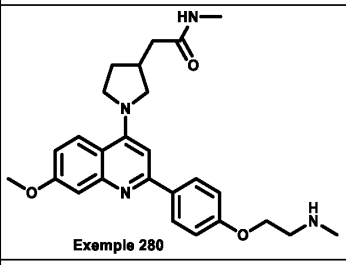
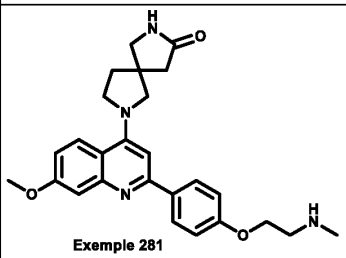
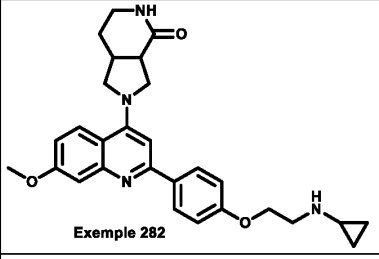
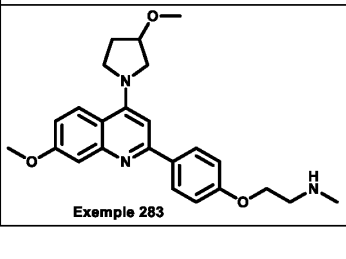
Ex. No.	Structure	Name
249	 Exemple 249	(S)-2-(4-(4-(3,3-difluoro-4-methoxypyrrolidin-1-yl)-7-methoxyquinolin-2-yl)phenoxy)-N-methylethan-1-amine
250	 Exemple 250	(cis)-2-[4-[6-fluoro-7-methoxy-4-(1-methyl-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrol-4-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine
251	 Exemple 251	3-[4-[6-fluoro-7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-propan-1-amine
252	 Exemple 252	2-[4-(azetidin-3-ylmethoxy)phenyl]-6-fluoro-7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinoline
253	 Exemple 253	2-[4-[4-[3-[(dimethylamino)methyl]pyrrolidin-1-yl]-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine
254	 Exemple 254	(cis)-2-[2-[4-(azetidin-3-ylmethoxy)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one

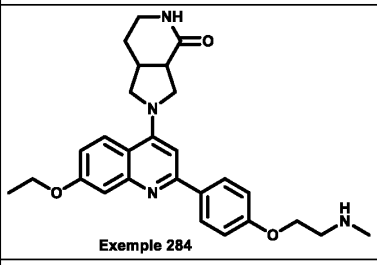
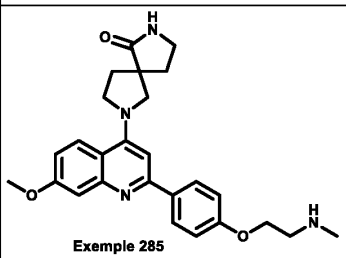
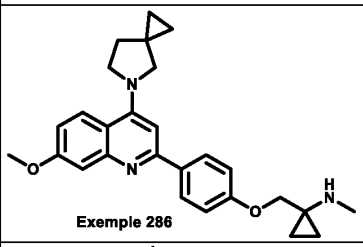
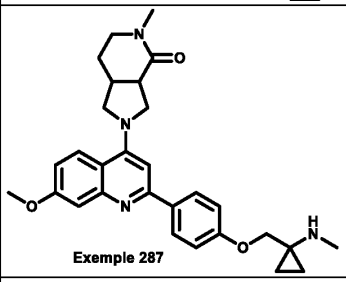
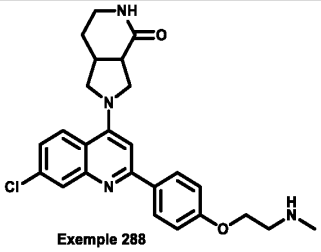
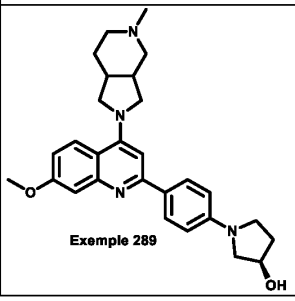
Ex. No.	Structure	Name
255	 Exemple 255	(cis)-(3R)-1-[5-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]pyrrolidin-3-ol
256	 Exemple 256	(cis)-2-[6-fluoro-7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
257	 Exemple 257	(cis)-(3S)-1-[5-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]pyrrolidin-3-ol
258	 Exemple 258	(3aS,7aR)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
259	 Exemple 259	(cis)-2-[4-[4-[5-(2,2-difluoroethyl)-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl]-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine

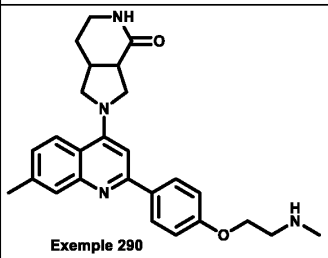
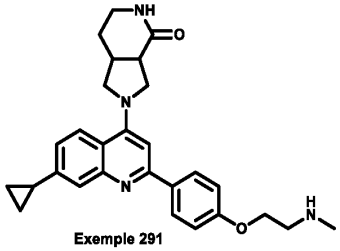
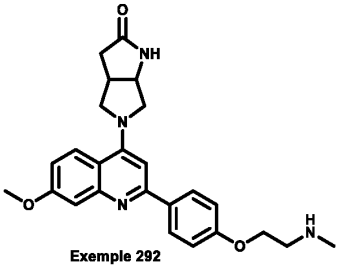
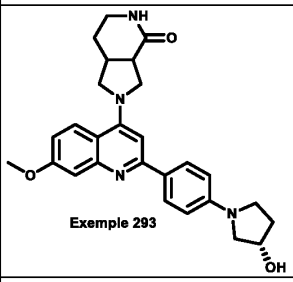
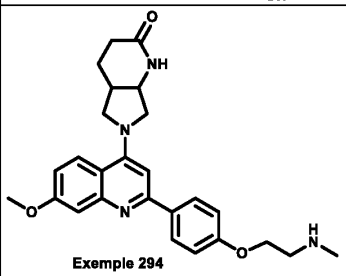
Ex. No.	Structure	Name
260	 Exemple 260	2-[[5-[7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine
261	 Exemple 261	2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-7-methyl-2,7-diazaspiro[4.4]nonan-8-one
262	 Exemple 262	2-[4-[7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine
263	 Exemple 263	(3S)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
264	 Exemple 264	7-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-1-one
265	 Exemple 265	2-[4-[4-(3,3-difluoropyrrolidin-1-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine

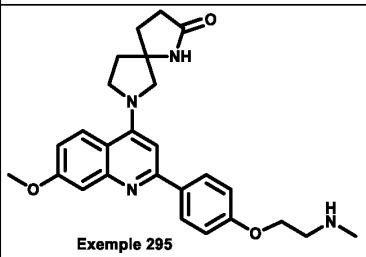
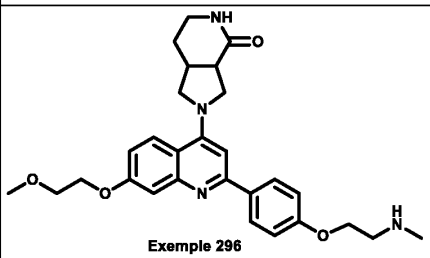
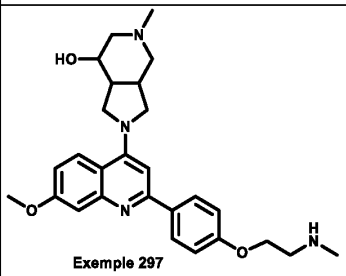
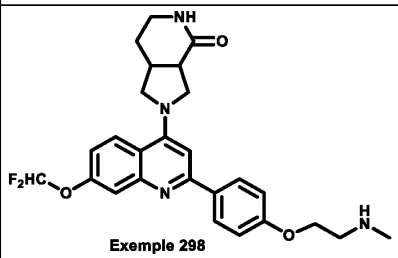
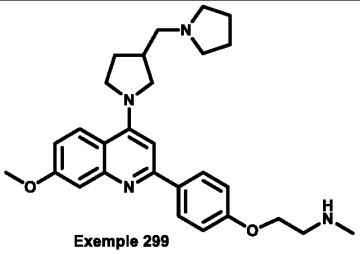
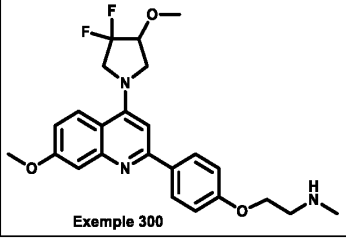
Ex. No.	Structure	Name
266	 Exemple 266	2-[4-[7-methoxy-4-(3-methyl-2,2-dioxo-2λ6-thia-3,7-diazaspiro[4.4]nonan-7-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine
267	 Exemple 267	2-[4-[4-(1,3-dimethyl-2,2-dioxo-2λ6-thia-3,7-diazaspiro[4.4]nonan-7-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine
268	 Exemple 268	(cis)-2-[6-fluoro-7-methoxy-2-[4-(2-methoxyethoxy)phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
269	 Exemple 269	(cis)-2-[6-fluoro-7-methoxy-2-[4-[2-(trideuteriomethoxy)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
270	 Exemple 270	2-[1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]-N-methyl-acetamide
271	 Exemple 271	(cis)-2-[2-[4-[2-(dimethylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one

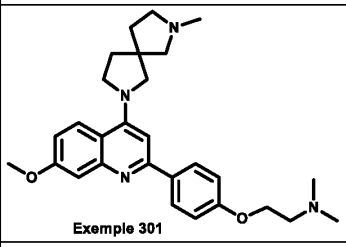
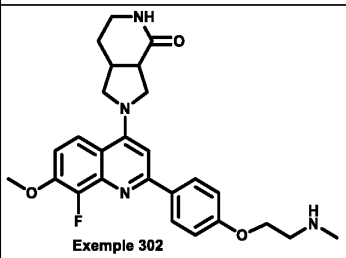
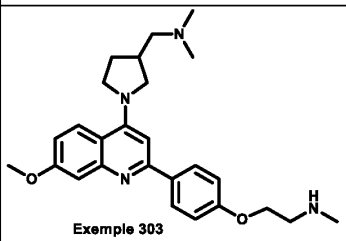
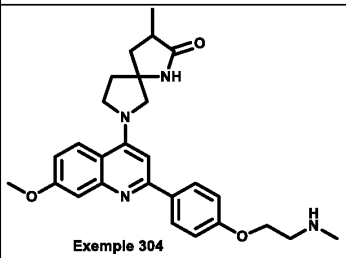
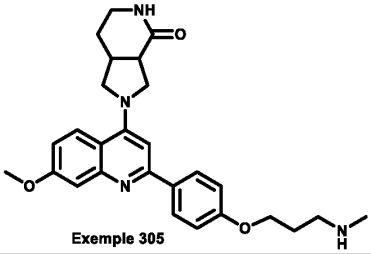
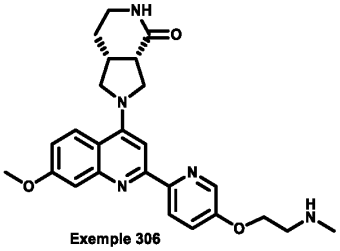
Ex. No.	Structure	Name
272	 Exemple 272	2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-8-one
273	 Exemple 273	(cis)-2-[2-[4-(azetidin-3-yloxy)phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
274	 Exemple 274	(cis)-2-[7-methoxy-2-[4-[(3S)-pyrrolidin-3-yl]oxyphenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
275	 Exemple 275	(3aR,7aS)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
276	 Exemple 276	(3aS,7aR)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
277	 Exemple 277	N-methyl-2-[4-[7-morpholino-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]ethanamine

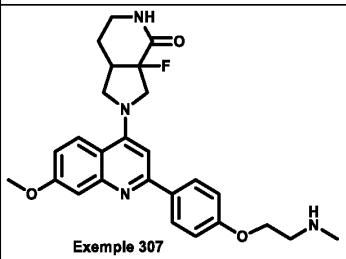
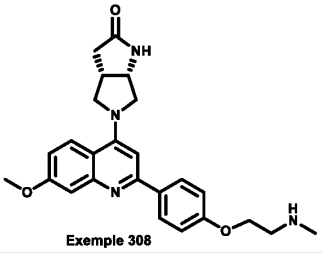
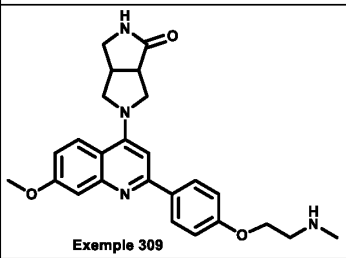
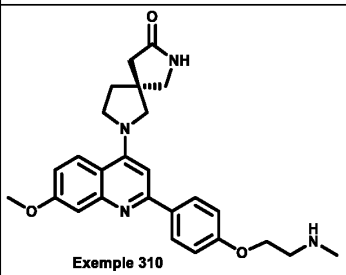
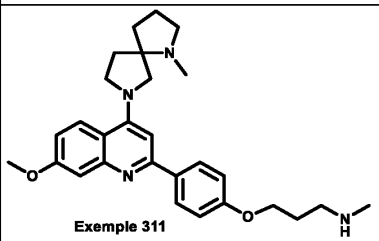
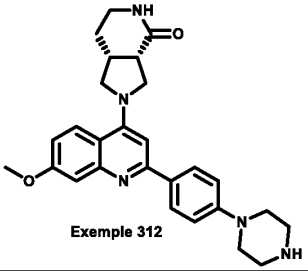
Ex. No.	Structure	Name
278	 Exemple 278	(cis)-2-[2-[4-[2-(methylamino)ethoxy]phenyl]-7-(trideuteriomethoxy)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
279	 Exemple 279	(cis)-2-[7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
280	 Exemple 280	2-[1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]-N-methyl-acetamide
281	 Exemple 281	2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-8-one
282	 Exemple 282	(cis)-2-[2-[4-[2-(cyclopropylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
283	 Exemple 283	2-[4-[7-methoxy-4-(3-methoxypyrrolidin-1-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine

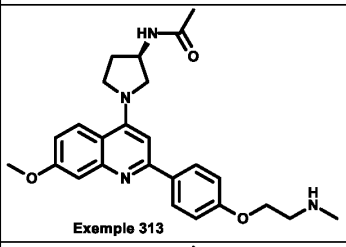
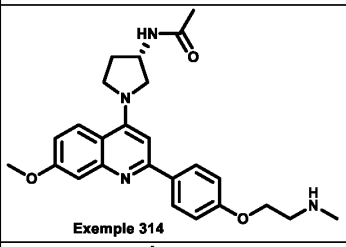
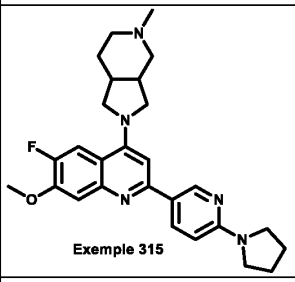
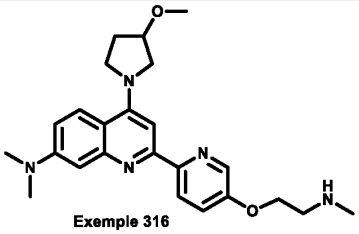
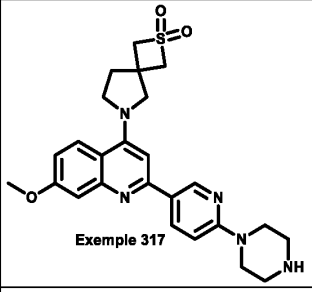
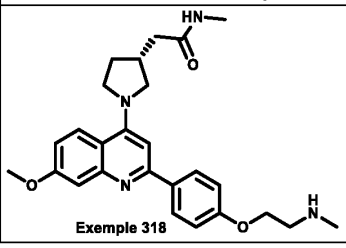
Ex. No.	Structure	Name
284	 Exemple 284	(cis)-2-[7-ethoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
285	 Exemple 285	7-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-1-one
286	 Exemple 286	1-[[4-[4-(5-azaspiro[2.4]heptan-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]methyl]-N-methyl-cyclopropanamine
287	 Exemple 287	(cis)-2-[7-methoxy-2-[4-[[1-(methylamino)cyclopropyl]methoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
288	 Exemple 288	(cis)-2-[7-chloro-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
289	 Exemple 289	(cis)-(3R)-1-[4-[7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenyl]pyrrolidin-3-ol

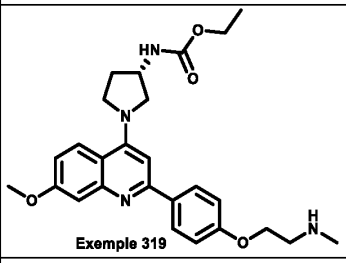
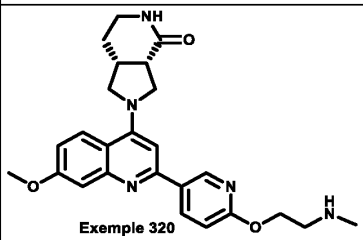
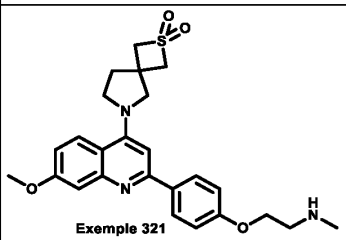
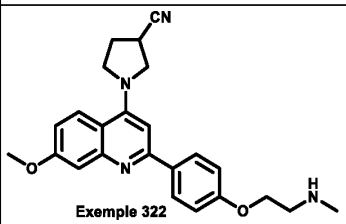
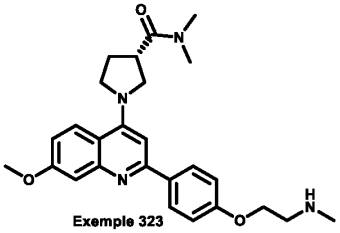
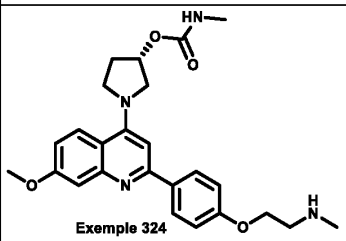
Ex. No.	Structure	Name
290	 Exemple 290	(cis)-2-[7-methyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
291	 Exemple 291	(cis)-2-[7-cyclopropyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
292	 Exemple 292	(cis)-5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-2-one
293	 Exemple 293	(cis)-2-[2-[4-[(3S)-3-hydroxypyrrolidin-1-yl]phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
294	 Exemple 294	(cis)-6-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,4,4a,5,7,7a-hexahydro-1H-pyrrolo[3,4-b]pyridin-2-one

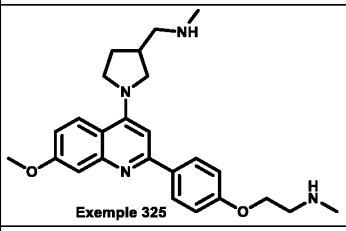
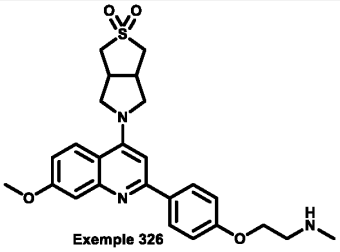
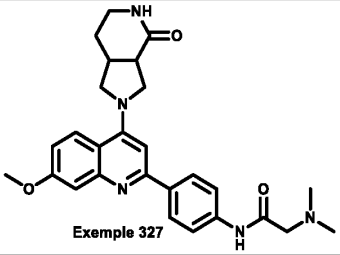
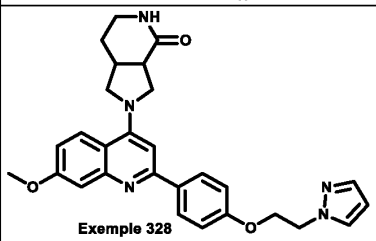
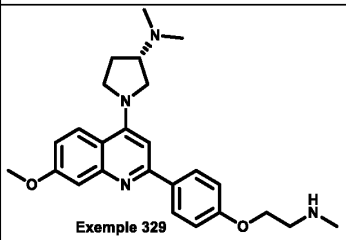
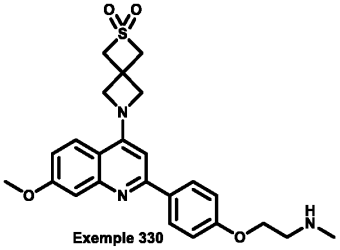
Ex. No.	Structure	Name
295	 Exemple 295	7-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,7-diazaspiro[4.4]nonan-2-one
296	 Exemple 296	(cis)-2-[7-(2-methoxyethoxy)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
297	 Exemple 297	(cis)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-7-ol
298	 Exemple 298	(cis)-2-[7-(difluoromethoxy)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
299	 Exemple 299	2-[4-[7-methoxy-4-[3-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine
300	 Exemple 300	2-[4-[4-(3,3-difluoro-4-methoxy-pyrrolidin-1-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine

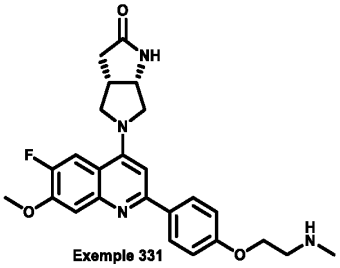
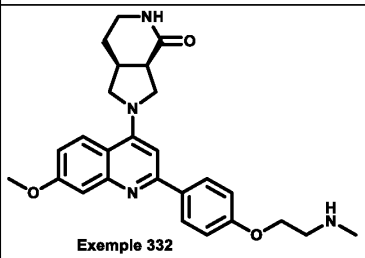
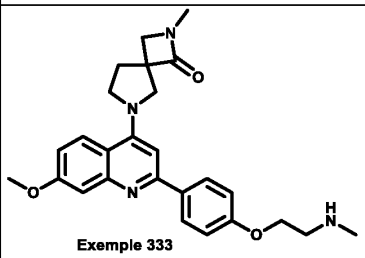
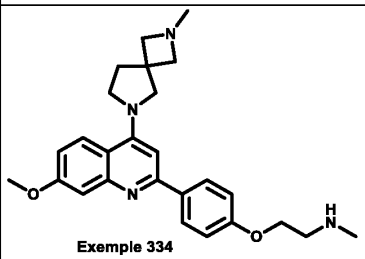
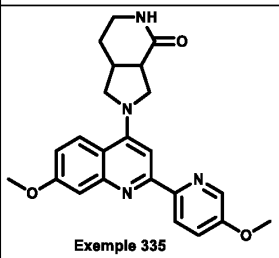
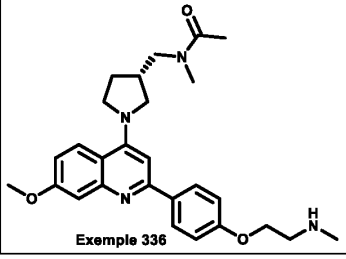
Ex. No.	Structure	Name
301	 Exemple 301	2-[4-[7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N,N-dimethyl-ethanamine
302	 Exemple 302	(cis)-2-[8-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
303	 Exemple 303	2-[4-[4-[3-[(dimethylamino)methyl]pyrrolidin-1-yl]-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine
304	 Exemple 304	7-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3-methyl-1,7-diazaspiro[4.4]nonan-2-one
305	 Exemple 305	(cis)-2-[7-methoxy-2-[4-[3-(methylamino)propoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
306	 Exemple 306	(3aS,7aR)-2-[7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one

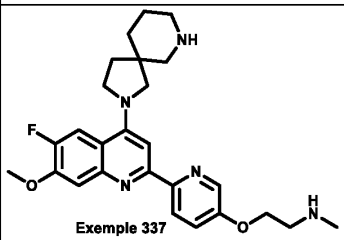
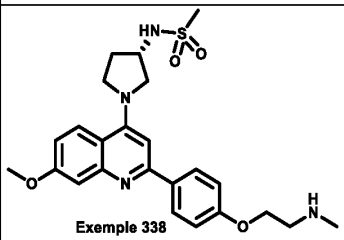
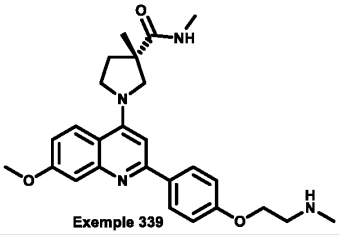
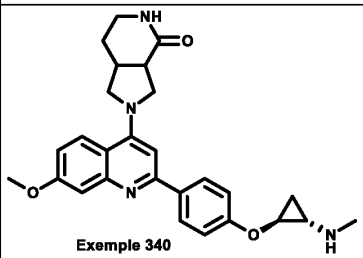
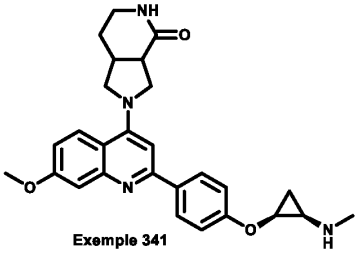
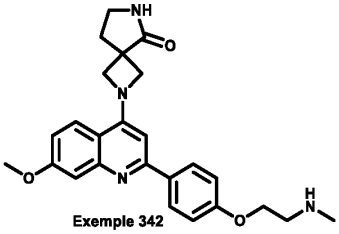
Ex. No.	Structure	Name
307	 Exemple 307	(cis)-3a-fluoro-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,5,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one
308	 Exemple 308	(3aR,6aR)-5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-2-one
309	 Exemple 309	(cis)-5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one
310	 Exemple 310	(5R)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-8-one
311	 Exemple 311	3-[4-[7-methoxy-4-(1-methyl-1,7-diazaspiro[4.4]nonan-7-yl)-2-quinolyl]phenoxy]-N-methyl-propan-1-amine
312	 Exemple 312	(3aS,7aR)-2-(7-methoxy-2-(4-(piperazin-1-yl)phenyl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one

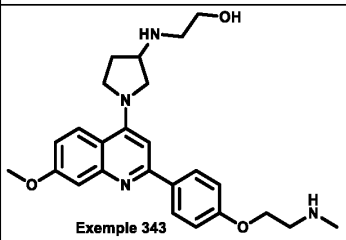
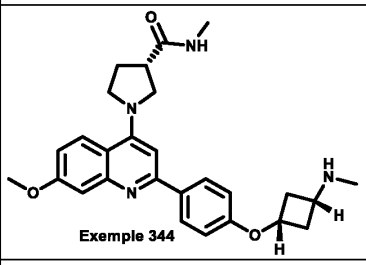
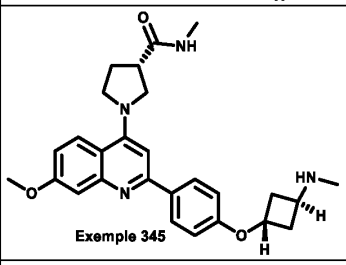
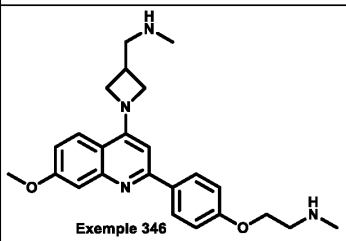
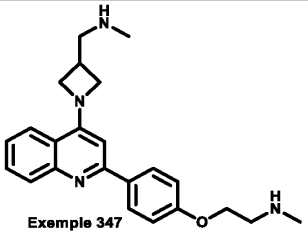
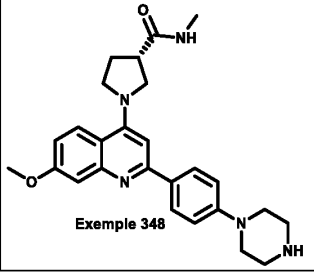
Ex. No.	Structure	Name
313	 Exemple 313	(R)-N-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)acetamide
314	 Exemple 314	(S)-N-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)acetamide
315	 Exemple 315	(cis)-6-fluoro-7-methoxy-4-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-2-(6-(pyrrolidin-1-yl)pyridin-3-yl)quinoline
316	 Exemple 316	4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(5-(2-(methylamino)ethoxy)pyridin-2-yl)quinolin-7-amine
317	 Exemple 317	6-(7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)-2-thia-6-azaspiro[3.4]octane 2,2-dioxide
318	 Exemple 318	(R)-2-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)-N-methylacetamide

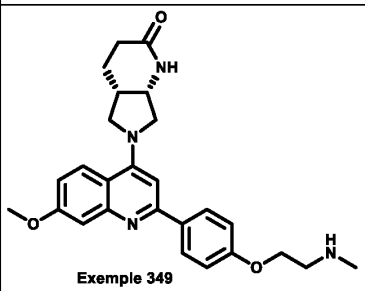
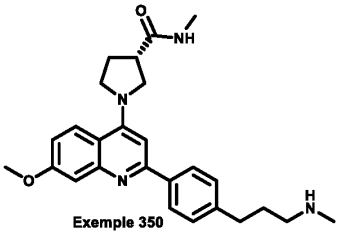
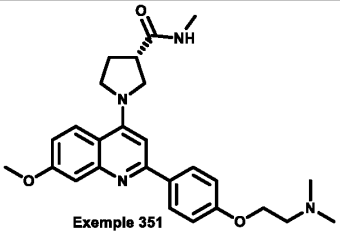
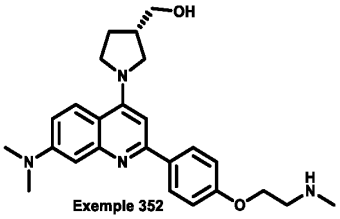
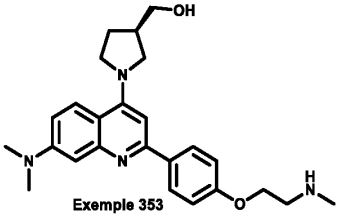
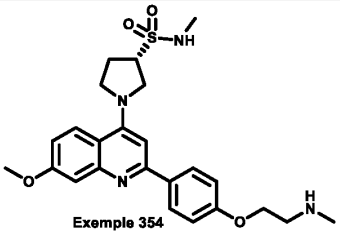
Ex. No.	Structure	Name
319	 Exemple 319	ethyl (S)-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)carbamate
320	 Exemple 320	(3aS,7aR)-2-(7-methoxy-2-(6-(2-(methylamino)ethoxy)pyridin-3-yl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one
321	 Exemple 321	6-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-2-thia-6-azaspiro[3.4]octane 2,2-dioxide
322	 Exemple 322	1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidine-3-carbonitrile
323	 Exemple 323	(S)-1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-N,N-dimethylpyrrolidine-3-carboxamide
324	 Exemple 324	(S)-1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl methylcarbamate

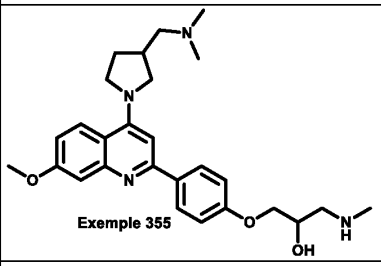
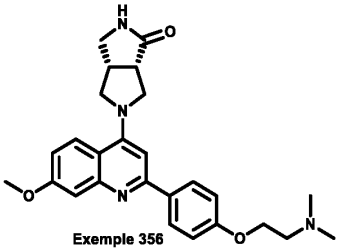
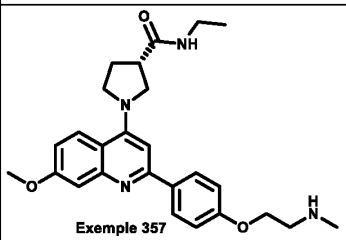
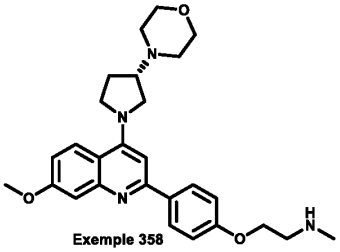
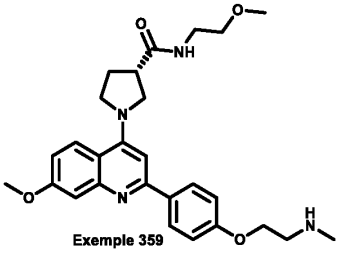
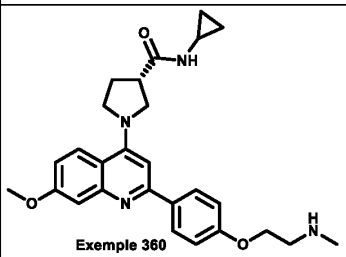
Ex. No.	Structure	Name
325	 Exemple 325	2-(4-(7-methoxy-4-(3-((methylamino)methyl)pyrrolidin-1-yl)quinolin-2-yl)phenoxy)-N-methylethan-1-amine
326	 Exemple 326	(cis)-5-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)hexahydro-1H-thieno[3,4-c]pyrrole 2,2-dioxide
327	 Exemple 327	(cis)-2-(dimethylamino)-N-(4-(7-methoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)acetamide
328	 Exemple 328	(cis)-2-(2-(4-(2-(1H-pyrazol-1-yl)ethoxy)phenyl)-7-methoxyquinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one
329	 Exemple 329	(S)-1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-N,N-dimethylpyrrolidin-3-amine
330	 Exemple 330	6-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-2-thia-6-azaspiro[3.3]heptane 2,2-dioxide

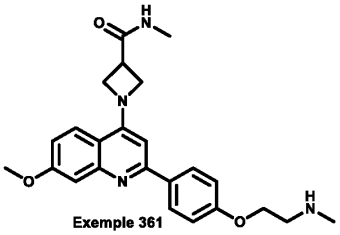
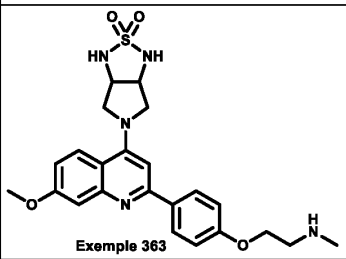
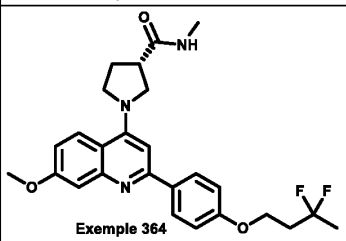
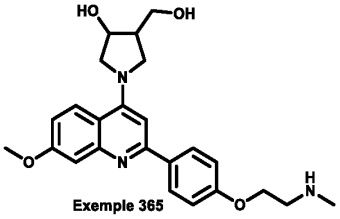
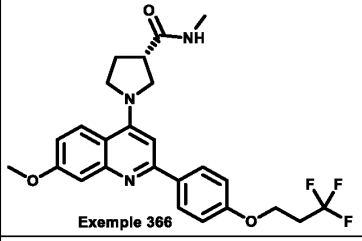
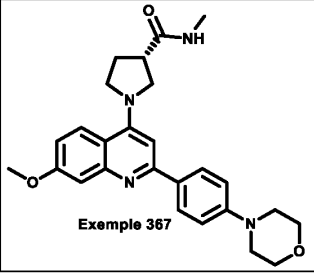
Ex. No.	Structure	Name
331	 Exemple 331	(3aS,6aS)-5-(6-fluoro-7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)hexahydropyrrolo[3,4-b]pyrrol-2(1H)-one
332	 Exemple 332	(3aR,7aS)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
333	 Exemple 333	6-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2-methyl-2,6-diazaspiro[3.4]octan-3-one
334	 Exemple 334	2-[4-[7-methoxy-4-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine
335	 Exemple 335	(cis)-2-[7-methoxy-2-(5-methoxy-2-pyridyl)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one
336	 Exemple 336	N-[[(3S)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methyl]-N-methyl-acetamide

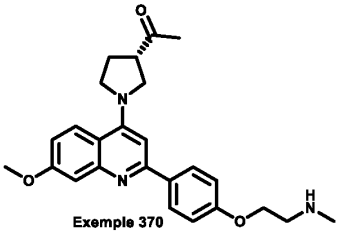
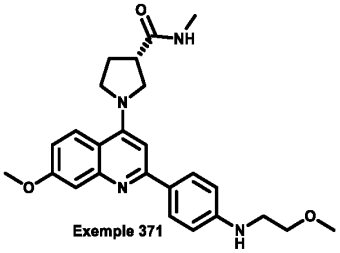
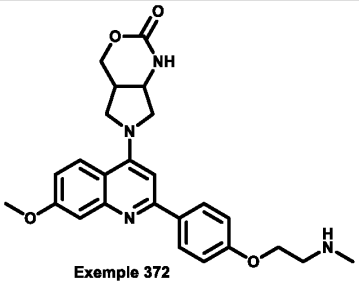
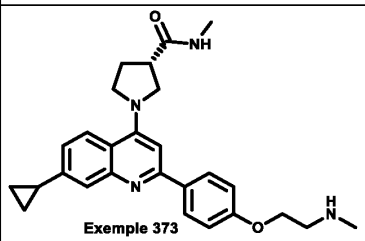
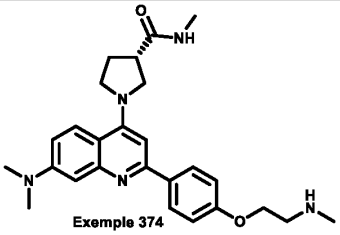
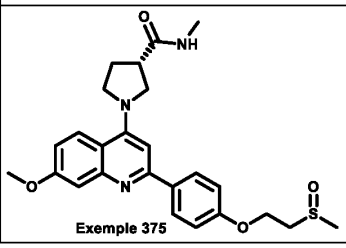
Ex. No.	Structure	Name
337	 Exemple 337	2-[[6-[4-(2,9-diazaspiro[4.5]decan-2-yl)-6-fluoro-7-methoxy-2-quinolyl]-3-pyridyl]oxy]-N-methyl-ethanamine
338	 Exemple 338	N-[(3S)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanesulfonamide
339	 Exemple 339	(3S)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N,3-dimethyl-pyrrolidine-3-carboxamide
340	 Exemple 340	(cis)-2-(7-methoxy-2-(4-((1S,2S)-2-(methylamino)cyclopropoxy)phenyl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one
341	 Exemple 341	(cis)-2-(7-methoxy-2-(4-((1S,2R)-2-(methylamino)cyclopropoxy)phenyl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one
342	 Exemple 342	2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,6-diazaspiro[3.4]octan-5-one

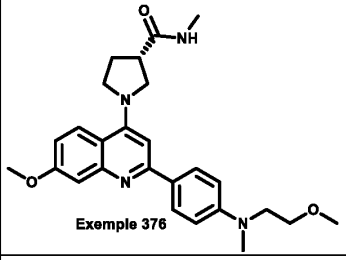
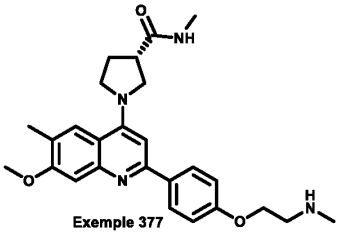
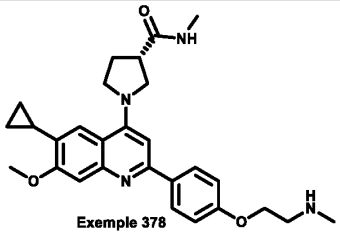
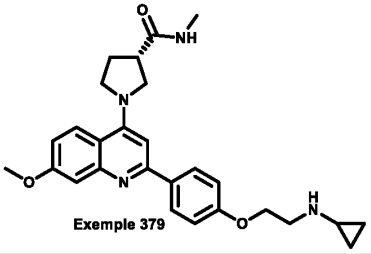
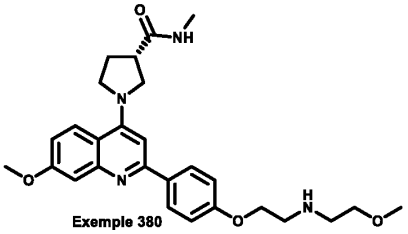
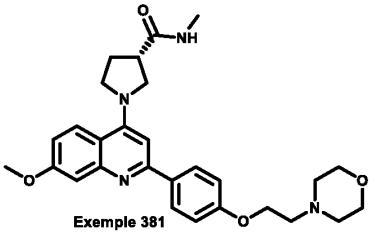
Ex. No.	Structure	Name
343	 Exemple 343	2-[[1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]amino]ethanol
344	 Exemple 344	(S)-1-(7-methoxy-2-(4-((1s,3R)-3-(methylamino)cyclobutoxy)phenyl)quinolin-4-yl)-N-methylpyrrolidine-3-carboxamide
345	 Exemple 345	(S)-1-(7-methoxy-2-(4-((1r,3S)-3-(methylamino)cyclobutoxy)phenyl)quinolin-4-yl)-N-methylpyrrolidine-3-carboxamide
346	 Exemple 346	2-[4-[7-methoxy-4-[3-(methylaminomethyl)azetidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine
347	 Exemple 347	N-methyl-2-[4-[4-[3-(methylaminomethyl)azetidin-1-yl]-2-quinolyl]phenoxy]ethanamine
348	 Exemple 348	(3S)-1-[7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide

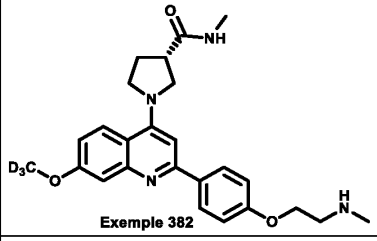
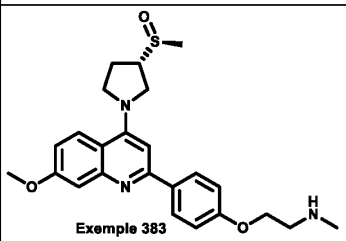
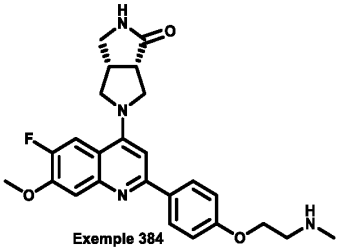
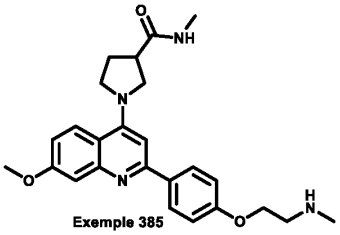
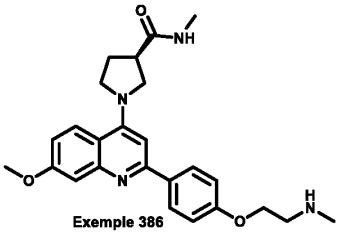
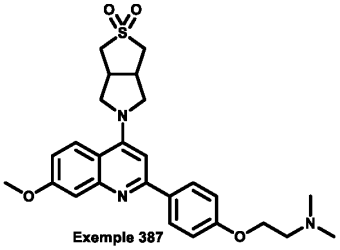
Ex. No.	Structure	Name
349	 Exemple 349	(4aS,7aS)-6-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,4,4a,5,7,7a-hexahydro-1H-pyrrolo[3,4-b]pyridin-2-one
350	 Exemple 350	(3S)-1-[7-methoxy-2-[4-[3-(methylamino)propyl]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
351	 Exemple 351	(3S)-1-[2-[4-[2-(dimethylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
352	 Exemple 352	[(3S)-1-[7-(dimethylamino)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol
353	 Exemple 353	[(3R)-1-[7-(dimethylamino)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol
354	 Exemple 354	(3S)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-sulfonamide

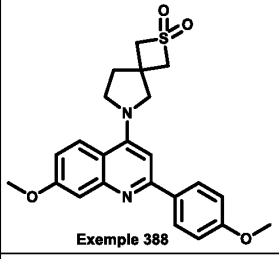
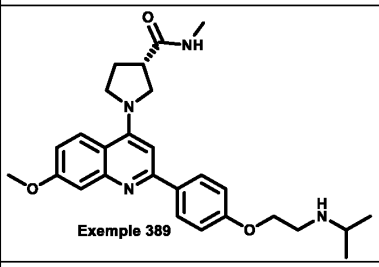
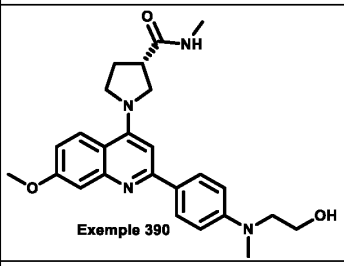
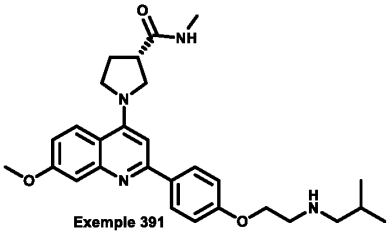
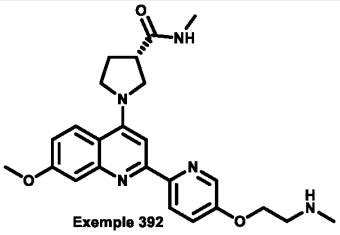
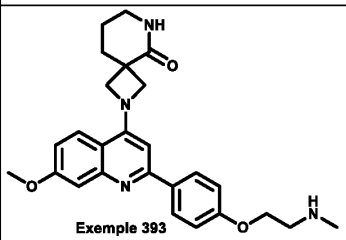
Ex. No.	Structure	Name
355	 Exemple 355	1-[4-[4-[3-[(dimethylamino)methyl]pyrrolidin-1-yl]-7-methoxy-2-quinolyl]phenoxy]-3-(methylamino)propan-2-ol
356	 Exemple 356	(3aS,6aS)-5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one
357	 Exemple 357	(3S)-N-ethyl-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidine-3-carboxamide
358	 Exemple 358	2-[4-[7-methoxy-4-[(3S)-3-morpholinopyrrolidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine
359	 Exemple 359	(3S)-N-(2-methoxyethyl)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidine-3-carboxamide
360	 Exemple 360	(3S)-N-cyclopropyl-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidine-3-carboxamide

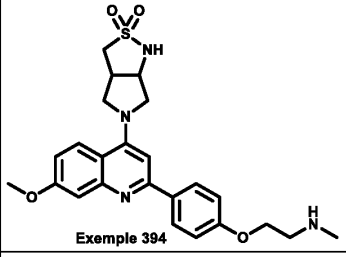
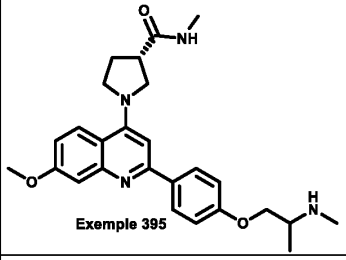
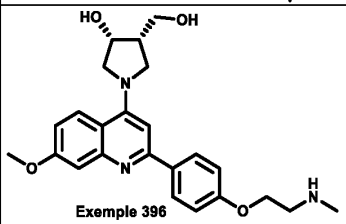
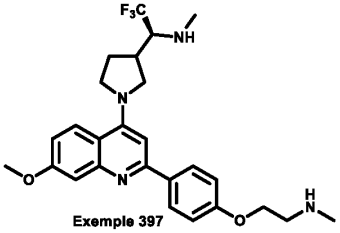
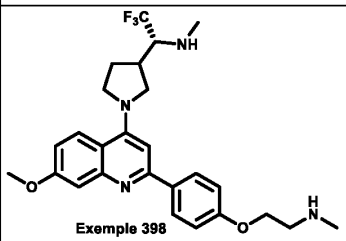
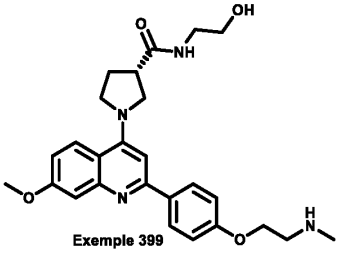
Ex. No.	Structure	Name
361	 Exemple 361	1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-azetidine-3-carboxamide
363	 Exemple 363	2-[4-[4-(2,2-dioxo-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c][1,2,5]thiadiazol-5-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine
364	 Exemple 364	(3S)-1-[2-[4-(3,3-difluorobutoxy)phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
365	 Exemple 365	4-(hydroxymethyl)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-ol
366	 Exemple 366	(3S)-1-[7-methoxy-2-[4-(3,3,3-trifluoropropoxy)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
367	 Exemple 367	(3S)-1-[7-methoxy-2-(4-morpholinophenyl)-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide

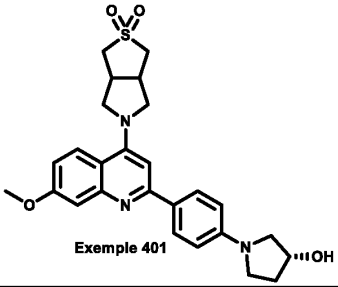
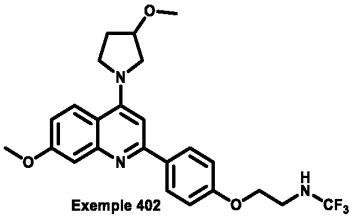
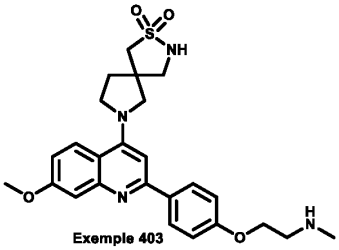
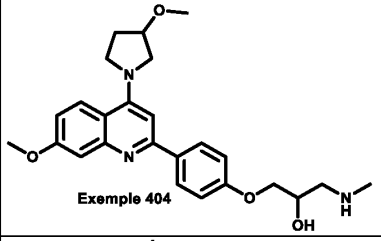
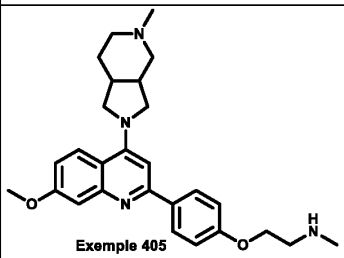
Ex. No.	Structure	Name
370	 Exemple 370	1-[(3S)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]ethanone
371	 Exemple 371	(3S)-1-[7-methoxy-2-[4-(2-methoxyethylamino)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
372	 Exemple 372	(cis)-6-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,4,4a,5,7,7a-hexahydropyrrolo[3,4-d][1,3]oxazin-2-one
373	 Exemple 373	(3S)-1-[7-cyclopropyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
374	 Exemple 374	(3S)-1-[7-(dimethylamino)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
375	 Exemple 375	(3S)-1-[7-methoxy-2-[4-(2-methylsulfinylethoxy)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide

Ex. No.	Structure	Name
376	 Exemple 376	(3S)-1-[7-methoxy-2-[4-[2-methoxyethyl(methyl)amino]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
377	 Exemple 377	(3S)-1-[7-methoxy-6-methyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
378	 Exemple 378	(3S)-1-[6-cyclopropyl-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
379	 Exemple 379	(3S)-1-[2-[4-[2-(cyclopropylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
380	 Exemple 380	(3S)-1-[7-methoxy-2-[4-[2-(2-methoxyethylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
381	 Exemple 381	(3S)-1-[7-methoxy-2-[4-(2-morpholinoethoxy)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide

Ex. No.	Structure	Name
382	 Exemple 382	(3S)-N-methyl-1-[2-[4-[2-(methylamino)ethoxy]phenyl]-7-(trideuteriomethoxy)-4-quinolyl]pyrrolidine-3-carboxamide
383	 Exemple 383	2-[4-[7-methoxy-4-[(3S)-3-[(S)-methylsulfinyl]pyrrolidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine
384	 Exemple 384	(3aS,6aS)-5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one
385	 Exemple 385	1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
386	 Exemple 386	(3R)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
387	 Exemple 387	(cis)-2-[4-[4-(2,2-dioxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrol-5-yl)-7-methoxy-2-quinolyl]phenoxy]-N,N-dimethyl-ethanamine

Ex. No.	Structure	Name
388	 Exemple 388	7-[7-methoxy-2-(4-methoxyphenyl)-4-quinolyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide
389	 Exemple 389	(3S)-1-[2-[4-[2-(isopropylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
390	 Exemple 390	(3S)-1-[2-[4-[2-hydroxyethyl(methyl)amino]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
391	 Exemple 391	(3S)-1-[2-[4-[2-(isobutylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
392	 Exemple 392	(3S)-1-[7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide
393	 Exemple 393	2-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-2,6-diazaspiro[3.5]nonan-5-one

Ex. No.	Structure	Name
394	 Exemple 394	(cis)-5-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)hexahydro-1H-pyrrolo[3,4-c]isothiazole 2,2-dioxide
395	 Exemple 395	(3S)-1-(7-methoxy-2-(4-(2-(methylamino)propoxy)phenyl)quinolin-4-yl)-N-methylpyrrolidine-3-carboxamide
396	 Exemple 396	(3R,4S)-4-(hydroxymethyl)-1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-ol
397	 Exemple 397	(1S)-2,2,2-trifluoro-1-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)-N-methylethan-1-amine
398	 Exemple 398	(1R)-2,2,2-trifluoro-1-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)-N-methylethan-1-amine
399	 Exemple 399	(S)-N-(2-hydroxyethyl)-1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidine-3-carboxamide

Ex. No.	Structure	Name
401	 Exemple 401	(cis)-5-(2-(4-((R)-3-hydroxypyrrolidin-1-yl)phenyl)-7-methoxyquinolin-4-yl)hexahydro-1H-thieno[3,4-c]pyrrole 2,2-dioxide
402	 Exemple 402	2-(4-(7-methoxy-4-(3-methoxypyrrolidin-1-yl)quinolin-2-yl)phenoxy)-N-(trifluoromethyl)ethan-1-amine
403	 Exemple 403	7-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-2-thia-3,7-diazaspiro[4.4]nonane 2,2-dioxide
404	 Exemple 404	1-(4-(7-methoxy-4-(3-methoxypyrrolidin-1-yl)quinolin-2-yl)phenoxy)-3-(methylamino)propan-2-ol
405	 Exemple 405	(cis)-2-(4-(7-methoxy-4-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)-N-methylethan-1-amine

[0111] In some embodiments, provided herein is a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein the compound is selected from the group consisting of

1-(4-(5-(6,7-dimethoxy-4-(pyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-one;

(1-(2-(6-(azetidin-1-yl) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol;

2-(4-(5-(6-fluoro-4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-ol;

(1-(2-(2-(azetidin-1-yl) thiazol-5-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol;

(1-(2-(6-(azetidin-1-yl) pyridin-3-yl)-7-(dimethylamino)-6-fluoroquinolin-4-yl) pyrrolidin-3-yl) methanol;

2-(2-(6-(dimethylamino) pyridin-3-yl)-7-methoxyquinolin-4-yl) octahydro-6H-pyrrolo[3,4-c] pyridin-6-one;

6,7-dimethoxy-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(pyrrolidin-1-yl) quinoline;

2-(4-(5-(6,7-dimethoxy-4-(pyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-ol;

1-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-3-methylpyrrolidin-3-ol;

(1-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol;

2-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane;

4-(2-methylpyrrolidin-1-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(pyrrolidin-1-yl) quinoline;

2-(2-(6-(azetidin-3-yl) pyridin-3-yl)-7-methoxyquinolin-4-yl)-2,7-diazaspiro [4.5] decane;

6-methoxy-4-(3-methoxypyrrolidin-1-yl)-*N*, *N*-dimethyl-2-(4-(2-(methylamino) ethoxy) phenyl) quinolin-7-amine;

4-(3-methoxypyrrolidin-1-yl)-*N*, *N*-dimethyl-2-(6-(2-(methylamino) ethoxy) pyridin-3-yl) quinolin-7-amine;

2-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane;

(1-(6-fluoro-7-methoxy-2-(6-(methylamino) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol;

5-(6-fluoro-7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl)-*N*-methylpyridin-2-amine;

2-(6-(piperazin-1-yl)pyridin-3-yl)-4-(2,6-diazaspiro[3.4]octan-6-yl)quinoline;

(1-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol;

2-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-7-methyl-2,7-diazaspiro [4.5] decane;

7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,6-diazaspiro [3.4] octan-6-yl) quinoline;

2-(7-methoxy-2-(4-(piperazin-1-yl) phenyl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane;

2-(4-(7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenoxy)-*N*-methylethan-1-amine;

6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

6-fluoro-*N*, *N*-dimethyl-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-7-amine;

2-(4-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenoxy)-*N*-methylethan-1-amine;

5-(7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl)-*N*, *N*-dimethylpyridin-2-amine;

(1-(2-(6-(2-(cyclopropylamino) ethoxy) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol;

2-amino-1-(5-(6-fluoro-4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) propan-1-one;

2-(2-(6-(azetidin-1-yl) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl)-2,7-diazaspiro [4.5] decane;

2-amino-1-(4-(5-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) propan-1-one;

4-hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

1-(4-(5-(4-(3,6-diazabicyclo [3.2.0] heptan-3-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-2-aminopropan-1-one;

2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(1,6-diazaspiro [3.4] octan-6-yl) quinoline;

2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.4] nonan-2-yl) quinoline;

4-(hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

4-(3,6-diazabicyclo [3.2.0] heptan-3-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

4-(3,6-diazabicyclo [3.2.0] heptan-6-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

2-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane;

2-amino-1-(4-(4-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) phenyl) piperazin-1-yl) propan-1-one;

4-(1,4-diazepan-1-yl)-6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

2-amino-1-(4-(4-(7-methoxy-4-(3-methoxypyrrolidin-1-yl) quinolin-2-yl) phenyl) piperazin-1-yl) propan-1-one;

2-amino-1-(4-(5-(7-(dimethylamino)-4-(3-methoxypyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) propan-1-one;

ethyl (2-(6-(methylamino) pyridin-3-yl)-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-7-yl) carbamate;

2-amino-*N*-(4-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenyl)-3-methylbutanamide;

2-amino-1-(4-(5-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-2-methylpropan-1-one;

5-[4-(2, 9-diazaspiro[4.5]decan-2-yl) -7-methoxy-2-quinolyl]-*N*, *N*-dimethyl-pyridin-2-amine;

2-(4-(piperazin-1-yl) phenyl)-4-(pyrrolidin-1-yl) quinoline;

(1-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol;

(1-(6-amino-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol;

2-amino-1-(5-(6-fluoro-7-methoxy-4-(2,7-diazaspiro[4.5]decan-2-yl)quinolin-2-yl)pyridin-2-yl)propan-1-one;

[4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazin-1-yl]-pyrrolidin-2-yl-methanone;

2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.4] nonan-2-yl) quinoline;

6-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2-oxa-6-azaspiro [3.4] octane;

2-((5-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) pyridin-2-yl) oxy)-N-methylethan-1-amine;

2-amino-1-(4-(5-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)piperazin-1-yl)propan-1-one;

2-amino-1-[5-[4-(2,9-diazaspiro [4.5]decan-2-yl)-7-(dimethylamino)-6-fluoro-2-quinolyl]-2-pyridyl]propan-1-one;

2-((5-(6-fluoro-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)-*N*-methylethan-1-amine;

2-((5-(6,7-difluoro-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)-N-methylethan-1-amine;

N-[4-[4-(2, 9-diazaspiro[4.5]decan-2-yl) -6-fluoro-7-methoxy-2-quinolyl]phenyl]acetamide;

5-[7-chloro-4-(2, 9-diazaspiro[4.5]decan-2-yl)-2-quinolyl]-*N*-methyl-pyridin-2-amine;

2-(6-piperazin-1-yl-3-pyridyl)-4-[3,6-diazabicyclo [3.2.0] heptan-6-yl] quinoline;

2-amino-1-(4-(5-(4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-3-methylbutan-1-one;

2-amino-1-[4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazin-1-yl]-4-methyl-pentan-1-one; and

2-(azetidin-1-yl)-5-[4-(2,9-diazaspiro [4.5]decan-2-yl)-7-methoxy-2-quinolyl]thiazole.

[0112] In some embodiments, the compound is selected from the group consisting of

1-(4-(5-(6,7-dimethoxy-4-(pyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-one;

(1-(2-(6-(azetidin-1-yl) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol;

2-(4-(5-(6-fluoro-4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-ol;

(1-(2-(2-(azetidin-1-yl) thiazol-5-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol;

(1-(2-(6-(azetidin-1-yl) pyridin-3-yl)-7-(dimethylamino)-6-fluoroquinolin-4-yl) pyrrolidin-3-yl) methanol;

2-(2-(6-(dimethylamino) pyridin-3-yl)-7-methoxyquinolin-4-yl) octahydro-6H-pyrrolo[3,4-c] pyridin-6-one;

6,7-dimethoxy-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(pyrrolidin-1-yl) quinoline;

2-(4-(5-(6,7-dimethoxy-4-(pyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-ol;

1-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-3-methylpyrrolidin-3-ol;

(1-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol;

2-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane;

4-(2-methylpyrrolidin-1-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(pyrrolidin-1-yl) quinoline;

2-(2-(6-(azetidin-3-yl) pyridin-3-yl)-7-methoxyquinolin-4-yl)-2,7-diazaspiro [4.5] decane;

6-methoxy-4-(3-methoxypyrrolidin-1-yl)-*N*, *N*-dimethyl-2-(4-(2-(methylamino) ethoxy) phenyl) quinolin-7-amine;

4-(3-methoxypyrrolidin-1-yl)-*N*, *N*-dimethyl-2-(6-(2-(methylamino) ethoxy) pyridin-3-yl) quinolin-7-amine;

2-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane;

(1-(6-fluoro-7-methoxy-2-(6-(methylamino) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol;

5-(6-fluoro-7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl)-*N*-methylpyridin-2-amine;

2-(6-(piperazin-1-yl)pyridin-3-yl)-4-(2,6-diazaspiro[3.4]octan-6-yl)quinoline;

(1-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol;

2-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-7-methyl-2,7-diazaspiro [4.5] decane;

7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,6-diazaspiro [3.4] octan-6-yl) quinoline;

2-(7-methoxy-2-(4-(piperazin-1-yl) phenyl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane;

2-(4-(7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenoxy)-*N*-methylethan-1-amine;

6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

6-fluoro-*N*, *N*-dimethyl-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-7-amine;

2-(4-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenoxy)-*N*-methylethan-1-amine;

5-(7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl)-*N*, *N*-dimethylpyridin-2-amine;

(1-(2-(6-(2-(cyclopropylamino) ethoxy) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol;

2-amino-1-(5-(6-fluoro-4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) propan-1-one;

2-(2-(6-(azetidin-1-yl) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl)-2,7-diazaspiro [4.5] decane;

2-amino-1-(4-(5-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) propan-1-one;

4-hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

1-(4-(5-(4-(3,6-diazabicyclo [3.2.0] heptan-3-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-2-aminopropan-1-one;

2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(1,6-diazaspiro [3.4] octan-6-yl) quinoline;

2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.4] nonan-2-yl) quinoline;

4-(3,6-diazabicyclo [3.2.0] heptan-6-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

4-(3,6-diazabicyclo [3.2.0] heptan-3-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

2-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane;

2-amino-1-(4-(4-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) phenyl) piperazin-1-yl) propan-1-one;

4-(1,4-diazepan-1-yl)-6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline;

2-amino-1-(4-(4-(7-methoxy-4-(3-methoxypyrrolidin-1-yl) quinolin-2-yl) phenyl) piperazin-1-yl) propan-1-one;

2-amino-1-(4-(5-(7-(dimethylamino)-4-(3-methoxypyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) propan-1-one;

ethyl (2-(6-(methylamino) pyridin-3-yl)-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-7-yl) carbamate;

2-amino-*N*-(4-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenyl)-3-methylbutanamide;

2-amino-1-(4-(5-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-2-methylpropan-1-one;

5-[4-(2, 9-diazaspiro[4.5]decan-2-yl) -7-methoxy-2-quinolyl]-*N*, *N*-dimethyl-pyridin-2-amine;

2-(4-(piperazin-1-yl) phenyl)-4-(pyrrolidin-1-yl) quinoline;

(1-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol;

(1-(6-amino-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol;

2-amino-1-(5-(6-fluoro-7-methoxy-4-(2,7-diazaspiro[4.5]decan-2-yl)quinolin-2-yl)pyridin-2-yl)propan-1-one;

[4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazin-1-yl]-pyrrolidin-2-yl-methanone;

2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.4] nonan-2-yl) quinoline;

6-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2-oxa-6-azaspiro [3.4] octane;

2-((5-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) pyridin-2-yl) oxy)-N-methylethan-1-amine;

2-amino-1-(4-(5-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)piperazin-1-yl)propan-1-one;

2-amino-1-[5-[4-(2,9-diazaspiro [4.5]decan-2-yl)-7-(dimethylamino)-6-fluoro-2-quinolyl]-2-pyridyl]propan-1-one;

2-((5-(6-fluoro-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)-*N*-methylethan-1-amine;

2-((5-(6,7-difluoro-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)-N-methylethan-1-amine;

N-[4-[4-(2, 9-diazaspiro[4.5]decan-2-yl) -6-fluoro-7-methoxy-2-quinolyl]phenyl]acetamide;

5-[7-chloro-4-(2, 9-diazaspiro[4.5]decan-2-yl)-2-quinolyl]-*N*-methyl-pyridin-2-amine;

2-(6-piperazin-1-yl-3-pyridyl)-4-[3,6-diazabicyclo [3.2.0] heptan-6-yl] quinoline;

2-amino-1-(4-(5-(4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-3-methylbutan-1-one;

2-amino-1-[4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazin-1-yl]-4-methyl-pentan-1-one;

2-(azetidin-1-yl)-5-[4-(2,9-diazaspiro [4.5]decan-2-yl)-7-methoxy-2-quinolyl]thiazole;

4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(2-(piperazin-1-yl)thiazol-5-yl)quinolin-7-amine;

2-(4-(5-(6-fluoro-4-(3-(hydroxymethyl)pyrrolidin-1-yl)-7-methoxyquinolin-2-yl)pyridin-2-yl)piperazin-1-yl)ethan-1-ol;

2-amino-1-(5-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)propan-1-one;

2-amino-1-(4-(5-(4-(3-(hydroxymethyl)pyrrolidin-1-yl)-7-methoxyquinolin-2-yl)pyridin-2-yl)piperazin-1-yl)propan-1-one;

2-(4-(6-fluoro-7-(methoxy-d3)-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)-N-methylethan-1-amine;

(1-(2-(6-(5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)pyridin-3-yl)-7-methoxyquinolin-4-yl)pyrrolidin-3-yl)methanol;

(1-(7-(dimethylamino)-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol;

2-(7-(methoxy-d3)-2-(4-(piperazin-1-yl)phenyl)quinolin-4-yl)-2,7-diazaspiro[4.5]decane;

(1-(7-methoxy-2-(6-(2-(methylamino)ethoxy)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol;

2-amino-N-(5-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)-N-methylpropanamide;

ethyl (2-(2-(azetidin-1-yl)thiazol-5-yl)-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-7-yl)carbamate;

2-amino-1-(4-(7-(methoxy-d3)-4-(2,7-diazaspiro[4.5]decan-2-yl)quinolin-2-yl)phenyl)propan-1-one;

2-amino-1-(4-(7-(methoxy-d3)-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)propan-1-one;

2-amino-1-(4-(6-fluoro-7-(methoxy-d3)-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)propan-1-one;

2-amino-1-(4-(7-(dimethylamino)-6-fluoro-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)propan-1-one;

2-(4-(6-fluoro-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-7-(pent-4-yn-1-yloxy)quinolin-2-yl)phenoxy)-N-methylethan-1-amine;

2-(6-(azetidin-1-yl)pyridin-3-yl)-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinoline;

2-(6-(azetidin-1-yl)pyridin-3-yl)-6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinoline;

2-(4-(6-fluoro-7-methoxy-4-(2,7-diazaspiro[4.5]decan-2-yl)quinolin-2-yl)phenoxy)-N-methylethan-1-amine;

2-(2-(4-(azetidin-1-yl)phenyl)-6-fluoro-7-methoxyquinolin-4-yl)-2,7-diazaspiro[4.5]decane;

2-amino-N-(5-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)-2-methylpropanamide;

(1-(2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)methanol;

(1-(7-methoxy-2-(4-(piperazin-1-yl)phenyl)quinolin-4-yl)pyrrolidin-3-yl)methanol;

4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-7-amine;

2-(6-(piperazin-1-yl)pyridin-3-yl)-4-(2,6-diazaspiro[3.4]octan-2-yl)quinoline;

2-amino-N-(5-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)propanamide;

2-(2-(6-(azetidin-1-yl)pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl)-2,7-diazaspiro[4.5]decan-8-one;

(1-(6-fluoro-7-methoxy-2-(6-(methyl(2-(methylamino)ethyl)amino)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol;

(1-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol;

[1-[7-(dimethylamino)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol;

[1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol;

[1-[6-fluoro-2-[4-[2-(methylamino)ethoxy]phenyl]-7-(trideuteriomethoxy)-4-quinolyl]pyrrolidin-3-yl]methanol;

2-[4-[4-(2,9-diazaspiro[4.5]decan-2-yl)-6-fluoro-7-(trideuteriomethoxy)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[4-[6-fluoro-7-methoxy-4-(9-methyl-2,9-diazaspiro[4.5]decan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

5-[7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-N,N-dimethyl-pyridin-2-amine;

7-[7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]-2-oxa-7-azaspiro[3.4]octane;

[1-[6-fluoro-7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol;

[1-[7-chloro-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol;

2-[2-[6-(dimethylamino)-3-pyridyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-(2-(4-(azetidin-3-yloxy)phenyl)-7-methoxyquinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one;

2-[4-[7-methoxy-4-(9-methyl-2,9-diazaspiro[4.5]decan-2-yl)-2-quinolyl]phenoxy]-N-methyl-acetamide;

2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.5]decan-6-one;

2-[4-[4-(2,9-diazaspiro[4.5]decan-2-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-acetamide;

[1-[7-(dimethylamino)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol;

ethyl N-[4-[3-(hydroxymethyl)pyrrolidin-1-yl]-2-[4-[2-(methylamino)ethoxy]phenyl]-7-quinolyl]carbamate;

[1-[2-(4-piperazin-1-ylphenyl)-4-quinolyl]pyrrolidin-3-yl]methanol;

[1-[7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]azetidin-3-yl]methanol;

[1-[7-[2-(dimethylamino)ethoxy]-2-(4-pyrrolidin-1-ylphenyl)-4-quinolyl]pyrrolidin-3-yl]methanol;

[1-[7-(dimethylamino)-2-[4-(methylamino)phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol;

N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine;

N,N-dimethyl-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]quinolin-7-amine;

N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-pyrrolidin-1-yl-quinolin-7-amine;

2-(4-(4-(3,3-difluoro-4-methoxypyrrolidin-1-yl)-7-methoxyquinolin-2-yl)phenoxy)-N-methylethan-1-amine;

[1-[7-(dimethylamino)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]azetidin-3-yl]methanol;

2-[[5-[7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)quinolin-7-amine;

2-[4-[7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

7-[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide;

N-methyl-2-[[5-[7-morpholino-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-2-pyridyl]oxy]ethanamine;

[1-[7-(dimethylamino)-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol;

2-(5-methoxy-2-pyridyl)-N,N-dimethyl-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine;

[1-[2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-7-morpholino-4-quinolyl]pyrrolidin-3-yl]methanol;

N,N-dimethyl-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine;

N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinolin-7-amine;

7-methoxy-4-(3-methoxypyrrolidin-1-yl)-2-(4-piperazin-1-ylphenyl)quinoline;

ethyl N-[4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[6-(methylamino)-3-pyridyl]-7-quinolyl]carbamate;

4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(6-piperazin-1-yl-3-pyridyl)quinolin-7-amine;

[1-[7-(dimethylamino)-2-(5-methoxy-2-pyridyl)-4-quinolyl]pyrrolidin-3-yl]methanol;

N-methyl-1-[1-[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]azetidin-3-yl]methanamine;

[1-[7-methoxy-2-(5-piperazin-1-yl-2-pyridyl)-4-quinolyl]pyrrolidin-3-yl]methanol;

7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(4-piperazin-1-ylphenyl)quinoline;

N,N-dimethyl-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[4-[2-(methylamino)ethoxy]phenyl]quinolin-7-amine;

N-methyl-2-[[6-[7-morpholino-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-3-pyridyl]oxy]ethanamine;

N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-[3-(trifluoromethoxy)pyrrolidin-1-yl]quinolin-7-amine;

4-(3-ethoxypyrrolidin-1-yl)-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]quinolin-7-amine;

2-[[5-[4-(3-methoxypyrrolidin-1-yl)-7-pyrrolidin-1-yl-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-[6-(2-pyrrolidin-1-ylethoxy)-3-pyridyl]quinolin-7-amine;

2-[[5-[4-(3-methoxypyrrolidin-1-yl)-7-morpholino-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

[1-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol;

7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(5-pyrrolidin-1-yl-2-pyridyl)quinoline;

2-[[5-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

4-(1,3,3a,4,5,6,7,7a-octahydropyrrolo[3,4-c]pyridin-2-yl)-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)quinoline;

6-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)octahydropyrrolo[3,4-e][1,2]thiazine 1,1-dioxide;

1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

6-fluoro-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinolin-7-amine;

N-methyl-1-[1-[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]pyrrolidin-3-yl]methanamine;

4-[3-(difluoromethoxy)pyrrolidin-1-yl]-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]quinolin-7-amine;

2-[7-methoxy-2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[[5-[7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.5]decan-6-one;

5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one;

2-[[5-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

N'-[5-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]-N,N'-dimethyl-ethane-1,2-diamine;

2-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[4-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-70methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2-[2-[4-(azetidin-1-yl)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[2-[6-(dimethylamino)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

N-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-2-quinolyl]phenyl]-2-pyrrolidin-1-yl-acetamide;

1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N,N-dimethyl-pyrrolidine-3-carboxamide;

2-[7-(dimethylamino)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

7-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2λ6-thia-7-azaspiro[4.4]nonane 2,2-dioxide;

2-[4-[4-(2,2-dioxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

6-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-2λ6-thia-6-azaspiro[3.3]heptane 2,2-dioxide;

2-[2-[4-(azetidin-3-yloxy)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[6-fluoro-7-methoxy-2-(4-pyrrolidin-3-yloxyphenyl)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

1-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

2-[6-fluoro-7-methoxy-2-[4-[pyrrolidin-3-yl]oxyphenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

7-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2λ6-thia-3,7-diazaspiro[4.4]nonane 2,2-dioxide;

6-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2-methyl-3,4,4a,5,7,7a-hexahydropyrrolo[3,4-e]thiazine 1,1-dioxide;

2-[6-fluoro-7-methoxy-2-[4-[pyrrolidin-3-yl]oxyphenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2-[4-[4-(7,7-difluoro-5-methyl-1,3,3a,4,6,7a-hexahydropyrrolo[3,4-c]pyridin-2-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[6-(2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline;

2-[6-(1,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline;

2-[6-(azetidin-3-ylmethoxy)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline;

2-[6-(azetidin-2-ylmethoxy)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline;

2-[4-(azetidin-3-yloxy)phenyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline;

6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(4-pyrrolidin-3-yloxyphenyl)quinoline;

2-[4-[6-fluoro-7-methoxy-4-(8-methyl-2,8-diazaspiro[3.5]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[4-[6-fluoro-7-methoxy-4-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[[5-[6-fluoro-7-methoxy-4-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

2-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-9-methyl-2,6,9-triazaspiro[4.5]decan-8-one;

2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6,7-difluoro-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[6,7-difluoro-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

7-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-3-methyl-2λ6-thia-3,7-diazaspiro[4.4]nonane 2,2-dioxide;

6-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-2-methyl-2,6-diazaspiro[3.4]octan-3-one;

2-[[5-[4-(7,7-difluoro-5-methyl-1,3,3a,4,6,7a-hexahydropyrrolo[3,4-c]pyridin-2-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

4-[5-(2,2-difluoroethyl)-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl]-6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)quinoline;

2-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-9-methyl-2,6,9-triazaspiro[4.5]decan-7-one;

2-[4-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenyl]sulfanyl-N-methyl-ethanamine;

6-fluoro-2-[4-(1H-imidazol-4-yloxy)phenyl]-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline;

2-[6-fluoro-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

6-fluoro-4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-[4-[2-(methylamino)ethoxy]phenyl]quinolin-7-amine;

2-[[5-(6-fluoro-7-methoxy-4-pyrrolidin-1-yl-2-quinolyl)-2-pyridyl]oxy]-N-methyl-ethanamine;

2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-pent-4-ynoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-one;

2-[4-[4-(2,3,3a,4,6,6a-hexahydrofuro[2,3-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[4-[4-(1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[[5-[4-(1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

7-[6-fluoro-2-[4-(1H-imidazol-4-yloxy)phenyl]-7-methoxy-4-quinolyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide;

5-[6-fluoro-7-methoxy-2-(4-pyrrolidin-1-ylphenyl)-4-quinolyl]-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrole 2,2-dioxide;

6-fluoro-N,N-dimethyl-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[4-[2-(methylamino)ethoxy]phenyl]quinolin-7-amine;

6-fluoro-N,N-dimethyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine;

2-[4-[6-fluoro-7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(4-piperazin-1-ylphenyl)quinoline;

6-fluoro-N,N-dimethyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinolin-7-amine;

2-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-thiopyrano[3,4-c]pyrrole 5,5-dioxide;

2-[[6-[4-(2,9-diazaspiro[4.5]decan-2-yl)-6-fluoro-7-(trideuteriomethoxy)-2-quinolyl]-3-pyridyl]oxy]-N-methyl-ethanamine;

[1-[6-fluoro-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-7-(trideuteriomethoxy)-4-quinolyl]pyrrolidin-3-yl]methanol;

2-[[5-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N,N-dimethyl-ethanamine;

2-[4-[6-fluoro-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-7-(trideuteriomethoxy)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(6-piperazin-1-yl-3-pyridyl)quinoline;

5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-2-one;

2-[[5-[4-(9,9-difluoro-7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

2-[4-[4-(9,9-difluoro-7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2-[2-[4-[2-(dimethylamino)ethoxy]phenyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N,N-dimethyl-ethanamine;

5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2-methyl-3a,4,6,6a-tetrahydro-1H-pyrrolo[3,4-c]pyrrol-3-one;

2-[2-[4-(azetidin-3-yloxy)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2,2-difluoro-N-[2-[4-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenoxy]ethyl]ethanamine;

6-fluoro-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)quinolin-7-amine;

2-[[5-[6-fluoro-7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

2-[4-[6-fluoro-7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[6-fluoro-7-methoxy-2-[4-[2-24(methylamino)ethoxy]phenyl]-4-quinolyl]-6-methyl-2,6-diazaspiro[3.5]nonan-5-one;

4,4-difluoro-7-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2-methyl-2,7-diazaspiro[4.4]nonan-1-one;

2-(4-(4-(3,3-difluoro-4-methoxypyrrolidin-1-yl)-7-methoxyquinolin-2-yl)phenoxy)-N-methylethan-1-amine;

2-[4-[6-fluoro-7-methoxy-4-(1-methyl-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrol-4-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

3-[4-[6-fluoro-7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-propan-1-amine;

2-[4-(azetidin-3-ylmethoxy)phenyl]-6-fluoro-7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinoline;

2-[4-[4-[3-[(dimethylamino)methyl]pyrrolidin-1-yl]-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[2-[4-(azetidin-3-ylmethoxy)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

1-[5-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]pyrrolidin-3-ol;

2-[6-fluoro-7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2-[4-[4-[5-(2,2-difluoroethyl)-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl]-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[[5-[7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine;

2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-7-methyl-2,7-diazaspiro[4.4]nonan-8-one;

2-[4-[7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

7-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-1-one;

2-[4-[4-(3,3-difluoropyrrolidin-1-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[4-[7-methoxy-4-(3-methyl-2,2-dioxo-2λ6-thia-3,7-diazaspiro[4.4]nonan-7-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[4-[4-(1,3-dimethyl-2,2-dioxo-2λ6-thia-3,7-diazaspiro[4.4]nonan-7-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[6-fluoro-7-methoxy-2-[4-(2-methoxyethoxy)phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[6-fluoro-7-methoxy-2-[4-[2-(trideuteriomethoxy)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]-N-methyl-acetamide;

2-[2-[4-[2-(dimethylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-8-one;

2-[2-[4-(azetidin-3-yloxy)phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[7-methoxy-2-[4-[pyrrolidin-3-yl]oxyphenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

N-methyl-2-[4-[7-morpholino-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]ethanamine;

2-[2-[4-[2-(methylamino)ethoxy]phenyl]-7-(trideuteriomethoxy)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]-N-methyl-acetamide;

2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-8-one;

2-[2-[4-[2-(cyclopropylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[4-[7-methoxy-4-(3-methoxypyrrolidin-1-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[7-ethoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

7-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-1-one;

1-[[4-[4-(5-azaspiro[2.4]heptan-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]methyl]-N-methyl-cyclopropanamine;

2-[7-methoxy-2-[4-[[1-(methylamino)cyclopropyl]methoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

2-[7-chloro-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

1-[4-[7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenyl]pyrrolidin-3-ol;

2-[7-methyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[7-cyclopropyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-2-one;

2-[2-[4-[3-hydroxypyrrolidin-1-yl]phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

6-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,4,4a,5,7,7a-hexahydro-1H-pyrrolo[3,4-b]pyridin-2-one;

7-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,7-diazaspiro[4.4]nonan-2-one;

2-[7-(2-methoxyethoxy)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-7-ol;

2-[7-(difluoromethoxy)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[4-[7-methoxy-4-[3-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[4-[4-(3,3-difluoro-4-methoxy-pyrrolidin-1-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[4-[7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N,N-dimethyl-ethanamine;

2-[8-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[4-[4-[3-[(dimethylamino)methyl]pyrrolidin-1-yl]-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

7-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3-methyl-1,7-diazaspiro[4.4]nonan-2-one;

2-[7-methoxy-2-[4-[3-(methylamino)propoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

2-[7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

3a-fluoro-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,5,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one;

5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-2-one;

5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one;

2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-8-one;

3-[4-[7-methoxy-4-(1-methyl-1,7-diazaspiro[4.4]nonan-7-yl)-2-quinolyl]phenoxy]-N-methyl-propan-1-amine;

2-(7-methoxy-2-(4-(piperazin-1-yl)phenyl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one;

N-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)acetamide;

6-fluoro-7-methoxy-4-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-2-(6-(pyrrolidin-1-yl)pyridin-3-yl)quinoline;

4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(5-(2-(methylamino)ethoxy)pyridin-2-yl)quinolin-7-amine;

6-(7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)-2-thia-6-azaspiro[3.4]octane 2,2-dioxide;

2-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)-N-methylacetamide;

ethyl (1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)carbamate;

2-(7-methoxy-2-(6-(2-(methylamino)ethoxy)pyridin-3-yl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one;

6-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-2-thia-6-azaspiro[3.4]octane 2,2-dioxide;

1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidine-3-carbonitrile;

1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-N,N-dimethylpyrrolidine-3-carboxamide;

1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl methylcarbamate;

2-(4-(7-methoxy-4-(3-((methylamino)methyl)pyrrolidin-1-yl)quinolin-2-yl)phenoxy)-N-methylethan-1-amine;

5-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)hexahydro-1H-thieno[3,4-c]pyrrole 2,2-dioxide;

2-(dimethylamino)-N-(4-(7-methoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)acetamide;

2-(2-(4-(2-(1H-pyrazol-1-yl)ethoxy)phenyl)-7-methoxyquinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one;

1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-N,N-dimethylpyrrolidin-3-amine;

6-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-2-thia-6-azaspiro[3.3]heptane 2,2-dioxide;

5-(6-fluoro-7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)hexahydropyrrolo[3,4-b]pyrrol-2(1H)-one;

2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

6-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2-methyl-2,6-diazaspiro[3.4]octan-3-one;

2-[4-[7-methoxy-4-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine;

2-[7-methoxy-2-(5-methoxy-2-pyridyl)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one;

N-[[1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methyl]-N-methyl-acetamide;

2-[[6-[4-(2,9-diazaspiro[4.5]decan-2-yl)-6-fluoro-7-methoxy-2-quinolyl]-3-pyridyl]oxy]-N-methyl-ethanamine;

N-[1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanesulfonamide;

1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N,3-dimethyl-pyrrolidine-3-carboxamide;

2-(7-methoxy-2-(4-(2-(methylamino)cyclopropoxy)phenyl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one;

2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,6-diazaspiro[3.4]octan-5-one;

2-[[1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]amino]etanol;

1-(7-methoxy-2-(4-(3-(methylamino)cyclobutoxy)phenyl)quinolin-4-yl)-N-methylpyrrolidine-3-carboxamide;

2-[4-[7-methoxy-4-[3-(methylaminomethyl)azetidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine;

N-methyl-2-[4-[4-[3-(methylaminomethyl)azetidin-1-yl]-2-quinolyl]phenoxy]ethanamine;

1-[7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

6-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,4,4a,5,7,7a-hexahydro-1H-pyrrolo[3,4-b]pyridin-2-one;

1-[7-methoxy-2-[4-[3-(methylamino)propyl]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[2-[4-[2-(dimethylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

[1-[7-(dimethylamino)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol;

1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-sulfonamide;

1-[4-[4-[3-[(dimethylamino)methyl]pyrrolidin-1-yl]-7-methoxy-2-quinolyl]phenoxy]-3-(methylamino)propan-2-ol;

5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one;

N-ethyl-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidine-3-carboxamide;

2-[4-[7-methoxy-4-[3-morpholinopyrrolidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine;

N-(2-methoxyethyl)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidine-3-carboxamide;

N-cyclopropyl-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidine-3-carboxamide;

1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-azetidine-3-carboxamide;

2-[4-[4-(2,2-dioxo-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c][1,2,5]thiadiazol-5-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine;

1-[2-[4-(3,3-difluorobutoxy)phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

4-(hydroxymethyl)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-ol;

1-[7-methoxy-2-[4-(3,3,3-trifluoropropoxy)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[7-methoxy-2-(4-morpholinophenyl)-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]ethanone;

1-[7-methoxy-2-[4-(2-methoxyethylamino)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

6-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,4,4a,5,7,7a-hexahydropyrrolo[3,4-d][1,3]oxazin-2-one;

1-[7-cyclopropyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[7-(dimethylamino)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[7-methoxy-2-[4-(2-methylsulfinylethoxy)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[7-methoxy-2-[4-[2-methoxyethyl(methyl)amino]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[7-methoxy-6-methyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[6-cyclopropyl-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[2-[4-[2-(cyclopropylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[7-methoxy-2-[4-[2-(2-methoxyethylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[7-methoxy-2-[4-(2-morpholinoethoxy)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

N-methyl-1-[2-[4-[2-(methylamino)ethoxy]phenyl]-7-(trideuteriomethoxy)-4-quinolyl]pyrrolidine-3-carboxamide;

2-[4-[7-methoxy-4-[3-[methylsulfinyl]pyrrolidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine;

5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one;

1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

2-[4-[4-(2,2-dioxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrol-5-yl)-7-methoxy-2-quinolyl]phenoxy]-N,N-dimethyl-ethanamine;

7-[7-methoxy-2-(4-methoxyphenyl)-4-quinolyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide;

1-[2-[4-[2-(isopropylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[2-[4-[2-hydroxyethyl(methyl)amino]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[2-[4-[2-(isobutylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

1-[7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide;

2-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-2,6-diazaspiro[3.5]nonan-5-one;

5-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)hexahydro-1H-pyrrolo[3,4-c]isothiazole 2,2-dioxide;

1-(7-methoxy-2-(4-(2-(methylamino)propoxy)phenyl)quinolin-4-yl)-N-methylpyrrolidine-3-carboxamide;

4-(hydroxymethyl)-1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-ol;

2,2,2-trifluoro-1-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)-N-methylethan-1-amine;

2,2,2-trifluoro-1-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)-N-methylethan-1-amine;

N-(2-hydroxyethyl)-1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidine-3-carboxamide;

5-(2-(4-(3-hydroxypyrrolidin-1-yl)phenyl)-7-methoxyquinolin-4-yl)hexahydro-1H-thieno[3,4-c]pyrrole 2,2-dioxide;

2-(4-(7-methoxy-4-(3-methoxypyrrolidin-1-yl)quinolin-2-yl)phenoxy)-N-(trifluoromethyl)ethan-1-amine;

7-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-2-thia-3,7-diazaspiro[4.4]nonane 2,2-dioxide;

1-(4-(7-methoxy-4-(3-methoxypyrrolidin-1-yl)quinolin-2-yl)phenoxy)-3-(methylamino)propan-2-ol; and

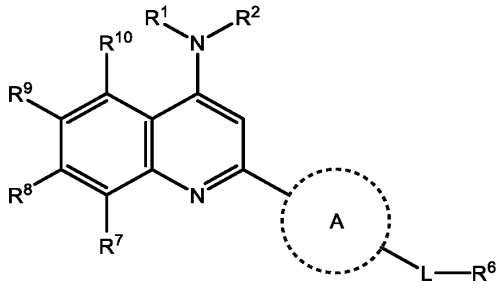
2-(4-(7-methoxy-4-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)-N-methylethan-1-amine.

PHARMACEUTICAL COMPOSITIONS

[0113] Provided herein are pharmaceutical compositions comprising a compound of formula (I), or any variation or embodiment thereof or a stereoisomer or tautomer thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (IV), or (IV-A), or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, as described elsewhere herein. In some embodiments, provided herein is a pharmaceutical composition comprising (i) a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (IV), or (IV-A), or a pharmaceutically acceptable salt, hydrate, or solvate of

any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients. In another variation, provided herein is a pharmaceutical composition comprising (i) a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (IV), or (IV-A), or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients. In some embodiments, the composition comprises a therapeutically effective amount of the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In some embodiments, the composition comprises a therapeutically effective amount of the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0114] In some embodiments, provided herein are pharmaceutical compositions comprising (i) a compound of formula (I),



(I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, and (ii) one or more pharmaceutically acceptable excipients, wherein

R^1 and R^2 are taken together with the N to which they are attached to form a saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 10-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl, wherein

the saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 9-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl is optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, oxo, $-OR^{12}$, $-N(R^x)(R^y)$, or $-C(=O)N(R^{13})(R^{14})$, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a};

Ring A is 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 8-membered unsaturated heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, or $-OR^{12}$;

L is a bond, C_{1-6}alkyl, -O-(C_{1-6}alkyl)-, -S-(C_{1-6}alkyl)-, or -N(R^5)(C_{1-6}alkyl)-;

R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, or $-OR^{12}$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is $-OR^{12}$, -O-(3- to 12-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, -C(=O)(C_{1-6}alkyl)$N(R^x)(R^y)$, $-C(=O)N(R^{13})(R^{14})$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, -($C_{3-8}$cycloalkyl)$N(R^x)(R^y)$, or 3- to 8-membered N-containing heterocyclyl, wherein

the -O-(3- to 8-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), or 3- to 8-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 8-membered N-containing heterocyclyl of R^6 optionally further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7 is H or halo;

R^8 and R^9 are each independently H, halo, C_{1-6}alkyl, $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(O)R^{14}$, $-N(R^{13})C(O)OR^{14}$, $-N(R^{13})C(O)N(R^{13})R^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{14}$, $-OC(O)N(R^{13})R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^8 or R^9 is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl of R^8 is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^8 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

R^{10} is H;

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently $-OR^{12}$ or $-N(R^x)(R^y)$;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, or $-N(R^x)(R^y)$, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H or C_{1-6}alkyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, $-O(C_{1-6}$alkyl), or $-N(R^x)(R^y)$;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, $-O(C_{1-6}$alkyl), -SH, $-S(C_{1-6}$alkyl), $-(C=O)NH_2$, -(C=O)OH, $-O(C=O)C_{1-8}$alkyl), $-NH(C=NH)NH_2$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the 6- to 10-membered aryl of R^{14} is optionally substituted by -OH, and

the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, -OH, or $-N(R^x)(R^y)$;

each R^{15} is independently H or C_{1-6}alkyl; and

each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, $-C(=O)(C_{1-6}$alkyl), or $-C(=O)O(C_{1-6}$alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with halo, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, $-NH_2$, $NH(C_{1-6}$alkyl), or $-N(C_{1-6}$alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of $-C(=O)(C_{1-6}$alkyl) or $-C(=O)O(C_{1-6}$alkyl) is optionally substituted with $-O(C=O)C_{1-8}$alkyl), wherein

when Ring A is phenyl, then $-L-R^6$ is not $-NH_2$ or $-OCH_3$.

[0115] Suitable pharmaceutically acceptable excipients may include, for example, fillers, diluents, sterile aqueous solutions and various organic solvents, permeation enhancers, solubilizers, and adjuvants. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating,

compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Examples of suitable excipients are well-known to those skilled in the art. See, *e.g.*, *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press (2017), which is incorporated herein by reference in its entirety. Such compositions are prepared in a manner well known in the pharmaceutical art. *See*, *e.g.*, *Remington's Pharmaceutical Sciences*, Academic Press, 23rd ed. (2020), which is incorporated herein by reference in its entirety.

METHODS OF TREATMENT

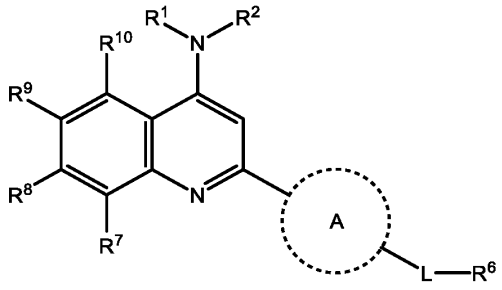
[0116] Traumatic brain injury (TBI) is a risk factor for ALS as demonstrated by the significantly higher incidence of disease in professional athletes and military veterans [See, *e.g.*, Lehman *et al. Neurology 79,* 1970-1974 (2012); McKee *et al. J. Neuropathol. Exp. Neurol.* 69, 989-929 (2010); Chio *et al. Brain* 128, 472-476 (2005), and Sagiraju *et al. Mil. Med.* 185 e501-e509 (2020), each of which is incorporated herein by reference in its entirety]. Cytoplasmic accumulation of TDP-43 has been shown in ~80% brains of patients with repeated head traumas [McKee *et al. J. Neuropathol. Exp. Neurol.* 69, 989-929 (2010), which is incorporated herein by reference in its entirety]. TDP-43 proteinopathy and loss-of-function has been shown to be a driver of neurodegeneration and pathology in preclinical models of brain injury and ALS [Lai *et al. Cell Stem Cell* 31, 519-536 (2024); Dogan *et al. Acta Neuropathol Commun* 11, 206 (2023); and *Kahriman et al. Brain* 146, 5139-5152 (2023), each of which is incorporated herein by reference in its entirety]. Neurofilament light chain (NfL) and glial fibrillary acid protein (GFAP) are prognostic neurodegeneration biomarkers for both TBI [Shahim *et al. Neurology* 95, e610-e622 (2020); Shahim *et al. Sci Rep* 6, 36791 (2016) and Abdelhak *et al. Nat Rev Neuro* 18, 158-172 (2022), each of which is incorporated herein by reference in its entirety] and ALS [Lu *et al. Neurology* 84, 2247-2257); and Benninger *et al. J Clin Neurosci* 26, 75-78 (2016), each of which is incorporated herein by reference in its entirety].

[0117] In one aspect, provided is a method for treating a disease or condition mediated by TDP-43, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or

embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, provided is a method for treating a disease or condition mediated by TDP-43, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, a therapeutically effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients is administered. In some embodiments, a therapeutically effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients is administered. In some embodiments, the methods selectively modulate TDP-43. In some embodiments, the methods reduce TDP-43 cytoplasmic inclusions, improve nuclear TDP-43 function, or reduce neurodegeneration. In some embodiments, the methods reduce TDP-43 cytoplasmic inclusions. In some embodiments, the methods improve nuclear TDP-43 function. In some embodiments, the methods reduce neurodegeneration. In some embodiments, the methods mitigate TDP-43 cytoplasmic

condensates in motor neurons. In some embodiments, the motor neurons are iPSC-derived motor neurons. In some embodiments, *STMN2* and *POLDIP3* splicing in iPSC-derived motor neurons is restored.

[0118] In some embodiments, provided herein is a method for treating a disease or condition mediated by TDP-43, comprising administering to an individual in need thereof a compound of formula (I),



(I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of formula (I) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein

R^1 and R^2 are taken together with the N to which they are attached to form a saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 10-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl, wherein

the saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 9-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl is optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, oxo, $-OR^{12}$, $-N(R^x)(R^y)$, or $-C(=O)N(R^{13})(R^{14})$, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a};

Ring A is 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 8-membered unsaturated heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, or $-OR^{12}$;

L is a bond, C_{1-6}alkyl, $-O-(C_{1-6}$alkyl$)-$, $-S-(C_{1-6}$alkyl$)-$, or $-N(R^5)(C_{1-6}$alkyl$)-$;

R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, or $-OR^{12}$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is $-OR^{12}$, -O-(3- to 12-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-C(=O)N(R^{13})(R^{14})$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, $-(C_{3-8}cycloalkyl)N(R^x)(R^y)$, or 3- to 8-membered N-containing heterocyclyl, wherein

the -O-(3- to 8-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), or 3- to 8-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 8-membered N-containing heterocyclyl of R^6 optionally further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7 is H or halo;

R^8 and R^9 are each independently H, halo, C_{1-6}alkyl, $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(O)R^{14}$, $-N(R^{13})C(O)OR^{14}$, $-N(R^{13})C(O)N(R^{13})R^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{14}$, $-OC(O)N(R^{13})R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^8 or R^9 is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl of R^8 is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^8 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

R^{10} is H;

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently $-OR^{12}$ or $-N(R^x)(R^y)$;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, or $-N(R^x)(R^y)$, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H or C_{1-6}alkyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, -$O(C_{1-6}$alkyl), or -$N(R^x)(R^y)$;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, -$O(C_{1-6}$alkyl), -SH, -$S(C_{1-6}$alkyl), -$(C=O)NH_2$, -(C=O)OH, -$O(C=O)C_{1-8}$alkyl), -$NH(C=NH)NH_2$, -$N(R^x)(R^y)$, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the 6- to 10-membered aryl of R^{14} is optionally substituted by -OH, and

the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, -OH, or -$N(R^x)(R^y)$;

each R^{15} is independently H or C_{1-6}alkyl; and

each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -$C(=O)(C_{1-6}$alkyl), or -$C(=O)O(C_{1-6}$alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with halo, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -NH_2, $NH(C_{1-6}$alkyl), or -$N(C_{1-6}$alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of -$C(=O)(C_{1-6}$alkyl) or -$C(=O)O(C_{1-6}$alkyl) is optionally substituted with -$O(C=O)C_{1-8}$alkyl), wherein

when Ring A is phenyl, then -L-R^6 is not -NH_2 or -OCH_3.

[0119] In some embodiments, the disease or condition is a neurological disease or condition. In some embodiments, the disease or condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), frontotemporal dementia (FTD), inclusion body myositis, Perry syndrome, corticobasal degeneration, spinocerebellar ataxia type 3, and amyotrophic lateral sclerosis (ALS).

[0120] In some embodiments, the disease or condition is traumatic brain injury (TBI).

[0121] In some embodiments, the disease or condition is frontotemporal dementia (FTD).

[0122] In some embodiments, the disease or condition is amyotrophic lateral sclerosis (ALS). In some variations, the amyotrophic lateral sclerosis is sporadic amyotrophic lateral sclerosis or C9ORF72 amyotrophic lateral sclerosis.

[0123] In some embodiments, the individual is a human.

[0124] In one aspect, provided herein is a method of reducing neurodegeneration, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, provided herein is a method of reducing neurodegeneration, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, the individual has a neurological disease or condition. In some embodiments, the individual has a disease or condition selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), frontotemporal dementia (FTD), inclusion body myositis, Perry syndrome, corticobasal degeneration, spinocerebellar ataxia type 3, and amyotrophic lateral sclerosis (ALS). In some embodiments, the individual has frontotemporal dementia (FTD). In some embodiments, the individual has a traumatic brain injury or ALS. In some embodiments, the individual has a traumatic brain injury. In some embodiments, the individual has ALS. In some variations, the amyotrophic lateral sclerosis is sporadic amyotrophic lateral sclerosis or C9ORF72 amyotrophic lateral sclerosis.

[0125] In one aspect, provided herein is a method of reducing neurodegeneration from traumatic brain injury, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a

pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, provided herein is a method of reducing neurodegeneration from traumatic brain injury, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0126] In one aspect, provided herein is a method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, provided herein is a method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, modulating TDP-43 comprises modulating TDP-43 incorporation into condensates, modulating TDP-43 binding to RNA in condensates, modulating TDP-43 aggregation, or modulating TDP43 protein-protein interactions. In some

embodiments, modulating TDP-43 comprises modulating TDP-43 incorporation into condensates. In some embodiments, modulating TDP-43 comprises modulating TDP-43 binding to RNA in condensates. In some embodiments, modulating TDP-43 comprises modulating TDP-43 aggregation. In some embodiments, modulating TDP-43 comprises modulating TDP43 protein-protein interactions. In some embodiments, modulating TDP-43 comprises mitigating TDP-43 interaction to RNA condensates, mitigating TDP-43 aggregation, or mitigating TDP-43 protein-protein interactions. In some embodiments, modulating TDP-43 comprises mitigating TDP-43 interaction to RNA condensates. In some embodiments, modulating TDP-43 comprises mitigating TDP-43 aggregation. In some embodiments, modulating TDP-43 comprises mitigating TDP-43 protein-protein interactions.

[0127] In one aspect, provided herein is a method of directly modulating TDP-43, comprising contacting a cell with an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, provided herein is a method of directly modulating TDP-43, comprising contacting a cell with an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, the methods selectively modulate TDP-43. In some embodiments, the methods reduce TDP-43 cytoplasmic inclusions, improve nuclear TDP-43 function, or reduce neurodegeneration. In some embodiments, the methods reduce TDP-43 cytoplasmic inclusions. In some embodiments, the methods improve nuclear TDP-43 function. In some embodiments, the methods reduce neurodegeneration. In some embodiments, the methods mitigate TDP-43 cytoplasmic condensates in motor neurons. In some embodiments, the motor neurons are iPSC-derived

motor neurons. In some embodiments, *STMN2* and *POLDIP3* splicing in iPSC-derived motor neurons is restored.

[0128] In one aspect, provided herein is a method of modulating TDP-43 driven gene expression levels, comprising contacting a cell with an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, provided herein is a method of modulating TDP-43 driven gene expression levels, comprising contacting a cell with an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, the gene expression levels are for *STMN2* or *POLDIP3*. In some embodiments, the gene expression levels are for *STMN2*. In some embodiments, the gene expression levels are for *POLDIP3*. In some embodiments, the methods selectively modulate TDP-43. In some embodiments, the methods reduce TDP-43 cytoplasmic inclusions, improve nuclear TDP-43 function, or reduce neurodegeneration. In some embodiments, the methods reduce TDP-43 cytoplasmic inclusions. In some embodiments, the methods improve nuclear TDP-43 function. In some embodiments, the methods reduce neurodegeneration. In some embodiments, the methods mitigate TDP-43 cytoplasmic condensates in motor neurons. In some embodiments, the motor neurons are iPSC-derived motor neurons. In some embodiments, *STMN2* and *POLDIP3* splicing in iPSC-derived motor neurons is restored.

[0129] In one aspect, provided herein is a compound of formula (I), or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically

acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I), or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients, for use in the treatment of a disease or condition mediated by TDP-43. In some embodiments, provided herein is a compound of formula (I), or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I), or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients, for use in the treatment of a disease or condition mediated by TDP-43.

[0130] In one aspect, provided herein is the use of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients, in the manufacture a medicament for the treatment of a disease or condition mediated by TDP-43. In some embodiments, provided herein is the use of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients, in the manufacture a medicament for the treatment of a disease or condition mediated by TDP-43.

KITS

[0131] The present disclosure further provides kits for carrying out the methods disclosed herein. The kits may comprise a compound, or stereoisomer or tautomer thereof, or pharmaceutically acceptable salt, hydrate, or solvate thereof as described herein and suitable packaging. The kits may comprise one or more containers comprising any compound described herein. In one aspect, a kit includes a compound of the disclosure or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and a label and/or instructions for use of the compound in the treatment of a disease or disorder described herein. The kits may comprise a unit dosage form of the compound. In some embodiments, the kits may comprise a compound, or stereoisomer or tautomer thereof, or pharmaceutically acceptable salt thereof.

[0132] Provided herein are kits, comprising (i) an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and (ii) instructions for use in treating a TDP-43 mediated disease, disorder, or condition in an individual in need thereof. In some embodiments, the kits comprise (i) a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) instructions for use in treating a TDP-43 mediated disease, disorder, or condition in an individual in need thereof. In some embodiments, the kits comprise (i) an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) instructions for use in treating a TDP-43 mediated disease, disorder, or condition in an individual in need thereof. Also provided herein are kits, comprising (i) a pharmaceutical composition comprising an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients; and (ii) instructions for use in treating a TDP-43 mediated disease, disorder, or condition in an individual in need thereof. In some embodiments, the kits comprise (i) a

pharmaceutical composition comprising an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients; and (ii) instructions for use in treating a TDP-43 mediated disease, disorder, or condition in an individual in need thereof.

[0133] In some embodiments, the individual is a human.

[0134] Articles of manufacture are also provided, wherein the article of manufacture comprises a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, in a suitable container. In some embodiments, the article of manufacture comprises a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in a suitable container. Also provided herein are articles of manufacture, comprising a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, in a suitable container. In some embodiments, the articles of manufacture comprise a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (II-D), (II-D-1), (II-D-2), (III), (III-A), (III-B), (IV), or (IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in a suitable container. The container may be a vial, jar, ampoule, preloaded syringe, or intravenous bag.

METHODS OF PREPARING

[0135] The present disclosure further provides processes for preparing the compounds of present invention. In some aspects, provided herein are processes of preparing a compound of formula (I), or any variation or embodiment thereof or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In some embodiments, provided herein are processes of preparing a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically

acceptable salt of any of the foregoing. In some embodiments, provided herein are processes of preparing a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof.

[0136] The following synthetic reaction schemes, which are detailed in the Schemes and Examples, are merely illustrative of some of the methods by which the compounds of the present disclosure, or an embodiment or aspect thereof, can be synthesized. Various modifications to these synthetic reaction schemes can be made, as will be apparent to those of ordinary skill in the art.

[0137] As depicted in the Schemes and Examples below, in certain exemplary embodiments, compounds of formula (I), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, are prepared according to the general procedures. The general methods below, and other methods known to synthetic chemists of ordinary skill in the art, can be applied to all formulae, embodiments, and species described herein.

[0138] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including, but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

[0139] Although certain exemplary embodiments are depicted and described herein, the compounds of the present disclosure, or any variation or embodiment thereof, may be prepared using appropriate starting materials according to the methods described generally herein and/or by methods available to one of ordinary skill in the art.

[0140] All the products generated from the following reactions can be isolated and purified employing standard techniques, such as extraction, prep-TLC, ion exchange chromatography, chromatography on silica gel, prep-HPLC. Specific purification steps and methods were set up and will be referred to in the text as follows.

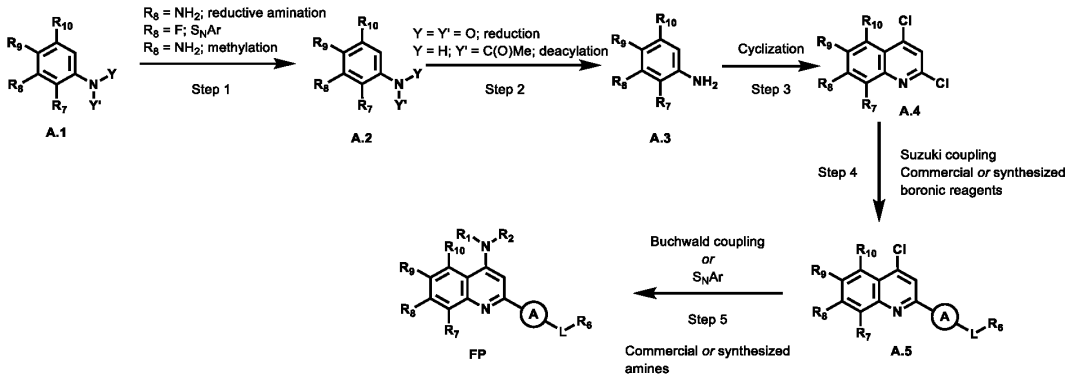
[0141] Compounds may be prepared by methods known in the art of organic chemistry as set forth in part by the following synthesis schemes. In all the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P.G.M. Wuts (1991) *Protecting Groups in Organic Synthesis*, John Wiley et Sons, hereby incorporated by reference in its entirety). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art.

The compound may be represented as a mixture of enantiomers, which may be resolved into the individual pure R- or S-enantiomers.

[0142] Commercial nitrobenzene and aniline were used as starting material **A.1** (Schemes 1, 2, 3 and 4) for the synthesis of 6,7-disubstituted 2,4-dichloroquinoline **A.4**. Commercial materials were used as such for cyclization step (step 3) to form the quinolines **A.4** or underwent two former steps: a first step to further substitute compound **A.1** in position 3 by reductive amination, aromatic nucleophilic substitution, or methylation to get **A.2**, and a second step for the reduction of nitro-groups or deacylation of methylamide to get the free aniline **A.3**. The derivative 2,4-dichloroquinoline **A.4** was then formed by cyclization of **A.3** with malonic acid in phosphoryl chloride.

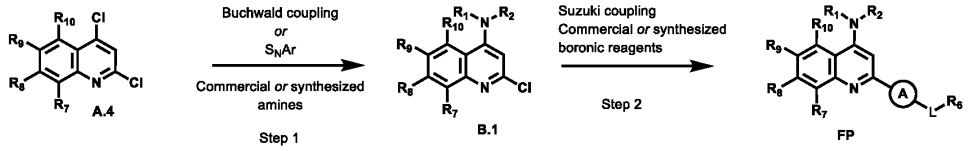
[0143] The 2,4-dichloroquinoline **A.4** underwent a Suzuki cross coupling with commercially available or synthesized boronic ester reagents (Scheme 1). Quinolines **A.4** were selectively substituted in position 2 to give compounds **A.5**. The substitution of position 4 of compound **A.5** was realized by Buchwald cross coupling or by aromatic nucleophilic substitution with commercial or synthesized amines and allowed the formation of **FP** (Final Product).

SCHEME 1.



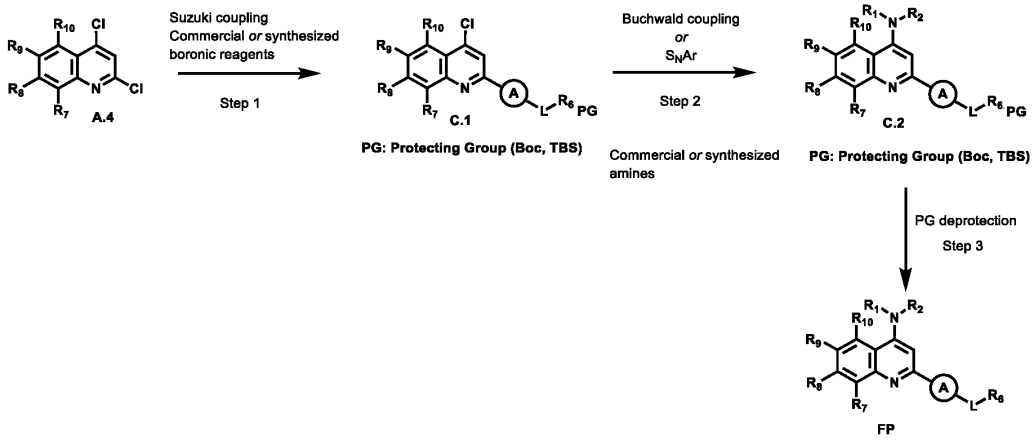
[0144] Similarly to Scheme 1, other **FP** were synthesized applying first the Buchwald coupling or the nucleophilic aromatic substitution of position 4 of quinolines **A.4** to give derivatives **B.1** (Scheme 2). This step was then followed by a Suzuki coupling to give **FP**.

SCHEME 2.



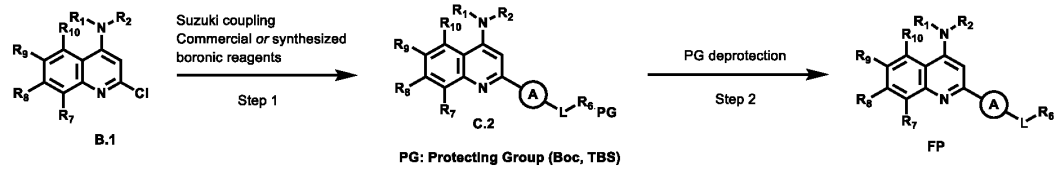
[0145] In some cases, the substituted (hetero)aromatic ring added during the Suzuki coupling on quinolines **A.4** contains a **PG** (Protecting Group, Schemes 3 and 4). In these cases, **FP** were obtained after an additional step of deprotection. Scheme 3 describes the synthetic sequence similar to Scheme 1, with a Suzuki cross coupling realized first on quinolines **A.4**, followed by the substitution of quinolines **C.1** using a Buchwald reaction or a nucleophilic aromatic substitution to give compounds **C2**. Compound **C.2** underwent then a deprotection step to give **FP**.

SCHEME 3.



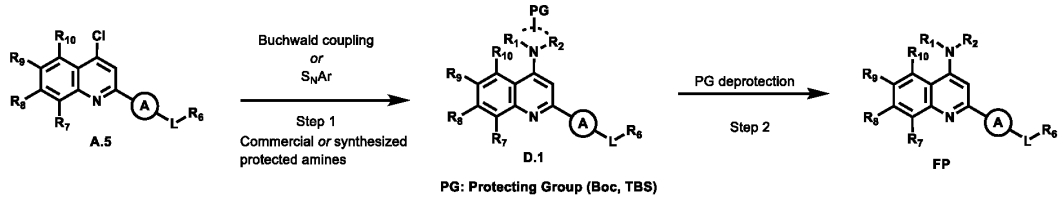
[0146] Scheme 4 describes a synthetic sequence similar to Scheme 2, where derivative **B.1** is obtained after a Buchwald or aromatic nucleophilic substitution realized on quinolines **A.4** and followed by a Suzuki cross coupling, and coupling **FP** are obtained by deprotection of compounds **C.2**.

SCHEME 4.



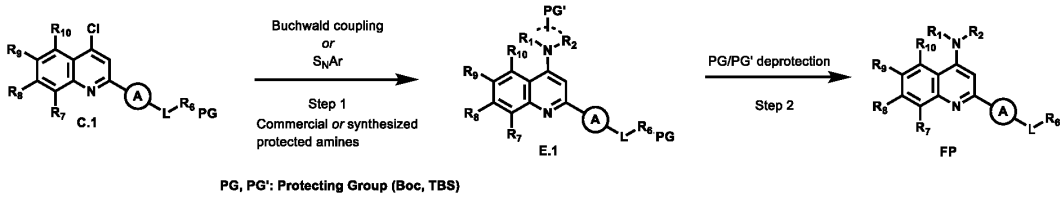
[0147] Scheme 5 describes a synthetic sequence where **A.5** was obtained following Scheme 1 and where the Buchwald coupling reaction is done with an opened or cyclized amine linked to a **PG**. to get **D.1** intermediates. **FP** is obtained after an additional step of deprotection.

SCHEME 5.



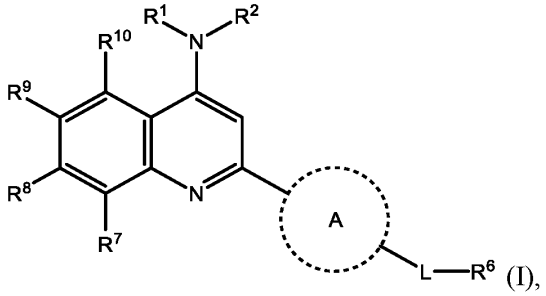
[0148] Scheme 6 describes a synthetic sequence where an opened or cyclized amine used for the Buchwald coupling or aromatic substitution on **C.1**, obtained from Scheme 3, held a protecting group PG' to get compound **E.1**. Compound **E.1** is then fully deprotected to give **FP**.

SCHEME 6.



Enumerated Embodiments

[0149] Enumerated Embodiment 1. A compound of formula (I):



(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

R^1 and R^2 are each independently C_{1-6}alkyl, C_{2-6}alkenyl, $-C(=O)R^{14}$, $-C(=O)OR^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl wherein

the C_{1-6}alkyl of R^1 or R^2 is optionally substituted with one or more R^{1a},

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^1 or R^2 is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C_{1-6}alkyl, C_{2-6}alkenyl, $-C(=O)R^{14}$, $-C(=O)OR^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or C_{3-8}cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1b};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein

the 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of R^1 and R^2 is optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, oxo, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with one or more R^{3a}, and

optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b};

Ring A is 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 4- to 12-membered cycloalkenyl, 4- to 12-membered unsaturated heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 12-membered unsaturated heterocyclyl or 5- to 10-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^4 is optionally substituted by one or more R^{4a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^4 is optionally substituted with one or more R^{4b}, and

the 3- to 8-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

L is a bond, C_{1-6}alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^5)(C_{1-6}alkyl)-$, wherein

the C_{1-6}alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^5)(C_{1-6}alkyl)-$ is optionally substituted by one or more R^L;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a C_{3-8}cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-C(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, or $-S(=O)_2N(R^{13})(R^{14})$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^6 is optionally substituted by one or more R^{6a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 8-membered heterocyclyl of R^6 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^6 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{6b};

R^7, R^8, R^9, and R^{10} are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{11}$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^7, R^8, R^9, or R^{10} is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^7, R^8, R^9, or R^{10} is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^7, R^8, R^9, or R^{10} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^7, R^8, R^9, or R^{10} are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=NR^{15})R^{14}$, $-S(=NR^{15})N(R^{13})R^{14}$, $-S(=NR^{15})OR^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, $-N(R^x)(R^y)$, oxo, -CN, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;

each R^{11} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^{11} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, or $-N(R^x)(R^y)$, and

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{11} is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, C_{1-6}alkoxy, -$N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, -O(C_{1-6}alkyl), -SH, -S(C_{1-6}alkyl), -(C=O)NH_2, -(C=O)OH, -O(C=O)C_{1-8}alkyl), -NH(C=NH)NH_2, -$N(R^x)(R^y)$, C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the 6- to 10-membered aryl is optionally substituted by -OH, and

the C_{3-8}cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, -OH, or -$N(R^x)(R^y)$;

each R^{15} is independently H or C_{1-6}alkyl; and

each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -C(=O)(C_{1-6}alkyl), or -C(=O)O(C_{1-6}alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -NH_2, NH(C_{1-6}alkyl), or -N(C_{1-6}alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of -C(=O)(C_{1-6}alkyl) or -C(=O)O(C_{1-6}alkyl) is optionally substituted with -O(C=O)C_{1-8}alkyl).

[0150] Enumerated Embodiment 2. The compound of Enumerated Embodiment 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

R^1 and R^2 are each independently C_{1-6}alkyl, C_{2-6}alkenyl, -C(=O)R^{14}, -C(=O)OR^{14}, -C(=O)N(R^{13})(R^{14}), or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^1 or R^2 is optionally substituted with one or more R^{1a},

the C_{3-8}cycloalkyl of R^1 or R^2 is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C_{1-6}alkyl, C_{2-6}alkenyl, -C(=O)R^{14}, -C(=O)OR^{14}, -C(=O)N(R^{13})(R^{14}), or C_{3-8}cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1b};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

Ring A is 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the 4- to 8-membered monocyclic cycloalkenyl, 4- to 8-membered unsaturated monocyclic heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 8-membered unsaturated monocyclic heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S; and

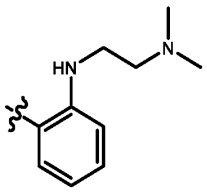
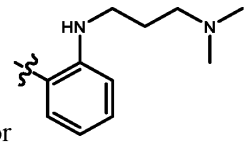
R^6 is $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)(C_{1\text{-}6}alkyl)N(R^x)(R^y)$, $-C(=O)N(R^{13})(R^{14})$, $-C(=NR^{15})N(R^{13})R^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or 3- to 12-membered N-containing heterocyclyl, wherein

the 3- to 12-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 12-membered N-containing heterocyclyl of R^6 further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

wherein

(i) when Ring A is phenyl and R^6 is selected from the group consisting of $-NH_2$, $-NHCH_3$, and $-N(CH_3)_3$, R^1 and R^2 are not both $C_{1\text{-}2}$alkyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form a 4-methylpiperazinyl, -(Ring A)-X-L-R^6 is not  or  ;

(iii) when R^1 and R^2 are taken together with the N to which they are attached to form a morpholinyl, R^6 is not selected from the group consisting of $-NH_2$, $-NHC(O)CH_3$, and $-NHC(O)O\text{-}C(CH_3)_3$; and

(iv) when Ring A is pyridin-4yl substituted with $-NHC(CH_3)$phenyl, R^1 and R^2 are not taken together with the N to which they are attached to form an optionally substituted 2,5-diazabicyclo[2.2.2]octanyl.

[0151] Enumerated Embodiment 3. The compound of Enumerated Embodiment 1 or 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

R^1 and R^2 are each independently C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^1 or R^2 is optionally substituted with one or more R^{1a},

the C_{3-8}cycloalkyl of R^1 or R^2 is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C_{1-6}alkyl, C_{2-6}alkenyl, or C_{3-8}cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1b};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, oxo, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with one or more R^{3a}, and

optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b};

each R^4 is independently halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, -

$S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^4 is optionally substituted by one or more R^{4a},

the C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^4 is optionally substituted with one or more R^{4b}, and

the 3- to 8-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

R^5 is H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, or $-S(=O)_2N(R^{13})(R^{14})$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)(C_{1-6}\text{alkyl})N(R^x)(R^y)$, $-C(=O)N(R^{13})(R^{14})$, $-C(=NR^{15})N(R^{13})R^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, or 3- to 12-membered N-containing heterocyclyl, wherein

the 3- to 12-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 12-membered N-containing heterocyclyl of R^6 further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7, R^8, R^9, and R^{10} are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-OR^{11}$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{1-6}alkyl of R^7, R^8, R^9, or R^{10} is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^7, R^8, R^9, or R^{10} is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^7, R^8, R^9, or R^{10} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R^7, R^8, R^9, or R^{10} are taken together with the atoms to which they are attached form a C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{12}$, $-SR^{12}$, $-SF_5$, $-NO_2$, -CN, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)R^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-OC(=O)OR^{14}$, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, $-C(=O)OR^{14}$, $-C(=NR^{15})R^{14}$, $-C(=NOR^{14})R^{14}$, $-C(=NR^{15})N(R^{13})R^{14}$, $-C(=NR^{15})OR^{14}$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)OR^{14}$, $-S(=O)_2R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8}cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, $-N(R^x)(R^y)$, oxo, -CN, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C_{1-6}alkyl of R^{11} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, or $-N(R^x)(R^y)$, and

the phenyl or 5- to 6-membered heteroaryl of R^{11} is optionally substituted with halo, C_{1-3}alkyl, C_{1-3}alkoxy, $-N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl;

each R^{12} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, C_{1-6}alkoxy, -$N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl;

each R^{13} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, -O(C_{1-6}alkyl), -$N(R^x)(R^y)$, C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, or -$N(R^x)(R^y)$; and

each R^{15} is independently H or C_{1-6}alkyl.

[0152] Enumerated Embodiment 4. The compound of any of Enumerated Embodiments 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

R^1 and R^2 are each independently C_{1-6}alkyl optionally substituted with one or more R^{1a};

or R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, oxo, -OR^{12}, or -$N(R^x)(R^y)$ wherein

the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a};

R^4 is halo, C_{1-6}alkyl, or -OR^{12};

L is a bond, C_{1-6}alkyl, -O-(C_{1-6}alkyl)-, -S-(C_{1-6}alkyl)-, or -$N(R^5)$(C_{1-6}alkyl)-;

R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, -$N(R^x)(R^y)$, or -OR^{12}, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is -$N(R^x)(R^y)$, -$N(R^{13})C(=O)R^{14}$, -$N(R^{13})C(=O)N(R^{13})R^{14}$, -$N(R^{13})C(=O)OR^{14}$, -$OC(=O)N(R^{13})R^{14}$, -$C(=O)$($C_{1-6}$alkyl)$N(R^x)(R^y)$, -$C(=O)N(R^{13})(R^{14})$, -$N(R^{13})S(=O)_2R^{14}$, -$S(=O)N(R^{13})R^{14}$, -$S(=O)_2N(R^{13})(R^{14})$, or 3- to 12-membered N-containing heterocyclyl, wherein

the 3- to 12-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, -$C(=O)R^{14}$, -$C(=O)N(R^{13})(R^{14})$, or -$C(=O)OR^{14}$, and

the 3- to 12-membered N-containing heterocyclyl of R^6 further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7 is H;

R^8 and R^9 are each independently H, halo, C_{1-6}alkyl, $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(O)R^{14}$, $-N(R^{13})C(O)OR^{14}$, $-N(R^{13})C(O)N(R^{13})R^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{14}$, $-OC(O)N(R^{13})R^{14}$, $-C(O)R^{14}$, $-C(O)OR^{14}$, or $-C(O)N(R^{13})(R^{14})$, wherein

the C_{1-6}alkyl of R^8 or R^9 is optionally substituted by one or more R^{7a};

R^{10} is H;

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently $-OR^{12}$ or $-N(R^x)(R^y)$;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, or $-N(R^x)(R^y)$, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

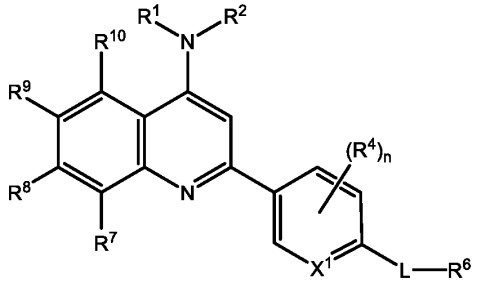
each R^{11} is independently H or C_{1-6}alkyl;

each R^{12} is independently H, C_{1-6}alkyl, or C_{3-8}cycloalkyl,

wherein the C_{1-6}alkyl is optionally substituted with one or more halo, deuterium, or $-N(R^x)(R^y)$; and

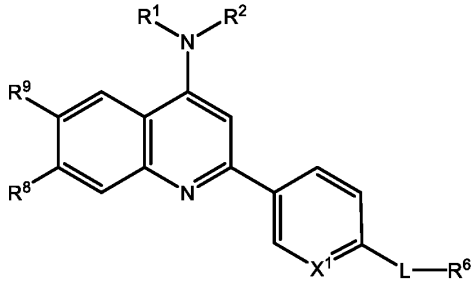
each R^{13} is independently H or C_{1-6}alkyl.

[0153] Enumerated Embodiment 5. The compound of any of Enumerated Embodiments 1-4, wherein the compound is a compound of formula (II):



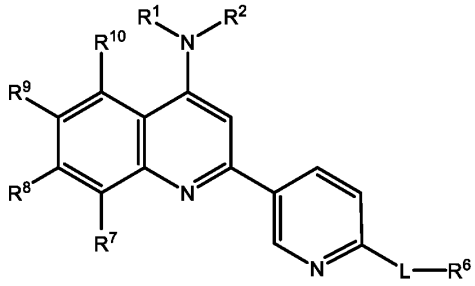
(II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^1 is N or CH, and n is 0, 1, 2, 3, or 4.

[0154] Enumerated Embodiment 6. The compound of Enumerated Embodiment 5, wherein the compound is a compound of formula (II-A):



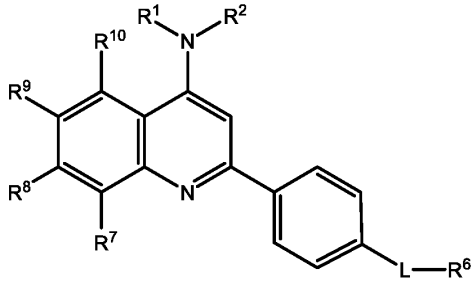
(II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing.

[0155] Enumerated Embodiment 7. The compound of Enumerated Embodiment 5, wherein the compound is a compound of formula (II-B):



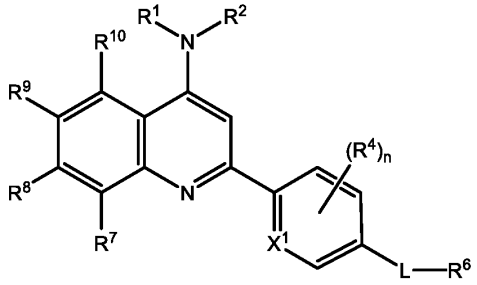
(II-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing.

[0156] Enumerated Embodiment 8. The compound of Enumerated Embodiment 5, wherein the compound is a compound of formula (II-C):



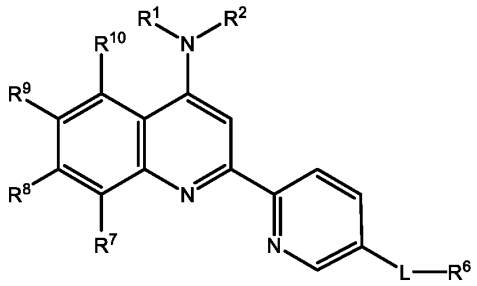
(II-C), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing.

[0157] Enumerated Embodiment 9. The compound of any of Enumerated Embodiments 1-4, wherein the compound is a compound of formula (III):



(III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^1 is N or CH; and n is 0, 1, 2, 3, or 4.

[0158] Enumerated Embodiment 10. The compound of Enumerated Embodiment 9, wherein the compound is a compound of formula (III-B):



(III-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing.

[0159] Enumerated Embodiment 11. The compound of any of Enumerated Embodiments 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3;

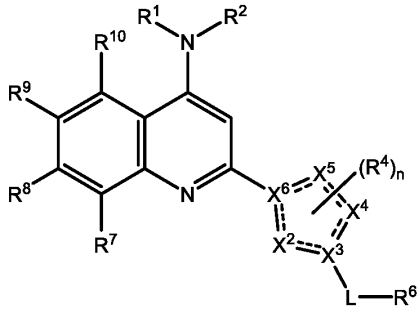
R^8 is H, halo, C_{1-6}alkyl, $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(O)R^{14}$, $-N(R^{13})C(O)OR^{14}$, $-N(R^{13})C(O)N(R^{13})R^{14}$, $-C(O)N(R^{13})(R^{14})$, or C_{3-6}cycloalkyl, wherein

the C_{1-6}alkyl of R^8 is optionally substituted by one or more R^{7a}; and

R^9 is H, halo, C_{1-6}alkyl, $-OR^{12}$, -CN, or C_{3-6}cycloalkyl, wherein

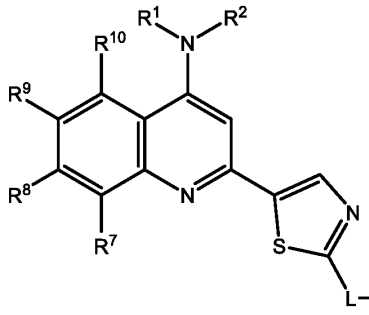
the C_{1-6}alkyl of R^9 is optionally substituted by one or more R^{7a}.

[0160] Enumerated Embodiment 12. The compound of any of Enumerated Embodiments 1-4, wherein the compound is a compound of formula (III):



(III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^2, X^4 and X^5 are each independently C, N, O or S; X^3 and X^6 are each independently C or N; and n is 0, 1, 2, or 3.

[0161] Enumerated Embodiment 13. The compound of Enumerated Embodiment 10, wherein the compound is a compound of formula (III-A):



(III-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing.

[0162] Enumerated Embodiment 14. The compound of any of Enumerated Embodiments 1-4, wherein Ring A is phenyl or 5- to 6-membered heteroaryl.

[0163] Enumerated Embodiment 15. The compound of Enumerated Embodiment 14, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein Ring A is selected from the group consisting of phenyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, furan, thiophene, oxazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

[0164] Enumerated Embodiment 16. The compound of Enumerated Embodiment 15, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein Ring A is phenyl, thiazolyl, or pyridinyl.

[0165] Enumerated Embodiment 17. The compound of any of Enumerated Embodiments 1-10, or 12-16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt,

hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are each independently C_{1-6}alkyl optionally substituted with one or more R^{1a}.

[0166] Enumerated Embodiment 18. The compound of Enumerated Embodiment 17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are each independently C_{1-4}alkyl optionally substituted with one or more R^{1a}.

[0167] Enumerated Embodiment 19. The compound of Enumerated Embodiment 17 or 18, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein each R^{1a} is independently -OH, $-NH_2$, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)(C_{1-6}alkyl), -NH(C_{3-6}cycloalkyl), or -N(C_{1-6}alkyl)(C_{3-6}cycloalkyl).

[0168] Enumerated Embodiment 20. The compound of any of Enumerated Embodiments 17-19, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein each R^{1a} is independently -OH, $-NH_2$, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)(C_{1-4}alkyl), -NH(C_{3-6}cycloalkyl), or -N(C_{1-4}alkyl)(C_{3-6}cycloalkyl).

[0169] Enumerated Embodiment 21. The compound of any of Enumerated Embodiments 17-20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein each R^{1a} is independently -OH, $-NH_2$, -NH(CH_3), -N(CH_3)(CH_3), -NH(CH_2CH_3), -N(CH_3)(CH_2CH_3), or -N(CH_2CH_3)(CH_2CH_3).

[0170] Enumerated Embodiment 22. The compound of any of Enumerated Embodiments 1-16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3, wherein

the 3- to 12-membered heterocyclyl comprises a 3- to 8-membered monocyclic heterocyclyl, a 5- to 12-membered fused heterocyclyl, or a 6- to 12-membered spirocyclic heterocyclyl.

[0171] Enumerated Embodiment 23. The compound of any of Enumerated Embodiments 1-16, or 22, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a 4- to 12-membered heterocyclyl optionally substituted with one or more R^3.

[0172] Enumerated Embodiment 24. The compound of Enumerated Embodiment 22 or 23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they

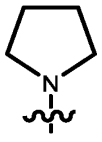
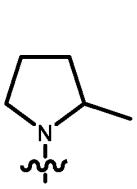
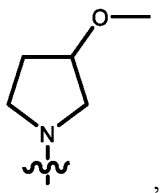
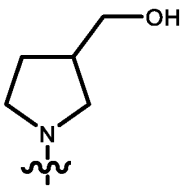
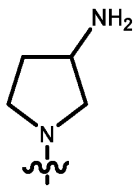
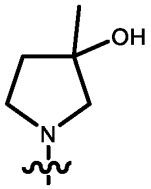
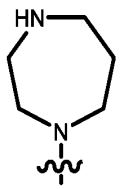
are attached to form a 4- to 7-membered monocyclic heterocyclyl optionally substituted with one or more R^3.

[0173] Enumerated Embodiment 25. The compound of any of Enumerated Embodiments 22-24, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they are attached to form a pyrrolidinyl or diazepanyl optionally substituted with one or more R^3.

[0174] Enumerated Embodiment 26. The compound of any of Enumerated Embodiments 22-25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein each R^3 is independently -OH, C_{1-6}alkyl, C_{1-6}alkoxy, or -N(R^x)(R^y) wherein the C_{1-6}alkyl of the R^3 is optionally substituted with R^{3a}.

[0175] Enumerated Embodiment 27. The compound of Enumerated Embodiment 26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein each R^3 is independently -OH, C_{1-4}alkyl, C_{1-4}alkoxy, -NH_2, -NH(C_{1-4}alkyl), -N(C_{1-4}alkyl)(C_{1-4}alkyl), -NH(C_{3-6}cycloalkyl), or -N(C_{1-4}alkyl)(C_{3-6}cycloalkyl), wherein the C_{1-4}alkyl of the R^3 is optionally substituted with R^{3a}.

[0176] Enumerated Embodiment 28. The compound of Enumerated Embodiment 27, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein each R^3 is independently -OH, -CH_3, -CH_2OH, -OCH_3, or -NH_2.

[0177] Enumerated Embodiment 29. The compound of any of Enumerated Embodiments 22-25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of  ,  ,  ,  ,  ,  , and  .

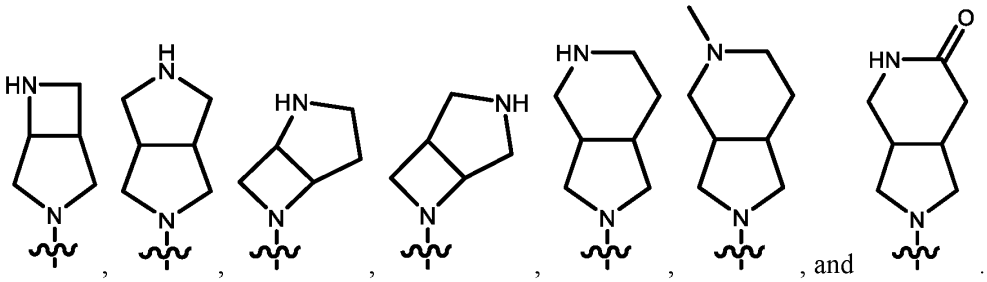
[0178] Enumerated Embodiment 30. The compound of Enumerated Embodiment 22 or 23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they

are attached to form a 6- to 12-membered fused heterocyclyl optionally substituted with one or more R^3.

[0179] Enumerated Embodiment 31. The compound of Enumerated Embodiment 30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein each R^3 is independently $C_{1\text{-}6}$alkyl or oxo.

[0180] Enumerated Embodiment 32. The compound of Enumerated Embodiment 31, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein each R^3 is independently -CH_3 or oxo.

[0181] Enumerated Embodiment 33. The compound of any of Enumerated Embodiments 22, 23 or 30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of



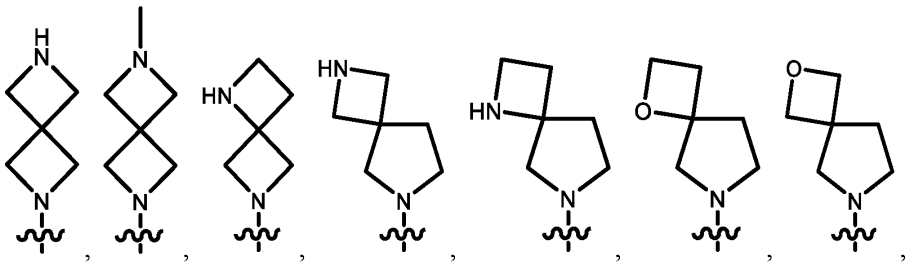
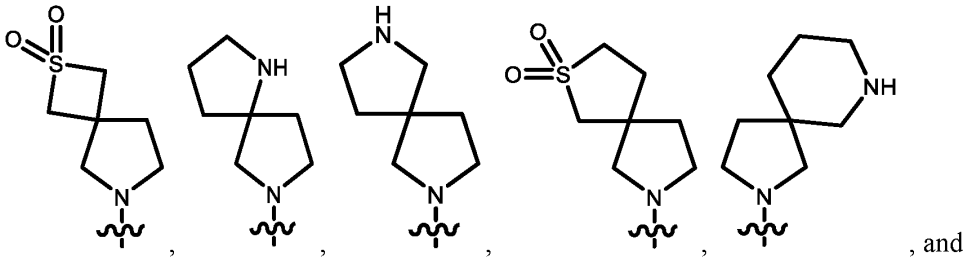
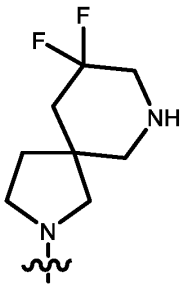
, , , , , , and .

[0182] Enumerated Embodiment 34. The compound of Enumerated Embodiment 22 or 23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they are attached to form a 6- to 12-membered spirocyclic heterocyclyl optionally substituted with one or more R^3.

[0183] Enumerated Embodiment 35. The compound of Enumerated Embodiment 34, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein each R^3 is halo.

[0184] Enumerated Embodiment 36. The compound of Enumerated Embodiment 35, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein each R^3 is F.

[0185] Enumerated Embodiment 37. The compound of any of Enumerated Embodiments 22, 23 or 34, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of




, and

[0186] Enumerated Embodiment 38. The compound of any of Enumerated Embodiments 1-5, 12, or 14-37, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^4 is halo or -O-(C_{1-6}alkyl).

[0187] Enumerated Embodiment 39. The compound of any of Enumerated Embodiments 1-5, 12, or 14-38, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^4 is halo or -OCH_3.

[0188] Enumerated Embodiment 40. The compound of any of Enumerated Embodiments 1-39, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, -$N(R^x)(R^y)$, -OR^{12}, and

the C_{3-8}cycloalkyl of R^5 is optionally substituted with one or more R^{5b}.

[0189] Enumerated Embodiment 41. The compound of any of Enumerated Embodiments 1-40, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl.

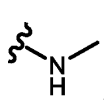
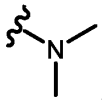
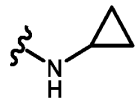
[0190] Enumerated Embodiment 42. The compound of any of Enumerated Embodiments 1-41, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^5 is H or C_{1-6}alkyl.

[0191] Enumerated Embodiment 43. The compound of any of Enumerated Embodiments 1-42, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^5 is H.

[0192] Enumerated Embodiment 44. The compound of any of Enumerated Embodiments 1-39, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein L is a bond or -O-(C_{1-6}alkyl)-.

[0193] Enumerated Embodiment 45. The compound of any of Enumerated Embodiments 1-39, or 44, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein L is a bond or -O-(CH_2CH_2)-.

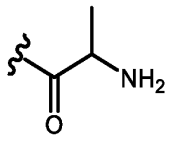
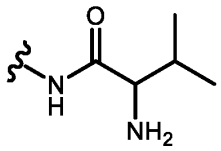
[0194] Enumerated Embodiment 46. The compound of any of Enumerated Embodiments 1-45, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^6 is -N(R^x)(R^y).

[0195] Enumerated Embodiment 47. The compound of Enumerated Embodiment 1-46, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^6 is selected from the group consisting of  ,  , and  .

[0196] Enumerated Embodiment 48. The compound of any of Enumerated Embodiments 1-45, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^6 is -N(R^{13})C(O)R^{14}, -N(R^{13})C(O)OR^{14}, -N(R^{13})C(O)N(R^{13})R^{14}, -C(O)N(R^{13})(R^{14}), -C(O)(C_{1-6}alkyl)N(R^{13})(R^{14}).

[0197] Enumerated Embodiment 49. The compound of any of Enumerated Embodiments 1-45 or 48, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^6 is -N(R^{13})C(O)R^{14} or -C(O)(C_{1-6}alkyl)N(R^{13})(R^{14}).

[0198] Enumerated Embodiment 50. The compound of any of Enumerated Embodiments 1-45, 46, or 49, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt,

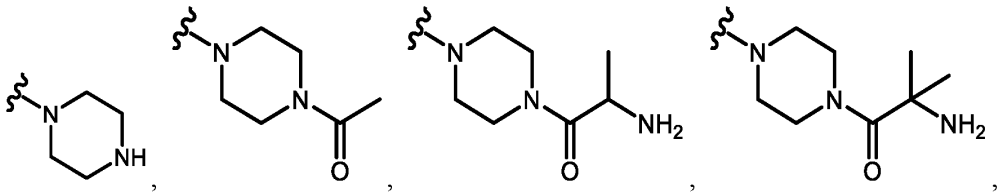
hydrate, or solvate of any of the foregoing, wherein R^6 is  or  .

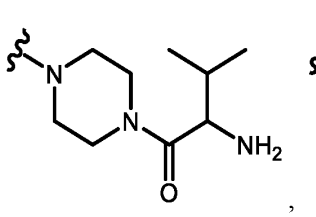
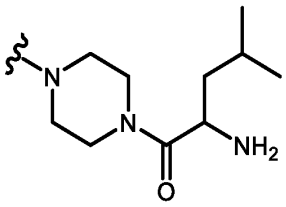
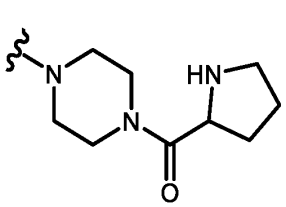
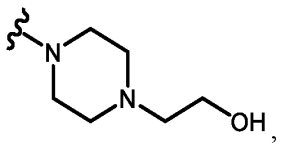
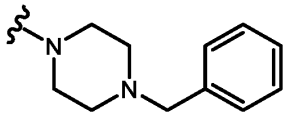
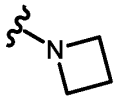
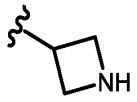
[0199] Enumerated Embodiment 51. The compound of any of Enumerated Embodiments 1-45, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^6 is 3- to 12-membered N-containing heterocyclyl optionally substituted with one or more R^{6b}.

[0200] Enumerated Embodiment 52. The compound of any of Enumerated Embodiments 1-45 or 50, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein L is a bond and R^6 is 3- to 12-membered N-containing heterocyclyl optionally substituted with one or more R^{6b}.

[0201] Enumerated Embodiment 53. The compound of any of Enumerated Embodiments 1-44, 50, or 52, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^6 is azetidinyl, pyrrolidinyl, or piperazinyl, wherein the azetidinyl, pyrrolidinyl, or piperazinyl is optionally substituted with one or more R^{6b}.

[0202] Enumerated Embodiment 54. The compound of Enumerated Embodiment 1-45 or 51-53, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^6 is selected from the group consisting of









and


[0203] Enumerated Embodiment 55. The compound of any of Enumerated Embodiments 1-10, or 12-54, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^8 and R^9 are each independently H, halo, $-N(R^x)(R^y)$, $-OR^{11}$, $-N(R^{13})C(O)R^{14}$, or $-N(R^{13})C(O)OR^{14}$.

[0204] Enumerated Embodiment 56. The compound of Enumerated Embodiment 55, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^8 and R^9 are each independently H, halo, $-NH_2$, $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$, $-O(C_{1-6}alkyl)$, $-NHC(O)$(5- to 6-membered aryl), or $-NHC(O)O(C_{1-6}alkyl)$, wherein

the 5- to 6-membered aryl of $-NHC(O)$(5- to 6-membered aryl) is optionally substituted with $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$.

[0205] Enumerated Embodiment 57. The compound of Enumerated Embodiment 56, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^8 and R^9 are each independently H, F, Cl, $-NH_2$, $-N(CH_3)(CH_3)$, $-OCH_3$, $-NHC(O)$(phenyl), or $-NHC(O)O(CH_2CH_3)$, wherein

the phenyl of $-NHC(O)$(phenyl) is substituted with $-N(CH_3)(CH_3)$.

[0206] Enumerated Embodiment 58. The compound of any of Enumerated Embodiments 1-57, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^8 and R^9 are each H.

[0207] Enumerated Embodiment 59. The compound of any of Enumerated Embodiments 1-4, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

R^1 and R^2 are taken together with the N to which they are attached to form a 4- to 12-membered heterocyclyl optionally substituted with one or more R^3;

Ring A is pyridinyl; and

L is a bond or $-O-(C_{1-6}alkyl)-$.

[0208] Enumerated Embodiment 60. The compound of Enumerated Embodiment 59, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

R^1 and R^2 are taken together with the N to which they are attached to form a 4- to 12-membered heterocyclyl optionally substituted with one or more R^3;

Ring A is pyridinyl;

L is a bond; and

R^6 is piperazinyl optionally substituted with one or more R^{6b}.

[0209] Enumerated Embodiment 61. The compound of any of Enumerated Embodiments 1-4, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

R^1 and R^2 are taken together with the N to which they are attached to form a 4- to 12-membered heterocyclyl optionally substituted with one or more R^3; and

R^8 and R^9 are each independently H, F, $-N(CH_3)(CH_3)$, $-OCH_3$ or $-OCD_3$.

[0210] Enumerated Embodiment 62. The compound of Enumerated Embodiment 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein the compound is selected from Table 1.

[0211] Enumerated Embodiment 63. A pharmaceutical composition comprising a compound of any of Enumerated Embodiments 1-62, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients or carriers.

[0212] Enumerated Embodiment 64. A method for treating a disease or condition mediated by TDP-43, comprising administering to a subject in need thereof a compound of any of Enumerated Embodiments 1-62, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or the pharmaceutical composition of Enumerated Embodiment 63.

[0213] Enumerated Embodiment 65. The method of Enumerated Embodiment 64, wherein a therapeutically effective amount of the compound is administered.

[0214] Enumerated Embodiment 66. The method of Enumerated Embodiment 64 or 65, wherein said disease or condition mediated by TDP-43 is a neurological disease or condition.

[0215] Enumerated Embodiment 67. The method of Enumerated Embodiment 66, wherein the neurological disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), frontotemporal dementia (FTD), inclusion body myositis, Perry

syndrome, corticobasaldegeneration, spinocerebellar ataxia type 3, and amyotrophic lateral sclerosis (ALS).

[0216] Enumerated Embodiment 68. The method of Enumerated Embodiment 66 or 67, wherein the neurological disease or condition is traumatic brain injury (TBI).

[0217] Enumerated Embodiment 69. The method of Enumerated Embodiment 66 or 67, wherein the neurological disease or condition is frontotemporal dementia (FTD).

[0218] Enumerated Embodiment 70. The method of Enumerated Embodiment 66 or 67, wherein the neurological disease or condition is amyotrophic lateral sclerosis (ALS).

[0219] Enumerated Embodiment 71. The method of any of Enumerated Embodiments 66, 67, or 70, wherein the neurological disease or condition is sporadic amyotrophic lateral sclerosis or C9ORF72 amyotrophic lateral sclerosis.

[0220] Enumerated Embodiment 72. The method of any of Enumerated Embodiments 64-71, wherein the subject is a human.

[0221] Enumerated Embodiment 73. A method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of any of Enumerated Embodiments 1-62, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or the pharmaceutical composition of Enumerated Embodiment 63, wherein

modulating TDP-43 comprises modulating TDP-43 incorporation into condensates, modulating TDP-43 binding to RNA in condensates, modulating TDP-43 aggregation, or modulating TDP43 protein-protein interactions.

[0222] Enumerated Embodiment 74. A method of modulating TDP-43 driven gene expression levels, comprising contacting a cell with an effective amount of a compound of any of Enumerated Embodiments 1-62, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or the pharmaceutical composition of Enumerated Embodiment 63.

[0223] Enumerated Embodiment 75. The method of Enumerated Embodiment 74, wherein the gene expression levels are for *STMN2*.

[0224] Enumerated Embodiment 76. The method of Enumerated Embodiment 74, wherein the gene expression levels are for *POLDIP3*.

[0225] Enumerated Embodiment 77. The compound of any of Enumerated Embodiments 1-62, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, or the pharmaceutical composition of Enumerated Embodiment 63 for use in the treatment of a disease or condition mediated by TDP-43.

[0226] Enumerated Embodiment 78. Use of a compound of any of Enumerated Embodiments 1-62, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate thereof in the manufacture of a medicament for the treatment of a disease or condition mediated by TDP-43.

[0227] Enumerated Embodiment 79. A kit, comprising (i) a compound of any one of Enumerated Embodiments 1-62, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or the pharmaceutical composition of Enumerated Embodiment 63 and (ii) instructions for use in treating a TDP-43 mediated disease or condition in an individual in need thereof.

EXAMPLES

[0228] The reagents and starting materials are commercially available and/or, using well-known techniques, can be readily synthesized by one of ordinary skill in the art. Unless otherwise noted, all commercially starting materials were used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification.

Table 2.

g (grams)	LCMS (Liquid Chromatography Mass Spectrum)
mg (milligrams)	HPLC (High Pressure Liquid Chromatography)
mL (milliliters)	NMR (Nuclear Magnetic Resonance)
μL (microliters)	^{1}H (proton)
μmol (micromoles)	rt (room temperature)
M (molar)	mmol (millimoles)
MHz (megahertz)	min (minutes)
Hz (hertz)	PE (petroleum ether)
EtOAc (ethyl acetate)	MeOH (methanol)
DCM (dichloromethane)	SCX (Strong Cation Exchange Resin)
OTs (tosylate)	ACN (acetonitrile)
HCl (Hydrochloric acid)	mm (micrometers)
mm (millimeters)	MPLC (Medium Pressure Liquid Chromatography)
h (hours)	% (percent)

UV (ultraviolet)	HATU (Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium)
TFA (trifluoroacetic acid)	THF (tetrahydrofuran)
FA (formic acid)	$NaHCO_3$ (sodium bicarbonate)
NaOH (sodium hydroxy)	Na_2SO_4 (sodium sulfate)
prep- (preparative)	DIEA (diisopropyl ethyl amine)
TLC (thin layer chromatography)	SiO_2 (silica)
TBS (*tert*-butyl dimethyl)	DMSO (dimethyl sulfoxide)
Fmoc (fluorenyl methoxycarbonyl)	DMF (dimethylformamide)
LED (light-emitting diode)	KOAc (potassium acetate)
ESI (electrospray ionization)	Pd $(PPh_3)_4$ (palladium tetrakistriphenylphosphine)
DME (dimethoxyethane)	Pd(dppf)Cl_2 ([1,1'-Bis(diphenylphosphino)ferrocene] palladium (II) dichloride)
CbzCl (Benzyl chloroformate)	BrettPhosPdG3 [2-Dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biohenyl)-2-(2'-amino-1,1'-biphenyl)] palladium (II) - methansulfonat
SPhosPdG3 (2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl) [2-(2'-amino-1,1'-biphenyl)] palladium (II)-methansulfonat	
XPhos Pd G4 ((*SP*-4-3)-[Dicyclohexyl[2′,4′,6′-tris(1-methylethyl) [1,1′-biphenyl]-2-yl] phosphine] (methanesulfonato-κ*O*) [2′-(methylamino-κN) [1,1′-biphenyl]-2-yl-κ*C*] palladium)	
[Pd $(OAc)_2]_3$ (palladium II acetate)	CPhos Pd G3 [(2-Dicyclohexylphosphino-2',6'-bis (*N*, *N*-dimethylamino)-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium (II) methansulfonate
BINAP (1.1'-binaphtyl-2.2'-diphemyl phosphine)	Pd$[P(t\text{-}Bu)_3]_2$ (palladium bis tri(tert-butyl)phosphine)

[0229] SCX general protocol. The hydrochloride salt product was neutralized by *Strong Cation Exchange Resin*. The resin was first washed with two volumes of deionized water. The compound to neutralized was absorbed to the resin by washing the resin with a solution

of the compound in methanol. The resin was then washed with deionized water until the pH of the solution is neutral. A solution of ammonium hydroxide and methanol was used to release compound from the resin. Solvents were then concentrated and lyophilized to get the desired product.

[0230] Prep-HPLC. Experiments were carried out at room temperature and detection was done by UV at 220 and 254 nm. The different methods used are described as follows.

1: ACSWH-GX-N; YMC triart C18 column 150 x 25 mm x 5 mm; mobile phase: water (HCl)-ACN

2: ACSWH-GX-N; Phenomenex Luna C18 column 150 x 25 mm x 10 mm; mobile phase: water (FA)-ACN

3: ACSWH-GX-N; Phenomenex Luna C18 column 150 x 25 mm x 10 mm; mobile phase: water (TFA)-ACN

4: ACSWH-GX-N; Unisil 3-100 C18 ultra column 150 x 50 mm x 3 mm; mobile phase: water (0.23% FA)-ACN

5: Agilent Infinity II 1260/1290, Agilent Infinity Lab Poroshell 1204; HPH-C18 column 21.2 x 150 mm; mobile phase: water (0.1% FA)-ACN (0.1% FA)

6 (basic system): Agilent Infinity II 1260/1290, Agilent Infinity Lab Poroshell 1204; HPH-C18 column 21.2 x 150 mm; mobile phase: water-ACN (0.1 % NH_3)

7: ACSWH-GX-N; Waters Xbridge 150 x 25 mm x 5 mm; mobile phase: water (ammonia hydroxide v/v)-ACN

8: ACSWH-GX-O; Phenomenex luna C_{18} 150 x 25 mm x 10 mm; mobile phase: water (HCl)-ACN

9: ACSWH-GX-A; YMC Triart C18 150 x 25 mm x 5 mm); mobile phase: water (ammonia hydroxide v/v)-ACN

10: ACSWH-GX-N; Welch Xtimate C18 150 x2 5mm x 5um; mobile phase: water (FA)-ACN

11: ACSWH-GX-N; Waters Xbridge 150 x 25 mm x 5 mm; mobile phase: water (water (FA)-ACN

[0231] Flash silica gel chromatography. ISCO®; SepaFlash® Silica Flash Column, Eluent Ethyl acetate/Petroleum ether gradient

[0232] Flash chromatography. Puri Flash XS520Plus, Interchim, PF-30SIHP-JP-F00xx, 30 μm

[0233] NMR and LCMS. The analytical characterization of synthesized compounds was done by NMR and LCMS. ^{1}H NMR spectra were recorded on a Bruker AVANCE III 400, Bruker AVANCE NEO 400, Bruker AVANCE III HD 400 or on a Jeol ECZ 400

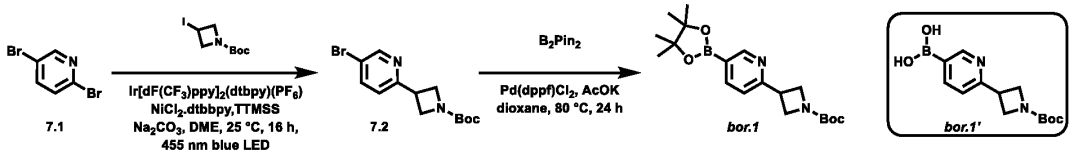
spectrometer at 400 MHz Data are reported as follows: chemical shift in ppm, deuterated solvent ($CDCl_3$ for deuterated chloroform, DMSO-d_6 for deuterated dimethylsulfoxide and methanol-d_4 for deuterated methanol), multiplicity (s = singulet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances, integration, br = broad singulet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, dq = doublet of quintuplet). Coupling constants *J* were measured in Hertz.

[0234] LCMS spectra were recorded according to the following conditions:

- SHIMADZU LCMS-2020 using LabSolution software Version 5.89 and 5.93; HALO C18 column 3.0 x 30 mm x 5.0 um or Kinetex EVO C18 column 2.1 x 30 mm x 5 um; mobile phase: water (0.04% TFA)-ACN (0.02% TFA), at 50 °C on a 1 to 2 minutes gradient (flow rate 1.5 to 2.0 mL/min) with UV detection at 220 and 254 nm; ESI for mass spectra.
- Agilent 1260 Infinity II, Agilent Poroshell 120 EC C18 or HPH C18 column 2.7 µm 2.1 x 50 mm; mobile phase: water (0.1% FA)-ACN on a two-minute gradient (flow rate 0.6 mL/min) or mobile phase: water (0.1% FA)-ACN on a five-minute gradient (flow rate 0.6 mL/min) or water (0.1% NH_3)-ACN (flow rate 0.7 mL/min) with UV detection at 220 and 254 nm; ESI for mass spectra.

Synthesis of non-commercially available boronic acids and esters

bor.1': [6-(1-*tert*-butoxycarbonylazetidin-3-yl)-3-pyridyl] boronic acid

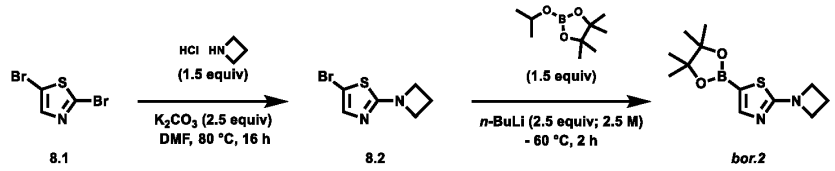


[0235] Step 1: To a solution of 2,5-dibromopyridine **7.1** (3.0 g, 13 mmol, 1.0 eq) and *tert*-butyl 3-iodoazetidine-1-carboxylate (4.7 g, 16.5 mmol, 1.3 eq) in DME (30 mL) were added [4,4′-*Bis*(1,1-dimethylethyl)-2,2′-bipyridine-*N*1,*N*1′]*bis*[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate (0.14 g, 0.13 mmol, 0.01 eq), [4,4′-Bis(1,1-dimethylethyl)-2,2′-bipyridine] nickel (II) dichloride (25 mg, 0.06 mmol, 0.005 eq), bis(trimethylsilyl)silyl-trimethyl-silane (3.15 g, 13 mmol, 1.0 eq) and Na_2CO_3 (2.7 g, 25 mmol, 2.0 eq) at 25 °C. After stirring at 25 °C for 16 h under irradiation with a 455 nm blue LED, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The remaining mixture was purified by Flash chromatography (20 g column, Eluent

of 0~60% EtOAc/PE gradient at 40 mL/min) to give *tert*-butyl 3-(5-bromo-2-pyridyl) azetidine-1-carboxylate **7.2** (1.0 g, 2.75 mmol, 22% yield, 86% purity) as yellow oil. MS m/z (ESI) $[M-55]^+$ = 259.0.

[0236] Step 2: To a solution of *tert*-butyl 3-(5-bromo-2-pyridyl)azetidine-1-carboxylate **7.2** (1.0 g, 2.75 mmol, 1.0 eq) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (0.91 g, 3.6 mmol, 1.3 eq) in dioxane (25 mL) was added 1,1-bis(diphenylphosphino) ferrocene palladium(II) dichloride (0.20 g, 0.28 mmol, 0.10 eq) and potassium acetate (1.1 g, 11 mmol, 4.0 eq) at 20 °C. After stirring at 80 °C for 24 h, the reaction mixture was diluted with water (30 mL) and then extracted with ethyl acetate (30 mL, three times), the combined organic phase was washed with brine (10 mL, three times), dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~50% EtOAc/PE gradient at 40 mL/min) to give ***bor.1'*** (0.45 g, 1.5 mmol, 54% yield, 91% purity) as a yellow gum. MS m/z (ESI) $[M-80]^+$ = 223.3.

***bor.2*: 2-(azetidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) thiazole**

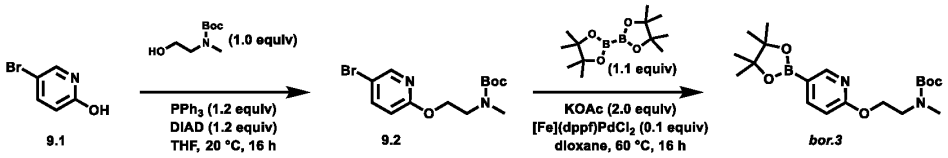


[0237] Step 1: To a solution of 2,5-dibromothiazole **8.1** (1.0 g, 4.1 mmol, 1.0 eq) in *N*, *N*-dimethylformamide (10 mL) was added potassium carbonate (1.1 g, 8.2 mmol, 2.0 eq) and azetidine (0.60 g, 6.4 mmol, 0.71 mL, 1.6 eq, HCl salt) at 25 °C. After stirring at 80 °C for 16 h, the reaction mixture was added into water (50 mL) and extracted with ethyl acetate 60 mL (20 mL, three times). The combined organic layers were washed with brine 60 mL (20 mL, three times), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (24g column, Eluent of 0~15% EtOAc/PE gradient at 45 mL/min) to give 2-(azetidin-1-yl)-5-bromo-thiazole **8.2** (0.50 g, 2.3 mmol, 55% yield, 99% purity) as a white solid. MS m/z (ESI) $[M+H]^+$= 221.0.

[0238] Step 2: To a solution of 2-(azetidin-1-yl)-5-bromo-thiazole **8.2** (0.25 g, 1.1 mmol, 1.0 eq) in THF (10 mL) was added *n*-BuLi (2.5 M, 1.0 mL, 2.2 eq) at – 60 °C. After stirring 0.5 h, the 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.32 g, 1.7 mmol, 0.35 mL, 1.5 eq) was added into the mixture at – 60 °C .Then, the mixture was stirred at – 60 °C for 2 h

and heated to room temperature. The reaction mixture was added into saturated aqueous solution of ammonium chloride (20 mL) and extracted with ethyl acetate 45 mL (15 mL, three times). The combined organic layers were washed with brine 15 mL, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give ***bor.2*** (0.20 g, 0.38 mmol, 33% yield, 50% purity) as a brown solid. MS m/z (ESI) $[M+H]^+$= 267.1.

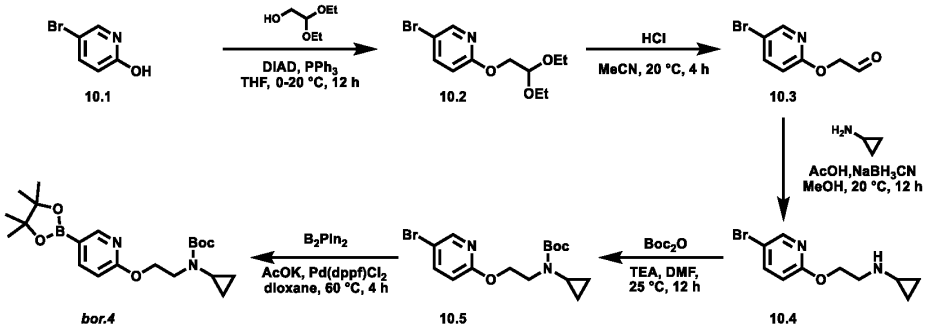
bor.3**:** *tert*-butyl *N*-methyl-*N*-[2-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl] oxy] ethyl] carbamate



[0239] Step 1: To a solution of 5-bromopyridin-2-ol **9.1** (1.0 g, 5.8 mmol, 1.0 eq) and *tert*-butyl *N*-(2-hydroxyethyl)-*N*-methylcarbamate (1.2 g, 6.9 mmol, 1.2 eq) in THF (20 mL) was added triphenylphosphine (1.8 g, 6.9 mmol, 1.2 eq) and diisopropyl azodicarboxylate (1.4 g, 6.9 mmol, 1.3 mL, 1.2 eq) at 25 °C. After stirring at 25 °C for 16 h, the reaction mixture was concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (40 g column, Eluent of 0~15% EtOAc/PE gradient at 30 mL/min) to give tert-butyl *N*-[2-[(5-bromo-2-pyridyl) oxy] ethyl]-*N*-methylcarbamate **9.2** (1.0 g, 2.9 mmol, 50% yield, 95% purity) as colorless oil. MS m/z (ESI) $[M-55]^+$= 241.0.

[0240] Step 2: A mixture of *tert*-butyl *N*-[2-[(5-bromo-2-pyridyl)oxy]ethyl]-*N*-methyl-carbamate **9.2** (0.50 g, 1.5 mmol, 1.0 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (0.42 g, 1.7 mmol, 1.1 eq), bis[3-(diphenylphosphanyl)cyclopenta-2,4-dien-1-yl]iron; dichloropalladium (0.11 g, 0.15 mmol, 0.10 eq), potassium acetate (0.30 g, 3.0 mmol, 2.0 eq) in dioxane (10 mL) was degassed and purged with nitrogen for 3 times at 25 °C. After stirring at 80 °C for 16 h under nitrogen atmosphere, the reaction mixture was concentrated under reduce pressure. The residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~10% EtOAc/PE gradient at 50 mL/min) to give ***bor.3*** (0.50 g, 1.15 mmol, 76% yield, 87% purity) as colorless oil. MS m/z (ESI) $[M-100+H]^+$= 297.1.

***bor.4*: *tert*-butyl *N*-cyclopropyl-*N*-[2-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl] oxy] ethyl] carbamate**



[0241] Step 1: To a solution of 5-bromopyridin-2-ol **10.1** (2.0 g, 11.5 mmol, 1.0 eq), 2,2-diethoxyethanol (1.9 g, 14 mmol, 1.2 eq) in THF (20 mL) were added triphenylphosphine (3.6 g, 14 mmol, 1.2 eq) and diisopropyl azodiformate (2.8 g, 14 mmol, 1.2 eq) at 0 °C. After stirring at 20 °C for 12 h, the reaction mixture was concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (40 g column, Eluent of 0~40% EtOAc/PE gradient at 40 mL/min) to give 5-bromo-2-(2,2-diethoxyethoxy) pyridine **10.2** (3.0 g, 10 mmol, 90% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) d (ppm): 7.87 (d, J = 2.8 Hz, 1H) ,7.54 (dd, J = 10, 2.8 Hz, 1H), 6.38 (d, J = 9.8 Hz, 1H), 4.71 - 4.66 (m, 1H), 3.94 (d, J = 5.5 Hz, 2H), 3.70 - 3.55 (m, 4H), 1.05 (t, J = 7.0 Hz, 6H).

[0242] Step 2: To a solution of 5-bromo-2-(2,2-diethoxyethoxy) pyridine **10.2** (2.8 g, 10 mmol, 1.0 eq) in acetonitrile (20 mL) was added hydrochloric acid (4 M, 6.0 mL, 2.5 eq) at 20 °C. The mixture was stirred at 20 °C for 4 h. The reaction mixture was diluted with water (20 mL) and then extracted with ethyl acetate (30.0 mL, three times). The combined organic layers were washed with brine (10 mL, three times), dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give 2-[(5-bromo-2-pyridyl) oxy] acetaldehyde **10.3** (2.2 g, crude) as an off-white solid.

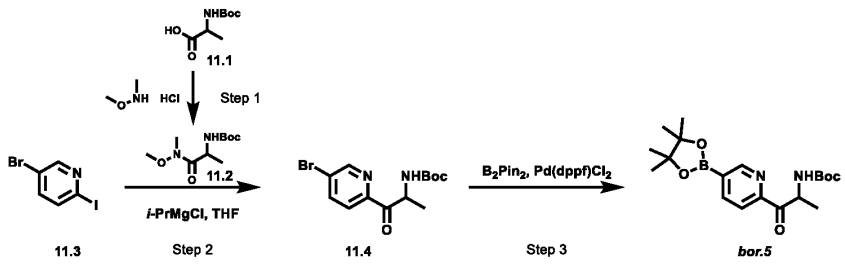
[0243] Step 3: To a solution of 2-[(5-bromo-2-pyridyl) oxy] acetaldehyde **10.3** (1.1 g, 5.1 mmol, 1.0 eq) and cyclopropanamine (0.26 g, 4.6 mmol, 0.90 eq) in methanol (15 mL) were added acetic acid (0.92 g, 15 mmol, 3.0 eq) and sodium cyanoborohydride (0.48 g, 7.6 mmol, 1.5 eq) at 20 °C. After stirring at 20 °C for 12 h, the reaction mixture was concentrated under reduced pressure. The residue obtained was diluted with water (15 mL) and then extracted with ethyl acetate (15 mL, three times). The combined organic phases were washed with brine (5.0 mL, three times), dried with anhydrous sodium sulfate, filtered and the filtrate was

concentrated under reduced pressure to give *N*-[2-[(5-bromo-2-pyridyl)oxy]ethyl]cyclopropanamine **10.4** (0.80 g, 2.4 mmol, 47% yield, 77% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 259.1.

[0244] Step 4: To a solution of *N*-[2-[(5-bromo-2-pyridyl)oxy]ethyl]cyclopropanamine **10.4** (0.80 g, 2.4 mmol, 1.0 eq) in *N*,*N*-dimethylformamide (10 mL) were added triethylamine (0.73 g, 7.2 mmol, 1.0 mL, 3.0 eq) and *tert*-butyl (2-methylpropan-2-yl)oxycarbonyl carbonate (1.1 g, 4.8 mmol, 1.1 mL, 2.0 eq) at 20 °C. The mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted with water (20 mL) and then extracted with ethyl acetate (20.0 mL, three times). The combined organic phases were washed with brine (10 mL, three times), dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~25% EtOAc/PE gradient at 40 mL/min) to give *tert*-butyl *N*-[2-[(5-bromo-2-pyridyl) oxy] ethyl]-N-cyclopropyl-carbamate **10.5** (0.60 g, 1.4 mmol, 60% yield, 86% purity) as a yellow solid. MS m/z (ESI) $[M-100]^+$ = 257.2.

[0245] Step 5: To a mixture of *tert*-butyl *N*-[2-[(5-bromo-2-pyridyl)oxy]ethyl]-*N*-cyclopropyl-carbamate **10.5** (0.60 g, 1.4 mmol, 1.0 eq) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- 1,3,2-dioxaborolane (0.44 g, 1.7 mmol, 1.2 eq) in dioxane (10 mL) were added 1,1-bis(diphenylphosphino)ferrocene palladium(II)dichloride (53 mg, 0.07 mmol, 0.05 eq) and potassium acetate (0.28 g, 2.9 mmol, 2.0 eq) at 25 °C. The mixture was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 60 °C for 4 h under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (10 mL), then the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~25% EtOAc/PE gradient at 40 mL/min) to give ***bor.4*** (0.40 g, 0.73 mmol, 51% yield, 74% purity) as a brown solid. MS m/z (ESI) $[M+H]^+$ = 405.3.

***bor.5*: *tert*-butyl *N*-[1-methyl-2-oxo-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl] ethyl] carbamate**

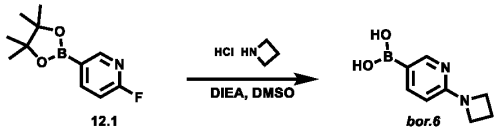


[0246] Step 1: To a solution of 2-(*tert*-butoxycarbonylamino) propanoic acid **11.1** (10 g, 53 mmol, 1.0 eq) in DMF (100 mL) was added HATU (25 g, 66 mmol, 1.2 eq), the reaction mixture was stirred at 25 °C for 10 min. Then to the mixture was added DIEA (19 g, 0.14 mol, 25 mL, 2.7 eq) and *N*-methoxymethanamine (6.0 g, 62 mmol, 1.2 eq, HCl). The mixture was stirred at 25 °C for another 5 h. The reaction mixture was extracted with EtOAc (400 mL) and H_2O (300 mL). The combined organic layers were washed with *saturated* aqueous NH_4Cl (300 mL), saturated aqueous $NaHCO_3$ (300 mL) and *saturated* aqueous NaCl (300 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (80 g column, Eluent of 0~50% EtOAc/PE gradient at 100 mL/min) to give *tert*-butyl *N*-[2-[methoxy(methyl)amino]-1-methyl-2-oxo-ethyl] carbamate **11.2** (9.0 g, 37 mmol, 70% yield, 95% purity) as a white solid.

[0247] Step 2: To a solution of 5-bromo-2-iodo-pyridine **11.3** (9.7 g, 34 mmol, 1.0 eq) in THF (150 mL) was added *tert*-butyl *N*-[2-[methoxy(methyl)amino]-1-methyl-2-oxo-ethyl]carbamate (8.0 g, 34 mmol, 1.0 eq) , the reaction mixture was degassed and purged with N_2 for three times, then *i*-PrMgCl (2 M, 35 mL, 2.0 eq) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 25 °C for 1 h under N_2 atmosphere. The reaction mixture was quenched with *saturated* aqueous NH_4Cl (300 mL) and extracted with EtOAc (500 mL, twice). The combined organic layers were washed with *saturated* aqueous NaCl (400 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (80 g column, Eluent of 0~9% EtOAc/PE gradient at 100 mL/min) to give the desired compound as a yellow solid, which was further purified by reversed-phase MPLC (0.1%FA condition) to give *tert*-butyl *N*-[2-(5-bromo-2-pyridyl)-1-methyl-2-oxo-ethyl]carbamate **11.4** (4.0 g, 12 mmol, 36% yield, 100% purity) as a white solid.

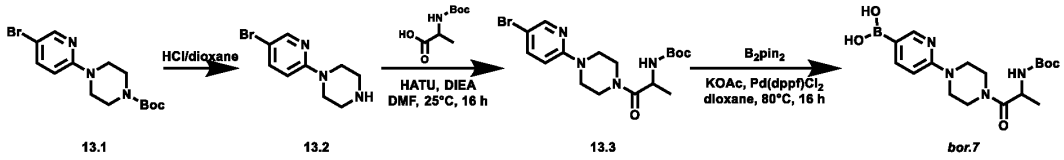
[0248] Step 3: To a solution of *tert*-butyl *N*-[2-(5-bromo-2-pyridyl)-1-methyl-2-oxo-ethyl]carbamate **11.4** (0.36 g, 1.1 mmol, 1.0 eq) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (0.44 g, 1.7 mmol, 1.6 eq) in dioxane (5.0 mL) was added $Pd(dppf)Cl_2$ (72 mg, 98 μmol, 0.09 eq) and KOAc (0.33 g, 3.3 mmol, 3.0 eq). The reaction mixture was degassed and purged with N_2 for three times. The mixture was stirred at 80 °C for 5 h under N_2 atmosphere. After filtration and concentration under reduced pressure the crude product ***bor.5*** (0.42 g, crude) was directly used into the next step without further purification as a black liquid.

***bor.6*:** [6-(azetidin-1-yl)-3-pyridyl] boronic acid



[0249] To a solution of 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyridine **12.1** (4.5 g, 20 mmol, 1.0 eq) and azetidine (2.3 g, 24 mmol, 2.7 mL, 1.2 eq, HCl) in DMSO (40 mL) was added K_2CO_3 (8.4 g, 61 mmol, 3.0 eq) at 25 °C. The mixture was stirred at 100 °C for 16 h. Then the mixture was diluted with water (50 mL) and extracted with ethyl acetate (60 mL, three times). The combined organic phases were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue obtained was purified by prep-HPLC **3** (gradient: 0%-30% ACN over 10 min) to give ***bor.6*** (2.2 g, 12 mmol, 61% yield, 99% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 178.9.

bor.7: (6-(4-((*tert*-butoxycarbonyl) alanyl) piperazin-1-yl) pyridin-3-yl) boronic acid



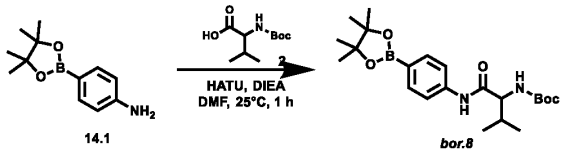
[0250] Step 1: To a solution of tert-butyl 4-(5-bromo-2-pyridyl) piperazine-1-carboxylate **13.1** (1.0 g, 2.9 mmol, 1.0 eq) in dioxane (0.5 mL) was added HCl/dioxane (2.0 M, 2.0 mL) at 25 °C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give 1-(5-bromo-2-pyridyl) piperazine **13.2** (0.80 g, 2.8 mmol, 96% yield, 98% purity, HCl). MS m/z (ESI) $[M+H]^+$ = 242.0.

[0251] Step 2: To a solution of 1-(5-bromo-2-pyridyl)piperazine **13.2** (0.80 g, 2.9 mmol, 1.0 eq, HCl) in DMF (3.0 mL) was added 2-(*tert*-butoxycarbonylamino)propanoic acid (0.65 g, 3.4 mmol, 1.2 eq), HATU (2.2 g, 5.7 mmol, 2.0 eq) and DIEA (1.5 g, 11 mmol, 2.0 mL, 4 eq). The mixture was stirred at 25 °C for 16 h. The reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl *N*-[2-[4-(5-bromo-2-pyridyl) piperazin-1-yl]-1-methyl-2-oxo-ethyl] carbamate **13.3** (1.1 g, 2.6 mmol, 92% yield, 99% purity). MS m/z (ESI) $[M+H]^+$ = 413.1.

[0252] Step 3: A mixture of *tert*-butyl *N*-[2-[4-(5-bromo-2-pyridyl)piperazin-1-yl]-1-methyl-2-oxo-ethyl]carbamate **13.3** (1.1 g, 2.7 mmol, 1 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-

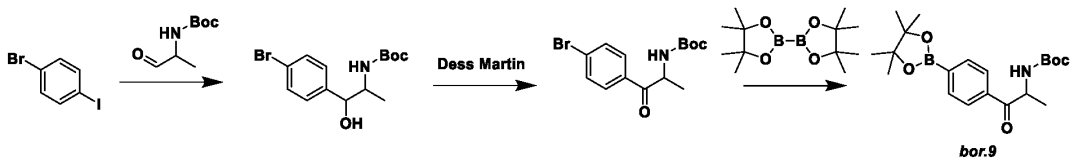
tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.0 g, 4.0 mmol, 1.5 eq), $Pd(dppf)Cl_2$ (0.20 g, 0.27 mmol, 0.10 eq) and AcOK (0.79 g, 8.0 mmol, 3.0 eq) in dioxane (3.0 mL) was degassed and purged with N_2 three times at 25 °C. Then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (30 mL) and extracted with EtOAc (35 mL, three times). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The new residue obtained was purified by prep-HPLC **2** (gradient:10%-40% ACN over 15 min) to give ***bor.7*** (0.48 g, 1.3 mmol, 48% yield, 100% purity). MS m/z (ESI) $[M+H]^+$ = 379.2.

bor.8: tert-butyl (3-methyl-1-oxo-1-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) amino) butan-2-yl) carbamate



[0253] To a solution of 4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) aniline **14.1** (1.0 g, 4.6 mmol, 1.0 eq) and 2-(tert-butoxycarbonylamino) -3-methyl-butanoic acid (1.0 g, 4.6 mmol, 1.0 eq) in DMF (20 mL) was added HATU (2.6 g, 6.9 mmol, 1.5 eq) and DIEA (2.0 g, 15 mmol, 2.7 mL, 3.4 eq) in turns, then the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with EtOAc (50 mL), washed with *sat.*NH_4Cl (50 mL, twice)., saturated aqueous $NaHCO_3$ (50 mL, twice), brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give crude material. The residue obtained was purified by Flash chromatography (40 g Column, Eluent of 0 to 40% EtOAc/PE gradient at 40 mL/min) to give ***bor.8*** (1.2 g, 2.2 mmol, 48% yield, 76% purity) as white solid. MS m/z (ESI) $[M+H]^+$ = 419.3.

bor.9: tert-butyl (1-oxo-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-2-yl)carbamate



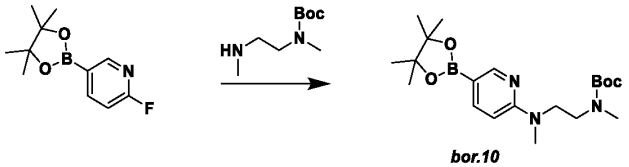
[0254] Step 1: To a solution of 1-bromo-4-iodo-benzene (0.5 g, 1.77 mmol, 1 eq) and tert-butyl (1-oxopropan-2-yl)carbamate (306.13 mg, 1.77 mmol, 1 eq) in THF (10 mL) was added

i-PrMgCl (1.3 M, 2.72 mL, 2 eq) at 0 °C .The mixture was stirred at 25 °C for 2 hours under N_2 atmosphere. The reaction mixture was quenched by saturated ammonium chloride aqueous solution (30 mL) at 0°C, and then extracted with ethyl acetate (15 mL, three times). The combined organic layers were washed with saturated brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 40mL/min) to give *tert*-butyl (1-(4-bromophenyl)-1-hydroxypropan-2-yl)carbamate (380 mg, 1.04 mmol, 58.60% yield, 90% purity) as colorless oil . ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.48 - 7.45 (m, 2H), 7.22 (d, J = 8.3 Hz, 2H), 4.71 - 4.64 (m, 1H), 4.54 (d, J = 5.5 Hz, 1H), 3.86 - 3.75 (m, 1H), 3.61 - 3.51 (m, 1H), 1.47 - 1.40 (m, 12H), 1.08 (d, J = 6.7 Hz, 2H).

[0255] Step 2: To a solution of tert-butyl (1-(4-bromophenyl)-1-hydroxypropan-2-yl)carbamate (0.38 g, 1.15 mmol, 1 eq) in DCM (4 mL) was added (1,1-diacetoxy-3-oxo-1,2-benziodoxol-1-yl) acetate (0.98 g, 2.30 mmol, 713.05 µL, 2 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hours. The mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give tert-butyl (1-(4-bromophenyl)-1-oxopropan-2-yl)carbamate (0.27 g, 806.21 µmol, 70% yield, 98% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+$ = 229.

[0256] Step 3: A mixture of tert-butyl (1-(4-bromophenyl)-1-oxopropan-2-yl)carbamate (0.27 mg, 822.67 µmol, 1 eq) , 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (0.313 g, 1.23 mmol, 1.5 eq), KOAc (0.24 g, 2.47 mmol, 3 eq) and $Pd(dppf)Cl_2$ (0.06 g, 82.27 µmol, 0.1 eq) in dioxane (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 hours under N_2 atmosphere. The reaction mixture was used next step directly without purification. ***bor.9*** (0.31 g, crude) was obtained as black oil.

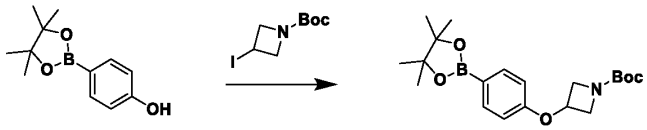
bor.10: tert-butyl N-methyl-N-[2-[methyl-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]amino]ethyl]carbamate



bor.10

[0257] To a solution of 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1 g, 4.48 mmol, 1 eq) and tert-butyl N-methyl-N-[2-(methylamino)ethyl]carbamate (0.84 g, 4.48 mmol, 1 eq) in DMF (10 mL) was added K_2CO_3 (1.86 g, 13.45 mmol, 3 eq) at 25 °C. The mixture was stirred at 80 °C for 16 hours. The mixture was diluted with water (100mL) and extracted with ethyl acetate (100 mL, three times). The organic phase was washed with brine (200 mL, three times), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 3/1). ***bor.10*** (300 mg, 689.99 μmol, 15.39% yield, 90% purity) was obtained as a white solid. MS m/z (ESI) $[M-82+H]^+$ = 310.2 (boric acid).

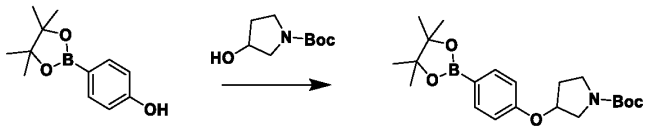
bor.11: tert-butyl 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]azetidine-1-carboxylate



bor.11

[0258] To a solution of tert-butyl 3-iodoazetidine-1-carboxylate (1.00 g, 3.53 mmol, 1.00 eq) and K_2CO_3 (0.98 g, 7.06 mmol, 2.00 eq) in DMF (10.0 mL) was added 4-(4,4,5,5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) phenol (0.85 g, 3.89 mmol, 1.10 eq) at 20 °C. The reaction mixture was stirred at 80 °C for 16 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate= 10/1 to 1/1) to give ***bor.11*** (1.00 g, 2.66 mmol, 75.4% yield) as a yellow solid. MS m/z (ESI) $[M-56+H]^+$ = 320.2.

bor.12: tert-butyl 3-[4-(4, 4, 5, 5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]pyrrolidine-1-carboxylate

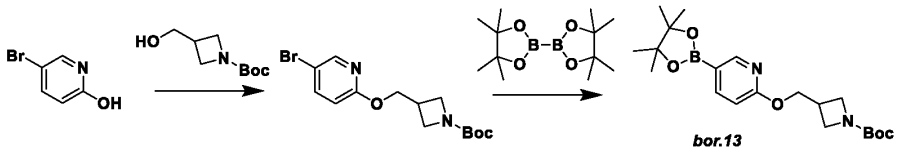


bor.12

[0259] To a solution of 4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) phenol (1.00 g, 4.54 mmol, 1.00 eq), tert-butyl 3-hydroxypyrrolidine-1-carboxylate (1.02 g, 5.45 mmol, 1.20 eq) and PPh_3 (1.79 g, 6.82 mmol, 1.50 eq) in THF (15.0 mL) was added (3E)-3-(dimethylcarbamoylimino)-1,1-dimethyl-urea (1.17 g, 6.82 mmol, 1.50 eq) at 0 °C. The reaction mixture was stirred at 20 °C for 16 hours. The reaction mixture was quenched by addition of water (15.0 mL) at 20 °C, and then extracted with EtOAc (15.0 mL, three times).

The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 2/1) to give *bor.12* (1.00 g, 2.57 mmol, 56.5% yield) as a white solid. MS m/z (ESI) = 334.1.

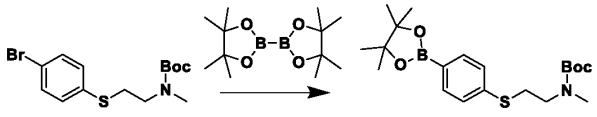
bor.13: tert-butyl 3-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxymethyl]azetidine-1-carboxylate



[0260] Step 1: To a solution of 5-bromopyridin-2-ol (1 g, 5.75 mmol, 1 eq), tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (1.61 g, 8.62 mmol, 1.5 eq) in THF (10 mL) was added DIAD (1.74 g, 8.62 mmol, 1.67 mL, 1.5 eq) and PPh_3 (2.26 g, 8.62 mmol, 1.5 eq) at 0°C. After stirring at 25°C for 16 hours, the reaction mixture was added into water(10 mL) and extracted with ethyl acetate30 mL (10 mL, three times). The combined organic layers were washed withbrine (10 mL, three times), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give tert-butyl 3-[(5-bromo-2-pyridyl)oxymethyl]azetidine-1-carboxylate (1.2 g, 3.15 mmol, 54.75% yield, 90% purity) as colorless oil. MS m/z (ESI) $[M+H]^+$ = 343.1.

[0261] Step 2: To a solution of tert-butyl 3-[(5-bromo-2-pyridyl)oxymethyl]azetidine-1-carboxylate (0.5 g, 1.46 mmol, 1 eq) , 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (0.55 g, 2.19 mmol, 1.5 eq) in dioxane (4 mL) was added $Pd(dppf)Cl_2$ (0.01 g, 145.68 μmol, 0.1 eq) and AcOK (0.43 g, 4.37 mmol, 3 eq) at 25°C. After stirring at 80°C for 16 hours, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~22% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give ***bor.13*** (0.5 g, 1.15 mmol, 79.15% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 391.3.

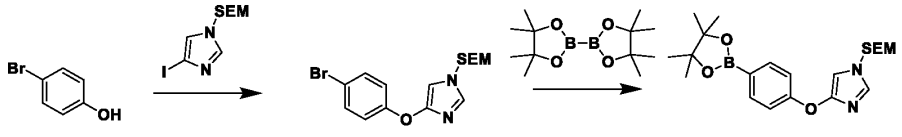
bor.14: tert-butyl N-methyl-N-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfanylethyl]carbamate



bor.14

[0262] A mixture of tert-butyl N-[2-(4-bromophenyl)sulfanylethyl]-N-methyl-carbamate (1.7 g, 4.91 mmol, 1 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.87 g, 7.36 mmol, 1.5 eq), $Pd(dppf)Cl_2$ (359 mg, 490.64 μmol, 0.1 eq) and KOAc (1.45 g, 14.73 mmol, 3 eq) in dioxane (20 mL) was stirred at 80 °C for 12hours under N_2. The mixture was concentrated and the residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~5% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give ***bor.14*** (1.9 g, 4.35 mmol, 88.55% yield, 90% purity) as light yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.58 (d, J = 8.1 Hz, 2H), 7.33 (br d, J = 7.0 Hz, 2H), 3.37 (br d, J = 6.3 Hz, 2H), 3.14 (br t, J = 6.7 Hz, 2H), 2.78 (br s, 3H), 1.42 - 1.32 (m, 9H), 1.28 (s, 12H). MS m/z (ESI) $[M-100+H]^+$ = 294.1.

bor.15: trimethyl-[2-[[4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy] imidazol-1-yl]methoxy]ethyl]silane

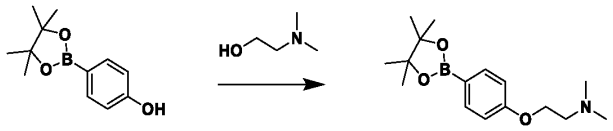


bor.15

[0263] Step 1: To a solution of 2-[(4-iodoimidazol-1-yl)methoxy]ethyl-trimethyl-silane (5.00 g, 15.42 mmol, 0.5 eq) in dioxane (70 mL) was added 4-bromophenol (8.07 g, 46.67 mmol, 1.5 eq) , Cs_2CO_3 (30.00 g, 92.08 mmol, 2.96 eq), bis[(Z)-1-methyl-3-oxo-but-1-enoxy]copper (800 mg, 3.06 mmol, 0.1 eq), then the resulting mixture was purged with N_2 three times and stirred at 120°C for 12 hours. The reaction mixture was partitioned between EtOAc(400 mL) and water(250 mL), washed with brine(200 mL), died over Na_2SO_4, filtered and evaporated under reduced pressure to give the crude product. The crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give a yellow solid. The yellow solid was purified by reversed-phase HPLC(0.1% FA condition) to give the 2-[[4-(4-bromophenoxy)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (1.5 g, 3.76 mmol, 12.10% yield, 92.7% purity) as a white solid. MS m/z (ESI) $[M+H]^+$= 371.1.

[0264] Step 2: To a solution of 2-[[4-(4-bromophenoxy)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (1.2 g, 3.25 mmol, 1 eq) in dioxane (15 mL) was added KOAc (960.00 mg, 9.78 mmol, 3.01 eq) , $Pd(dppf)Cl_2$ (360.00 mg, 492.00 μmol, 1.51e-1 eq) , 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1 g, 3.94 mmol, 1.21 eq), then the resulting mixture was purged with N_2 three timesand stirred at 80°C for 12 hours. The reaction mixture was filtered and evaporated under reduced pressure to give the crude product. The crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give ***bor.15*** (1 g, 2.17 mmol, 66.67% yield, 90.2% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 417.2.

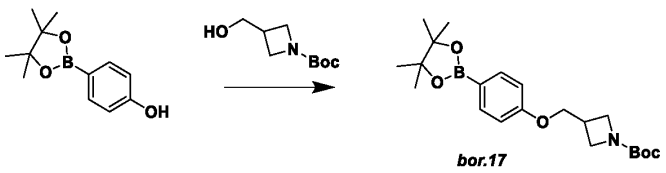
bor.16:N,N-dimethyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethanamine



bor.16

[0265] To a mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (10 g, 45.44 mmol, 1 eq), 2-(dimethylamino)ethanol (6.08 g, 68.16 mmol, 6.84 mL, 1.5 eq) and PPh_3 (21.45 g, 81.79 mmol, 1.8 eq) in THF (180 mL) was added DIAD (16.54 g, 81.79 mmol, 15.86 mL, 1.8 eq) at 0 °C. The mixture was stirred at 0~25 °C for 12hours under N_2. The mixture was concentrated and the residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give a crude product. The crude product was triturated with PE/EtOAc (v/v = 2/1, 60 ml) and then purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~35% THF/Petroleum ether gradient @ 100 mL/min). The product obtained was triturated with PE/EtOAc (v/v = 2/1, 21 ml) to give ***bor.16*** (3.1 g, 3.19 mmol, 7.03% yield, 30% purity) as brown oil. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.57 - 7.51 (m, 2H), 6.92 (d, J = 8.5 Hz, 2H), 4.09 - 4.03 (m, 2H), 2.61 (t, J = 5.8 Hz, 2H), 2.20 (s, 6H), 1.22 - 1.16 (m, 12H). MS m/z (ESI) $[M+H]^+$= 292.2.

bor.17: tert-butyl 3-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]methyl]azetidine-1-carboxylate

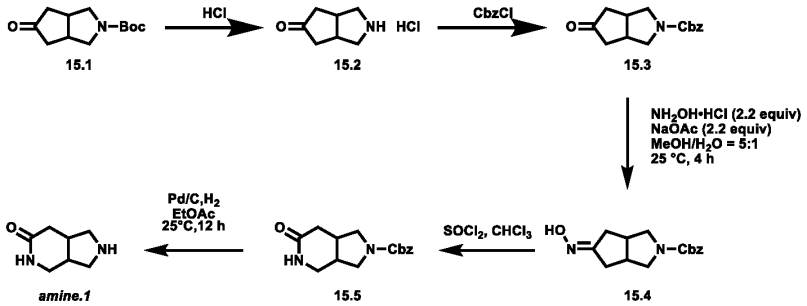


bor.17

[0266] To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (5 g, 22.72 mmol, 1 eq) tert-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (4.4 g, 23.50 mmol, 1.03 eq) and PPh_3 (9 g, 34.31 mmol, 1.51 eq) in THF (60 mL) was added DIAD (7.30 g, 36.11 mmol, 7 mL, 1.59 eq) at 0 °C under N_2, The reaction solution was stirred at 25°C for 12 hours. The reaction mixture was partitioned between EtOAc (1 L) and water (500 mL), washed with brine (400 mL), died over Na2SO4, filtered and evaporated under reduced pressure. The crude product was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give a residue. The residue was purified by reversed-phase HPLC (0.1% FA condition) to ***bor.17*** (5 g, 10.53 mmol, 46.36% yield, 82% purity) as a red oil. MS m/z (ESI) $[M+Na]^+$= 412.2.

Synthesis of amine intermediates

amine.1**:** 1, 2, 3, 3a, 4, 5, 7, 7a-octahydropyrrolo [3, 4-c] pyridin-6-one



[0267] Step 1: Tert-butyl 5-oxo-1,3,3a,4,6,6a-hexahydrocyclopenta[c]pyrrole-2-carboxylate **15.1** (5.0 g, 22 mmol, 1.0 eq) was added to HCl/dioxane (2 M, 40 mL, 3.6 eq). The reaction solution was stirred at 25 °C for 1 h. The solution was concentrated under *vacuum* to give 2,3,3a,4,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-5-one **15.2** (5.0 g, crude, HCl) as a yellow solid which was used for next step without further purification.

[0268] Step 2: To a solution of 2,3,3a,4,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-5-one **15.2** (3.6 g, 22 mmol, 1.0 eq, HCl) and TEA (7.3 g, 72 mmol, 10 mL, 3.2 eq) in DCM (40 mL) was added CbzCl (4.6 g, 27 mmol, 3.8 mL, 1.2 eq) at 0 °C, The reaction solution was stirred at 25 °C for 1 h. The residue was partitioned between EtOAc (50 mL) and water (50 mL). The combine organic phases were washed by sat. NaCl (50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give a crude material. The residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~20% EtOAc/PE gradient at 40 mL/min) to afford benzyl 5-oxo-1,3,3a,4,6,6a-hexahydrocyclopenta[c]pyrrole-2-carboxylate **15.3** (1.2 g, 3.4 mmol, 15% yield, 73% purity) as a light-yellow oil.

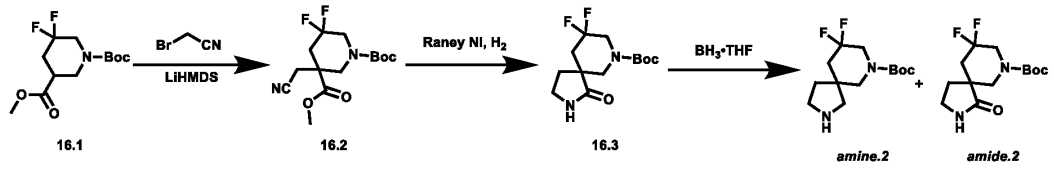
[0269] Step 3: To a solution of benzyl 5-oxo-1,3,3a,4,6,6a-hexahydrocyclopenta[c]pyrrole-2-carboxylate **15.3** (1.2 g, 4.6 mmol, 1.0 eq) in MeOH (20 mL) /H_2O (5 mL) was added $NH_2OH.HCl$ (0.72 g, 10 mmol, 2.2 eq) and NaOAc (1.1 g, 13 mmol, 2.8 eq). The reaction solution was stirred at 25 °C for 1 h. The residue was partitioned between EtOAc (500 mL) and water (500 mL). The combine organic phases were washed by sat. NaCl (500 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give a crude material. The residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~20% EtOAc/PE gradient at 40 mL/min) to afford benzyl 5-hydroxyimino-1,3,3a,4,6,6a-hexahydrocyclopenta[c]pyrrole-2-carboxylate **15.4** (1.2 g, 4.4 mmol, 95% yield) as a light-yellow oil. ^1H NMR (400 MHz, $CDCl_3$) *d* (ppm): 7.38 - 7.33 (m, 5H), 5.14 (d, *J* = 4.9 Hz, 2H), 3.71 - 3.63 (m, 2H), 3.33 - 3.18 (m, 2H), 2.83 - 2.65 (m, 4H), 2.44 - 2.34 (m, 2H).

[0270] Step 4: To a solution of benzyl 5-hydroxyimino-1,3,3a,4,6,6a-hexahydrocyclopenta[c]pyrrole-2-carboxylate **15.4** (1.2 g, 4.4 mmol, 1.0 eq) in THF (10 mL) was added $SOCl_2$ (1.6 g, 14 mmol, 1.0 mL, 3.2 eq) at 0 °C. The solution was stirred at 25 °C for 2 h. The residue was partitioned between EtOAc (500 mL) and water (500 mL). The combined organic phases were washed by sat. NaCl (500 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give a crude material. The residue obtained was purified by prep-HPLC **2** (gradient: 23%-53% ACN over 15 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give benzyl 6-oxo-3,3a,4,5,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridine-2-carboxylate **15.5** (0.60 g, 2.2 mmol, 50% yield, 100% purity) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) *d* (ppm): 7.40 - 7.37 (m, 5H), 5.16 (s, 2H), 3.79 - 3.62 (m, 3H), 3.45 - 3.28 (m, 3H), 2.94 - 2.60 (m, 3H), 2.47 (br dd, *J* = 3.7, 17.9 Hz, 1H). MS m/z (ESI) $[M+H]^+$ = 275.2.

[0271] Step 5: To a solution of Pd/C (20 mg, 10% purity) in EtOAc (5.0 mL) was added benzyl 6-oxo-3, 3a, 4, 5, 7, 7a-hexahydro-1H-pyrrolo[3, 4-c]pyridine-2-carboxylate **15.5** (0.10 g, 0.36 mmol, 1.0 eq) under N_2. The reaction solution was degassed and purged under H_2 for three times. The reaction solution was stirred at 25 °C for 12 h. The reaction solution was filtered, and the filtrate was concentrated under vacuum to give 1, 2, 3, 3a, 4, 5, 7, 7a-octahydropyrrolo [3, 4-c] pyridin-6-one ***amine.1*** (50 mg, crude) as a yellow oil was used for next step without purification.

Amine.2: tert-butyl 9,9-difluoro-2,7-diazaspiro [4.5] decane-7-carboxylate

Amide.2: tert-butyl 9,9-difluoro-1-oxo-2,7-diazaspiro [4.5] decane-7-carboxylate



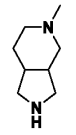
[0272] Step 1: A solution of 1-(tert-butyl) 3-methyl 5,5-difluoropiperidine-1,3-dicarboxylate **16.1** (0.80 g, 2.9 mmol, 1.0 eq) in THF (10 mL) was degassed and purged with nitrogen three times. To the mixture was added LiHMDS (1 M, 4.50 mL, 1.6 eq) at -78 °C. After stirring at -78 °C for 0.5 h, was added 2-bromoacetonitrile (0.70 g, 5.8 mmol, 2.0 eq) at -78 °C. Then the mixture was stirred at 25 °C for another 1.5 h under nitrogen atmosphere. The reaction mixture was quenched by saturated ammonium chloride aqueous solution (20 mL) and saturated sodium bicarbonate solution (20 mL). The mixture was then extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 10 mL), dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue obtained was purified by Flash chromatography **2** (12 g column, Eluent of 0 to 20% EtOAc/PE gradient at 30 mL/min) to give 1-(tert-butyl) 3-methyl 3-(cyanomethyl)-5,5-difluoropiperidine-1,3-dicarboxylate **16.2** (0.90 g, 2.8 mmol, 99% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.87 - 3.74 (m, 2H), 3.71 (s, 3H), 3.67 - 3.53 (m, 2H), 2.84 (s, 2H), 2.63 - 2.52 (m, 1H), 2.34 - 2.20 (m, 1H), 1.42 (s, 9H).

[0273] Step 2: To a solution of 1-(tert-butyl) 3-methyl 3-(cyanomethyl)-5,5-difluoropiperidine-1,3-dicarboxylate **16.2** (0.90 g, 2.8 mmol, 1.0 eq) in MeOH (20 mL) was added Raney-Ni (0.10 g) at 25 °C in a high-pressure reaction reactor. The mixture was stirred at 25 °C for under hydrogen (50 Psi) for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give tert-butyl 7,7-difluoro-1-oxo-2,9-diazaspiro [4.5] decane-9-carboxylate **16.3** (0.75 g, 2.6 mmol, 91% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.94 (s, 1H), 4.28 - 4.05 (m, 1H), 3.95 - 3.73 (m, 1H), 3.30 - 3.09 (m, 3H), 2.88 - 2.65 (m, 1H), 2.31 - 2.13 (m, 1H), 2.04 – 1.83 (m, 3H), 1.41 (s, 9H).

[0274] Step 3: To a solution of tert-butyl 7,7-difluoro-1-oxo-2,9-diazaspiro [4.5] decane-9-carboxylate **16.3** (0.70 g, 2.4 mmol, 1.0 eq) in THF (10 mL) was added BH_3/Me_2S (10 M, 3.0 mL, 12 eq) at 25 °C. The mixture was stirred at 50 °C for 3 h. The reaction mixture was quenched with saturated ammonium chloride aqueous solution (30 mL) and then extracted

with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (3 × 10 mL), dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a mixture of ***amine.2*** and ***amide.2*** (650 mg, crude) as a white solid.

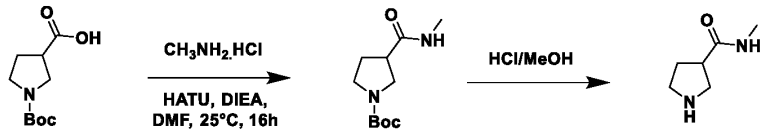
amine.3: cis-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine



amine 3

[0275] To a solution of tert-butyl cis-octahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate (1.5 g, 5.71 mmol, 1 *eq*, HCl salt) in THF (30 mL) was added dropwise $LiAlH_4$ (2.5 M, 7 mL, 3 *eq*) at 0 °C over 1 min. After addition, the mixture was stirred at 50 °C for 16 hours under N_2 atmosphere. The reaction mixture was added Na_2SO_4 (2 g) and water (0.5 mL) at 20 °C, and then diluted with EtOAc (20 mL) filtered and concentrated under reduced pressure to give ***amine.3*** (800 mg, crude) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.06 - 2.52 (m, 8H), 2.24 - 2.22 (m, 3H), 1.81 - 1.60 (m, 4H).

amine.4: N-methylpyrrolidine-3-carboxamide



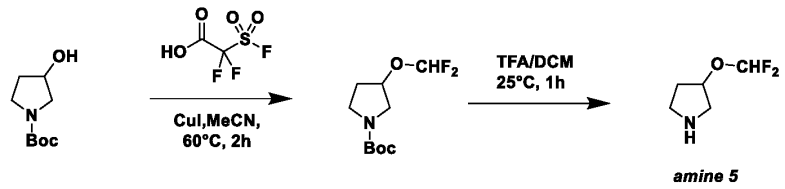
amine 4

[0276] Step 1: To a solution of 1-tert-butoxycarbonylpyrrolidine-3-carboxylic acid (2 g, 9.29 mmol, 1 eq) in DMF (20 mL) was added methanamine;hydrochloride (750 mg, 11.11 mmol, 1.2 eq), HATU (5.30 g, 13.94 mmol, 1.5 eq) and DIEA (3.60 g, 27.88 mmol, 4.86 mL, 3 eq) at 25°C.The mixture was stirred at 25 °C for 16 hours . The reaction mixture was diluted with water (35 mL) and extracted with ethyl acetate (25 mL, three times). The combined organic layers were washed with brine (30 mL) and saturated $NaHCO_3$ solution (30 ml), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 3-(methylcarbamoyl)pyrrolidine-1-carboxylate (950 mg, crude). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.87 (s, 1H), 3.44 - 3.33 (m, 2H), 3.24 - 3.15 (m, 2H), 2.91 - 2.80 (m, 1H), 2.57 (d, J = 4.5 Hz, 3H), 1.98 - 1.81 (m, 2H), 1.39 (s, 9H).

[0277] Step 2: To a solution of tert-butyl 3-(methylcarbamoyl)pyrrolidine-1-carboxylate (950 mg, 4.16 mmol, 1 eq) in MeOH (1 mL) was added HCl/MeOH (2 M, 3 mL) at 25°C .The

mixture was stirred at 25 °C for 4 hours . The reaction mixture was filtered and concentrated under reduced pressure to give ***amine.4*** (700 mg, crude). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.56 - 9.31 (m, 1H), 9.17 (d, J = 4.9 Hz, 1H), 8.19 (d, J = 3.1 Hz, 1H), 3.34 - 3.25 (m, 1H), 3.20 - 3.12 (m, 3H), 3.01 (q, J = 7.7 Hz, 1H), 2.59 (d, J = 4.6 Hz, 3H), 2.16 - 2.05 (m, 1H), 1.96 - 1.85 (m, 1H).

amine.5**:** 3-(difluoromethoxy)pyrrolidine

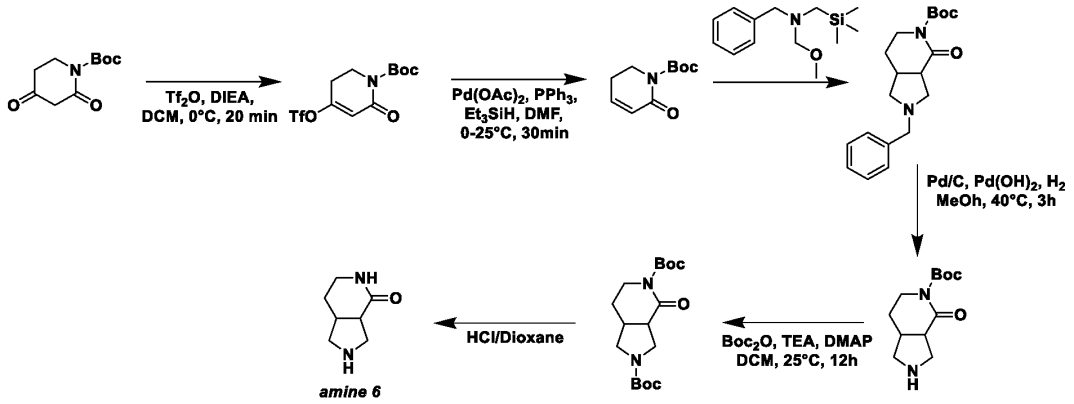


amine 5

[0278] Step 1: To a solution of tert-butyl 3-hydroxypyrrolidine-1-carboxylate (1 g, 5.34 mmol, 1 eq) in MeCN (20 mL) was added CuI (250 mg, 1.31 mmol, 0.25 eq) , 2,2-difluoro-2-fluorosulfonyl-acetic acid (2.30 g, 12.90 mmol, 1.33 mL, 2.42 eq), 2,2-difluoro-2-fluorosulfonyl-acetic acid (2.30 g, 12.90 mmol, 1.33 mL, 2.42 eq) , then the resulting mixture was stirred at 60°C for 2 hours. The reaction mixture was partitioned between EtOAc (150 mL) and water (80 mL), washed with brine (70 mL), died over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give tert-butyl 3-(difluoromethoxy)pyrrolidine-1-carboxylate (400 mg, 1.69 mmol, 31.57% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.45 - 6.01 (m, 1H), 3.63 - 3.36 (m, 4H), 2.14 - 2.05 (m, 2H), 1.47 (s, 9H).

[0279] Step 2: To a solution of tert-butyl 3-(difluoromethoxy)pyrrolidine-1-carboxylate (300 mg, 1.26 mmol, 1 eq) in DCM (2 mL) was added TFA (767.50 mg, 6.73 mmol, 0.5 mL, 5.32 eq), then resulting mixture was stirred at 25°C for 1 hour. The reaction mixture was filtered and evaporated under reduced pressure to give the ***amine.5*** (200 mg, crude) as colourless oil which was used without further purification.

***amine.6*:** cis-octahydro-4H-pyrrolo[3,4-c]pyridin-4-one



[0280] Step 1: To a solution of tert-butyl 2,4-dioxopiperidine-1-carboxylate (20 g, 93.80 mmol, 1 eq) and DIEA (22.26 g, 172.24 mmol, 30 mL, 1.84 eq) in DCM (200 mL) was added trifluoromethylsulfonyl trifluoromethanesulfonate (31 g, 109.87 mmol, 18.13 mL, 1.17 eq) at 0 °C. The reaction solution was stirred at 0 °C for another 30 min. The residue was partitioned between EtOAc (500 mL) and water (500 mL). The organic phase was washed by saturated NaCl (50 mL) . The combined organic layers were dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% eToaC/Petroleum ether gradient @ 40 mL/min) to afford tert-butyl 6-oxo-4-(trifluoromethylsulfonyloxy)-2,3-dihydropyridine-1-carboxylate (28 g, 81.09 mmol, 86.45% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.02 (s, 1H), 3.99 (t, J = 6.6 Hz, 2H), 2.77 (t, J = 6.5 Hz, 2H), 1.55 (s, 9H).

[0281] Step 2: Under nitrogen, to a solution of tert-butyl 6-oxo-4-(trifluoromethylsulfonyloxy)-2,3-dihydropyridine-1-carboxylate (26 g, 75.30 mmol, 1 eq), Pd(OAc)2 (3.40 g, 15.14 mmol, 2.01e-1 eq) , and PPh3 (7.80 g, 29.74 mmol, 3.95e-1 eq) in DMF (300 mL) was added Et_3SiH (17.47 g, 150.26 mmol, 24 mL, 2 eq) at 0 °C. The mixture was then stirred at 25 °C for 30 minutes. The residue was partitioned between EtOAc (500 mL) and water (500 mL). The organic phase was washed by saturated NaCl (50 mL). The combined organic layers were dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc/Petroleum ether gradient @ 40 mL/min) to afford tert-butyl 6-oxo-2,3-dihydropyridine-1-carboxylate (10 g, 50.70 mmol, 67.33% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 6.86 - 6.67 (m, 1H), 6.03 - 5.85 (m, 1H), 3.86 (dt, J = 3.2, 6.4 Hz, 2H), 2.41 (td, J = 2.0, 4.2 Hz, 2H), 1.54 (d, J = 3.4 Hz, 9H).

[0282] Step 3: To a solution of tert-butyl 6-oxo-2,3-dihydropyridine-1-carboxylate (10 g, 50.70 mmol, 1 eq) in MeCN (100 mL) was added N-(methoxymethyl)-1-phenyl-N-(trimethylsilylmethyl)methanamine (24 g, 101.09 mmol, 1.99 eq). The reaction solution was stirred at 25 °C for 12 hours. The reaction solution concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% THF/Petroleum ether gradient @ 100 mL/min) to afford tert-butyl cis-2-benzyl-4-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate (16 g, 48.42 mmol, 95.51% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.34 - 7.23 (m, 5H), 3.95 (ddd, J = 3.1, 6.2, 13.1 Hz, 1H), 3.61 - 3.43 (m, 3H), 3.14 - 3.04 (m, 1H), 2.97 - 2.77 (m, 3H), 2.69 - 2.54 (m, 1H), 2.21 (dd, J = 6.1, 9.2 Hz, 1H), 2.00 - 1.87 (m, 1H), 1.60 - 1.47 (m, 10H).

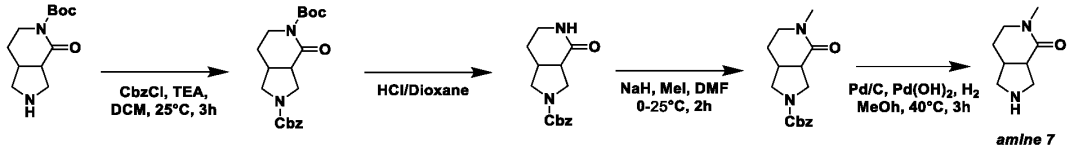
[0283] Step 4: To a solution of tert-butyl cis-2-benzyl-4-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate (8 g, 24.21 mmol, 1 eq) in MeOH (300 mL) was added Pd/C (1 g, 10% purity and $Pd(OH)_2$ (1 g, 20% purity) under N_2, The reaction solution was degassed and purged under H_2 for three times, The reaction solution was stirred at 40 °C for 3 hours. The reaction solution was filtered and filtrate was concentrated under vacuum to give tert-butyl cis-4-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate (4.8 g, crude) as a yellow oil which was used for next step without further confirmed.

[0284] Step 5: To a solution of tert-butyl cis-4-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate (4.8 g, 19.98 mmol, 1 eq) in DCM (50 mL) was added $(Boc)_2O$ (5.23 g, 23.97 mmol, 5.51 mL, 1.2 eq) ,TEA (6.54 g, 64.66 mmol, 9 mL, 3.24 eq) and DMAP (250 mg, 2.05 mmol, 0.1 eq) ,The reaction solution was stirred at 25 °C for 1 hour. The residue was partitioned between EtOAc (300 mL) and water (300 mL). The organic phase was washed by saturated NaCl (300 mL) . The combined organic layers were dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% THF/Petroleum ether gradient @ 100 mL/min) to afford di-tert-butyl cis-4-oxohexahydro-2H-pyrrolo[3,4-c]pyridine-2,5(3H)-dicarboxylate (5.5 g, 14.38 mmol, 71.99% yield, 89% purity) as a yellow oil. MS m/z (ESI) $[M+Na]^+$= 363.1.

[0285] Step 6: Di-tert-butyl cis-4-oxohexahydro-2H-pyrrolo[3,4-c]pyridine-2,5(3H)-dicarboxylate (5.5 g, 16.16 mmol, 1 eq) was added to HCl/dioxane (2 M, 50 mL, 6.19 eq). The reaction solution was stirred at 25 °C for 1 hour. The reaction solution was concentrated

under vacuum to give ***amine.6*** (3 g, crude, HCl) as a white solid which was used for next step without further purification.

***amine.7*:** cis-5-methyloctahydro-4H-pyrrolo[3,4-c]pyridin-4-one



amine 7

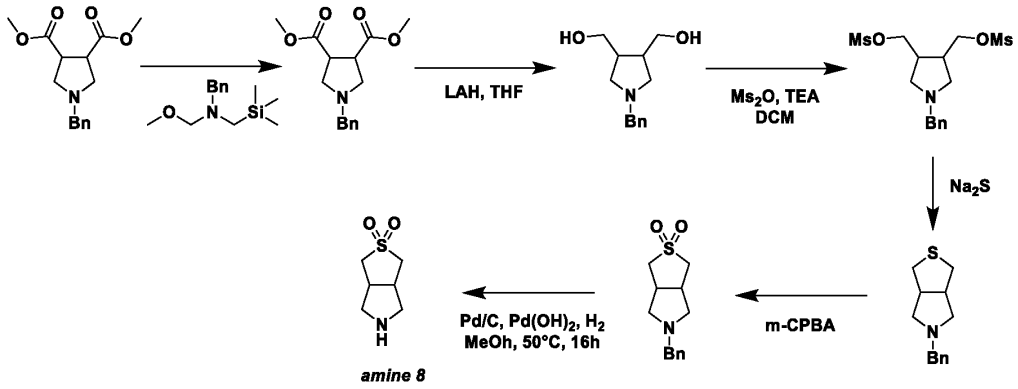
[0286] Step 1: To a solution of tert-butyl cis-4-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate (13.6 g, 56.60 mmol, 1 eq) in DCM (150 mL) was added CbzCl (9.80 g, 57.44 mmol, 8.2 mL, 1.01 eq) and TEA (14.54 g, 143.69 mmol, 20 mL, 2.54 eq). The reaction solution was stirred at 25 °C for 1 hour. The mixture was diluted with water (60 ml), and then extracted with EtOAc (50 mL, twice). The combined organic phase was washed with brine (50 ml, three times), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~3% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give 2-benzyl 5-(tert-butyl) cis-4-oxohexahydro-2H-pyrrolo[3,4-c]pyridine-2,5(3H)-dicarboxylate (6 g, 14.74 mmol, 26.05% yield, 92% purity) as a colorless oil. MS m/z (ESI) $[M+Na]^+$= 397.1.

[0287] Step 2: 2-benzyl 5-(tert-butyl) cis-4-oxohexahydro-2H-pyrrolo[3,4-c]pyridine-2,5(3H)-dicarboxylate (5 g, 13.35 mmol, 1 eq) was added to HCl/dioxane (2 M, 100 mL). The reaction solution was stirred at 25 °C for 1 hour. The reaction solution was concentrated under vacuum to give benzyl cis-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate (4 g, crude) as a yellow oil which was used for next step without further purification.

[0288] Step 3: To a solution of benzyl cis-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate (3.5 g, 12.76 mmol, 1 eq) in DMF (40 mL) was added NaH (1.5 g, 37.50 mmol, 60% purity, 2.94 eq) at 0 °C under N_2. The reaction solution was stirred at 25 °C for 1 hour. MeI (2.28 g, 16.06 mmol, 1 mL, 1.26 eq) was added to the solution at 0 °C and stirred at 25 °C for another 1 hour. The mixture was quenched by H_2O (100 mL), then the aqueous phase was extracted with EtOAc (100 mL, three times). The combined organic layers were dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~70% THF/Petroleum ether gradient @ 100 mL/min) to give benzyl cis-5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate (2.6 g, 8.66 mmol, 67.85% yield, 96% purity) as a colorless oil. MS m/z (ESI) $[M+H]^+$= 289.1.

[0289] Step 4: To a solution of benzyl cis-5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate (2.5 g, 8.67 mmol, 1 eq) in MeOH (200 mL) was added Pd/C (300 mg, 10% purity) and $Pd(OH)_2$ (300 mg, 20% purity) under N_2. The reaction solution was degassed and purged under H_2 for three times. The reaction solution was stirred at 40 °C for 3 hours. The reaction solution was filtered and the filtrate was concentrated under vacuum to give ***amine.7*** (1.5 g, crude) as a colorless oil which was used for next step without further purification.

amine.8**:** 3,3a,4,5,6,6a-hexahydro-1H-thieno[3,4-c]pyrrole 2,2-dioxide



[0290] Step 1: To a solution of dimethyl (Z)-but-2-enedioate (1 g, 6.94 mmol, 871.08 μL, 1 eq) in CH_3CN (10 mL) was added N-(methoxymethyl)-1-phenyl-N-(trimethylsilylmethyl)methanamine (3.29 g, 13.88 mmol, 2 eq) at 0 °C .The mixture was stirred at 25 °C for 2 hours. The mixture was diluted with water (30mL) and extracted with EtOAc (30 mL, three times). The organic phase was washed with brine (40 mL), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give dimethyl 1-benzylpyrrolidine-3,4-dicarboxylate (1.1 g, 3.81 mmol, 54.88% yield, 96% purity) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26 - 7.19 (m, 5H), 3.60 (s, 8H), 3.28 - 3.22 (m, 2H), 3.12 - 3.05 (m, 2H), 2.70 - 2.63 (m, 2H).

[0291] Step 2: To a solution of dimethyl 1-benzylpyrrolidine-3,4-dicarboxylate (1 g, 3.61 mmol, 1 eq) in THF (10 mL)was added $LiAlH_4$ (2.5 M, 5.7 mL, 3.95 eq) at 0 °C. The mixture was stirred at 60 °C for 16 hours under N_2atmosphere.The reaction mixture was added Na2SO4.10 H_2O (6 g) at 0 °C, and then diluted with EtOAc (20mL) filtered and concentrated under reduced pressure to give [1-benzyl-4-(hydroxymethyl)pyrrolidin-3-yl]methanol (700

mg, 3.16 mmol, 87.72% yield) as colorless oil. The crude was used next step without purification. MS m/z (ESI) $[M+H]^+$= 222.2.

[0292] Step 3: To a solution of [1-benzyl-4-(hydroxymethyl)pyrrolidin-3-yl]methanol (600 mg, 2.71 mmol, 1 eq) and TEA (1.65 g, 16.27 mmol, 2.26 mL, 6 eq) in DCM (10 mL) was added methylsulfonyl methanesulfonate (1.42 g, 8.13 mmol, 3 eq) at 0 °C. The mixture was stirred at 25 °C for 16 hours. The mixture was diluted with water (20 mL) and extracted with DCM (20 mL *3). The organic phase was washed with brine (40 mL), dried over Na_2SO_4, filtrated and evaporated to give [1-benzyl-4-(methylsulfonyloxymethyl)pyrrolidin-3-yl]methyl methanesulfonate (1.1 g, crude) as yellow oil. The crude was used next step without purification.

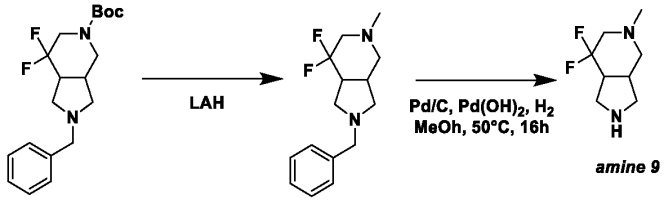
[0293] Step 4: To a solution of [1-benzyl-4-(methylsulfonyloxymethyl)pyrrolidin-3-yl]methyl methanesulfonate (1.1 g, 2.91 mmol, 1 eq) in DMF (11 mL) was added Na_2S (682.29 mg, 8.74 mmol, 366.82 μL, 3 eq) at 25 °C. The mixture was stirred at 60 °C for 16 hours. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL, three times). The organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 20g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give 5-benzyl-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrole (600 mg, 2.19 mmol, 75.09% yield, 80% purity) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 - 7.26 (m, 5H), 3.58 (s, 2H), 3.04 - 2.84 (m, 6H), 2.60 - 2.55 (m, 2H), 2.16 - 2.15 (m, 2H).

[0294] Step 5: To a solution of 5-benzyl-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrole (600 mg, 2.74 mmol, 1 eq) in DCM (10 mL) was added m-CPBA (1.67 g, 8.21 mmol, 85% purity, 3 eq) at 0°C, the mixture was stirred at 25 °C for 16 hours. The reaction mixture was quenched with sat.aturated Na_2SO_3 (50 mL) and extracted with EtOAc (60 mL, three times). The combined organic phase was washed with saturated NaCl (150 mL), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by prep-TLC (SiO2, Petroleum ether : Ethyl acetate = 0:1) to give 5-benzyl-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrole 2,2-dioxide (370 mg, 1.47 mmol, 53.82% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 - 7.28 (m, 5H), 3.68 (s, 2H), 3.22 (dd, J = 7.8, 12.8 Hz, 2H), 3.06 (d, J = 1.8 Hz, 2H), 2.98 - 2.87 (m, 4H), 2.67 (s, 2H).

[0295] Step 6: To a solution of Pd/C (37 mg, 10% purity) and $Pd(OH)_2$ (37 mg, 20% purity) inMeOH MeOH (10 mL) was added 5-benzyl-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrole 2,2-dioxide (370 mg, 1.47 mmol, 1 eq) at 25 °C under N_2. The suspension was degassed

under vacuum and purged with H_2 three times. The mixture was stirred under H_2 (50 psi) at 50°C for 16 hours. The reaction mixture was diluted with MeOH (10 mL). Then the mixture was filtered through a pad of celite and the filtrate was concentrated to give ***amine.8*** (200 mg, crude) as a white solid. The crude was used next step without purification. MS m/z (ESI) $[M+H]^+$= 162.2.

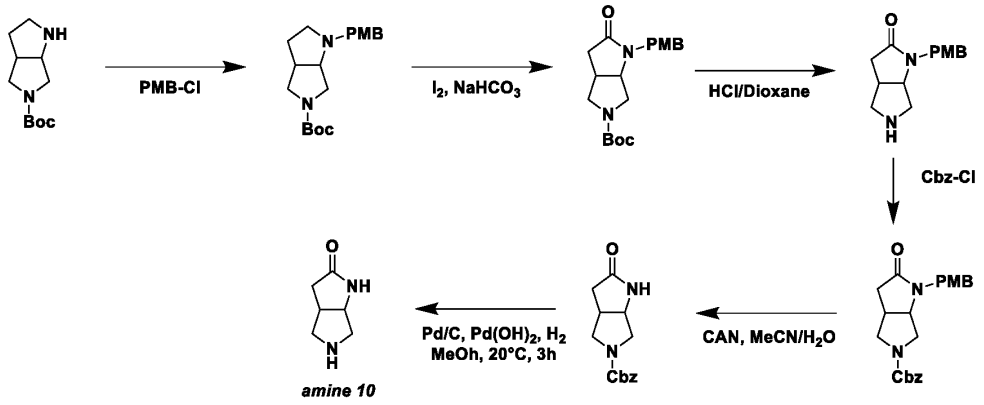
amine.9**:** cis-7,7-difluoro-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine



[0296] Step 1: To a solution of tert-butyl cis-2-benzyl-7,7-difluorooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate (500.00 mg, 1.42 mmol, 1 eq) in THF (10 mL) was added LAH (2.5 M, 850.00 µL, 1.5 eq) at 0 °C. The mixture was stirred at 50 °C for 16 hours under N_2 atmosphere. The reaction mixture was added $Na_2SO_4.10\ H_2O$ (750 mg) at 0 °C, and then diluted with EtOAc(20 mL) filtered and concentrated under reduced pressure to give cis-2-benzyl-7,7-difluoro-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine (440 mg, crude) was obtained as yellow oil. The crude was used next step without purification. MS m/z (ESI) $[M+H]^+$= 267.1.

[0297] Step 2: To a solution of Pd/C (44 mg, 10% purity) and $Pd(OH)_2$ (44 mg, 20% purity) in MeOH (10 mL) was added cis-2-benzyl-7,7-difluoro-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine (440 mg, 1.65 mmol, 1 eq) at 25 °C under N_2. The suspension was degassed under vacuum and purged with H_2 three times. The mixture was stirred under H_2 (50psi) at 50 °C for 16 hours. The reaction mixture was diluted with MeOH (20 mL),the mixture was filtered through a pad of celite and the filtrate was concentrated to give ***amine.9*** (300 mg, crude) as colorless oil. The crude was used next step without purification.

amine.10: 3,3a,4,5,6,6a-hexahydro-1H-pyrrolo[3,4-b]pyrrol-2-one



[0298] Step 1: To a solution of tert-butyl 2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-b]pyrrole-5-carboxylate (2.5 g, 11.78 mmol, 1 eq) in DMF (35 mL) were added K_2CO_3 (4.88 g, 35.33 mmol, 3 eq) and PMB-Cl (1.94 g, 12.37 mmol, 1.68 mL, 1.05 eq) at 20°C, The mixture was stirred at 20 °C for 24 hours. The reaction mixture was diluted with water (50 ml) and then extracted with ethyl acetate(50 mL, three times). The combined organic phase was washed with brine (20 mL, three times), dried with Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~40%Ethylacetate/Petroleum ether gradient @40 mL/min) to give tert-butyl1-[(4-methoxyphenyl)methyl]-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrole-5-carboxylate (2.8 g, 8.17 mmol, 69.38% yield, 97% purity) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.17 (d, J = 8.44 Hz, 2 H), 6.86 (d, J =8.44 Hz, 2 H), 3.72 (s, 3 H), 3.29 (s, 2 H), 3.15 - 3.03 (m, 2 H), 2.97 (t, J =6.30 Hz, 1 H), 2.83 (s, 1 H), 2.69 (s, 1 H), 2.21 (d, J =7.95 Hz, 1 H), 1.91 (d, J =9.54 Hz, 1 H), 1.50 - 1.41 (m, 1 H), 1.38 (s, 9 H). MS m/z (ESI) $[M+H]^+$= 333.3.

[0299] Step 2: To a solution of tert-butyl 1-[(4-methoxyphenyl)methyl]-2,3,3a,4,6,6a-hexahydropyrrolo [3,4-b]pyrrole-5-carboxylate (2.8 g, 8.42 mmol, 1 eq) in THF (30 mL) was added H_2O (10 mL), I_2 (16.03 g, 63.17 mmol, 7.5 eq) and $NaHCO_3$ (7.08 g, 84.23 mmol, 10 eq) at 20°C, the mixture was stirred at 20 °C for12 hours. The reaction mixture was diluted with water (20mL) and then extracted with ethyl acetate(30mL, three times), the combined organic phase was washed with brine (10mL, three times) ,dried with Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50%tetrahydrofuran/Petroleum ether gradient @ 40 mL/min) to give tert-butyl1-[(4-methoxyphenyl)methyl]-2-oxo-3a,4,6,6a-tetrahydro-

3H-pyrrolo [3,4-b]pyrrole-5-carboxylate (1.1 g, 2.54 mmol, 30.16% yield, 80% purity) as a yellow gum. MS m/z (ESI) $[M-55]^+$= 291.3.

[0300] Step 3: To a solution of tert-butyl1-[(4-methoxyphenyl)methyl]-2-oxo-3a,4,6,6a-tetrahydro-3H- pyrrolo[3,4-b]pyrrole-5-carboxylate (1.1 g, 3.18 mmol, 1 eq) in dioxane (2 mL) was added HCl/dioxane (2.5 M, 15 mL, 11.8 eq) at 20°C. The mixture was stirred at 20 °C for 12 hours. The reaction mixture was concentrated under reduce presser to give crude 1-[(4-methoxyphenyl) methyl]-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-b]pyrrol-2-one (1 g, crude, HCl) as yellow gum which was used in the next step directly without further purification.

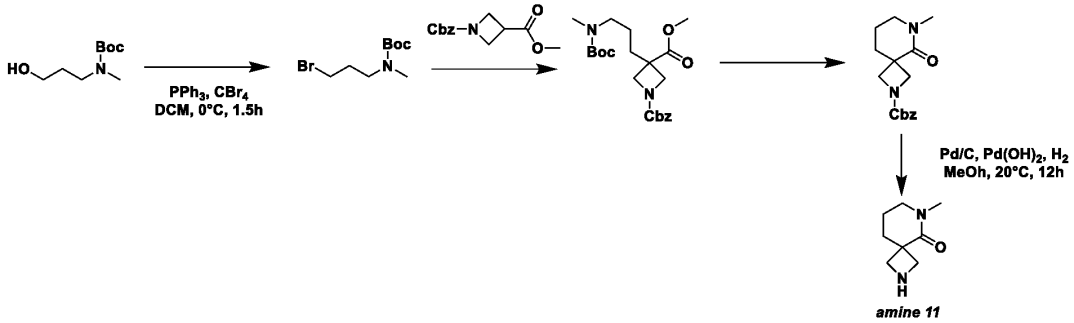
[0301] Step 4: To a solution of 1-[(4-methoxyphenyl)methyl]-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-b] pyrrol-2-one (1 g, 3.15 mmol, 1 eq, HCl) in THF (15 mL), H_2O (2 mL) were added $NaHCO_3$ (1.32 g, 15.74 mmol, 5 eq) and Cbz-Cl (800 mg, 4.69 mmol, 1.49 eq) at 20°C. The mixture was stirred at 20°C for 12 hours. The reaction mixture was diluted with water (20 mL) and then extracted with ethyl acetate (30 mL, three times), the combined organic phase was washed with brine (10mL, 3 times), dried with Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~55%Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give benzyl1-[(4-methoxyphenyl)methyl]- 2-oxo-3a,4,6,6a-tetrahydro-3H-pyrrolo[3,4-b]pyrrole-5-carboxylate (1.2 g, 2.40 mmol, 76.16% yield, 76% purity) as yellow gum. MS m/z (ESI) $[M+H]^+$= 381.1.

[0302] Step 5: To a solution of benzyl1-[(4-methoxyphenyl)methyl]-2-oxo-3a,4,6,6a-tetrahydro-3H-pyrrolo [3,4-b]pyrrole-5-carboxylate (1.2 g, 2.49 mmol, 1 eq) in MeCN (20 mL), H_2O (2 mL) was added ceric ammonium nitrate (6.8 g, 12.40 mmol, 6.18 mL, 4.98 eq) at 20°C. The mixture was stirred at 20°C for 12 hours. The reaction mixture was diluted with water (10 mL), quenched with saturated sodium sulfite solution (20 mL), and then extracted with ethyl acetate (30mL, three times). The combined organic phase was washed with brine (10 mL, three times), dried with Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 20g SepaFlash® Silica Flash Column, Eluent of 0~80% tetrahydrofuran/Petroleum ether gradient @ 40 mL/min)to give crude product as a yellow solid. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm*10um;mobile phase: [water(FA)-ACN]; gradient:12%-42% B over 10 min) to give benzyl 2-oxo-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrole-5-carboxylate (0.15 g, 576.29 μmol, 23.13% yield, 100% purity) as a white solid. MS m/z (ESI) $[M+H]^+$= 261.2.

[0303] Step 6: To a mixture of benzyl 2-oxo-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrole-5-carboxylate (140 mg, 537.87 μmol, 1 eq) in MeOH (20 mL) were added Pd/C (186.67 mg,

175.41 μmol, 10% purity, 0.033 eq) at 20 °C. The suspension was degassed under vacuum and purged with H_2 three times. The mixture was stirred under H_2 (50psi) at 20 °C for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give crude ***amine.10*** as a white solid which was used in the next step directly without further purification.

amine.11: 6-methyl-2,6-diazaspiro[3.5]nonan-5-one



[0304] Step 1: To a mixture of tert-butyl N-(3-hydroxypropyl)-N-methyl-carbamate (8 g, 42.27 mmol, 1 eq) and PPh_3 (14.41 g, 54.95 mmol, 1.3 eq) in DCM (80 mL) was added CBr_4 (18.22 g, 54.95 mmol, 1.3 eq) at 0 °C. The mixture was stirred at 0 °C for 1.5 hours under N_2. The mixture was washed with water (50 ml), saturated sodium bicarbonate solution (50 ml), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~6% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give tert-butyl N-(3-bromopropyl)-N-methyl-carbamate (8.65 g, 34.31 mmol, 81.15% yield, 100% purity) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.44 - 3.28 (m, 4H), 2.86 (s, 3H), 2.13 - 2.01 (m, 2H), 1.45 (s, 9H). MS m/z (ESI) $[M-56+H]^+$= 198.0.

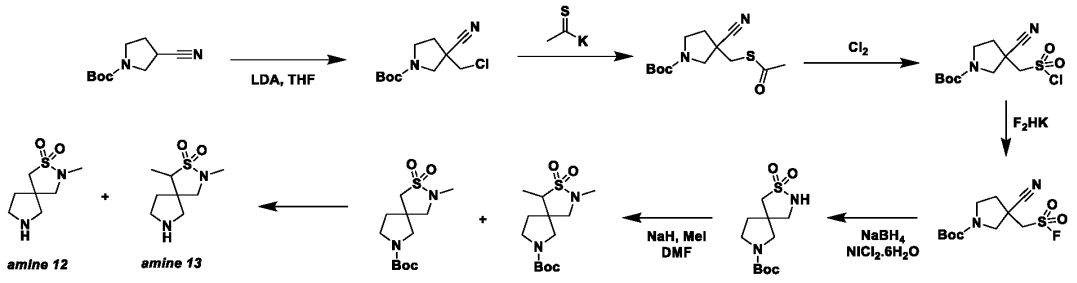
[0305] Step 2: To a mixture of O1-benzyl O3-methyl azetidine-1,3-dicarboxylate (5 g, 20.06 mmol, 1 eq) in THF (50 mL) was added LiHMDS (1 M, 26 mL, 1.3 eq) at -40 °C under N_2. The mixture was stirred at -40 °C for 0.5 hour under N_2, and then a solution of tert-butyl N-(3-bromopropyl)-N-methyl-carbamate (6.07 g, 24.07 mmol, 1.2 eq) in THF (10 mL) was added. The mixture was stirred at -40~10 °C for 12 hours under N_2. The mixture was quenched with sat.NH_4Cl solution (50 ml) at 0 °C, and then extracted with EtOAc (30 mL, 2 times). The combined organic phase was washed with brine, dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give O1-benzyl O3-methyl 3-[3-[tert-

butoxycarbonyl(methyl)amino]propyl]azetidine-1,3-dicarboxylate (700 mg, 1.07 mmol, 5.35% yield, 64.5% purity) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.41 - 7.29 (m, 5H), 5.03 (s, 2H), 4.19 - 4.04 (m, 2H), 3.86 - 3.60 (m, 5H), 3.13 (br t, J = 6.9 Hz, 2H), 2.74 (s, 3H), 1.83 - 1.71 (m, 2H), 1.37 (s, 11H). MS m/z (ESI) $[M-11+H]^+$= 321.1.

[0306] Step 3: A mixture of O1-benzyl O3-methyl 3-[3-[tert-butoxycarbonyl(methyl)amino]propyl]azetidine-1,3-dicarboxylate (360 mg, 856.13 µmol, 1 eq) and TFA (1.07 g, 9.42 mmol, 0.7 mL, 11.01 eq) in DCM (7 mL) was stirred at 20 °C for 1 hour, and then the mixture was adjusted to pH= 8 with saturated sodium bicarbonate solution. The mixture was stirred at 20 °C for 12 hours. The mixture (combined with another two batch) was separated, the aqueous phase was extracted with ethyl acetate (30 mL, 2 times). The combined organic phase was washed with brine, dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give benzyl 6-methyl-5-oxo-2,6-diazaspiro[3.5]nonane-2-carboxylate (550 mg, 1.91 mmol, 74.27% yield, 100% purity) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.45 - 7.24 (m, 5H), 5.04 (s, 2H), 4.19 - 4.02 (m, 2H), 3.70 - 3.51 (m, 2H), 3.23 (t, J = 6.1 Hz, 2H), 2.82 (s, 3H), 2.08 - 1.98 (m, 2H), 1.77 - 1.63 (m, 2H). MS m/z (ESI) $[M+H]^+$= 289.1.

[0307] Step 4: To a mixture of Pd/C (60 mg, 56.38 µmol, 10% purity) in MeOH (10 mL) was added benzyl 6-methyl-5-oxo-2,6-diazaspiro[3.5]nonane-2-carboxylate (550 mg, 1.91 mmol, 1 eq) . The mixture was stirred at 20 °C for 12 hours under H_2 (50 Psi). The mixture was filtered by celite. The filtrate was concentrated to give ***amine.11*** (294 mg, 1.90 mmol, 99.65% yield, 99.7% purity) as colorless oil. MS m/z (ESI) $[M + H]^+$. $[M+H]^+$= 155.1.

amine.12 & 13**:** 1,3-dimethyl-2thia-3,7-diazaspiro[4.4]nonane 2,2-dioxide & 3-methyl-2thia-3,7-diazaspiro[4.4]nonane 2,2-dioxide



[0308] Step 1: To a solution of tert-butyl 3-cyanopyrrolidine-1-carboxylate (3 g, 15.29 mmol, 1 *eq*) in THF (30 mL) was added LDA (2 M, 15.29 mL, 2 *eq*) at -78 °C. The reaction mixture

was stirred at -78°C for 1 hour. A solution of chloro(iodo)methane (4.04 g, 22.93 mmol, 1.66 mL, 1.5 *eq*) in THF (20 mL) was added dropwise into reaction mixture at -78°C. The reaction mixture was warmed up to 20 °C and stirred 1 hour at 20 °C. The reaction mixture was quenched by addition NH_4Cl (50 mL) at 0 °C, and then extracted with EtOAc (50 mL, 3 times). The combined organic layers were dried over Na_2SO_4, filtrated and evaporated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 2/1). Compound tert-butyl 3-(chloromethyl) -3-cyano-pyrrolidine-1-carboxylate (2.5 g, 10.22 mmol, 66.83% yield) was obtained as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.95 - 3.79 (m, 1H), 3.73 - 3.47 (m, 5H), 2.48 - 2.37 (m, 1H), 2.25 - 2.12 (m, 1H), 1.48 (s, 9H).

[0309] Step 2: To a solution of tert-butyl 3-(chloromethyl) -3-cyano-pyrrolidine-1-carboxylate (2.5 g, 10.22 mmol, 1 *eq*) in DMF (25 mL) was added acetylsulfanylpotassium (1.63 g, 14.30 mmol, 1.4 *eq*) at 20 °C. The reaction mixture was stirred at 60 °C for 16 hours. The reaction mixture was quenched by addition of water (50 mL) at 20 °C, and then extracted with EtOAc (40 mL, 3 times). The combined organic layers were dried over Na_2SO_4, filtrated and evaporated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 2/1). Compound tert-butyl 3-(acetylsulfanylmethyl) -3-cyano-pyrrolidine-1-carboxylate (2 g, 7.03 mmol, 68.84% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.87 - 3.75 (m, 1H), 3.62 - 3.51 (m, 2H), 3.22 (s, 3H), 2.42 (s, 3H), 2.36 - 2.28 (m, 1H), 2.04 (s, 1H), 1.46 (s, 9H).

[0310] Step 3: To a solution of tert-butyl 3-(acetylsulfanylmethyl) -3-cyano-pyrrolidine-1-carboxylate (2 g, 7.03 mmol, 1 *eq*) in DCM (20 mL) / Water (10 mL) was bubbled Cl_2 (5.0 g, 70.52 mmol, 10.03 *eq*) at 0 °C for 0.5 hour. The reaction mixture was quenched by addition $NaHSO_3$ (50 mL) at 20 °C, and then extracted with DCM (50 mL, 3 times). The combined organic layers were dried over Na_2SO_4, filtrated and evaporated. The crude product tert-butyl 3-(chlorosulfonylmethyl) -3-cyano-pyrrolidine-1-carboxylate (2 g, 6.48 mmol, 92.10% yield) as yellow oil was used into the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.04 – 3.97 (m, 3H), 3.58 - 3.52 (m, 3H), 2.55 – 2.53 (m, 1H), 2.23 - 2.21 (m, 1H), 1.46 (s, 9H).

[0311] Step 4: To a solution of tert-butyl 3-(chlorosulfonylmethyl) -3-cyano-pyrrolidine-1-carboxylate (2 g, 6.48 mmol, 1 *eq*) in MeOH (10 mL) / Water (10 mL) was added KHF_2 (5.06 g, 64.77 mmol, 2.13 mL, 10 *eq*) at 20 °C. The reaction mixture was stirred at 20 °C for 16 hours. The reaction mixture was extracted with DCM (50 mL, 3 times). The combined organic layers were dried over Na_2SO_4, filtrated and evaporated. The residue was purified by

column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1/1). Compound tert-butyl 3-cyano-3-(fluorosulfonylmethyl) pyrrolidine-1-carboxylate (1.4 g, 4.79 mmol, 73.94% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.09 (s, 1H), 3.87 - 3.59 (m, 4H), 3.51 (br s, 1H), 2.68 - 2.54 (m, 1H), 2.31 - 2.21 (m, 1H), 1.48 (s, 9H).

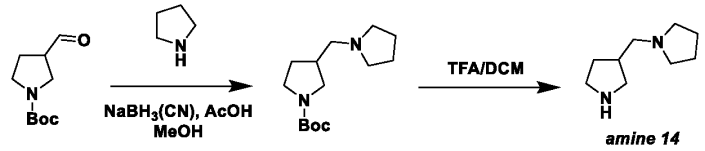
[0312] Step 5: To a solution of tert-butyl 3-cyano-3-(fluorosulfonylmethyl) pyrrolidine-1-carboxylate (500 mg, 1.71 mmol, 1 *eq*) and $NiCl_2 \cdot 6H_2O$ (447.21 mg, 1.88 mmol, 1.1 *eq*) in EtOH (10 mL) was cooled to -20 °C. Then $NaBH_4$ (170 mg, 4.49 mmol, 2.63 *eq*) was added into the mixture at -20 °C. The reaction mixture was warmed up to 20 °C and stirred at 20 °C for 16 hours. The reaction was quenched with HCl (1 M) and the mixture was adjusted to pH 6~7. Then the mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL, 3 times). The organic phase was dried over Na_2SO_4, filtrated and evaporated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1/1). Compound tert-butyl 2, 2-dioxo-2thia-3, 7-diazaspiro[4.4]nonane-7-carboxylate (250 mg, 904.64 μmol, 52.89% yield) was obtained as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.92 - 4.55 (m, 1H), 3.53 - 2.99 (m, 8H), 2.06 - 1.93 (m, 2H), 1.39 (s, 9H).

[0313] Step 6: To a solution of tert-butyl 2, 2-dioxo-2thia-3, 7-diazaspiro[4.4]nonane-7-carboxylate (250 mg, 904.64 μmol, 1 eq) in THF (2.50 mL) was added NaH (43.42 mg, 1.09 mmol, 60% purity, 1.2 eq) at 0 °C under N_2. The reaction solution was stirred at 20 °C for 30 min. Then CH_3I (128.40 mg, 904.64 μmol, 56.32 μL, 1 eq) was added to the solution at 0 °C and stirred at 20 °C for another 12 h under N_2. Water (10.0 mL) was added to the solution to quench the unfinished NaH. The residue was partitioned between EtOAc (20.0 mL, 2 times) and water (20.0 mL). The combined organic layers were washed by brine (20.0 mL) and dried over Na_2SO_4, filtrated and evaporated. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 1/1). Compound tert-butyl 1, 3-dimethyl-2, 2-dioxo-2thia-3, 7-diazaspiro[4.4]nonane-7-carboxylate;tert-butyl 3-methyl-2, 2-dioxo-2thia-3, 7-diazaspiro[4.4]nonane-7-carboxylate (230 mg, 386.70 μmol, 42.75% yield) was obtained as yellow oil. MS m/z (ESI) $[M-56+H]^+$= 235.2 & MS m/z (ESI) $[M-56+H]^+$= 249.2.

[0314] Step 7: To a solution of tert-butyl 1, 3-dimethyl-2, 2-dioxo-2thia-3, 7-diazaspiro[4.4]nonane-7-carboxylate;tert-butyl 3-methyl-2, 2-dioxo-2thia-3, 7-diazaspiro[4.4]nonane-7-carboxylate (230.00 mg, 386.70 μmol, 1 eq) in EtOAc (0.50 mL) was added HCl/dioxane (2 M, 2.00 mL, 10.34 eq) at 20 °C. The reaction mixture was stirred at 20 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give the

crude ***amine.13*** (130 mg, 329.49 μmol, 85.21% yield) as brown oil used into the next step without further purification.

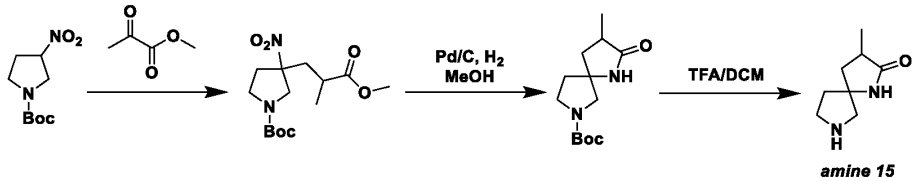
amine.14: 1-(pyrrolidin-3-ylmethyl)pyrrolidine



[0315] Step 1: To a solution of tert-butyl 3-formylpyrrolidine-1-carboxylate (1 g, 5.02 mmol, 1 eq) in dioxane MeOH (10 mL) was added pyrrolidine (400 mg, 5.62 mmol, 469.48 μL, 1.12 eq) , AcOH (1.05 g, 17.47 mmol, 1 mL, 3.48 eq) and $NaBH_3CN$ (1 g, 15.91 mmol, 3.17 eq). Then the resulting mixture was purged with N_2 three timesand stirred at 25°C for 12 hours. The reaction mixture was partitioned between EtOAc (150 mL) and water (80 mL), washed with brine (70 mL), died over Na_2SO_4, filtrated and evaporated. The crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give tert-butyl 3-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carboxylate (450 mg, 1.77 mmol, 35.25% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.92 - 3.64 (m, 4H), 3.39 - 3.30 (m, 2H), 3.23 - 3.14 (m, 2H), 3.08 (br dd, J = 8.4, 10.8 Hz, 1H), 2.66 - 2.56 (m, 1H), 2.26 - 2.14 (m, 5H), 1.86 - 1.65 (m, 2H), 1.46 (s, 9H).

[0316] Step 2: To a solution of tert-butyl 3-(pyrrolidin-1-ylmethyl)pyrrolidine-1-carboxylate (450 mg, 1.77 mmol, 1 eq) in DCM (4 mL) was added TFA (3.07 g, 26.92 mmol, 2 mL, 15.22 eq) , then the resulting mixture was stirred at 25°C for 1 hours. The reaction mixture was evaporated under reduced pressure. The ***amine.14*** was obtained (250 mg, crude) as the colorless oil was used without further purification. MS m/z (ESI) $[M+H]^+$= 155.3.

amine.15: 3-methyl-1,7-diazaspiro[4.4]nonan-2-one



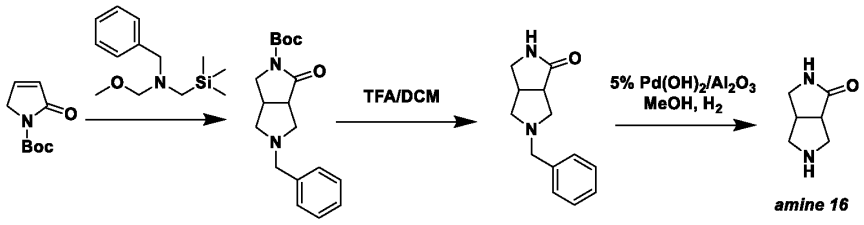
[0317] Step 1: To a solution of tert-butyl 3-nitropyrrolidine-1-carboxylate (1 g, 4.62 mmol, 1 eq) and methyl 2-methylprop-2-enoate (509.30 mg, 5.09 mmol, 1.1 eq) in THF (10 mL) was added TBAF (1 M, 9.25 mL, 2 eq) at 25 °C . The mixture was stirred at 70 °C for 16 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL, 3 times). The

organic phase was washed with brine (40 mL), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 20g SepaFlash® Silica Flash Column, Eluent of 0~50% EtOAc/PE gradient @ 40 mL/min) to give tert-butyl 3-(3-methoxy-2-methyl-3-oxo-propyl)-3-nitro-pyrrolidine-1-carboxylate (580 mg, 1.83 mmol, 39.64% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.38 - 4.19 (m, 1H), 3.70 (s, 3H), 3.62 - 3.27 (m, 3H), 2.84 - 2.68 (m, 1H), 2.59 - 2.40 (m, 2H), 2.22 - 1.96 (m, 2H), 1.50 - 1.42 (m, 9H), 1.23 - 1.18 (m, 3H).

[0318] Step 2: To a solution of Pd/C (58 mg, 10% purity) in MeOH (10 mL)/THF (10 mL) was added tert-butyl 3-(3-methoxy-2-methyl-3-oxo-propyl)-3-nitro-pyrrolidine-1-carboxylate (580 mg, 1.83 mmol, 1 eq) under N_2. The suspension was degassed under vacuum and purged with H_2 three times. The mixture was stirred under H_2 (1 Mpa) at 40°C for 16 hours. The reaction mixture was diluted with MeOH (10 mL) then mixture was filtered through a pad of celite and the filtrate was concentrated to give residue. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~50% EtOAc/PE gradient @ 40 mL/min) to give tert-butyl 3-methyl-2-oxo-1,7-diazaspiro[4.4]nonane-7-carboxylate (180 mg, 707.76 µmol, 38.60% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.51 - 3.28 (m, 3H), 2.67-2.57 (m, 1H), 2.46 - 2.29 (m, 1H), 2.04 - 1.84 (m, 2H), 1.72 - 1.59 (m, 2H), 1.47 (s, 8H), 1.24 (d, J = 7.2 Hz, 3H).

[0319] Step 3: To a solution of tert-butyl 3-methyl-2-oxo-1,7-diazaspiro[4.4]nonane-7-carboxylate (180 mg, 707.76 µmol, 1 eq) in DCM (1 mL) was added TFA (307.00 mg, 2.69 mmol, 0.2 mL, 3.80 eq) at 25 °C. The mixture was stirred at 25 °C for 2 hours. The mixture was concentrated under reduced pressure to ***give amine 15*** (120 mg, crude) as a yellow solid. The crude was used next step without purification.

***amine.16*:** hexahydropyrrolo[3,4-c]pyrrol-1(2H)-one



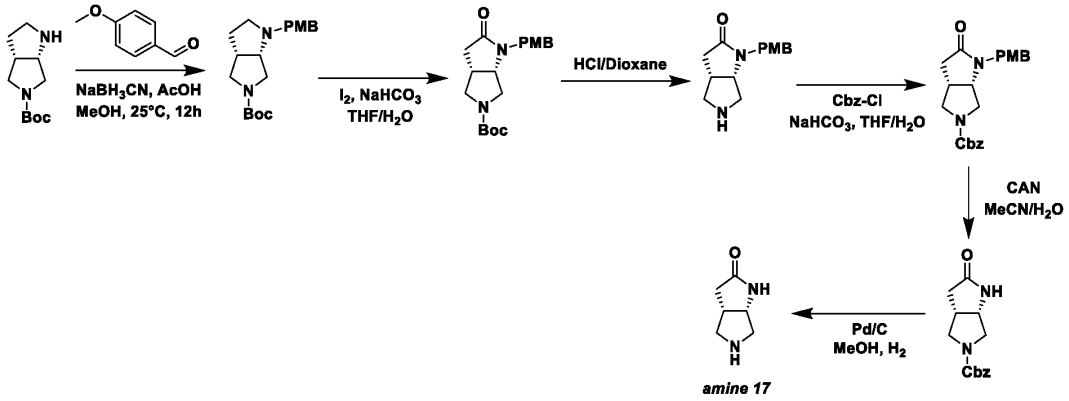
[0320] Step 1: To a solution of tert-butyl 5-oxo-2H-pyrrole-1-carboxylate (2 g, 10.92 mmol, 1 eq) in MeCN (25 mL) was added N-(methoxymethyl)-1-phenyl-N-(trimethylsilylmethyl)methanamine (3.9 g, 16.43 mmol, 1.5 eq). The mixture was stirred at 25°C for 12 hours. The reaction mixture was filtered and evaporated under reduced pressure to give the crude product. The crude product was purified by reversed-phase HPLC (0.1% FA

condition) and lyophilized to give the tert-butyl 5-benzyl-1-oxohexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (1.2 g, 3.79 mmol, 34.74% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 - 7.28 (m, 5H), 3.90 (d, J = 8.7, 11.2 Hz, 1H), 3.83 - 3.74 (m, 1H), 3.72 - 3.63 (m, 1H), 3.54 (d, J = 3.0, 11.3 Hz, 1H), 3.28 - 3.11 (m, 2H), 2.92 - 2.78 (m, 3H), 2.72 - 2.64 (m, 1H), 1.54 (s, 9H).

[0321] Step 2: To a solution of tert-butyl 5-benzyl-1-oxohexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (600 mg, 1.90 mmol, 1 eq) in DCM (5 mL) was added TFA (3.07 g, 26.92 mmol, 2 mL, 14.20 eq), then the resulting mixture was stirred at 25°C for 1 hour. The reaction mixture was evaporated under reduced pressure to give the crude product. The 5-benzylhexahydropyrrolo[3,4-c]pyrrol-1(2H)-one (600 mg, crude) as the yellow oil was used without further purification. MS m/z (ESI) $[M+H]^+$= 217.3.

[0322] Step 3: 5-benzylhexahydropyrrolo[3,4-c]pyrrol-1(2H)-one (600 mg, 2.77 mmol, 1 eq) in MeOH (50 mL), The fixed bed (FLR1, volume 5 mL) was completely packed with granular catalyst 5%$Pd(OH)_2/Al_2O_3$ (1.00 eq). The H_2 back pressure regulator was adjusted to 1.5 MPa, and the flow rate of H_2 was 20 mL/min. Then the solution S1 was pumped by Pump 1 {S1, P1, 0.4 mL/min } to fixed bed {FLR1,SS,Fixed bed,6.350(1/4'') mm, 1 mL, 45°C }. Then the reaction mixture was collected from the reactor output. The fixed bed was washed by extra {MeOH,50 mL}. The fixed bed was evaporated under reduced pressure to give ***amine 16*** (400 mg, crude) as a white solid.

amine.17: (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-2(1H)-one



[0323] Step 1: To a solution of tert-butyl (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrole-5(1H)-carboxylate (1.00 g, 4.71 mmol, 1.00 eq), 4-methoxybenzaldehyde (830 mg, 6.10 mmol, 1.29 eq) in MeOH (20.0 mL) were added acetic acid (141 mg, 2.36 mmol, 0.500 eq) and sodium cyanoborohydride (590 mg, 9.39 mmol, 1.99 eq) at 0°C. The mixture was stirred at 25 °C for 12 hours. The reaction mixture was diluted with water (30.0 mL) and then extracted with

EtOAc (30.0 mL, 3 times). The combined organic phase was washed with brine (10.0 mL, 3 times), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~20% THF/PE gradient @ 40 mL/min) to give tert-butyl (3aS,6aS)-1-(4-methoxybenzyl)hexahydropyrrolo[3,4-b]pyrrole-5(1H)-carboxylate (1.00 g, 2.91 mmol, 61.9% yield, 96.9% purity) as colorless oil. MS m/z (ESI) $[M+H]^+$= 333.3.

[0324] Step 2: To a solution of tert-butyl (3aS,6aS)-1-(4-methoxybenzyl)hexahydropyrrolo[3,4-b]pyrrole-5(1H)-carboxylate (1.00 g, 96.9% purity, 3.01 mmol, 1.00 eq) in THF (35.0 mL) were added H_2O (15.0 mL), I_2 (4.50 g, 17.7 mmol, 5.89 eq) and $NaHCO_3$ (2.55 g, 30.35 mmol, 10.1 eq) at 25°C. The mixture was stirred at 25 °C for 0.5 hour. The reaction mixture was diluted with water (50.0 mL), quenched with sodium sulfite (20.0 g), extracted with EtOAc (50.0 mL, 3 times), the combined organic phase was washed with brine (20.0 mL, 3 times), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~28% EtOAc/PE gradient @ 40 mL/min) to give tert-butyl (3aS,6aS)-1-(4-methoxybenzyl)-2-oxohexahydropyrrolo[3,4-b]pyrrole-5(1H)-carboxylate (700 mg, 1.79 mmol, 59.7% yield, 88.8% purity) as a yellow gum. MS m/z (ESI) $[M-55]^+$= 291.1.

[0325] Step 3: To a solution of tert-butyl (3aS,6aS)-1-(4-methoxybenzyl)-2-oxohexahydropyrrolo[3,4-b]pyrrole-5(1H)-carboxylate (700 mg, 1.80 mmol, 1.00 eq) in dioxane (5.00 mL) was added HCl / dioxane (2.00 M, 15.0 mL) at 25°C. The mixture was stirred at 25°C for 4 hours. The reaction mixture was concentrated under reduce presser to give crude (3aS,6aS)-1-(4-methoxybenzyl)hexahydropyrrolo[3,4-b]pyrrol-2(1H)-one (550 mg, crude, HCl) as yellow gum which was used in the next step directly without further purification.

[0326] Step 4: To a solution of (3aS,6aS)-1-(4-methoxybenzyl)hexahydropyrrolo[3,4-b]pyrrol-2(1H)-one (crude 550 mg, 1.95 mmol, 1.00 eq, HCl) in THF (10.0 mL), H_2O (2.00 mL) were added $NaHCO_3$ (1.50 g, 17.86 mmol, 9.18 eq) and benzyl carbonochloridate (600 mg, 3.52 mmol, 1.81 eq) at 25°C. The mixture was stirred at 25 °C for 12 hours. The reaction mixture was diluted with water (20.0 mL) and then extracted with EtOAc (30.0 mL, 3 times), the combined organic phase was washed with brine (10.0 mL, 3 times), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% THF/PE gradient @ 40 mL/min) to give benzyl (3aS,6aS)-1-(4-methoxybenzyl)-2-oxohexahydropyrrolo[3,4-

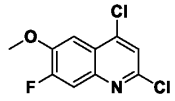
b]pyrrole-5(1H)-carboxylate (550 mg, 1.43 mmol, 72.8% yield, 98.5% purity) as yellow gum. MS m/z (ESI) $[M+H]^+$= 381.3.

[0327] Step 5: To a solution of benzyl (3aS,6aS)-1-(4-methoxybenzyl)-2-oxohexahydropyrrolo[3,4-b]pyrrole-5(1H)-carboxylate (550 mg, 98.5% purity, 1.43 mmol, 1.00 eq) in MeCN (10 mL), H_2O (4.00 mL) was added ceric ammonium nitrate (1.71 g, 3.12 mmol, 2.20 eq) at 25°C. The mixture was stirred at 25°C for 0.5 hour. The reaction mixture was diluted with water (50.0 mL), quenched with sodium sulfite (20.0 g). extracted with EtOAc (30. 0ml), the combined organic phase was washed with brine (10.0 mL), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 40g SepaFlash® Silica Flash Column, Eluent of 0~50% THF/PE gradient @ 40 mL/min) to give crude product as yellow gum, the crude product was then purified by prep-TLC (SiO_2: ethyl acetate : methanol= 10:1) to give benzyl (3aS,6aS)-2-oxohexahydropyrrolo[3,4-b]pyrrole-5(1H)-carboxylate (120 mg, 374 μmol, 26.4% yield, 81.5% purity) as yellow gum. MS m/z (ESI) $[M+H]^+$= 521.3.

[0328] Step 6: To a solution of benzyl (3aS,6aS)-2-oxohexahydropyrrolo[3,4-b]pyrrole-5(1H)-carboxylate (120 mg, 81.5% purity, 374 μmol, 1.00 eq) in MeOH (10.0 mL) was added Pd/C (100 mg, 94.0 μmol, 10.0 % purity, 2.52e-1 eq) at 25°C. The mixture was stirred at 25°C for 2 hours under H_2 atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give crude ***amine 17*** (50.0 mg, crude) as yellow gum which was used in the next step directly without further purification.

*Synthesis of substituted dichloroquinoline intermediates **A.4***

A.4a (R_7 = -H; R_8 = -F; R_9 = -OCH_3; R_{10} = -H): 2, 4-dichloro-7-fluoro-6-methoxy-quinoline

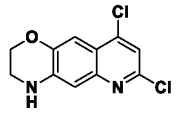


A.4a

[0329] According to Scheme 1 Step 3: To a solution of 3-fluoro-4-methoxy-aniline **A.3a** (2.0 g, 14 mmol, 1.0 eq) and malonic acid (1.6 g, 15 mmol, 1.6 mL, 1.1 eq) in $POCl_3$ (33 g, 215 mmol, 20 mL, 15 eq) at 25 °C. The mixture was stirred at 25 °C for 3 h, then stirred at 90 °C for 12 h. The reaction mixture was added into H_2O and held the temperature at 20 °C ~ 30 °C, washed with aq. $NaHCO_3$ then was partitioned between ethyl acetate (30 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (30 mL) twice. The combined organic layers were dried over Na_2SO_4 and evaporated to give a crude material. The residue

obtained was purified by Flash chromatography (40 g column, Eluent of 0~10% EtOAc/PE gradient at 40 mL/min) to afford **A.4a** (1.9 g, 7.7 mmol, 54% yield, 100% purity) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.89 (m, 2H), 7.59 (d, J = 8.9 Hz, 1H), 4.06 (s, 3H). MS m/z (ESI) $[M+H]^+$ = 246.0.

A.4b (R_8-R_9 = -$NHCH_2CH_2O$-; $R_{7,10}$ = -H): 7,9-dichloro-3,4-dihydro-2H-pyrido[2,3-g] [1,4] benzoxazine



A.4b

[0330] According to Scheme 1 Step 1: To a solution of 6-nitro-3,4-dihydro-2H-1,4-benzoxazine **A.1b** (4.2 g, 23 mmol, 1.0 eq) and NaOH (2.8 g, 70 mmol, 1.3 mL, 3.0 eq) in THF (40 mL) was added Fmoc-Cl (7.2 g, 28 mmol, 1.2 eq) at 0 °C. The mixture was stirred at 25 °C for 1 h. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (100 mL, three times). The combined organic phases were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue obtained was purified by Flash chromatography (120 g column, Eluent of 0~100% EtOAc/PE gradient at 50 mL/min) to give 9H-fluoren-9-ylmethyl 6-nitro-2,3-dihydro-1,4-benzoxazine-4-carboxylate **A.2b** (7.6 g, 17 mmol, 71% yield, 88% purity) as a yellow solid. MS m/z (ESI) $[M+Na]^+$ = 425.1.

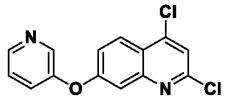
[0331] According to Scheme 1 Step 2: To a solution of **A.2b** (7.6 g, 19 mmol, 1.0 eq) and NH_4Cl (6.1 g, 113 mmol, 6.0 eq) in EtOH (60 mL) / H_2O (60 mL) was added Fe (5.3 g, 94 mmol, 5.0 eq) at 60 °C, the mixture was stirred at 60 °C for 16 h. The mixture was diluted with water (200 mL) and extracted with ethyl acetate (200 mL, three times). The combined organic phases were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue obtained was purified by Flash chromatography (Eluent of 0~100% EtOAc/PE gradient at 50 mL/min) to give 9H-fluoren-9-ylmethyl 6-amino-2,3-dihydro-1,4-benzoxazine-4-carboxylate **A.3b** (6.0 g, 13 mmol, 68% yield, 80% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 373.2.

[0332] According to Scheme 1 Step 3: A mixture of **A.3b** (5.0 g, 13 mmol, 1.0 eq) and malonic acid (1.6 g, 15 mmol, 1.6 mL, 1.1 eq) in $POCl_3$ (50 mL) was stirred at 100 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove $POCl_3$, the reaction mixture was quenched with water (200 mL) at 25 °C, the mixture was adjusted to pH = 7~8 with $NaHCO_3$.The mixture was diluted with water (200 mL) and extracted with ethyl

acetate (200 mL, three times). The combined organic phases were washed with brine (400 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The mixture was concentrated to give a residue. The residue obtained was purified by Flash chromatography (25 g column, Eluent of 0~100% EtOAc/PE gradient at 50 mL/min) to give 9H-fluoren-9-ylmethyl 7,9-dichloro-2,3-dihydropyrido[2,3-g] [1,4] benzoxazine-4-carboxylate **A.4b'** (1.0 g, 1.3 mmol, 9.8% yield, 63% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 477.1.

[0333] *Intermediate **A.4b'** underwent an additional step of deprotection.* To a solution of **A.4b'** (0.90 g, 1.9 mmol, 1.0 eq) in DCM (5.0 mL) was added diethylamine (3.2 g, 44 mmol, 4.5 mL, 23 eq) at 25 °C. The mixture was stirred at 60 °C for 2 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL, three times). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated to give a residue. The residue obtained was purified by Flash chromatography (20 g column, Eluent of 0~50% EtOAc/PE gradient at 40 mL/min) to give **A.4b** (0.15 g, 0.59 mmol, 31% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.45 (s, 1H), 7.29 (s, 1H), 7.24 (s, 1H), 4.33 - 4.29 (m, 2H), 3.59 - 3.54 (m, 2H).

A.4c (R_8 = -O-pyridine; $R_{7,9,10}$ = -H): 2,4-dichloro-7-(3-pyridyloxy) quinoline



A.4c

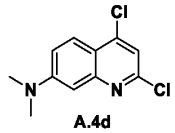
[0334] According to Scheme 1 Step 1: To a mixture of 1-fluoro-3-nitrobenzene **A.1c** (10 g, 71 mmol, 7.6 mL, 1.0 eq) and pyridin-3-ol (8.1 g, 85 mmol, 1.2 eq) in DMF (100 mL) was added potassium carbonate (20 g, 0.14 mol, 2.0 eq) at 20 °C. The reaction mixture was stirred at 130 °C for 48 h. The reaction mixture was quenched with water (500 mL) and extracted with ethyl acetate (500 mL, twice). The combined organic phases were washed with brine (500 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to give a crude product. The crude product was purified by column chromatography (SiO_2, PE/EtOAc = 10:1 to 3:1) to give 3-(3-nitrophenoxy) pyridine **A.2.c** (7.0 g, 45% yield) as a yellow oil. MS m/z (ESI) $[M+H]^+$ = 216.9.

[0335] According to Scheme 1 Step 2: To a mixture of **A.2c** (7.0 g, 32 mmol, 1.0 eq) in a mixed solution of ethanol (80 mL) and water (10 mL) was added ammonium chloride (14 g, 0.26 mol, 8.0 eq) at 20 °C. The reaction mixture was stirred at 80 °C and Fe (9.0 g, 0.16 mol, 5.0 eq) was added to the reaction mixture in batches at 80 °C. Then the reaction mixture was

stirred at 80 °C for 3 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* to give a crude product. The crude product was purified by column chromatography (SiO_2, PE/EtOAc = 5:1 to 1:1) to give 3-(3-pyridyloxy) aniline **A.3c** (4.0 g, 66% yield) as yellow oil.

[0336] According to Scheme 1 Step 3: A mixture of **A.3c** (4.0 g, 22 mmol, 1.0 eq) and malonic acid (2.5 g, 24 mmol, 2.5 mL, 1.1 eq) in phosphorus oxychloride (40 mL) as stirred at 110 °C for 16 h. The reaction mixture was cooled to room temperature and most of the phosphorus oxychloride was removed by decompress distillation to give a residue. The residue was quenched with saturated sodium hydrogen carbonate solution (500 mL) and extracted with ethyl acetate (500 mL, twice). The combined organic phase was washed with brine (500 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to give the crude product. The crude product was purified by column chromatography (SiO_2, PE/EtOAc = 10:1 to 3:1) and prep-TLC (SiO_2, PE/EtOAc = 3:1) to afford **A.4c** (0.20 g, 3% yield) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 290.9.

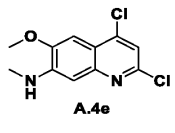
A.4d (R_8 = -$N(CH_3)_2$; $R_{7,9,10}$ = -H): 2,4-dichloro-*N*, *N*-dimethyl-quinolin-7-amine



A.4d

[0337] According to Scheme 1 Step 3: To a solution of N_1, N_1-dimethylbenzene-1,3-diamine **A.3d** (10 g, 73 mmol, 1.0 eq) in phosphorus oxychloride (90 mL) was added malonic acid (10 g, 96 mmol, 10 mL, 1.3 eq) at 25 °C. After stirring at 110 °C for 16 h, the reaction mixture was added into saturated sodium bicarbonate (200 mL) and extracted with ethyl acetate 300 mL (3 x 100 mL). The combined organic layers were washed with brine 300 mL (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (80 g column, Eluent of 0~7% EtOAc/PE gradient at 30 mL/min) to give **A.4d** (1.5 g, 5.9 mmol, 8.1% yield, 95% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 241.0.

A.4e (R_8 = -$NHCH_3$; R_9 = -OCH_3; $R_{7,10}$ = -H): 2,4-dichloro-6-methoxy-*N*-methyl-quinolin-7-amine



A.4e

[0338] According to Scheme 1 Step 1: To a solution of *N*-(3-amino-4-methoxy-phenyl) acetamide **A.1e** (12 g, 67 mmol, 1.0 eq) in methyl alcohol (100 mL) / acetic acid (10 mL) was added formaldehyde (2.0 g, 67 mmol, 1.8 mL, 1.0 eq) and sodium cyanoborohydride (13 g, 0.20 mol, 3.0 eq) at 25 °C. After stirring at 25 °C for 16 h, the reaction mixture was added into water (200 mL) and adjusted the pH = 7-8 and then extracted with ethyl acetate 300 mL (3 x 100 mL). The combined organic layers were washed with brine 300 mL (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (80 g column, Eluent of 0~50% EtOAc/PE gradient at 60 mL/min) to give *N*-[4-methoxy-3-(methylamino) phenyl] acetamide **A.2e'** (7.0 g, 24 mmol, 36% yield, 66% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 195.0.

[0339] *Intermediate A.2e' underwent an additional step of protection.* To a solution of **A.2e'** (6.5 g, 22 mmol, 1.0 eq) in dioxane (100 mL) was added sodium bicarbonate (5.6 g, 66 mmol, 2.6 mL, 3.0 eq) and 9H-fluoren-9-ylmethyl carbonochloridate (6.3 g, 24 mmol, 1.1 eq) at 0 °C. After stirring at 25 °C for 16 h, the reaction mixture was added into water (100 mL) and extracted with ethyl acetate 120 mL (3 x 40 mL). The combined organic layers were washed with brine 120 mL (3 x 40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (80 g column, Eluent of 0~50% EtOAc/PE gradient at 60 mL/min) to give 9H-fluoren-9-ylmethyl N-(5-acetamido-2-methoxy-phenyl)-*N*-methylcarbamate **A.2e** (10 g, 19 mmol, 87% yield, 80% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 417.2.

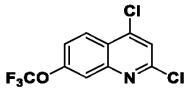
[0340] According to Scheme 1 Step 2: To a solution of **A.2e** (9.9 g, 24 mmol, 1.0 eq) in MeOH (100 mL) was added sulfuric acid (12 M, 20 mL, 10 eq) at 25 °C. After stirring at 60 °C for 16 h, the reaction mixture was added into water and adjusted the pH to 7-8, extracted with ethyl acetate 120 mL (3 x 40 mL). The combined organic layers were washed with brine 120 mL (3 x 40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 9H-fluoren-9-ylmethyl *N*-(5-amino-2-methoxy-phenyl)-*N*-methylcarbamate **A.3e** (11 g, 24 mmol, 99% yield, 80% purity) as a yellow gum. MS m/z (ESI) $[M+H]^+$ = 375.1.

[0341] According to Scheme 1 Step 3: To a solution of **A.3e** (10 g, 27 mmol, 1.0 eq) in phosphorus oxychloride (90 mL) was added malonic acid (3.5 g, 34 mmol, 3.5 mL, 1.3 eq) at 25 °C. After stirring at 110°C for 16 h, the reaction mixture was concentrated under reduced pressure. The residue was added into saturated sodium bicarbonate (200 mL) and extracted with ethyl acetate 300 mL (3 x 100 mL). The combined organic layers were washed with water (100 mL) and brine 300 mL (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by Flash

chromatography (40 g column, Eluent of 0~20% EtOAc/PE gradient at 60 mL/min) to give 9H-fluoren-9-ylmethyl *N*-(2,4-dichloro-6-methoxy-7-quinolyl)-*N*-methylcarbamate **A.4e'** (2.0 g, 3.3 mmol, 12% yield, 78% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 479.1.

[0342] *Intermediate **A.4e'** underwent an additional step of deprotection.* To a solution of **A.4e'** (2.0 g, 4.2 mmol, 1.0 eq) in dichloromethane (20 mL) was added piperidine (8.6 g, 0.10 mol, 10 mL, 24 eq) at 25 °C. After stirring at 60 °C for 2 h, the reaction mixture was added into water and extracted with ethyl acetate 60 mL (3 x 20 mL). The combined organic layers were washed with brine 60 mL (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~30% EtOAc/PE gradient at 45 mL/min) to give **A.4e** (0.60 g, 1.6 mmol, 39% yield, 70% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 256.9.

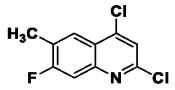
A.4f (R_8 = -OCF_3; $R_{7,9,10}$ = -H): 2,4-dichloro-7-(trifluoromethoxy) quinoline



A.4f

[0343] According to Scheme 1 Step 3: To a solution of 3-(trifluoromethoxy) aniline **A.3f** (10 g, 56 mmol, 7.6 mL, 1.0 eq) in $POCl_3$ (90 mL) was added malonic acid (7.5 g, 72 mmol, 7.5 mL, 1.3 eq) at 20 °C. The reaction mixture was stirred at 20 °C for 2 h, then the reaction mixture was stirred at 110 °C for 12 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with *saturated aqueous* $NaHCO_3$ (500 mL). The mixture was then extracted with ethyl acetate (1000 mL, three times). The combined organic phases were washed with brine (1000 mL, three times), dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (80g column, Eluent of 0~10% EtOAc/PE gradient at 40 mL/min) to afford **A.4f** (5.2 g, 18 mmol, 33% yield) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.28 (d, J = 9.2 Hz, 1H), 7.91 (d, J = 0.7 Hz, 1H), 7.59 - 7.50 (m, 2H).

A.4g (R_8 = -F; R_9 = -CH_3; $R_{7,10}$ = -H): 2,4-dichloro-6-fluoro-*N*, *N*-dimethyl-quinolin-7-amine



A.4g

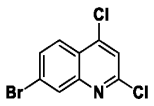
[0344] According to Scheme 1 Step 1: To a solution of 2-fluoro-5-nitro-aniline **A.1g** (10 g, 64 mmol, 1.0 eq) in MeOH (100 mL) /AcOH (10 mL) was added HCHO (5.8 g, 192 mmol,

5.3 mL, 3.0 eq) at 25 °C. After stirring at 25 °C for 48 h. The reaction mixture was added into saturated aqueous solution of ammonium chloride (200 mL) and extracted with ethyl acetate 300 mL (100 mL, three times). The combined organic layers were washed with brine 300 mL (100 mL, three times), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (40 g column, Eluent of 0~5% EtOAc/PE gradient at 45mL/min) to give 2-fluoro-*N*, *N*-dimethyl-5-nitro-aniline **A.2g** (7.0 g, 36 mmol, 56% yield, 95% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$ = 185.1.

[0345] According to Scheme 1 Step 2: To a solution of Pd/C (0.10 g, 10% purity) in ethyl acetate (20 mL) was added **A.2g** (1.0 g, 5.4 mmol, 1.0 eq) under N_2 atmosphere at 25 °C. The suspension was degassed and purged with H_2 three times at 25 °C. After stirring under H_2 (15 Psi) at 25 °C for 16 h, the reaction mixture was filtered and concentrated under reduced pressure to give 4-fluoro-*N3*, *N3*-dimethyl-benzene-1,3-diamine **A.3g** (0.70 g, 4.1 mmol, 75% yield, 90% purity) as brown oil. MS m/z (ESI) $[M+H]^+$ = 155.1.

[0346] According to Scheme 1 Step 3: To a solution of **A.3g** (0.70 g, 4.5 mmol, 1.0 eq), malonic acid (0.5 g, 4.8 mmol, 0.50 mL, 1.1 eq) in $POCl_3$ (7.0 mL) at 25 °C. After stirring at 100 °C for 16 h, the reaction mixture was added into *saturated* sodium bicarbonate aqueous solution (100 mL) and extracted with ethyl acetate 60 mL (20 mL, three times). The combined organic layers were washed with brine 60 mL (20 mL, three times), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (40 g column, Eluent of 0~5% EtOAc/PE gradient at 45 mL/min) to give **A.4g** (0.17 g, 0.59 mmol, 13% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 259.1.

A.4h (R_8 = -Br; $R_{7,9,10}$ = -H): 7-bromo-2,4-dichloro-quinoline

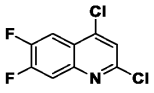


A.4h

[0347] According to Scheme 1 Step 3: To a solution of 3-bromoaniline **A.3h** (10 g, 58 mmol, 6.3 mL, 1 eq) and malonic acid (6.7 g, 64 mmol, 6.7 mL, 1.1 eq) in $POCl_3$ (100 mL) at 25 °C. The mixture was stirred at 25 °C for 1 h. Then the mixture was stirred at 100 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove $POCl_3$. The reaction mixture was quenched with water (200 mL) at 25 °C, the mixture was adjusted to pH=7~8 with $NaHCO_3$.The mixture was diluted with water (200 mL) and extracted with ethyl acetate (200 mL, three times). The combined organic phases were washed with brine (600 mL), dried

over anhydrous Na_2SO_4, filtered and the filtrate was concentrated. The residue obtained was purified by column chromatography (SiO_2, PE/EtOAc). **A.4h** (3.0 g, 11 mmol, 19% yield, 100% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+$ = 277.9.

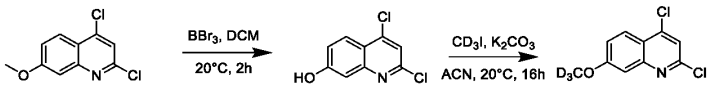
A.4i ($R_{8,9}$ = -F; $R_{7,10}$ = -H): 2, 4-dichloro-6, 7-difluoro-quinoline



A.4i

[0348] According to Scheme 1 Step 3: To a solution of malonic acid (9.0 g, 86 mmol, 9.0 mL, 1.1 eq) in $POCl_3$ (80 mL) was added 3, 4-difluoroaniline **A.3i** (10 g, 77 mmol, 1.0 eq) at 25 °C. The mixture was stirred at 110 °C for 12 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with ethyl acetate (0.10 L). The pH of the mixture was adjusted with sodium bicarbonate solution (2.0 M). The mixture was extracted with EtOAc (0.10 L, twice). The combined organic layers were washed with saturated salt solution (0.10 L, twice), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (SiO_2, PE/EtOAc = 10:1 to 5:1) to give **A.4i** (3.0 g, 12 mmol, 15% yield, 90% purity) as a yellow solid.

A.4j (R_8 = -OCD_3; $R_{7,9,10}$ = -H): 2,4-dichloro-7-(trideuteriomethoxy) quinoline



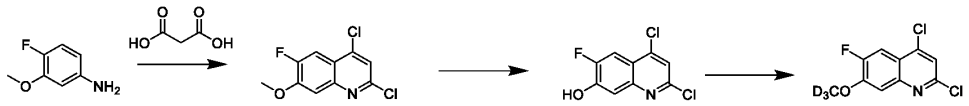
A.4J

[0349] Step 1: To a solution of 2,4-dichloro-7-methoxy-quinoline (1.0 g, 4.4 mmol, 1.0 eq) in DCM (15 mL) was added boron tribromide (2.6 g, 10 mmol, 2.4 eq) at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by methanol (20 mL), the mixture was diluted with water (50 mL) and then to the mixture was added sodium bicarbonate until the pH = 7. The above mixture was then extracted with DCM (50 mL, three times), washed with brine (20 mL, three times), dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (20 g column, Eluent of 0~30% EtOAc/PE gradient at 40 mL/min) to give 2,4-dichloroquinolin-7-ol (0.85 g, 3.7 mmol, 84% yield, 93% purity) as a white solid. MS m/z (ESI) $[M+H]^+$ = 214.1.

[0350] Step 2: To a solution of 2,4-dichloroquinolin-7-ol (0.40 g, 1.9 mmol, 1.0 eq) in ACN (8.0 mL) was added potassium carbonate (0.52 g, 3.7 mmol, 2.0 eq) and

trideuterio(iodo)methane (0.35 g, 2.4 mmol, 1.3 eq) at 20 °C. The mixture was stirred at 20 °C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~20% EtOAc/PE gradient at 30 mL/min) to give **A.4j** (0.30 g, 1.3 mmol, 70% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.11 - 8.03 (m, 1H), 7.73 (s, 1H), 7.46 - 7.37 (m, 2H). MS m/z (ESI) $[M+H]^+$ = 231.2.

A.4k (R_8 = -OCD_3; R_9 = -F; $R_{7,10}$ = -H): 4 - 2,4-dichloro-6-fluoro-7-(trideuteriomethoxy)quinoline



A.4k

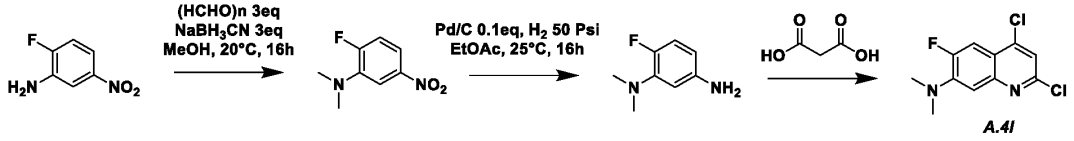
[0351] Step 1: To a solution of 4-fluoro-3-methoxy-aniline (10 g, 70.85 mmol, 1 *eq*) in $POCl_3$ (164.50 g, 1.07 mol, 100 mL, 15.14 *eq*) was added malonic acid (7.4 g, 71.11 mmol, 7.40 mL, 1 *eq*), the reaction mixture was stirred at 110 °C for 12 hours. TLC (PE:EA=5:1, Rf=0.53) showed one major spot was detected. The reaction solution was quenched by H_2O (100 mL). The pH of the residue was adjusted to 8 by adding sat. $NaHCO_3$. The residue was extracted by EtOAc (300 mL, 2 times), The organic phase was washed by sat. $NaHCO_3$ (200 mL, 3 times). The combined organic layers were dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to afford 2, 4-dichloro-6-fluoro-7-methoxy-quinoline (15 g, 60.17 mmol, 84.92% yield, 98.7% purity) as a light green solid. MS m/z (ESI) $[M+H]^+$.= 246.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.04 (s, 3 H) 7.43 (s, 1 H) 7.47 (d, *J*=7.95 Hz, 1 H) 7.81 (d, *J*=11.37 Hz, 1 H) .

[0352] Step 2: To a soluton of 2, 4-dichloro-6-fluoro-7-methoxy-quinoline (10 g, 40.64 mmol, 1 *eq*) in DCM (100 mL) was added BBr_3 (2 M, 42 mL, 2.07 *eq*) at 0 °C. The mixture was stirred at 0°C for 2 hours. TLC (PE/EtOAc=3/1, Rf=0.32) showed one major spot was observed. The reaction mixture was quenched with methanol (100 mL), the mixture was diluted with water (200mL) and then treated with sodium bicarbonate to attend pH=7. The mixture was extracted with ethyl acetate (100mL, 3 times), the combined organic phase was washed with brine (2100mL, 2 times), dried with anhydrous Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®;80 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @

100 mL/min) to afford 2, 4-dichloro-6-fluoro-quinolin-7-ol (9.4 g, 40.51 mmol, 99.68% yield, 100% purity) as white solid. MS m/z (ESI) $[M+H]^+$ = 232.0.

[0353] Step 3: To a solution of 2, 4-dichloro-6-fluoro-quinolin-7-ol (9.4 g, 40.51 mmol, 1 *eq*) in DMF (100 mL) was added trideuterio (iodo) methane (7.2 g, 49.67 mmol, 3.09 mL, 1.23 *eq*) and K_2CO_3 (17 g, 123.00 mmol, 3.04 *eq*), the reaction mixture was stirred at 25 °C for 12 hours. TLC (PE/EtOAc=5/1, Rf=0.32) showed one major spot was observed. The reaction mixture was filtered and the filtrate was poured into water (1000 mL), extracted with EtOAc (500 mL, 3 times). The combined organic phase was washed with saturated brine (500 mL, 2 times), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to afford **A.4k** (6.4 g, 25.69 mmol, 63.43% yield, 100% purity) as white solid. MS m/z (ESI) $[M+H]^+$= 249.1. ^1H NMR (400 MHz, CD_3OD) δ (ppm): 7.59 (br d, *J*=7.34 Hz, 1 H) 7.70 (br s, 1 H) 7.97 (br d, *J*=10.39 Hz, 1 H).

A.4l (R_8 = -$N(CH_3)_2$; R_9 = -F; $R_{7,10}$ = -H): 2,4-dichloro-6-fluoro-N,N-dimethylquinolin-7-amine



A.4l

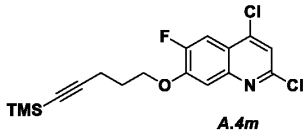
[0354] Step 1: To a solution of 2-fluoro-5-nitro-aniline (10 g, 64.06 mmol, 1 eq) in MeOH (100 mL)/AcOH (10 mL) was added HCHO (5.77 g, 192.17 mmol, 5.29 mL, 3 eq) at 25°C. After stirring at 25 °C for 48 hours the reaction mixture was added into saturated aqueous solution of ammonium chloride (200 mL) and extracted with ethyl acetate (100 mL, 3 times). The combined organic layers were washed with brine (100 mL, 3 times), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~5% Ethylacetate/Petroleum ether gradient @ 45mL/min) to give 2-fluoro-N,N-dimethyl-5-nitro-aniline (7 g, 36.11 mmol, 56.37% yield, 95% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$ = 185.1.

[0355] Step 2: To a solution of Pd/C (0.1 g, 10% purity) in ethyl acetate (20 mL) was added 2-fluoro-N,N-dimethyl-5-nitro-aniline (1 g, 5.43 mmol, 1 eq) under N_2 atmosphere at 25°C. The suspension was degassed and purged with H_2 3 times at 25°C. After stirring under H_2 (15 Psi) at 25 °C for 16 hours, the reaction mixture was filtered and concentrated under reduced

pressure to give 4-fluoro-N3,N3-dimethyl-benzene-1,3-diamine (0.7 g, 4.09 mmol, 75.25% yield, 90% purity) as brown oil. MS m/z (ESI) $[M+H]^+$ = 155.1.

[0356] Step 3: To a solution of 6-fluoro-N^1,N^1-dimethylbenzene-1,3-diamine (0.7 g, 4.54 mmol, 1 eq), malonic acid (0.5 g, 4.80 mmol, 500.00 μL, 1.06 eq) in POCl3 (7 mL) at 25°C. After stirring at 100°C for 16 hours, the reaction mixture was added into saturated sodium bicarbonate aqueous solution (100 mL) and extracted with ethyl acetate 60 mL (20 mL, 3 times). The combined organic layers were washed with brine 60 mL (20 mL , 3 times), dried over Na_2SO_4, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~5% Ethylacetate/Petroleum ether gradient @ 45 mL/min) to give **A.4l** (0.17 g, 590.49 μmol, 13.01% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 259.1.

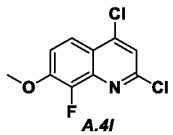
A.4m: 5-[(2,4-dichloro-6-fluoro-7-quinolyl)oxy]pent-1-ynyl-trimethyl-silane



A.4m

[0357] To a solution of 2,4-dichloro-6-fluoro-quinolin-7-ol (400 mg, 1.72 mmol, 1 eq) in DCM (2 mL) was added 5-trimethylsilylpent-4-yn-1-ol (400 mg, 2.56 mmol, 1.48 eq) , PPh_3 (1.36 g, 5.17 mmol, 3 eq), then the resulting mixture was purged with N_2 three times and followed by the addition of DIAD (1.05 g, 5.17 mmol, 1.00 mL, 3 eq) at 0°C, then stirred at 25°C for 12 hours. The reaction mixture was partitioned between EtOAc (80 mL) and water (40 mL), washed with brine (50 mL), died over Na_2SO_4, filtered and evaporated. The crude product was purified by flash silica gel chromatography (ISCO; 12 g SepaFlash Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **A.4m** (380 mg, 1.03 mmol, 59.53% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.81 (d, J = 11.4 Hz, 1H), 7.48 - 7.45 (m, 1H), 7.42 - 7.40 (m, 1H), 4.28 (t, J = 6.1 Hz, 2H), 2.51 (t, J = 6.9 Hz, 2H), 2.19 - 2.08 (m, 2H), 0.15 (s, 9H).

A.4n: 2,4-dichloro-8-fluoro-7-methoxy-quinoline



A.4l

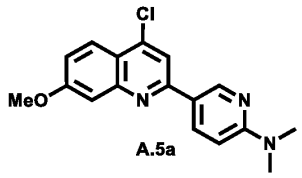
[0358] To a solution of 2-fluoro-3-methoxy-aniline (5 g, 35.43 mmol, 1 eq) in POCl3 (60 mL) was added malonic acid (4.2 g, 40.36 mmol, 4.20 mL, 1.14 eq), then the resulting mixture was stirred at 100°C for 12 hours. The reaction mixture was partitioned between

EtOAc (250 mL, 3 times) and $NaHCO_3$ (200 mL), water (200 mL), washed with brine (180 mL, 2 times), died over Na_2SO_4, filtered and evaporated. The crude product was purified by flash silica gel chromatography (ISCO; 80 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **A.4n** (3.2 g, 13.00 mmol, 36.71% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.95 (d, J = 9.3 Hz, 1H), 7.50 - 7.39 (m, 2H), 4.09 (s, 3H).

General procedure for Suzuki coupling reaction: Intermediates A.5 (Scheme 1; Step 4), C.1 (Scheme 3; Step 1), C.2 (Scheme 4; Step1) have been obtained following the synthetic conditions described below:

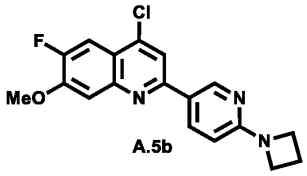
[0359] A mixture of 2,4-dichloroquinoline derivative **A.4** (1.0 eq), boronic ester derivatives (***bor.*** when not commercially available) (1.2 eq), Na_2CO_3 (3.0 eq), $Pd(PPh_3)_4$ (0.10 eq) in **S1:** dioxane/H_2O (0.85:0.15; 0.16M) *or* **S2:** EtOH/toluene/H_2O (0.45:0.45:0.10; 0.17M) was degassed and purged with N_2 three times at 25 °C, and then the mixture was stirred at 80 °C for 16 h under N_2 atmosphere. The mixture was diluted with water and extracted with ethyl acetate (three times). The combined organic phases were washed with brine (three times), dried over *anhydrous* Na_2SO_4, filtered and the filtrate was concentrated to give a residue.

A.5a: 5-(4-chloro-7-methoxy-2-quinolyl)-*N*, *N*-dimethyl-pyridin-2-amine



[0360] According to Scheme 1 Step 4: 2,4-Dichloro-7-methoxy-quinoline (0.30 g, 1.3 mmol, 1.0 eq) and (6-(dimethylamino)pyridin-3-yl)boronic acid (0.26 g, 1.56 mmol, 1.2 eq) were mixed in **S1** (8 mL). After work-up the residue obtained was purified by prep-TLC (SiO_2, DCM/MeOH = 10:1) to give compound **A.5a** (0.15 g, 0.45 mmol, 35% yield, 95% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 314.1.

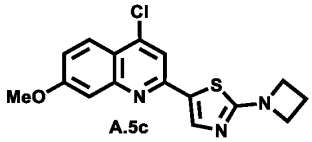
A.5b: 2-[6-(azetidin-1-yl)-3-pyridyl]-4-chloro-6-fluoro-7-methoxy-quinoline



[0361] According to Scheme 1 Step 4: 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.20 g, 0.81 mmol, 1.0 eq) and boronic acid ***bor.6*** (0.17 g, 0.97 mmol, 1.2 eq) were mixed in **S1** (5

mL). After work-up the residue obtained was triturated with ethyl acetate (5.0 mL) at 25 °C for 10 min to give compound **A.5b** (0.15 g, 0.41 mmol, 50% yield, 93% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 344.0.

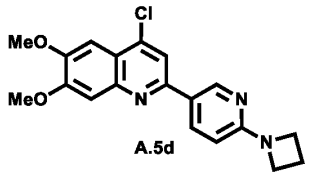
A.5c: 2-(azetidin-1-yl)-5-(4-chloro-7-methoxy-2-quinolyl) thiazole.



A.5c

[0362] According to Scheme 1 Step 4: 2,4-dichloro-7-methoxy-quinoline (0.60 g, 2.6 mmol, 1.0 eq) and boronic ester ***bor.2*** (0.83 g, 3.12 mmol, 1.2 eq) in **S2** (15 mL). The reaction mixture was stirred at 60 °C for 16 h. After work-up the residue obtained was triturated with EtOAc (30 mL) at 25 °C for 20 min and the resulting solid was filtered and washed by EtOAc (10 mL). The filter cake was concentrated to give **A.5c** (0.45 g, 0.93 mmol, 35% yield, 68% purity) as yellow solid. MS m/z (ESI) $[M+H]^+$ = 332.1.

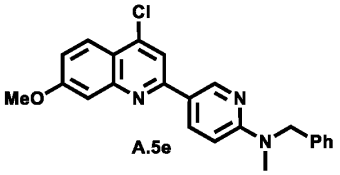
A.5d: 2-[6-(azetidin-1-yl)-3-pyridyl]-4-chloro-6,7-dimethoxy-quinoline



A.5d

[0363] According to Scheme 1 Step 4: 2,4-Dichloro-6,7-dimethoxy-quinoline (0.40 g, 1.6 mmol, 1.0 eq) and boronic acid ***bor.6*** (0.34 g, 1.92 mmol, 1.2 eq) in **S1** (10 mL). After work-up the residue obtained was purified by Flash chromatography (20g column, Eluent of 0~100% EtOAc/PE gradient at 40mL/min) to give compound **A.5d** (0.22 g, 0.42 mmol, 27% yield, 68% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 356.0.

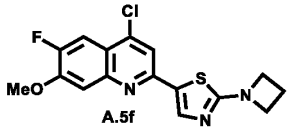
A.5e: *N*-benzyl-5-(4-chloro-7-methoxy-2-quinolyl) -*N*- methyl-pyridin-2-amine



A.5e

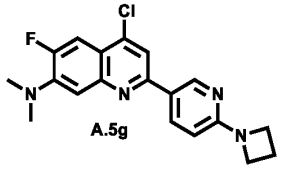
[0364] According to Scheme 1 Step 4: 2,4-Dichloro-7-methoxy-quinoline (0.20 g, 0.88 mmol, 1.0 eq) and (6-(benzyl(methyl)amino)pyridin-3-yl)boronic acid (0.25 g, 1.05 mmol, 1.2 eq) in **S1** (5.5 mL). After work-up the residue obtained was purified by prep-TLC (Plate 1: PE/EtOAc = 3:1) to give compound **A.5e** (0.13 g, 0.30 mmol, 34% yield, 90% purity) as a white solid.

A.5f: 2-(azetidin-1-yl)-5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) thiazole



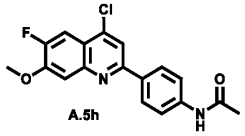
[0365] According to Scheme 1 Step 4: 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.30 g, 1.2 mmol, 1.0 eq) and boronic ester ***bor.2*** (0.38 g, 1.44 mmol, 1.2 eq) in **S1** (7.5 mL). After work-up the residue obtained was purified by prep-TLC (SiO_2, PE/EtOAc = 3:1) to give compound **A.5f** (50 mg, 0.10 mmol, 8.2% yield, 70% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$ = 350.0.

A.5g: 2-[6-(azetidin-1-yl)-3-pyridyl]-4-chloro-6-fluoro-*N*, *N*-dimethyl-quinolin-7-amine



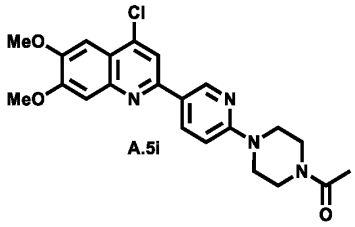
[0366] According to Scheme 1 Step 4: 2,4-Dichloro-6-fluoro-*N*, *N*-dimethyl-quinolin-7-amine (0.17 g, 0.66 mmol, 1.0 eq) and boronic acid ***bor.6*** (0.14 g, 0.8 mmol, 1.2 eq) in **S1** (10 mL). After work-up the residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~20% EtOAc/PE gradient at 45 mL/min) to give compound **A.5g** (0.12 g, 0.30 mmol, 46% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ = 357.1.

A.5h: N-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenyl] acetamide



[0367] According to Scheme 1 Step 4: To a mixture of 2, 4-dichloro-6-fluoro-7-methoxy-quinoline (0.20 g, 0.81 mmol, 1.0 eq) in dioxane (3.0 mL) / H_2O (0.30 mL) was added N-[4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) phenyl]acetamide (0.21 g, 0.80 mmol, 0.99 eq), $Pd(PPh_3)_2Cl_2$ (60 mg, 85 μmol, 0.11 eq) and Na_2CO_3 (0.26 g, 2.5 mmol, 3.0 eq), then the mixture was stirred at 60 °C under N_2 for 12 h. The reaction mixture was filtered and concentrated the filter liquor. The residue obtained was purified by flash chromatography (12 g column, Eluent of 0 to 50% EtOAc/PE gradient at 20 mL/min) to afford **A.5h** (0.11 g, 0.30 mmol, 37% yield, 94% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$ = 345.1.

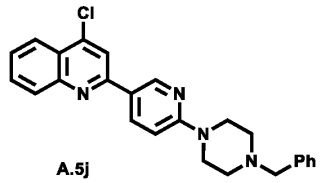
A.5i: 1-[4-[5-(4-chloro-6,7-dimethoxy-2-quinolyl)-2-pyridyl] piperazin-1-yl] ethanone



A.5i

[0368] According to Scheme 1 Step 4: 2,4-Dichloro-6,7-dimethoxy-quinoline (0.25 g, 0.97 mmol, 1.0 eq) and (6-(4-acetylpiperazin-1-yl)pyridin-3-yl)boronic acid (0.29 g, 1.16 mmol, 1.2 eq) in **S1** (6 mL). After work-up the residue obtained was purified by prep-TLC (SiO_2, PE/EtOAc = 1:1) to give compound **A.5i** (0.27 g, 0.59 mmol, 61% yield, 94% purity) was obtained as a brown solid. MS m/z (ESI) $[M+H]^+$ = 427.1.

A.5j: 2-(6-(4-benzylpiperazin-1-yl) pyridin-3-yl)-4-chloroquinoline



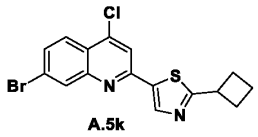
A.5j

[0369] A solution of **C.1a** (33 g, 78 mmol, 1.0 eq) in EtOAc (0.10 L) was degassed and purged with N_2 three times. HCl/EtOAc (2.0 M, 0.50 mL, 13 eq) was added dropwise under N_2. The reaction mixture was stirred at room temperature for 1 h under N_2. The reaction mixture was filtered and gave the HCl.salt (40 g, crude) as a yellow solid. To the crude (70 g from two batches) was added H_2O (1.0 L) at room temperature. pH was adjusted to 11~12 with saturated K_2CO_3 aqueous solution. The mixture was extracted with EtOAc (1.0 L, four times) and concentrated under vacuum. The crude product (around 40 g) was triturated with MTBE at room temperature for 12 h to obtain 4-chloro-2-(6-(piperazin-1-yl)pyridin-3-yl)quinoline **A.5k** (34 g, 0.10 mol, 60% yield, 96% purity) was obtained as a light yellow solid. MS m/z (ESI) $[M+H]^+$ = 325.0. ^1H NMR (400 MHz, $CDCl_3$) *d* (ppm): 8.92 (d, *J* = 2.4 Hz, 1H), 8.35 (dd, *J* = 2.4, 8.8 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H), 7.7-7.8 (m, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 9.2 Hz, 1H), 3.6-3.7 (m, 4H), 3.0-3.1 (m, 4H).

[0370] Free amine **A.5k** (1.5 g, 4.6 mmol, 1.0 eq) was mixed with cesium carbonate (3.0 g, 9.2 mmol, 2.0 eq) and (chloromethyl)benzene (0.64 mL, 5.5 mmol, 1.2 eq) in 100 mL flask. DMF (37 mL) was added, and the reaction was stirred at room temperature for 3 days. The reaction mixture was transferred to a 0.50 L flask and diluted with EtOAc (0.20 L) and

washed with water (0.20 L) and brine (0.20 L). The crude material was obtained as 2.7 g of yellow oil. The oil was diluted with DCM (4.0 mL) and subjected to purification by fully automated flash chromatography (heptane/EtOAc, 0–40% in 0–15 CV). Compound **A.5j** (0.71 g, 1.7 mmol, 37% yield) was obtained as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) *d* (ppm): 8.96 (d, *J* = 2.4 Hz, 1H), 7.50–8.05 (m, 6H), 7.39 (s, 5H), 6.79 (d, *J* = 9.0 Hz, 1H), 3.73 (t, *J* = 5.6 Hz, 4H), 3.63 (s, 2H), 2.63 (t, *J* = 5.1 Hz, 4H).

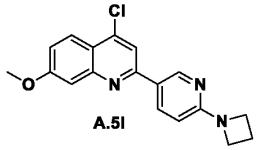
A.5k: 2-(azetidin-1-yl)-5-(7-bromo-4-chloro-2-quinolyl)thiazole



A.5k

[0371] According to Scheme 1 Step 4: 7-bromo-2,4-dichloro-quinoline (500 mg, 1.81 mmol, 1 eq) and 2-(azetidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (480.54 mg, 1.81 mmol, 1 eq) in **S1** (1 mL). After work-up the residue was triturated with Petroleum ether : Ethyl acetate (1:1, 5 ml) at 25 °C for 0.5 hours to give **A.5k** (250 mg, 591.03 µmol, 32.74% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 381.9.

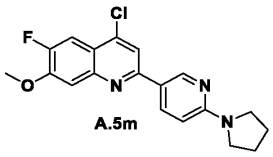
A.5l: 2-[6-(azetidin-1-yl)-3-pyridyl]-4-chloro-7-methoxy-quinoline



A.5l

[0372] According to Scheme 1 Step 4: 2, 4-dichloro-7-methoxy-quinoline (200 mg, 876.91 µmol, 1 eq) and 2-(azetidin-1-yl) -5-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) pyridine (230 mg, 884.14 µmol, 1.01 eq) in **S1** (3.2 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 40~60% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to afford **A.5l** (250 mg, 736.67 µmol, 84.01% yield, 96% purity) as yellow oil.

A.5m: 4-chloro-6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)quinoline

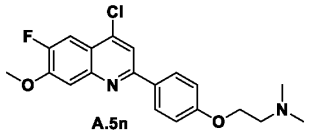


A.5m

[0373] According to Scheme 1 Step 4: To a screw-cap vial equipped with a magnetic stir bar was added 2, 4-dichloro-6-fluoro-7-methoxy-quinoline (600 mg, 2.44 mmol, 1 eq) and dioxane (10 mL) and H_2O (2 mL) and 2-pyrrolidin-1-yl-5-(4, 4, 5, 5-tetramethyl-1, 3, 2-

dioxaborolan-2-yl) pyridine (670 mg, 2.44 mmol, 1 eq) and Na_2CO_3 (800 mg, 7.55 mmol, 3.10 eq) and $Pd(PPh_3)_4$ (280 mg, 242 μmol, 0.1 eq) sequentially. The vial was sealed with a teflon-lined septum, evacuated and backfilled with nitrogen. Then the mixture was stirred at 80 °C for 16 hours under nitrogen atmosphere. TLC (Petroleum ether/Ethylacetate=1/1, NH3.H2O, Rf=0.43) indicated new spots formed. The reaction mixture was quenched by water (10 mL) and EtOAc (10 mL), and then the resulting mixture was filtered and the filter cake was concentrated in vacuum to give **A.5m** (650 mg, 1.82 mmol, 74.5% yield) as white solid.

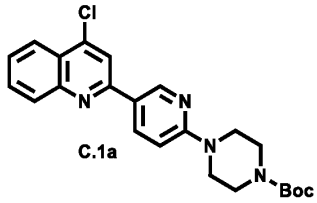
A.5n: 2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]-N,N-dimethyl-ethanamine



A.5n

[0374] According to Scheme 1 Step 4: A mixture of N,N-dimethyl-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethanamine (2.95 g, 3.04 mmol, 9.97e-1 eq), 2,4-dichloro-6-fluoro-7-methoxy-quinoline (750 mg, 3.05 mmol, 1 eq), Pd(PPh3)4 (352 mg, 304.61 μmol, 9.99e-2 eq) and Na2CO3 (969 mg, 9.14 mmol, 3 eq) in S2 (22 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~60% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **A.5n** (1 g, 2.29 mmol, 75.19% yield, 85.9% purity) as a brown solid. MS m/z (ESI) $[M+H]^+$ = 375.1.

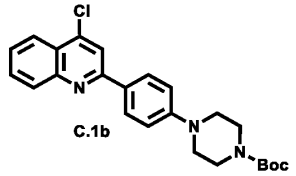
C.1a: *tert*-butyl 4-[5-(4-chloro-2-quinolyl) -2-pyridyl] piperazine-1-carboxylate



C.1a

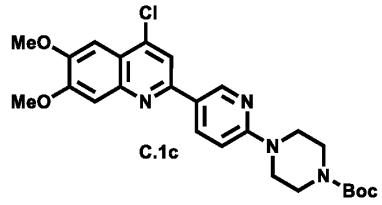
[0375] According to Scheme 3 Step 1: 2,4-Dichloroquinoline (0.35 g, 1.8 mmol, 1.0 eq) and (6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridin-3-yl)boronic acid (0.66 g, 2.16 mmol, 1.2 eq) in **S1** (11.25 mL). After work-up the residue was purified by Flash chromatography (40 g column, Eluent of 0-21% EtOAc/PE gradient at 40 mL/min) to give **C.1a** (0.65 g, 1.5 mmol, 87% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) *d* (ppm): 8.95 - 8.92 (m, 1H), 8.41 - 8.36 (m, 1H), 8.23 - 8.18 (m, 1H), 8.14 - 8.09 (m, 1H), 7.90 - 7.88 (m, 1H), 7.78 - 7.73 (m, 1H), 7.62 - 7.56 (m, 1H), 6.80 - 6.75 (m, 1H), 3.72 - 3.65 (m, 4H), 3.63 - 3.56 (m, 4H), 1.53 - 1.49 (m, 9H).

C.1b: tert-butyl 4-[4-(4-chloro-2-quinolyl) phenyl] piperazine-1-carboxylate



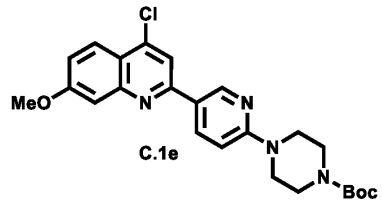
[0376] According to Scheme 3 Step 1: 2,4-Dichloroquinoline (2.0 g, 10 mmol, 1.0 eq) and (4-(4-(tert-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (3.67 g, 12 mmol, 1.2 eq) in **S1** (62.5 mL). After work-up the residue obtained was purified by column chromatography (SiO_2, PE/EtOAc = 20/1 to 3/1**)** to afford **C.1b** (3.0 g, 7.1 mmol, 70% yield) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 424.2.

C.1c: *tert*-butyl 4- [5-(4-chloro-6, 7-dimethoxy-2-quinolyl) -2-pyridyl] piperazine-1-carboxylate



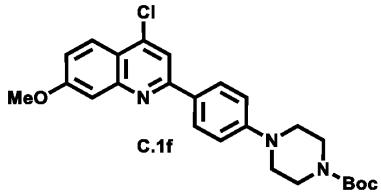
[0377] According to Scheme 3 Step 1: 2,4-Dichloro-6,7-dimethoxy-quinoline (0.20 g, 0.77 mmol, 1.0 eq) and (6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridin-3-yl)boronic acid (0.28 g, 0.92 mmol, 1.2 eq) in **S1** (4.8 mL). After work-up the residue obtained was purified by Flash chromatography (20 g column, Eluent of 0~50% EtOAc/PE gradient at 30 mL/min) to afford **C.1c** (0.35 g, 0.59 mmol, 76% yield, 82% purity) as yellow gum. MS m/z (ESI) $[M+H]^+$= 485.2.

C.1e: *tert*-butyl 4-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate



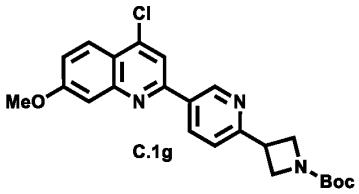
[0378] According to Scheme 3 Step 1: 2,4-Dichloro-7-methoxy-quinoline (0.30 g, 1.3 mmol, 1.0 eq) and (6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridin-3-yl)boronic acid (0.48 g, 1.56 mmol, 1.2 eq) in **S1** (8.1 mL). After work-up the residue obtained was purified by prep-TLC (SiO_2, PE/EtOAc = 2:1) to give **C.1e** (0.50 g, 1.0 mmol, 77% yield, 92% purity) was obtained as yellow oil. MS m/z (ESI) $[M+H]^+$= 455.2.

C.1f: *tert*-butyl 4-[4-(4-chloro-7-methoxy-2-quinolyl) phenyl] piperazine-1-carboxylate



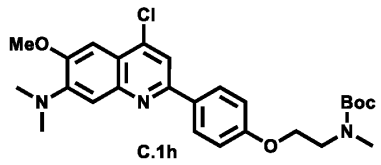
[0379] According to Scheme 3 Step 1: 2,4-Dichloro-7-methoxy-quinoline (0.40 g, 1.8 mmol, 1.0 eq) and (4-(4-(tert-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (0.66 g, 2.16 mmol, 1.2 eq) in **S1** (11.25 mL). After work-up the residue obtained was purified by Flash chromatography (12 g column, Eluent of 20~30% EtOAc/PE gradient at 40 mL/min) to afford **C.1f** (0.60 g, 1.3 mmol, 75% yield, 99% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$ = 454.2.

C.1g: *tert*-butyl 3-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl] azetidine-1-carboxylate



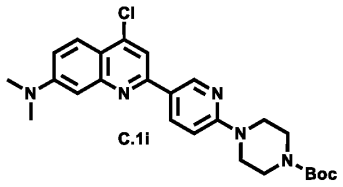
[0380] According to Scheme 3 Step 1: 2,4-Dichloro-7-methoxy-quinoline (0.40 g, 1.8 mmol, 1.0 eq), boronic acid ***bor.1'*** (0.48 g, 2.16 mmol, 1.2 eq) in **S1** (11.25 mL). After work-up the residue obtained was purified by Flash chromatography (40g column, Eluent of 0~10% EtOAc/PE gradient at 40 mL/min) to afford **C.1g** (0.36 g, 0.74 mmol, 42% yield, 88% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 426.1.

C.1h: *tert*-butyl *N*- [2- [4- [4-chloro-7-(dimethylamino)-6-methoxy-2-quinolyl] phenoxy] ethyl]-*N*-methylcarbamate



[0381] 2,4-Dichloro-6-methoxy-*N*, *N*-dimethyl-quinolin-7-amine (0.15 g, 0.55 mmol, 1.0 eq) and tert-butyl methyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)carbamate (0.25 g, 0.66 mmol, 1.2 eq) in **S1** (3.44 mL). After work-up the residue obtained was purified by prep-TLC (SiO_2, PE/EtOAc = 2:1) to give **C.1h** (0.16 g, 0.33 mmol, 60% yield, 100% purity) as a yellow oil. MS m/z (ESI) $[M+H]^+$= 486.3.

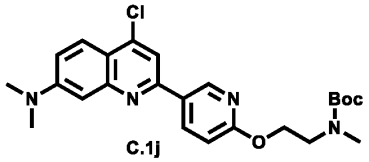
C.1i: *tert*-butyl 4-[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



C.1i

[0382] According to Scheme 3 Step 1: 2,4-Dichloro-*N*, *N*-dimethyl-quinolin-7-amine **A.4d** (0.50 g, 2.1 mmol, 1.0 eq) and (6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridin-3-yl)boronic acid (0.77 g, 2.52 mmol, 1.2 eq) in **S1** (13.1 mL). After work-up the residue obtained was not purified. **C.1i** (0.80 g, 1.2 mmol, 58% yield, 70% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+$= 468.2.

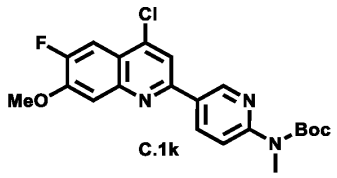
C.1j: *tert*-butyl *N*-[2-[[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl] oxy] ethyl]-*N*-methylcarbamate



C.1j

[0383] According to Scheme 3 Step 1: 2,4-Dichloro-*N*, *N*-dimethyl-quinolin-7-amine **A.4d** (0.30 g, 1.2 mmol, 1.0 eq) and tert-butyl methyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)carbamate (054 g, 1.44 mmol, 1.2 eq) in **S1** (7.5 mL). After work-up the residue obtained was not purified. **C.1j** (0.80 g, 1.2 mmol, 98% yield, 70% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 457.2.

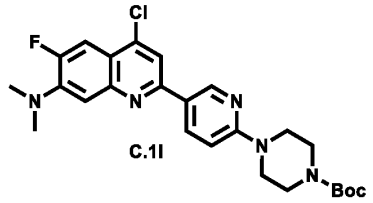
C.1k: *tert*-butyl *N*-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]-*N*-methylcarbamate



C.1k

[0384] According to Scheme 3 Step 1: 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.45 g, 1.8 mmol, 1.0 eq) and tert-butyl methyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (0.72 g, 2.16 mmol, 1.2 eq) in **S1** (11.2 mL). After work-up the residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~20% EtOAc/PE gradient at 40 mL/min) to afford **C.1k** (0.60 g, 1.2 mmol, 64% yield, 82% purity) as a light green solid. MS m/z (ESI) $[M+H]^+$= 418.1.

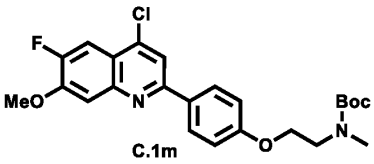
C.1l: *tert*-butyl 4-[5-[4-chloro-7-(dimethylamino)-6-fluoro-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



C.1l

[0385] According to Scheme 3 Step 1: 2,4-Dichloro-6-fluoro-*N*, *N*-dimethyl-quinolin-7-amine (0.30 g, 1.2 mmol, 1.0 eq) and (6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridin-3-yl)boronic acid (0.44 g, 1.44 mmol, 1.2 eq) in **S1** (7.5 mL). After work-up the residue obtained was purified by Flash chromatography (12 g column, Eluent of 0 to 15% EtOAc/PE gradient at 45 mL/min) to give **C.1l** (0.50 g, 0.84 mmol, 73% yield, 82% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 486.2.

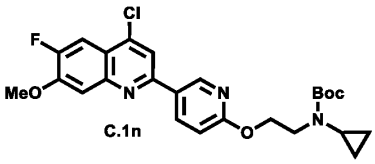
C.1m: *tert*-butyl *N*-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenoxy] ethyl]-*N*-methylcarbamate



C.1m

[0386] According to Scheme 3 Step 1: 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.30 g, 1.2 mmol, 1.0 eq) and tert-butyl methyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)carbamate (0.54 g, 1.44 mmol, 1.2 eq) in **S1** (7.5 mL). After work-up the residue obtained was purified by silica gel chromatography (Biotage, 100-200 mesh silica gel, product came out at B = 25% EtOAc/PE) to afford product **C.1m** (0.50 g, 1.1 mmol, 89% yield) as off-white solid.

C.1n: *tert*-butyl *N*-[2-[[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]oxy]ethyl]-*N*-cyclopropyl-carbamate

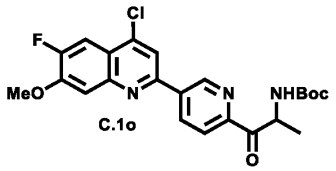


C.1n

[0387] According to Scheme 3 Step 1: 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.18 g, 0.73 mol, 1.0 eq) and *tert*-butyl *N*-cyclopropyl-*N*-[2-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy]ethyl]carbamate (0.36 g, 0.88 mmol, 1.2 eq) in **S1** (4.6 mL). After work-up the residue obtained was purified by Flash chromatography (20 g

column, Eluent of 0~30% EtOAc/PE gradient at 30 mL/min) to give **C.1n** (0.12 g, 0.17 mmol, 23% yield, 69% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 488.2.

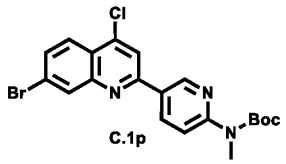
C.1o: *tert*-butyl *N*-[2-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]-1-methyl-2-oxo-ethyl] carbamate



C.1o

[0388] According to Scheme 3 Step 1: 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.30 g, 1.2 mmol, 1.0 eq) and *tert*-butyl *N*-[1-methyl-2-oxo-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl] ethyl] carbamate (0.54 g, 1.44 mmol, 1.2 eq) in **S1** (7.5 mL). After work-up the residue obtained was purified by Flash chromatography (20 g column, Eluent of 0~23% EtOAc/PE gradient at 60 mL/min) to give desired compound as a yellow solid, which was further triturated with EtOAc (50 mL) at 25 °C for 10 min, the resulting solid was filtered and washed by EtOAc (50 mL), the filter cake was concentrated to give **C.1o** (0.30 g, 0.65 mmol, 53% yield, 99% purity) as an off-white solid.

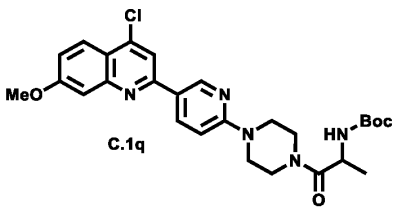
C.1p: *tert*-butyl *N*-[5-(7-bromo-4-chloro-2-quinolyl) -2-pyridyl]-N-methylcarbamate



C.1p

[0389] According to Scheme 3 Step 1: 7-Bromo-2,4-dichloro-quinoline **A.4h** (0.30 g, 1.1 mmol, 1.0 eq) and tert-butyl methyl(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (0.44 g, 1.32 mmol, 1.2 eq) in **S1** (6.9 mL). After work-up the residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~10% EtOAc/PE gradient at 40 mL/min) to afford **C.1p** (0.30 g, 0.66 mmol, 60% yield, 98% purity) as a white solid. MS m/z (ESI) $[M+H]^+$= 450.0.

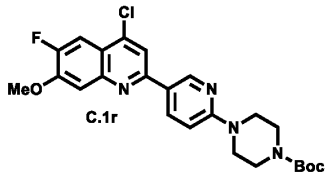
C.1q: *tert*-butyl *N*-[2-[4-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl] piperazin-1-yl]-1-methyl-2-oxo-ethyl] carbamate



C.1q

[0390] According to Scheme 3 Step 1: 2,4-Dichloro-7-methoxy-quinoline (0.25 g, 1.1 mmol, 1.0 eq),and [6-[4-[2-(tert-butoxycarbonylamino) propanoyl] piperazin-1-yl]-3-pyridyl] boronic acid ***bor.7*** (0.52 g, 1.3 mmol, 1.2 eq) in **S1** (6.9 mL). The crude product was triturated with EtOAc (30 mL) (at 25 °C for 30 min to give **C.1q** (0.23 g, 0.41 mmol, 37% yield, 94% purity). MS m/z (ESI) $[M+H]^+$= 526.2.

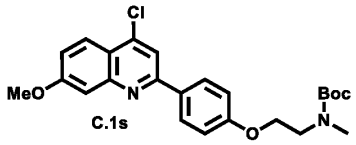
C.1r: *tert*-butyl 4-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate



C.1r

[0391] According to Scheme 3 Step 1: 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.30 g, 1.2 mmol, 1.0 eq) and (6-(4-(tert-butoxycarbonyl)piperazin-1-yl)pyridin-3-yl)boronic acid (0.44 g, 1.44 mmol, 1.2 eq) in **S1** (7.5 mL). After work-up the residue obtained was purified by Flash chromatography (40g column, Eluent of 0~25% EtOAc/PE gradient at 40 mL/min) to afford **C.1r** (0.55 g, 0.95 mmol, 78% yield, 82% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 473.2.

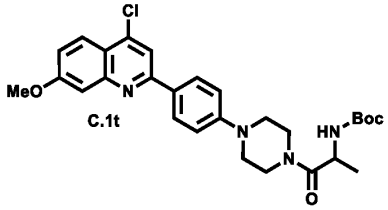
C.1s: tert-butyl methyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)carbamate



C.1s

[0392] According to Scheme 3 Step 1: 2,4-Dichloro-7-methoxy-quinoline (0.30 g, 1.3 mmol, 1.0 eq) and tert-butyl methyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)carbamate (0.59 g, 1.56 mmol, 1.2 eq) in **S1** (8.12 mL). After work-up the residue obtained was purified by Flash chromatography (20 g column, EtOAc/PE 0 to 21% at 60 mL/min) to give **C.1s** (0.60 g, 0.81 mmol, 62% yield, 60% purity) as a colourless gum.

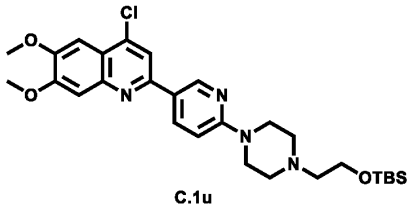
C.1t: tert-butyl (1-(4-(4-(4-chloro-7-methoxyquinolin-2-yl) phenyl) piperazin-1-yl)-1-oxopropan-2-yl) carbamate



C.1t

[0393] According to Scheme 3 Step 1: 2,4-Dichloro-7-methoxy-quinoline (0.10 mg, 0.44 mmol, 1.0 eq eq) and tert-butyl (1-oxo-1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperazin-1-yl)propan-2-yl)carbamate (0.24 g, 0.53 mmol, 1.2 eq) in S1 (2.8 mL). The crude product was triturated with Ethyl acetate (20 mL) at 25 °C for 20 min to give **C.1t** (0.13 mg, 0.25 mmol, 56% yield, 100% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+$= 525.2.

C.1u: *tert*-butyl-[2-[4-[5-(4-chloro-6,7-dimethoxy-2-quinolyl)-2-pyridyl] piperazin-1-yl] ethoxy]-dimethyl-silane

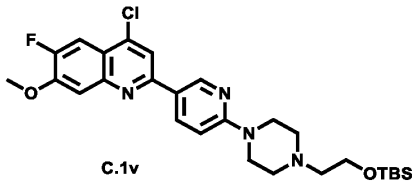


C.1u

[0394] To a solution of compound **C.1c** (0.68 g, 1.4 mmol, 1.0 eq) in dioxane (2.0 mL) was added HCl/dioxane (4.0 M, 5.0 mL) at 25 °C. The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give 4-chloro-6,7-dimethoxy-2-(6-piperazin-1-yl-3-pyridyl) quinoline (0.17 g, 0.44 mmol, 77% yield, 100% purity), which was obtained as a light-yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.56 (s, 2H), 9.00 (d, J = 2.1 Hz, 1H), 8.64 (d, J = 7.8 Hz, 1H), 8.32 (s, 1H), 7.78 (s, 1H), 7.40 (s, 1H), 7.27 (d, J = 9.3 Hz, 1H), 4.00 (s, 10H), 3.24 (s, 4H). MS m/z (ESI) $[M+H]^+$= 385.1.

[0395] To a solution of 4-chloro-6,7-dimethoxy-2-(6-piperazin-1-yl-3-pyridyl) quinoline (0.14 g, 0.36 mmol, 1.0 eq) in DMF (2.0 mL) was added 2-bromoethoxy-tert-butyl-dimethyl-silane (0.14 g, 0.59 mmol, 1.6 eq) and K_2CO_3 (0.21 g, 1.5 mmol, 4.2 eq) at 25 °C. The mixture was stirred at 60 °C for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with EtOAc (25 mL, three times). The combined organic layers were washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue obtained was purified by prep-TLC (SiO_2, PE/EtOAc = 1:1) to give **C.1u** (0.14 g, 0.25 mmol, 69% yield, 98% purity) was obtained as a yellow oil. MS m/z (ESI) $[M+H]^+$= 543.3.

C.1v: *tert*-butyl-[2-[4-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl] piperazin-1-yl] ethoxy]-dimethyl-silane

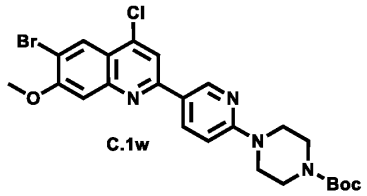


C.1v

[0396] To a solution of **C.1r** (0.19 g, 0.40 mmol, 1.0 eq) in dioxane (2.0 mL) was added HCl/dioxane (2.0 M, 5.0 mL, 25 eq). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated to give 4-chloro-6-fluoro-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl) quinoline (0.14 g, 0.38 mmol, 93% yield) as a white solid. The crude material was used in the next step without purification. MS m/z (ESI) $[M+H]^+$= 373.1.

[0397] To a solution of 4-chloro-6-fluoro-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl) quinoline (0.13 g, 0.35 mmol, 1.0 eq) and 2-bromoethoxy-*tert*-butyl-dimethyl-silane (0.17 g, 0.71 mmol, 2.0 eq) in DMF (5.0 mL) was added K_2CO_3 (0.10 g, 0.75 mmol, 2.2 eq) at 25 °C. The mixture was stirred at 60 °C for 5 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL, three times). The combined organic phases were washed with brine (50 mL, three times), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to give a residue. The residue obtained was purified by prep-HPLC **2** (gradient: 34%-64% B over 10 min) to give **C.1v** (0.15 g, 0.19 mmol, 55% yield, 68% purity) as a white solid. MS m/z (ESI) $[M+H]^+$= 531.3.

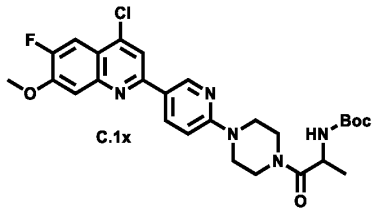
C.1w: tert-butyl 4-[5-(6-bromo-4-chloro-7-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate



C.1w

[0398] To a mixture of 6-bromo-2,4-dichloro-7-methoxy-quinoline (0.40 g, 1.3 mmol, 1.0 eq) and tert-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]piperazine-1-carboxylate (0.51 g, 1.3 mmol, 1.0 eq) in **S2** (7.65 mL) was added $Pd(PPh_3)_4$ (0.10 eq), sodium carbonate (2.0 eq). The mixture was stirred at 70 °C for 16 h. After work-up the residue was purified by Flash chromatography (12 g column, Eluent of 0 to 30% EtOAc/PE gradient at 40 mL/min) to give **C.1w** (0.34 g, 0.57 mmol, 44%, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 535.1.

C.1x: tert-butyl (1-(4-(5-(4-chloro-6-fluoro-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-1-oxopropan-2-yl) carbamate

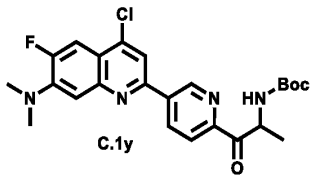


C.1x

[0399] **C.1r** (0.55 g, 1.2 mmol, 1.0 eq) was added to HCl/dioxane (2.0 M, 5.0 mL, 8.6 eq) and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated to give 4-chloro-6-fluoro-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl) quinoline (0.43 g, 1.2 mmol, 99% yield) as yellow solid, which was used in next step directly without further purification.

[0400] To a solution of 4-chloro-6-fluoro-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl)quinoline (0.20 g, 0.54 mmol, 1.0 eq) in DMF (10 mL) was added 2-(tert-butoxycarbonylamino)propanoic acid (0.16 g, 0.85 mmol, 1.6 eq), HATU (0.32 g, 0.84 mmol, 1.6 eq) and DIEA (0.22 g, 1.7 mmol, 0.30 mL, 3.2 eq). The reaction mixture was stirred at 25 °C for 1 h. The reaction was poured into water (0.10 L), extracted with EtOAc (0.10 L, three times). The combined organic phases were washed with saturated brine (100 mL, twice), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was triturated with EtOAc (30 mL) at 25 °C for 20 min and the resulting solid was filtered and washed by EtOAc (10 mL), the filter cake was concentrated to give **C.1x** (0.25 g, 0.44 mmol, 82% yield, 96% purity) as white solid. MS m/z (ESI) $[M+H]^+$= 544.2.

C.1y: tert-butyl N-[2-[5-[4-chloro-7-(dimethylamino)-6-fluoro-2-quinolyl]-2-pyridyl]-1-methyl-2-oxo-ethyl] carbamate

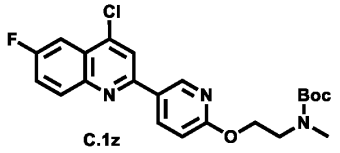


C.1y

[0401] According to Scheme 3 Step 1: To a solution of 2,4-dichloro-6-fluoro-N,N-dimethyl-quinolin-7-amine (0.10 g, 0.39 mmol, 1.0 eq) and tert-butyl N-[1-methyl-2-oxo-2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]ethyl]carbamate (0.28 g, 0.74 mmol, 1.9 eq) in dioxane (4.0 mL) / H_2O (0.40 mL) was added $Pd(PPh_3)_4$ (45 mg, 39 μmol, 0.10 eq) and Na_2CO_3 (0.12 g, 1.2 mmol, 3.0 eq) at 25 °C. After stirring at 60 °C for 16 h, the reaction mixture filtered and concentrated under reduced pressure. The residue obtained was purified

by prep-TLC (SiO_2, PE/EtOAc = 5:1) to give **C.1y** (0.90 g, 0.17 mmol, 44% yield, 90% purity) as a yellow oil. MS m/z (ESI) $[M+H]^+$= 473.1.

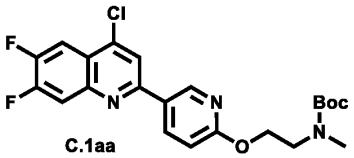
C.1z: tert-butyl N-[2-[[5-(4-chloro-6-fluoro-2-quinolyl)-2-pyridyl]oxy] ethyl]-N-methyl carbamate



C.1z

[0402] According to Scheme 3 Step 1: To a solution of 2, 4-dichloro-6-fluoro-quinoline (0.20 g, 0.93 mmol, 1.0 eq) and tert-butyl N-methyl-N-[2-[[5-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) -2-pyridyl]oxy]ethyl]carbamate (0.35 g, 0.93 mmol, 1.0 eq) in **S1** (5.8 mL) was added $Pd(PPh_3)_4$ (0.09 eq) and Na_2CO_3 (2.0 eq). Then the resulting mixture was stirred at 60 °C for 16 h under N_2. After work-up the residue obtained was purified by flash chromatography (20 g column, Eluent of 0 to 80% EtOAc/PE gradient at 40 mL/min) to give **C.1z** (0.30 g, 0.57 mmol, 61% yield, 82% purity) as colorless gum. MS m/z (ESI) $[M+Na]^+$= 454.3.

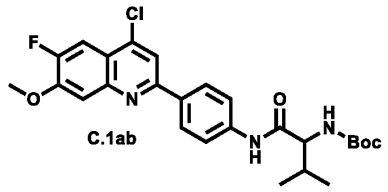
C.1aa: tert-butyl N-[2-[[5-(4-chloro-6, 7-difluoro-2-quinolyl)-2-pyridyl]oxy]ethyl]-N-methyl-carbamate



C.1aa

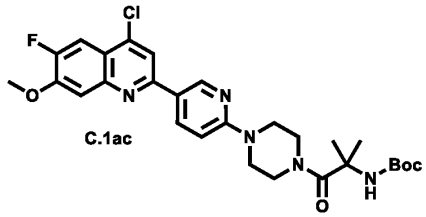
[0403] According to Scheme 3 Step 1: To a solution of **A.4i** (0.32 g, 0.85 mmol, 0.99 eq) and tert-butyl methyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)carbamate ***bor.3*** (0.39 g, 1.02 mmol, 1.2 eq) in **S2** (5 mL) was added $Pd(PPh_3)_4$ (0.10 g, 87 mmol, 0.10 eq) and sodium carbonate (0.19 g, 1.8 mmol, 2.0 eq) at 25 °C. The mixture was degassed and purged with N_2 three times, and then the mixture was stirred at 60 °C for 12 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure. The residue obtained was purified by prep-TLC (PE/EtOAc= 0:1) to give **C.1aa** (0.18 g, 0.36 mmol, 42% yield, 90% purity) as a yellow solid.

C.1ab: tert-butyl N-[1-[[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenyl] carbamoyl]-2-methyl-propyl] carbamate



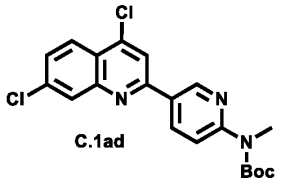
[0404] According to Scheme 3 Step 1: To a solution of 2, 4-dichloro-6-fluoro-7-methoxy-quinoline (0.20 g, 0.82 mmol, 1.0 eq) and ***bor.8*** (0.45 g, 0.99 mmol, 1.2 eq) in dioxane (4.0 mL) /H_2O (0.40 mL) was added $Pd(PPh_3)_4$ (0.10 g, 87 μmol, 0.11 eq) and Na_2CO_3 (0.20 g, 1.9 mmol, 2.3 eq), then the resulting mixture was stirred at 80 °C for 12 h under N_2. The reaction mixture was diluted with EtOAc (50 mL), washed with water (20 mL, twice). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give a crude material. The residue obtained was purified by Flash chromatography **(**4.0 g column, gradient: 0 to 100% EtOAc/PE at 20 mL/min**)** to give **C.1ab** (0.29 g, 0.56 mmol, 69% yield, 97% purity) as colorless gum. MS m/z (ESI) $[M+H]^+$= 502.4.

C.1ac: tert-butyl N-[2-[4-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl] piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl] carbamate



[0405] To a solution of 4-chloro-6-fluoro-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl)quinoline (0.20 g, 0.54 mmol, 1.0 eq) in DMF (10 mL) was added 2-(tert-butoxycarbonylamino)-2-methyl-propanoic acid (0.17 g, 0.84 mmol, 1.6 eq), HATU (0.32 g, 0.84 mmol, 1.6 eq) and DIEA (0.22 g, 1.7 mmol, 0.30 mL, 3.2 eq). The reaction mixture was stirred at 25 °C for 12 h. Then the reaction was poured into water (0.10 L), extracted with EtOAc (50 mL, three times). The combined organic phases were washed with saturated brine (50 mL, twice), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue obtained was purified by Flash chromatography (40 g column, gradient: 0 to 10% EtOAc/PE at 40 mL/min) to afford **C.5ac** (0.20 g, 0.34 mmol, 63% yield, 94% purity) as red oil. MS m/z (ESI) $[M+H]^+$= 558.2.

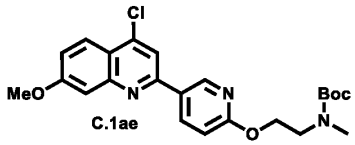
C.1ad: tert-butyl N-[5-(4, 7-dichloro-2-quinolyl) -2-pyridyl]-N-methyl-carbamate



C.1ad

[0406] According to Scheme 3 Step 1: To a solution of 2, 4, 7-trichloroquinoline (0.30 g, 1.3 mmol, 1.0 eq) and tert-butyl N-methyl-N-[5-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) -2-pyridyl]carbamate (0.40 g, 1.2 mmol, 0.93 eq) in **S2** (7.64 mL) were added $Pd(PPh_3)_4$ (0.15 g, 0.13 mmol, 0.10 eq) and Na_2CO_3 (0.28 g, 2.6 mmol, 2.1 eq) at 25 °C. The mixture was degassed and purged with N_2 three times, and then the mixture was stirred at 60 °C for 12 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (4 g column, gradient 0 to 10% EtOAc/PE at 30 mL/min) to give **C.1ad** (0.40 g, 0.94 mmol, 73% yield, 95% purity) as a white solid.

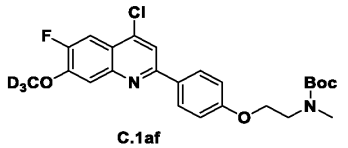
C.1ae: *tert*-butyl (2-((5-(4-chloro-7-methoxyquinolin-2-yl)pyridin-2l)oxy)ethyl)(methyl)carbamate



C.1ae

[0407] According to Scheme 3 Step 1: 2,4-Dichloro-7-methoxy-quinoline (0.30 g, 1.3 mmol, 1.0 eq) and tert-butyl methyl(2-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)ethyl)carbamate ***bor.3*** (0.46 g, 1.56 mmol, 1.2 eq) in **S1** (8.12 mL). After work-up the residue obtained was purified by Flash chromatography (20 g column, EtOAc/PE 0 to 21% at 60 mL/min) to give product **C.1ae** (0.60 g, 0.81 mmol, 60% yield, 65% purity) as a colourless gum.

C.1af: *tert*-butyl N-[2-[4-[4-chloro-6-fluoro-7-(trideuteriomethoxy)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate

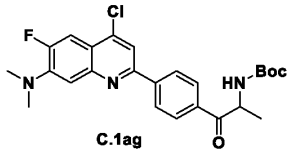


C.1af

[0408] According to Scheme 3 Step 1: To a solution of 2,4-dichloro-6-fluoro-7-(trideuteriomethoxy)quinoline (200 mg, 802.94 μmol, 1 *eq*) in **S1** (6 mL) was added tert-butyl N-methyl-N-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]carbamate

(300 mg, 795.16 µmol, 0.99 *eq*). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 40g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to afford **C.af** (350 mg, 703.10 µmol, 87.57% yield, 93.2% purity) as red oil. MS m/z (ESI) $[M+H]^+$= 464.2.

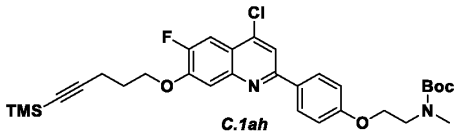
C.1ag: *tert*-butyl N-[2-[4-[4-chloro-7-(dimethylamino)-6-fluoro-2-quinolyl]phenyl]-1-methyl-2-oxo-ethyl]carbamate



C.1ag

[0409] To a solution of 2,4-dichloro-6-fluoro-N,N-dimethyl-quinolin-7-amine (300 mg, 1.16 mmol, 1 eq), tert-butyl N-[1-methyl-2-oxo-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl] carbamate (521.39 mg, 1.39 mmol, 1.2 eq) in **S1** (6.6 mL). After work-up residue was purified by prep-TLC (SiO2, Petroleum ether : Ethyl acetate= 1:1) to give **C.1ag** (0.3 g, 572.09 µmol, 49.41% yield, 90% purity) as a yellow solid.

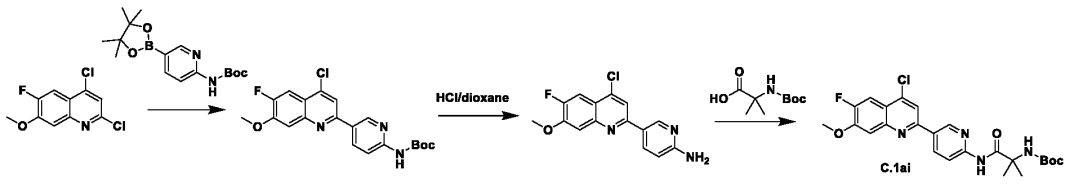
C.1ah: tert-butyl N-[2-[4-[4-chloro-6-fluoro-7-(5-trimethylsilylpent-4-ynoxy)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.1ah

[0410] According to Scheme 3 Step 1: To a solution of 5-[(2,4-dichloro-6-fluoro-7-quinolyl)oxy]pent-1-ynyl-trimethyl-silane (370 mg, 999.14 µmol, 1 eq) in **S1** (8.5 mL) was added tert-butyl N-methyl-N-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]carbamate (460 mg, 1.22 mmol, 1.22 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.1ah** (300 mg, 470.62 µmol, 47.10% yield, 91.8% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 585.2.

C.1ai: tert-butyl N-[2-[[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]amino]-1,1-dimethyl-2-oxo-ethyl]carbamate



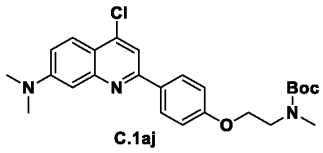
[0411] Step 1: To a screw-cap vial equipped with a magnetic stir bar was added 2, 4-dichloro-6-fluoro-7-methoxy-quinoline (500 mg, 2.03 mmol, 1 eq) and tert-butyl N-[5-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) -2-pyridyl]carbamate (640 mg, 2.00 mmol, 0.98 eq) and dioxane (7.5 mL) and H_2O (1.5 mL) and Na_2CO_3 (700 mg, 6.60 mmol, 3.2 eq) and $Pd(PPh_3)_4$ (240 mg, 207 μmol, 0.1 *eq*) sequentially. The vial was sealed with a teflon-lined septum, evacuated and backfilled with nitrogen. Then the mixture was stirred at 90 °C for 16 hours under nitrogen atmosphere. The reaction mixture was quenched by water (10 mL) and EtOAc (10 mL) and then filtered. The filter cake was collected as tert-butyl N-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) -2-pyridyl]carbamate (530 mg, 1.31 mmol, 64.5% yield). After work-up the residue was purified by silica gel chromatography (Biotage, 100-200 mesh silica gel, product came out at B=10%. A: Petroleum ether, B: Ethyl acetate) to afford tert-butyl N-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]carbamate (70 mg, 173 μmol, 8.5% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.10 (s, 1H), 9.14 (d, J = 2.2 Hz, 1H), 8.61 (dd, J = 2.4, 8.7 Hz, 1H), 8.33 (s, 1H), 8.03 - 7.88 (m, 2H), 7.71 (d, J = 8.2 Hz, 1H), 4.06 (s, 3H), 1.50 (s, 9H)

[0412] Step 2: To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl N-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]carbamate (430 mg, 1.06 mmol, 1 *eq*) and HCl/dioxane (2 M, 10 mL) sequentially. The vial was sealed with a teflon-lined septum. Then the mixture was stirred at 60 °C for 2 hours. LC-MS showed reactant remained. HCl/dioxane (2 M, 15 mL) was added and the mixture was stirred at 60 °C for 2 hours. The reaction mixture was concentrated in vacuum to give product 5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) pyridin-2-amine (390 mg, HCl salt) as yellow solid.

[0413] Step 3: To a screw-cap vial equipped with a magnetic stir bar was added 2-(tert-butoxycarbonylamino) -2-methyl-propanoic acid (200 mg, 984 μmol, 1.5 eq) and DCE (5 mL) and ethyl 2-ethoxy-2H-quinoline-1-carboxylate (350 mg, 1.42 mmol, 2.1 eq) and 5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) pyridin-2-amine (200 mg, 658 μmol, 1 eq) and DIPEA (300 mg, 2.32 mmol, 3.5 eq) sequentially. The vial was sealed with a teflon-lined septum. Then the mixture was stirred at 80 °C for 16 hours. LC-MS showed 45% of reactant amine remained. 2-(tert-butoxycarbonylamino)-2-methyl-propanoic acid (200 mg, 984 μmol, 1.5 eq) and ethyl 2-ethoxy-2H-quinoline-1-carboxylate (300 mg, 1.21 mmol, 1.8 eq) was added the mixture was stirred at 80°C for 5 hours. LC-MS showed not complete. 2-(tert-butoxycarbonylamino) -2-methyl-propanoic acid (200 mg, 984 μmol, 1.5 eq) and ethyl 2-ethoxy-2H-quinoline-1-carboxylate (300 mg, 1.21 mmol, 1.8 eq) was added and the mixture was stirred at 80°C for 16 hours. The reaction was diluted with DCM (20 mL) and water (20

mL) and then the resulting organic phase was extracted with DCM (10 mL, 3 times). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (Biotage, 100-200 mesh silica gel, product came out at B=40%. A: Petroleum ether, B: Ethyl acetate) to afford **C.1ai** (100 mg, 204 μmol, 31% yield) as yellow gum.

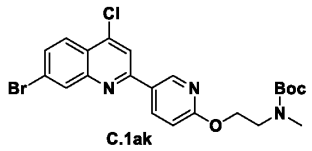
C.1aj: tert-butyl N-[2-[4-[4-chloro-7-(dimethylamino)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.1aj

[0414] According to Scheme 3 Step 1: A solution of 2,4-dichloro-N,N-dimethyl-quinolin-7-amine (200 mg, 829.48 μmol, 1 eq) and tert-butyl N-methyl-N-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]carbamate (312.95 mg, 829.48 μmol, 1 eq) in **S1** (6.6 mL). After work-up **C.1aj** (0.3 g, crude) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+$= 456.1.

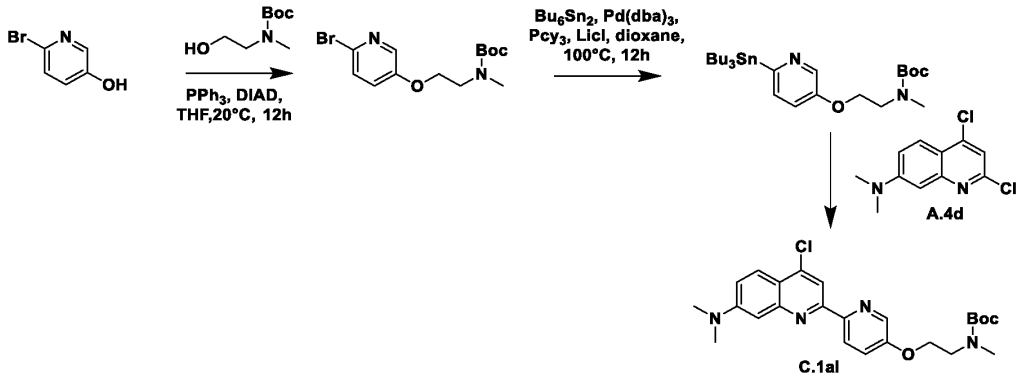
C.1ak: tert-butyl N-[2-[[5-(7-bromo-4-chloro-2-quinolyl)-2-pyridyl]oxy]ethyl]-N-methyl-carbamate



C.1ak

[0415] According to Scheme 3 Step 1: A mixture of 7-bromo-2,4-dichloro-quinoline (500 mg, 1.81 mmol, 1 eq) , tert-butyl N-methyl-N-[2-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy]ethyl]carbamate (615 mg, 1.63 mmol, 9.01e-1 eq) in **S2** (6.6 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethylacetate/Petroleum ether gradient @ 50 mL/min) to give **C.1ak** (650 mg, 1.12 mmol, 62.10% yield, 85% purity). MS m/z (ESI) $[M+H]^+$= 494.0.

C.1al: afford tert-butyl N-[2-[[6-[4-chloro-7-(dimethylamino)-2-quinolyl]-3-pyridyl]oxy]ethyl]-N-methyl-carbamate



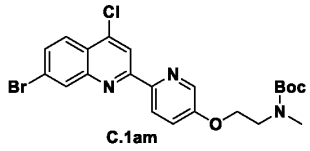
[0416] Step 1: To a solution of 6-bromopyridin-3-ol (17 g, 97.70 mmol, 1 eq), PPh_3 (28.19 g, 107.47 mmol, 1.1 eq) and tert-butyl N-(2-hydroxyethyl)-N-methyl-carbamate (20.54 g, 117.24 mmol, 1.2 eq) in THF (170 mL) was added DIAD (21.73 g, 107.47 mmol, 20.84 mL, 1.1 eq) at 0 °C under N_2. The reaction solution was stirred at 25 °C for 12 hours. The reaction mixture was partitioned between EtOAc (1000 mL) and water (500 mL), washed with brine(400 mL), died over Na_2SO_4, filtered and evaporated. The crude product was purified by flash silica gel chromatography (ISCO; 330 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give the tert-butyl N-[2-[(6-bromo-3-pyridyl)oxy]ethyl]-N-methyl-carbamate (6 g, 18.12 mmol, 18.54% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.05 (d, J = 3.0 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.10 (br d, J = 6.4 Hz, 1H), 4.15 - 4.07 (m, 2H), 3.61 (br t, J = 5.4 Hz, 2H), 2.97 (s, 3H), 1.46 (s, 9H).

[0417] Step 2: To a solution of tert-butyl N-[2-[(6-bromo-3-pyridyl)oxy]ethyl]-N-methyl-carbamate (4.3 g, 12.98 mmol, 1 eq), $Pd_2(dba)_3$ (1.2 g, 1.31 mmol, 1.01e-1 eq), PCy_3 (0.75 g, 2.67 mmol, 867.05 µL, 2.06e-1 eq) and LiCl (2.79 g, 65.93 mmol, 1.35 mL, 5.08 eq) in dioxane (40 mL) was added tributyl(tributylstannyl)stannane (22.03 g, 37.98 mmol, 19.02 mL, 2.93 eq) under N_2. The reaction solution was stirred at 110 °C for 12 hours. The reaction solution was extracted with EtOAc (200 mL, 3 times). The combined organic phase was washed with brine (200 mL, 2 times), dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~3% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give a residue. The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10um; mobile phase: [water (ammonia hydroxide v/v)-ACN]; gradient: 90%-100% B over 15

min). After Prep-HPLC purification, the eluent was concentrated to give tert-butyl N-methyl-N-[2-[(6-tributylstannyl-3-pyridyl)oxy]ethyl]carbamate (5 g, 4.80 mmol, 36.99% yield, 91% purity) as a colorless oil. MS m/z (ESI) $[M+H]^+$= 543.3.

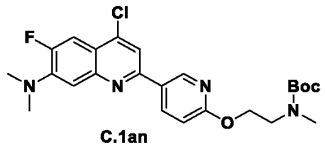
[0418] Step 3: To a solution of tert-butyl N-methyl-N-[2-[(6-tributylstannyl-3-pyridyl)oxy]ethyl]carbamate (1 g, 1.85 mmol, 1 eq) , 2,4-dichloro-N,N-dimethyl-quinolin-7-amine (600 mg, 2.49 mmol, 1.35 eq) and LiCl (420 mg, 9.91 mmol, 203.09 µL, 5.36 eq) in m-xylene (20 mL) was added $Pd(PPh_3)_2Cl_2$ (260 mg, 370.43 µmol, 2.01e-1 eq) under N_2. The reaction solution stirred at 130 °C for 12 hours. The reaction solution was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to **C.1al** (450 mg, 807.50 µmol, 43.71% yield, 82% purity) as a yellow oil. MS m/z (ESI) $[M+H]^+$= 457.2.

C.1am: tert-butylN-[2-[[6-(7-bromo-4-chloro-2-quinolyl)-3-pyridyl]oxy]ethyl]-N-methyl-carbamate



[0419] According to Scheme 3 Step 1: A mixture of 7-bromo-2,4-dichloro-quinoline (500 mg, 1.81 mmol, 1 eq), tert-butyl N-methyl-N-[2-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy]ethyl]carbamate (615 mg, 1.63 mmol, 9.01e-1 eq) in **S2** (6.6 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethylacetate/Petroleum ether gradient @ 50 mL/min) to give **C.1am** (650 mg, 1.12 mmol, 62.10% yield, 85% purity). MS m/z (ESI) $[M+H]^+$= 494.0.

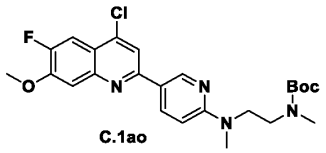
C.1an: tert-butyl N-[2-[[5-[4-chloro-7-(dimethylamino)-6-fluoro-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate



[0420] According to Scheme 3 Step 1: A mixture of 2,4-dichloro-6-fluoro-N,N-dimethyl-quinolin-7-amine (500 mg, 1.93 mmol, 1 eq), tert-butyl N-methyl-N-[2-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy]ethyl]carbamate (730 mg, 1.93 mmol, 1 eq) in **S2** (11 mL). After work-up the residue was purified by flash silica gel chromatography

(ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.1an** (800 mg, 1.68 mmol, 87.29% yield, 100% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 475.1.

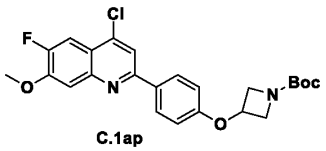
C.1ao: tert-butyl N-[2-[[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]-methyl-amino]ethyl]-N-methyl-carbamate



C.1ao

[0421] According to Scheme 3 Step 1: A mixture of 2,4-dichloro-6-fluoro-7-methoxy-quinoline (0.200 g, 0.813 mmol, 1.00 eq) ,tert-butyl N-methyl-N-[2-[methyl-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl] amino]ethyl]carbamate (318 mg, 0.813 mmol, 1.00 eq) in **S2** (4.5 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~60% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.1ao** (350 mg, 0.538 mmol, 66.2% yield, 73% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 475.3.

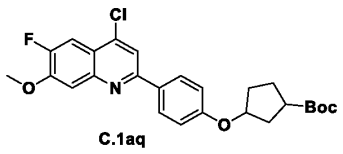
C.1ap: tert-butyl 3-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenoxy]azetidine-1-carboxylate



C.1ap

[0422] According to Scheme 3 Step 1: A solution of 2, 4-dichloro-6-fluoro-7-methoxy-quinoline (200 mg, 813 μmol, 1.00 eq), tert-butyl 3-[4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) phenoxy]azetidine-1-carboxylate (305 mg, 813 μmol, 1.00 eq) in **S2** (4.4 mL). After work-up the residue was purified by prep-TLC (SiO2, PE: EtOAc = 3:1) to give **C.1ap** (230 mg, 501 μmol, 61.7% yield) as yellow oil. MS m/z (ESI) $[M+H]^+$= 459.1.

C.1aq: tert-butyl 3-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenoxy]pyrrolidine-1-carboxylate

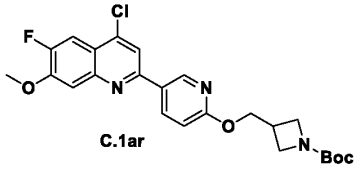


C.1aq

[0423] According to Scheme 3 Step 1: A solution of 2, 4-dichloro-6-fluoro-7-methoxy-quinoline (200 mg, 813 μmol, 1.00 eq), tert-butyl 3-[4-(4, 4, 5, 5-tetramethyl-1, 3, 2-

dioxaborolan-2-yl) phenoxy]pyrrolidine-1-carboxylate (316.4 mg, 813 µmol, 1.00 eq) in **S2** (4.4 mL). After work-up the residue was purified by prep-TLC (SiO2, PE: EtOAc = 3:1) to give **C.1aq** (260 mg, 550 µmol, 67.6% yield) as yellow oil. MS m/z (ESI) $[M+H]^+$= 473.3.

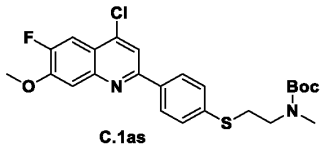
C.1ar: tert-butyl 3-[[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]oxymethyl]azetidine-1-carboxylate



C.1ar

[0424] According to Scheme 3 Step 1: A solution of 2,4-dichloro-6-fluoro-7-methoxy-quinoline (0.3 g, 1.22 mmol, 1 eq) , tert-butyl 3-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxymethyl]azetidine-1-carboxylate (475.83 mg, 1.22 mmol, 1 eq) in **S2** (11 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~15%Ethylacetate/Petroleum ether gradient @ 45 mL/min) to give C.1ar (400 mg, 759.62 µmol, 62.30% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 474.2.

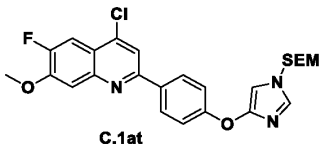
C.1as: tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenyl]sulfanylethyl]-N-methyl-carbamate



C.1as

[0425] According to Scheme 3 Step 1: A mixture of tert-butyl N-methyl-N-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]sulfanylethyl]carbamate (320 mg, 813.53 µmol, 1 eq), 2,4-dichloro-6-fluoro-7-methoxy-quinoline (200 mg, 812.79 µmol, 1 eq) in **S2** (5.5 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) to give **C.1as** (250 mg, 486.91 µmol, 59.91% yield, 92.9% purity) as colorless oil. MS m/z (ESI) $[M+H]^+$= 477.1.

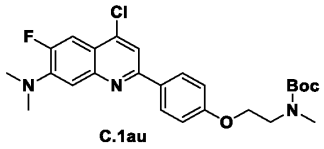
C.1at: 2-[[4-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]imidazol-1-yl]methoxy]ethyl-trimethyl-silane



C.1at

[0426] According to Scheme 3 Step 1: A solution of 2,4-dichloro-6-fluoro-7-methoxy-quinoline (350 mg, 1.42 mmol, 1 eq), trimethyl-[2-[[4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]imidazol-1-yl]methoxy]ethyl]silane (550 mg, 1.32 mmol, 9.29e-1 eq)) in **S2** (4.5 mL). After work-up the crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.1at** (450 mg, 818.94 µmol, 57.58% yield, 91% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 500.1.

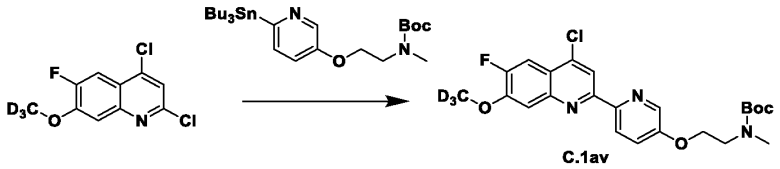
C.1au: tert-butyl N-[2-[4-[4-chloro-7-(dimethylamino)-6-fluoro-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.1au

[0427] According to Scheme 3 Step 1: A solution of 2,4-dichloro-6-fluoro-N,N-dimethyl-quinolin-7-amine (150 mg, 578.91 µmol, 1 eq) , tert-butyl N-methyl-N-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]carbamate (218.41 mg, 578.91 µmol, 1 eq) in **S1** (4.4 mL). After work-up the residue was purified by prep-TLC (Petroleum ether : Ethyl acetate=3:1) to give **C.1au** (0.2 g, 379.77 µmol, 65.60% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 474.2.

C.1av: tert-butyl N-[2-[[6-[4-chloro-6-fluoro-7-(trideuteriomethoxy)-2-quinolyl]-3-pyridyl]oxy]ethyl]-N-methyl-carbamate

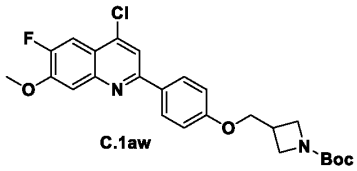


C.1av

[0428] According to Scheme 3 Step 1: To a solution of 2,4-dichloro-6-fluoro-7-(trideuteriomethoxy)quinoline (260 mg, 1.04 mmol, 1 eq) in o-xylene (10 mL) was added tert-butyl N-methyl-N-[2-[(6-tributylstannyl-3-pyridyl)oxy]ethyl]carbamate (650.00 mg, 1.20 mmol, 1.15 eq) , LiCl (195.00 mg, 4.60 mmol, 94.29 µL, 4.41 eq), $PdCl_2(PPh_3)_2$ (195.00 mg, 277.82 µmol, 2.66e-1 eq), then the resulting mixture was purged with N_2 three times and stirred at 100°C for 12 hours. The reaction mixture was partitioned between EtOAc (60 mL) and water (30 mL), washed with brine(30 mL), died over Na_2SO_4, filtered and evaporated. The crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min)

to give **C.1av** (450 mg, 967.88 μmol, 92.72% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.55 - 8.48 (m, 2H), 8.40 (d, J = 2.9 Hz, 1H), 7.86 (d, J = 11.6 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 2.6, 8.6 Hz, 1H), 4.24 (br d, J = 2.3 Hz, 2H), 3.74 - 3.60 (m, 2H), 3.03 (s, 3H), 1.49 (s, 9H).

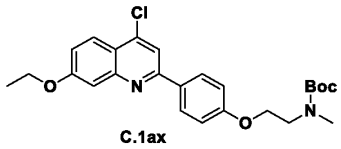
C.1aw: tert-butyl 3-[[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]methyl]azetidine-1-carboxylate



C.1aw

[0429] According to Scheme 3 Step 1: A solution of 2,4-dichloro-6-fluoro-7-methoxy-quinoline (500 mg, 2.03 mmol, 1 eq), tert-butyl 3-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]methyl]azetidine-1-carboxylate (790 mg, 2.03 mmol, 9.99e-1 eq) in **S1** (7 mL).After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~40% PE:EtOAc gradient @ 40 mL/min) to afford **C.1aw** (500 mg, 919.79 μmol, 45.27% yield, 87% purity) as a yellow oil. MS (ESI) m/z $[M+H]^+$= 473.2.

C.1ax: tert-butyl (2-(4-(7-ethoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.1ax

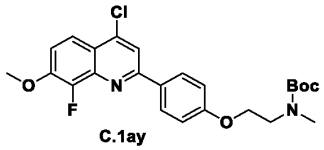
[0430] Step1: To a solution of 2,4-dichloro-7-methoxy-quinoline (7 g, 30.69 mmol, 1 *eq*) in DCM (100 mL) was added BBr_3 (2 M, 46 mL, 3 *eq*) at 0°C under N_2 and stirred at 0°C for 2 hours. The reaction solution was quenched by H_2O (200 mL). The mixture was extracted with ethyl acetate (300 mL, 2 times). The combined organic phases were washed with brine (300 mL), dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=1/0 to 20/1) to give 2,4-dichloroquinolin-7-ol (5 g, 22.89 mmol, 74.59% yield, 98% purity) as a white solid. MS m/z (ESI) $[M+H]^+$= 241.1.

[0431] Step 2: According to Scheme 3 Step 1: A solution of 2,4-dichloroquinolin-7-ol (1.3 g, 6.07 mmol, 1 *eq*), tert-butyl N-methyl-N-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]ethyl]carbamate (1.46 g, 3.88 mmol, 6.38e-1 *eq*) in **S1** (11 mL). After work-up

the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% DCM/MeOH gradient @ 40 mL/min) to afford tert-butyl N-[2-[4-(4-chloro-7-hydroxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (760 mg, 1.20 mmol, 19.84% yield, 68% purity) as a yellow oil. MS m/z (ESI) $[M+H]^+$= 429.2.

[0432] Step 3: To a solution of tert-butyl N-[2-[4-(4-chloro-7-hydroxy-2-quinolyl) phenoxy]ethyl]-N-methyl-carbamate (250 mg, 582.88 µmol, 1 eq) in MeCN (5 mL) was added iodoethane (130 mg, 833.52 µmol, 66.67 µL, 1.43 eq) and K_2CO_3 (240 mg, 1.74 mmol, 2.98 eq). The reaction mixture was stirred at 60 °C for 12 hours. The residue was partitioned between ethyl acetate (10 mL) and water (20mL). The aqueous layer was extracted with ethyl acetate (20mL, 2 times). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 20~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to afford **C.1ax** (180 mg, 393.91 µmol, 67.58% yield, 100% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 457.3.

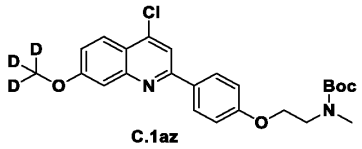
C.1ay: tert-butyl N-[2-[4-(4-chloro-8-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate



C.1ay

[0433] According to Scheme 3 Step1: A solution of 2,4-dichloro-8-fluoro-7-methoxy-quinoline (300 mg, 1.22 mmol, 1 eq) in toluene (3mL) and tert-butyl N-methyl-N-[2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenoxy]ethyl]carbamate (450 mg, 1.19 mmol, 9.78e-1 eq) in **S2** (6.6 mL). After work-up the crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.1ay** (120 mg, 260.35 µmol, 21.35% yield, 100% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 461.2.

C.1az: 1-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]pyrrolidin-2-one



C.1az

To a solution of tert-butyl N-[2-[4-(4-chloro-7-hydroxy-2-quinolyl) phenoxy]ethyl]-N-methyl-carbamate (250 mg, 582.88 µmol, 1 eq) in MeCN (5 mL) was added trideuterio (iodo) methane (120 mg, 827.83 µmol, 51.52 µL, 1.42 eq) and K_2CO_3 (240 mg, 1.74 mmol, 2.98 eq).

The reaction mixture was stirred at 60°C for 12 hours. The residue was partitioned between EtOAc (10 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (20mL, 2 times). The combined organic layers were dried over (Na_2SO_4) and evaporated to give a crude material which was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 20~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to afford **C.1az** (200 mg, 448.48 μmol, 76.94% yield, 100% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 446.2.

General procedures for Buchwald coupling and S_NAr reactions: Intermediates B.1 (Scheme 2; Step 1), C.2 (Scheme 3; Step 2), D.1 (Scheme 5; Step 1), E.1 (Scheme 6; Step 1)

[0434] Conditions 1 Buchwald. A mixture of derivative **A.4**, **A.5 or C.1** (1.0 eq), amine (2.0 eq), BrettPhos Pd G3 (0.10 eq), *t*-BuONa (3.0 eq) in dioxane (0.10 M) was degassed and purged with N_2 three times at 25 °C, and then the mixture was stirred at 80 °C for 16 hours under N_2 atmosphere. The mixture was diluted with water and extracted with EtOAc (3 times). The combine organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give a residue.

[0435] Conditions 2 Buchwald. A mixture of derivative **A.4**, **A.5 or C.1** (1.0 eq), amine (1.3 eq), $PdP(t\text{-Bu})_3$ (0.10 eq), *t*-BuONa (3.0 eq) in dioxane (0.15 M) was degassed and purged with N_2 three times at 25 °C, and then the mixture was stirred at 80 °C for 16 hours under N_2 atmosphere. The mixture was diluted with water and extracted with EtOAc (3 times). The combine organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give a residue.

[0436] Conditions 3 Buchwald. A mixture of derivative **A.4**, **A.5 or C.1** (1.0 eq), amine (3.0 eq), CPhos Pd G3 (0.10 eq), $CsCO_3$ (2.0 eq) in dioxane (0.10 M) was degassed and purged with N_2 three times at 25 °C, and then the mixture was stirred at 80 °C for 16 hours under N_2 atmosphere. The mixture was diluted with water and extracted with EtOAc (3 times). The combine organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give a residue.

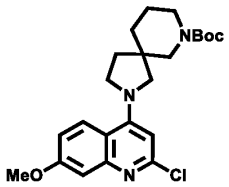
[0437] Conditions 4 Buchwald. A mixture of derivative **A.4**, **A.5 or C.1** (1.0 eq), amine (1.2 eq), SPhos Pd G_3 (0.10 eq), Cs_2CO_3 (3.0 eq) in dioxane was degassed and purged with N_2 for three times, and then the mixture was stirred at 80 °C for 16 hours under N_2 atmosphere. The mixture was diluted with water and extracted with ethyl acetate (3 times). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to give a residue.

[0438] Conditions 1 SNAr: To a solution of quinoline **A.4**, **A.5 or C.1** (1.0 eq), amine (1.5 eq) in dimethyl sulfoxide (0.40 M) was added cesium fluoride (2.0 eq) at 25 °C. After stirring at 130 °C for 16 hours, the reaction mixture was added into water (0.08 M) and extracted with ethyl acetate (3 times). The combined organic layers were washed with brine (three times), dried over sodium sulfate, filtered, and concentrated under reduced pressure.

[0439] Conditions 2 SNAr: To a screw-cap vial equipped with a magnetic stir bar was added **A.4**, **A.5 or C.1** (1.0 eq), and amine (> 10 eq) sequentially. The vial was sealed with a Teflon-lined septum. Then the mixture was stirred at 130 °C for 16 h. The reaction mixture was diluted with EtOAc and water, and then the resulting organic phase was extracted with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and the filtrate was concentrated *in vacuum* to give the product.

[0440] Conditions 3 SNAr: To a solution of **A.4**, **A.5 or C.1** (1.0 eq) in DMSO (0.40 M) was added amine (3.0 eq) and DIEA (1.7 eq) at 25 °C. The mixture was stirred at 100 °C for 16 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (three times). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure.

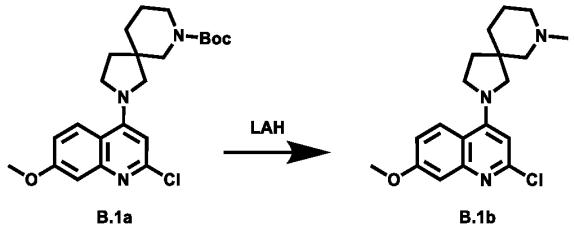
B.1a: *tert*-butyl 2-(2-chloro-7-methoxyquinolin-4-yl)-2,7-diazaspiro [4.5] decane-7-carboxylate



B.1a

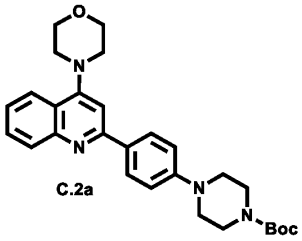
[0441] According to Scheme 2 Step 1: Conditions 3 SNAr: To 2,4-Dichloro-7-methoxyquinoline (0.38 g, 1.7 mmol, 1.0 eq) in DMSO (1.7 M) was added DIEA and amine (1.5 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 25%-55% over 15 min). The eluent was lyophilized to give **B.1a** (0.33 g, 0.76 mmol, 46% yield, 100% purity) as a yellow solid.

B.1b: 2-(2-chloro-7-methoxyquinolin-4-yl)-7-methyl-2,7-diazaspiro [4.5] decane



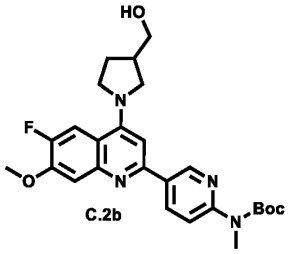
[0442] To a solution **B.1a** (0.28 g, 0.64 mmol, 1.0 eq) in THF (4.0 mL) was added $LiAlH_4$ (2.5 M, 1.0 mL, 3.9 eq) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at 25 °C for 10 min, then the mixture was stirred at 50 °C for 2 h. To the reaction mixture was added THF (20 mL) to dilute the reaction solution, then to the mixture was added Na_2SO_4. To the reaction mixture was added H_2O dropwise until there was no air bubble in the reaction system. Then the reaction mixture was filtered and concentrated under reduced pressure to give the residue. The residue obtained was purified by prep-TLC (SiO_2, PE/EtOAc = 1:1) to give **B.1b** (80 mg, 0.22 mmol, 35% yield, 95% purity) as a colorless gum.

C.2a: *tert*-butyl 4-(4-(4-morpholinoquinolin-2-yl)phenyl)piperazine-1-carboxylate



[0443] According to Scheme 3 Step 2: Conditions 1 Buchwald with **C.1b** (0.20 g, 0.47 mmol, 1.0 eq). After work-up the residue was purified by Flash chromatography (40 g column, Eluent of 0-21% EtOAc/PE gradient at 40 mL/min) to give **C.2a** (0.65 g, 1.5 mmol, 87% yield) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 475.3.

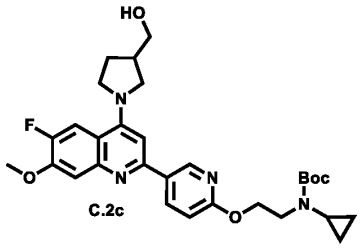
C.2b: *tert*-butyl *N*-[5-[6-fluoro-4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl]-*N*-methylcarbamate



[0444] According to Scheme 3 Step 2: Conditions 1 Buchwald with **C.1k** (0.15 g, 0.36 mmol, 1.0 eq). After work-up the residue obtained was purified by Flash chromatography (12

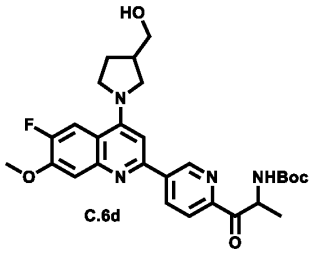
g column, eluent of 0~20% EtOAc/PE gradient at 40 mL/min) to afford **C.2b** (40 mg, 43 μmol, 12% yield, 52% purity) as a light-yellow oil. MS m/z (ESI) $[M+H]^+$= 483.2.

C.2c: *tert*-butyl *N*-cyclopropyl-N-[2-[[5-[6-fluoro-4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy -2-quinolyl]-2-pyridyl] oxy] ethyl] carbamate



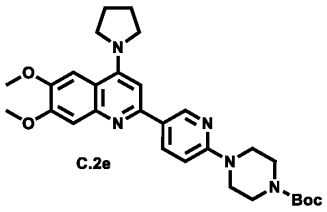
[0445] According to Scheme 3 Step 2: Conditions 4 Buchwald with **C.1n** (0.12 g, 0.17 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-TLC (petroleum ether: ethyl acetate = 0:1) to give **C.2c** (50 mg, 0.06 mmol, 35% yield, 65% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 553.3.

C.2d: *tert*-butyl *N*-[2-[5-[6-fluoro-4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl]-1-methyl-2-oxo-ethyl] carbamate



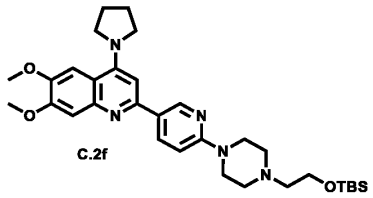
[0446] According to Scheme 3 Step 2: Conditions 4 Buchwald with **C.1o** (0.24 g, 0.52 mmol, 1.0 eq). After work-up the residue obtained was purified by Flash chromatography (20 g column, Eluent of 0~75% EtOAc/PE gradient at 60 mL/min) to give **C.2d** (0.16 g, 0.28 mmol, 53% yield, 91% purity) as an orange solid.

C.2e: *tert*-butyl 4- [5-(6, 7-dimethoxy-4-pyrrolidin-1-yl-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate



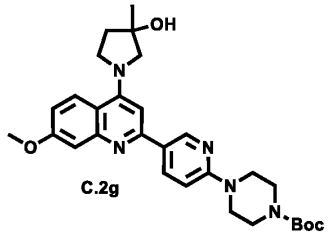
[0447] According to Scheme 3 Step 2: Conditions 2 S_NAr with **C.1c** (0.45 g, 0.93 mmol, 1.0 eq) and pyrrolidine (54 eq). After work-up **C.2e** (0.50 mg, crude) was obtained as brown oil.

C.2f: *tert*-butyl-[2-[4-[5-(6,7-dimethoxy-4-pyrrolidin-1-yl-2-quinolyl)-2-pyridyl] piperazin-1-yl] ethoxy]-dimethyl-silane



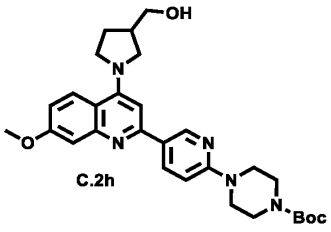
[0448] According to Scheme 3 Step 2: Conditions 3 S_NAr with **C.1u** (0.12 g, 0.22 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 20%-50% over 10 min) to give **C.2f** (80 mg, 0.12 mmol, 56% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 578.4.

C.2g: *tert*-butyl 4-[5-[4-(3-hydroxy-3-methyl-pyrrolidin-1-yl)-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



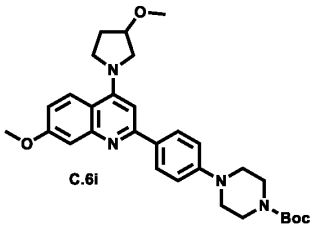
[0449] According to Scheme 3 Step 2: Conditions 3 S_NAr with **C.1e** (100 mg, 219.81 μmol, 1 eq). After work-up the crude product was used in the next step without purification. **C.2g** (0.10 g, 0.17 mmol, 77% yield, 88% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+$= 502.5.

C.2h: *tert*-butyl 4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



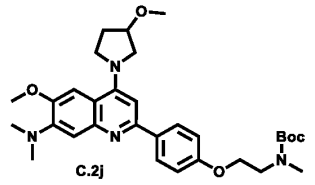
[0450] According to Scheme 3 Step 2: Conditions 3 S_NAr with **C.1e** (0.20 g, 0.31 mmol, 1.0 eq). After work-up the crude product was used in the next step without purification. **C.2h** (0.15 g, 0.25 mmol, 81% yield, 86% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+$= 520.3.

C.2i: *tert*-butyl 4-[4-[7-methoxy-4-(3-methoxypyrrolidin-1-yl) -2-quinolyl] phenyl] piperazine-1-carboxylate



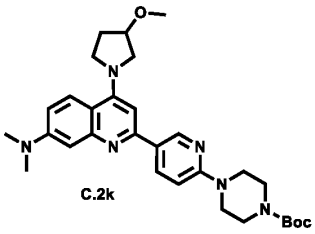
[0451] According to Scheme 3 Step 2: Conditions 3 S_NAr with **C.1f** (0.55 g, 1.2 mmol, 1.0 eq*)*. After work-up **C.2i** (0.55 g, crude) was obtained as a white solid. MS m/z (ESI) $[M+H]^+$= 519.3.

C.2j: *tert*-butyl *N*-[2-[4-[7-(dimethylamino)-6-methoxy-4-(3-methoxypyrrolidin-1-yl)-2-quinolyl] phenoxy] ethyl]-*N*-methylcarbamate



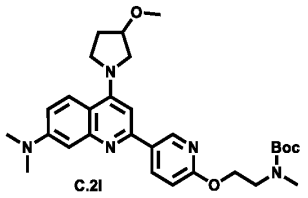
[0452] According to Scheme 3 Step 2: Conditions 2 S_NAr with **C.1h** (0.14 g, 0.29 mmol, 1.0 eq and 3-methoxypyrrolidine (10 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 30%-60% over 10 min) to give **C.2j** (0.10 g, 0.18 mmol, 63% yield, 100% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 511.4.

C.2k: *tert*-butyl 4-[5-[7-(dimethylamino)-4-(3-methoxypyrrolidin-1-yl)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



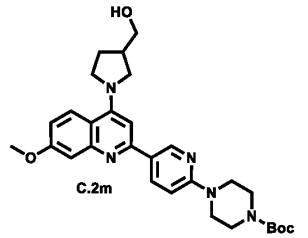
[0453] According to Scheme 3 Step 2: Conditions 2 S_NAr with **C.1i** (0.50 g, 1.1 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 27%-47% B over 10 min) to give **C.2k** (0.3 g, 0.54 mmol, 50% yield, 95% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$ =533.3.

C.2l: *tert*-butyl *N*-[2-[[5-[7-(dimethylamino)-4-(3-methoxypyrrolidin-1-yl)-2-quinolyl]-2-pyridyl] oxy] ethyl] -*N*-methylcarbamate



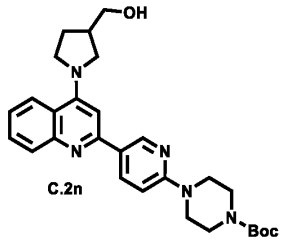
[0454] According to Scheme 3 Step 2: Conditions 2 S_NAr with *tert*-butyl N-[2-[[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl] oxy] ethyl]-N-methyl-carbamate **C.1j** (0.80 g, 1.1 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 23%-53% over 15 min) to give **C.2l** (0.20 g, 0.36 mmol, 35% yield, 95% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 522.3.

C.2m: *tert*-butyl 4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



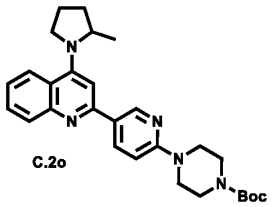
[0455] According to Scheme 3 Step 2: Conditions 3 S_NAr with **C.1e** (0.57 g, 1.3 mmol, 1.0 eq). After work-up **C.2m** (0.70 g, 1.2 mmol, 96% yield, 89% purity) was obtained as a yellow oil. MS m/z (ESI) $[M+H]^+$=520.3.

C.2n: *tert*-butyl 4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



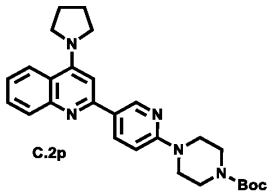
[0456] According to Scheme 3 Step 2: Conditions 3 S_NAr with **C.1a** (0.20 g, 0.47 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-TLC (SiO_2, DCM/MeOH = 10:1) to give **C.2n** (0.15 g, 291.05 μmol, 61.84% yield, 95% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 490.2.

C.2o: tert-butyl 4-(5-(4-(2-methylpyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazine-1-carboxylate



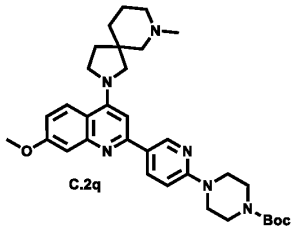
[0457] According to Scheme 3 Step 2: Conditions 2 S_NAr with **C.1a** (0.15 g, 0.35 mmol, 1.0 eq), 2-methylpyrrolidine (30 eq). The reaction mixture was evaporated under *vacuo* and purification was done by flash chromatography (DCM/MeOH: 0% to 10%) to give **C.2o** (0.16 g, 0.27 mmol, 75%).

C.2p: *tert*-butyl 4-(5-(4-(pyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazine-1-carboxylate



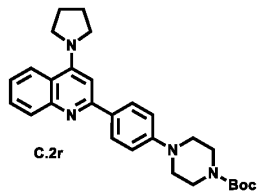
[0458] According to Scheme 3 Step 2: Conditions 2 S_NAr with **C.1a** (0.15 g, 0.35 mmol, 1.0 eq), pyrrolidine (30 eq). At 90 °C. The reaction mixture was evaporated in *vacuo* and purified by flash chromatography (DCM/MeOH 0% to 10%) to give **C.2p** (0.16 g, 0.35 mmol, 98%).

C.2q: *tert*-butyl 4-(5-(7-methoxy-4-(7-methyl-2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) pyridin-2-yl) piperazine-1-carboxylate



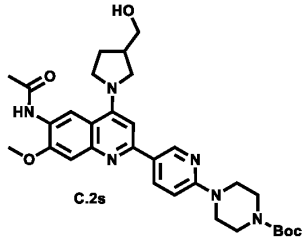
[0459] According to Scheme 4 Step 1: To a solution of **B.1b** (80 mg, 0.23 mmol, 1.0 eq) and tert-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]piperazine-1-carboxylate (0.11 g, 0.28 mmol, 1.0 eq) in **S2** (1.35 mL) was added $Pd(PPh_3)_4$ (0.10 eq), sodium carbonate (2.0 eq). After work-up the residue was purified by Flash chromatography (12 g column, Eluent of 0 to 30% EtOAc/PE gradient at 40 mL/min) then by prep-TLC (SiO_2, PE/EtOAc = 1:1) to give **C.2q** (0.10 g, 0.16 mmol, 68% yield, 90% purity) as a colourless gum.

C.2r: *tert*-butyl 4-[4-(4-pyrrolidin-1-yl-2-quinolyl) phenyl] piperazine-1-carboxylate



[0460] According to Scheme 3 Step 2: Conditions 2 Buchwald: **C.1b** (0.30 g, 0.57 mmol, 1.0 eq, 80% purity) and pyrrolidine (48 mg, 0.68 mmol, 57 mL, 1.2 eq) were stirred in dioxane (5.0 mL) at 100 °C for 16 hours. The mixture was concentrated to give a residue. The crude product was used in the next step without purification. **C.2r** (0.30 g, 0.46 mmol, 81% yield, 70% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+$=459.4.

C.2s: tert-butyl 4-(5-(6-acetamido-4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazine-1-carboxylate

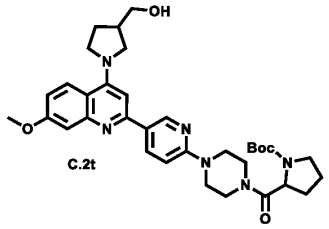


[0461] According to Scheme 3 Step 2: To a solution of **C.1w** (0.32 g, 0.54 mmol, 1.0 eq) in DMSO (3.0 mL) were added pyrrolidin-3-ylmethanol (0.11 g, 1.1 mmol, 2.0 eq) and *N*, *N*-diisopropylethylamine (0.28 g, 2.2 mmol, 4.0 eq) at 20 °C. The mixture was stirred at 100 °C for 16 hours and then concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (4 g column, EtOAc/PE gradient at 40 mL/min) to give tert-butyl 4-[5-[6-bromo-4-[3- (hydroxymethyl)pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate (0.30 g, 0.49 mmol, 91% yield, 98% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$=600.2.

[0462] To a mixture of tert-butyl 4-[5-[6-bromo-4-[3-(hydroxymethyl)pyrrolidin-1-yl]-7-methoxy -2-quinolyl]-2-pyridyl]piperazine-1-carboxylate (0.28 g, 0.47 mmol, 1.0 eq) and acetamide (55 mg, 0.94 mmol, 2.0 eq) in dioxane (3.0 mL) were added Xantphos-Pd G4 (45 mg, 0.05 mmol, 0.10 eq) and $CsCO_3$ (0.31 g, 0.94 mmol, 2.0 eq) at 20 °C. The mixture was stirred at 100 °C for 6 hours under N_2 atmosphere. The reaction mixture was diluted with ethyl acetate (10 mL), then the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (12 g column,

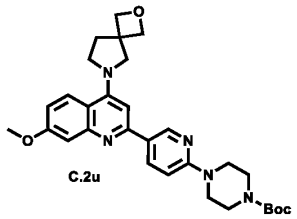
Eluent of 0% to 5% MeOH/EtOAc gradient at 30 mL/min) to give **C.2s** (0.20 g, 0.29 mmol, 62% yield, 83% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 577.3.

C.2t: *tert*-butyl 2-(4-(5-(4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazine-1-carbonyl) pyrrolidine-1-carboxylate



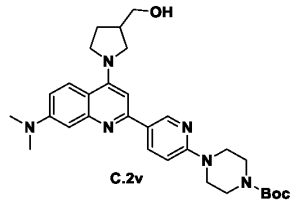
[0463] To a solution of **Example 10** (0.15 g, 0.36 mmol, 1.0 eq) in DMF (2.0 mL) was added HATU (0.21 g, 0.54 mmol, 1.5 eq), 1-tert-butoxycarbonylpyrrolidine-2-carboxylic acid (90 mg, 0.42 mmol, 1.2 eq) and DIEA (0.14 g, 1.1 mmol, 0.19 mL, 3.0 eq) at 25 °C. The mixture was stirred at 25 °C for 4 hours. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL, three times). The combined organic layers were washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue obtained was purified by prep-TLC (SiO_2, PE/EtOAc = 0:1) to give **C.2t** (0.12 g, 0.14 mmol, 38% yield, 70% purity) as yellow gum. MS m/z (ESI) $[M+H]^+$= 617.3.

C.2u: tert-butyl 4-(5-(7-methoxy-4-(2-oxa-6-azaspiro[3.4]octan-6-yl)quinolin-2-yl)pyridin-2-yl)piperazine-1-carboxylate



[0464] According to Scheme 3 Step 2: To a solution of tert-butyl 4-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate (0.25 g, 0.54 mmol, 1.0 eq) in DMSO (3.0 mL) were added 2-oxa-6-azaspiro[3.4]octane (0.12 g, 1.1 mmol, 2.0 eq) and *N*, *N*-diisopropylethylamine (0.28 g, 2.2 mmol, 4.0 eq) at 25 °C. The mixture was stirred at 100 °C for 16 hours then the reaction mixture was concentrated under reduced pressure. The residue obtained was purified by Flash chromatography (4 g column, EtOAc/PE gradient at 40 mL/min) to give **C.2u** (0.27 g, 0.50 mmol, 91% yield, 98% purity).

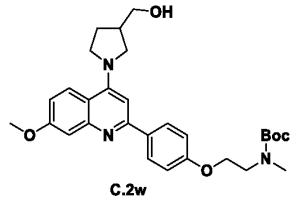
C.2v: tert-butyl 4-[5-[7-(dimethylamino)-4-[3-(hydroxymethyl)pyrrolidin-1-yl]-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate



C.2v

[0465] According to Scheme 3 Step 2: To a solution of tert-butyl 4-[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate (0.12 g, 256.42 µmol, 1 eq), pyrrolidin-3-ylmethanol (51.87 mg, 512.83 µmol, 2 eq) in DMSO (0.5 mL) was added CsF (116.85 mg, 769.25 µmol, 3 eq) at 25°C. After stirring at 130°C for 16 hours, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN];gradient:20%-50% B over 10 min) to give **C.2v** (65 mg, 109.82 µmol, 42.83% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 533.2.

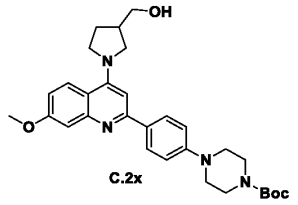
C.2w: *tert*-butyl N-[2-[4-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2w

[0466] According to Scheme 3 Step 2: To a solution of tert-butyl N-[2-[4-(4-chloro-7-methoxy-2-quinolyl) phenoxy]ethyl]-N-methyl-carbamate (300 mg, 677.30 µmol, 1 *eq*) and DIEA (262.61 mg, 2.03 mmol, 353.92 µL, 3 *eq*) in DMSO (0.5 mL) was added pyrrolidin-3-ylmethanol (342.53 mg, 3.39 mmol, 5.0 *eq*) at 20 °C. The reaction mixture was stirred at 100 °C for 16 hours. The reaction mixture was quenched by addition of water (10 mL) at 20 °C, and then extracted with EtOAc (10 mL, 3 times). After work-up the crude **C.2w** (270 mg, 531.89 µmol, 78.53% yield) as yellow oil was used into the next step without further purification.

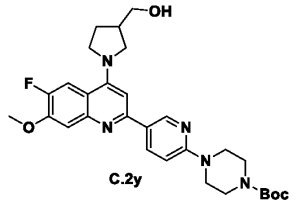
C.2x: tert-butyl 4-[4-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]phenyl]piperazine-1-carboxylate



C.2x

[0467] According to Scheme 3 Step 2: To a solution of tert-butyl 4-[4-(4-chloro-7-methoxy-2-quinolyl) phenyl]piperazine-1-carboxylate (400 mg, 722.53 μmol, 1 eq) in DMSO (3 mL) was added pyrrolidin-3-ylmethanol (200 mg, 1.98 mmol, 2.74 eq) and CsF (300 mg, 1.97 mmol, 2.73 eq) in turns, then the resulting mixture was stirred at 90 °C for 16 hours. The reaction mixture was diluted with EtOAc (100 mL), washed with water (50 mL, 2 times), brine (50 mL). After work-up the crude material was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 25 mL/min) to give **C.2x** (280 mg, 518.27 μmol, 71.73% yield, 96% purity) as yellow gum. MS m/z (ESI) $[M+H]^+$= 519.3.

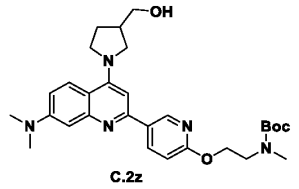
C.2y: tert-butyl 4-[5-[7-(dimethylamino)-4-[3-(hydroxymethyl)pyrrolidin-1-yl]-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate



C.2y

[0468] According to Scheme 3 Step 2: To a solution of tert-butyl 4-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) -2-pyridyl]piperazine-1-carboxylate (250 mg, 528.61 μmol, 1 eq) and pyrrolidin-3-ylmethanol (100 mg, 988.66 μmol, 1.87 eq) in dioxane (5 mL) was added SPhos Pd G3 (50 mg, 64.08 μmol, 1.21e-1 eq) and Cs_2CO_3 (400 mg, 1.23 mmol, 2.32 eq), then the resulting mixture was stirred at 80°C for 12 hours under N_2. The reaction mixture was diluted with EtOAc (100 mL), washed with water (50 mL, 2 times), brine (50 mL). After work-up the crude material was purified by flash silica gel chromatography (ISCO®; 12 SepaFlash® Silica Flash Column, Eluent of 0~100 Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.2y** (250 mg, 443.39 μmol, 83.88% yield, 95.35% purity) as colorless gum. MS m/z (ESI) $[M+H]^+$= 538.3.

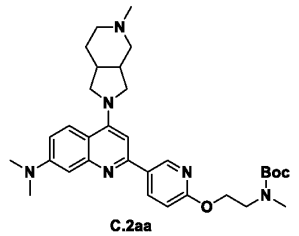
C.2z: tert-butyl N-[2-[[5-[7-(dimethylamino)-4-[3-(hydroxymethyl)pyrrolidin-1-yl]-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate



C.2z

[0469] According to Scheme 3 Step 2: Conditions 1 SNAr: To a solution of tert-butyl N-[2-[[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (0.2 g, 437.67 μmol, 1 eq), pyrrolidin-3-ylmethanol (88.54 mg, 875.34 μmol, 2 eq) in DMSO (0.5 mL) was added CsF (99.73 mg, 656.51 μmol, 1.5 eq). After work-up the residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN]; gradient:18%-48% B over 10 min) to give **C.2z** (130 mg, 249.21 μmol, 56.94% yield, 100% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 522.2.

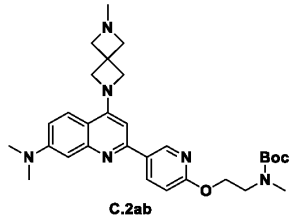
C.2aa: tert-butyl (2-((5-(7-(dimethylamino)-4-((cis)-5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)ethyl)(methyl)carbamate



C.2aa

[0470] According to Scheme 3 Step 2: Condition 4 Buchwald: A mixture of tert-butyl N-[2-[[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (300 mg, 656.51 μmol, 1 eq), cis 5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine (110.47 mg, 787.81 μmol, 1.2 eq), Cs_2CO_3 (641.71 mg, 1.97 mmol, 3 eq) , SPhos Pd G3 (51.22 mg, 65.65 μmol, 0.1 eq) in dioxane (3 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.2aa** (200 mg, 356.68 μmol, 54.33% yield, 100% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 521.2.

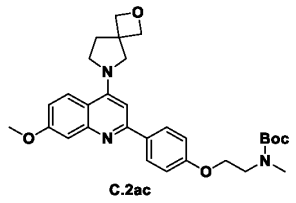
C.2ab: tert-butyl N-[2-[[5-[7-(dimethylamino)-4-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate



C.2ab

[0471] According to Scheme 3 Step 2: Conditions 1 SNAr: To a solution of tert-butyl N-[2-[[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (300 mg, 656.51 μmol, 1 eq) , 2-methyl-2,6-diazaspiro[3.3]heptane (182.27 mg, 984.76 μmol, 1.5 eq, 2HCl) in DMSO (2 mL) was added CsF (498.63 mg, 3.28 mmol, 5 eq). After work-up the residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um;mobile phase: [water(FA)-ACN]; gradient:8%-38% B over 10 min) to give **C.2ab** (200 mg, 356.69 μmol, 54.33% yield, 95% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 533.3.

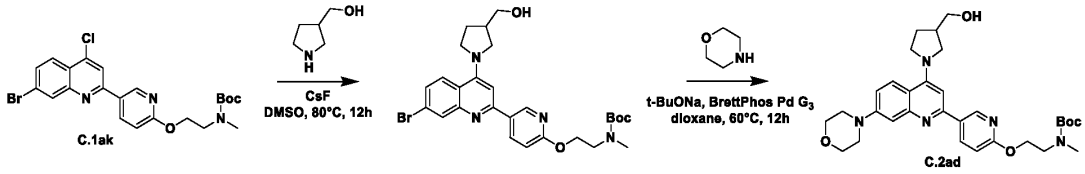
C.2ac: tert-butyl N-[2-[4-[7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl) -2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2ac

[0472] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-7-methoxy-2-quinolyl) phenoxy]ethyl]-N-methyl-carbamate (270 mg, 609.57 μmol, 1 eq), 2-oxa-7-azaspiro[3.4]octane oxalate (106.06 mg, 670.53 μmol, 1.1 eq) and Cs_2CO_3 (397.22 mg, 1.22 mmol, 2.0 eq) in dioxane (2 mL) was added SPhos Pd G3 (47.56 mg, 60.96 μmol, 0.1 eq After work-up the residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1). **C.2ac** (240 mg, 461.87 μmol, 75.77% yield) was obtained as yellow oil. MS m/z (ESI) $[M+H]^+$= 520.4.

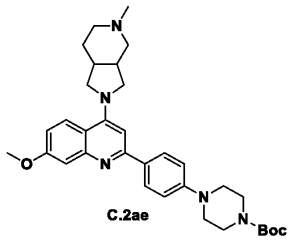
C.2ad: tert-butyl N-[2-[[5-[4-[3-(hydroxymethyl)pyrrolidin-1-yl]-7-morpholino-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate



[0473] Step 1: Conditions 1 SNAr: To a solution of tert-butyl N-[2-[[5-(7-bromo-4-chloro-2-quinolyl)-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (650 mg, 1.32 mmol, 1 eq) in DMSO (5 mL) was added CsF (600 mg, 3.95 mmol, 2.99 eq) and pyrrolidin-3-ylmethanol (145 mg, 1.43 mmol, 1.09 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethylacetate/Petroleum ether gradient @ 60 mL/min) to give tert-butyl N-[2-[[5-[7-bromo-4-[3-(hydroxymethyl)pyrrolidin-1-yl]-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (300 mg, 462.80 μmol, 35.09% yield, 86% purity). MS m/z (ESI) $[M+H]^+$= 557.2.

[0474] Step 2: A mixture of tert-butyl N-[2-[[5-[7-bromo-4-[3-(hydroxymethyl)pyrrolidin-1-yl]-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (280 mg, 502.26 μmol, 1 eq), morpholine (55 mg, 631.31 μmol, 55.56 μL, 1.26 eq), t-BuONa (140.00 mg, 1.46 mmol, 2.90 eq), BrettPhos Pd G3 (45 mg, 49.64 μmol, 9.88e-2 eq) in dioxane (5 mL). The reaction mixture was stirred at 80 °C for 16 hours under N_2 atmosphere. After work-up the residue was purified by prep-TLC (SiO2, Dichloromethane : Methanol = 10:1) to give **C.2ad** (50 mg, 70.07 μmol, 13.95% yield, 79% purity). MS m/z (ESI) $[M+H]^+$= 564.2.

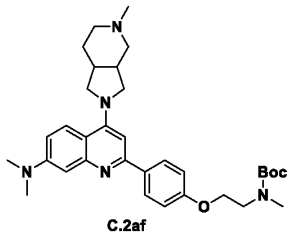
C.2ae: tert-butyl 4-(4-(7-methoxy-4-(cis-5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)piperazine-1-carboxylate



[0475] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl 4-[4-(4-chloro-7-methoxy-2-quinolyl)phenyl]piperazine-1-carboxylate (740 mg, 1.63 mmol, 1 eq), cis-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine (274.30 mg, 1.96 mmol, 1.2 eq) and Cs_2CO_3 (1.06 g, 3.26 mmol, 2 eq) in dioxane (8 mL) was added SPhos Pd G3 (127.19 mg, 163.01 μmol, 0.1 eq). After work-up the residue was purified by column

chromatography (SiO_2, Petroleum ether/Ethyl acetate=5/1 to 0/1). **C.2ae** (700 mg, 1.26 mmol, 77.00% yield) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+$= 558.3.

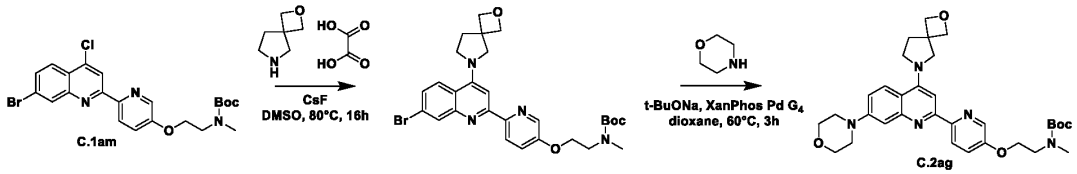
C.2af: tert-butyl (2-(4-(7-(dimethylamino)-4-(cis-5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2af

[0476] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-[4-chloro-7-(dimethylamino)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (350 mg, 767.58 µmol, 1 eq) and Cs_2CO_3 (600 mg, 1.84 mmol, 2.40 eq) in dioxane (5 mL) was added SPhos Pd G3 (120 mg, 153.80 µmol, 0.2 eq) and cis-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine (130 mg, 927.08 µmol, 1.21 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% DCM/MeOH gradient @ 40 mL/min) to afford **C.2af** (300 mg, 535.96 µmol, 69.82% yield, 100% purity) as a yellow oil. MS m/z (ESI) $[M+H]^+$= 560.5.

C.2ag: tert-butyl methyl(2-((6-(7-morpholino-4-(2-oxa-6-azaspiro[3.4]octan-6-yl)quinolin-2-yl)pyridin-3-yl)oxy)ethyl)carbamate

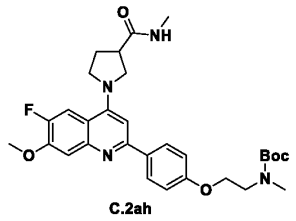


C.2ag

[0477] Step 1: Conditions 1 SNAr: To a mixture of tert-butylN-[2-[[6-(7-bromo-4-chloro-2-quinolyl)-3-pyridyl]oxy]ethyl]-N- methyl-carbamate (240 mg, 0.404 mmol, 1 eq), 2-oxa-7-azaspiro[3.4]octane oxalate (70.3 mg, 0.445 mmol, 1.1 eq) in dimethyl sulfoxide (1 mL) was added CsF (184 mg, 1.21 mmol, 3 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% dichloromethane / methanol gradient @ 25 mL/min) to give tert-butyl N-[2-[[6-[7-bromo-4-(2- oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-3-pyridyl]oxy]ethyl]-N-methyl-carbamate (120 mg, 202.29 µmol, 50.04% yield, 96% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 571.2.

[0478] Step 2: To a mixture of tert-butyl N-[2-[[6-[7-bromo-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl] -3-pyridyl]oxy]ethyl]-N-methyl-carbamate (120 mg, 0.202 mmol, 1 eq), morpholine (35.3 mg, 0.405 mmol, 2 eq) in dioxane (2 mL) were added sodium tert-butoxide (38.9 mg, 0.405 mmol, 2 eq), Xantphos Pd G4 (19.5 mg, 0.020 mmol, 0.1 eq) at 20 °C. The mixture was stirred at 60 °C for 3 hours under nitrogen atmosphere. After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~80% Ethyl acetate/Petroleum ether gradient @ 20mL/min) to give **C.2ag** (90.0 mg, 0.100 mmol, 49.5% yield, 64% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 576.3.

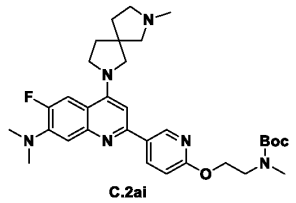
C.2ah: tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-[3-(methylcarbamoyl)pyrrolidin-1-yl]-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2ah

[0479] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (200 mg, 433.91 µmol, 1 eq), N-methylpyrrolidine-3-carboxamide (110 mg, 668.15 µmol, 1.54 eq, HCl), Cs_2CO_3 (425 mg, 1.30 mmol, 3.01 eq), SPhos Pd G3 (35 mg, 44.86 µmol, 1.03e-1 eq) in dioxane (4 mL). After work-up **C.2ah** (250 mg, 343.81 µmol, 79.23% yield, 76% purity) was obtained. MS m/z (ESI) $[M+H]^+$= 553.3.

C.2ai: tert-butyl N-[2-[[5-[7-(dimethylamino)-6-fluoro-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate

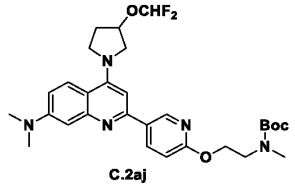


C.2ai

[0480] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[[5-[4-chloro-7-(dimethylamino)-6-fluoro-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (200 mg, 421.09 µmol, 1 eq), 2-methyl-2,7-diazaspiro[4.4]nonane (89 mg, 634.69 µmol, 1.51 eq), SPhos Pd G3 (33 mg, 42.29 µmol, 0.1 eq) and Cs_2CO_3 (412 mg, 1.26 mmol,

3 eq) in dioxane (5 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient, then 0~30% MeOH/Ethyl acetate @ 18 mL/min) to give **C.2ai** (240 mg, 348.36 μmol, 82.73% yield, 84% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 579.4.

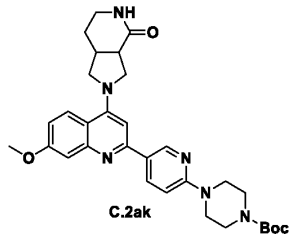
C.2aj: tert-butyl N-[2-[[5-[4-[3-(difluoromethoxy)pyrrolidin-1-yl]-7-(dimethylamino)-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate



C.2aj

[0481] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (250 mg, 547.09 μmol, 1 eq) in dioxane (3 mL) was added 3-(difluoromethoxy)pyrrolidine (110 mg, 802.17 μmol, 1.47 eq), Cs_2CO_3 (600 mg, 1.84 mmol, 3.37 eq), SPhos Pd G3 (80 mg, 102.53 μmol, 1.87e-1 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.2aj** (280 mg, 482.04 μmol, 88.11% yield, 96% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 558.4.

C.2ak: tert-butyl 4-(5-(7-methoxy-4-(cis-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)piperazine-1-carboxylate

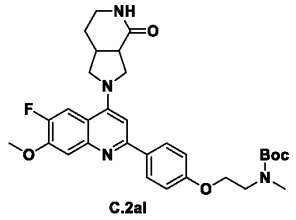


C.2ak

[0482] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl 4-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl]piperazine-1-carboxylate (200 mg, 439.61 μmol, 1 eq), cis-octahydro-4H-pyrrolo[3,4-c]pyridin-4-one (140.52 mg, 659.42 μmol, 1.5 eq, 2.0 HCl) and Cs_2CO_3 (600 mg, 1.84 mmol, 4.19 eq) in dioxane (3 mL)was added SPhos Pd G3 (70 mg, 89.71 μmol, 2.04e-1 eq). After work-up the residue was purified by silica gel

chromatography column (EA:MeOH:NH_3H_2O=12:1:0.5) to get **C.2ak** (200 mg, 247.02 μmol, 56.19% yield, 69% purity) as a yellow oil. MS m/z (ESI) $[M+H]^+$= 559.3.

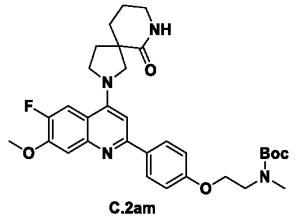
C.2al: tert-butyl (2-(4-(6-fluoro-7-methoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2al

[0483] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (200 mg, 433.91 μmol, 1 eq) in dioxane (3 mL) was added cis-octahydro-4H-pyrrolo[3,4-c]pyridin-4-one (140 mg, 656.96 μmol, 1.52 eq, HCl), SPhos Pd G3 (338.56 mg, 433.91 μmol, 1 eq), Cs_2CO_3 (526 mg, 1.61 mmol, 3.00 eq). After work-up the crude product was purified by prep-TLC (SiO_2, PE: EA = 1:1, Rf=0.1) to give **C.2al** (190 mg, 97.58 μmol, 22.49% yield, 29% purity) as a white solid. MS m/z (ESI) $[M+H]^+$= 565.2.

C.2am: tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(6-oxo-2,7-diazaspiro[4.5]decan-2-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



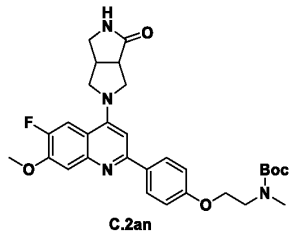
C.2am

[0484] Step 1: To a solution of tert-butyl 6-oxo-2,7-diazaspiro[4.5]decane-2-carboxylate (300 mg, 1.18 mmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 2 mL) at 25°C .The mixture was stirred at 25 °C for 2 hours. The reaction mixture was filtered and concentrated under reduced pressure to give 2,7-diazaspiro[4.5]decan-6-one (220 mg, crude, HCl). ^1H NMR (400 MHz, CD_3OD) δ (ppm): 3.64 (d, J = 11.7 Hz, 1H), 3.55 - 3.40 (m, 2H), 3.37 - 3.32 (m, 2H), 3.02 (d, J = 11.7 Hz, 1H), 2.43 (ddd, J = 5.1, 8.0, 13.3 Hz, 1H), 2.05 - 1.85 (m, 5H).

[0485] Step 2: According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (250 mg, 542.39 μmol, 1 eq), 2,7-diazaspiro[4.5]decan-6-one (100 mg, 648.47 μmol, 1.2 eq),

Cs_2CO_3 (530 mg, 1.63 mmol, 3 eq), SPhos Pd G3 (45 mg, 57.67 μmol, 1.06e-1 eq) in dioxane (5 mL). After work-up the residue was purified by prep-TLC (SiO_2, Petroleum ether : Ethyl acetate = 0:1) to give **C.2am** (125 mg, 166.11 μmol, 30.63% yield, 76.9% purity). MS m/z (ESI) $[M+H]^+$= 579.3.

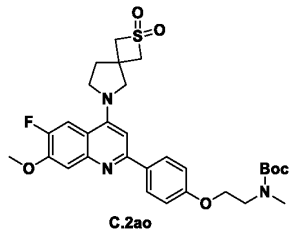
C.2an: tert-butyl (2-(4-(6-fluoro-7-methoxy-4-(4-oxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2an

[0486] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (250 mg, 541.23 μmol, 1 eq) in dioxane (5 mL) was added hexahydropyrrolo[3,4-c]pyrrol-1(2H)-one (150 mg, 662.92 μmol, 1.22 eq) , SPhos Pd G3 (70 mg, 89.71 μmol, 1.66e-1 eq) , Cs_2CO_3 (600 mg, 1.84 mmol, 3.40 eq). After work-up the crude product was purified by prep-TLC (SiO_2, PE: EA = 1:1, Rf=0.1) to give **C.2an** (350 mg, 158.91 μmol, 29.36% yield, 25% purity) as a white solid. MS m/z (ESI) $[M+H]^+$= 551.3.

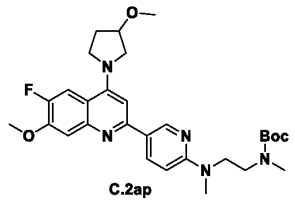
C.2ao: tert-butyl N-[2-[4-[4-(2,2-dioxo-2thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2ao

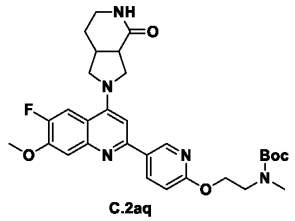
[0487] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (200 mg, 433.91 μmol, 1 eq) , 2thia-7-azaspiro[3.4]octane 2,2-dioxide (100 mg, 505.86 μmol, 1.17 eq, HCl) , Cs_2CO_3 (425 mg, 1.30 mmol, 3.01 eq) , SPhos Pd G3 (35 mg, 44.86 μmol, 1.03e-1 eq) in dioxane (5 mL) . After work-up the residue was triturated with Ethyl acetate (10 ml) at 25°C for 30 min to give **C.2ao** (160 mg, 256.79 μmol, 59.18% yield, 94% purity). MS m/z (ESI) $[M+H]^+$= 586.2.

C.2ap: tert-butylN-[2-[[5-[6-fluoro-7-methoxy-4-(3-methoxypyrrolidin-1-yl)-2-quinolyl] -2-pyridyl] -methyl-amino]ethyl]-N-methyl-carbamate



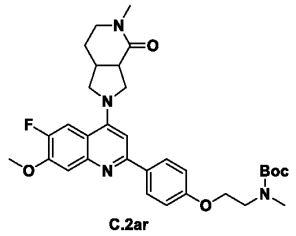
[0488] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a mixture of tert-butyl N-[2-[[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]- methyl-amino]ethyl]-N-methyl-carbamate (350 mg, 0.538 mmol, 1 eq), 3-methoxypyrrolidine (111 mg, 0.807 mmol, 1.5 eq, HCl) in dioxane (3.0 mL) were added Xanphos Pd G4 (42.0 mg, 0.0538 μmol, 0.1 eq), Cs_2CO_3 (526 mg, 1.61 mmol, 3 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give **C.2ap** (270 mg, 0.470 mmol, 87.4% yield, 94% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 540.4.

C.2aq: tert-butyl (2-((5-(6-fluoro-7-methoxy-4-(cis-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)ethyl)(methyl)carbamate



[0489] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (200 mg, 432.98 μmol, 1 eq) , cis-octahydro-4H-pyrrolo[3,4-c]pyridin-4-one (140 mg, 656.96 μmol, 1.52 eq, HCl), Cs_2CO_3 (425 mg, 1.30 mmol, 3.01 eq), SPhos Pd G3 (35 mg, 44.86 μmol, 1.04e-1 eq) in dioxane (3 mL). After work-up the residue was purified by prep-TLC (SiO2, Petroleum ether: Ethyl acetate = 0:1) to give **C.2aq** (70 mg, 95.79 μmol, 22.12% yield, 77.4% purity). MS m/z (ESI) $[M+H]^+$= 566.2.

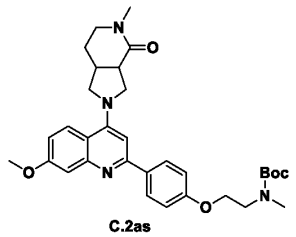
C.2ar: tert-butyl (2-(4-(6-fluoro-7-methoxy-4-(cis-5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2ar

[0490] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (250 mg, 542.39 μmol, 1 eq) in dioxane (3 mL) was added cis-5-methyloctahydro-4H-pyrrolo[3,4-c]pyridin-4-one (120 mg, 778.16 μmol, 1.43 eq), SPhos Pd G3 (70 mg, 89.71 μmol, 1.65e-1 eq), Cs_2CO_3 (600 mg, 1.84 mmol, 3.4 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash? Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.2ar** (270 mg, 443.26 μmol, 81.72% yield, 95% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 579.3.

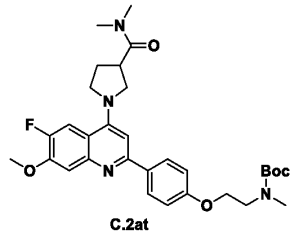
C.2as: tert-butyl (2-(4-(7-methoxy-4-cis-5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2as

[0491] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[4-(4-chloro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (200 mg, 451.53 μmol, 1 eq), cis-5-methyloctahydro-4H-pyrrolo[3,4-c]pyridin-4-one (104.45 mg, 677.30 μmol, 1.5 eq), SPhos Pd G3 (35.23 mg, 45.15 μmol, 0.1 eq), Cs_2CO_3 (441.36 mg, 1.35 mmol, 3 eq) in dioxane (2 mL). After work-up the residue was purified by prep-TLC (SiO2, PE:EtOAc = 0:1) to give **C.2as** (200 mg, 353.14 μmol, 78.21% yield, 99% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 561.3.

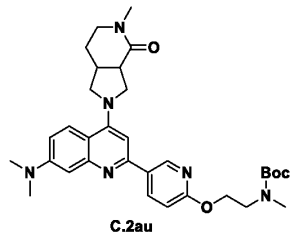
C.2at: tert-butyl N-[2-[4-[4-[3-(dimethylcarbamoyl)pyrrolidin-1-yl]-6-fluoro-7-methoxy-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2at

[0492] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (250 mg, 542.39 µmol, 1 eq), N,N-dimethylpyrrolidine-3-carboxamide (145 mg, 811.60 µmol, 1.5 eq, HCl), Cs_2CO_3 (530 mg, 1.63 mmol, 3 eq), SPhos Pd G3 (45 mg, 57.67 µmol, 1.06e-1 eq) in dioxane (3 mL). After work-up **C.2at** (280 mg, 380.47 µmol, 70.15% yield, 77% purity) was obtained. MS m/z (ESI) $[M+H]^+$= 567.4.

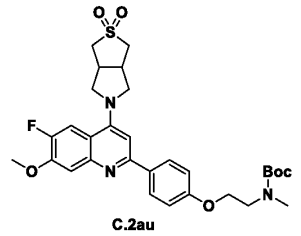
C.2au: tert-butyl (2-((5-(7-(dimethylamino)-4-(cis-5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)ethyl)(methyl)carbamate



C.2au

[0493] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (250 mg, 547.09 µmol, 1 eq) in dioxane (2 mL) was added cis-5-methyloctahydro-4H-pyrrolo[3,4-c]pyridin-4-one (120 mg, 778.16 µmol, 1.42 eq), SPhos Pd G3 (80 mg, 102.53 µmol, 1.87e-1 eq), Cs_2CO_3 (600 mg, 1.84 mmol, 3.37 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/PE gradient @ 40 mL/min) to give **C.2au** (270 mg, 401.68 µmol, 73.42% yield, 85.5% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 575.2.

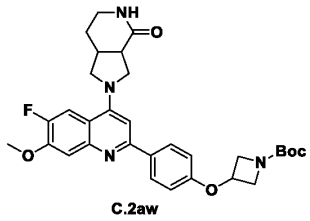
C.2av: tert-butyl N-[2-[4-[4-(2,2-dioxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2au

[0494] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (150 mg, 325.43 µmol, 1 eq), 3,3a,4,5,6,6a-hexahydro-1H-thieno[3,4-c]pyrrole 2,2-dioxide (78.70 mg, 488.15 µmol, 1.5 eq), Cs_2CO_3 (318.10 mg, 976.30 µmol, 3 eq), SPhos Pd G3 (25.39 mg, 32.54 µmol, 0.1 eq) in dioxane (2 mL). After work-up the residue was purified by prep-TLC (SiO_2, PE:Ethyl acetate = 0:1) to give **C.2av** (180 mg, 255.09 µmol, 78.38% yield, 83% purity) as a white solid. MS m/z (ESI) $[M+H]^+$= 586.4.

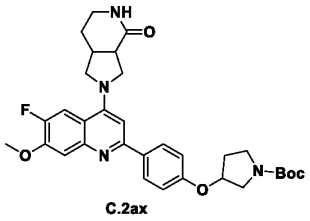
C.2aw: tert-butyl 3-(4-(6-fluoro-7-methoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)azetidine-1-carboxylate



C.2aw

[0495] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl 3-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenoxy]azetidine-1-carboxylate (230 mg, 501 µmol, 1 eq), cis -octahydropyrrolo[3, 4-c]pyridin-4-one (70.3 mg, 501 µmol, 1 eq) and Cs_2CO_3 (163.3 mg, 501.2 µmol, 1 eq) in dioxane (2.50 mL) was added SPhos Pd G3 (39.1 mg, 50.1 µmol, 0.1 eq). After work-up the residue was purified by prep-TLC (SiO_2, PE:EtOAc = 1:1) to give compound **C.2aw** (140 mg, 248.8 µmol, 49.7% yield) as yellow oil. MS m/z (ESI) $[M+H]^+$= 563.3.

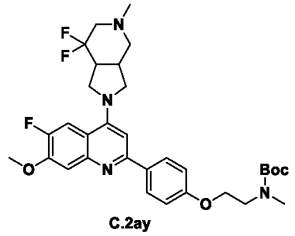
C.2ax: tert-butyl 3-(4-(6-fluoro-7-methoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)pyrrolidine-1-carboxylate



C.2ax

[0496] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl 3-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenoxy]pyrrolidine-1-carboxylate (260 mg, 550 µmol, 1 eq), cis-octahydropyrrolo[3, 4-c]pyridin-4-one (77.07 mg, 550 µmol, 1 eq) and Cs_2CO_3 (358 mg, 1.1 mmol, 2 eq) in dioxane (3 mL) was added SPhos Pd G3 (42.9 mg, 54.9 µmol, 0.1 eq). After work-up the residue was purified by prep-TLC (SiO_2, PE:EtOAc = 1:1) to give **C.2ax** (200 mg, 347 µmol, 63.1% yield) as yellow oil. MS m/z (ESI) $[M+H]^+$= 577.3.

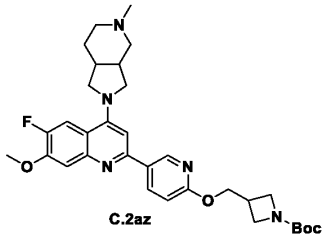
C.2ay: tert-butyl (2-(4-(4-(cis-7,7-difluoro-5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-6-fluoro-7-methoxyquinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2ay

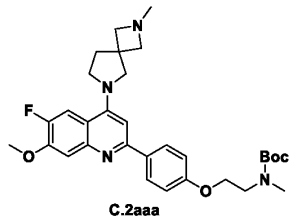
[0497] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (150 mg, 325.43 µmol, 1 eq), cis-7,7-difluoro-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine (114.69 mg, 650.87 µmol, 2 eq), SPhos Pd G3 (25.39 mg, 32.54 µmol, 0.1 eq), Cs_2CO_3 (318.10 mg, 976.30 µmol, 3 eq) in dioxane (2 mL). After work-up the residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give **C.2ay** (52 mg, 82.24 µmol, 25.27% yield, 95% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 601.3.

C.2az: tert-butyl 3-(((5-(6-fluoro-7-methoxy-4-(cis-5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)methyl)azetidine-1-carboxylate



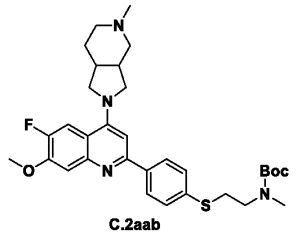
[0498] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl 3-[[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]oxymethyl]azetidine-1-carboxylate (0.3 g, 633.01 µmol, 1 eq) , cis-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine (100 mg, 713.14 µmol, 1.13 eq) in dioxane (6 mL) was added SPhos Pd G3 (49.39 mg, 63.30 µmol, 0.1 eq) and Cs_2CO_3 (618.74 mg, 1.90 mmol, 3 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Dichloromethane : Methanol gradient @ 60mL/min) to **C.2az** (150 mg, 233.69 µmol, 36.92% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 578.4.

C.2aaa: tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(2-methyl-2, 6-diazaspiro[3.4]octan-6-yl) -2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



[0499] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenoxy]ethyl]-N-methyl-carbamate (250 mg, 542.39 µmol, 1 eq) and 2-methyl-2, 7-diazaspiro[3.4]octane (100.00 mg, 792.40 µmol, 1.46 eq) in dioxane (5 mL) was added SPhos Pd G3 (60 mg, 76.90 µmol, 1.42e-1 eq) and Cs_2CO_3 (500.00 mg, 1.53 mmol, 2.83 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/ Ethyl acetate (1% $NH_3 \cdot H_2O$) gradient @ 50 mL/min) to give **C.2aaa** (250 mg, 454.00 µmol, 83.70% yield, 100% purity) as yellow gum. MS m/z (ESI) $[M+H]^+$= 551.4.

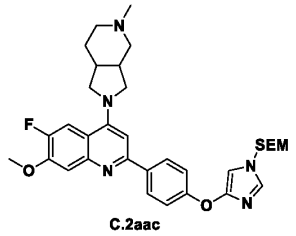
C.2aab: tert-butyl (2-((4-(6-fluoro-7-methoxy-4-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)thio)ethyl)(methyl)carbamate



C.2aab

[0500] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenyl]sulfanylethyl]-N-methyl-carbamate (250 mg, 524.12 µmol, 1 eq), cis-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine (110 mg, 784.45 µmol, 1.5 eq), SPhos Pd G3 (41 mg, 52.55 µmol, 0.1 eq) and Cs_2CO_3 (512 mg, 1.57 mmol, 3 eq) in dioxane (5 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) to give C.2aab (180 mg, 213.86 µmol, 40.80% yield, 69% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 581.3.

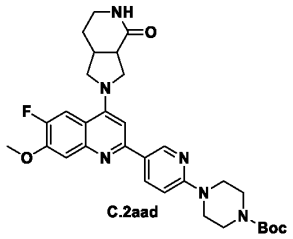
C.2aac: 6-fluoro-7-methoxy-4-(cis-5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-2-(4-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)oxy)phenyl)quinoline



C.2aac

[0501] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of 2-[[4-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]imidazol-1-yl]methoxy]ethyl-trimethyl-silane (350 mg, 699.95 µmol, 1 eq) in dioxane (3 mL) was added cis-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine (210.00 mg, 1.19 mmol, 1.70 eq, HCl), Cs_2CO_3 (700.00 mg, 2.15 mmol, 3.07 eq), SPhos Pd G3 (61.25 mg, 78.50 µmol, 1.12e-1 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.2aac** (290 mg, 416.89 µmol, 59.56% yield, 86.8% purity) as a yellow solid.

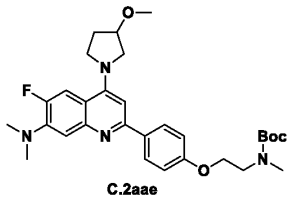
C.2aad: tert-butyl 4-(5-(6-fluoro-7-methoxy-4-(cis-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)piperazine-1-carboxylate



C.2aad

[0502] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl 4-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]piperazine-1-carboxylate (300 mg, 634.33 µmol, 1 eq), octahydro-4H-pyrrolo[3,4-c]pyridin-4-one (109 mg, 707.45 µmol, 1.12 eq) in dioxane (5 mL) were added SPhos Pd G3 (50 mg, 64.08 µmol, 1.01e-1 eq) and Cs_2CO_3 (420 mg, 1.29 mmol, 2.03 eq). After work-up the residue was purified by prep-TLC (Plate 1: Petroleum ether : Ethyl acetate=0:1) to give **C.2aad** (160 mg, 141.85 µmol, 22.36% yield, 60% purity) as a yellow solid.

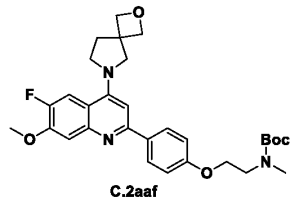
C.2aae: tert-butyl N-[2-[4-[7-(dimethylamino)-6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2aae

[0503] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-[4-chloro-7-(dimethylamino)-6-fluoro-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (200 mg, 421.97 µmol, 1 eq), 3-methoxypyrrolidine (87.10 mg, 632.96 µmol, 1.5 eq, HCl) in dioxane (4 mL) was added SPhos Pd G3 (32.92 mg, 42.20 µmol, 0.1 eq) and Cs_2CO_3 (412.46 mg, 1.27 mmol, 3 eq) at 25°C. After work-up **C.2aae** (0.2 g, 371.30 µmol, 87.99% yield) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+$= 539.2.

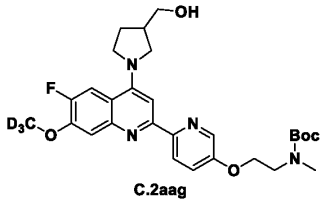
C.2aaf: tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2aaf

[0504] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate oxalate (200 mg, 433.91 µmol, 1 eq) , 2-oxa-7-azaspiro[3.4]octane (90.00 mg, 568.99 µmol, 1.31 eq), Cs_2CO_3 (425.00 mg, 1.30 mmol, 3.01 eq), SPhos Pd G3 (40.00 mg, 51.27 µmol, 1.18e-1 eq) in dioxane (3 mL). After work-up **C.2aaf** (200 mg, 279.01 µmol, 64.30% yield, 75% purity) was obtained. MS m/z (ESI) $[M+H]^+$= 538.4.

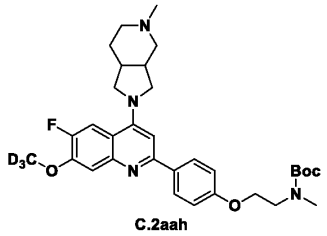
C.2aag: tert-butyl N-[2-[[6-[6-fluoro-4-[3-(hydroxymethyl)pyrrolidin-1-yl]-7-(trideuteriomethoxy)-2-quinolyl]-3-pyridyl]oxy]ethyl]-N-methyl-carbamate



C.2aag

[0505] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[[6-[4-chloro-6-fluoro-7-(trideuteriomethoxy)-2-quinolyl]-3-pyridyl]oxy]ethyl]-N-methyl-carbamate (180 mg, 387.15 µmol, 1 eq) in dioxane (3 mL) was added pyrrolidin-3-ylmethanol (90.00 mg, 889.80 µmol, 2.30 eq), SPhos Pd G3 (90.00 mg, 115.35 µmol, 2.98e-1 eq), Cs_2CO_3 (450.00 mg, 1.38 mmol, 3.57 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.2aag** (190 mg, 335.07 µmol, 86.55% yield, 93.4% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 530.2.

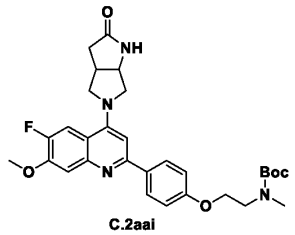
C.2aah: tert-butyl cis-tert-butyl (2-(4-(6-fluoro-7-(methoxy-d3)-4-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2aah

[0506] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-[4-chloro-6-fluoro-7-(trideuteromethoxy) -2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (200 mg, 431.09 µmol, 1 eq) in dioxane (5 mL) was added SPhos Pd G3 (40 mg, 51.27 µmol, 1.19e-1 eq) and cis-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine (400 mg, 2.26 mmol, 5.25 eq, HCl), Cs_2CO_3 (700 mg, 2.15 mmol, 4.98 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Dichloromethane /Methanol gradient @ 40 mL/min) to afford **C.2aah** (100 mg, 176.15 µmol, 40.86% yield, 100% purity) as yellow oil. MS (ESI) $[M+H]^+$= 568.4.

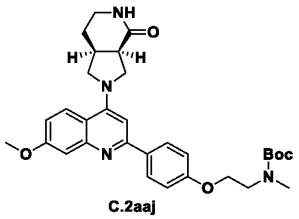
C.2aai: tert-butylN-[2-[4-[6-fluoro-7-methoxy-4-(2-oxo-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol -5-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



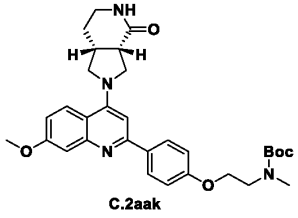
C.2aai

[0507] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a mixture of tert-butylN-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]- N-methyl-carbamate (200 mg, 433.91 µmol, 1 eq), 3,3a,4,5,6,6a-hexahydro-1H-pyrrolo[3,4-b] pyrrol-2-one (65 mg, 515.24 µmol, 1.19 eq) in dioxane (3 mL) were added SPhos Pd G3 (35 mg, 44.86 µmol, 1.03e-1 eq), Cs_2CO_3 (300 mg, 920.76 µmol, 2.12 eq). After work-up the residue was purified by prep-TLC (SiO_2: petroleum ether: ethyl acetate = 1:1) to give **C.2aai** (150 mg, 266.97 µmol, 61.53% yield, 98% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 551.3.

C.2aaj, C.2aak: tert-butyl (2-(4-(7-methoxy-4-((3aR,7aS)-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate& tert-butyl (2-(4-(7-methoxy-4-((3aS,7aR)-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



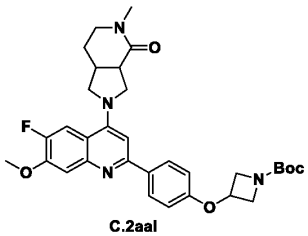
C.2aaj



C.2aak

[0508] According to Scheme 3 Step 2: Conditions 1 SNAr: To a solution of tert-butyl N-[2-[4-(4-chloro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (1 g, 2.26 mmol, 1 eq) in DMSO (20 mL) was added cis-octahydro-4H-pyrrolo[3,4-c]pyridin-4-one hydrochloride (1 g, 4.69 mmol, 2.08 eq, 2 HCl) and CsF (1.00 g, 6.58 mmol, 2.92 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc/Petroleum ether gradient @ 100 mL/min) to afford a residue. The residue was purified by prep-SFC (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um);mobile phase: [CO_2-ACN/i-PrOH (0.1% NH_3H_2O)]; B%:70%, isocratic elution mode). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to **C.2aaj** (200 mg, 365.86 µmol, 16.21% yield, 100% purity) as a colorless oil MS m/z (ESI) $[M+H]^+$= 547.3 and **C.2aak** (200 mg, 362.20 µmol, 16.04% yield, 99% purity) as a colorless oil MS m/z (ESI) $[M+H]^+$= 547.3.

C.2aal: tert-butyl 3-(4-(6-fluoro-7-methoxy-4-(5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)azetidine-1-carboxylate

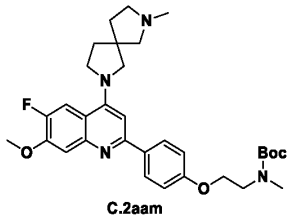


C.2aal

[0509] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl 3-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]azetidine-1-carboxylate (140 mg, 305.07 µmol, 1 eq), cis-5-methyloctahydro-4H-pyrrolo[3,4-c]pyridin-4-one (94.09 mg, 610.14 µmol, 2 eq), SPhos Pd G3 (23.80 mg, 30.51 µmol, 0.1 eq), Cs_2CO_3 (298.19 mg, 915.21 µmol, 3 eq)

in dioxane (2 mL). After work-up the residue was purified by prep-TLC (SiO_2, Ethyl acetate : Methanol = 10:1) to give **C.2aal** (120 mg, 181.04 µmol, 59.34% yield, 87% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 577.3.

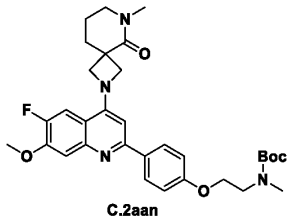
C.2aam: tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2aam

[0510] According to Scheme 3 Step 2: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (150 mg, 325.43 µmol, 1 eq), 2-methyl-2,7-diazaspiro[4.4]nonane (69 mg, 492.06 µmol, 1.51 eq), SPhos Pd G3 (25 mg, 32.04 µmol, 9.85e-2 eq) and Cs_2CO_3 (318 mg, 976.00 µmol, 3 eq) in dioxane (5 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) to give **C.2aam** (150 mg, 254.21 µmol, 78.11% yield, 95.7% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 565.3.

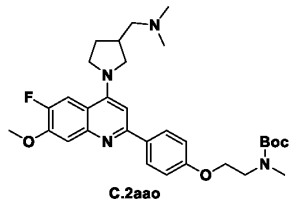
C.2aan: tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(6-methyl-5-oxo-2,6-diazaspiro[3.5]nonan-2-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2aan

[0511] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (300 mg, 650.87 µmol, 1 eq) in dioxane (3 mL) was added 6-methyl-2,6-diazaspiro[3.5]nonan-5-one (120 mg, 778.16 µmol, 1.20 eq) , SPhos Pd G3 (80 mg, 102.53 µmol, 1.58e-1 eq) , Cs_2CO_3 (650 mg, 1.99 mmol, 3.07 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.2aan** (350 mg, 575.80 µmol, 88.47% yield, 95.2% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 579.3.

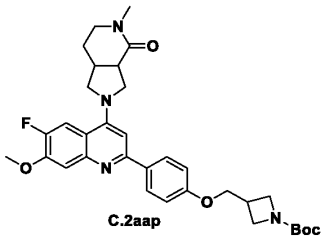
C.2aao: tert-butyl N-[2-[4-[4-[3-[(dimethylamino) methyl]pyrrolidin-1-yl]-6-fluoro-7-methoxy-2-quinolyl]phenoxy] ethyl]-N-methyl-carbamate



C.2aao

[0512] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenoxy]ethyl]-N-methyl-carbamate (170.00 mg, 368.82 µmol, 1 eq) and N, N-dimethyl-1-pyrrolidin-3-yl-methanamine (100 mg, 779.94 µmol, 2.11 eq) in dioxane (5 mL) was added SPhos Pd G3 (50 mg, 64.08 µmol, 1.74e-1 eq) and Cs_2CO_3 (400 mg, 1.23 mmol, 3.33 eq). After work-up the crude material was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/ Ethyl acetate (1% NH_3•H_2O) gradient @ 50 mL/min) to give **C.2aao** (160 mg, 277.92 µmol, 75.35% yield, 96% purity) as yellow solid. MS m/z (ESI) $[M+H]^+$= 553.4.

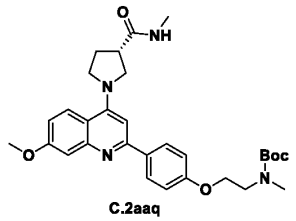
C.2aap: tert-butyl 3-((4-(6-fluoro-7-methoxy-4-(5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)methyl)azetidine-1-carboxylate



C.2aap

[0513] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl 3-[[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]methyl]azetidine-1-carboxylate (200 mg, 422.89 µmol, 1 eq), cis-5-methyloctahydro-4H-pyrrolo[3,4-c]pyridin-4-one (80 mg, 518.78 µmol, 1.23 eq) and Cs_2CO_3 (400 mg, 1.23 mmol, 2.90 eq) in dioxane (3 mL) was added SPhos Pd G3 (30 mg, 38.45 µmol, 9.09e-2 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% DCM/MeOH gradient @ 40 mL/min) to **C.2aap** (140 mg, 231.80 µmol, 54.81% yield, 97.8% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 591.3.

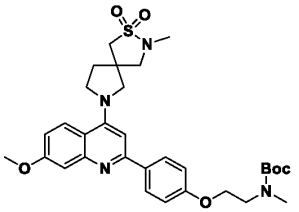
C.2aaq: tert-butyl N-[2-[4-[7-methoxy-4-[(3S) -3-(methylcarbamoyl) pyrrolidin-1-yl]-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



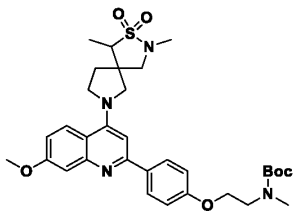
C.2aaq

[0514] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-7-methoxy-2-quinolyl) phenoxy]ethyl]-N-methyl-carbamate (150 mg, 338.65 µmol, 1 eq) (EW30832-1647-P1) and (3S) -N-methylpyrrolidine-3-carboxamide (100 mg, 607.41 µmol, 1.79 eq, HCl) in dioxane (5 mL) was added SPhos Pd G3 (40 mg, 51.26 µmol, 1.51e-1 eq) and Cs_2CO_3 (400 mg, 1.23 mmol, 3.63 eq). After work-up the crude material was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/ Ethyl acetate gradient @ 50 mL/min) to give **C.2aaq** (120 mg, 220.09 µmol, 64.99% yield, 98.06% purity) as yellow solid. MS m/z (ESI) $[M+H]^+$= 535.4.

C.2aar & C.2aas: tert-butyl N-[2-[4-[7-methoxy-4-(3-methyl-2,2-dioxo-2thia-3,7-diazaspiro[4.4]nonan-7-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate & tert-butyl N-[2-[4-[4-(1,3-dimethyl-2,2-dioxo-2thia-3,7-diazaspiro[4.4]nonan-7-yl)-7-methoxy-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



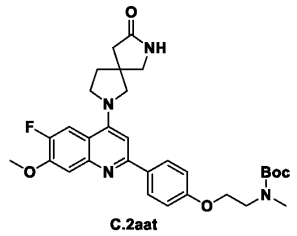
C.2aar



C.2aas

[0515] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-7-methoxy-2-quinolyl) phenoxy]ethyl]-N-methyl-carbamate (200 mg, 451.53 µmol, 1 eq), 1, 3-dimethyl-2thia-3,7-diazaspiro[4.4]nonane 2, 2-dioxide/3-methyl-2thia-3,7-diazaspiro[4.4]nonane 2, 2-dioxide (124.71 mg, 316.07 µmol, 0.7 eq) and Cs_2CO_3 (588.47 mg, 1.81 mmol, 4 eq) in dioxane (4.00 mL) was added SPhos Pd G3 (35.23 mg, 45.15 µmol, 0.1 eq). After work-up the residue was purified by prep-TLC (SiO_2, PE: EtOAc = 1:1). **C.2aar** & **C.2aas** (150 mg, 124.22 µmol, 27.51% yield) were obtained as yellow oil. MS m/z (ESI) $[M+H]^+$= 597.3 & MS m/z (ESI) $[M+H]^+$= 611.3.

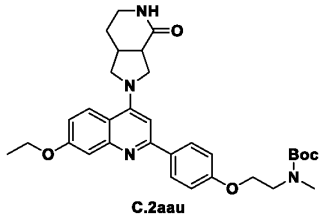
C.2aat: tert-butylN-[2-[4-[6-fluoro-7-methoxy-4-(8-oxo-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2aat

[0516] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (200 mg, 433.91 µmol, 1 eq) in dioxane (2 mL) was added 2,7-diazaspiro[4.4]nonan-3-one (80 mg, 570.68 µmol, 1.32 eq), SPhos Pd G3 (70 mg, 89.71 µmol, 2.07e-1 eq), Cs_2CO_3 (500 mg, 1.53 mmol, 3.54 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.2aat** (130 mg, 206.98 µmol, 47.70% yield, 89.9% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 565.4.

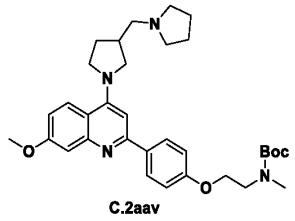
C.2aau: tert-butyl (2-(4-(7-ethoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2aau

[0517] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-7-ethoxy-2-quinolyl) phenoxy]ethyl]-N-methyl-carbamate (180 mg, 393.91 µmol, 1 eq) in dioxane (2 mL) was added cis-ydro-4H-pyrrolo[3,4-c]pyridin-4-one (65 mg, 463.68 µmol, 1.18 eq), SPhos Pd G3 (30 mg, 38.45 µmol, 9.76e-2 eq) and Cs_2CO_3 (390 mg, 1.20 mmol, 3.04 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate / Methanol gradient @ 40 mL/min) to afford **C.2aau** (100 mg, 178.35 µmol, 45.28% yield, 100% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 561.3.

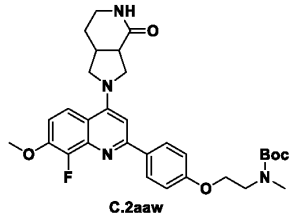
C.2aav: tert-butyl N-[2-[4-[7-methoxy-4-[3-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2aav

[0518] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (250 mg, 564.42 µmol, 1 eq) in dioxane (3 mL) was added 1-(pyrrolidin-3-ylmethyl)pyrrolidine (100 mg, 648.29 µmol, 1.15 eq), SPhos Pd G3 (50 mg, 64.08 µmol, 1.14e-1 eq), Cs_2CO_3 (600 mg, 1.84 mmol, 3.26 eq. After work-up the crude product was purified by flash silica gel chromatography (ISCO; 12 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give **C.2aav** (150 mg, 267.51 µmol, 47.40% yield, 100% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 561.4.

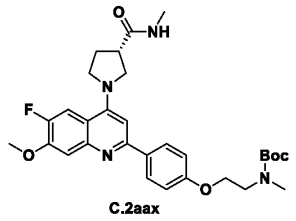
C.2aaw: tert-butyl (2-(4-(8-fluoro-7-methoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2aaw

[0519] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-8-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (80 mg, 173.56 µmol, 1 eq) in dioxane (2 mL) was added cis-octahydro-4H-pyrrolo[3,4-c]pyridin-4-one (40 mg, 285.34 µmol, 1.64 eq), SPhos Pd G3 (50 mg, 64.08 µmol, 3.69e-1 eq), Cs_2CO_3 (200 mg, 613.84 µmol, 3.54 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO; 12 g SepaFlash Silica Flash Column, Eluent of 0~10% DCM/MeOH ether gradient @ 40 mL/min) to give **C.2aaw** (80 mg, 138.14 µmol, 79.59% yield, 97.5% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 565.2.

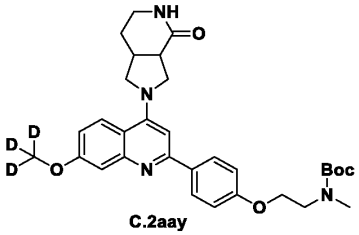
C.2aax: tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-[(3S) -3-(methylcarbamoyl) pyrrolidin-1-yl]-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2aax

[0520] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenoxy]ethyl]-N-methyl-carbamate (200 mg, 433.91 μmol, 1 eq) and (3S) -N-methylpyrrolidine-3-carboxamide (120 mg, 728.90 μmol, 1.68 eq, HCl) in dioxane (5 mL) was added SPhos Pd G_3 (50.00 mg, 64.08 μmol, 1.48e-1 eq) and Cs_2CO_3 (400 mg, 1.23 mmol, 2.83 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/ Ethyl acetate gradient @ 50 mL/min) to give **C.2aax** (220 mg, 346.34 μmol, 79.82% yield, 87% purity) as yellow solid. MS m/z (ESI) $[M+H]^+$= 553.3.

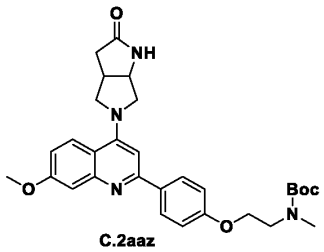
C.2aay: cis-tert-butyl (2-(4-(7-(methoxy-d3)-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2aay

[0521] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-[4-chloro-7-(trideuteriomethoxy) -2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (200 mg, 448.48 μmol, 1 eq) in dioxane (3 mL) was added cis-octahydro-4H-pyrrolo[3,4-c]pyridin-4-one (80 mg, 570.68 μmol, 1.27 eq), SPhos Pd G_3 (40 mg, 51.27 μmol, 1.14e-1 eq) and Cs_2CO_3 (440 mg, 1.35 mmol, 3.01 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate /Methano gradient @ 40 mL/min) to afford **C.2aay** (210 mg, 382.04 μmol, 85.19% yield, 100% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 550.5.

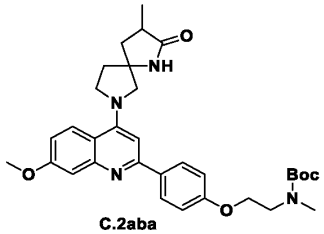
C.2aaz: cis-tert-butyl (2-(4-(7-methoxy-4-(2-oxohexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2aaz

[0522] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a mixture of tert-butyl N-[2-[4-(4-chloro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl- carbamate (500 mg, 1.13 mmol, 1 eq), cis-hexahydropyrrolo[3,4-b]pyrrol-2(1H)-one (200 mg, 1.59 mmol, 1.4 eq) in dioxane (8 mL) were added SPhos Pd G_3 (90.0 mg, 0.115 mmol, 1.02e-1 eq) and Cs_2CO_3 (1.10 g, 3.39 mmol, 3.00 eq) at 25°C. After work-up the crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% EtOAc/PE gradient @ 40 mL/min) to give **C.2aaz** (120 mg, 0.153 mmol, 13.6% yield, 68% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 553.3.

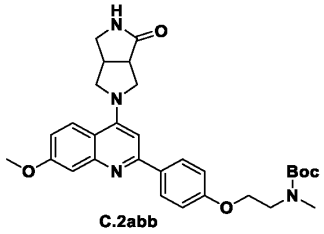
C.2aba: tert-butyl N-[2-[4-[7-methoxy-4-(3-methyl-2-oxo-1,7-diazaspiro[4.4]nonan-7-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2aba

[0523] According to Scheme 3 Step 2: Conditions 3 Buchwald: To mixture of tert-butyl N-[2-[4-(4-chloro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (130 mg, 293.50 μmol, 1 eq) , 3-methyl-1,7-diazaspiro[4.4]nonan-2-one (84.50 mg, 443.17 μmol, 1.51 eq, HCl) were added SPhos Pd G_3 (26.00 mg, 33.32 μmol, 1.14e-1 eq) , Cs_2CO_3 (383.50 mg, 1.18 mmol, 4.01 eq) in dioxane (2 mL). After work-up the crude product was purified by prep-TLC (SiO_2, PE/EtOAc 10/1) to give **C.aba** (80 mg, 119.85 μmol, 40.84% yield, 84% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 561.4.

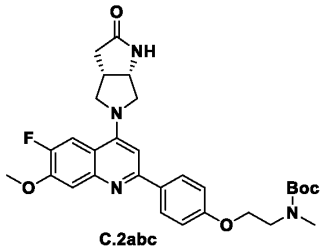
C.2abb: cis-tert-butyl N-[2-[4-[4-(2,2-dioxo-2thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-pent-4-ynoxy-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate



C.2abb

[0524] According to Scheme 3 Step 2: Conditions 1 SNAr: To a solution of tert-butyl N-[2-[4-(4-chloro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (250 mg, 564.42 μmol, 1 eq) in DMSO (2 mL) was added hexahydropyrrolo[3,4-c]pyrrol-1(2H)-one (120.00 mg, 951.20 μmol, 1.69 eq), CsF (300 mg, 1.97 mmol, 3.50 eq), then the resulting mixture was purged with N_2 for three times and stirred at 100°C for 12 hours. The reaction mixture was partitioned between EtOAc (100 mL) and water (80 mL), washed with brine(70 mL), died over Na_2SO_4, filtered and evaporated under reduced pressure to give the crude product. The crude product was purified by flash silica gel chromatography (ISCO; 20 g SepaFlash Silica Flash Column, Eluent of 0~30% EtOAc/PE gradient @ 40 mL/min) to give **C.2abb** (160 mg, 277.57 μmol, 49.18% yield, 92.4% purity) as a yellow solid.

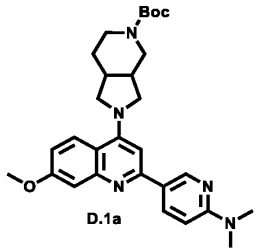
C.2abc: tert-butyl (2-(4-(6-fluoro-7-methoxy-4-((3aS,6aS)-2-oxohexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate



C.2abc

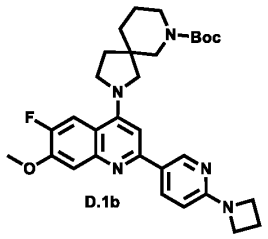
[0525] According to Scheme 3 Step 2: Conditions 3 Buchwald: To a mixture of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (150 mg, 325 μmol, 1.00 eq), (3aS,6aS)-hexahydropyrrolo[3,4-b]pyrrol-2(1H)-one (crude 50.0 mg, 396 μmol, 1.22 eq) in dioxane (3.00 mL) were added SPhos Pd G3 (32.0 mg, 41.01 μmol, 1.26e-1 eq) and Cs_2CO_3 (370 mg, 1.14 mmol, 3.49 eq) at 25°C. After work-up the crude product was purified by prep-TLC (SiO_2: EtOAc/MeOH 10/1) to give **C.2abc** (60.0 mg, 105 μmol, 32.1% yield, 97.0% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 551.2.

D.1a: *tert*-butyl (cis)-2-[2-[6-(dimethylamino)-3-pyridyl]-7-methoxy-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridine-5-carboxylate



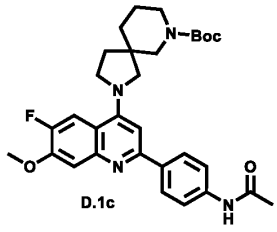
[0526] According to Scheme 5 Step 1: Conditions 4 Buchwald: 5-(4-chloro-7-methoxy-2-quinolyl)-*N*, *N*-dimethyl-pyridin-2-amine **A.5a** (0.20 g, 0.64 mmol, 1.0 eq) in dioxane (4 mL). After work-up the residue obtained was purified by prep-TLC (SiO_2, PE/EtOAc = 0:1) to give **D.1a** (0.30 g, 0.59 mmol, 92% yield, 98% purity), which was obtained as black, brown oil. MS m/z (ESI) $[M+H]^+$= 504.3.

D.1b: tert-butyl 2-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



[0527] According to Scheme 5 Step 1: Conditions 1 Buchwald: 2-[6-(azetidin-1-yl) -3-pyridyl]-4-chloro-6-fluoro-7-methoxy-quinoline **A.5b** (0.20 g, 0.58 mmol, 1.0 eq). After work-up **D.1b** (0.30 g, crude) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+$= 548.3.

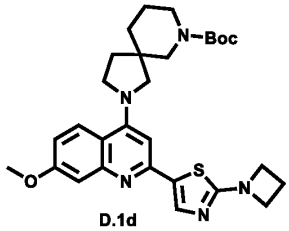
D.1c: tert-butyl 2-[2-(4-acetamidophenyl)-6-fluoro-7-methoxy-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



[0528] According to Scheme 5 Step 1: Conditions 1 Buchwald: To a mixture of **A.5i** (0.11 g, 0.32 mmol, 1.0 eq) in dioxane (3.0 mL) was added tert-butyl 2, 7-diazaspiro[4.5]decane-7-carboxylate (90 mg, 0.37 mmol, 1.2 eq), BrettPhos Pd G_3 (30 mg, 33 μmol, 0.10 eq) and *t*-BuONa (90 mg, 0.94 mmol, 2.9 eq). After work-up the residue obtained was purified by

Flash chromatography (12 g column, Eluent of 0 to 30% EtOAc/PE gradient at 20 mL/min) to afford **D.1c** (0.11 g, 0.18 mmol, 55% yield, 88% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 549.3.

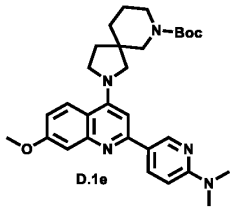
D.1d: tert-butyl 2-[2-[2-(azetidin-1-yl) thiazol-5-yl]-7-methoxy-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



D.1d

[0529] According to Scheme 5 Step 1: Conditions 4 Buchwald: To a solution of **A.5c** (0.10 g, 0.30 mmol, 1.0 eq) in dioxane (2.0 mL) was added tert-butyl 2,7-diazaspiro [4.5] decane-7-carboxylate (90 mg, 0.37 mmol, 1.2 eq), SPhos Pd G3 (25 mg, 32 μmol, 0.1 eq) and Cs_2CO_3 (0.30 g, 0.92 mmol, 3.1 eq). After work-up the crude product was purified by prep-TLC (PE/EtOAc = 3:1) to give **D.1d** (0.15 g, 0.24 mmol, 80% yield, 86% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 536.3.

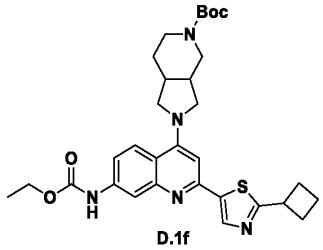
D.1e: tert-butyl 2-[2-[6-(dimethylamino) -3-pyridyl]-7-methoxy-4-quinolyl]-2, 7-diazaspiro [4.5] decane-7-carboxylate



D.1e

[0530] According to Scheme 5 Step 1: Conditions 4 Buchwald: **A.5a** (0.10 g, 0.32 mmol, 1.0 eq), tert-butyl 2, 7-diazaspiro [4.5] decane-7-carboxylate (0.15 g, 0.62 mmol, 2.0 eq) in dioxane (2 mL), SPhos Pd G_3 (0.1 eq), Cs_2CO_3 (2.0 eq). No work-up. The reaction mixture was filtered and concentrated under reduced pressure. The residue obtained was purified by prep-TLC (PE/EtOAc = 1:1) to give **D.1e** (0.10 g, 0.17 mmol, 55% yield, 90% purity) as a white solid.

D.1f: tert-butyl 2-[2-[2-(azetidin-1-yl)thiazol-5-yl]-7-(ethoxycarbonylamino)-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridine-5-carboxylate

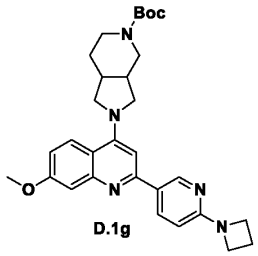


D.1f

[0531] According to Scheme 5 Step 1: Conditions 4 Buchwald: To a solution of **A.5k** (120 mg, 315.22 μmol, 1 eq) in DMSO (0.5 mL) was added CsF (143.65 mg, 945.65 μmol, 3 eq) and tert-butyl 1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,4-c]pyridine-5-carboxylate (85.53 mg, 315.22 μmol, 1 eq, 0.5 oxalic acid). After work-up **D.1f** (100 mg, 157.74 μmol, 50.04% yield, 90% purity) was obtained as yellow oil. MS m/z (ESI) $[M+H]^+$= 572.2.

[0532] To a solution of tert-butyl 2-[2-[2-(azetidin-1-yl)thiazol-5-yl]-7-bromo-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridine-5-carboxylate (100 mg, 175.27 μmol, 1 eq), ethyl carbamate (23.42 mg, 262.91 μmol, 1.5 eq) in dioxane (4 mL) was added t-BuONa (50.53 mg, 525.81 μmol, 3 eq) and BrettPhos Pd G3 (15.89 mg, 17.53 μmol, 0.1 eq). After work-up the residue was purified by prep-TLC (SiO_2, DCM:MeOH = 10:1) to give **D.1f** (60 mg, 93.31 μmol, 53.24% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 579.3.

D.1g: 5- tert-butyl 2-[2-[6-(azetidin-1-yl)-3-pyridyl]-7-methoxy-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridine-5-carboxylate

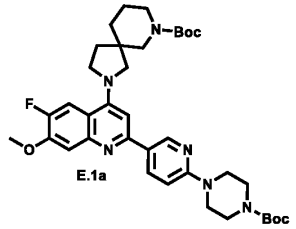


D.1g

[0533] According to Scheme 5 Step 1: To a solution of 2-[6-(azetidin-1-yl) -3-pyridyl]-4-chloro-7-methoxy-quinoline (250 mg, 767.36 μmol, 1 eq) in dioxane (5 mL) was added tert-butyl 1, 2, 3, 3a, 4, 6, 7, 7a-octahydropyrrolo[3, 4-c]pyridine-5-carboxylate (210 mg, 927.91 μmol, 1.21 eq), SPhos Pd G_3 (60 mg, 76.90 μmol, 0.1 eq) and Cs_2CO_3 (750 mg, 2.30 mmol, 3 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 70~100% Ethyl acetate/Petroleum ether gradient

@ 40 mL/min) to afford **D.1g** (250 mg, 460.59 μmol, 60.02% yield, 95% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 516.2.

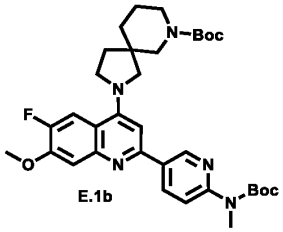
E.1a: tert-butyl 2-[2-[6-(4-tert-butoxycarbonylpiperazin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



E.1a

[0534] According to Scheme 5 Step 1: Conditions 2 Buchwald: **C.1r** (0.20 g, 0.42 mmol, 1.0 eq). After work-up the filtrate was concentrated *in vacuo* to give **E.1a** (0.20 g, 55% yield) as a white solid. MS m/z (ESI) $[M+H]^+$= 677.6.

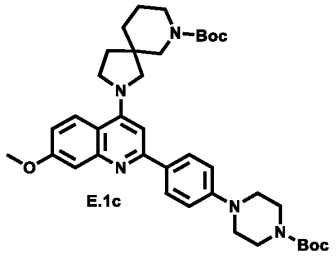
E.1b: *tert*-butyl 2-[2-[6-[tert-butoxycarbonyl(methyl)amino]-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



E.1b

[0535] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1k** (0.15 g, 0.36 mmol, 1.0 eq). After work-up the residue obtained was purified by Flash chromatography (12 g column, Eluent of 0~20% EtOAc/PE gradient at 40 mL/min) to afford **E.1b** (0.13 g, 0.21 mmol, 58% yield, 100% purity) as a light-yellow oil. MS m/z (ESI) $[M+H]^+$= 622.3.

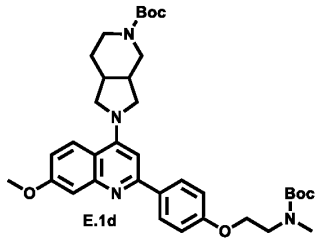
E.1c: tert-butyl 2-(2-(4-(4-(tert-butoxycarbonyl) piperazin-1-yl) phenyl)-7-methoxyquinolin-4-yl)-2,7-diazaspiro [4.5] decane-7-carboxylate



E.1c

[0536] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1f** (0.40 g, 0.88 mmol, 1.0 eq). Work-up was done and the combined organic layers were dried over Na_2SO_4 and evaporated to give a crude **E.1c**. MS m/z (ESI) $[M+H]^+$= 658.4.

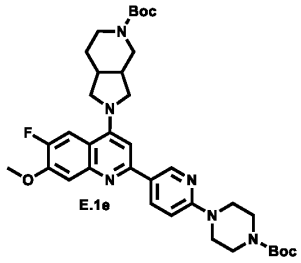
E.1d: tert-butyl (cis)-2-(2-(4-(2-((tert-butoxycarbonyl)(methyl)amino)ethoxy)phenyl)-7-methoxyquinolin-4-yl)octahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate



E.1d

[0537] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1s** (0.10 g, 0.23 mmol, 1.0 eq). After work-up **E.1d** (0.10 g, crude) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+$= 633.4.

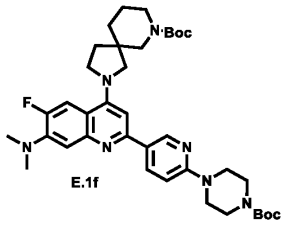
E.1e: *tert*-butyl (cis)-2-[2-[6-(4-tert-butoxycarbonylpiperazin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridine-5-carboxylate



E.1e

[0538] According to Scheme 5 Step 1: Conditions 4 Buchwald: **C.1r** (0.10 g, 0.21 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-TLC (SiO_2, PE/EtOAc = 0:1) to give **E.1e** (0.12 g, 0.16 mmol, 73% yield, 95% purity) as yellow gum. MS m/z (ESI) $[M+H]^+$= 663.3.

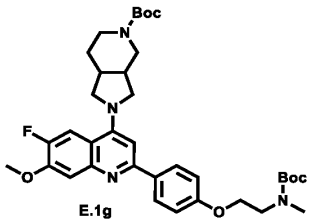
E.1f: *tert*-butyl 2-[2-[6-(4-*tert*-butoxycarbonylpiperazin-1-yl)-3-pyridyl]-7-(dimethylamino)-6-fluoro-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



E.1f

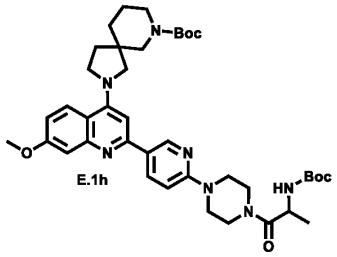
[0539] According to Scheme 5 Step 1: Conditions 4 Buchwald: **C.1l** (0.20 g, 0.41 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-TLC (SiO_2, EtOAc/MeOH = 10:1) to give **E.1f** (0.15 g, 0.17 mmol, 42% yield, 80% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 690.4.

E.1g: *tert*-butyl (cis)-2-[2-[4-[2-[tert-butoxycarbonyl (methyl) amino]ethoxy]phenyl]-6-fluoro-7-methoxy-4-quinolyl]-3, 3a,4,6,7,7a-hexahydro-1H-pyrrolo[3, 4-c]pyridine-5-carboxylate



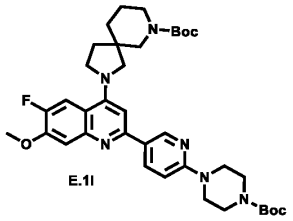
[0540] According to Scheme 5 Step 1: Conditions 2 Buchwald: **C.1m** (0.20 g, 0.43 mmol, 1.0 eq). After work-up the residue obtained was purified by silica gel chromatography (Biotage, 100-200 mesh silica gel) to afford **E.1g** (0.18 g, 0.28 mmol, 64% yield) as yellow solid.

E.1h: *tert*-butyl 2-[2-[6-[4-[2-(tert-butoxycarbonylamino) propanoyl] piperazin-1-yl]-3-pyridyl]-7-methoxy-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



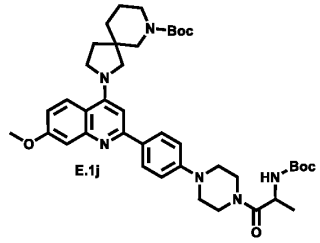
[0541] According to Scheme 5 Step 1: Conditions 2 Buchwald: **C.1q** (0.23 g, 0.44 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-TLC (SiO_2, PE/EtOAc = 0:1) to give **E.1h** (0.23 g, 0.28 mmol, 64% yield, 89% purity). MS m/z (ESI) $[M+H]^+$= 730.4.

E.1i: tert-butyl 2-[2-[6-(4-tert-butoxycarbonylpiperazin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



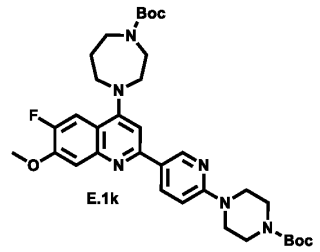
[0542] According to Scheme 5 Step 1: Conditions 2 Buchwald: **C.1r** (0.20 g, 0.42 mmol, 1.0 eq). After work-up the filtrate was concentrated *in vacuo* to give **E.1i** (200 mg, 55% yield) as a white solid. MS m/z (ESI) $[M+H]^+$= 677.6.

E.1j: *tert*-butyl 2-[2-[4-[4-[2-(tert-butoxycarbonylamino) propanoyl] piperazin-1-yl] phenyl]-7-methoxy-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



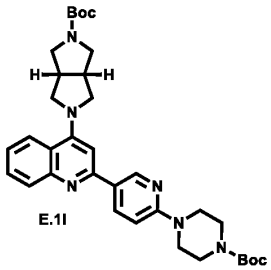
[0543] According to Scheme 5 Step 1: Conditions 4 Buchwald: **C.1q** (0.13 g, 0.25 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 30%-60% over 10 min) to give **E.1j** (80 mg, 0.11 mmol, 44% yield, 100% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+$= 729.4.

E.1k: *tert*-butyl 4-[2-[6-(4-tert-butoxycarbonylpiperazin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-1,4-diazepane-1-carboxylate



[0544] According to Scheme 5 Step 1: Conditions 4 Buchwald: **C.1r** (0.30 g, 0.63 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 30%-60% over 10 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **E.1k** (0.26 g, 0.21 mmol, 33% yield, 52% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 637.3.

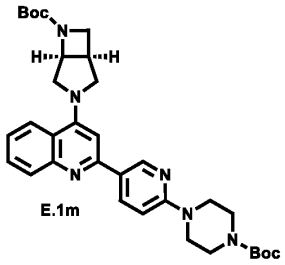
E.1l: *tert*-butyl (cis)-5-(2-(6-(4-(*tert*-butoxycarbonyl) piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) hexahydropyrrolo[3,4-c] pyrrole-2(1H)-carboxylate



[0545] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1a** (0.25 g, 0.59 mmol, 1.0 eq), 120 °C for 72 h. After work-up the residue was purified by Flash chromatography (12g

column, DCM/MeOH (100/0 to 60/40) to get **E.1l** (0.62 mg, 0.62 mmol, 60% purity, *quant.*) as yellow oil. MS m/z (ESI) $[M+H]^+$= 601.

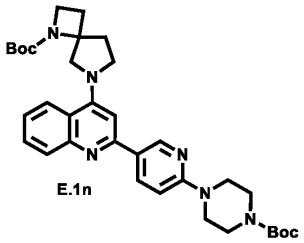
E.1m: *tert*-butyl (1R,5S)-3-(2-(6-(4-(*tert*-butoxycarbonyl) piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-3,6-diazabicyclo [3.2.0] heptane-6-carboxylate



E.1m

[0546] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1a** (0. 27 g, 0.64 mmol, 1.0 eq), 120 °C for 72 h. After work-up the residue was purified by Flash chromatography (12g column, DCM/MeOH (100/0 to 60/40) to get **E.1m** (0.50 g, 0.68 mmol, 80% purity, *quant.*) was obtained as a yellow oil. MS m/z (ESI) $[M+H]^+$= 587.

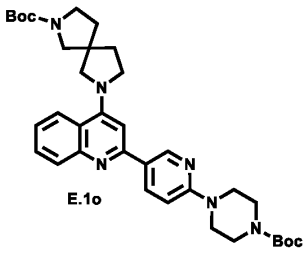
E.1n: *tert*-butyl 6-(2-(6-(4-(*tert*-butoxycarbonyl) piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-1,6-diazaspiro [3.4] octane-1-carboxylate



E.1n

[0547] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1a** (0.18 g, 0.42 mmol, 1.0 eq), 120 °C for 72 h. After work-up the residue was purified by Flash chromatography (12g column, DCM/MeOH (100/0 to 60/40) to get **E.1n** was obtained as a brown solid (0.41 g, 0.45 mmol, 65% purity, *quant.*) MS m/z (ESI) $[M+H]^+$= 601.

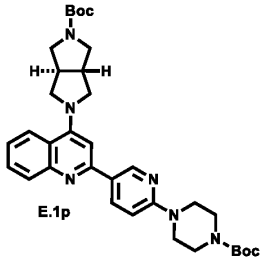
E.1o: tert-butyl 7-(2-(6-(4-(tert-butoxycarbonyl) piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.4] nonane-2-carboxylate



E.1o

[0548] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1a** (0.18 g, 0.42 mmol, 1.0 eq), 120 °C for 72 h. After work-up the residue was purified by Flash chromatography (12g column, DCM/MeOH (100/0 to 60/40) to get **E.1o** (0.28 g, 0.45 mmol, *quant.*) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+$= 615.

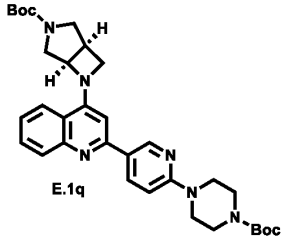
E.1p: *tert*-butyl (trans)-5-(2-(6-(4-(*tert*-butoxycarbonyl) piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) hexahydropyrrolo[3,4-c] pyrrole-2(1H)-carboxylate



E.1p

[0549] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1a** (0.18 g, 0.42 mmol, 1.0 eq), 120 °C for 72 h. After work-up the residue was purified by Flash chromatography (12g column, DCM/MeOH (100/0 to 60/40) to get **E.1p** was obtained as a yellow solid (0.18 g, 0.30 mmol, 71%) MS m/z (ESI) $[M+H]^+$= 601.

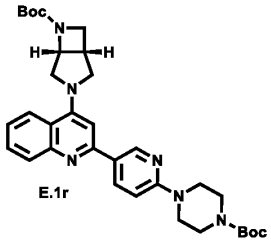
E.1q: *tert*-butyl (1R,5R)-6-(2-(6-(4-(*tert*-butoxycarbonyl) piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-3,6-diazabicyclo [3.2.0] heptane-3-carboxylate



E.1q

[0550] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1a** (0.23 g, 0.54 mmol, 1.0 eq), 120 °C for 72 h. After work-up the residue was purified by Flash chromatography (12g column, DCM/MeOH (100/0 to 60/40) to get **E.1q** (0.16 g, 0.27 mmol, 51%) was obtained as a yellow oil. MS m/z (ESI) $[M+H]^+$= 587.

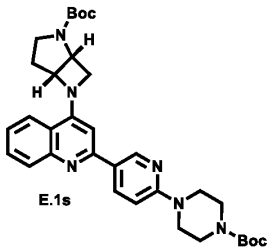
E.1r: *tert*-butyl (1S,5R)-3-(2-(6-(4-(*tert*-butoxycarbonyl) piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-3,6-diazabicyclo [3.2.0] heptane-6-carboxylate



E.1r

[0551] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1a** (0.27 g, 0.64 mmol, 1.0 eq), 120 °C for 72 h. No work-up. After work-up the residue was purified by prep-HPLC **6**, and **E.1r** (0.11 g, 0.19 mmol, 30%) was obtained after lyophilization as a yellow powder. MS m/z (ESI) $[M+H]^+$= 587.

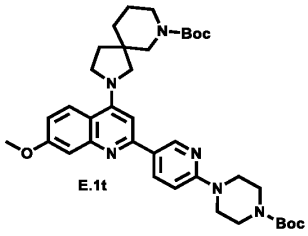
E.1s: *tert*-butyl (cis)-6-(2-(6-(4-(*tert*-butoxycarbonyl) piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,6-diazabicyclo [3.2.0] heptane-2-carboxylate



E.1s

[0552] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1a** (0.27 g, 0.64 mmol, 1.0 eq), 120 °C for 72 h. No work-up. After work-up the residue was purified by prep-HPLC **6** and **E.1s** (0.16 g, 0.27 mmol, 42%) was obtained after lyophilization as a yellow powder. MS m/z (ESI) $[M+H]^+$= 587.

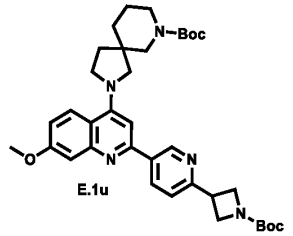
E.1t: tert-butyl 2-[2-[6-(4-tert-butoxycarbonylpiperazin-1-yl)-3-pyridyl]-7-methoxy-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



E.1t

[0553] According to Scheme 5 Step 1: Conditions 3 S_NAr: **C.1e** (0.20 g, 0.44 mmol, 1.0 eq). After work-up the crude material was used in the next step without purification. **E.1t** (0.10 g, 0.13 mmol, 29% yield, 85% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+$= 659.6.

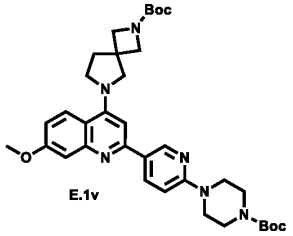
E.1u: *tert*-butyl 2-[2-[6-(1-tert-butoxycarbonylazetidin-3-yl)-3-pyridyl]-7-methoxy-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



E.1u

[0554] According to Scheme 5 Step 1: Conditions 3 S_NAr: **C.1g** (0.15 g, 0.35 mmol, 1.0 eq). After work-up **E.1u** (0.41 g, crude) was obtained as brown solid.

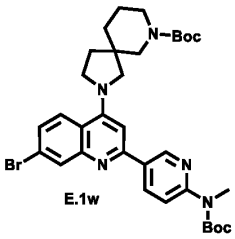
E.1v: *tert*-butyl 7-[2-[6-(4-tert-butoxycarbonylpiperazin-1-yl)-3-pyridyl]-7-methoxy-4-quinolyl]-2,7-diazaspiro [3.4] octane-2-carboxylate



E.1v

[0555] According to Scheme 5 Step 1: Conditions 3 S_NAr: **C.1e** (0.20 g, 0.44 mmol, 1.0 eq). After work-up **E.1v** (0.40 g, crude) was directly used into the next step without further purification as a brown gum.

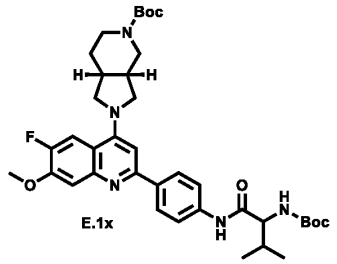
E.1w: *tert*-butyl 2-[7-bromo-2-[6-(methylamino) -3-pyridyl]-4-quinolyl]-2, 7-diazaspiro [4.5] decane-7-carboxylate



E.1w

[0556] According to Scheme 5 Step 1: Conditions 1 S_NAr: **C.1p** (0.28 g, 0.62 mmol, 1.0 eq). After work-up the residue obtained was purified by Flash chromatography (12 g column, Eluent of 80~100% EtOAc/PE gradient at 30 mL/min) to afford **E.1w** (0.30 g, 0.53 mmol, 85% yield, 98% purity) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 - 7.33 (m, 5H), 5.14 (d, J = 4.9 Hz, 2H), 3.71 - 3.63 (m, 2H), 3.33 - 3.18 (m, 2H), 2.83 - 2.65 (m, 4H), 2.44 - 2.34 (m, 2H). MS m/z (ESI) $[M+H]^+$= 450.0.

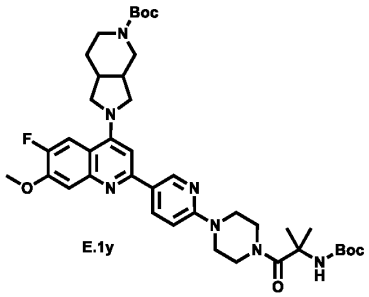
E.1x: tert-butyl (cis)-2-(2-(4-(2-((tert-butoxycarbonyl) amino)-3-methylbutanamido) phenyl)-6-fluoro-7-methoxyquinolin-4-yl) octahydro-5H-pyrrolo [3,4-c] pyridine-5-carboxylate



E.1x

[0557] According to Scheme 5 Step 1: Conditions 4 Buchwald: **C.1ab** (0.29 g, 0.58 mmol, 1.0 eq), tert-butyl 1, 2, 3, 3a, 4, 6, 7, 7a-octahydropyrrolo [3, 4-c] pyridine-5-carboxylate oxalate (0.15 g, 0.55 mmol, 1.0 eq) in dioxane (4.0 mL), SPhos Pd G_3 (0.10 eq), Cs_2CO_3 (3.2 eq). After work-up the residue obtained was purified by Flash chromatography (12 g column, Eluent of 0 to 100% EtOAc/PE gradient at 40 mL/min) to give **E.1x** (0.20 g, 0.28 mmol, 49% yield, 97% purity) as colorless gum. MS m/z (ESI) $[M+H]^+$= 692.2.

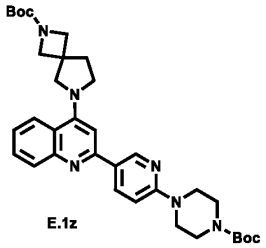
E.1y: tert-butyl (cis)-2-[2-[6-[4-[2-(tert-butoxycarbonylamino)-2-methyl-propanoyl] piperazin-1-yl]-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridine-5-carboxylate



E.1y

[0558] According to Scheme 5 Step 1: Conditions 4 Buchwald: **C.1ac** (0.20 g, 0.36 mmol, 1.0 eq) in dioxane (10 mL), at 80 °C for 2 h. After work-up the residue obtained was purified by prep-TLC (PE/EtOAc = 1:1) to give **E.1y** (0.19 g, 0.20 mmol, 56% yield, 79% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 748.4.

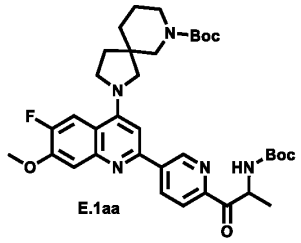
E.1z: tert-butyl 6-(2-(6-(4-(tert-butoxycarbonyl) piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,6-diazaspiro [3.4] octane-2-carboxylate



E.1z

[0559] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1a** (0.25 g, 0.59 mmol, 1.0 eq), tert-butyl 2,7-diazaspiro [3.4]octane-2-carboxylate (0.25 g, 1.2 mmol, 2.0 eq), BrettPhos Pd G3 (0.10 eq), *t*-BuONa (1.2 eq), 120 °C for 12 h. After work-up the residue obtained was purified by Flash chromatography (12 g column, DCM/MeOH = 100:0 to 60:40) to give **E.1z** (0.41 g, 0.61 mmol, *quant.*).

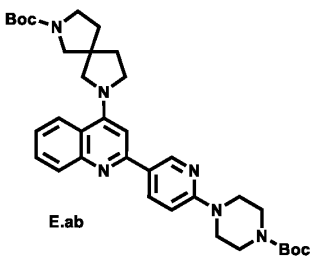
E.1aa: tert-butyl 2-[2-[6-[2-(tert-butoxycarbonylamino) propanoyl]-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate.



E.1aa

[0560] According to Scheme 5 Step 1: Conditions 4 Buchwald: To a solution of **C.1o** (0.20 g, 0.43 mmol, 1.0 eq) and tert-butyl 2,7-diazaspiro [4.5] decane-7-carboxylate (0.18 g, 0.66 mmol, 1.5 eq, HCl) in dioxane (5.0 mL) was added SPhos-Pd-G3 (0.09 eq) and Cs_2CO_3 (4.1 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 29%-59% over 10 min). The eluent was lyophilized to give **E.1aa** (35 mg, 52 μmol, 12% yield, 98% purity) as a yellow gum.

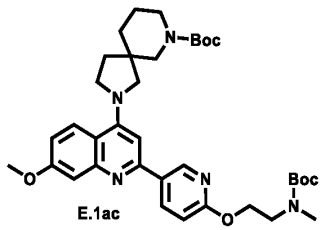
E.1ab: tert-butyl 7-(2-(6-(4-(tert-butoxycarbonyl) piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.4] nonane-2-carboxylate



E.ab

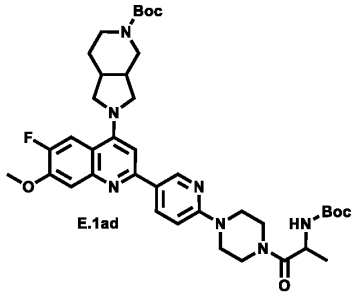
[0561] According to Scheme 5 Step 1: Conditions 4 Buchwald: **C.1a** (0.18 g, 0.42 mmol, 1.0 eq), SPhos-Pd-G3 (0.04 mmol), tert-butyl 2,7-diazaspiro [4.4]nonane-2-carboxylate;oxalic acid (0.27 g, 0.85 mmol, 2.0 eq) and sodium tert-butoxide (0.18 mL, 1.7 mmol, 4.0 eq), for 12 h at 120 °C. After work-up the residue obtained was purified by Flash chromatography (12 g column, DCM/MeOH 100:0 to 60:40) to give **E.1ab** (0.28 g, 0.45 mmol, *quant.*).

E.1ac: tert-butyl 2-[2-[6-[2-[tert-butoxycarbonyl (methyl) amino]ethoxy]-3-pyridyl]-7-methoxy-4-quinolyl]-2, 7-diazaspiro[4.5]decane-7-carboxylate



[0562] According to Scheme 5 Step 1: Conditions 4 Buchwald: **C.1ae** (0.11 g, 0.29 mmol, 1.0 eq), tert-butyl 2, 7-diazaspiro [4.5] decane-7-carboxylate (89 mg, 0.32 mmol, 1.1 eq, HCl) and Cs_2CO_3 (2.0 eq) in 1, 4-dioxane (2.0 mL) was added SPhos Pd G_3 (0.10 eq) at 20 °C. The reaction mixture was degassed and purged with N_2 three times, and then the reaction mixture was stirred at 80 °C for 16 h under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue which was purified by prep-TLC (SiO_2, DCM/MeOH = 10:1) to give **E.1ac** (0.10 g, 0.15 mmol, 53% yield) was obtained as yellow oil. MS m/z (ESI) $[M+H]^+$= 648.3.

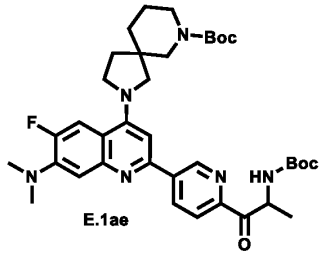
E.1ad: tert-butyl (cis)-2-[2-[6-[4-[2-(tert-butoxycarbonylamino) propanoyl] piperazin-1-yl]-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridine-5-carboxylate



[0563] According to Scheme 5 Step 1: Conditions 4 Buchwald: **C.1x** (0.23 g, 0.42 mmol, 1.0 eq), 1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,4-c] pyridine-5-carboxylate (0.12 g, 0.51 mmol, 1.2 eq), SPhos-Pd-G3 (0.10 eq) and Cs_2CO_3 (0.42 g, 1.3 mmol, 3.1 eq). After work-up the residue obtained was purified by Flash chromatography (40 g column, Eluent of 0 to 10%

EtOAc/PE gradient at 40 mL/min) to afford **E.1ad** (0.30 g, 0.30 mmol, 71% yield, 73% purity) as red oil. MS m/z (ESI) $[M+H]^+$= 734.2.

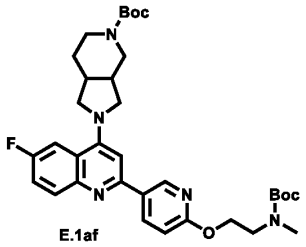
E.1ae: tert-butyl 2-[2-[6-[2-(tert-butoxycarbonylamino) propanoyl]-3-pyridyl]-7-(dimethylamino)-6-fluoro-4-quinolyl]-2,7-diazaspiro [4.5] decane-7-carboxylate



E.1ae

[0564] According to Scheme 5 Step 1: Conditions 4 Buchwald: To a mixture of **C.1y** (80 mg, 0.17 mmol, 1.0 eq), tert-butyl 2,7-diazaspiro[4.5]decane-7-carboxylate (50 mg, 0.21 mmol, 1.2 eq) in dioxane (3.0 mL) was added SPhos Pd G3 (0.10 eq) and Cs_2CO_3 (3.0 eq) at 25°C. After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 30%-60% over 10 min) to give **E.1ae** (50 mg, 70 μmol, 41% yield, 95% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 677.4.

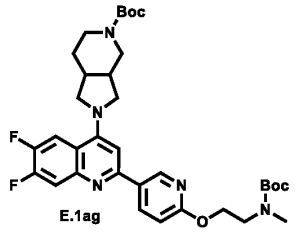
E.1af: tert-butyl (cis)-2-[2-[6-[2-[tert-butoxycarbonyl (methyl) amino]ethoxy]-3-pyridyl]-6-fluoro-4-quinolyl]-3, 3a, 4, 6, 7, 7a-hexahydro-1H-pyrrolo[3, 4-c]pyridine-5-carboxylate



E.1af

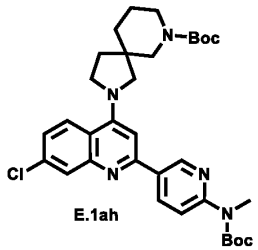
[0565] According to Scheme 5 Step 1: Conditions 4 Buckwald: **C.1z** (0.30 g, 0.57 mmol, 1.0 eq) and tert-butyl 1, 2, 3, 3a, 4, 6, 7, 7a-octahydropyrrolo [3, 4-c] pyridine-5-carboxylate (0.15 g, 0.55 mmol, 0.98 eq, 0.5 oxalic acid) in dioxane (7.0 mL). After work-up the residue obtained was purified by Flash chromatography (4 g column, Eluent of 0 to 100% EtOAc/PE gradient at 20 mL/min) to give **E.1af** (0.19 mg, 0.25 mmol, 44% yield, 84% purity) as colorless gum. MS m/z (ESI) $[M+H]^+$= 622.4.

E.1ag: tert-butyl (cis)-2-[2-[6-[2-[tert-butoxycarbonyl (methyl) amino]ethoxy]-3-pyridyl]-6, 7-difluoro-4-quinolyl]-3, 3a, 4, 6, 7, 7a-hexahydro-1H-pyrrolo[3, 4-c]pyridine-5-carboxylate



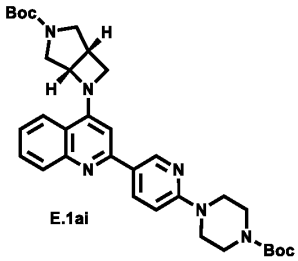
[0566] According to Scheme 5 Step 1: Conditions 4 Buchwald: To a solution of **C.1aa** (0.18 g, 0.40 mmol, 1.0 eq), tert-butyl 1, 2, 3, 3a, 4, 6, 7, 7a-octahydropyrrolo [3, 4-c] pyridine-5-carboxylate (0.10 g, 0.44 mmol, 1.1 eq) in dioxane (5.0 mL) were added SPhos Pd G_3 (0.10 eq) and Cs_2CO_3 (2.3 eq). After work-up the residue obtained was purified by prep-TLC (PE/EtOAc = 0:1) to give **E.1ag** (0.15 g, 0.20 mmol, 50% yield, 85% purity) as a yellow solid.

E.1ah: *tert*-butyl 2-[2-[6-[tert-butoxycarbonyl (methyl) amino]-3-pyridyl]-7-chloro-4-quinolyl]-2, 7-diazaspiro[4.5]decane-7-carboxylate



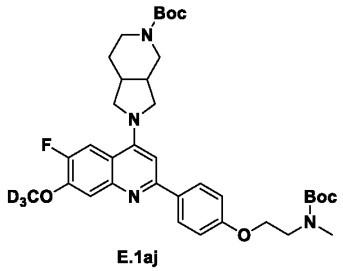
[0567] According to Scheme 5 Step 1: Conditions 2 Buchwald: To a solution of **C.1ad** (0.20 g, 0.49 mmol, 1.0 eq), tert-butyl 2, 7-diazaspiro [4.5] decane-7-carboxylate (1.5 eq) in dioxane (3.0 mL) were added Pd(*t*-$Bu_3P)_2$ (30 mg, 59 μmol, 0.12 eq) and *t*-BuONa (2.1 eq). After work-up the residue obtained was purified by prep-TLC (PE/EtOAc = 0:1) to give **E.1ah** (0.15 g, 0.18 mmol, 37% yield, 75% purity) as a white solid.

E.1ai: *tert*-butyl (1S,5S)-6-[2-[6-(4-tert-butoxycarbonylpiperazin-1-yl)-3-pyridyl]-4-quinolyl]-3,6-diazabicyclo [3.2.0] heptane-3-carboxylate



[0568] According to Scheme 5 Step 1: Conditions 1 Buchwald: **C.1a** (0.27 g, 0.64 mmol, 1.0 eq), tert-butyl (1S,5S)-3,6-diazabicyclo[3.2.0]heptane-3-carboxylate (0.25 g, 1.3 mmol, 2.0 eq) *[cis-pure]*, BrettPhos Pd G4 (0.10 eq) and sodium tert-butoxide (0.13 mL, 1.3 mmol, 2.0 eq). After work-up the residue obtained was purified by prep-HPLC **5** to give **E.1ai** (75 mg, 0.13 mmol, 20%) as a yellow powder.

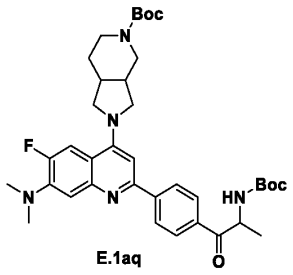
E.1aj: *tert*-butyl 2-[2-[4-[2-[tert-butoxycarbonyl(methyl)amino]ethoxy]phenyl]-6-fluoro-7-(trideuteriomethoxy)-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridine-5-carboxylate



E.1aj

[0569] According to Scheme 6 Step 1: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-[4-chloro-6-fluoro-7-(trideuteriomethoxy)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (260 mg, 560.41 μmol, 1 eq) in dioxane (10 mL) was added tert-butyl 1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,4-c]pyridine-5-carboxylate (150 mg, 662.79 μmol, 1.18 eq), SPhos Pd G3 (50 mg, 64.08 μmol, 1.14e-1 eq) and Cs_2CO_3 (550 mg, 1.69 mmol, 3.01 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 40g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to **E.1aj** (350 mg, 518.74 μmol, 92.56% yield, 96.9% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 654.3.

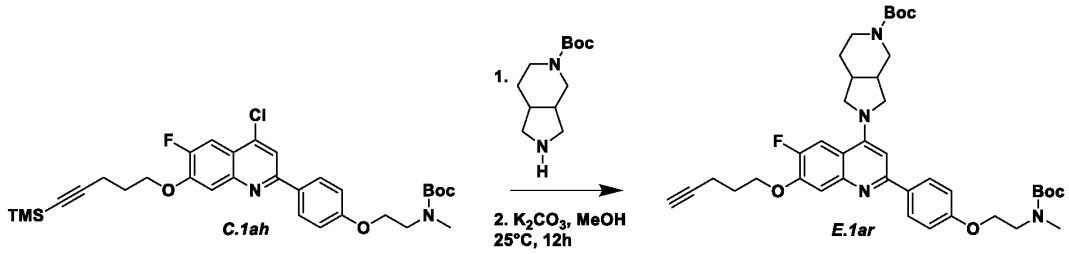
E.1aq: tert-butyl 2-[2-[4-[2-(tert-butoxycarbonylamino)propanoyl]phenyl]-7-(dimethylamino)-6-fluoro-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridine-5-carboxylate



E.1aq

[0570] According to Scheme 6 Step 1: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-[4-chloro-7-(dimethylamino)-6-fluoro-2-quinolyl]phenyl]-1-methyl-2-oxo-ethyl]carbamate (150 mg, 317.83 µmol, 1 eq), tert-butyl 1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,4-c]pyridine-5-carboxylate (107.89 mg, 476.74 µmol, 1.5 eq) in dioxane (4 mL) was added SPhos Pd G3 (24.80 mg, 31.78 µmol, 0.1 eq) and Cs_2CO_3 (310.67 mg, 953.49 µmol, 3 eq). After work-up the residue was purified by prep-TLC (SiO_2, Petroleum ether : Ethyl acetate= 1:1) to give **E.1aq** (120 mg, 163.19 µmol, 51.35% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 662.2.

E.1ar: tert-butyl2-[2-[4-[2-[tert-butoxycarbonyl(methyl)amino]ethoxy]phenyl]-6-fluoro-7-pent-4-ynoxy-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridine-5-carboxylate

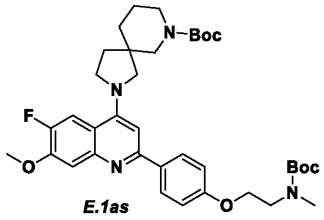


[0571] Step 1: According to Scheme 6 Step 1: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-[4-chloro-6-fluoro-7-(5-trimethylsilylpent-4-ynoxy)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (250 mg, 427.22 µmol, 1 eq) in dioxane (4 mL) was added tert-butyl 1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,4-c]pyridine-5-carboxylate (120 mg, 530.24 µmol, 1.24 eq), Cs_2CO_3 (450 mg, 1.38 mmol, 3.23 eq), SPhos Pd G_3 (40 mg, 51.27 µmol, 0.12 eq). After work-up the crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give tert-butyl 2-[2-[4-[2-[tert-butoxycarbonyl(methyl)amino]ethoxy]phenyl]-6-fluoro-7-(5-trimethylsilylpent-4-ynoxy)-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridine-5-carboxylate (200 mg, 229.67 µmol, 53.76% yield, 89% purity) a yellow solid. MS m/z (ESI) $[M+H]^+$= 755.4.

[0572] Step2: To a solution of tert-butyl 2-[2-[4-[2-[tert-butoxycarbonyl(methyl)amino]ethoxy]phenyl]-6-fluoro-7-(5-trimethylsilylpent-4-ynoxy)-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridine-5-carboxylate (150 mg, 193.54 µmol, 1 eq) in MeOH (2 mL) was added K_2CO_3 (70 mg, 506.49 µmol, 2.62 eq), then the resulting mixture was stirred at 25°C for 12 hours. The reaction mixture was filtered to give

the crude product. The crude product evaporated under reduced pressure to give E.1ar (140 mg, crude) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 703.3.

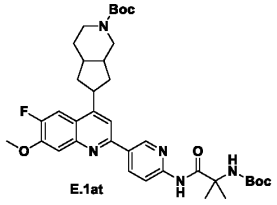
E.1as: tert-butyl 2-[2-[4-[2-[tert-butoxycarbonyl(methyl)amino]ethoxy]phenyl]-6-fluoro-7-methoxy-4-quinolyl]-2,7-diazaspiro[4.5]decane-7-carboxylate



E.1as

[0573] According to Scheme 6 Step 1: Conditions 3 Buchwald: To a solution of tert-butyl N-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenoxy]ethyl]-N-methyl-carbamate (200 mg, 433.91 μmol, 1 eq) in dioxane (10 mL) was added tert-butyl 2, 7-diazaspiro[4.5]decane-7-carboxylate (145 mg, 523.84 μmol, 1.21 eq, HCl), Cs_2CO_3 (425 mg, 1.30 mmol, 3.01 eq) and SPhos Pd G_3 (35 mg, 44.86 μmol, 1.03e-1 eq). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to afford **E.1as** (222 mg, 330.59 μmol, 76.19% yield, 99% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 665.5.

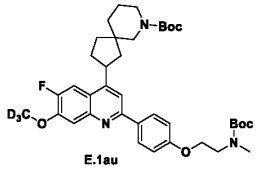
E.1at: tert-butyl 2-[2-[6-[[2-(tert-butoxycarbonylamino) -2-methyl-propanoyl]amino]-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-3, 3a, 4, 6, 7, 7a-hexahydro-1H-pyrrolo[3, 4-c]pyridine-5-carboxylate



E.1at

[0574] According to Scheme 6 Step 1: Conditions 3 Buchwald: To a screw-cap vial equipped with a magnetic stir bar was added tert-butyl N-[2-[[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) -2-pyridyl]amino]-1, 1-dimethyl-2-oxo-ethyl]carbamate (80 mg, 163 μmol, 1 eq) and dioxane (1.5 mL) and tert-butyl 1, 2, 3, 3a, 4, 6, 7, 7a-octahydropyrrolo[3, 4-c]pyridine-5-carboxylate oxalate (50 mg, 184.28 μmol, 1.13 eq) and Cs_2CO_3 (160 mg, 491 μmol, 3 eq) and SPhos Pd G3 (15 mg, 19.2 μmol, 0.1 eq) sequentially. After work-up the residue was purified by prep-TLC (Petroleum ether/Ethylacetate=0/1, Rf=0.43) to give **E.1at** (30 mg, 44.2 μmol, 27% yield) as yellow solid.

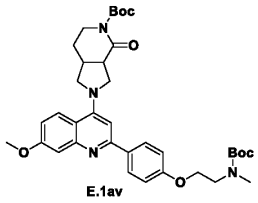
E.1au: tert-butyl 2-[2-[4-[2-[tert-butoxycarbonyl(methyl)amino]ethoxy]phenyl]-6-fluoro-7-(trideuteriomethoxy)-4-quinolyl]-2,7-diazaspiro[4.5]decane-7-carboxylate



E.1au

[0575] According to Scheme 6 Step 1: Conditions 3 Buchwald: A mixture of tert-butyl N-[2-[4-[4-chloro-6-fluoro-7-(trideuteriomethoxy)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (200 mg, 431.09 µmol, 1 eq), tert-butyl 2,7-diazaspiro[4.5]decane-7-carboxylate (124.33 mg, 517.30 µmol, 1.2 eq), SPhos Pd G3 (33.64 mg, 43.11 µmol, 0.1 eq), Cs_2CO_3 (421.37 mg, 1.29 mmol, 3 eq) in dioxane (2 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 40mL/min) to give **E.1au** (200 mg, 299.48 µmol, 69.47% yield, 100% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 668.4.

E.1av: tert-butyl cis-2-(2-(4-(2-((tert-butoxycarbonyl)(methyl)amino)ethoxy)phenyl)-7-methoxyquinolin-4-yl)-4-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate



E.1av

[0576] According to Scheme 6 Step 1: Condition 4 Buckwald: A mixture of tert-butyl N-[2-[4-(4-chloro-7-methoxy-2-quinolyl)phenoxy]ethyl]-N-methyl-carbamate (300 mg, 677.30 µmol, 1 eq), tert-butyl cis-4-oxooctahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate (325.51 mg, 1.35 mmol, 2 eq), SPhos Pd G3 (52.85 mg, 67.73 µmol, 0.1 eq), Cs_2CO_3 (662.03 mg, 2.03 mmol, 3 eq) in dioxane (3 mL). After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 40mL/min) to give **E.1av** (200 mg, 240.37 µmol, 35.49% yield, 65.7% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 547.3.

Synthesis of final products

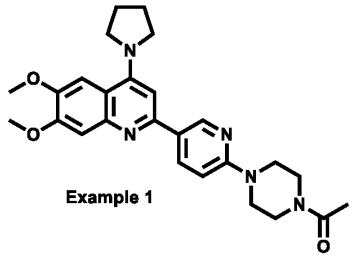
[0577] Final products from Suzuki coupling (Scheme 2; Step 2), Buchwald coupling or SNAr (Scheme 1; step 5) – See above protocols. Final products from deprotection step (Scheme 3; Step 3), (Schemes 4, 5 and 6; Step 2) – See protocols below.

[0578] Conditions 1 HCl: To a solution of substrate **C.2** or **D.1** or **E.1** (1.0 eq) in dioxane (0.06M) was added HCl/dioxane (> 20 eq). The mixture was stirred at 25 °C for 2 h. The mixture was concentrated to give a residue. Purifications described below.

[0579] Conditions 2 TFA: To a solution of substrate **C.2** or **D.1** or **E.1** (1.0 eq) in DCM (0.15M) was added TFA (> 10 eq) at 25 °C. After stirring at 25 °C for 4 h, the reaction mixture was filtered and concentrated under reduced pressure. Purifications described below.

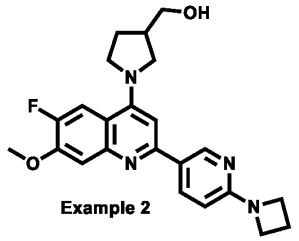
[0580] Conditions 3 TMSOTf: To a solution of substrate **C.2** or **D.1** or **E.1** (1.0 eq) in DCM (0.15M) was added TMSOTf (> 3 eq) and 2,6-dimethylpyridine (>9 eq) at 0°C. After stirring at 0°C for 0.5 hours, the reaction mixture was concentrated under reduced pressure to give a residue at 25°C. Purifications described below.

Example 1: 1-(4-(5-(6,7-dimethoxy-4-(pyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-one



[0581] According to Scheme 1 Step 5: Conditions 3 S_NAr with substrate **A.5i** (0.10 g, 0.23 mmol, 1.0 eq). After work-up the crude product was triturated with MeOH (10 mL) at 25 °C for 20 min to give **Example 1** (32 mg, 68 μmol, 29% yield, 99% purity) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (d, J = 1.2 Hz, 1H), 8.37 - 8.28 (m, 1H), 7.49 (s, 1H), 7.24 (s, 1H), 7.00 - 6.88 (m, 2H), 3.89 (d, J = 12 Hz, 6H), 3.70 (s, 4H), 3.65 (d, J = 2.7 Hz, 2H), 3.57 (s, 6H), 2.06 (s, 3H), 1.99 (s, 4H). MS m/z (ESI) $[M+H]^+$= 462.2.

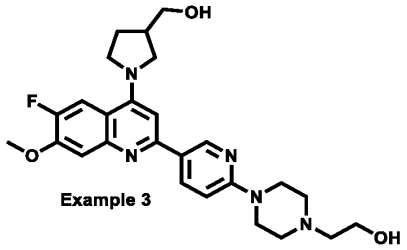
Example 2: (1-(2-(6-(azetidin-1-yl) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol



[0582] According to Scheme 1 Step 5: Conditions 4 Buchwald with substrate **A.5b** (0.10 mg, 0.29 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC 7 (gradient: 30%-50% over 8 min) to give **Example 2** (84 mg, 0.21 mmol, 71% yield, 100%

purity), which was obtained as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.86 (d, J = 2.0 Hz, 1H), 8.27 (dd, J = 2.4, 8.8 Hz, 1H), 7.94 (d, J = 14 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 6.83 (s, 1H), 6.42 (d, J = 8.6 Hz, 1H), 4.75 (t, J = 5.4 Hz, 1H), 4.01 (t, J = 7.6 Hz, 4H), 3.97 (s, 3H), 3.73 - 3.68 (m, 2H), 3.58 - 3.43 (m, 4H), 2.47 - 2.40 (m, 1H), 2.39 - 2.32 (m, 2H), 2.09 - 2.01 (m, 1H), 1.80 - 1.72 (m, 1H). MS m/z (ESI) $[M+H]^+$= 409.2.

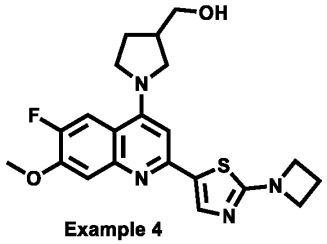
Example 3: 2-(4-(5-(6-fluoro-4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-ol



Example 3

[0583] According to Scheme 1 Step 5: Conditions 4 Buchwald with substrate **C.1v** (0.10 g, 0.19 mmol, 1.0 eq), only 3 h. After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 15%-45% over 10 min) to give pure product. The residue was further purified by SCX (see general protocol) to give **Example 3** (39 mg, 80 µmol, 42% yield, 98% purity) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.69 (d, J = 2.3 Hz, 1H), 8.12 (dd, J = 2.5, 9.0 Hz, 1H), 8.01 (d, J = 14 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 6.73 (s, 1H), 4.02 (s, 3H), 3.86 - 3.65 (m, 12H), 2.70 - 2.66 (m, 4H), 2.61 (t, J = 5.9 Hz, 2H), 2.59 - 2.54 (m, 1H), 2.23 - 2.10 (m, 1H), 1.94 - 1.85 (m, 1H). MS m/z (ESI) $[M+H]^+$= 482.3.

Example 4: (1-(2-(2-(azetidin-1-yl) thiazol-5-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol

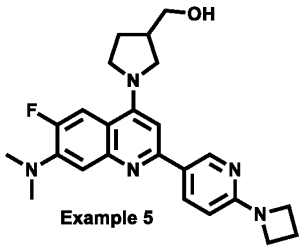


Example 4

[0584] According to Scheme 1 Step 5: Conditions 1 Buchwald with substrate **A.5f** (40 mg, 80 µmol, 1.0 eq). The reaction mixture was filtered and concentrated under reduced pressure. The residue obtained was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give the crude product. The crude product was purified by prep-HPLC **7** (gradient: 34%-54% over 8 min) to give **Example 4** (1.9 mg, 4.5 µmol, 5.7% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.94 (s, 1H), 7.91 (d, J = 14 Hz, 1H), 7.23 (d, J = 9.0

Hz, 1H), 6.82 (s, 1H), 4.75 (t, J = 5.3 Hz, 1H), 4.06 (t, J = 7.5 Hz, 4H), 3.95 (s, 3H), 3.61 - 3.78 (m, 3H), 3.44 - 3.59 (m, 3H), 2.36 - 2.48 (m, 3H), 2.05 (dq, J = 12, 6.1 Hz, 1H), 1.65 - 1.85 (m, 1H). MS m/z (ESI) $[M+H]^+$ = 415.1.

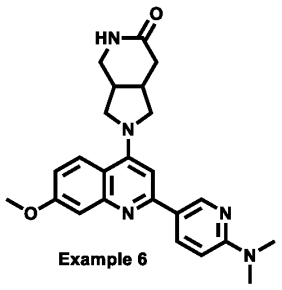
Example 5: (1-(2-(6-(azetidin-1-yl) pyridin-3-yl)-7-(dimethylamino)-6-fluoroquinolin-4-yl) pyrrolidin-3-yl) methanol



Example 5

[0585] According to Scheme 1 Step 5: Conditions 1 Buchwald with substrate **A.5g** (0.12 g, 0.34 mmol, 1.0 eq). The reaction mixture was concentrated under reduced pressure. The residue obtained was purified by prep-TLC (SiO_2, DCM/MeOH = 10:1) to give the crude product. The crude product was purified by prep-HPLC **7** (gradient: 34%-54% over 8 min) to give **Example 5** (22 mg, 52 µmol, 15% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.83 (d, J = 2.1 Hz, 1H), 8.25 (dd, J = 8.7, 1.9 Hz, 1H), 7.85 (d, J = 16 Hz, 1H), 7.17 (d, J = 9.5 Hz, 1H), 6.77 (s, 1H), 6.42 (d, J = 8.8 Hz, 1H), 4.69 (t, J = 5.3 Hz, 1H), 4.02 (t, J = 7.3 Hz, 4H), 3.64 - 3.82 (m, 3H), 3.42 - 3.61 (m, 3H), 2.93 (s, 6H), 2.41 - 2.46 (m, 1H), 2.31 - 2.39 (m, 2H), 2.06 (dq, J = 12, 6.1 Hz, 1H), 1.69 - 1.85 (m, 1H). MS m/z (ESI) $[M+H]^+$ = 422.3.

Example 6: (cis)-2-(2-(6-(dimethylamino) pyridin-3-yl)-7-methoxyquinolin-4-yl) octahydro-6H-pyrrolo[3,4-c] pyridin-6-one

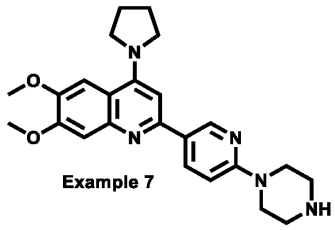


Example 6

[0586] According to Scheme 1 Step 5: Conditions 1 Buchwald with substrate **A.5a** (0.10 g, 0.32 mmol, 1.0 eq) and ***amine.1***. After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 6%-26% over 10 min) then the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 6** (7 mg, 16.77 µmol, 5.26% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm):

8.68 (d, J = 2.4 Hz, 1H), 8.52 (s, 1H), 8.40 (d, J = 9.5 Hz, 1H), 8.08 (dd, J = 2.6, 9.1 Hz, 1H), 7.35 (d, J = 2.5 Hz, 1H), 7.18 (dd, J = 2.6, 9.5 Hz, 1H), 6.83 (d, J = 9.1 Hz, 1H), 6.79 (s, 1H), 4.24 - 4.13 (m, 2H), 3.99 (s, 3H), 3.93 - 3.84 (m, 2H), 3.57 (dd, J = 5.8, 13 Hz, 1H), 3.39 (dd, J = 6.1, 13 Hz, 1H), 3.20 (s, 6H), 3.00 - 2.91 (m, 1H), 2.91 - 2.82 (m, 1H), 2.66 (dd, J = 7.6, 18 Hz, 1H), 2.37 (dd, J = 5.6, 18 Hz, 1H). MS m/z (ESI) $[M+H]^+$ = 418.2.

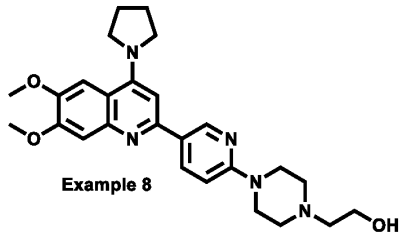
Example 7: 6,7-dimethoxy-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(pyrrolidin-1-yl) quinoline



Example 7

[0587] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2e** (0.40 g, 0.77 mmol, 1.0 eq). TAftert work-up the residue obtained was purified by prep-HPLC 7 (gradient: 15%-45% over 10 min), followed by lyophilization to give **Example 7** (0.17 g, 0.40 mmol, 52% yield, 99% purity) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) : 8.88 (d, J = 2.3 Hz, 1H), 8.29 (dd, J = 2.5, 9.0 Hz, 1H), 7.47 (s, 1H), 7.23 (s, 1H), 6.90 (s, 1H), 6.87 (d, J = 8.9 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.75 - 3.64 (m, 4H), 3.53 - 3.45 (m, 4H), 2.85 - 2.75 (m, 4H), 2.06 - 1.92 (m, 4H). MS m/z (ESI) $[M+H]^+$= 420.3.

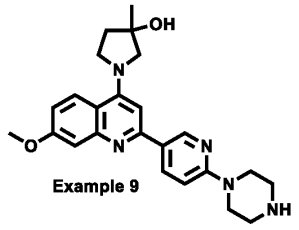
Example 8: 2-(4-(5-(6,7-dimethoxy-4-(pyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-ol



Example 8

[0588] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2f** (70 mg, 0.12 mmol, 1.0 eq). The reaction mixture was concentrated under reduced pressure to give a crude product purified with SCX (see general protocol). **Example 8** (40 mg, 86 μmol, 86% yield, 99% purity) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.87 (d, J = 2.4 Hz, 1H), 8.28 (dd, J = 2.4, 8.9 Hz, 1H), 7.49 (s, 1H), 7.25 (s, 1H), 6.94 - 6.87 (m, 2H), 4.46 (d, J = 1.1 Hz, 1H), 3.89 (d, J = 11 Hz, 6H), 3.71 (s, 4H), 3.57 (d, J = 4.6 Hz, 6H), 2.54 (d, J = 5.1 Hz, 4H), 2.47 - 2.43 (m, 2H), 1.99 (s, 4H). MS m/z (ESI) $[M+H]^+$= 464.2.

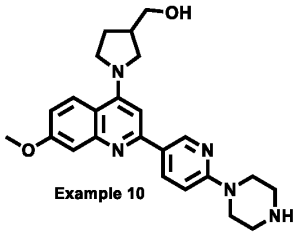
Example 9: 1-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-3-methylpyrrolidin-3-ol



Example 9

[0589] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2g** (0.10 g, 0.19 mmol, 1.0 eq) in MeOH (1.0 mL). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 6%-36% over 8 min). Then the product was further purified with SCX (see general protocol). **Example 9** (19 mg, 45 µmol, 24% yield, 100% purity) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) : 8.93 (d, J = 2.4 Hz, 1H), 8.36 - 8.30 (m, 1H), 8.11 (d, J = 9.2 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 6.95 - 6.87 (m, 2H), 6.82 - 6.77 (m, 1H), 4.86 (br s, 1H), 3.99 - 3.92 (m, 1H), 3.8 (s, 3H), 3.81 (br d, J = 10.4 Hz, 1H), 3.66 - 3.61 (m, 1H), 3.58 - 3.52 (m, 5H), 2.90 - 2.79 (m, 4H), 2.01 - 1.86 (m, 2H), 1.40 (s, 3H). MS m/z (ESI)[M+H]$^+$= 420.2.

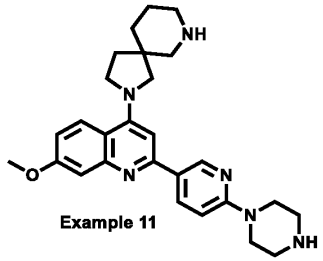
Example 10: (1-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol



Example 10

[0590] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2m** (0.10 g, 0.19 mmol, 1.0 eq) in MeOH (5.0 mL). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 5%-35% over 8 min). Then the crude product was further purified with SCX (see general protocol). **Example 10** (47 mg, 0.11 mmol, 57% yield, 98% purity) was obtained as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (d, J = 2.4 Hz, 1H), 8.31 (dd, J = 8.8, 2.4 Hz, 1H) 8.14 (d, J = 9.2 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 6.97 - 6.80 (m, 3H), 4.74 (br s, 1H), 3.88 (s, 3H), 3.78 - 3.65 (m, 3H), 3.59 - 3.65 (m, 7H), 2.86 - 2.76 (m, 4H), 2.47 - 2.39 (m, 1H), 2.06 (dq, J = 11.6, 6.0 Hz, 1H), 1.77 (dq, J = 12.4, 8.0 Hz, 1H). MS m/z (ESI) [M+H] $^+$= 420.3.

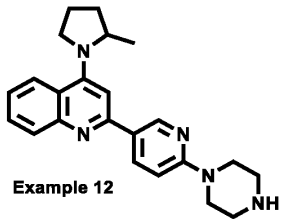
Example 11: 2-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane



Example 11

[0591] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1t** (0.10 g, 0.15 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 2%-30% over 8 min). **Example 11** (59 mg, 0.13 mmol, 84% yield, 100% purity) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.92 (d, J = 1.6 Hz, 1H), 8.32 (dd, J = 8.8, 2.0 Hz, 1H), 8.16 (d, J = 9.2 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 6.98 - 6.81 (m, 3H), 3.88 (s, 3H), 3.84 - 3.75 (m, 1H), 3.73 - 3.63 (m, 2H), 3.56 - 3.53 (m, 1H), 3.51 (br s, 4H), 2.80 (br s, 4H), 2.76 - 3.53 (m, 4H), 2.02 - 1.87 (m, 1H), 1.84 - 1.44 (m, 5H). MS m/z (ESI) $[M+H]^+$= 459.4.

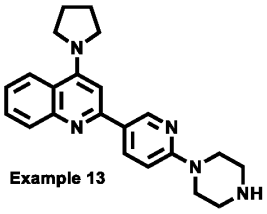
Example 12: 4-(2-methylpyrrolidin-1-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline



Example 12

[0592] According to Scheme 3 Step 3: Conditions 2 TFA with subtrate **C.2o** (0.16 mg, 0.33 mmol, 1.0 eq), TFA (26 eq). After work-up the reaction mixture was concentrated and purified by prep-HPLC **6** to give after lyophilization **Example 12** (0.13 g, 0.35 mmol, *quant.*) as a yellow fluffy powder. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.80 (d, J = 2.5 Hz, 1H), 8.47 (d, J = 7.3 Hz, 1H), 8.21 (dd, J = 8.9, 2.7 Hz, 1H), 7.98 (dd, J = 8.5, 1.4 Hz, 1H), 7.88 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.61 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.13 (d, J = 8.9 Hz, 1H), 6.96 (s, 1H), 4.60 (h, J = 6.5 Hz, 1H), 4.37 – 4.26 (m, 1H), 4.07 (m, 1H), 4.01 – 3.95 (m, 4H), 3.37 – 3.30 (m, 5H), 2.49 – 2.38 (m, 1H), 2.23 (m, 1H), 2.04 – 1.86 (m, 2H), 1.47 (d, J = 6.2 Hz, 3H). MS m/z (ESI) $[M+H]^+$= 374.20.

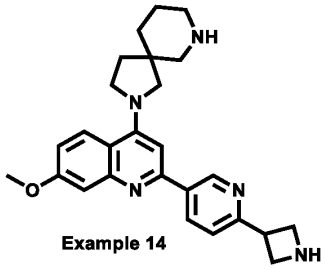
Example 13: 2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(pyrrolidin-1-yl) quinoline



Example 13

[0593] According to Scheme 3 Step 3: Conditions 2 TFA with substrate **C.2p** (0.16 g, 0.35 mmol, 1.0 eq), TFA (25 eq) was added. After work-up the residue obtained was purified by prep-HPLC **6** to give after lyophilization **Example 13** (50 mg, 0.14 mmol, 40%) as a yellow fluffy powder. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.80 (d, J = 2.5 Hz, 1H), 8.58 (d, J = 7.8 Hz, 1H), 8.21 (dd, J = 9.0, 2.6 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.88 (t, J = 7.7 Hz, 1H), 7.62 (t, J = 7.1 Hz, 1H), 7.11 (d, J = 9.1 Hz, 1H), 6.89 (s, 1H), 4.07 (s, 4H), 3.99 – 3.92 (m, 4H), 3.34 – 3.24 (m, 4H), 2.26 – 2.15 (m, 4H). MS m/z (ESI) $[M+H]^+$= 360.20.

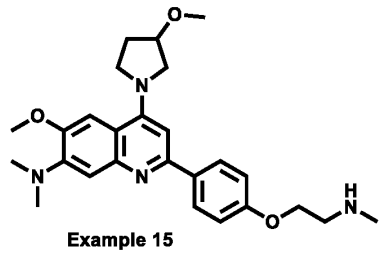
Example 14: 2-(2-(6-(azetidin-3-yl) pyridin-3-yl)-7-methoxyquinolin-4-yl)-2,7-diazaspiro [4.5] decane



Example 14

[0594] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1u** (0.41 g, 0.65 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 1%-20% over 10 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 14** (33 mg, 77 μmol, 12% yield, 99% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.35 (d, J = 1.8 Hz, 1H), 8.49 (dd, J = 2.1, 8.1 Hz, 1H), 8.24 (d, J = 9.4 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 7.01 (dd, J = 2.8, 9.4 Hz, 1H), 6.95 (s, 1H), 4.18 (br s, 1H), 4.07 - 3.94 (m, 4H), 3.91 (s, 3H), 3.86 - 3.81 (m, 1H), 3.75 (br d, J = 9.5 Hz, 2H), 3.58 - 3.55 (m, 2H), 2.75 - 2.55 (m, 5H), 2.02 - 1.95 (m, 1H), 1.82 - 1.75 (m, 1H), 1.52 (br s, 4H). MS m/z (ESI) $[M+H]^+$= 430.2.

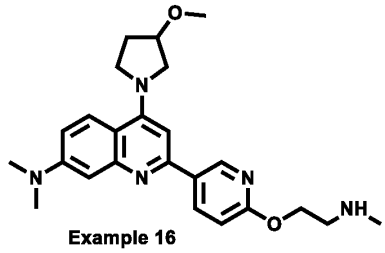
Example 15: 6-methoxy-4-(3-methoxypyrrolidin-1-yl)-*N*, *N*-dimethyl-2-(4-(2-(methylamino) ethoxy) phenyl) quinolin-7-amine



Example 15

[0595] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2j** (0.10 g, 0.18 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 8%-38% over 9 min) to give pure product. Then the residue was further purified with SCX (see general protocol) to give **Example 15** (45 mg, 97 μmol, 53% yield, 98% purity) as yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.10 (d, J = 8.8 Hz, 2H), 7.41 (s, 1H), 7.16 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.89 (s, 1H), 4.12 - 4.07 (m, 3H), 3.95 (d, J = 4.6 Hz, 1H), 3.92 (s, 3H), 3.85 - 3.78 (m, 1H), 3.65 - 3.60 (m, 2H), 3.29 (s, 3H), 2.89 (t, J = 5.6 Hz, 2H), 2.85 (s, 6H), 2.37 (s, 3H), 2.15 - 2.06 (m, 2H). MS m/z (ESI) $[M+H]^+$= 451.2.

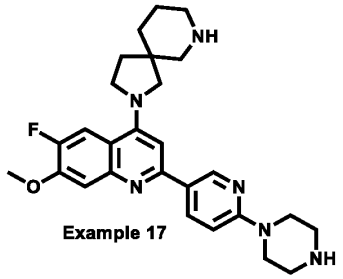
Example 16: 4-(3-methoxypyrrolidin-1-yl)-*N*, *N*-dimethyl-2-(6-(2-(methylamino) ethoxy) pyridin-3-yl) quinolin-7-amine



Example 16

[0596] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2l** (0.10 g, 0.19 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 5%-35% over 9 min) to give (4-(3-methoxypyrrolidin-1-yl)-*N*, *N*-dimethyl-2-[6-[2-(methylamino) ethoxy]-3-pyridyl] quinolin-7-amine (HCl salt)). Then the salt was purified with SCX (see general protocol) to give **Example 16** (34 mg, 81 μmol, 42% yield, 100% purity) as a yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (d, J = 2.2 Hz, 1H), 8.46 (dd, J = 8.7, 2.5 Hz, 1H), 8.07 (d, J = 9.4 Hz, 1H), 6.85 - 7.06 (m, 3H), 6.75 (s, 1H), 4.37 (t, J = 5.8 Hz, 2H), 4.10 (d, J = 2.1 Hz, 1H), 3.93 (dd, J = 11, 4.4 Hz, 1H), 3.76 - 3.86 (m, 1H), 3.58 - 3.71 (m, 2H), 3.28 (s, 3H), 3.03 (s, 6H), 2.88 (t, J = 5.7 Hz, 2H), 2.36 (s, 3H), 2.01 - 2.17 (m, 2H). MS m/z (ESI) $[M+H]^+$= 422.2.

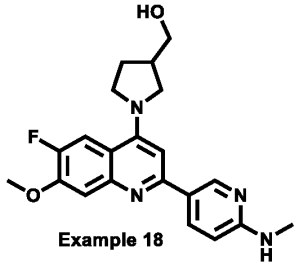
Example 17: 2-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane



Example 17

[0597] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1a** (0.20 g, 0.30 mmol, 1.0 eq) in methanol (1.0 mL). After work-up the residue obtained was purified by prep-HPLC **3** (gradient: 10%-40% over 10 min) and then prep-HPLC **8** (gradient: 1%-30% over 9 min) to give **Example 17** (51 mg, 36% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.85 (s, 1H), 8.60 (d, J = 4.4 Hz, 1H), 8.32 (d, J = 13.2 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 6.96 (s, 1H), 4.26-4.22 (m, 3H), 4.16 (t, J = 5.2 Hz, 4H), 4.10 (s, 3H), 4.09-4.07 (m, 1H), 3.52 (t, J = 5.2 Hz, 4H), 3.32-3.19 (m, 4H), 2.29-2.17 (m, 2H), 2.00-1.63 (m, 4H). MS m/z (ESI) $[M+H]^+$= 477.4.

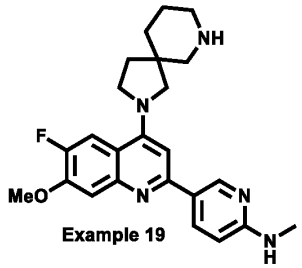
Example 18: (1-(6-fluoro-7-methoxy-2-(6-(methylamino) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol



Example 18

[0598] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2b** (50 mg, 0.10 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 4%-34% over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 18** (8.3 mg, 21 μmol, 20% yield, 98% purity) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d$_4$) δ (ppm): 8.55 (d, J = 1.8 Hz, 1H), 8.52 (br s, 1H), 8.18 (d, J = 13 Hz, 1H), 8.00 - 7.89 (m, 1H), 7.46 (br d, J = 8.1 Hz, 1H), 6.70 (s, 1H), 6.66 (d, J = 8.8 Hz, 1H), 4.08 - 3.95 (m, 6H), 3.80 (br dd, J = 8.1, 11 Hz, 1H), 3.76 - 3.70 (m, 1H), 3.69 - 3.62 (m, 1H), 2.96 - 2.96 (m, 1H), 2.96 (s, 2H), 2.67 - 2.58 (m, 1H), 2.25 (qd, J = 5.9, 11.6 Hz, 1H), 2.00 - 1.89 (m, 1H). MS m/z (ESI) $[M+H]^+$= 383.2.

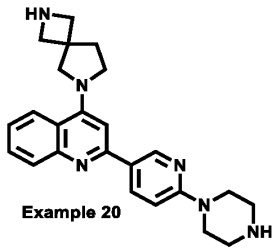
Example 19: 5-(6-fluoro-7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl)-*N*-methylpyridin-2-amine



Example 19

[0599] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1b** (50 mg, 80 μmol, 1.0 eq). Aftzer work-up the residue obtained was purified by prep-HPLC **2** (gradient:1%-25% over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 19** as a yellow solid. Then the residue was further purified with SCX (see general protocol). ^{1}H NMR (400 MHz, methanol-d$_4$) δ (ppm): 8.57 (d, J = 2.2 Hz, 1H), 8.04 (dd, J = 2.3, 8.8 Hz, 1H), 7.93 (d, J = 13.8 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H), 6.69 (s, 1H), 6.61 (d, J = 8.9 Hz, 1H), 3.99 (s, 3H), 3.84 - 3.70 (m, 2H), 3.67 - 3.53 (m, 2H), 2.94 (s, 3H), 2.92 - 2.62 (m, 4H), 2.05 - 1.95 (m, 1H), 1.91 - 1.81 (m, 1H), 1.78 - 1.56 (m, 4H). MS m/z (ESI) $[M+H]^+$= 422.2.

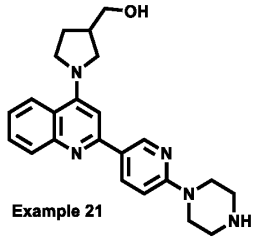
Example 20: 2-(6-(piperazin-1-yl)pyridin-3-yl)-4-(2,6-diazaspiro[3.4]octan-6-yl)quinoline



Example 20

[0600] According to Scheme 6 Step 2: Conditions 2 TFA with substrate **E.1z** (0.41 g, 0.68 mmol, 1.0 eq) in DCM (6.0 mL) and TFA (1.0 mL, 13 mmol, 19 eq). The mixture was stirred for 12 h at room temperature. After work-up the residue obtained was purified by prep-HPLC **5** to give **Example 20** (0.17 g, 0.42 mmol, 62%) as a yellow powder. MS m/z (ESI) $[M+H]^+$= 401.2

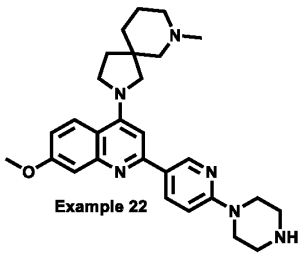
Example 21: (1-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol



Example 21

[0601] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2n** (0.10 g, 0.20 mmol, 1.0 eq). After work-up the residue was first purified by prep-HPLC **8** (gradient:10%-40% over 9 min) and then purified with SCX (see general protocol) to give **Example 21** (0.35 g, 89 μmol, 43% yield, 100% purity) as a yellow solid. ^{1} H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.92 (d, J = 2.4 Hz, 1H), 8.32 (dd, J = 9.0, 2.4 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H), 7.82 (dd, J = 8.4, 1.1 Hz, 1H), 7.58 (td, J = 7.6, 1.0 Hz, 1H), 7.31 (td, J = 7.7, 1.2 Hz, 1H), 6.94 (s, 1H), 6.89 (d, J = 9.0 Hz, 1H), 4.77 (s, 1H), 3.68 - 3.82 (m, 3H), 3.59 (dd, J = 9.8, 7.3 Hz, 1H), 3.49 - 3.53 (m, 4H), 3.21 - 3.32 (m, 2H), 2.71 - 2.91 (m, 4H), 2.39 - 2.48 (m, 1H), 2.02 - 2.14 (m, 1H), 1.78 - 2.00 (m, 1H). MS m/z (ESI) $[M+H]^+$= 390.2.

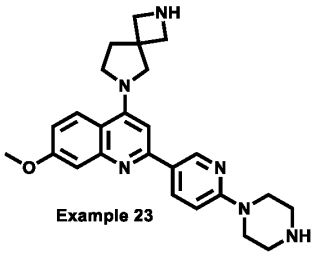
Example 22: 2-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-7-methyl-2,7-diazaspiro [4.5] decane



Example 22

[0602] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2q** (0.10 g, 0.17 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 1%-31% over 10 min). The eluent was lyophilized to give **Example 22** (19 mg, 41 μmol, 23% yield, 99% purity) as a yellow solid. Then the product was further purified with SCX (see general protocol). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.98 - 8.88 (m, 1H), 8.39 - 8.30 (m, 1H), 8.20 - 8.08 (m, 1H), 7.25 - 7.18 (m, 1H), 7.00 - 6.89 (m, 2H), 6.85 - 6.80 (m, 1H), 3.92 - 3.86 (m, 3H), 3.83 - 3.77 (m, 1H), 3.72 - 3.65 (m, 2H), 3.63 - 3.58 (m, 4H), 3.53 (br d, J = 9.8 Hz, 2H), 3.00 - 2.88 (m, 4H), 2.45 - 2.26 (m, 2H), 2.24 - 2.03 (m, 5H), 2.00 - 1.89 (m, 1H), 1.83 - 1.73 (m, 1H), 1.63 - 1.55 (m, 2H), 1.54 - 1.45 (m, 1H), 1.45 - 1.34 (m, 1H). MS m/z (ESI) $[M+H]^+$= 473.3.

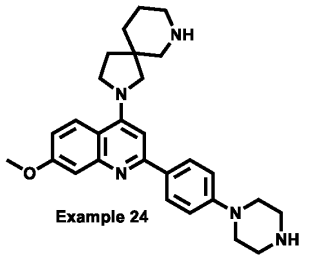
Example 23: 7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,6-diazaspiro [3.4] octan-6-yl) quinoline



Example 23

[0603] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1v** (0.40 g, 0.63 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 0%-20% over 9 min). The eluent was lyophilized to give **Example 23** (62 mg, 0.14 mmol, 23% yield, 100% purity) as a yellow solid. Then the product was further purified / neutralized with SCX (see general protocol). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.96 - 8.89 (m, 1H), 8.38 - 8.27 (m, 1H), 8.17 - 8.06 (m, 1H), 7.28 - 7.20 (m, 1H), 7.01 - 6.89 (m, 2H), 6.87 - 6.81 (m, 1H), 3.99 - 3.91 (m, 4H), 3.89 (s, 3H), 3.87 - 3.83 (m, 2H), 3.73 - 3.69 (m, 2H), 3.56 (br s, 4H), 2.92 - 2.82 (m, 4H), 2.59 (br d, J = 3.0 Hz, 2H), 2.32 - 2.22 (m, 2H). MS m/z (ESI) $[M+H]^+$= 431.2.

Example 24: 2-(7-methoxy-2-(4-(piperazin-1-yl) phenyl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane

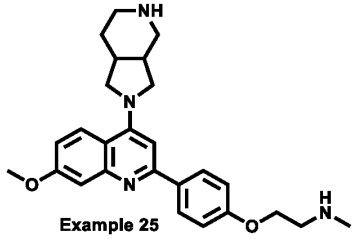


Example 24

[0604] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1c** (0.20 g, 0.30 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 2%-32% over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give 2-[7-methoxy-2-(4-piperazin-1-ylphenyl) -4-quinolyl]-2, 9-diazaspiro [4.5] decane as a yellow solid. Then the product was further purified with SCX (see general protocol) to give **Example 24** (17 mg, 37 μmol, 12% yield, 100% purity), which was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.15 (d, J = 9.4 Hz, 1H), 8.06 (br d, J = 8.8 Hz, 2H), 7.22 (d, J = 2.8 Hz, 1H), 7.01 (br d, J = 8.9 Hz, 2H), 6.94 (dd, J = 2.6, 9.3 Hz, 1H), 6.84 (s, 1H), 3.89 (s, 3H),

3.84 - 3.77 (m, 1H), 3.73 - 3.67 (m, 2H), 3.53 (br d, *J* = 10.3 Hz, 2H), 3.19 - 3.15 (m, 4H), 2.92 - 2.85 (m, 4H), 2.81 - 2.65 (m, 4H), 2.04 - 1.94 (m, 1H), 1.81 - 1.64 (m, 2H), 1.54 (br s, 2H). MS m/z (ESI) $[M+H]^+$= 458.3.

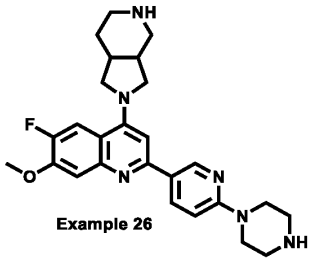
Example 25: (cis)-2-(4-(7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenoxy)-*N*-methylethan-1-amine



Example 25

[0605] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1d** (50 mg, 79 μmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **3** (gradient: 0%-30% B over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give 2-[4-[4-(1, 3, 3a, 4, 5, 6, 7, 7a-octahydropyrrolo[3, 4-c]pyridin-2-yl) -7-methoxy-2-quinolyl]phenoxy]-*N*-methyl-ethanamine as a yellow solid. Then the product was further purified with SCX (see general protocol) to give **Example 25** (11 mg, 26 μmol, 33% yield, 99% purity), which was obtained as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.23 (d, *J* = 9.4 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.99 (dd, *J* = 1.7, 9.3 Hz, 1H), 6.72 (s, 1H), 4.17 (t, *J* = 5.0 Hz, 2H), 3.93 (s, 3H), 3.90 - 3.82 (m, 2H), 3.75 - 3.64 (m, 2H), 3.04 - 2.92 (m, 4H), 2.91 - 2.82 (m, 1H), 2.75 - 2.64 (m, 1H), 2.49 (s, 3H), 2.48 - 2.40 (m, 2H), 1.73 (br d, *J* = 9.0 Hz, 1H), 1.62 - 1.48 (m, 1H). MS m/z (ESI) $[M+H]^+$= 433.3.

Example 26: (cis)-6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline

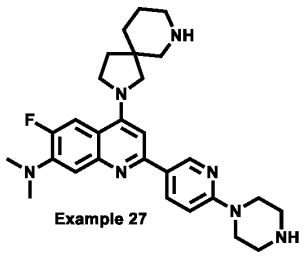


Example 26

[0606] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.6e** (0.12 mg, 0.17 μmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 3%-33% over 9 min) to give 4-(1,3,3a,4,5,6,7,7a-octahydropyrrolo[3,4-c] pyridin-2-yl)-6-

fluoro-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl) quinoline (HCl salt). Then this salt was basified with SCX (see general protocol) to give to give **Example 26** (36 mg, 76 µmol, 44% yield, 99% purity), which was obtained as yellow solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ (ppm): 8.86 (d, J = 2.0 Hz, 1H), 8.27 (dd, J = 2.1, 8.9 Hz, 1H), 7.97 (d, J = 14 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 9.1 Hz, 1H), 6.82 (s, 1H), 3.95 (s, 3H), 3.87 - 3.80 (m, 1H), 3.76 (dd, J = 5.6, 8.9 Hz, 1H), 3.64 (s, 2H), 3.54 - 3.49 (m, 4H), 3.00 - 2.90 (m, 2H), 2.86 (d, J = 3.0 Hz, 1H), 2.79 (s, 4H), 2.73 - 2.64 (m, 1H), 2.41 (s, 2H), 1.68 (d, J = 9.8 Hz, 1H), 1.50 (dd, J = 1.5, 7.9 Hz, 1H). MS m/z (ESI) $[M+H]^+$= 463.2.

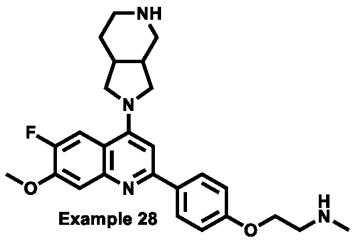
Example 27: 6-fluoro-*N*, *N*-dimethyl-2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-7-amine



Example 27

[0607] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.6f** (0.15 g, 0.17 mmol, 1.0 eq). After work-up the residue was first purified by prep-HPLC **8** (gradient: 0%-30% over 9 min) and then basified with SCX (see general protocol) to give **Example 27** (23 mg, 46 µmol, 26% yield, 98% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.90 (d, J = 1.8 Hz, 1 H), 8.29 (dd, J = 8.9, 2.1 Hz, 1H), 7.86 (d, J = 16 Hz, 1H), 7.16 (d, J = 9.5 Hz, 1H), 6.87 (d, J = 9.2 Hz, 1H), 6.81 (s, 1H), 3.75 - 3.84 (m, 1H), 3.62 - 3.73 (m, 2H), 3.47 - 3.53 (m, 5H), 2.86 - 3.00 (m, 7H), 2.76 - 2.84 (m, 4H), 2.58 - 2.75 (m, 4H), 1.87 - 2.03 (m, 1H), 1.70 - 1.81 (m, 1H), 1.59 - 1.69 (m, 1H), 1.40 - 1.58 (m, 3H). MS m/z (ESI) $[M+H]^+$= 490.3.

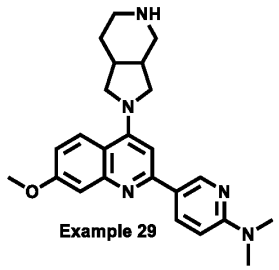
Example 28: (cis)-2-(4-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenoxy)-*N*-methylethan-1-amine



Example 28

[0608] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1g** (0.17 mg, 0.25 mmol, 1.0 eq). The reaction was diluted with water (0.50 mL) and purified by prep-HPLC **8** (gradient: 0%-30% over 9 min), followed by lyophilization. The product (HCl salt) was basified by SCX (see general protocol). **Example 28** (41 mg, 91 μmol, 36% yield, 100% purity) was obtained as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.13 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 14 Hz, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.05 (d, J = 8.9 Hz, 2H), 6.89 (s, 1H), 4.09 (t, J = 5.6 Hz, 2H), 3.99 (s, 3H), 3.91 (br dd, J = 7.5, 8.7 Hz, 1H), 3.83 (br dd, J = 5.9, 9.8 Hz, 1H), 3.67 - 3.61 (m, 1H), 3.57 (br dd, J = 3.1, 9.6 Hz, 1H), 2.94 - 2.81 (m, 5H), 2.61 - 2.57 (m, 1H), 2.37 (s, 3H), 2.36 - 2.30 (m, 2H), 1.67 - 1.54 (m, 1H), 1.49 - 1.37 (m, 1H). MS m/z (ESI) $[M+H]^+$= 451.4.

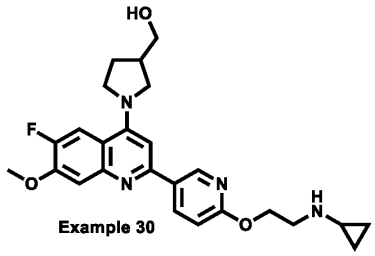
Example 29: (cis)-5-(7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl)-*N*, *N*-dimethylpyridin-2-amine



Example 29

[0609] According to Scheme 5 Step 2: Conditions 1 HCl with substrate **D.1a** (0.30 g, 0.60 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 0%-30% over 9 min) to give 5-[4-(1,3,3a,4,5,6,7,7a-octahydropyrrolo[3,4-c] pyridin-2-yl)-7-methoxy-2-quinolyl]-*N*, *N*-dimethyl-pyridin-2-amine (HCl salt). Then 5-[4-(1,3,3a,4,5,6,7,7a-octahydropyrrolo[3,4-c] pyridin-2-yl)-7-methoxy-2-quinolyl]-*N*, *N*-dimethyl-pyridin-2-amine (HCl salt) was basified with SCX (see general protocol) to give **Example 29** (24 mg, 60 μmol, 10% yield, 100% purity), which was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (d, J = 2.1 Hz, 1H), 8.30 (dd, J = 2.4, 8.9 Hz, 1H), 8.17 (d, J = 9.4 Hz, 1H), 7.20 (d, J = 2.8 Hz, 1H), 6.92 (dd, J = 2.6, 9.4 Hz, 1H), 6.81 (s, 1H), 6.72 (d, J = 9.0 Hz, 1H), 3.93 - 3.89 (m, 1H), 3.88 (s, 3H), 3.81 (dd, J = 5.9, 9.8 Hz, 1H), 3.64 - 3.59 (m, 1H), 3.55 (dd, J = 3.2, 9.6 Hz, 1H), 3.10 (s, 6H), 2.88 - 2.76 (m, 3H), 2.55 (d, J = 9.3 Hz, 1H), 2.33 (d, J = 4.6 Hz, 2H), 1.63 - 1.51 (m, 1H), 1.45 - 1.33 (m, 1H). MS m/z (ESI) $[M+H]^+$= 404.2.

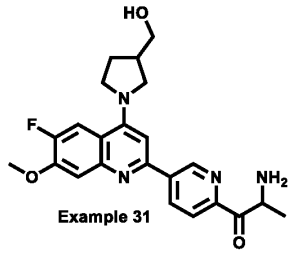
Example 30: (1-(2-(6-(2-(cyclopropylamino) ethoxy) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl) pyrrolidin-3-yl) methanol



Example 30

[0610] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2c** (50 mg, 0.06 mmol, 65% purity, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 2%-30% over 9 min) to give **Example 30** (10 mg, 0.02 mmol, 34% yield, 98% purity, HCl) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.77 (s, 1H), 8.28 (d, J = 13 Hz, 1H), 8.11 (d, J = 9.3 Hz, 1H), 7.76 (d, J = 7.96 Hz, 1H), 6.84 (s, 1H), 6.77 (d, J = 9.6 Hz, 1H), 4.52 (t, J = 5.6 Hz, 2H), 4.23 - 4.02 (m, 6H), 3.96 - 3.85 (m, 1H), 3.77 - 3.65 (m, 4H), 2.93 - 2.84 (m, 1H), 2.72 - 2.60 (m, 1H), 2.33 - 2.23 (m, 1H), 2.05 – 1.93 (m, 1H), 1.05 – 0.97 (m, 2H), 0.97 - 0.91 (m, 2H). MS m/z (ESI) $[M+H]^+$= 453.3.

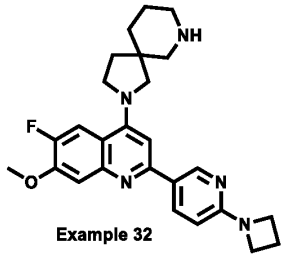
Example 31: 2-amino-1-(5-(6-fluoro-4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) propan-1-one



Example 31

[0611] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2d** (0.16 g, 0.31 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 5%-35% over 9 min). The eluent was lyophilized to give **Example 31** (21 mg, 48 μmol, 16% yield, 96% purity) as a yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 14.69 - 14.43 (m, 1H), 9.52 - 9.44 (m, 1H), 8.85 - 8.77 (m, 1H), 8.65 - 8.51 (m, 3H), 8.38 - 8.28 (m, 2H), 8.23 - 8.13 (m, 1H), 7.17 - 6.98 (m, 1H), 5.30 - 5.18 (m, 1H), 4.22 - 4.06 (m, 3H), 4.05 - 4.02 (m, 3H), 3.94 - 3.82 (m, 1H), 3.55 - 3.50 (m, 2H), 2.68 - 2.59 (m, 1H), 2.20 - 2.08 (m, 1H), 1.93 - 1.81 (m, 1H), 1.61 - 1.52 (m, 3H). MS m/z (ESI) $[M+H]^+$= 425.2.

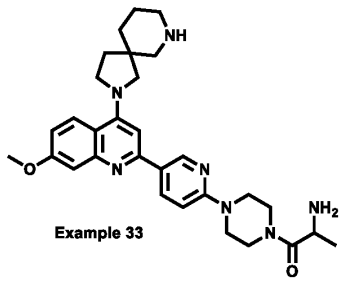
Example 32: 2-(2-(6-(azetidin-1-yl) pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl)-2,7-diazaspiro [4.5] decane



Example 32

[0612] According to Scheme 5 Step 2: Conditions 2 TFA with substrate **D.1b** (0.10 g, 0.18 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 4%-24% over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give 2-[2-[6-(azetidin-1-yl) -3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2, 9-diazaspiro [4.5] decane as a white solid. The crude product was purified by prep-TLC with DCM/MeOH = 10:1 to give 2-[2-[6-(azetidin-1-yl) -3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2, 9-diazaspiro [4.5] decane as yellow oil. Then the product was neutralized with SCX (see general protocol) to give **Example 32** (12 mg, 27 μmol, 15% yield, 98% purity), which was obtained as a white solid. ^{1}H NMR (400 MHz, methanol-d$_4$) δ (ppm): 8.62 (d, J = 2.1 Hz, 1H), 8.14 (dd, J = 2.4, 8.8 Hz, 1H), 7.98 (d, J = 13.8 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 6.75 (s, 1H), 6.48 (d, J = 8.8 Hz, 1H), 4.13 (t, J = 7.4 Hz, 4H), 4.01 (s, 3H), 3.88 - 3.75 (m, 2H), 3.73 - 3.66 (m, 1H), 3.64 - 3.58 (m, 1H), 2.91 - 2.75 (m, 4H), 2.46 (quin, J = 7.5 Hz, 2H), 2.10 - 1.98 (m, 1H), 1.96 - 1.84 (m, 1H), 1.80 - 1.72 (m, 1H), 1.71 - 1.58 (m, 3H). MS m/z (ESI) $[M+H]^+$= 488.3.

Example 33: 2-amino-1-(4-(5-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) propan-1-one

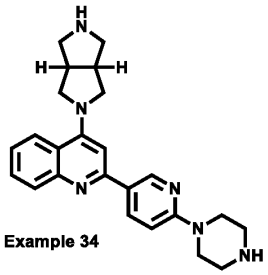


Example 33

[0613] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1h** (0.23 g, 0.32 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 2%-30% over 9 min) to give 2-amino-1-[4-[5-[4-(2,9-diazaspiro [4.5]decan-2-yl)-7-methoxy-2-quinolyl]-2-pyridyl]piperazin-1-yl]propan-1-one (HCl salt). Then this salt was basified

with SCX (see general protocol) to give **Example 33** (16 mg, 28 μmol, 8.9% yield, 96% purity). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.96 (d, J = 1.8 Hz, 1H), 8.36 (dd, J = 2.2, 8.9 Hz, 1H), 8.17 (d, J = 9.2 Hz, 1H), 7.22 (d, J = 2.7 Hz, 1H), 6.95 d, J = 9.0 Hz, 2H), 6.85 (s, 1H), 3.90 - 3.82 (m, 5H), 3.70 - 3.59 (m, 9H), 3.52 (d, J = 10.0 Hz, 2H), 2.71 - 2.57 (m, 4H), 1.99 - 1.92 (m, 1H), 1.79 - 1.73 (m, 1H), 1.65 - 1.48 (m, 4H), 1.12 (d, J = 6.7 Hz, 3H). MS m/z (ESI) $[M+H]^+$= 530.4.

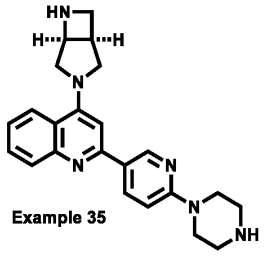
Example 34: 4-(cis)-hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline



Example 34

[0614] According to Scheme 6 Step 2: Conditions 2 TFA with substrate **E.1l** (0.62 g, 1.0 mmol, 1.0 eq). The reaction mixture was evaporated and purified by prep-HPLC **6** and then prep-HPLC 7. After lyophilization, **Example 34** was obtained (21 mg, 0.05 mmol, 5%) as a light-yellow powder. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.80 (s, 1H), 8.47 (d, J = 11 Hz, 1H), 8.22 (d, J = 8.9 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.86 (t, J = 8.7 Hz, 1H), 7.61 (t, J = 8.8 Hz, 1H), 7.10 (d, J = 6.4 Hz, 1H), 6.96 (s, 1H), 4.25 – 4.16 (m, 2H), 4.07 (m, 2H), 3.99 (s, 4H), 3.65 (m, 2H), 3.47 – 3.29 (m, 11H). MS m/z (ESI) $[M+H]^+$= 401.20.

Example 35: (cis)-1-(4-(5-(4-((1S,5S)-3,6-diazabicyclo [3.2.0] heptan-3-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-2-aminopropan-1-one

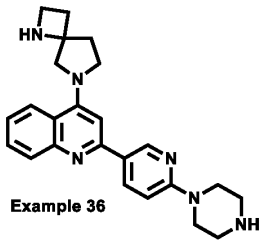


Example 35

[0615] According to Scheme 6 Step 2: Conditions 2 TFA with substrate **E.1m** (0.52 g, 0.85 mmol, 1.0 eq). The reaction mixture was evaporated and purified by prep-HPLC **6**. After lyophilization, **Example 35** was obtained (0.32 g, 0.83 mmol, 97%) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.89 (d, J = 2.6 Hz, 1H), 8.60 (d, J = 8.2 Hz, 1H), 8.30 (dd, J = 9.0, 2.7 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.99 (t, J = 7.7 Hz, 1H), 7.74 (t, J =

7.8 Hz, 1H), 7.32 (s, 1H), 7.18 (d, J = 9.1 Hz, 1H), 5.29 – 5.21 (m, 1H), 4.72 (d, J = 12.3 Hz, 1H), 4.37 (dd, J = 11.4, 8.3 Hz, 1H), 4.17 (dd, J = 14.0, 5.7 Hz, 1H), 4.10 – 4.03 (m, 4H), 3.96 (dd, J = 11.4, 5.2 Hz, 2zH), 3.71 (p, J = 7.6 Hz, 1H), 3.40 (t, J = 5.3 Hz, 4H). 3.38 (s, 6H). MS m/z (ESI) $[M+H]^+$= 387.20.

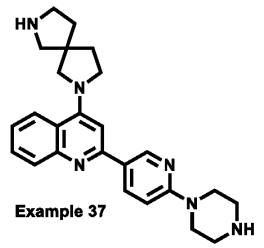
Example 36: 2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(1,6-diazaspiro [3.4] octan-6-yl) quinoline



Example 36

[0616] According to Scheme 6 Step 2: Conditions 2 TFA with substrate **E.1n** (0.41 mg, 0.69 mmol, 1.0 eq). The reaction mixture was evaporated and purified by prep-HPLC **6**. After lyophilization, **Example 36** was obtained (0.16 g, 0.39 mmol, 57%) as a yellow powder. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.77 (d, J = 2.6 Hz, 1H), 8.47 (d, J = 8.6 Hz, 1H), 8.18 (dd, J = 9.1, 2.7 Hz, 1H), 8.00 (d, J = 7.5 Hz, 1H), 7.89 (t, J = 7.8 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.09 (d, J = 9.1 Hz, 1H), 6.89 (s, 1H), 4.80 (m, 2H), 4.44 (d, J = 13.0 Hz, 1H), 4.25 – 4.16 (m, 2H), 4.09 – 4.02 (m, 2H), 4.02 – 3.96 (m, 4H), 3.37 – 3.27 (m, 4H), 2.97 – 2.74 (m, 3H), 2.53 (m, 1H). MS m/z (ESI) $[M+H]^+$= 401.20.

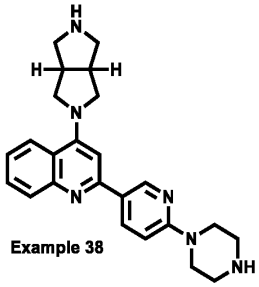
Example 37: 2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.4] nonan-2-yl) quinoline



Example 37

[0617] According to Scheme 6 Step 2: Conditions 2 TFA with substrate **E.1o** (0.28 g, 0.45 mmol, 1.0 eq). The reaction mixture was evaporated and purified by prep-HPLC **6**. After lyophilization, **Example 37** (80 mg, 0.19 mmol, 43%) was obtained as a yellow powder. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.81 (d, J = 2.6 Hz, 1H), 8.56 (d, J = 8.1 Hz, 1H), 8.22 (dd, J = 9.0, 2.6 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.92 (t, J = 7.8 Hz, 1H), 7.66 (t, J = 8.5 Hz, 1H), 7.14 (d, J = 9.0 Hz, 1H), 6.91 (s, 1H), 4.27 – 4.13 (m, 4H), 4.07 – 4.00 (m, 4H), 3.56 – 3.40 (m, 4H), 3.40 – 3.34 (m, 4H), 2.39 – 2.14 (m, 4H). MS m/z (ESI) $[M+H]^+$= 415.20.

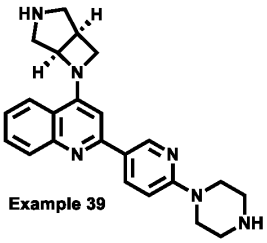
Example 38: 4-((trans)-hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline



Example 38

[0618] According to Scheme 6 Step 2: Conditions 2 TFA with substrate **E.1p** (0.18 g, 0.30 mmol, 1.0 eq). The reaction mixture was evaporated and purified by prep-HPLC **6**. After lyophilization, **Example 38** (36 mg, 0.09 mmol, 30%) was obtained as a yellow powder. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.81 (s, 1H), 8.51 (d, J = 8.6 Hz, 1H), 8.22 (d, J = 6.4 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.93 (t, J = 7.7 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 9.0 Hz, 1H), 6.94 (s, 1H), 4.23 (s, 2H), 4.13 – 4.00 (m, 6H), 3.70 (m, 2H), 3.41 – 3.34 (m, 4H), 3.27 (t, J = 11.3 Hz, 2H), 2.78 (m, 2H). MS m/z (ESI) $[M+H]^+$= 401.20.

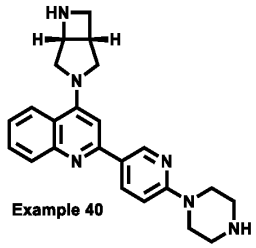
Example 39: 4-((1S,5R)-3,6-diazabicyclo [3.2.0] heptan-6-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline



Example 39

[0619] According to Scheme 6 Step 2: Substrate **E.1q** (0.16 mg, 0.27 mmol, 1.0 eq) was dissolved into DCM (2.7 mL). and 2,2-difluoropropanoic acid (1.0 mL, 12 mmol, 44 eq) was added. The reaction was stirred for 12 h at rt. The reaction mixture was evaporated and purified twice by prep-HPLC **6**. **Example 39** (33 mg, 0.09 mmol, 31%) was obtained after lyophilization. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.78 (d, J = 2.6 Hz, 1H), 8.20 (dd, J = 9.0, 2.6 Hz,1H), 8.12 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.84 (t, J = 8.3 Hz, 1H), 7.58 (t, J = 7.1 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 6.71 (s, 1H), 5.68 – 5.61 (m, 1H), 4.83 (m, 1H), 4.64 (dd, J = 10.1, 4.3 Hz, 1H), 4.01 – 3.96 (m, 4H), 3.93 (m, 1H), 3.74 (d, J = 12.5 Hz, 1H), 3.68 – 3.59 (m, 1H), 3.37 (m, 1H), 3.35 – 3.30 (m, 5H). MS m/z (ESI) $[M+H]^+$= 387.20.

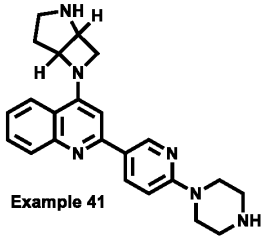
Example 40: 4-((1R,5R)-3,6-diazabicyclo [3.2.0] heptan-3-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline



Example 40

[0620] According to Scheme 6 Step 2: Conditions 2 TFA with substrate **E.1r** (0.11 g, 0.19 mmol, 1.0 eq). After work-up the crude was purified by prep-HPLC **6**. After lyophilization, **Example 40** (46 mg, 0.12 mmol, 62%) was obtained as a yellow powder. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.84 (d, J = 2.1 Hz, 1H), 8.55 (d, J = 8.8 Hz, 1H), 8.25 (dd, J = 9.0, 2.6 Hz, 1H), 8.05 (m, 1H), 7.94 (t, J = 8.4 Hz, 1H), 7.73 – 7.64 (m, 1H), 7.27 (s, 1H), 7.12 (d, J = 8.5 Hz, 1H), 5.23 – 5.15 (m, 1H), 4.66 (d, J = 12.2 Hz, 1H), 4.31 (dd, J = 11.3, 8.5 Hz, 1H), 4.10 (dd, J = 13.8, 5.9 Hz, 1H), 4.01 (t, J = 5.4 Hz, 4H), 3.90 (dd, J = 11.5, 5.2 Hz, 2H), 3.66 (m, 1H), 3.35 (m, 4H), 3.32 (s, 1H). MS m/z (ESI) $[M+H]^+$= 387.20.

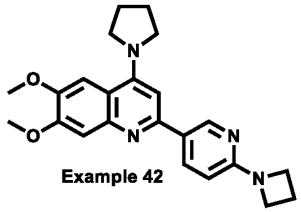
Example 41: 4-((cis)-3,6-diazabicyclo [3.2.0] heptan-6-yl)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline



Example 41

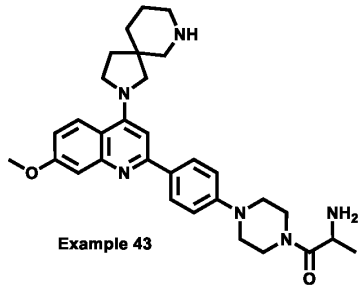
[0621] According to Scheme 6 Step 2: Conditions 2 TFA with substrate **E.1s** (0.16 g, 0.27 mmol, 1.0 eq). After work-up the crude was purified by prep-HPLC **6** twice. After lyophilization, **Example 41** (42 mg, 0.11 mmol, 41%) was obtained as a yellow powder. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.74 (m, 1H), 8.15 (m, 2H), 7.95 – 7.82 (m, 1H), 7.68 – 7.56 (m, 1H), 7.06 (m, 1H), 6.66 (s, 1H), 5.69 (m, 1H), 4.98 (m, 2H), 4.79 – 4.67 (m, 2H), 4.07 – 3.93 (m, 5H), 3.74 – 3.53 (m, 2H), 3.35 – 3.27 (m, 5H), 2.55 (m, 1H), 2.25 – 2.10 (m, 1H). MS m/z (ESI) $[M+H]^+$= 387.20.

Example 42: 2-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2,7-diazaspiro [4.5] decane



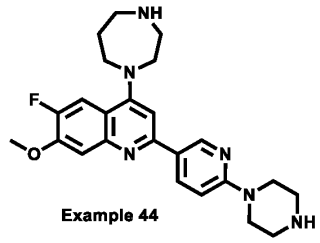
[0622] According to Scheme 1 Step 5: Conditions 2 S_NAr: Substrate **A.5d** (0.10 g, 0.28 mmol, 1.0 eq) in pyrrolidine (2.0 mL) was stirred at 100 °C for 16 h. After cooling at room temperature and work-up the residue obtained was purified by prep-HPLC **7** (gradient: 39%-69% over 10 min) to give **Example 42** (46 mg, 0.12 mmol, 46% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.84 (d, J = 2.4 Hz, 1H), 8.27 (dd, J = 2.4, 8.6 Hz, 1H), 7.47 (s, 1H), 7.22 (s, 1H), 6.88 (s, 1H), 6.43 (d, J = 8.8 Hz, 1H), 4.01 (t, J = 7.6 Hz, 4H), 3.89 (d, J = 12 Hz, 6H), 3.71 - 3.66 (m, 4H), 2.39 - 2.32 (m, 2H), 1.99 (t, J = 6.0 Hz, 4H). MS m/z (ESI) $[M+H]^+$= 391.1.

Example 43: 2-amino-1-(4-(4-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) phenyl) piperazin-1-yl) propan-1-one



[0623] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1j** (80 mg, 0.11 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 3%-30% over 9 min) to give 2-amino-1-[4-[4-[4-(2,9-diazaspiro [4.5]decan-2-yl)-7-methoxy-2-quinolyl]phenyl]piperazin-1-yl]propan-1-one (HCl salt). Then the salt was basified with SCX (see general protocol) to give **Example 43** (25 mg, 48 µmol, 43% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.16 (d, J = 9.5 Hz, 1H), 8.08 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 2.7 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 6.94 (dd, J = 2.6, 9.4 Hz, 1H), 6.85 (s, 1H), 3.90 - 3.85 (m, 4H), 3.82 - 3.76 (m, 1H), 3.72 - 3.62 (m, 6H), 3.51 (d, J = 9.4 Hz, 1H), 3.28 - 3.23 (m, 4H), 2.73 - 2.57 (m, 4H), 2.01 - 1.91 (m, 1H), 1.81 - 1.71 (m, 1H), 1.67 - 1.60 (m, 1H), 1.57 - 1.46 (m, 3H), 1.13 (d, J = 6.7 Hz, 3H). MS m/z (ESI) $[M+H]^+$= 529.5.

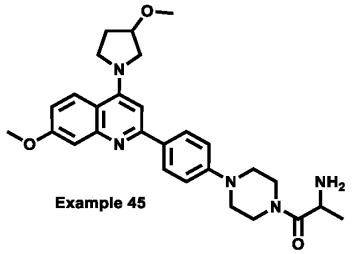
Example 44: 4-(1,4-diazepan-1-yl)-6-fluoro-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline



Example 44

[0624] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1k** (0.26 g, 0.41 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient:1%-23% over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 44** (37 mg, 85 μmol, 21% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 2.14 (br t, J = 4.9 Hz, 2H) 2.93 - 3.05 (m, 4H) 3.15 - 3.20 (m, 2H) 3.21 - 3.27 (m, 2H) 3.57 - 3.70 (m, 8H) 4.04 (s, 3H) 6.94 (d, J = 8.9 Hz, 1H) 7.24 (s, 1H) 7.49 (d, J = 8.3 Hz, 1H) 7.72 (d, J = 13 Hz, 1H) 8.22 (dd, J = 9.0, 2.4 Hz, 1H) 8.78 (d, J = 2.2 Hz, 1H). MS m/z (ESI) $[M+H]^+$= 437.3.

Example 45: 2-amino-1-(4-(4-(7-methoxy-4-(3-methoxypyrrolidin-1-yl) quinolin-2-yl) phenyl) piperazin-1-yl) propan-1-one



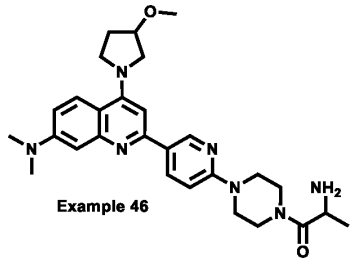
Example 45

[0625] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2i** (0.50 g, 1.2 mmol, 1.0 eq). After work-up the residue obtained was solubilized in DMF (5.0 mL) and 2-(*tert*-butoxycarbonylamino) propanoic acid (0.27 g, 1.4 mmol, 1.2 eq), HATU (0.88 g, 2.3 mmol, 1.9 eq) and DIEA (0.45 g, 3.4 mmol, 0.60 mL, 2.9 eq) were added. The reaction mixture was stirred at 25 °C for 1 h. The residue was partitioned between ethyl acetate (20 mL) and water (30 mL). The aqueous layer was extracted with ethyl acetate (20 mL) twice. The combined organic layers were dried over (Na_2SO_4) and evaporated to give a crude material. The residue obtained was purified by Flash chromatography (12 g column, Eluent of 90~100% DCM/MeOH gradient at 40 mL/min) to afford *tert*-butyl *N*-[2-[4-[4-[7-methoxy-4-(3-methoxypyrrolidin-1-yl) -2-quinolyl]phenyl]piperazin-1-yl]-1-methyl-2-oxo-

ethyl]carbamate (0.28 g, 0.47 mmol, 40% yield, 80% purity) as yellow oil. MS m/z (ESI) $[M+H]^+$= 590.3.

[0626] The same Conditions 1 HCl was used with the previous compound (0.28 g, 0.47 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 15%-45% over 10 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 45** (20 mg, 41 µmol, 8.7% yield, 100% purity) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.14 - 8.08 (m, 3H), 7.24 (d, J = 2.8 Hz, 1H), 7.06 (d, J = 8.9 Hz, 2H), 6.95 (dd, J = 2.8, 9.4 Hz, 1H), 6.87 (s, 1H), 4.12 (br s, 1H), 3.98 - 3.91 (m, 2H), 3.90 (s, 3H), 3.89 - 3.78 (m, 2H), 3.72 - 3.58 (m, 7H), 3.29 (s, 5H), 2.16 - 2.06 (m, 2H), 1.15 (d, J = 6.7 Hz, 3H). MS m/z (ESI) $[M+H]^+$= 490.3.

Example 46: 2-amino-1-(4-(5-(7-(dimethylamino)-4-(3-methoxypyrrolidin-1-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl) propan-1-one



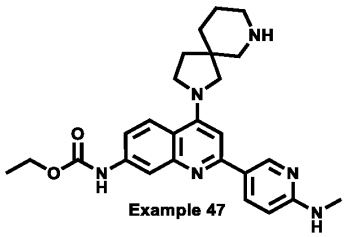
Example 46

[0627] According to Scheme 3 Step 3: Conditions 1 HCl with substrate **C.2k** (0.17 g, 0.36 mmol, 1.0 eq). After work-up the residue obtained was solubilized in DMF (2.0 mL) and 2-(tert-butoxycarbonylamino) propanoic acid (0.14 mg, 0.73 mmol, 2.0 eq), HATU (0.41 g, 1.1 mmol, 3.0 eq) and *N*-ethyl-*N*-propan-2-ylpropan-2-amine (0.23 g, 1.8 mmol, 0.32 µL, 5.0 eq) were added. After stirring at 25 °C for 16 h, the reaction mixture was concentrated under reduced pressure. The residue obtained was purified by prep-HPLC **2** (gradient: 22%-52% over 10 min) to give tert-butyl *N*-[2-[4-[5-[7-(dimethylamino)-4-(3-methoxypyrrolidin-1-yl)-2-quinolyl]-2-pyridyl]piperazin-1-yl]-1-methyl-2-oxo-ethyl]carbamate (0.2 g, 0.30 mmol, 82% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+$= 604.8.

[0628] The same Conditions 1 HCl was used with the previous compound (0.10 g, 0.17 mmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 10%-40% over 9 min), to give 2-amino-1-[4-[5-[7-(dimethylamino)-4-(3-methoxypyrrolidin-1-yl)-2-quinolyl]-2-pyridyl] piperazin-1-yl] propan-1-one (HCl salt). Then the salt was basified with SCX (see general protocol) to give **Example 46** (23 mg, 46 µmol, 28% yield, 100% purity) as a yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.09 (s, 1H), 8.88

(d, J = 2.3 Hz, 1H), 8.19 - 8.45 (m, 5H), 7.35 (d, J = 2.58 Hz, 1H), 6.98 - 7.19 (m, 2H), 6.66 (s, 1H), 3.43 - 4.22 (m, 14H), 3.30 (s, 3H), 3.11 (s, 6H), 2.02 - 2.29 (m, 2H), 1.36 (d, J = 7.0 Hz, 3H). MS m/z (ESI) $[M+H]^+$= 504.2.

Example 47: ethyl (2-(6-(methylamino) pyridin-3-yl)-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-7-yl) carbamate

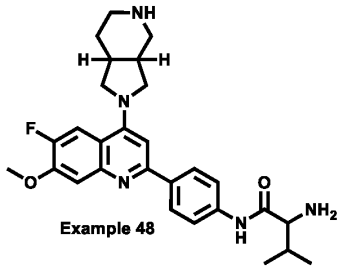


Example 47

[0629] To a solution of **E.1w** (0.15 g, 0.27 mmol, 1.0 eq) in dioxane (3.0 mL) was added ethyl carbamate (35 mg, 0.39 mmol, 1.5 eq), BrettPhos Pd G_3 (25 mg, 28 μmol, 0.10 eq) and *t*-BuONa (80 mg, 0.83 mmol, 3.1 eq), The mixture was degassed and purged with nitrogen three times, then the resulting mixture was stirred at 60 °C for 12 h. The residue was partitioned between ethyl acetate (10 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL) twice. The combined organic layers were dried over (Na_2SO_4) and evaporated to give a crude material. Compound tert-butyl 2-[7-(ethoxycarbonylamino) -2-[6-(methylamino) -3-pyridyl]-4-quinolyl]-2, 7-diazaspiro [4.5] decane-7-carboxylate (100 mg, crude) was obtained as yellow oil. MS m/z (ESI) $[M+H]^+$= 561.4

[0630] According to Scheme 3 Step 3: Conditions 1 HCl with tert-butyl 2-[7-(ethoxycarbonylamino) -2-[6-(methylamino) -3-pyridyl]-4-quinolyl]-2, 7-diazaspiro [4.5] decane-7-carboxylate (20 mg, 36 μmol, 1.0 eq). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 2%-32% over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 47** (4.6 mg, 9.9 μmol, 28% yield, 100% purity) as yellow oil. ^1H NMR (400 MHz, methanol-d_4) δ (ppm): 8.57 (d, J = 2.3 Hz, 1H), 8.51 (s, 2H), 8.44 - 8.35 (m, 2H), 7.97 (dd, J = 2.4, 8.9 Hz, 1H), 7.46 (dd, J = 2.2, 9.4 Hz, 1H), 6.73 - 6.65 (m, 2H), 4.27 (q, J = 7.1 Hz, 2H), 4.13 (br t, J = 6.6 Hz, 2H), 4.08 - 3.93 (m, 2H), 3.26 - 3.19 (m, 2H), 3.19 - 3.10 (m, 2H), 2.97 (s, 3H), 2.26 - 2.07 (m, 2H), 1.95 - 1.77 (m, 4H), 1.35 (t, J = 7.1 Hz, 3H). MS m/z (ESI) $[M+H]^+$= 461.3.

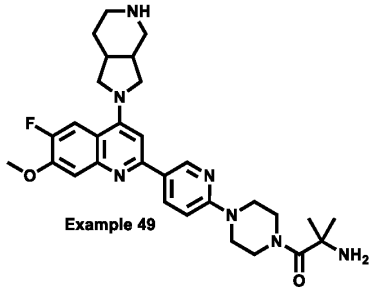
Example 48: 2-amino-N-(4-(6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) phenyl)-3-methylbutanamide



Example 48

[0631] According to Scheme 6 Step 2: Conditions 1 HCl with substrate **E.1x** (0.20 g, 0.29 mmol, 1,0 eq) stirred with HCl/dioxane (2 mL) for 1 h. After work-up the residue was purified by prep-HPLC **2** (gradient:1%-25% over 4 min). The eluent was lyophilized directly to give the title compound as formate. Then the formate was neutralized with SCX (see general protocol) to give **Example 48** (20 mg, 41 μmol, 14% yield, 100% purity) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.14 (d, J = 8.7 Hz, 2H), 8.01 (d, J = 14 Hz, 1H), 7.76 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 9.0 Hz, 1H), 6.91 (s, 1H), 3.98 (s, 3H), 3.91 (t, J = 8.3 Hz, 1H), 3.82 (dd, J = 6.2, 9.4 Hz, 1H), 3.63 (t, J = 8.3 Hz, 1H), 3.59-3.53 (m, 1H), 3.14 (d, J = 5.5 Hz, 2H), 2.92 - 2.78 (m, 3H), 2.62 - 2.54 (m, 2H), 2.41 - 2.31 (m, 2H), 2.03 - 1.90 (m, 1H), 1.66-1.55 (m, 1H), 1.49 - 1.35 (m, 1H), 1.00 - 0.82 (m, 6H). MS m/z (ESI) $[M+H]^+$= 492.3.

Example 49: 2-amino-1-(4-(5-(6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl) quinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-2-methylpropan-1-one

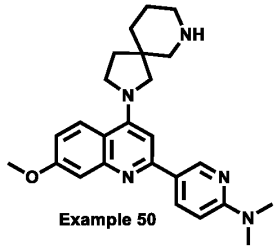


Example 49

[0632] According to Scheme 6 Step 2: Conditions 1 HCl: Substrate **E.1y** (0.19 g, 0.25 mmol, 1.0 eq) was added to HCl/dioxane (2 M, 2.0 mL, 16 eq) and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated to give a residue. The residue obtained was purified by prep-HPLC **7** (gradient: 0%-30% over 9 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 49** (22 mg, 39 μmol, 16% yield, 100% purity) as a

white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 1.56 (s, 6 H) 1.62 - 1.75 (m, 1 H) 1.80 - 1.90 (m, 1 H) 2.57 (br s, 2 H) 2.80 - 2.91 (m, 1 H) 2.96 - 3.04 (m, 1 H) 3.06 - 3.14 (m, 2 H) 3.68 - 3.82 (m, 6 H) 3.91 (br s, 6 H) 4.03 (s, 3 H) 6.80 (s, 1 H) 6.97 (d, J = 8.9 Hz, 1 H) 7.44 (d, J = 8.7 Hz, 1 H) 8.02 (d, J = 14 Hz, 1 H) 8.20 (dd, J = 8.9, 2.5 Hz, 1 H) 8.77 (d, J = 2.2 Hz, 1 H). MS m/z (ESI) $[M+H]^+$= 548.4.

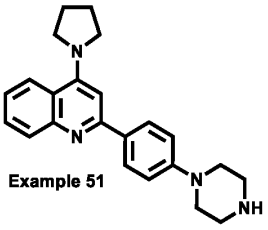
Example 50: 5-[4-(2, 9-diazaspiro[4.5]decan-2-yl) -7-methoxy-2-quinolyl]-N, N-dimethyl-pyridin-2-amine



Example 50

[0633] According to Scheme 5 Step 2: Conditions 1 HCl: On substrate **D.1e** (0.10 g, 0.19 mmol, 1.0 eq) in dioxane (2.0 mL) was added HCl/dioxane (2 M) and the reaction mixture was stirred at 25 °C for 2 h. After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 0%-30% over 10 min). Then the solid was neutralized with SCX (see general protocol to give **Example 50** (20 mg, 46 μmol, 24% yield, 95% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (d, J = 2.2 Hz, 1H), 8.31 (dd, J = 2.4, 8.8 Hz, 1H), 8.16 (d, J = 9.4 Hz, 1H), 7.20 (d, J = 2.6 Hz, 1H), 6.93 (dd, J = 2.8, 9.4 Hz, 1H), 6.84 (s, 1H), 6.72 (d, J = 9.0 Hz, 1H), 3.88 (s, 3H), 3.84 - 3.76 (m, 1H), 3.74 - 3.63 (m, 2H), 3.52 (d, J = 10.0 Hz, 1H), 3.10 (s, 6H), 2.71 - 2.55 (m, 4H), 2.02 - 1.91 (m, 1H), 1.81 - 1.70 (m, 1H), 1.69 - 1.59 (m, 1H), 1.58 - 1.43 (m, 3H). MS m/z (ESI) $[M+H]^+$= 418.3.

Example 51: 2-(4-(piperazin-1-yl) phenyl)-4-(pyrrolidin-1-yl) quinoline

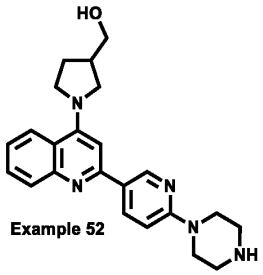


Example 51

[0634] According to Scheme 3 Step 3: Conditions 1 HCl: On substrate **C.2r** (0.30 g, 0.65 mmol, 1.0 eq) in dioxane (5.0 mL) was added HCl/dioxane (4.0 M, 2.0 mL, 12 eq). The mixture was stirred 2 h at 25 °C. After work-up the residue was poured into ACN (10 mL) and was added K_2CO_3 (35 mg, 0.25 mmol, 1.0 eq). The mixture was stirred at 25 °C for 16 h. The mixture was adjusted to pH = 7~8 with $NH_3.H_2O$. The mixture was concentrated to give

a residue. After work-up, purification was done by prep-HPLC **9** (gradient: 0-10 minutes 8~38%) to give **Example 51**(17 mg, 47 mmol, 19% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.23 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 7.2 Hz, 1H), 7.30 (t, J = 6.8 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.96 (s, 1H), 3.71 (t, J = 6.0 Hz, 4H), 3.17 - 3.10 (m, 4H), 2.88 - 2.82 (m, 4H), 2.03 - 1.95 (m, 4H). MS m/z (ESI) $[M+H]^+$= 359.3.

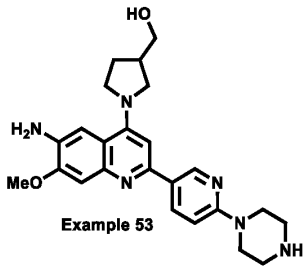
Example 52: (1-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol



Example 52

[0635] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of **C.2n** (0.10 g, 0.20 mmol, 1.0 eq) in dioxane (1.0 mL) was added HCl/dioxane (2 M, 2.0 mL, 20 eq). After stirring at 25 °C for 4 h, the reaction mixture was concentrated under reduced pressure. The residue obtained was purified by prep-HPLC **8** (gradient: 10%-40% over 9 min) to and neutralized with SCX (see general protocol) to give **Example 52** (35 mg, 89 μmol, 43% yield, 100% purity) as a yellow solid. ^{1} H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.92 (d, J = 2.4 Hz, 1H), 8.32 (dd, J = 9.0, 2.4 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H), 7.82 (dd, J = 8.4, 1.1 Hz, 1H), 7.58 (td, J = 7.6, 1.0 Hz, 1H), 7.31 (td, J = 7.7, 1.2 Hz, 1H), 6.94 (s, 1H), 6.89 (d, J = 9.0 Hz, 1H), 4.77 (s, 1H), 3.68 - 3.82 (m, 3H), 3.59 (dd, J = 9.8, 7.3 Hz, 1H), 3.49 - 3.53 (m, 4H), 3.21 - 3.32 (m, 2H), 2.71 - 2.91 (m, 4H), 2.39 - 2.48 (m, 1H), 2.02 - 2.14 (m, 1H), 1.78-2.001 (m, 1H). MS m/z (ESI) $[M+H]^+$= 390.2.

Example 53: (1-(6-amino-7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) pyrrolidin-3-yl) methanol

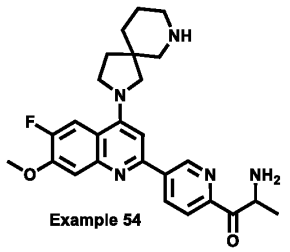


Example 53

[0636] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of **C.2s** (0.20 g, 0.29 mmol, 1.0 eq) in MeOH (5.0 mL) was added TFA (0.33 g, 2.9 mmol, 10 eq) at 25 °C. The

mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue, The residue obtained was purified by prep-HPLC **8** (gradient: 0%-30% over 10 min) to give *N*-(4-(3-(hydroxymethyl)pyrrolidin-1-yl)-7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-6-yl)acetamide HCl salt and **Example 53** HCl salt as a yellow solid. The HCl salt products were neutralized by SCX (see general protocol) to give *N*-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl)-6-quinolyl]acetamide (25 mg, 0.05 μmol, 18% yield, 98% purity) as a yellow solid and **Example 53** (35 mg, 0.08 mmol, 28% yield, 100% purity) as a yellow solid. Acetamide product: MS m/z (ESI) $[M+H]^+$ = 477.3. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.84 (d, J = 2.0 Hz, 1H), 8.24 (dd, J = 8.8, 2.0 Hz, 1H), 7.33 (s, 1H) ,7.14 (s, 1H), 6.80 - 6.89 (m, 2H), 5.06 (s, 2H), 4.80-4.65 (m, 1H), 3.92 (s, 3H), 3.64 - 3.59 (m, 2H), 3.53 - 3.41 (m, 8H), 2.81 (s, 4H), 2.47 - 2.40 (m, 1H), 2.05 (dd, J = 12, 5.6 Hz, 1H), 1.80 - 1.68 (m, 1H). MS m/z (ESI) $[M+H]^+$= 435.3.

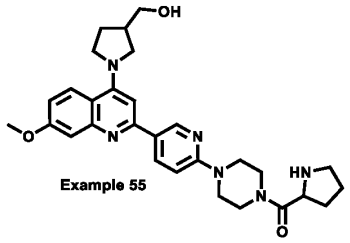
Example 54: 2-amino-1-(5-(6-fluoro-7-methoxy-4-(2,7-diazaspiro[4.5]decan-2-yl)quinolin-2-yl)pyridin-2-yl)propan-1-one



Example 54

[0637] According to Scheme 6 Step 2: Conditions 1 HCl: On substrate **E.1aa** (35 mg, 53 μmol, 1.0 eq)was added HCl/dioxane (2 M, 26 μL, 1.0 eq). The mixture was stirred 2 h at 25 °C. After work-up the residue obtained was purified by prep-HPLC **8** (gradient: 1%-30% over 10 min). The eluent was lyophilized to give **Example 54** (5.4 mg, 12 μmol, 22% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d$_4$) δ (ppm): 9.40 - 9.34 (m, 1H), 8.71 - 8.62 (m, 1H), 8.43 - 8.35 (m, 2H), 7.66 - 7.62 (m, 1H), 7.09 (br d, J = 2.0 Hz, 1H), 5.44 (s, 1H), 4.35 - 4.17 (m, 4H), 4.14 - 4.06 (m, 5H), 3.24 - 3.20 (m, 2H), 2.28 - 2.19 (m, 2H), 1.97 - 1.87 (m, 4H), 1.73 - 1.67 (m, 3H). MS m/z (ESI) $[M+H]^+$= 464.3.

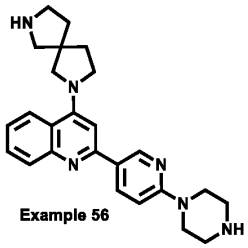
Example 55: [4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazin-1-yl]-pyrrolidin-2-yl-methanone



Example 55

[0638] According to Scheme 3 Step 3: Conditions 1 HCl: On substrate **C.2t** (0.12 g, 0.19 mmol, 1.0 eq) was added HCl/dioxane (2 M, 1.0 mL) and the mixture was stirred at 25 °C for 4 h. After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 4%-34% over 10 min) and product was neutralized by SCX (see general protocol) to give **Example 55** (24 mg, 43 µmol, 22% yield, 96% purity) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.94 (d, J = 2.3 Hz, 1H), 8.35 (dd, J = 2.3, 8.9 Hz, 1H), 8.15 (d, J = 9.4 Hz, 1H), 7.22 (d, J = 2.8 Hz, 1H), 6.95 (td, J = 2.7, 9.2 Hz, 2H), 6.84 (s, 1H), 4.79 - 4.66 (m, 1H), 3.96 (dd, J = 6.1, 7.7 Hz, 1H), 3.89 (s, 3H), 3.78 - 3.71 (m, 3H), 3.66 - 3.57 (m, 8H), 3.52 - 3.44 (m, 4H), 3.06 - 2.99 (m, 1H), 2.71 (td, J = 6.8, 10.7 Hz, 1H), 2.46 - 2.40 (m, 1H), 2.11 - 2.01 (m, 2H), 1.82 - 1.60 (m, 4H). MS m/z (ESI) $[M+H]^+$= 517.3.

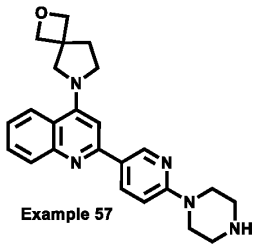
Example 56: 2-(6-(piperazin-1-yl) pyridin-3-yl)-4-(2,7-diazaspiro [4.4] nonan-2-yl) quinoline



Example 56

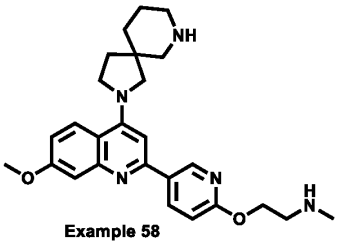
[0639] According to Scheme 6 Step 2: Conditions 2 TFA.: On substrate **E.1ab** (0.28 g, 0.45 mmol, 1.0 eq) was added TFA (29 eq) and the mixture was stirred 12 h at 25 °C. After work-up the residue obtained was purified by prep-HPLC 5 to give **Example 56** (80 mg, 0.19 mmol, 43%) as a yellow powder. MS m/z (ESI) $[M+H]^+$= 415.2.

Example 57: 6-(2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-2-oxa-6-azaspiro [3.4] octane



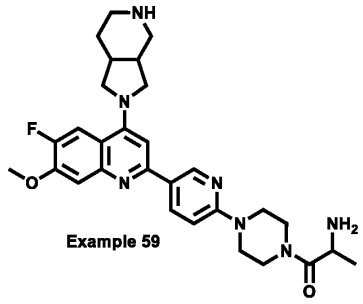
[0640] According to Scheme 3 Step 3: Conditions 2 TFA: To a substrate **C.2u** (0.11 g, 0.21 mmol, 1.0 eq) was added TFA (62 eq) and the mixture was stirred12 h at 25 °C. After work-up the residue obtained was purified by prep-HPLC **5** to give **Example 57** (48 mg, 0.12 mmol, 57%) as a yellow powder. MS m/z (ESI) [M+H]+= 401.2.

Example 58: 2-((5-(7-methoxy-4-(2,7-diazaspiro [4.5] decan-2-yl) quinolin-2-yl) pyridin-2-yl) oxy)-N-methylethan-1-amine



[0641] According to Scheme 6 Step 2: Conditions 1 HCl: To a substrate **E.1ac** (0.10 g, 0.15 mmol, 1.0 eq) in EtOAc (0.5 mL) was added HCl/EtOAc (4.0 M, 2.0 mL, 52 eq) and the mixture was stirred 1 h at 25 °C. The reaction mixture was concentrated under reduced pressure. The residue obtained was purified by prep-HPLC **2** (gradient: 2-8 min 10-34%) and product was then neutralized by SCX (see general protocol) to give **Example 58** (18 mg, 39 μmol, 25% yield, 97% purity) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.51-8.50 (m, 1H), 8.31- .30 (m, 1H), 8.18- 8.16 (m, 1H), 7.20- 7.19 (m, 1H), 6.97 – 6.96 (m, 1H), 6.76 (s, 1H), 6.49 – 6.46 (m, 1H), 4.09- 4.07 (m, 2H), 3.88 (s, 3H), 3.78 - 3.75 (m, 1H), 3.64- 3.62 (m, 2H), 3.55 - 3.52 (m, 1H), 2.83 – 2.81 (m, 2H), 2.66-2.63 (m, 4H), 2.31 (s, 3H), 1.79-1.77 (m, 1H), 1.62- 1.59 (m, 1H), 1.56- 1.53 (m, 4H). MS m/z (ESI) $[M+H]^+$= 448.2.

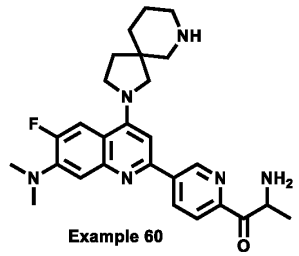
Example 59: 2-amino-1-(4-(5-(6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)piperazin-1-yl)propan-1-one



Example 59

[0642] According to Scheme 6 Step 2: Conditions 1 HCl: Substrate **E.1ad** (0.20 g, 0.27 mmol, 1.0 eq) was added to HCl/dioxane (2.0 M, 2.0 mL, 15 eq) and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated to give a residue. The residue obtained was purified by prep-HPLC **8** (gradient: 0%-29% over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 59** (24 mg, 46 μmol, 17% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 1.31 (d, J = 6.9 Hz, 3H), 1.55 - 1.69 (m, 1H), 1.72 - 1.86 (m, 1H), 2.53 (br d, J = 3.1 Hz, 2H), 2.74 - 2.83 (m, 1H), 2.92 - 2.99 (m, 1H), 3.01 - 3.08 (m, 2H), 3.64 - 3.73 (m, 4H), 3.74 - 3.82 (m, 6H), 3.86 - 3.94 (m, 2H), 4.01 (s, 1H), 4.03 (s, 3H), 6.79 (s, 1H), 6.98 (d, J = 8.9 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 8.02 (d, J = 14 Hz, 1H) 8.20 (dd, J = 8.9, 2.5 Hz, 1H), 8.77 (d, J = 2.2 Hz, 1H). MS m/z (ESI) $[M+H]^+$ = 534.2.

Example 60: 2-amino-1-[5-[4-(2,9-diazaspiro [4.5]decan-2-yl)-7-(dimethylamino)-6-fluoro-2-quinolyl]-2-pyridyl]propan-1-one

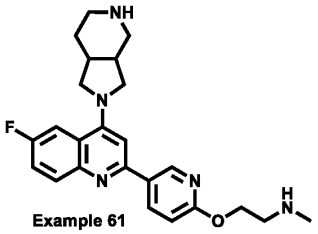


Example 60

[0643] According to Scheme 6 Step 2: Conditions 1 HCl: To a substrate **E.1ae** (50 mg, 74 μmol, 1.0 eq) in dioxane (1.0 mL) was added HCl/dioxane (2.0 M, 4.0 mL) at 25 °C. After stirring at 25 °C for 1 h, the reaction mixture was concentrated under reduced pressure. The residue obtained was purified by prep-HPLC **5** (gradient: 1%-31% over 9 min) to give **Example 60** (15 mg, 30 μmol, 40% yield, 100% purity, HCl) as an orange gum. ^{1}H NMR

(400 MHz, DMSO-d_6) δ (ppm): 9.18 - 9.60 (m, 3H) 8.82 (dd, J = 8.2, 2.2 Hz, 1H) 8.52 (s, 3H) 8.27 (d, J = 8.3 Hz, 1H) 8.19 (d, J = 17 Hz, 1H) 7.77 (d, J = 9.0 Hz, 1) 6.93 (s, 1H) 5.11 - 5.38 (m, 1H) 4.33 (dd, J = 12, 3.2 Hz, 1H) 4.09 - 4.24 (m, 2H) 3.97 (d, J = 12 Hz, 1 H) 3.14 (d, J = 1.8 Hz, 6H) 2.95 - 3.13 (m, 4H) 2.19 - 2.31 (m, 1H) 1.96 - 2.09 (m, 1H) 1.65 - 1.91 (m, 4H) 1.60 (d, J = 7.1 Hz, 3H). MS m/z (ESI) $[M+H]^+$= 477.2.

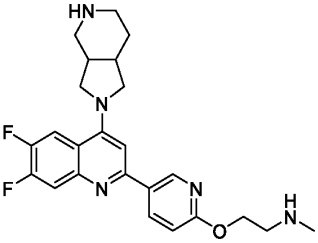
Example 61: 2-((5-(6-fluoro-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)-N-methylethan-1-amine



Example 61

[0644] According to Scheme 6 Step 2: Conditions 1 HCl: A substrate **E.1af** (0.19 g, 0.25 mmol, 1.0 eq) was added into HCl/dioxane (4.0 mL), and then the resulting mixture was stirred at 25 °C for 1 h. The crude material was purified by prep-HPLC **2** (gradient: 1%-10% over 10 min). The eluent was lyophilized directly to give the title compound as formate. Then the formate was neutralized with SCX (see general protocol) to give **Example 61** (30 mg, 71 μmol, 29% yield, 100% purity) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.51 (d, J = 2.3 Hz, 1H), 8.30 (dd, J = 2.4, 9.5 Hz, 1H), 7.99 (dd, J = 2.5, 12 Hz, 1H), 7.85 (dd, J = 6.1, 9.2 Hz, 1H), 7.56 - 7.45 (m, 1H), 6.86 (s, 1H), 6.49 (d, J = 9.5 Hz, 1H), 4.08 (t, J = 6.2 Hz, 2H), 3.94 (t, J = 8.6 Hz, 1H), 3.87-3.79 (m, 1H), 3.67 - 3.61 (m, 1H), 3.58-3.54 (m, 1H), 2.91 - 2.75 (m, 5H), 2.59 - 2.53 (m, 1H), 2.41 - 2.31 (m, 2H), 2.30 (s, 3H), 1.64 - 1.54 (m, 1H), 1.47 - 1.35 (m, 1H). MS m/z (ESI) $[M+H]^+$= 422.2.

Example 62: 2-((5-(6,7-difluoro-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)-N-methylethan-1-amine

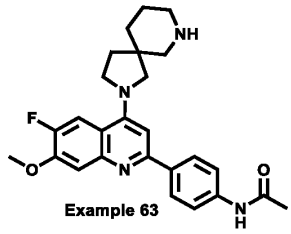


Example 62

[0645] According to Scheme 6 Step 2: To a substrate **E.1ag** (100 mg, 156.32 μmol, 1 *eq*) in dioxane (2 mL) was added HCl/dioxane (2 M, 2 mL) at 25 °C. The mixture was stirred at 25

°C for 12 hours. The reaction mixture was concentrated under reduced pressure. The residue obtained was purified by prep-HPLC **2** (gradient: 1%-10% over 10 min). Then the solid was neutralized with SCX (see general protocol) to give **Example 62** (20 mg, 46 μmol, 29% yield, 100% purity) as yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.52 (d, J = 2.4 Hz, 1H), 8.34 - 8.16 (m, 2H), 7.71 (dd, J = 8.4, 12.2 Hz, 1H), 6.86 (s, 1H), 6.49 (d, J = 9.6 Hz, 1H), 4.07 (t, J = 6.2 Hz, 2H), 3.98 - 3.88 (m, 1H), 3.83 (dd, J = 6.2, 9.6 Hz, 1H), 3.69 - 3.61 (m, 1H), 3.60 - 3.53 (m, 1H), 2.91 - 2.74 (m, 5H), 2.61 - 2.53 (m, 1H), 2.42 - 2.33 (m, 3H), 2.30 (s, 3H), 1.59 (dd, J = 2.6, 11.6 Hz, 1H), 1.48 - 1.32 (m, 1H). MS m/z (ESI) $[M+H]^+$= 440.2.

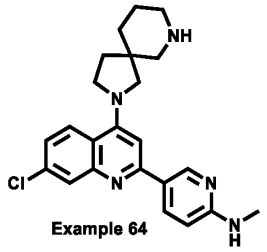
Example 63: N-[4-[4-(2, 9-diazaspiro[4.5]decan-2-yl) -6-fluoro-7-methoxy-2-quinolyl]phenyl]acetamide



Example 63

[0646] According to Scheme 5 Step 2: To a substrate **D.1c** (0.10 g, 0.18 mmol, 1.0 eq) in DCM (1.0 mL) was added 2, 6-dimethylpyridine (0.37 g, 3.4 mmol, 0.40 mL, 19 eq). Then TMSOTf (0.25 g, 1.1 mmol, 0.20 mL, 6.1 eq) was added into the mixture at 0 °C. The resulting solution was stirred at 25 °C for 1 h. The reaction mixture was concentrated to give a residue. The filter liquor was purified by prep-HPLC **2** (gradient: 4%-34% over 10 min), and the product was then neutralized with SCX (see general protocol) to give **Example 63** (11 mg, 25 μmol, 14% yield, 100% purity) off-white solid. ^{1}H NMR (400 MHz, methanol-d_4, 298 K) δ (ppm): 8.01 (d, J = 13.6 Hz, 1H), 7.92 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.6 Hz, 1H), 6.84 (s, 1H), 4.02 (s, 3H), 3.90 - 3.80 (m, 2H), 3.75 - 3.70 (m, 1H), 3.67 - 3.61 (m, 1H), 2.95 - 2.83 (m, 4H), 2.17 (s, 3H), 2.05 (td, J = 6.6, 12.8 Hz, 1H), 1.98 - 1.91 (m, 1H), 1.80 - 1.66 (m, 4H). MS m/z (ESI) $[M+H]^+$= 449.3.

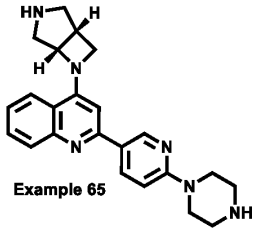
Example 64: 5-[7-chloro-4-(2, 9-diazaspiro[4.5]decan-2-yl) -2-quinolyl]-N-methyl-pyridin-2-amine



Example 64

[0647] According to Scheme 6 Step 2: Conditions 1 HCl: To a solution of **E.1ah** (0.10 g, 0.16 mmol, 1.0 eq) in dioxane (3.0 mL) was added HCl/dioxane (1.0 M, 2.0 mL) at 25 °C. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure. The residue obtained was purified by prep-HPLC **8** (gradient: 5%-35% over 10 min). Then the solid was purified with SCX (see general protocol) to give **Example 64** (25 mg, 58 μmol, 35% yield, 95% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.86 (s, 1H), 8.37 - 8.11 (m, 2H), 7.79 (d, J = 1.6 Hz, 1H), 7.29 (dd, J = 1.8, 9.2 Hz, 1H), 6.95 - 6.77 (m, 2H), 6.54 (d, J = 8.8 Hz, 1H), 3.91 - 3.77 (m, 1H), 3.77 - 3.64 (m, 2H), 3.54 (d, J = 10.0 Hz, 1H), 2.85 (d, J = 4.6 Hz, 3H), 2.75 - 2.53 (m, 4H), 2.03 - 1.90 (m, 1H), 1.82 - 1.71 (m, 1H), 1.67 - 1.43 (m, 4H). MS m/z (ESI) $[M+H]^+$= 408.2.

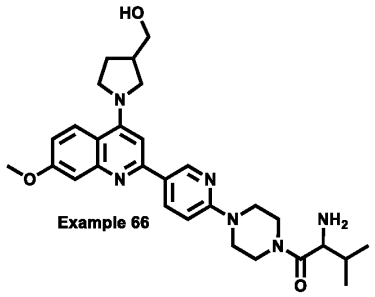
Example 65: 2-(6-piperazin-1-yl-3-pyridyl)-4-[(1R,5S)-3,6-diazabicyclo [3.2.0] heptan-6-yl] quinoline



Example 65

[0648] According to Scheme 6 Step 2: Conditions 2 TFA: To a solution of **E.1ai** (75 mg, 0.13 mmol, 1.0 eq) TFA (101 eq) was added at at 25 °C. The mixture was stirred at 25 °C for 24 h. After work-up the residue obtained was purified by prep-HPLC **5** to give **Example 65** (66 mg, 0.17 mmol, *quant.*) as a yellow powder. MS m/z (ESI) $[M+H]^+$= 387.1.

Example 66: 2-amino-1-(4-(5-(4-(3-(hydroxymethyl) pyrrolidin-1-yl)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-3-methylbutan-1-one

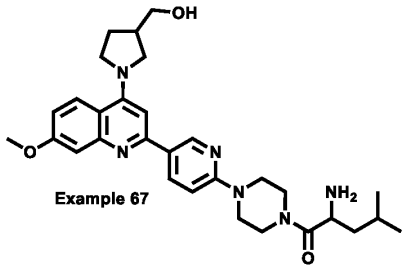


Example 66

[0649] To a solution of **Example 10** (0.15 g, 0.36 mmol, 1.0 eq) in DMF (2.0 mL) was added HATU (0.21 g, 0.54 mmol, 1.5 eq), 2-(tert-butoxycarbonylamino)-3-methyl-butanoic acid (90 mg, 0.41 mmol, 1.2 eq) and DIEA (0.14 g, 1.1 mmol, 0.19 mL, 3.0 eq) at 25 °C. The mixture was stirred at 25 °C for 16 h. After work-up tert-butyl N-[1-[4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carbonyl]-2-methyl-propyl] carbamate (0.23 g, 0.28 mmol, 79% yield, 76% purity) was obtained as yellow gum. MS m/z (ESI) $[M+H]^+$= 619.3

[0650] According to Scheme 3 Step 3: To a solution of tert-butyl N-[1-[4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carbonyl]-2-methyl-propyl] carbamate (0.23 g, 0.37 mmol, 1.0 eq) in dioxane (1.0 mL) was added HCl/dioxane (2 M, 1.0 mL) at 25 °C. The mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure. The residue obtained was purified by prep-HPLC **2** (gradient:4%-34% over 10 min) to give 2-amino-1-[4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazin-1-yl]-3-methyl-butan-1-one (FA salt). Then the salt was basified with SCX (see general protocol) to give **Example 66** (22 mg, 39 μmol, 11% yield, 94% purity) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.94 (d, J = 2.3 Hz, 1H), 8.35 (dd, J = 2.3, 8.9 Hz, 1H), 8.15 (d, J = 9.4 Hz, 1H), 7.22 (d, J = 2.8 Hz, 1H), 6.97 - 6.92 (m, 2H), 6.84 (s, 1H), 4.74 (s, 1H), 3.89 (s, 3H), 3.78 - 3.46 (m, 17H), 2.46 - 2.40 (m, 1H), 2.11 - 2.03 (m, 1H), 1.82 - 1.71 (m, 2H), 0.91 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H). MS m/z (ESI) $[M+H]^+$= 519.3.

Example 67: 2-amino-1-[4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazin-1-yl]-4-methyl-pentan-1-one

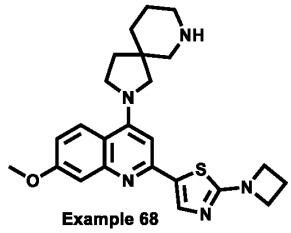


Example 67

[0651] To a solution of **Example 10** (0.15 g, 0.36 mmol, 1.0 eq) in DMF (2.0 mL) was added HATU (0.21 g, 0.54 mmol, 1.5 eq), 2-(tert-butoxycarbonylamino)-4-methyl-pentanoic acid (90 mg, 0.39 mmol, 1.1 eq) and DIEA (0.14 g, 1.1 mmol, 0.19 mL, 3.0 eq) at 25 °C. The mixture was stirred at 25 °C for 4 h. After work-up tert-butyl N-[1-[4-[5-[4-[3-(hydroxymethyl) pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carbonyl]-3-methyl-butyl] carbamate (0.20 g, 0.19 mmol, 52% yield, 59% purity) was obtained as yellow gum. MS m/z (ESI) $[M+H]^+$= 633.4

[0652] According to Scheme 3 Step 3: To a solution of tert-butyl N-[1-[4-[5-[4-[3-(hydroxymethyl)pyrrolidin-1-yl]-7-methoxy-2-quinolyl]-2-pyridyl]piperazine-1-carbonyl]-3-methyl-butyl]carbamate (0.20 g, 0.19 mmol, 1.0 eq) in dioxane (0.50 mL) was added HCl/dioxane (2.0 M, 1.0 mL) at 25 °C. The mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure. The residue obtained was purified by prep-HPLC **2** (gradient: 2%-32% over 10 min) and neutralized with SCX (see general protocol) to give **Example 67** (27 mg, 50 μmol, 27% yield, 100% purity) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.94 (d, J = 2.1 Hz, 1H), 8.36 (dd, J = 2.3, 8.9 Hz, 1H), 8.15 (d, J = 9.4 Hz, 1H), 7.22 (d, J = 2.6 Hz, 1H), 6.95 (td, J = 2.5, 9.3 Hz, 2H), 6.84 (s, 1H), 4.95 - 4.54 (m, 1H), 3.89 (s, 3H), 3.84 - 3.44 (m, 17H), 2.47 - 2.39 (m, 1H), 2.06 (dq, J = 5.8, 11.4 Hz, 1H), 1.85 - 1.70 (m, 2H), 1.37 - 1.23 (m, 2H), 0.90 (dd, J = 6.8, 9.0 Hz, 6H). MS m/z (ESI) $[M+H]^+$= 533.20

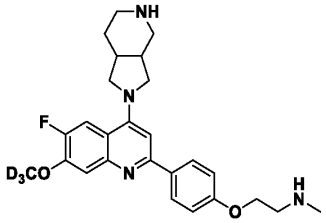
Example 68: 2-(azetidin-1-yl)-5-[4-(2,9-diazaspiro [4.5]decan-2-yl)-7-methoxy-2-quinolyl]thiazole



Example 68

[0653] According to Scheme 5 Step 2: Conditions 2 TFA: To a substrate **D.1d** (0.15 g, 0.28 mmol, 1.0 eq) was added TFA (1.0 mL). The mixture was stirred 1 h at 25 °Cwas added 2, 6-dimethylpyridine (0.37 g, 3.4 mmol, 0.40 mL, 19 eq). TFA (1.0 mL), stirred at rt for 1 h. After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 2%-32% over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 68** (25 mg, 58 μmol, 21% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 1.62 - 1.81 (m, 4H) 1.86 - 1.95 (m, 1H) 2.04 (dt, J = 13, 6.4 Hz, 1H) 2.56 (quin, J = 7.4 Hz, 2H) 2.76 - 2.92 (m, 4H) 3.54 - 3.72 (m, 2H) 3.75 - 3.87 (m, 2H) 3.93 (s, 3H) 4.19 (t, J = 7.4 Hz, 4H) 6.73 (s, 1H) 6.98 (br d, J = 9.3 Hz, 1H) 7.23 (d, J = 1.1 Hz, 1H) 7.81 (s, 1H) 8.17 (d, J = 9.7 Hz, 1H). MS m/z (ESI) $[M+H]^+$ = 436.3.

Example 73: 2-(4-(6-fluoro-7-(methoxy-d3)-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)-N-methylethan-1-amine

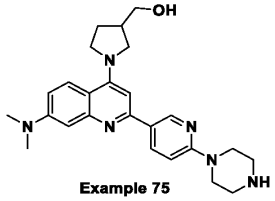


Example 73

[0654] According to Scheme 6 Step 2: Conditions 1 HCl: To a substrate **E.1aj** (350 mg, 535.33 μmol, 1 *eq*) was added to HCl/dioxane (2 M, 5 mL, 18.68 eq). The reaction mixture was stirred at 25°C for 1hour. The reaction mixture was concentrated and the residue was purified by prep-HPLC **1** (gradient:0%-30% over 9 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 73** (60.36 mg, 131.75 μmol, 24.61% yield, 99% purity) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 1.50 - 1.65 (m, 1 H) 1.69 - 1.80 (m, 1

H) 2.43 - 2.51 (m, 5 H) 2.71 (ddd, *J*=12.62, 8.89, 3.42 Hz, 1 H) 2.86 - 2.92 (m, 1 H) 2.95 - 3.02 (m, 4 H) 3.61 - 3.75 (m, 2 H) 3.81 - 3.93 (m, 2 H) 4.18 (t, *J*=5.26 Hz, 2 H) 6.79 (s, 1 H) 7.09 (d, *J*=8.80 Hz, 2 H) 7.43 (d, *J*=8.80 Hz, 1 H) 7.92 (d, *J*=8.68 Hz, 2 H) 8.00 (d, *J*=13.82 Hz, 1 H). MS m/z (ESI) $[M+H]^+$= 454.3.

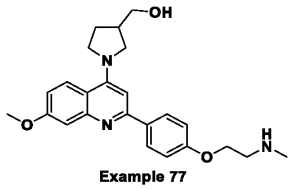
Example 75: (1-(7-(dimethylamino)-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol



Example 75

[0655] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of **C.2v** (60 mg, 112.64 µmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M) at 25°C. After stirring at 25 °C for 2 hours, the reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:10%-40% over 9 min) to give **Example 75** (32.17 mg, 68.59 µmol, 60.89% yield, 100% purity, HCl) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.01 (s, 1 H) 9.61 (s, 2 H) 8.87 (d, *J*=2.50 Hz, 1 H) 8.33 (dd, *J*=9.08, 2.56 Hz, 1 H) 8.26 (d, *J*=9.76 Hz, 1 H) 7.32 (d, *J*=2.63 Hz, 1 H) 7.14 (d, *J*=9.14 Hz, 1 H) 7.05 (dd, *J*=9.68, 2.68 Hz, 1 H) 6.62 (d, *J*=1.14 Hz, 1 H) 3.86 - 4.09 (m, 7 H) 3.70 - 3.85 (m, 1 H) 3.43 - 3.58 (m, 2 H) 3.19 (s, 4 H) 3.10 (s, 6 H) 2.41 - 2.49 (m, 1 H) 2.05 - 2.16 (m, 1 H) 1.83-1.80 (m, 1 H). MS m/z (ESI)433.1 $[M+H]^+$. $[M+H]^+$= 436.3.

Example 77: (1-(7-methoxy-2-(6-(2-(methylamino)ethoxy)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol

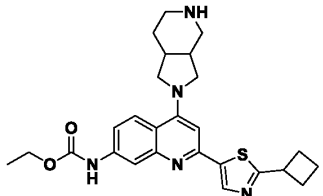


Example 77

[0656] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of **C.2w** (270 mg, 531.89 µmol, 1 *eq*) in EtOAc (0.5 mL) was added HCl/EtOAc (2 M, 3 mL, 11.28 *eq*) at 20 °C. The reaction mixture was stirred at 20 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC **1** (gradient: 2-9 min 11-41%). The salt was basified by strong cation exchange resin (CNWBOND SCX, SPE Cartridge). 1/ Wash resin with deionized water (10.0 mL). 2/ Wash resin with the salt in MeOH (2.0 mL) (target was adsorbed to the resin. 3/ Wash resin with

deionized water (5.0 mL) until the pH of the solution is neutral. 4/ Wash resin with $NH_3.H_2O$/MeOH=1/20 (10.0 mL), target was cleaved from the resin. 5/ Concentration and lyophilization give **Example 77** (22.25 mg, 51.38 μmol, 9.66% yield, 94.1% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.25-8.23 (m, 1H), 7.90-7.88 (m, 2H), 7.32-7.31 (m, 1H), 7.11-7.09 (m, 2H), 7.02-7.00 (m, 1H), 6.72 (s, 1H), 4.20-4.19 (m, 2H), 3.95 (s, 3H), 3.90 - 3.78 (m, 3H), 3.74 - 3.61 (m, 3H), 3.04-3.03 (m, 2H), 2.57 - 2.54 (m, 1H), 2.52 (s, 3H), 2.19-2.17 (m, 1H), 1.91 - 1.87 (m, 1H). MS m/z (ESI) $[M+H]^+$= 408.2.

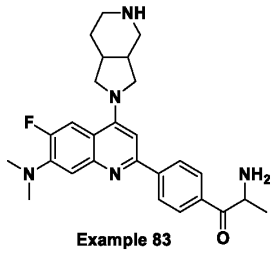
Example 79: ethyl (2-(2-(azetidin-1-yl)thiazol-5-yl)-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-7-yl)carbamate



Example 79

[0657] According to Scheme 5 Step 2: Conditions 3 TMSOTf: To a solution of **D.1f** (50 mg, 86.40 μmol, 1 eq) in DCM (1 mL) was added TMSOTf (61.50 mg, 276.71 μmol, 50 μL, 3.20 eq) and 2,6-dimethylpyridine (92.00 mg, 858.59 μmol, 100 μL, 9.94 eq) at 0°C. After stirring at 0°C for 0.5 hours, the reaction mixture was concentrated under reduced pressure to give a residue at 25°C. The residue was purified by prep-HPLC **2** (gradient:5%-35% over 10 min) to give **Example 79** (4.85 mg, 10.13 μmol, 11.73% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.94 (s, 1 H), 7.91 (d, *J*=14.14 Hz, 1 H), 7.23 (d, J=9.02 Hz, 1 H), 6.82 (s, 1 H), 4.75 (t, *J*=5.26 Hz, 1 H), 4.06 (t, *J*=7.50 Hz, 4 H), 3.95 (s, 3 H), 3.61 - 3.78 (m, 3 H), 3.44 - 3.59 (m, 3 H), 2.36 - 2.48 (m, 3 H), 2.05 (dq, *J*=11.94, 6.14 Hz, 1 H), 1.65 - 1.85 (m, 1 H). MS m/z (ESI) $[M+H]^+$= 479.1.

Example 83: 2-amino-1-(4-(7-(dimethylamino)-6-fluoro-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)propan-1-one

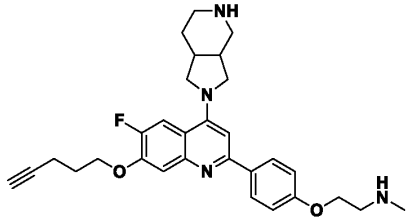


Example 83

[0658] According to Scheme 6 Step 2: Conditions 1 HCl: To a solution of **E.1aq** (0.1 g, 151.10 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 4 mL) at 25°C. After

stirring at 25°C for 1 hour, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC **1** (gradient:0%-30% over 9 min) to give **Example 83** (62.72 mg, 135.88 μmol, 89.93% yield, 100% purity) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 14.06 (s, 1 H) 9.42 - 9.89 (m, 2 H) 8.71 (d, J=3.76 Hz, 3 H) 8.22 - 8.41 (m, 4 H) 8.16 (d, J=16.76 Hz, 1 H) 7.88 (d, J=9.02 Hz, 1 H) 6.83 (s, 1 H) 5.21 - 5.33 (m, 1 H) 3.64 - 4.76 (m, 4 H) 3.20 (s, 2 H) 3.09 (s, 6 H) 2.96 - 3.06 (m, 1 H) 2.79 (d, J=5.76 Hz, 1 H) 2.58 - 2.70 (m, 1 H) 1.96 (s, 1 H) 1.79 (br d, J=11.64 Hz, 1 H) 1.48 (d, J=7.14 Hz, 3 H). MS m/z (ESI) $[M+H]^+$= 462-2.

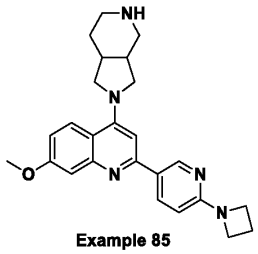
Example 84: 2-(4-(6-fluoro-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-7-(pent-4-yn-1-yloxy)quinolin-2-yl)phenoxy)-N-methylethan-1-amine



Example 84

[0659] According to Scheme 6 Step 2: Conditions 1 HCl: To a solution of **E.1ar** (120 mg, 170.73 μmol, 1 eq) in dioxane (2 mL) was added HCl/dioxane (4 M, 1 mL, 23.43 eq), then the resulting mixture was stirred at 25°C for 2 hours. The reaction mixture was filtered and evaporated under reduced pressure to give the crude product. The crude product was purified by prep-HPLC **2** (gradient:0%-30% over 10 min]; gradient:36%-56% B over min) to give **Example 84** (36.39 mg, 71.46 μmol, 41.85% yield, 98.7% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.32 (s, 2H), 8.06 - 7.97 (m, 3H), 7.44 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 6.80 (s, 1H), 4.30 - 4.21 (m, 5H), 3.84 - 3.70 (m, 4H), 3.33 (t, J = 4.6 Hz, 2H), 3.26 - 3.16 (m, 2H), 3.11 - 2.98 (m, 2H), 2.73 - 2.65 (m, 2H), 2.64 (s, 3H), 2.59 - 2.54 (m, 1H), 2.36 (dt, J = 2.4, 6.9 Hz, 2H), 2.03 - 1.95 (m, 2H), 1.91 (d, J = 8.1 Hz, 1H), 1.78 - 1.64 (m, 1H).MS m/z (ESI) $[M+H]^+$= 503.2.

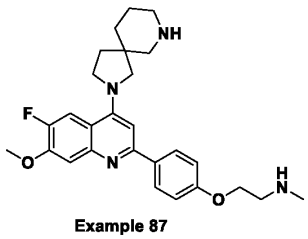
Example 85: 2-(6-(azetidin-1-yl)pyridin-3-yl)-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinoline



Example 85

[0660] According to Scheme 5 Step 2: Conditions 3 TMSOTf: To a solution of **D.1g** (100 mg, 193.93 μmol, 1 eq) in DCM (1 mL) was added 2, 6-dimethylpyridine (368.00 mg, 3.43 mmol, 0.4 mL, 17.71 eq) and TMSOTf (246.00 mg, 1.11 mmol, 0.2 mL, 5.71 eq). The reaction mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was concentrated to give a residue. The residue was purified by prep-HPLC **2** (gradient:1%-25% over 10 min). The salt was basified by strong cation exchange resin (CNWBOND SCX, SPE Cartridge). 1/ Wash resin with deionized water 10.0 mL. 2/ Wash resin with the salt in MeOH (2.0 mL) (target was adsorbed to the resin. 3/ Wash resin with deionized water (10.0 mL) until the pH of the solution is neutral. 4/ Wash resin with $NH_3.H_2O$/MeOH=1/20 (21 mL), target was cleaved from the resin. 5/ Concentration and lyophilization give **Example 85** (40.36 mg, 97.13 μmol, 50.08% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.87 (d, J = 2.3 Hz, 1H), 8.29 (dd, J = 2.3, 8.7 Hz, 1H), 8.18 (d, J = 9.4 Hz, 1H), 7.20 (d, J = 2.6 Hz, 1H), 6.92 (dd, J = 2.8, 9.4 Hz, 1H), 6.79 (s, 1H), 6.43 (d, J = 8.6 Hz, 1H), 4.01 (t, J = 7.4 Hz, 4H), 3.93 - 3.89 (m, 1H), 3.88 (s, 3H), 3.81 (br dd, J = 5.9, 9.4 Hz, 1H), 3.66 - 3.59 (m, 1H), 3.55 (br dd, J = 3.3, 9.5 Hz, 1H), 2.89 - 2.74 (m, 3H), 2.58 - 2.53 (m, 1H), 2.39 - 2.30 (m, 4H), 1.63 - 1.53 (m, 1H), 1.46 - 1.32 (m, 1H). MS m/z (ESI) $[M+H]^+$= 416.2.

Example 87: 2-(4-(6-fluoro-7-methoxy-4-(2,7-diazaspiro[4.5]decan-2-yl)quinolin-2-yl)phenoxy)-N-methylethan-1-amine

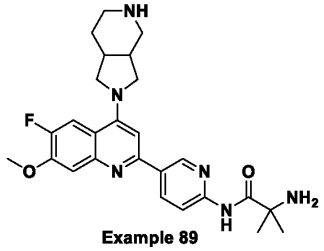


Example 87

[0661] According to Scheme 6 Step 2: Conditions 1 HCl: **E.1as** (222 mg, 333.93 μmol, 1 eq) was added to HCl/dioxane (2 M, 5 mL, 29.95 eq), the reaction mixture was stirred at 25 °C for 2 hours. LCMS showed desired MS was detected. The reaction mixture was concentrated

to give a residue. The residue was purified by prep-HPLC **1** (gradient:0%-30% over 9 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents to give **Example 87** (58.46 mg, 116.68 μmol, 34.94% yield, 100% purity, HCl) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.58 - 1.85 (m, 4 H) 1.89 - 2.03 (m, 1 H) 2.16 - 2.29 (m, 1 H) 2.63 (t, *J*=5.38 Hz, 3 H) 2.89 - 3.20 (m, 4 H) 3.31 - 3.42 (m, 2 H) 4.01 (s, 3 H) 4.05 - 4.20 (m, 2 H) 4.27 (br d, *J*=11.88 Hz, 1 H) 4.44 (br t, *J*=5.00 Hz, 2 H) 6.83 (s, 1 H) 7.24 (d, *J*=8.88 Hz, 2 H) 8.20 (d, *J*=8.88 Hz, 2 H) 8.26 - 8.37 (m, 2 H) 9.34 - 9.67 (m, 4 H) 13.97 (s, 1 H). MS m/z (ESI) $[M+H]^+$= 465.3.

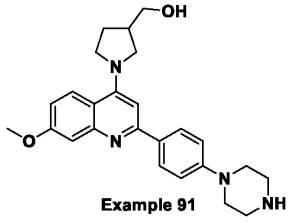
Example 89: 2-amino-N-(5-(6-fluoro-7-methoxy-4-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)-2-methylpropanamide



Example 89

[0662] According to Scheme 6 Step 2: Conditions 1 HCl: To a screw-cap vial equipped with a magnetic stir bar was added **E.1at** (30 mg, 44.2 μmol, 1 eq) and HCl/dioxane (2 M, 1 mL) sequentially. The vial was sealed with a teflon-lined septum. Then the mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated *in vacuum* to give a residue. The residue was purified by prep-HPLC **1** (gradient:0%-27% over 9 min), followed by lyophilization to **Example 89** (13 mg, 27.1 μmol, 61.4% yield, 99.9% purity, 3 HCl salt) as yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.99 (d, *J* = 1.8 Hz, 1H), 8.48 - 8.43 (m, 1H), 8.43 - 8.38 (m, 1H), 8.33 (d, *J* = 13.1 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 6.97 (s, 1H), 4.39 - 4.12 (m, 4H), 4.12 (s, 3H), 3.47 - 3.36 (m, 2H), 3.30 - 3.20 (m, 2H), 2.97 - 2.89 (m, 1H), 2.87 - 2.79 (m, 1H), 2.19 - 2.06 (m, 1H), 2.02 - 1.92 (m, 1H), 1.76 (s, 6H). MS (ESI) m/z=479.3 $[M+H]^+$. $[M+H]^+$= 479.3.

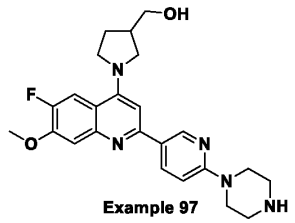
Example 91: (1-(7-methoxy-2-(4-(piperazin-1-yl)phenyl)quinolin-4-yl)pyrrolidin-3-yl)methanol



Example 91

[0663] According to Scheme 3 Step 3: Conditions 1 HCl: **C.2x** (280 mg, 539.87 µmol, 1 eq) was added to HCl/dioxane (5 mL), then the resulting mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated to give crude material which was purified by Prep-HPLC **2** (gradient:4%-34%over 10 min). The eluent was lyophilized directly to give **Example 91** (218 mg, 467.91 µmol, 86.67% yield, 99.71% purity, Formate) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.24 (s, 1H), 8.19 (d, J = 9.4 Hz, 1H), 8.07 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 2.6 Hz, 1H), 7.08 (d, J = 9.0 Hz, 2H), 6.98 (dd, J = 2.7, 9.3 Hz, 1H), 6.82 (s, 1H), 3.83 - 3.71 (m, 3H), 3.62-3.57 (m, 1H), 3.56 - 3.46 (m, 2H), 3.46 - 3.36 (m, 4H), 3.22-3.09 (m, 4H), 2.48 - 2.39 (m, 1H), 2.12-2.02 (m, 1H), 1.83-1.72 (m, 1H). MS m/z (ESI) $[M+H]^+$= 419.2.

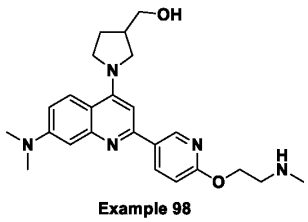
Example 97: (1-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol



Example 97

[0664] According to Scheme 3 Step 3: Conditions 1 HCl: A solution of **C.2y** (250 mg, 465.01 µmol, 1 eq) in HCl/dioxane (5 mL) was stirred at 25°C for 1 hour. The crude material was concentrated to give a crude material which was purified by Prep-HPLC **1** (gradient:6%-36% B over 9 min). The eluent was lyophilized directly to give the title compound as HCl salt. Then the HCl salt was basified with SCX cation exchange resin to **Example 97** (66 mg, 150.10 µmol, 32.28% yield, 99.5% purity) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (d, J = 2.0 Hz, 1H), 8.30 (dd, J = 2.3, 9.0 Hz, 1H), 7.95 (d, J = 14.2 Hz, 1H), 7.39 (d, J = 8.9 Hz, 1H), 6.92 - 6.82 (m, 2H), 4.74 (br t, J = 5.1 Hz, 1H), 3.98 (s, 3H), 3.77 - 3.65 (m, 3H), 3.60 - 3.43 (m, 7H), 2.85 - 2.75 (m, 4H), 2.46 - 2.39 (m, 1H), 2.11 - 2.01 (m, 1H), 1.83 - 1.71 (m, 1H). MS m/z (ESI) $[M+H]^+$= 438.2.

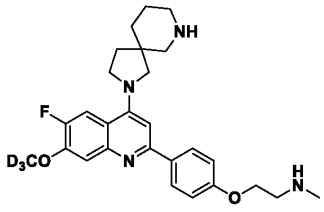
Example 98: [1-[7-(dimethylamino)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol



Example 98

[0665] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of **C.2z** (130 mg, 249.21 µmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 2 mL) and at 25°C .The mixture was stirred at 25°C for 2 hours, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC **2** (gradient:2%-32% over 10 min) to give **Example 98** (82.43 mg, 195.55 µmol, 78.47% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.90 (d, *J*=2.26 Hz, 1 H) 8.47 (dd, *J*=8.64, 2.50 Hz, 1 H) 8.26 (s, 2 H) 8.12 (d, *J*=9.52 Hz, 1 H) 6.89 - 7.02 (m, 3 H) 6.72 (s, 1 H) 4.54 (t, *J*=5.28 Hz, 2 H) 3.71 - 3.81 (m, 3 H) 3.43 - 3.61 (m, 3 H) 3.26 (t, *J*=5.28 Hz, 2 H) 3.04 (s, 6 H) 2.57 (s, 3 H) 2.37 - 2.48 (m, 1 H) 2.09 - 2.07 (m, 1 H) 1.79 - 1.77 (m, 1 H). MS m/z (ESI) $[M+H]^+$= 422.2.

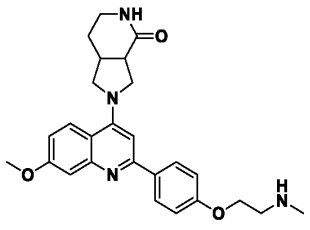
Example 101: 2-[4-[4-(2,9-diazaspiro[4.5]decan-2-yl)-6-fluoro-7-(trideuteriomethoxy)-2-quinolyl]phenoxy]-N-methyl-ethanamine



Example 101

[0666] According to Scheme 6 Step 2: Conditions 1 HCl: To a solution of **E.1au** (200 mg, 299.48 µmol, 1 eq) in dioxane (0.5 mL) was added HCl/dioxane (2 M, 2 mL, 13.36 eq) at 25°C. The mixture was stirred at 25°C for 2 hours, concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:1%-30% B over 9 min) to give **Example 101** (129.14 mg, 256.20 µmol, 85.55% yield, 100% purity, HCl) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.30 (d, *J* = 13.2 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 6.88 (s, 1H), 4.46 - 4.41 (m, 2H), 4.27 - 4.14 (m, 3H), 4.03 (d, *J* = 11.2 Hz, 1H), 3.53 (t, *J* = 4.8 Hz, 2H), 3.36 - 3.31 (m, 3H), 3.27 - 3.16 (m, 2H), 2.83 (s, 3H), 2.30 - 2.12 (m, 2H), 2.00 - 1.79 (m, 4H). MS m/z (ESI) $[M+H]^+$= 468.2.

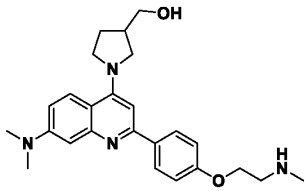
Example 110: (cis)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one



Example 110

[0667] According to Scheme 6 Step 2: Conditions 1 HCl: To a solution of **E.1av** (200 mg, 365.86 μmol, 1 eq) in dioxane (0.5 mL) was added HCl/dioxane (2 M, 2 mL) at 25°C. The mixture was stirred at 25°C for 2 hours. The mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:5%-35% over 0 min). The salt was basified by strong cation exchange resin (CNWBOND SCX, SPE Cartridge). 1/ Wash resin with deionized water 20.0 mL. 2/ Wash resin with the salt in MeOH (4.0 mL) (target was adsorbed to the resin. 3/ Wash resin with deionized water (20.0 mL) until the pH of the solution is neutral. 4/ Wash resin with $NH_3.H_2O$/MeOH=1/10 (21 mL), target was cleaved from the resin. 5/ Concentration and lyophilization give **Example 110** (62.55 mg, 135.31 μmol, 36.99% yield, 96.6% purity) as a off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.19 - 8.12 (m, 3H), 7.74 (s, 1H), 7.26 (d, J = 2.6 Hz, 1H), 7.06 (d, J = 8.8 Hz, 2H), 6.98 (dd, J = 2.8, 9.2 Hz, 1H), 6.93 (s, 1H), 4.16 (t, J = 5.4 Hz, 2H), 3.98 - 3.93 (m, 1H), 3.91 - 3.85 (m, 5H), 3.55 (dd, J = 5.2, 10.2 Hz, 1H), 3.31 - 3.22 (m, 2H), 3.04 - 2.98 (m, 3H), 2.81 - 2.72 (m, 1H), 2.45 (s, 3H), 1.94 - 1.85 (m, 1H), 1.73 - 1.61 (m, 1H). MS m/z (ESI) $[M+H]^+$= 447.3.

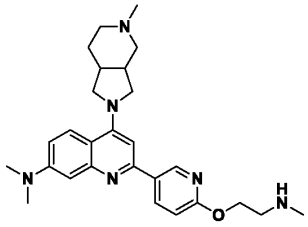
Example 113: [1-[7-(dimethylamino)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol



Example 113

[0668] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[7-(dimethylamino)-4-[3-(hydroxymethyl)pyrrolidin-1-yl]-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (300 mg, 576.19 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 10 mL) at 25°C. After stirring at 25°C for 1 hour, the reaction mixture was concentrated under reduced pressure and residue was purified by prep-HPLC **1** (gradient:8%-38% over 10 min) basified by SCX cation exchange resin to give **Example 113** (41 mg, 97.49 μmol, 16.92% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.01 - 8.18 (m, 3 H) 6.94 - 7.10 (m, 3 H) 6.91 (d, J=2.57 Hz, 1 H) 6.71 (s, 1 H) 4.47 (s, 1 H) 4.25 (2, 1 H) 4.08 (t, J=5.56 Hz, 2 H) 3.67 - 3.76 (m, 3 H) 3.44 - 3.57 (m, 3 H) 3.02 (s, 6 H) 2.83 - 2.95 (m, 2 H) 2.41 - 2.48 (m, 1 H) 2.36 (s, 3 H) 2.06 (dq, J=11.56, 5.74 Hz, 1 H) 1.69 - 1.83 (m, 1 H). MS m/z (ESI)421.2 $[M+H]^+$. $[M+H]^+$= 421.2.

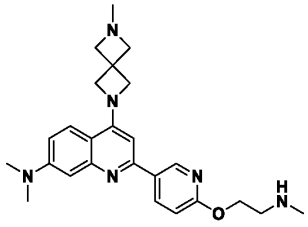
Example 120: (cis)-N,N-dimethyl-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]quinolin-7-amine



Example 120

[0669] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of **C.2aa** (200 mg, 356.68 µmol, 1 eq) in dioxane (0.5 mL) was added HCl/dioxane (2 M, 1.86 mL) at 25°C. The mixture was stirred at 25°C for 2 hours. The mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:1%-31% over 10 min) to give product. The product was purified by prep-TLC (SiO_2, DCM: MeOH= 8:1) to give **Example 120** (33.03 mg, 71.71 µmol, 20.10% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.67 (d, J = 2.4 Hz, 1H), 8.24 - 8.14 (m, 2H), 7.05 - 7.00 (m, 2H), 6.94 (d, J = 8.6 Hz, 1H), 6.56 (s, 1H), 4.47 (t, J = 5.3 Hz, 2H), 3.87 - 3.79 (m, 3H), 3.71 (dd, J = 5.6, 9.8 Hz, 1H), 3.08 (s, 7H), 2.99 (t, J = 5.4 Hz, 2H), 2.56 (s, 4H), 2.47 (s, 3H), 2.42 - 2.33 (m, 2H), 2.29 (s, 3H), 1.85 (dd, J = 4.2, 7.8 Hz, 1H), 1.73- 1.65 (m, 1H). MS m/z (ESI) $[M+H]^+$= 461.3.

Example 125: N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)quinolin-7-amine

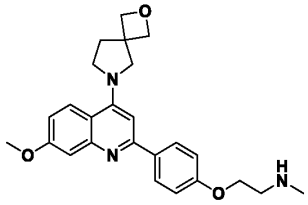


Example 125

[0670] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of **C.2ab** (150 mg, 281.60 µmol, 1 eq) in DCM (2 mL) was added TFA (614.00 mg, 5.38 mmol, 0.4 mL) at 25 °C .The mixture was stirred at 25 °C for 2 hours. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC **3** (gradient:4%-34% over 12 min) basified by SCX cation exchange resin to give **Example 125** (63.62 mg, 147.08 µmol, 52.23% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.80 (d, J = 2.2 Hz, 1H), 8.37 (dd, J = 2.4, 8.6 Hz, 1H), 7.75 (d, J = 9.4 Hz, 1H),

6.99 (dd, J = 2.4, 9.3 Hz, 1H), 6.92 - 6.87 (m, 2H), 6.41 (s, 1H), 4.39 - 4.32 (m, 6H), 3.32 (s, 4H), 2.99 (s, 6H), 2.85 (t, J = 5.5 Hz, 2H), 2.31 (s, 3H), 2.18 (s, 3H). MS m/z (ESI) $[M+H]^+$= 433.4.

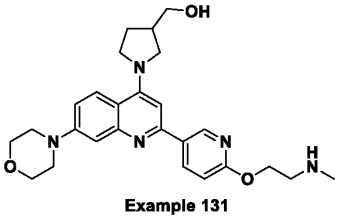
Example 126: 2-[4-[7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl) -2-quinolyl]phenoxy]-N-methyl-ethanamine



Example 126

[0671] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of **C.2ac** (240 mg, 461.87 µmol, 1 eq) in DCM (2.5 mL) was added TFA (767.50 mg, 6.73 mmol, 0.5 mL, 14.57 eq) at 20°C. The reaction mixture was stirred at 20°C for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (gradient: 3-12 min 9-39% flow 25 mL/min) basified by SCX cation exchange resin to give **Example 126** (91.97 mg, 204.26 µmol, 44.22% yield, 93.17% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.15 - 8.13 (m, 3H), 7.26-7.25 (m, 1H), 7.05-7.03 (m, 2H), 6.98-6.97 (m, 1H), 6.88 (s, 1H), 4.65-4.64 (m, 2H), 4.56-4.55 (m, 2H), 4.09-4.08 (m, 2H), 3.96 (s, 2H), 3.90 (s, 3H), 3.72-3.71 (m, 2H), 2.87-2.86 (m, 2H), 2.37 (s, 3H), 2.29-2.27 (m, 2H). MS m/z (ESI) $[M+H]^+$= 420.3.

Example 131: [1-[2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-7-morpholino-4-quinolyl]pyrrolidin-3-yl]methanol

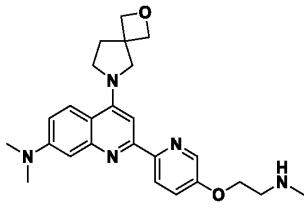


Example 131

[0672] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of **C.2ad** (50 mg, 88.70 µmol, 1 eq) in MeOH (1 mL) was added HCl/MeOH (2 M, 1 mL) at 25°C. The mixture was stirred at 25°C for 2 hours. The reaction mixture was added K_2CO_3 to adjust at pH>7. Then the mixture was diluted with water (20 mL) and extracted with ethyl acetate (25 mL, 3 times). The combined organic layers were washed with brine (35 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure and the residue was purified by prep-TLC

(SiO_2, Dichloromethane: Methanol=5:1) to give **Example 131** (12.85 mg, 27.72 μmol, 31.25% yield, 100% purity). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (d, J = 2.2 Hz, 1H), 8.51 - 8.40 (m, 1H), 8.13 (d, J = 9.3 Hz, 1H), 7.16 (dd, J = 2.6, 9.4 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 6.80 (s, 1H), 4.81 - 4.69 (m, 1H), 4.38 (t, J = 5.7 Hz, 2H), 3.81 - 3.70 (m, 7H), 3.57 (dd, J = 7.2, 9.6 Hz, 1H), 3.53 - 3.45 (m, 2H), 3.28 - 3.24 (m, 4H), 2.90 (t, J = 5.7 Hz, 2H), 2.46 - 2.40 (m, 1H), 2.37 (s, 3H), 2.11 - 2.02 (m, 1H), 1.83 - 1.72 (m, 1H). MS m/z (ESI)464.3 $[M+H]^+$. $[M+H]^+$= 464.3.

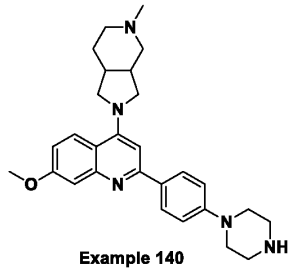
Example 132: N,N-dimethyl-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine



Example 132

[0673] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of tert-butyl N-[2-[[6-[7-(dimethylamino)-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-3-pyridyl]oxy]ethyl]-N-methyl-carbamate (450 mg, 843.23 μmol, 1 eq) in DCM (4 mL) was added TFA (6.14 g, 53.85 mmol, 4 mL, 63.86 eq) ,The reaction solution was stirred at 25°C for 1 hour. The reaction solution was concentrated and the residue was purified by prep-HPLC **2** (gradient:5%-35% over 10 min) basified by SCX cation exchange resin to give **Example 132** (130 mg, 287.86 μmol, 34.14% yield, 96% purity) as an off-white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.43 (d, J = 2.8 Hz, 1H), 8.25 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 10.1 Hz, 1H), 7.57 (dd, J = 2.9, 8.8 Hz, 1H), 7.13 - 7.00 (m, 3H), 4.79 - 4.74 (m, 2H), 4.73 - 4.65 (m, 2H), 4.26 (t, J = 5.2 Hz, 2H), 4.10 (s, 2H), 3.88 (t, J = 6.8 Hz, 2H), 3.12 (s, 6H), 3.03 (t, J = 5.1 Hz, 2H), 2.49 (s, 3H), 2.38 (t, J = 6.7 Hz, 2H). MS m/z (ESI) $[M+H]^+$= 434.3.

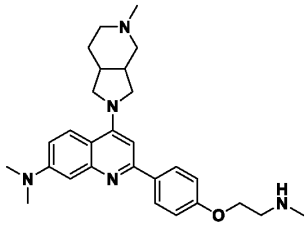
Example 140: (cis)-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(4-piperazin-1-ylphenyl)quinoline



Example 140

[0674] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl 4-(4-(7-methoxy-4-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)piperazine-1-carboxylate (700 mg, 1.26 mmol, 1 eq) in EtOAc (1 mL) was added HCl/EtOAc (2 M, 10 mL, 15.93 eq) at 20°C. The reaction mixture was stirred at 20°C for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient: 2-10 min 1-25%; flow 25 ml/min) basified by SCX cation exchange resin to give **Example 140** (197.65 mg, 431.92 μmol, 34.41% yield, 100% purity) was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.15 (d, J = 9.4 Hz, 1H), 8.06 (d, J = 8.9 Hz, 2H), 7.22-7.21 (m, 1H), 7.01 (d, J = 8.9 Hz, 2H), 6.93 (dd, J = 2.8, 9.4 Hz, 1H), 6.80 (s, 1H), 3.89 (s, 3H), 3.83-3.82 (m, 2H), 3.70 - 3.69 (m, 1H), 3.58-3.86 (m, 1H), 3.16 - 3.14 (m, 4H), 2.88 - 2.85 (m, 4H), 2.47 (s, 3H), 2.32-2.30 (m, 2H), 2.18 (s, 3H), 2.16 - 2.14 (m, 1H), 1.74 - 1.72 (m, 1H), 1.57 - 1.55 (m, 1H). MS m/z (ESI) $[M+H]^+$= 458.3.

Example 141: (cis)-N,N-dimethyl-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[4-[2-(methylamino)ethoxy]phenyl]quinolin-7-amine

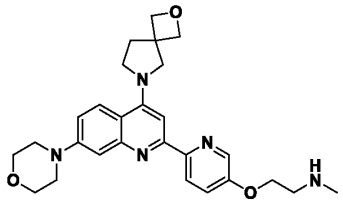


Example 141

[0675] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of tert-butyl (2-(4-(7-(dimethylamino)-4-(cis-5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (300 mg, 535.96 μmol, 1 eq) in DCM (4 mL) was added TFA (61.11 mg, 535.96 μmol, 39.81 μL, 1 eq). The reaction solution was stirred at 25°C for 1 hour. The reaction solution was concentrated and the residue was purified by

prep-HPLC **2** (gradient:0%-30% over 10 min) basified by SCX cation exchange resin to give **Example 141** (55 mg, 119.66 μmol, 22.33% yield, 100% purity) as off-white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.23 (dd, J = 2.2, 9.6 Hz, 1H), 7.87 (br d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.09 - 7.03 (m, 1H), 7.01 (br s, 1H), 6.60 (br d, J = 3.4 Hz, 1H), 4.19 (t, J = 5.2 Hz, 2H), 3.92 (br s, 3H), 3.79 (br d, J = 9.9 Hz, 1H), 3.13 (s, 6H), 3.01 (t, J = 5.1 Hz, 2H), 2.66 - 2.51 (m, 4H), 2.49 (s, 3H), 2.47 - 2.35 (m, 2H), 2.32 (s, 3H), 1.92 - 1.83 (m, 1H), 1.76 - 1.66 (m, 1H). MS m/z (ESI) $[M+H]^+$= 460.3.

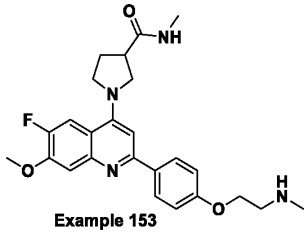
Example 142: N-methyl-2-[[6-[7-morpholino-4-(2-oxa-7- azaspiro[3.4]octan-7-yl)-2-quinolyl]-3-pyridyl]oxy]ethanamine



Example 142

[0676] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of **C.2ag** (90.0 mg, 0.100 mmol, 1 eq) in dichloromethane (5.00 mL) was added TFA (1.54 g, 13.5 mmol, 1.00 mL) at 20°C. The mixture was stirred at 20°C for 12 hours and the residue was purified by prep-HPLC **3** (gradient:12%-42% over 12 min) basified by SCX cation exchange resin to give **Example 142** (20.0 mg, 0.0409 mmol, 40.8% yield, 97.2% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.48 (d, J = 8.88 Hz, 1 H) 8.38 (d, J = 2.88 Hz, 1 H) 8.09 (d, J = 9.38 Hz, 1 H) 7.53 (dd, J = 8.82, 2.94 Hz, 1 H), 7.44 (s, 1 H), 7.24 - 7.14 (m, 2 H), 4.65 (d, J = 6.12 Hz, 2 H), 4.54 (d, J = 6.00 Hz, 2 H), 4.17 (t, J = 5.50 Hz, 2 H), 3.93 (s, 2 H), 3.84 - 3.76 (m, 4 H), 3.69 (s, 2 H), 3.30 - 3.24 (m, 4 H), 2.90 (t, J = 5.44 Hz, 2 H), 2.37 (s, 3 H), 2.29 (t, J = 6.64 Hz, 2 H). MS m/z (ESI) $[M+H]^+$= 476.3.

Example 153: 1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide

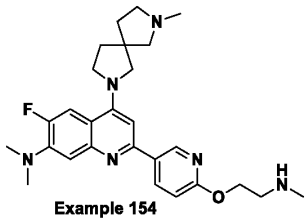


Example 153

[0677] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-[3-(methylcarbamoyl)pyrrolidin-1-yl]-2-quinolyl]phenoxy]ethyl]-N-

methyl-carbamate (250 mg, 452.38 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 2 mL) at 25°C .The mixture was stirred at 25°C for 4hours. The reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:2%-32% over 9 min) basified by SCX cation exchange resin to give **Example 153** (77.49 mg, 170.04 μmol, 37.59% yield, 99.3% purity). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.13 (d, J = 8.7 Hz, 2H), 8.02 (d, J = 4.6 Hz, 1H), 7.92 (d, J = 13.9 Hz, 1H), 7.43 (d, J = 8.9 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 6.91 (s, 1H), 4.17 - 4.07 (m, 2H), 3.98 (s, 3H), 3.83 - 3.75 (m, 3H), 3.71 - 3.66 (m, 1H), 3.07 (q, J = 7.7 Hz, 1H), 2.93 - 2.86 (m, 2H), 2.63 (d, J = 4.5 Hz, 3H), 2.37 (s, 3H), 2.23 - 2.07 (m, 2H). MS m/z (ESI) $[M+H]^+$= 453.2.

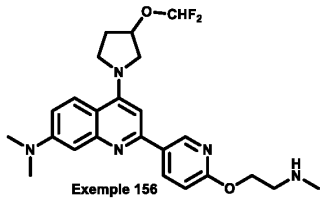
Example 154: 6-fluoro-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinolin-7-amine



Example 154

[0678] According to Scheme 3 Step 3: Conditions 1 HCl: A mixture of tert-butyl N-[2-[[5-[7-(dimethylamino)-6-fluoro-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (240 mg, 348.36 μmol, 1 eq) in HCl/MeOH (3 mL, 2M) was stirred at 20°C for 1hour. The mixture was concentrated to give a residue which was purified by prep-HPLC **1** (gradient: 1%-31% over 9 min) basified by SCX cation exchange resin to give **Example 154** (82.78 mg, 172.96 μmol, 49.65% yield, 100% purity) as yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (d, J = 2.3 Hz, 1H), 8.46 (dd, J = 2.4, 8.6 Hz, 1H), 7.85 (d, J = 16.3 Hz, 1H), 7.19 (d, J = 9.5 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.84 (s, 1H), 4.36 (t, J = 5.7 Hz, 2H), 3.74 (br t, J = 6.5 Hz, 2H), 3.70 - 3.59 (m, 2H), 2.94 - 2.84 (m, 8H), 2.62 - 2.53 (m, 2H), 2.48 - 2.44 (m, 1H), 2.40 (br d, J = 9.0 Hz, 1H), 2.35 (s, 3H), 2.23 (s, 3H), 2.05 - 1.74 (m, 4H). MS m/z (ESI) $[M+H]^+$= 479.2.

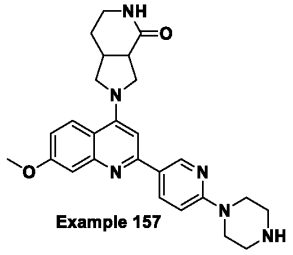
Example 156: 4-[3-(difluoromethoxy)pyrrolidin-1-yl]-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]quinolin-7-amine



Exemple 156

[0679] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of tert-butyl N-[2-[[5-[4-[3-(difluoromethoxy)pyrrolidin-1-yl]-7-(dimethylamino)-2-quinolyl]-2-pyridyl]oxy]ethyl]-N-methyl-carbamate (200 mg, 358.66 μmol, 1 eq) in DCM (2 mL) was added TFA (40.90 mg, 358.66 μmol, 26.64 μL, 1 eq), then the resulting mixture was stirred at 25°C for 3 hours. The reaction mixture was filtered, evaporated under reduced pressure and the crude product was purified by prep-HPLC **2** (gradient:8%-38% over 10 min) basified by SCX cation exchange resin to give **Example 156** (49.85 mg, 105.04 μmol, 29.29% yield, 96.4% purity) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.68 (d, J = 2.3 Hz, 1H), 8.23 (d, J = 2.5, 8.6 Hz, 1H), 8.14 (d, J = 9.4 Hz, 1H), 7.09 - 7.02 (m, 2H), 6.95 (d, J = 8.7 Hz, 1H), 6.69 (s, 1H), 6.63 (s, 1H), 6.50 (s, 1H), 6.32 (s, 1H), 5.02 (d, J = 2.6 Hz, 1H), 4.48 (t, J = 5.3 Hz, 2H), 4.13 (d, J = 4.5, 11.3 Hz, 1H), 4.00 (d, J = 8.7 Hz, 1H), 3.82 (d, J = 10.6 Hz, 2H), 3.10 (s, 6H), 3.01 (t, J = 5.4 Hz, 2H), 2.48 (s, 3H), 2.33 - 2.28 (m, 2H). MS m/z (ESI) $[M+H]^+$ = 458.2.

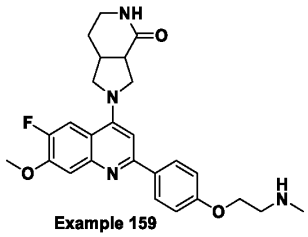
Example 157: (cis)-2-[7-methoxy-2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one



Example 157

[0680] According to Scheme 3 Step 3: Conditions 1 HCl: Tert-butyl 4-(5-(7-methoxy-4-(cis-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)piperazine-1-carboxylate (200 mg, 357.99 μmol, 1 eq) was added to HCl/dioxane (2 M, 2 mL). The reaction solution was stirred at 25 °C for 1 hour. The reaction solution was concentrated under *vacuum*. The residue was purified by prep-HPLC **2** (gradient:0%-30% over 10 min) basified by SCX cation exchange resin to give **Example 157** (20 mg, 42.52 μmol, 11.88% yield, 97.5% purity) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.63 (d, J = 2.4 Hz, 1H), 8.14 - 8.02 (m, 2H), 7.20 (d, J = 2.6 Hz, 1H), 6.94 (dd, J = 2.7, 9.4 Hz, 1H), 6.83 (d, J = 9.0 Hz, 1H), 6.68 (s, 1H), 4.00 - 3.87 (m, 3H), 3.84 (s, 3H), 3.59 - 3.50 (m, 5H), 3.40 - 3.26 (m, 2H), 3.07 (q, J = 7.8 Hz, 1H), 2.94 - 2.82 (m, 4H), 2.81 - 2.70 (m, 1H), 1.95 - 1.84 (m, 1H), 1.80 - 1.66 (m, 1H). MS m/z (ESI) $[M+H]^+$ = 459.2.

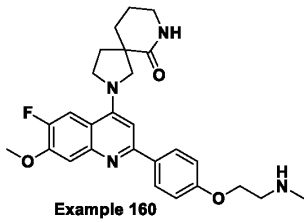
Example 159: (cis)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one



Example 159

[0681] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of cis-tert-butyl(2-(4-(6-fluoro-7-methoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (150 mg, 265.65 μmol, 1 eq) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 50.68 eq). Then the resulting mixture was stirred at 25°C for 1 hour. The reaction mixture was filtered and evaporated under reduced pressure and the crude product was purified by prep-HPLC **10** (gradient:2%-32% over 10 min) basified by SCX cation exchange resin to give **Example 159** (9.53 mg, 20.52 μmol, 7.72% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 7.96 - 7.91 (m, 3H), 7.46 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 8.8 Hz, 2H), 6.89 (s, 1H), 4.25 (t, J = 5.1 Hz, 2H), 4.02 (s, 3H), 3.99 (br d, J = 4.3 Hz, 2H), 3.60 (d, J = 3.9, 10.1 Hz, 1H), 3.49 - 3.34 (m, 3H), 3.20 - 3.15 (m, 3H), 2.90 - 2.83 (m, 1H), 2.61 (s, 3H), 2.05 - 1.97 (m, 1H), 1.83 (d, J = 4.7, 9.5, 14.2 Hz, 1H). MS m/z (ESI) $[M+H]^+$= 465.2.

Example 160: 2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.5]decan-6-one

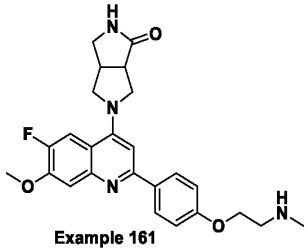


Example 160

[0682] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(6-oxo-2,7-diazaspiro[4.5]decan-2-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (125 mg, 216.01 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 2 mL) at 25°C. The mixture was stirred at 25 °C for 2hours. The reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:8%-38% over 9 min) basified by SCX cation exchange resin to give **Example 160** (63.20 mg, 125.86 μmol, 58.26% yield, 95.3% purity). ^{1}H NMR (400 MHz, DMSO-d_6) δ

(ppm): 8.15 (d, J = 8.9 Hz, 2H), 7.94 (d, J = 13.9 Hz, 1H), 7.61 (s, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 6.91 (s, 1H), 4.13 (t, J = 5.3 Hz, 2H), 3.98 (s, 3H), 3.95 (d, J = 9.8 Hz, 1H), 3.92 - 3.85 (m, 1H), 3.80 - 3.72 (m, 1H), 3.61 (d, J = 9.7 Hz, 1H), 3.18 (s, 2H), 2.96 (t, J = 5.4 Hz, 2H), 2.44 - 2.36 (m, 4H), 1.98 - 1.90 (m, 1H), 1.89 - 1.73 (m, 4H). MS m/z (ESI) $[M+H]^+$= 479.2.

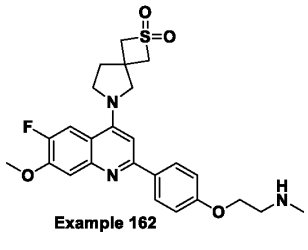
Example 161: (cis)-5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one



Example 161

[0683] According to Scheme 4 Step 2: Conditions 2 TFA: To a solution of tert-butyl (2-(4-(6-fluoro-7-methoxy-4-(4-oxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (180 mg, 326.90 μmol, 1 eq) in DCM (2 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 41.18 eq). Then the resulting mixture was stirred at 25°C for 1 hour. The reaction mixture was filtered and evaporated under reduced pressure and the crude product was purified by prep-HPLC **10** (gradient:8%-38% over 10 min) basified by SCX cation exchange resin to give **Example 161** (12.88 mg, 28.25 μmol, 8.64% yield, 98.8% purity) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 7.99 - 7.94 (m, 2H), 7.77 (d, J = 13.0 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.12 - 7.08 (m, 3H), 4.19 (t, J = 5.2 Hz, 2H), 4.02 (s, 3H), 3.99 (s, 1H), 3.76 (d, J = 7.3, 10.4 Hz, 1H), 3.71 - 3.65 (m, 1H), 3.58 (d, J = 3.4, 10.1 Hz, 1H), 3.50 (d, J = 6.8, 10.2 Hz, 1H), 3.38 (d, J = 1.6, 10.4 Hz, 1H), 3.27 - 3.19 (m, 2H), 3.04 (t, J = 5.1 Hz, 2H), 2.51 (s, 3H). MS m/z (ESI) $[M+H]^+$= 451.2.

Example 162: 2-[4-[4-(2,2-dioxo-2thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine

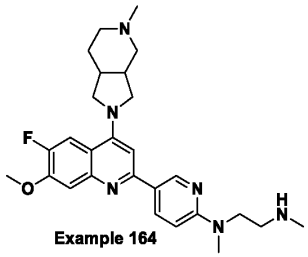


Example 162

[0684] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[4-(2,2-dioxo-2thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-

quinolyl]phenoxy]ethyl]-N-methyl-carbamate (160 mg, 273.18 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 2 mL) at 25°C. The mixture was stirred at 25°C for 2hours. The reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:2%-32% over 9 min) basified by SCX cation exchange resin to give **Example 162** (88.01 mg, 181.25 μmol, 66.35% yield, 100% purity). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.13 (d, J = 8.9 Hz, 2H), 7.90 (d, J = 14.0 Hz, 1H), 7.44 (d, J = 9.0 Hz, 1H), 7.05 (d, J = 8.9 Hz, 2H), 6.92 (s, 1H), 4.39 - 4.33 (m, 2H), 4.26 - 4.20 (m, 2H), 4.09 (t, J = 5.6 Hz, 2H), 3.99 (s, 5H), 3.79 (t, J = 6.5 Hz, 2H), 2.88 (t, J = 5.5 Hz, 2H), 2.37 (s, 3H), 2.31 (t, J = 6.3 Hz, 2H). MS m/z (ESI) $[M+H]^+$= 486.1.

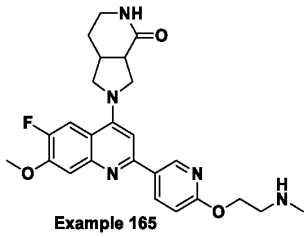
Example 164: (cis)-N'-[5-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]-N,N'-dimethyl-ethane-1,2-diamine



Example 164

[0685] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of tert-butyl tert-butyl(2-((5-(6-fluoro-7-methoxy-4-(5-methyloctahydro-2H- pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)(methyl)amino)ethyl)(methyl)carbamate (300 mg, 0.487 mmol, 1 eq) in dichloromethane (5.00 mL) was added trifluoroacetic acid (1.54 g, 13.5 mmol, 1.00 mL, 27.6 eq) at 20°C. The mixture was stirred at 20°C for 12 hours. The reaction mixture was concentrated under reduce pressure and the residue was purified by prep-HPLC **3** (gradient:2%-32% over 12 min) basified by SCX cation exchange resin to give **Example 164** (130 mg, 0.272 mmol, 55.7% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.88 (d, J = 2.32 Hz, 1 H), 8.28 (dd, J = 8.99, 2.38 Hz, 1 H), 7.95 (d, J = 14.06 Hz, 1 H), 7.37 (d, J = 9.05 Hz, 1 H), 6.82 (s, 1 H), 6.70 (d, J = 9.05 Hz, 1 H), 4.04 – 3.92 (m, 3 H), 3.84 - 3.71 (m, 3 H), 3.66 (t, J = 6.66 Hz, 2 H), 3.58 (dd, J = 9.78, 4.40 Hz, 1 H), 3.08 (s, 3 H), 2.73 (t, J = 6.66 Hz, 2 H), 2.49 - 2.38 (m, 3 H), 2.34 (s, 3 H), 2.33 - 2.24 (m, 2 H), 2.17 (s, 3 H), 2.15 - 2.07 (m, 1 H), 1.70 (d, J = 6.11 Hz, 1 H), 1.56 (dd, J = 8.68, 4.03 Hz, 1 H). MS m/z (ESI) $[M+H]^+$= 479.4.

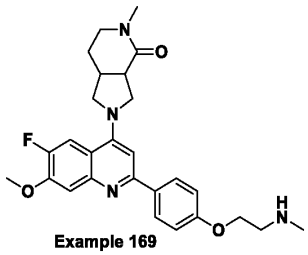
Example 165: (cis)-2-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one



Example 165

[0686] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl (2-((5-(6-fluoro-7-methoxy-4-(cis-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)ethyl)(methyl)carbamate (70 mg, 123.75 μmol, 1 eq) in MeOH (0.5 mL) was added HCl/MeOH (2 M, 1 mL) at 25°C .The mixture was stirred at 25°C for 2hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC **1** (gradient:3%-33% over 9 min) basified by SCX cation exchange resin to give **Example 165** (16.54 mg, 35.53 μmol, 28.71% yield, 100% purity). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.96 (d, J = 2.2 Hz, 1H), 8.50 (dd, J = 2.4, 8.7 Hz, 1H), 7.99 (d, J = 13.9 Hz, 1H), 7.74 s, 1H), 7.44 (d, J = 9.0 Hz, 1H), 7.00 (s, 1H), 6.92 (d, J = 8.6 Hz, 1H), 4.39 (t, J = 5.6 Hz, 2H), 4.01 - 3.95 (m, 4H), 3.92 - 3.83 (m, 2H), 3.56 (dd, J = 5.1, 10.0 Hz, 1H), 3.28 - 3.17 (m, 2H), 3.03 - 2.97 (m, 1H), 2.92 (t, J = 5.6 Hz, 2H), 2.76 (d, J = 3.2 Hz, 1H), 2.38 (s, 3H), 1.94 - 1.85 (m, 1H), 1.74 - 1.64 (m, 1H). MS m/z (ESI) $[M+H]^+$= 466.2.

Example 169: (cis)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-70methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one

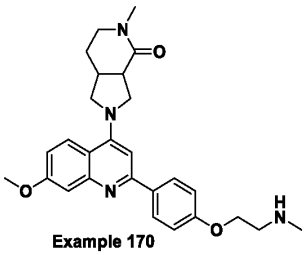


Example 169

[0687] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of tert-butyl (2-(4-(6-fluoro-7-methoxy-4-(cis-5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (250 mg, 432.02 μmol, 1 eq) in DCM (2 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 31.16 eq), then the resulting mixture was stirred at 25°C for 12 hours. The reaction mixture was filtered and evaporated under reduced pressure and the crude product was purified by prep-HPLC **10** (gradient:5%-35% over 10 min) basified by

SCX cation exchange resin to give **Example 169** (73.94 mg, 154.51 μmol, 35.76% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 7.96 - 7.88 (m, 3H), 7.45 (d, J = 8.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 2H), 6.86 (s, 1H), 4.20 (t, J = 5.1 Hz, 2H), 4.04 - 3.94 (m, 6H), 3.59 (d, J = 3.4, 10.0 Hz, 1H), 3.55 - 3.46 (m, 2H), 3.19 (d, J = 7.7 Hz, 1H), 3.08 (t, J = 5.1 Hz, 2H), 3.01 (s, 3H), 2.89 - 2.80 (m, 1H), 2.54 (s, 3H), 2.05 - 1.86 (m, 2H). MS m/z (ESI) $[M+H]^+$= 479.2

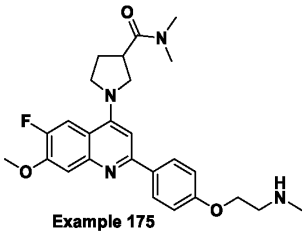
Example 170: (cis)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one



Example 170

[0688] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl (2-(4-(7-methoxy-4-cis-5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (200 mg, 356.71 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 178.35 μL) at 25°C .The mixture was stirred at 25°C for 2 hours. The mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:6%-36% over 9 min) basified by SCX cation exchange resin to give **Example 170** (138.46 mg, 300.63 μmol, 84.28% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.19 - 8.11 (m, 3H), 7.25 (d, J = 2.8 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.98 (dd, J = 2.8, 9.4 Hz, 1H), 6.90 (s, 1H), 4.08 (t, J = 5.6 Hz, 2H), 3.99 - 3.94 (m, 1H), 3.93 - 3.86 (m, 5H), 3.57 (dd, J = 4.8, 10.1 Hz, 1H), 3.41 (t, J = 5.8 Hz, 2H), 3.09 - 3.03 (m, 1H), 2.90 - 2.84 (m, 5H), 2.81 - 2.72 (m, 1H), 2.36 (s, 3H), 1.98 - 1.91 (m, 1H), 1.84 - 1.74 (m, 1H). MS m/z (ESI) $[M+H]^+$= 461.3.

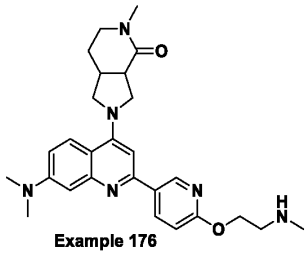
Example 175: 1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N,N-dimethyl-pyrrolidine-3-carboxamide



Example 175

[0689] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[4-[3-(dimethylcarbamoyl)pyrrolidin-1-yl]-6-fluoro-7-methoxy-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (280 mg, 494.12 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 247.06 μl, 1.00 eq) at 25°C .The mixture was stirred at 25°C for 4hours. The reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:7%-37% over 9 min) basified by SCX cation exchange resin to give **Example 175** (95.41 mg, 204.50 μmol, 41.39% yield, 100% purity). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.14 (d, J = 8.9 Hz, 2H), 7.95 (d, J = 13.9 Hz, 1H), 7.43 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 6.94 (s, 1H), 4.11 (t, J = 5.5 Hz, 2H), 3.99 (s, 3H), 3.82 (d, J = 7.1 Hz, 2H), 3.79 - 3.73 (m, 1H), 3.72 - 3.65 (m, 1H), 3.56 - 3.51 (m, 1H), 3.09 (s, 3H), 2.93 (t, J = 5.5 Hz, 2H), 2.87 (s, 3H), 2.40 (s, 3H), 2.29 - 2.19 (m, 1H), 2.15 - 2.05 (m, 1H). MS m/z (ESI) $[M+H]^+$= 467.2.

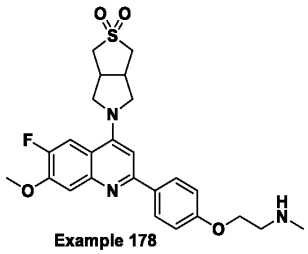
Example 176: (cis)-2-[7-(dimethylamino)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one



Example 176

[0690] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of tert-butyl (2-((5-(7-(dimethylamino)-4-((cis)-5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)ethyl)(methyl)carbamate (250 mg, 435.00 μmol, 1 eq) in DCM (2 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 30.95 eq) , then the resulting mixture was stirred at 25°C for 1 hour. The reaction mixture was filtered and evaporated under reduced pressure and the crude product was purified by prep-HPLC **10** (gradient:2%-32% over 10 min) basified by SCX cation exchange resin to give **Example 176** (91 mg, 191.74 μmol, 44.08% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.69 (d, J = 2.3 Hz, 1H), 8.23 (d, J = 2.5, 8.6 Hz, 1H), 8.14 (d, J = 9.4 Hz, 1H), 7.07 (d, J = 2.7, 9.4 Hz, 1H), 7.03 (d, J = 2.6 Hz, 1H), 6.95 (d, J = 8.7 Hz, 1H), 6.65 (s, 1H), 4.51 - 4.46 (m, 2H), 4.09 - 4.00 (m, 3H), 3.65 (d, J = 3.5, 10.3 Hz, 1H), 3.54 - 3.46 (m, 2H), 3.18 (d, J = 7.6 Hz, 1H), 3.10 (s, 6H), 3.03 - 2.99 (m, 5H), 2.88 - 2.81 (m, 1H), 2.49 (s, 3H), 2.05 - 1.98 (m, 1H), 1.92 (td, J = 4.7, 9.4 Hz, 1H). MS m/z (ESI) $[M+H]^+$= 475.4.

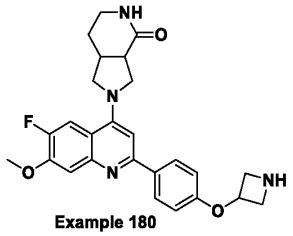
Example 178: (cis)-2-[4-[4-(2,2-dioxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine



Example 178

[0691] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[4-(2,2-dioxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (150 mg, 256.11 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 1 mL) at 25°C .The mixture was stirred at 25°C for 2 hours. The mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:5%-35% over 9 min) basified by SCX cation exchange resin to give **Example 178** (76.03 mg, 156.58 μmol, 61.14% yield, 100% purity) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.15 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 13.2 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.11 (s, 1H), 7.06 (d, J = 8.8 Hz, 2H), 4.10 (t, J = 5.6 Hz, 2H), 3.99 (s, 3H), 3.87 (dd, J = 6.2, 10.2 Hz, 2H), 3.57 (b dd, J = 3.8, 10.2 Hz, 2H), 3.42 (d, J = 5.2 Hz, 2H), 3.25 - 3.20 (m, 4H), 2.88 (t, J = 5.6 Hz, 2H), 2.37 (s, 3H). MS m/z (ESI) $[M+H]^+$= 486.3.

Example 180: (cis)-2-[2-[4-(azetidin-3-yloxy)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one

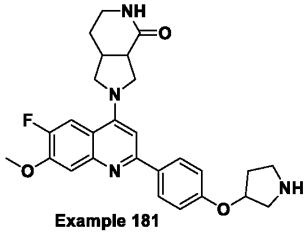


Example 180

[0692] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of cis-tert-butyl 3-(4-(6-fluoro-7-methoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)azetidine-1-carboxylate (140 mg, 248.8 μmol, 1 eq) in EtOAc (0.50 mL) was added HCl/EtOAc (2 M, 3.00 mL, 24.1 eq) at 20°C. The reaction mixture was stirred at 20°C for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient: 2-9 min 5-35%; flow 25 mL/min) basified by SCX cation exchange resin to give **Example 180** (45.07 mg, 97.5 μmol, 39.2% yield) as a white

solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.14 (br d, J = 8.6 Hz, 2H), 7.97 (d, J = 13.8 Hz, 1H), 7.75 (br s, 1H), 7.44 (d, J = 8.9 Hz, 1H), 6.97 (s, 1H), 6.91 (br d, J = 8.6 Hz, 2H), 5.14 - 4.98 (m, 1H), 3.99 (s, 3H), 3.96 - 3.77 (m, 5H), 3.57 - 3.51 (m, 3H), 3.26 - 3.18 (m, 2H), 3.01 (br d, J = 7.3 Hz, 1H), 2.80 - 2.75 (m, 1H), 1.95 - 1.86 (m, 1H), 1.69 (br d, J = 9.1 Hz, 1H). MS m/z (ESI) $[M+H]^+$= 463.2.

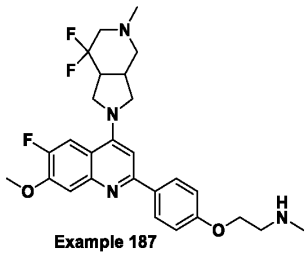
Example 181: (cis)-2-[6-fluoro-7-methoxy-2-(4-pyrrolidin-3-yloxyphenyl)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one



Example 181

[0693] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of cis-tert-butyl 3-(4-(6-fluoro-7-methoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)pyrrolidine-1-carboxylate (200 mg, 347 μmol, 1 eq) in EtOAc (0.500 mL) was added HCl/EtOAc (2 M, 5.00 mL, 28.8 eq) at 20°C. The reaction mixture was stirred at 20°C for 1 hour. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient: 2-9 min 3-33%; flow 25 mL/min) basified by SCX cation exchange resin to give **Example 181** (43.12 mg, 89.9 μmol, 25.9% yield, 99.4% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.15 (br d, J = 8.8 Hz, 2H), 7.97 (d, J = 14.0 Hz, 1H), 7.76 (br s, 1H), 7.44 (d, J = 8.9 Hz, 1H), 7.07 - 6.94 (m, 3H), 4.99 (br s, 1H), 4.00 (s, 3H), 3.96 - 3.80 (m, 3H), 3.56 - 3.52 (m, 1H), 3.25 - 3.11 (m, 3H), 3.06 - 2.85 (m, 4H), 2.82 - 2.72 (m, 1H), 2.10 (br dd, J = 6.3, 13.8 Hz, 1H), 1.97 - 1.81 (m, 2H), 1.77 - 1.61 (m, 1H). MS m/z (ESI) $[M+H]^+$= 472.2.

Example 187: (cis)-2-[4-[4-(7,7-difluoro-5-methyl-1,3,3a,4,6,7a-hexahydropyrrolo[3,4-c]pyridin-2-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine

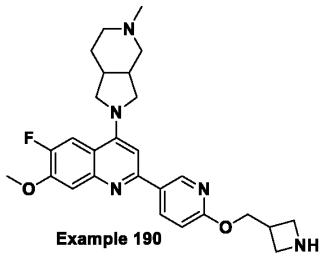


Example 187

[0694] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl (2-(4-(4-(cis-7,7-difluoro-5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-6-fluoro-7-

methoxyquinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (50 mg, 83.24 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 1 mL) at 25°C. The mixture was stirred at 25°C for 2 hours. The residue was purified by prep-TLC (Plate 1, SiO_2, Dichloromethane : Methanol= 10:1) to give Example **187** (23.5 mg, 46.95 μmol, 56.40% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 7.95 - 7.87 (m, 3H), 7.43 (d, J = 8.6 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 6.78 (s, 1H), 4.20 (t, J = 5.2 Hz, 2H), 4.03 - 3.96 (m, 4H), 3.94 - 3.85 (m, 2H), 3.73 - 3.66 (m, 1H), 3.07 (t, J = 5.2 Hz, 2H), 2.94 - 2.69 (m, 4H), 2.64 (dd, J = 4.2, 12.2 Hz, 1H), 2.53 (s, 3H), 2.46 (dd, J = 8.8, 12.2 Hz, 1H), 2.37 (s, 3H). MS m/z (ESI) $[M+H]^+$= 501.2.

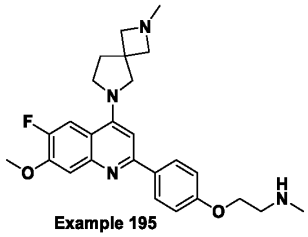
Example 190: (cis)-2-[6-(azetidin-3-ylmethoxy)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline



Example 190

[0695] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of tert-butyl 3-(((5-(6-fluoro-7-methoxy-4-(cis-5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)oxy)methyl)azetidine-1-carboxylate (120 mg, 207.72 μmol, 1 eq) in DCM (1 mL) was added TFA (307.00 mg, 2.69 mmol, 0.2 mL, 12.96 eq) at 25°C . After stirring at 25°C for 2 hours, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC **2** (gradient:1%-20% over 10 min) basified by SCX cation exchange resin to give **Example 190** (25 mg, 51.82 μmol, 24.95% yield, 99% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.94 (d, J = 2.0 Hz, 1H), 8.55 - 8.41 (m, 1H), 8.00 (d, J = 14.4 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 6.99 - 6.82 (m, 2H), 4.51 - 4.42 (m, 2H), 3.98 (s, 3H), 3.96-3.94 (m, 5H), 3.69 - 3.55 (m, 4H), 2.46 - 2.23 (m, 5H), 2.22 - 2.11 (m, 4H), 1.83 - 1.63 (m, 1H), 1.46 - 1.44 (m, 1H). MS m/z (ESI) $[M+H]^+$= 478.3.

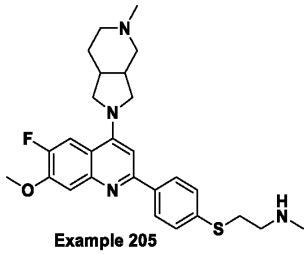
Example 195: 2-[4-[6-fluoro-7-methoxy-4-(2-methyl-2, 6-diazaspiro[3.4]octan-6-yl) -2-quinolyl]phenoxy]-N-methyl-ethanamine



Example 195

[0696] According to Scheme 3 Step 3: Conditions 2 TFA: A solution of tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(2-methyl-2, 6-diazaspiro[3.4]octan-6-yl) -2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (250 mg, 454.00 µmol, 1 eq) in TFA (1 mL)/DCM (3 mL) was stirred at 25°C for 2 hours then the reaction mixture was concentrated and the crude material was purified by Prep-HPLC **10** (gradient:1%-20% over 10 min) basified by SCX cation exchange resin to give **Example 195** (110 mg, 244.15 µmol, 53.78% yield, 100% purity) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.12 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 13.9 Hz, 1H), 7.42 (d, J = 8.9 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.88 (s, 1H), 4.08 (t, J = 5.6 Hz, 2H), 3.98 (s, 3H), 3.79 (s, 2H), 3.69 (br t, J = 6.5 Hz, 2H), 3.17 (d, J = 6.8 Hz, 2H), 3.13 (d, J = 6.8 Hz, 2H), 2.85 (t, J = 5.6 Hz, 2H), 2.35 (s, 3H), 2.23 (s, 3H), 2.13 (br t, J = 6.6 Hz, 2H). MS m/z (ESI) $[M+H]^+$= 451.3.

Example 205: (cis)-2-[4-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenyl]sulfanyl-N-methyl-ethanamine

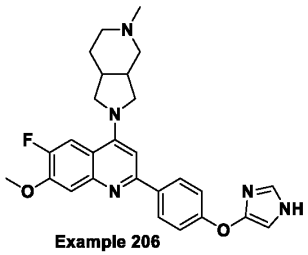


Example 205

[0697] According to Scheme 3 Step 3: Conditions 1 HCl: A mixture of cis-tert-butyl (2-((4-(6-fluoro-7-methoxy-4-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)thio)ethyl)(methyl)carbamate (180 mg, 213.86 µmol, 1 eq) in HCl/dioxane (3 mL, 2M) was stirred at 25°C for 1hour then mixture was concentrated and the residue was purified by prep-HPLC **1** (gradient: 0%-30% over 10 min), basified by SCX cation exchange resin to give **Example 205** (50.83 mg, 105.76 µmol, 49.45% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.12 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 14.1 Hz, 1H), 7.42 (br d, J = 8.1 Hz, 3H), 6.87 (s, 1H), 3.98 (s, 3H), 3.87 - 3.68 (m, 3H), 3.59 (br dd, J

= 4.3, 9.7 Hz, 1H), 3.40 (br d, J = 6.5 Hz, 2H), 3.11 (t, J = 6.9 Hz, 2H), 2.77 - 2.65 (m, 2H), 2.46 (br d, J = 7.0 Hz, 2H), 2.30 (s, 5H), 2.20 - 2.07 (m, 4H), 1.70 (br d, J = 10.5 Hz, 1H), 1.61 - 1.47 (m, 1H). MS m/z (ESI) $[M+H]^+$= 481.2.

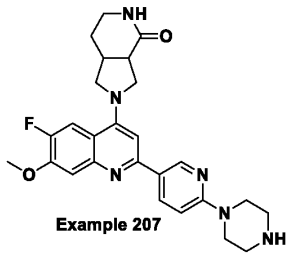
Example 206: (cis)-6-fluoro-2-[4-(1H-imidazol-4-yloxy)phenyl]-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline



Example 206

[0698] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of 6-fluoro-7-methoxy-4-(cis-5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-2-(4-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)oxy)phenyl)quinoline (290 mg, 480.29 μmol, 1 eq) in DCM (2 mL) was added TFA (54.76 mg, 480.29 μmol, 35.68 μL, 1 eq). Then the resulting mixture was stirred at 25°C for 2 hours, filtered and evaporated under reduced and the residue was purified by prep-HPLC **1** (gradient:0%-26% over 10 min) basified by SCX cation exchange resin to give **Example 206** (207.97 mg, 439.18 μmol, 91.44% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 14.21 (br d, J = 6.9 Hz, 1H), 11.16 (d, J = 1.6, 5.1 Hz, 1H), 8.58 (br d, J = 7.8 Hz, 1H), 8.37 - 8.19 (m, 4H), 7.42 - 7.32 (m, 3H), 6.83 (s, 1H), 4.00 (br d, J = 1.9 Hz, 4H), 3.75 - 3.52 (m, 2H), 3.30 (br d, J = 13.1 Hz, 2H), 3.09 - 2.84 (m, 2H), 2.73 (d, J = 4.0, 14.0 Hz, 4H), 2.60 - 2.51 (m, 2H), 2.37 - 1.79 (m, 2H). MS m/z (ESI) $[M+H]^+$= 474.3.

Example 207: (cis)-2-[6-fluoro-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one

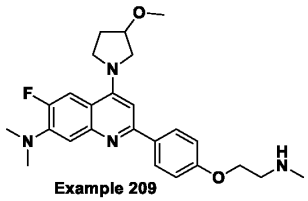


Example 207

[0699] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl 4-(5-(6-fluoro-7-methoxy-4-(cis-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)piperazine-1-carboxylate (160 mg, 141.85 μmol, 1 eq) in dioxane (1 mL) was

added HCl/dioxane (2 M, 1 mL) at 25°C.The mixture was stirred at 25°C for 2hours then concentrated under reduced pressure and the residue was purified by prep-HPLC **3** (gradient: 8%-38% B over 12 min) basified by SCX cation exchange resin to give **Example 207** (10 mg, 20.98 μmol, 14.79% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.94 (d, J = 2.2 Hz, 1H), 8.34 (dd, J = 2.4, 8.8 Hz, 1H), 7.94 (d, J = 13.8 Hz, 1H), 7.74 (s, 1H), 7.41 (d, J = 9.0 Hz, 1H), 6.96 (s, 1H), 6.89 (d, J = 8.8 Hz, 1H), 4.01 - 3.92 (m, 4H), 3.90 - 3.77 (m, 2H), 3.58 - 3.48 (m, 5H), 3.27 - 3.17 (m, 2H), 3.05 - 2.95 (m, 1H), 2.92 - 2.69 (m, 5H), 1.95 - 1.83 (m, 1H), 1.75 - 1.63 (m, 1H). MS m/z (ESI) $[M+H]^+$= 477.2.

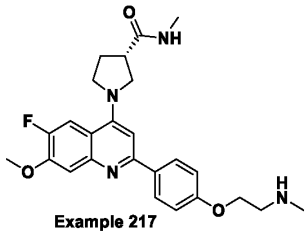
Example 209: 6-fluoro-4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-[4-[2-(methylamino)ethoxy]phenyl]quinolin-7-amine



Example 209

[0700] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[7-(dimethylamino)-6-fluoro-4-(3-methoxypyrrolidin-1-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (200 mg, 371.30 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 1 mL) at 25°C. After stirring at 25°C for 2 hours the reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient: 9%-39% over 10 min) basified by SCX cation exchange resin to give **Example 209** (50 mg, 114.02 μmol, 30.71% yield, 100% purity) as yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.11 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 16.4 Hz, 1H), 7.20 (d, J = 9.6 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.84 (s, 1H), 4.17 - 4.04 (m, 3H), 3.94 (dd, J = 4.4, 10.8 Hz, 1H), 3.84 - 3.75 (m, 1H), 3.91 - 3.64 (m, 1H), 3.67 - 3.59 (m, 2H), 3.28 (s, 3H), 2.92 (s, 6H), 2.86 (t, J = 5.6 Hz, 2H), 2.36 (s, 3H), 2.19 - 2.01 (m, 2H). MS m/z (ESI) $[M+H]^+$= 439.3.

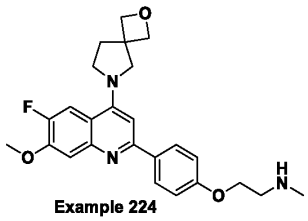
Example 217: (3S)-1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide



Example 217

[0701] According to Scheme 3 Step 3: Conditions 2 TFA: A solution of tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-[(3S) -3-(methylcarbamoyl) pyrrolidin-1-yl]-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (220 mg, 398.09 µmol, 1 eq) in TFA (1 mL)/DCM (3 mL) was stirred at 25°C for 1 hour then mixture was concentrated and the residue was purified by prep-HPLC **1** (gradient: 0%-30% over 10 min), basified by SCX cation exchange resin to give **Example 217** (80 mg, 174.31 µmol, 43.79% yield, 98.6% purity) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.13 (d, J = 8.9 Hz, 2H), 8.05 - 7.99 (m, 1H), 7.93 (d, J = 13.9 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 6.91 (s, 1H), 4.10 (t, J = 5.6 Hz, 2H), 3.98 (s, 3H), 3.85 - 3.75 (m, 3H), 3.73 - 3.66 (m, 1H), 3.13 - 3.03 (m, 1H), 2.90 (t, J = 5.6 Hz, 2H), 2.63 (d, J = 4.6 Hz, 3H), 2.27 - 2.06 (m, 2H). MS m/z (ESI) $[M+H]^+$= 453.2.

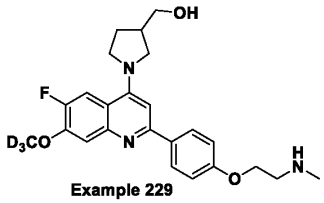
Example 224: 2-[4-[6-fluoro-7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine



Example 224

[0702] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (200 mg, 372.01 µmol, 1 eq) in DCM (2.5 mL) was added TFA (767.50 mg, 6.73 mmol, 0.5 mL, 18.09 eq) at 25°C. The mixture was stirred at 25°C for 1 hour then filtered and concentrated under reduced pressure and the residue was purified by prep-HPLC **3** (gradient: 10%-40% B over 10 min) basified by SCX cation exchange resin to give **Example 224** (116.67 mg, 266.67 µmol, 71.68% yield, 100% purity). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.13 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 13.8 Hz, 1H), 7.43 (d, J = 8.9 Hz, 1H), 7.04 (d, J = 8.7 Hz, 2H), 6.91 (s, 1H), 4.65 (d, J = 6.0 Hz, 2H), 4.55 (d, J = 6.0 Hz, 2H), 4.09 (t, J = 5.6 Hz, 2H), 3.98 (s, 3H), 3.95 (s, 2H), 3.71 (t, J = 6.5 Hz, 2H), 2.88 (t, J = 5.5 Hz, 2H), 2.37 (s, 3H), 2.28 (t, J = 6.6 Hz, 2H). MS m/z (ESI) $[M+H]^+$= 438.2.

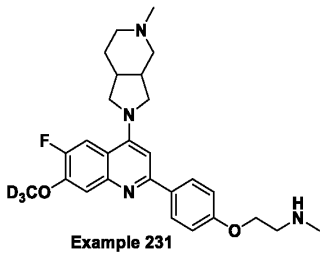
Example 229: [1-[6-fluoro-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-7-(trideuteriomethoxy)-4-quinolyl]pyrrolidin-3-yl]methanol



Example 229

[0703] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of tert-butyl N-[2-[[6-[6-fluoro-4-[3-(hydroxymethyl)pyrrolidin-1-yl]-7-(trideuteriomethoxy)-2-quinolyl]-3-pyridyl]oxy]ethyl]-N-methyl-carbamate (180 mg, 339.87 μmol, 1 eq) in DCM (2 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 39.61 eq). The resulting mixture was stirred at 25°C for 2 hours then filtered and evaporated under reduced pressure and the crude product was purified by prep-HPLC **2** (gradient:2%-30% over 10 min) basified by SCX cation exchange resin to give **Example 229** (57.24 mg, 132.60 μmol, 39.02% yield, 99.5% purity) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.38 (d, J = 2.7 Hz, 1H), 8.29 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 13.8 Hz, 1H), 7.56 (d, J = 2.9, 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.34 (s, 1H), 4.26 (t, J = 5.1 Hz, 2H), 3.86 - 3.78 (m, 3H), 3.71 - 3.61 (m, 3H), 3.04 (t, J = 5.1 Hz, 2H), 2.61 - 2.54 (m, 1H), 2.50 (s, 3H), 2.19 (d, J = 5.4, 11.8 Hz, 1H), 1.88 (br s, 1H). MS m/z (ESI) $[M+H]^+$ = 430.2.

Example 231: (cis)-2-[4-[6-fluoro-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-7-(trideuteriomethoxy)-2-quinolyl]phenoxy]-N-methyl-ethanamine

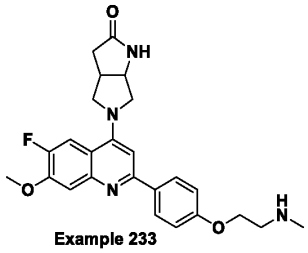


Example 231

[0704] According to Scheme 3 Step 3: Conditions 1 HCl: cis-tert-butyl (2-(4-(6-fluoro-7-(methoxy-d3)-4-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate was added to HCl/dioxane (2 M, 1 mL, 11.35 eq), the reaction mixture was stirred at 25°C for 1 hour, concentrated and the residue was purified by prep-HPLC **1** (gradient:0%-26% over 10 min) basified by SCX cation exchange resin to give **Example 231** (50.88 mg, 108.81 μmol, 61.77% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 14.06 - 13.69 (m, 1H), 11.12 - 10.84 (m, 1H), 9.45 - 9.08 (m, 2H), 8.51 - 7.93 (m, 4H), 7.25 (br d, J = 7.9 Hz, 2H), 6.85 (s, 1H), 4.42 (br t, J = 4.8

Hz, 2H), 4.09 - 3.47 (m, 4H), 3.33 - 3.22 (m, 4H), 3.07 - 2.80 (m, 2H), 2.78 - 2.69 (m, 3H), 2.64 (br s, 5H), 2.35 (s, 2H). MS m/z (ESI) $[M+H]^+$= 468.3.

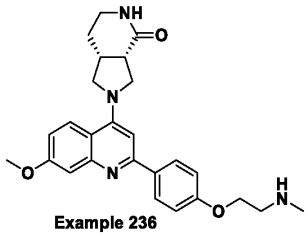
Example 233: (cis)-5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-2-one



Example 233

[0705] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(2-oxo-1,3,3a,4,6,6a- hexahydropyrrolo[3,4-b]pyrrol-5-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (150 mg, 266.97 µmol, 1 eq) in dioxane (3 mL)was added HCl/dioxane (2 M, 2 mL, 14.98 eq) at 20°C. The mixture was stirred at 20 °C for 2 hours concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:0%-30% over 10 min) basified by SCX cation exchange resin to give **Example 233** (40 mg, 88.79 µmol, 33.26% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.16 (d, J=8.80 Hz, 2 H), 7.91 (s, 1 H), 7.79 (d, J=13.20 Hz, 1 H), 7.49 (d, J=8.68 Hz, 1 H), 7.15 (s, 1 H), 7.06 (d, J=8.80 Hz, 2 H), 4.31 - 4.22 (m, 1 H), 4.11 (t, J=5.44 Hz, 2 H), 4.00 (s, 3 H), 3.64 (d, J=10.64 Hz, 1 H), 3.57 - 3.49 (m, 2 H), 3.42 (d, J = 4.78 Hz, 1 H), 3.15 - 3.04 (m, 1 H), 2.91 (t, J=5.40 Hz, 2 H), 2.59 (dd, J=17.2, 9.28 Hz, 1 H), 2.39 (s, 3 H),2.21(dd, J=17.12, 2.32 Hz, 1 H). MS m/z (ESI) $[M+H]^+$= 451.3.

Example 236: (3aS,7aR)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one

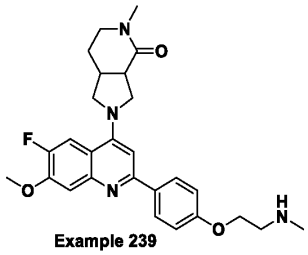


Example 236

[0706] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl (2-(4-(7-methoxy-4-((3aS,7aR)-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (150 mg, 274.40 µmol, 1 eq) in MeOH (2 mL) was added HCl/dioxane (2 M, 2 mL, 14.58 eq). The reaction solution was stirred at 25 °C for 1 hour, concentrated under *vacuum* and the residue was purified by prep-HPLC **1** (radient:6%-

36% over 10 min) basified by SCX cation exchange resin to give **Example 236** (60 mg, 134.37 µmol, 48.97% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.44 (s, 1H), 9.18 (br d, J = 6.5 Hz, 2H), 8.48 (d, J = 9.7 Hz, 1H), 8.12 (d, J = 8.9 Hz, 2H), 7.92 - 7.71 (m, 2H), 7.33 - 7.15 (m, 3H), 6.85 (s, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.34 - 4.14 (m, 3H), 4.02 - 3.86 (m, 4H), 3.43 - 3.24 (m, 4H), 3.16 - 3.07 (m, 1H), 2.91 - 2.80 (m, 1H), 2.67 - 2.62 (m, 3H), 1.99 - 1.87 (m, 1H), 1.79 - 1.66 (m, 1H). MS m/z (ESI) $[M+H]^+$= 447.3.

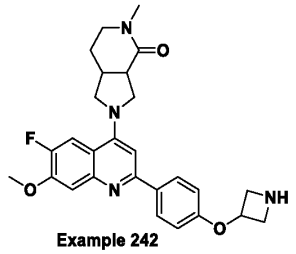
Example 239: (cis)-2-[2-[4-[2-(dimethylamino)ethoxy]phenyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one



Example 239

[0707] According to Scheme 1 Step 5: A mixture of 2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)phenoxy]-N,N-dimethyl-ethanamine (200 mg, 533.57 µmol, 1 eq), cis-5-methyloctahydro-4H-pyrrolo[3,4-c]pyridin-4-one (123 mg, 797.62 µmol, 1.49 eq), SPhos Pd G3 (42 mg, 53.83 µmol, 1.01e-1 eq) and Cs_2CO_3 (522 mg, 1.60 mmol, 3 eq) in dioxane (5 mL) was stirred at 80 °C for 12h under N_2. The mixture was diluted with EtOAc (15 ml), and then filtered. The filtrate was concentrated to give a residue which was purified by prep-HPLC **1** (gradient: 5%-35% over 10 min) to give **Example 239** (50.86 mg, 89.94 µmol, 16.86% yield, 100% purity, 2HCl) as yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.82 (br s, 1H), 10.83 (br s, 1H), 8.30 (br d, J = 13.5 Hz, 1H), 8.22 - 8.11 (m, 3H), 7.25 (br d, J = 8.6 Hz, 2H), 6.85 (s, 1H), 4.51 (br s, 2H), 4.32 - 4.14 (m, 3H), 4.06 - 3.91 (m, 4H), 3.48 - 3.35 (m, 3H), 3.14 (br d, J = 6.6 Hz, 1H), 2.96 - 2.78 (m, 11H), 2.04 - 1.92 (m, 1H), 1.89 - 1.78 (m, 1H). MS m/z (ESI) $[M+H]^+$= 493.2.

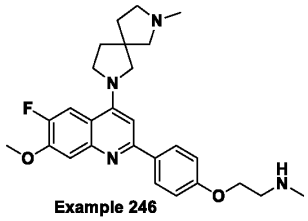
Example 242: (cis)-2-[2-[4-(azetidin-3-yloxy)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one



Example 242

[0708] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of cis-tert-butyl 3-(4-(6-fluoro-7-methoxy-4-(5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)azetidine-1-carboxylate (120 mg, 208.10 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (2 M, 1 mL) at 25 °C. The mixture was stirred at 25 °C for 2 hours, concentrated under reduced pressure and the residue was purified by prep-HPLC **1** (gradient:2%-32% over 10 min) basified by SCX cation exchange resin to give **Example 242** (54.93 mg, 115.27 μmol, 55.39% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.85 (s, 1H), 9.76 - 9.49 (m, 2H), 8.32 (d, J = 13.2 Hz, 1H), 8.19 - 8.10 (m, 3H), 7.13 (d, J = 8.8 Hz, 2H), 6.86 (s, 1H), 5.29 - 5.19 (m, 1H), 4.56 - 4.45 (m, 2H), 4.32 - 4.15 (m, 3H), 4.08 - 3.94 (m, 6H), 3.45 - 3.41 (m, 2H), 3.14 (q, J = 6.9 Hz, 1H), 2.90 - 2.82 (m, 4H), 2.03 - 1.92 (m, 1H), 1.89 - 1.77 (m, 1H). MS m/z (ESI) $[M+H]^+$= 477.2.

Example 246: 2-[4-[6-fluoro-7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine

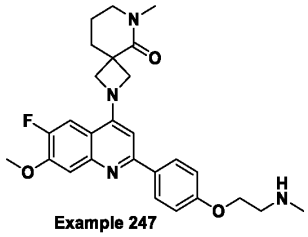


Example 246

[0709] According to Scheme 3 Step 3: Conditions 1 HCl: A mixture of tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (150 mg, 265.63 μmol, 1 eq) in HCl/dioxane (2 M, 3 mL) was stirred at 25 °C for 1hour, concentrated and the residue was purified by prep-HPLC **1** (gradient: 0%-26% over 10 min) to give **Example 246** (104.56 mg, 182.17 μmol, 68.58% yield, 100% purity, 3HCl) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.95 (br d, J = 13.9 Hz, 1H), 11.74 - 11.45 (m, 1H), 9.38 (br s, 2H), 8.32 - 8.21 (m, 2H), 8.19 - 8.12 (m, 2H), 7.25 (d, J = 8.9 Hz, 2H), 6.82 (br d, J = 11.9 Hz, 1H), 4.43 (br t, J = 4.9 Hz, 2H), 4.38 - 3.98 (m, 7H),

3.67 - 3.61 (m, 2H), 3.40 - 3.32 (m, 2H), 3.26 - 3.09 (m, 2H), 2.80 (d, J = 4.5 Hz, 3H), 2.63 (t, J = 5.4 Hz, 3H), 2.36 - 1.96 (m, 4H). MS m/z (ESI) $[M+H]^+$= 465.2.

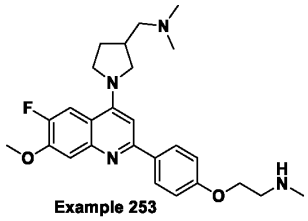
Example 247: 2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-6-methyl-2,6-diazaspiro[3.5]nonan-5-one



Example 247

[0710] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(6-methyl-5-oxo-2,6-diazaspiro[3.5]nonan-2-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (300 mg, 518.43 µmol, 1 eq) in DCM (2 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 25.97 eq). The resulting mixture was stirred at 25°C for 2 hours, filtered and evaporated under reduced pressure and the crude product was purified by prep-HPLC **11** (gradient:5%-35% over 2 min) basified by SCX cation exchange resin to give **Example 247** (98.77 mg, 206.39 µmol, 39.81% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 7.89 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 12.7 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.50 (s, 1H), 4.60 (d, J = 7.6 Hz, 2H), 4.20 - 4.10 (m, 4H), 3.98 (s, 3H), 3.38 (t, J = 6.0 Hz, 2H), 3.03 (br t, J = 4.8 Hz, 2H), 2.96 (s, 3H), 2.50 (s, 3H), 2.25 (td, J = 2.8, 5.8 Hz, 2H), 1.95 - 1.84 (m, 2H). MS m/z (ESI) $[M+H]^+$= 472.2.

Example 253: 2-[4-[4-[3-[(dimethylamino) methyl]pyrrolidin-1-yl]-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine

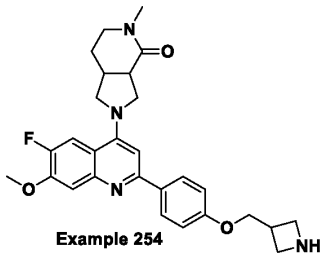


Example 253

[0711] According to Scheme 3 Step 3: Conditions 1 HCl: A solution of tert-butyl N-[2-[4-[4-[3-[(dimethylamino) methyl]pyrrolidin-1-yl]-6-fluoro-7-methoxy-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (160 mg, 289.50 µmol, 1 eq) in HCl/dioxane (5 mL) was stirred at 25°C for 1 hour, concentrated and the crude material was purified by Prep-HPLC **1** (gradient:0%-26% over 10 min) to give **Example 253** (128 mg, 227.78 µmol, 78.68% yield, 100% purity,

3HCl) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.86 (s, 1H), 11.06 (br s, 1H), 9.32 (br d, J = 2.8 Hz, 2H), 8.33 (br d, J = 13.3 Hz, 1H), 8.23 (d, J = 8.3 Hz, 1H), 8.17 (d, J = 8.9 Hz, 2H), 7.25 (d, J = 8.9 Hz, 2H), 6.85 (s, 1H), 4.43 (br t, J = 4.9 Hz, 2H), 4.32 (br dd, J = 6.2, 8.7 Hz, 1H), 4.10 - 3.95 (m, 6H), 3.40 - 3.32 (m, 2H), 3.28 (br t, J = 6.2 Hz, 2H), 2.91 - 2.83 (m, 1H), 2.80 (d, J = 4.8 Hz, 6H), 2.63 (t, J = 5.4 Hz, 3H), 2.36 - 2.25 (m, 1H), 1.95 - 1.82 (m, 1H). MS m/z (ESI) $[M+H]^+$= 453.3.

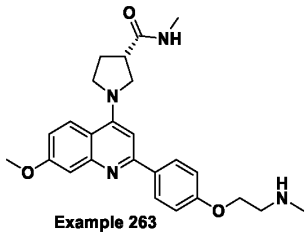
Example 254: (cis)-2-[2-[4-(azetidin-3-ylmethoxy)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one



Example 254

[0712] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of cis-tert-butyl 3-((4-(6-fluoro-7-methoxy-4-(5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)methyl)azetidine-1-carboxylate (140 mg, 237.01 μmol, 1 eq) in DCM (2 mL) was added TFA (767.50 mg, 6.73 mmol, 0.5 mL, 28.40 eq). The reaction solution was stirred at 25 °C for 1 hour, concentrated and the residue was purified by prep-HPLC **4** (gradient:1%-30% over 10 min) basified by SCX cation exchange resin to give **Example 254** (70 mg, 138.27 μmol, 58.34% yield, 96.9% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.15 (br d, J = 8.6 Hz, 2H), 7.95 (br d, J = 14.1 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.04 (br d, J = 8.6 Hz, 2H), 6.95 (s, 1H), 4.18 (br d, J = 6.7 Hz, 2H), 3.99 - 3.78 (m, 7H), 3.66 - 3.49 (m, 6H), 3.08 - 3.00 (m, 2H), 2.87 (s, 3H), 2.79 - 2.74 (m, 1H), 1.95 (br dd, J = 4.2, 13.1 Hz, 1H), 1.87 - 1.73 (m, 1H). MS m/z (ESI) $[M+H]^+$= 491.2.

Example 263: (3S) -1-[7-methoxy-2-[4-[2-(methylamino) ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide

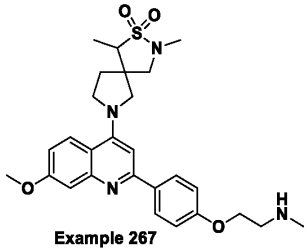


Example 263

[0713] According to Scheme 3 Step 3: Conditions 1 HCl: A solution of tert-butyl N-[2-[4-[7-methoxy-4-[(3S) -3-(methylcarbamoyl) pyrrolidin-1-yl]-2-quinolyl]phenoxy]ethyl]-N-

methyl-carbamate (120 mg, 224.45 μmol, 1 eq) in HCl/dioxane (4 mL) was stirred at 25°C for 1 hour, concentrated and the residue was purified by Prep-HPLC **1** (gradient:3%-33% over 20 min) to give **Example 263** (110 mg, 216.77 μmol, 96.58% yield, 100% purity, 2HCl) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.47 (s, 1H), 9.26 (s, 2H), 8.43 (d, J = 9.6 Hz, 1H), 8.23 (br d, J = 4.8 Hz, 1H), 8.11 (d, J = 8.9 Hz, 2H), 7.81 (d, J = 2.3 Hz, 1H), 7.31 - 7.15 (m, 3H), 6.81 (s, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.22 - 3.99 (m, 4H), 3.94 (s, 3H), 3.41 - 3.33 (m, 2H), 3.18 (quin, J = 7.3 Hz, 1H), 2.66 - 2.60 (m, 6H), 2.35 - 2.23 (m, 1H), 2.22 - 2.10 (m, 1H). MS m/z (ESI) $[M+H]^+$= 435.4.

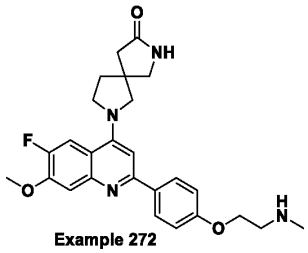
Example 267: 2-[4-[4-(1,3-dimethyl-2,2-dioxo-2thia-3,7-diazaspiro[4.4]nonan-7-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine



Example 267

[0714] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[4-(1, 3-dimethyl-2, 2-dioxo-2thia-3, 7-diazaspiro[4.4]nonan-7-yl) -7-methoxy-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate & tert-butyl N-[2-[4-[7-methoxy-4-(3-methyl-2, 2-dioxo-2thia-3, 7-diazaspiro[4.4]nonan-7-yl) -2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (150.00 mg, 124.22 μmol, 1 eq) in EtOAc (0.50 mL) was added HCl/EtOAc (2 M, 3.00 mL, 48.30 eq) at 20°C. The reaction mixture was stirred at 20°C for 1 hour, concentrated under reduced and the residue was purified by prep-HPLC **1** (gradient: 2-10 min 0-30%; flow 25 mL/min) basified by SCX cation exchange resin to give **Example 267** (23.11 mg, 45.26 μmol, 36.43% yield, 100% purity) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.19 - 8.08 (m, 3H), 7.27 (d, J = 2.4 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 6.99 (br dd, J = 2.9, 9.3 Hz, 1H), 6.95 - 6.89 (m, 1H), 4.09 (t, J = 5.6 Hz, 2H), 3.96 - 3.82 (m, 5H), 3.72 (s, 1H), 3.53 - 3.49 (m, 1H), 3.21 (br s, 3H), 2.86 (t, J = 5.4 Hz, 2H), 2.62 - 2.57 (m, 3H), 2.36 (s, 3H), 2.20 - 1.90 (m, 2H), 1.38 - 1.26 (m, 3H) MS m/z (ESI) $[M+H]^+$= 511.3.

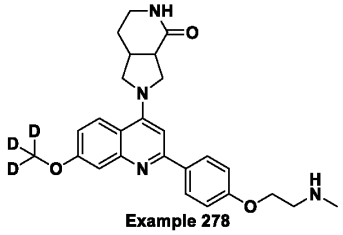
Example 272: 2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-8-one



Example 272

[0715] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[6-fluoro-7-methoxy-4-(8-oxo-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (100 mg, 177.10 μmol, 1 eq) in dioxane (1 mL) was added HCl/dioxane (4 M, 666.67 μL, 15.06 eq). The resulting mixture was stirred at 25°C for 1 hour, filtered and evaporated under reduced pressure and the crude product was purified by prep-HPLC **10** (gradient:2%-32% over 10 min) basified by SCX cation exchange resin to give **Example 272** (41.19 mg, 88.40 μmol, 49.92% yield, 99.7% purity) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 7.95 - 7.90 (m, 3H), 7.43 (d, J = 8.7 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 6.80 (s, 1H), 4.20 (t, J = 5.2 Hz, 2H), 4.00 (s, 3H), 3.90 - 3.84 (m, 2H), 3.76 (s, 2H), 3.45 (d, J = 3.3 Hz, 2H), 3.08 (t, J = 5.1 Hz, 2H), 2.54 (s, 3H), 2.51 - 2.44 (m, 2H), 2.14 (dt, J = 2.3, 6.7 Hz, 2H). MS m/z (ESI) $[M+H]^+$= 465.3.

Example 278: cis-2-(7-(methoxy-d3)-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one

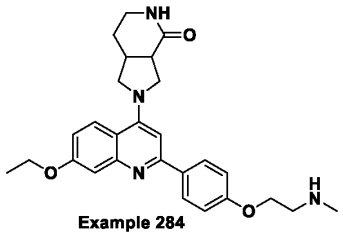


Example 278

[0716] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of cis-tert-butyl (2-(4-(7-(methoxy-d_3) -4-(4-oxooctahydro-2H-pyrrolo[3, 4-c]pyridin-2-yl) quinolin-2-yl) phenoxy) ethyl) (methyl) carbamate (210 mg, 382.04 μmol, 1 eq) in DCM (3 mL) was added TFA (767.50 mg, 6.73 mmol, 0.5 mL, 17.62 eq), the reaction mixture was stirred at 25°C for 1 hour. The resulting mixture was stirred at 25°C for 2 hours, filtered and evaporated under reduced pressure and the crude product was purified by prep-HPLC **8** (gradient:2%-32% over 20 min) basified by SCX cation exchange resin to give **Example 278** (42.28 mg, 90.57 μmol, 23.71% yield, 96.3% purity) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.19 - 8.12 (m, 3H), 7.74 (br s, 1H), 7.25 (d, J = 2.8 Hz, 1H), 7.05 (d, J = 8.9 Hz, 2H), 6.98 (dd, J = 2.8, 9.3 Hz, 1H), 6.92 (s, 1H), 4.14 (t, J = 5.4 Hz, 2H), 3.99 - 3.92 (m, 1H), 3.91 -

3.83 (m, 2H), 3.55 (br d, J = 5.1 Hz, 1H), 3.24 (br dd, J = 4.4, 8.4 Hz, 2H), 3.03 - 2.98 (m, 3H), 2.77 (br dd, J = 2.1, 5.2 Hz, 1H), 2.44 (s, 3H), 1.95 - 1.87 (m, 1H), 1.74 - 1.63 (m, 1H). MS m/z (ESI) $[M+H]^+$= 450.2.

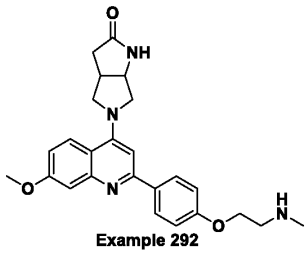
Example 284: (cis)-2-[7-ethoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one



Example 284

[0717] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of cis-tert-butyl (2-(4-(7-ethoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (100 mg, 178.35 μmol, 1 eq) in DCM (1 mL) was added TFA (460.50 mg, 4.04 mmol, 0.3 mL, 22.64 eq). The reaction mixture was stirred at 25 °C for 1 hour, concentrated and the residue was purified by prep-HPLC **3** (gradient:0%-28% B over 10 min) basified by SCX cation exchange resin to give **Example 284** (50.15 mg, 108.89 μmol, 61.05% yield, 100% purity) was obtained as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.22 (d, J = 9.4 Hz, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 2.7 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.06 (dd, J = 2.5, 9.5 Hz, 1H), 6.82 (s, 1H), 4.25 (t, J = 5.1 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 4.13 - 4.00 (m, 3H), 3.68 (dd, J = 3.8, 10.3 Hz, 1H), 3.46 - 3.39 (m, 2H), 3.22 - 3.14 (m, 3H), 2.92 - 2.82 (m, 1H), 2.59 (s, 3H), 2.00 (qd, J = 4.5, 13.7 Hz, 1H), 1.90 - 1.75 (m, 1H), 1.48 (t, J = 7.0 Hz, 3H). MS m/z (ESI) $[M+H]^+$= 461.3.

Example 292: cis-5-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)hexahydropyrrolo[3,4-b]pyrrol-2(1H)-one

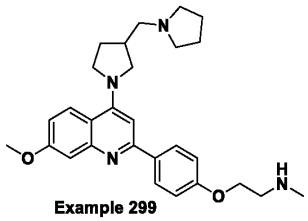


Example 292

[0718] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of cis-tert-butyl(2-(4-(7-methoxy-4-(2-oxohexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl) quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (120 mg, 0.153 mmol, 68% purity, 1.00 eq) in dioxane (2.00 mL) was added HCl/dioxane (2.00 M, 3.00 mL) at 25°C. The mixture was stirred at

25°C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC **8** (gradient:5%-35% B over 20 min). The salt was basified by Strong Cation Exchange Resin. 1) Wash resin with deionized water 20 mL; 2) Wash resin with the salt in methanol (target was adsorbed to the resin); 3) Wash resin with deionized water until the pH of the solution is neutral; 4) Wash resin with ammonium hydroxide/methanol, target was cleaved from the resin; 5) concentration and lyophilization give **Example 292** (35.0 mg, 0.0794 mmol, 51.8% yield, 98.1% purity) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.18 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 9.4 Hz, 1H), 7.89 (s, 1H), 7.30 (d, J = 2.6 Hz, 1H), 7.12 - 7.02 (m, 4H), 4.29 - 4.22 (m, 1H), 4.14 (t, J = 5.4 Hz, 2H), 3.91 (s, 3H), 3.65 (d, J = 10.9 Hz, 1H), 3.57 - 3.52 (m, 2H), 3.47 - 3.44 (m, 1H), 3.15 - 3.05 (m, 1H), 2.98 (t, J = 5.4 Hz, 2H), 2.59 (dd, J = 9.1, 17.1 Hz, 1H), 2.43 (s, 3H), 2.22 (dd, J = 2.4, 17.1 Hz, 1H). MS m/z (ESI) $[M+H]^+$= 433.2.

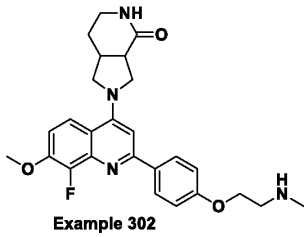
Example 299: 2-[4-[7-methoxy-4-[3-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine



Example 299

[0719] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl N-[2-[4-[7-methoxy-4-[3-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (150 mg, 267.51 μmol, 1 eq) in dioxane (2 mL) was added HCl/dioxane (4 M, 0.5 mL, 7.48 eq). The resulting mixture was stirred at 25°C for 1 hours, concentrated and the crude product was purified by prep-HPLC **10** (gradient:1%-25% over 10.0 min) basified by SCX cation exchange resin to give **Example 299** (44.43 mg, 95.98 μmol, 35.88% yield, 99.5% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.58 (br s, 1H), 11.28 (br s, 1H), 9.33 (br s, 2H), 8.55 (br d, J = 9.5 Hz, 1H), 8.15 (d, J = 8.6 Hz, 2H), 7.90 (s, 1H), 7.25 (d, J = 8.9 Hz, 2H), 7.18 (d, J = 2.4, 9.5 Hz, 1H), 6.82 (s, 1H), 4.43 (br t, J = 4.8 Hz, 2H), 4.35 (br d, J = 1.6 Hz, 1H), 4.17 - 3.86 (m, 7H), 3.39 - 3.32 (m, 4H), 3.04 (br s, 2H), 2.84 (br s, 1H), 2.64 (t, J = 5.4 Hz, 3H), 2.32 (d, J = 3.3, 6.8 Hz, 1H), 2.10 - 1.82 (m, 6H). MS m/z (ESI)461.3$[M+H]^+$. $[M+H]^+$= 461.3.

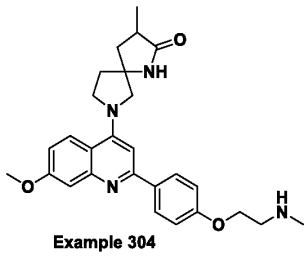
Example 302: (cis)-2-[8-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one



Example 302

[0720] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of cis-tert-butyl (2-(4-(8-fluoro-7-methoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (80 mg, 141.68 µmol, 1 eq) in DCM (2 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 95.02 eq). The resulting mixture was stirred at 25°C for 12 hours, filtered and concentrated and the crude product was purified by prep-HPLC **10** (gradient:0%-30% over 10.0 min) basified by SCX cation exchange resin to give **Example 302** (35.67 mg, 76.79 µmol, 54.20% yield, 100% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.19 (d, J = 9.0 Hz, 2H), 8.06 (br d, J = 10.0 Hz, 1H), 7.74 (br s, 1H), 7.30 (t, J = 8.9 Hz, 1H), 7.06 (br d, J = 8.8 Hz, 2H), 6.95 (s, 1H), 4.14 (br t, J = 5.4 Hz, 2H), 4.03 - 3.94 (m, 5H), 3.91 (br d, J = 8.1 Hz, 2H), 3.61 - 3.56 (m, 1H), 3.26 - 3.22 (m, 1H), 3.05 - 2.96 (m, 3H), 2.78 (br s, 1H), 2.43 (s, 3H), 1.94 - 1.87 (m, 1H), 1.69 (br s, 1H). MS m/z (ESI) $[M+H]^+$= 465.4.

Example 304: 7-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3-methyl-1,7-diazaspiro[4.4]nonan-2-one

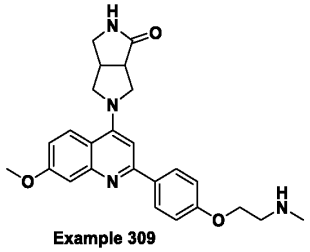


Example 304

[0721] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of tert-butyl N-[2-[4-[7-methoxy-4-(3-methyl-2-oxo-1,7-diazaspiro[4.4]nonan-7-yl)-2-quinolyl]phenoxy]ethyl]-N-methyl-carbamate (80 mg, 142.68 µmol, 1 eq) in DCM (1 mL) was added TFA (307.00 mg, 2.69 mmol, 0.2 mL, 18.87 eq) at 25°C. The mixture was stirred at 25°C for 2 hours. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO2, DCM : MeOH : $NH_3.H_2O$ = 10:1:0.1) to give **Example 304** (30.8 mg, 66.87 µmol, 46.87% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ

(ppm): 8.21 (d, J = 16.4 Hz, 1H), 8.17 - 8.09 (m, 3H), 7.25 (d, J = 2.5 Hz, 1H), 7.04 (d, J = 8.2 Hz, 2H), 6.98 (d, J = 9.4 Hz, 1H), 6.87 (d, J = 4.2 Hz, 1H), 4.09 (t, J = 5.6 Hz, 2H), 3.89 (s, 4H), 3.83 - 3.74 (m, 2H), 3.64 (dd, J = 9.8, 14.4 Hz, 1H), 2.91 - 2.84 (m, 2H), 2.44 - 2.30 (m, 4H), 2.15 - 2.00 (m, 2H), 1.81 - 1.65 (m, 1H), 1.08 (t, J = 6.4 Hz, 3H). MS m/z (ESI) $[M+H]^+$= 461.4.

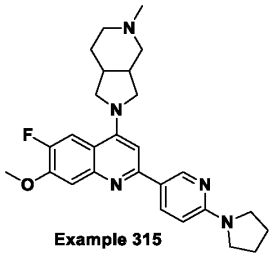
Example 309: 7-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3-methyl-1,7-diazaspiro[4.4]nonan-2-one



Example 309

[0722] According to Scheme 3 Step 3: Conditions 2 TFA: To a solution of give tert-butyl (2-(4-(7-methoxy-4-(4-oxohexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (150 mg, 281.62 μmol, 1 eq) in DCM (2 mL) was added TFA (32.11 mg, 281.62 μmol, 20.92 μL, 1 eq). The resulting mixture was stirred at 25°C for 1 hour. The reaction mixture was filtered and evaporated under reduced pressure to give the crude product. The crude product was purified by prep-HPLC (Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [H_2O(0.05%HCl)-ACN];gradient:1%-29% B over 10.0 min) to give the **Example 309** (17.96 mg, 40.65 μmol, 14.44% yield, 97.9% purity) as a yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.30 - 8.14 (m, 3H), 8.10 - 8.03 (m, 1H), 8.06 (d, J = 9.4 Hz, 1H), 7.85 - 7.81 (m, 1H), 7.82 (s, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.09 - 7.02 (m, 4H), 4.16 (br t, J = 5.3 Hz, 2H), 3.90 (s, 3H), 3.85 (br d, J = 10.0 Hz, 1H), 3.69 (br d, J = 8.3 Hz, 2H), 3.65 - 3.62 (m, 2H), 3.56 (br d, J = 2.3 Hz, 3H), 3.05 - 3.01 (m, 2H), 2.45 (s, 3H). MS m/z (ESI) $[M+H]^+$= 433.3.

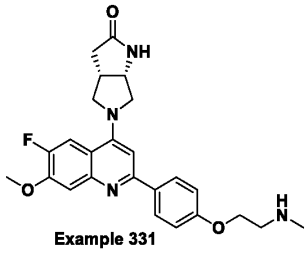
Example 315: (cis)-6-fluoro-7-methoxy-4-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-2-(6-(pyrrolidin-1-yl)pyridin-3-yl)quinoline



Example 315

[0723] According to Scheme 1 Step 5: Conditions 4 Buchwald: To a screw-cap vial equipped with a magnetic stir bar was added 4-chloro-6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl) quinoline (200 mg, 558 μmol, 1 eq) and dioxane (4 mL) and cis-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine (140 mg, 998 μmol, 1.8 eq) and Cs_2CO_3 (550 mg, 1.69 mmol, 3 eq) and SPhos Pd G3 (50 mg, 64.0 μmol, 0.1 eq) sequentially. After work-up the reaction mixture was diluted with DCM/MeOH (10 mL, 10/1) and purified by silica gel chromatography (100-200 mesh silica gel, DCM/MeOH =10/1) to give crude product. The crude product was purified by prep-HPLC **2** (gradient:2%-26% over 10 min) basified by SCX cation exchange resin to give **Example 315** (68 mg, 147 μmol, 64.8% yield, 99.9% purity) as yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ (ppm): 8.65 (d, J = 2.2 Hz, 1H), 8.13 (dd, J = 2.4, 9.0 Hz, 1H), 8.00 (d, J = 13.8 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 6.75 (s, 1H), 6.62 (d, J = 8.8 Hz, 1H), 4.01 (s, 3H), 3.95 - 3.76 (m, 3H), 3.75 - 3.67 (m, 1H), 3.53 (br t, J = 6.5 Hz, 4H), 2.69 - 2.49 (m, 4H), 2.49 - 2.41 (m, 1H), 2.41 - 2.34 (m, 1H), 2.32 (s, 3H), 2.08 (br t, J = 6.7 Hz, 4H), 1.88 (tt, J = 4.3, 8.1 Hz, 1H), 1.80 - 1.68 (m, 1H). MS m/z (ESI) $[M+H]^+$= 462.2.

Example 331: (3aS,6aS)-5-(6-fluoro-7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)hexahydropyrrolo[3,4-b]pyrrol-2(1H)-one

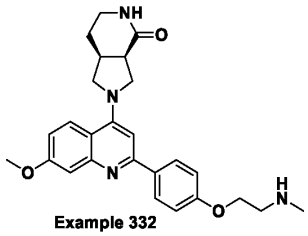


Example 331

[0724] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl (2-(4-(6-fluoro-7-methoxy-4-((3aS,6aS)-2-oxohexahydropyrrolo[3,4-b]pyrrol-5(1H)-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (60.0 mg, 97.0% purity, 105 μmol, 1.00 eq) in dioxane (2.00 mL) was added HCl/dioxane (2 M, 6.00 mL, 115 eq) at 25°C. The mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated under reduce presser to give a residue, The residue was purified by prep-HPLC **8** (gradient:1%-27% B over 20 min). The salt was basified by Strong Cation Exchange Resin. 1) Wash resin with deionized water 20 mL; 2) Wash resin with the salt in methanol (target was adsorbed to the resin); 3) Wash resin with deionized water until the pH of the solution is neutral; 4) Wash resin with ammonium hydroxide/methanol, target was cleaved from the resin; 5) concentration and lyophilization give **Example 311** (16.0 mg, 35.5 μmol, 33.9% yield, 100% purity) as a yellow solid. ^{1}H

NMR (400 MHz, methanol-d_4) δ (ppm): 8.16 (d, J = 8.80 Hz, 2H), 7.91 (s, 1H), 7.79 (d, J = 13.2 Hz, 1H), 7.49 (d, J = 8.80 Hz, 1H), 7.16 (s, 1H), 7.06 (d, J = 8.80 Hz, 2H), 4.29 - 4.21 (m, 1H), 4.10 (t, J = 5.60 Hz, 2H), 4.00 (s, 3H), 3.64 (d, J = 10.8 Hz, 1H), 3.58 - 3.48 (m, 2H), 3.41 (dd, J = 4.92, 10.8 Hz, 1H), 3.13 - 3.06 (m, 1H), 2.88 (t, J = 5.52 Hz, 2H), 2.59 (dd, J = 9.32, 17.2 Hz, 1H), 2.37 (s, 3H), 2.21 (dd, J = 2.40, 17.2 Hz, 1H). MS m/z (ESI) $[M+H]^+$= 451.2.

Example 332: (3aR,7aS)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one

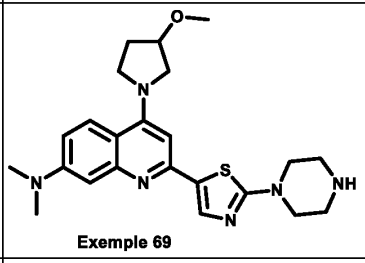
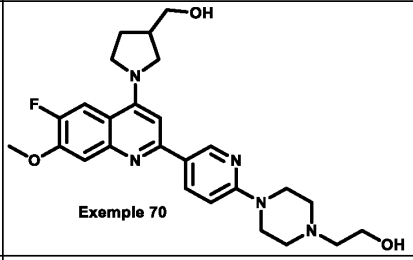
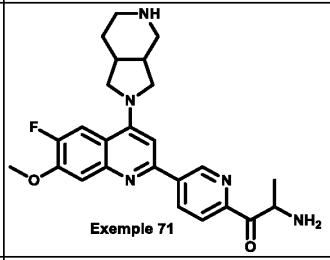
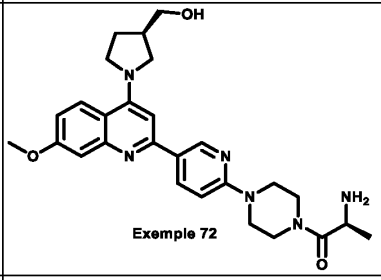
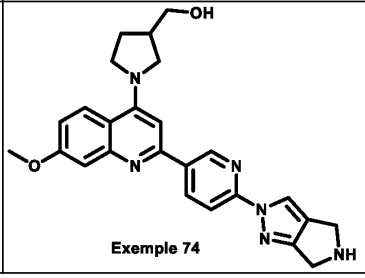


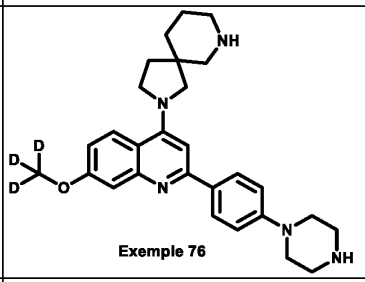
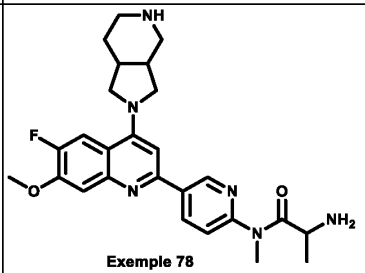
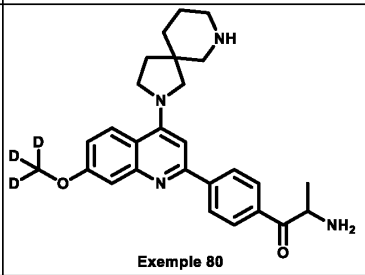
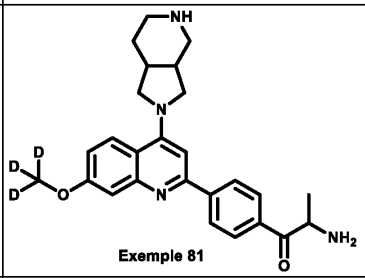
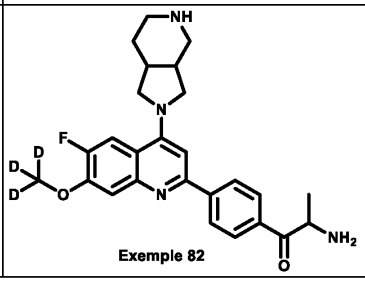
Example 332

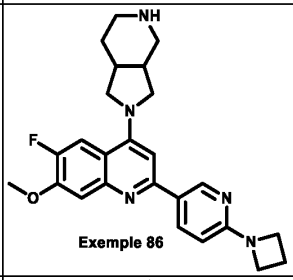
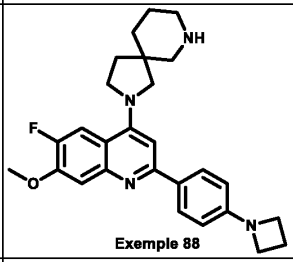
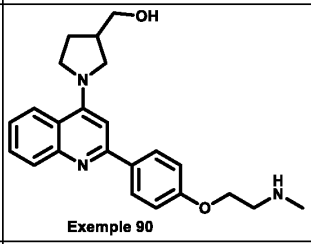
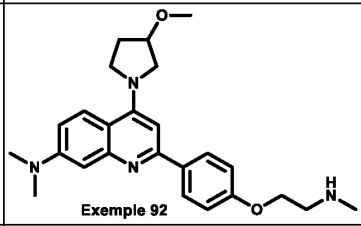
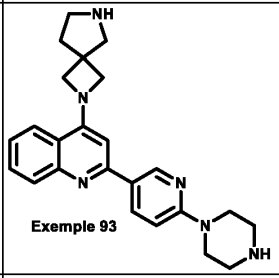
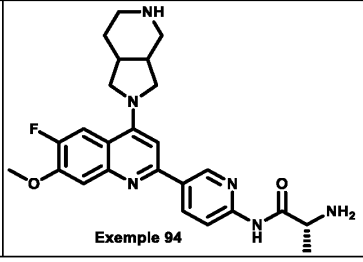
[0725] According to Scheme 3 Step 3: Conditions 1 HCl: To a solution of tert-butyl (2-(4-(7-methoxy-4-((3aR,7aS)-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenoxy)ethyl)(methyl)carbamate (150 mg, 274.40 µmol, 1 eq) in MeOH (2 mL) was added HCl/dioxane (2 M, 2 mL, 14.58 eq). The reaction solution was stirred at 25°C for 1 hour, concentrated under vacuum nand the crude product was purified by prep-HPLC **10** (gradient:1%-25% over 10.0 min) basified by SCX cation exchange resin to give **Example 332** (95 mg, 208.92 µmol, 76.14% yield, 98.2% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.42 (s, 1H), 9.31 - 9.07 (m, 2H), 8.48 (d, J = 9.5 Hz, 1H), 8.12 (d, J = 8.8 Hz, 2H), 7.83 (br s, 1H), 7.76 (d, J = 1.8 Hz, 1H), 7.28 - 7.19 (m, 3H), 6.85 (s, 1H), 4.41 (t, J = 5.0 Hz, 2H), 4.34 - 4.14 (m, 3H), 3.99 - 3.87 (m, 4H), 3.39 - 3.23 (m, 4H), 3.11 (q, J = 6.8 Hz, 1H), 2.95 - 2.78 (m, 1H), 2.67 - 2.62 (m, 3H), 2.00 - 1.87 (m, 1H), 1.79 - 1.65 (m, 1H). MS m/z (ESI) $[M+H]^+$= 447.3.

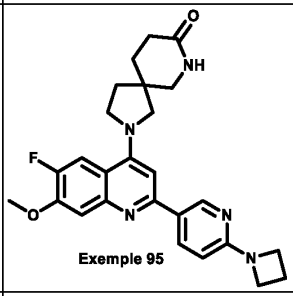
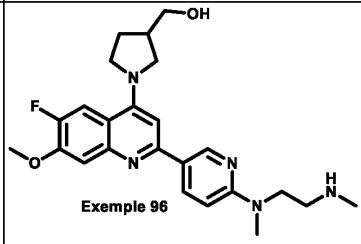
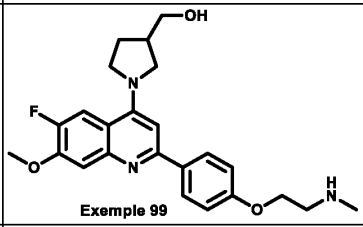
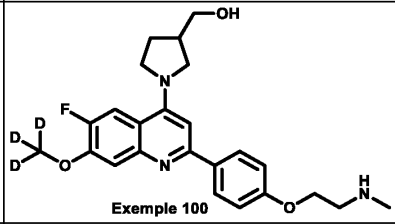
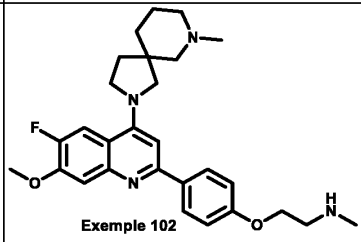
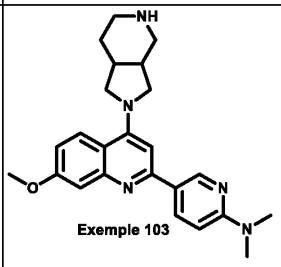
[0726] The compounds in **Table 3** were synthesized using methods similar to those disclosed elsewhere herein.

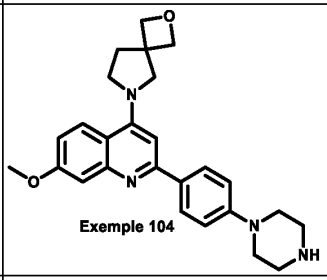
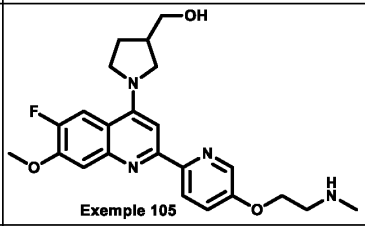
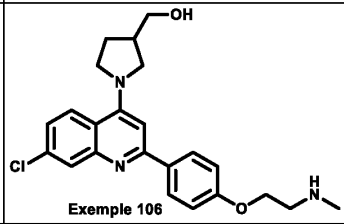
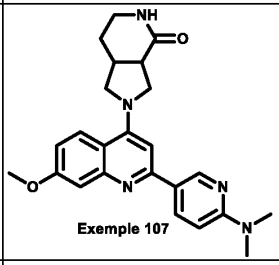
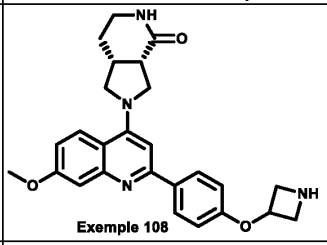
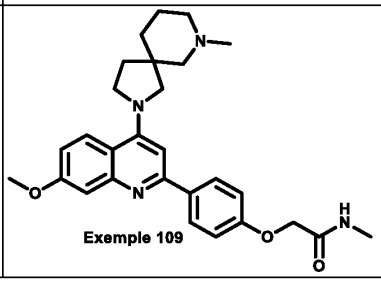
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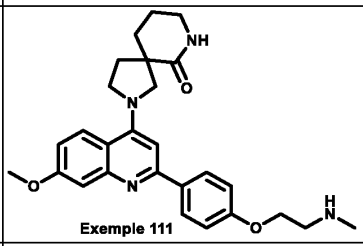
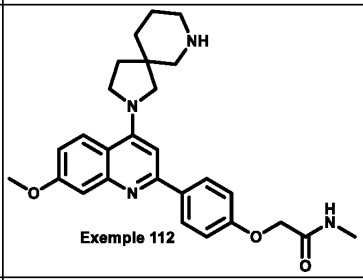
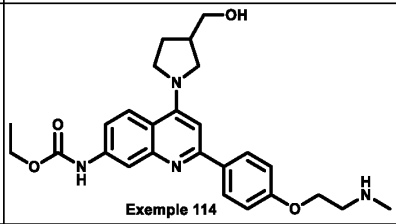
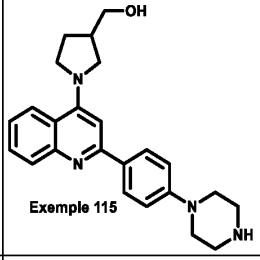
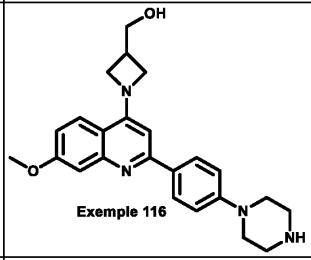
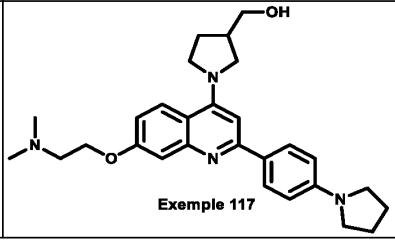
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
69	 Exemple 69	4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(2-(piperazin-1-yl)thiazol-5-yl)quinolin-7-amine	439.2
70	 Exemple 70	2-(4-(5-(6-fluoro-4-(3-(hydroxymethyl)pyrrolidin-1-yl)-7-methoxyquinolin-2-yl)pyridin-2-yl)piperazin-1-yl)ethan-1-ol	482.3
71	 Exemple 71	2-amino-1-(5-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)propan-1-one	450.3
72	 Exemple 72	(S)-2-amino-1-(4-(5-(4-((R)-3-(hydroxymethyl)pyrrolidin-1-yl)-7-methoxyquinolin-2-yl)pyridin-2-yl)piperazin-1-yl)propan-1-one	491.3
74	 Exemple 74	(1-(2-(6-(5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)pyridin-3-yl)-7-methoxyquinolin-4-yl)pyrrolidin-3-yl)methanol	443.3

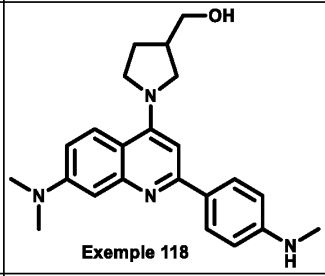
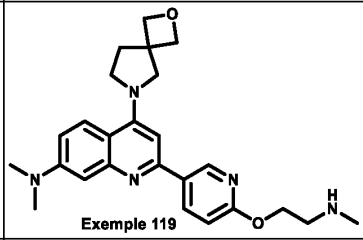
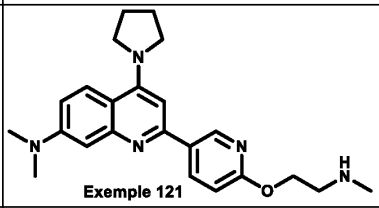
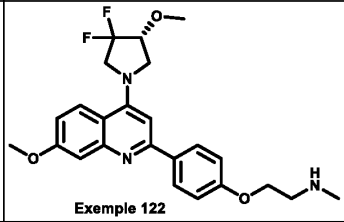
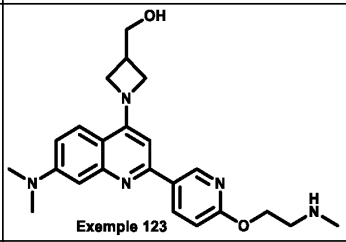
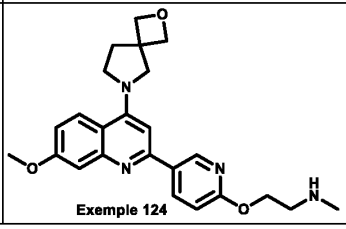
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
76	 Exemple 76	2-(7-(methoxy-d3)-2-(4-(piperazin-1-yl)phenyl)quinolin-4-yl)-2,7-diazaspiro[4.5]decane	461.4
78	 Exemple 78	2-amino-N-(5-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)-N-methylpropanamide	479.3
80	 Exemple 80	2-amino-1-(4-(7-(methoxy-d3)-4-(2,7-diazaspiro[4.5]decan-2-yl)quinolin-2-yl)phenyl)propan-1-one	448.2
81	 Exemple 81	2-amino-1-(4-(7-(methoxy-d3)-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)propan-1-one	434.2
82	 Exemple 82	2-amino-1-(4-(6-fluoro-7-(methoxy-d3)-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)propan-1-one	449.2

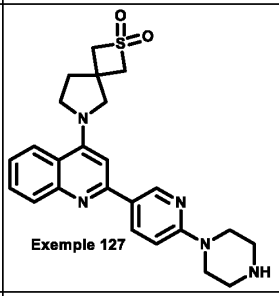
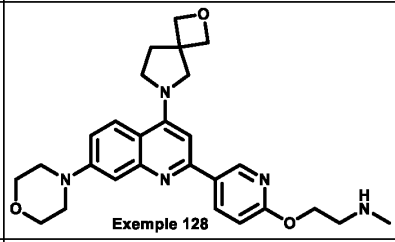
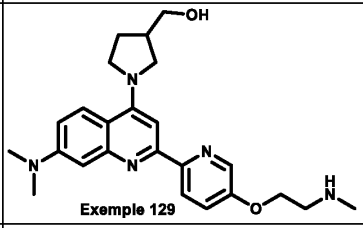
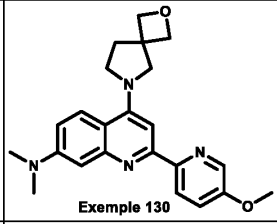
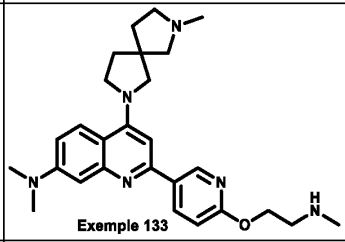
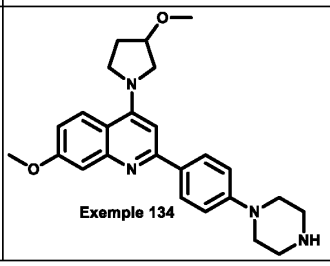
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
86	 Exemple 86	2-(6-(azetidin-1-yl)pyridin-3-yl)-6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinoline	434.2
88	 Exemple 88	2-(2-(4-(azetidin-1-yl)phenyl)-6-fluoro-7-methoxyquinolin-4-yl)-2,7-diazaspiro[4.5]decane	447.4
90	 Exemple 90	(1-(2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)methanol	378.3
92	 Exemple 92	4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-7-amine	421.3
93	 Exemple 93	2-(6-(piperazin-1-yl)pyridin-3-yl)-4-(2,6-diazaspiro[3.4]octan-2-yl)quinoline	401.2
94	 Exemple 94	(2R)-2-amino-N-(5-(6-fluoro-7-methoxy-4-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)pyridin-2-yl)propanamide	465.3

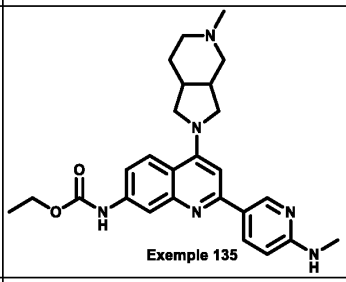
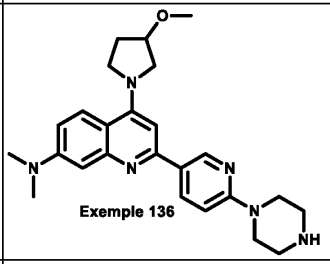
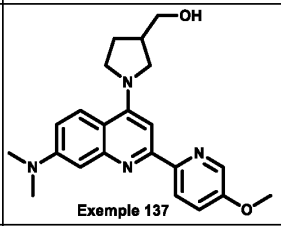
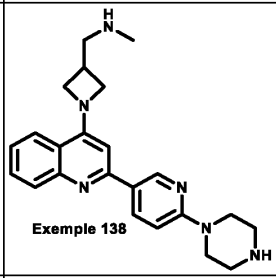
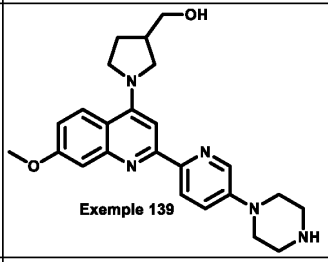
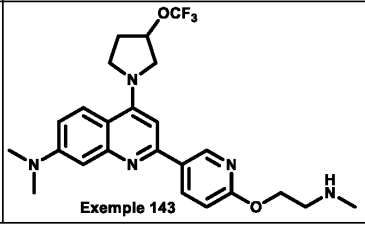
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
95	 Exemple 95	2-(2-(6-(azetidin-1-yl)pyridin-3-yl)-6-fluoro-7-methoxyquinolin-4-yl)-2,7-diazaspiro[4.5]decan-8-one	462.2
96	 Exemple 96	(1-(6-fluoro-7-methoxy-2-(6-(methyl(2-(methylamino)ethyl)amino)pyridin-3-yl)quinolin-4-yl)pyrrolidin-3-yl)methanol	440.3
99	 Exemple 99	[1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol	426.2
100	 Exemple 100	[1-[6-fluoro-2-[4-[2-(methylamino)ethoxy]phenyl]-7-(trideuteriomethoxy)-4-quinolyl]pyrrolidin-3-yl]methanol	429.2
102	 Exemple 102	2-[4-[6-fluoro-7-methoxy-4-(9-methyl-2,9-diazaspiro[4.5]decan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine	479.2
103	 Exemple 103	5-[7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-N,N-dimethyl-pyridin-2-amine	418.2

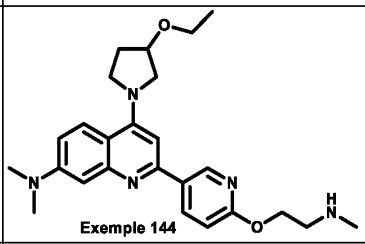
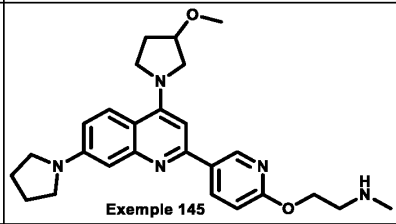
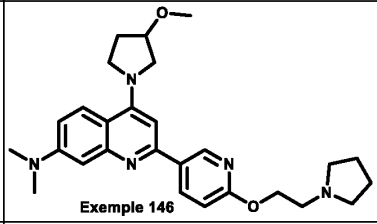
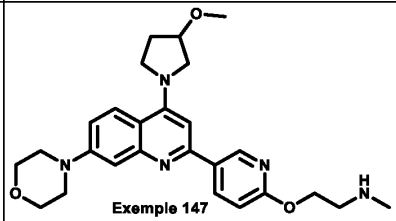
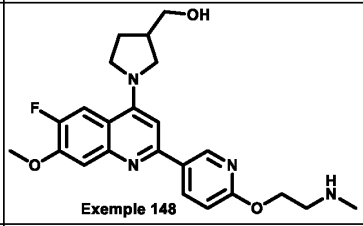
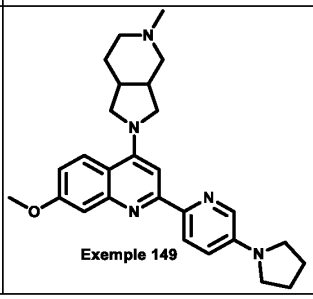
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
104	 Exemple 104	7-[7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]-2-oxa-7-azaspiro[3.4]octane	431.2
105	 Exemple 105	[1-[6-fluoro-7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol	427.2
106	 Exemple 106	[1-[7-chloro-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol	412.1
107	 Exemple 107	2-[2-[6-(dimethylamino)-3-pyridyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	418.2
108	 Exemple 108	(3aS,7aR)-2-(2-(4-(azetidin-3-yloxy)phenyl)-7-methoxyquinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one	445.4
109	 Exemple 109	2-[4-[7-methoxy-4-(9-methyl-2,9-diazaspiro[4.5]decan-2-yl)-2-quinolyl]phenoxy]-N-methyl-acetamide	475.2

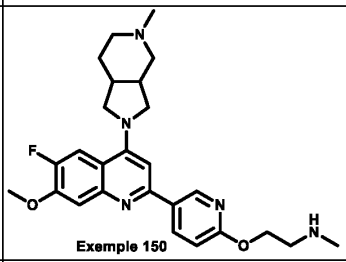
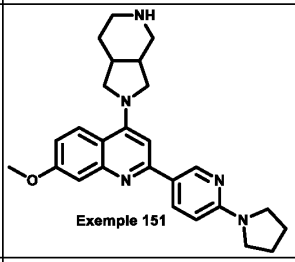
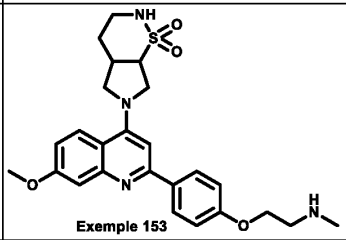
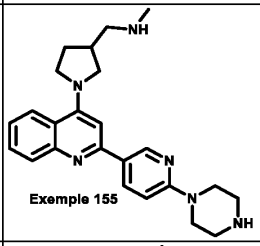
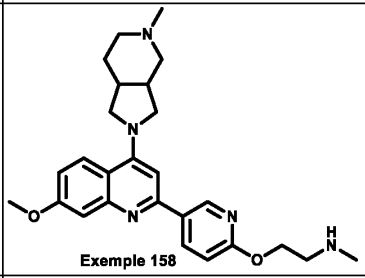
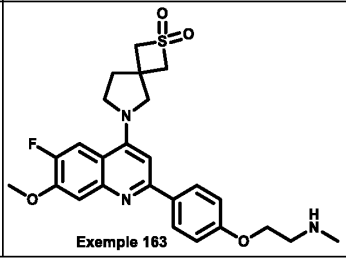
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
111	 Exemple 111	2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.5]decan-6-one	461.2
112	 Exemple 112	2-[4-[4-(2,9-diazaspiro[4.5]decan-2-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-acetamide	461.2
114	 Exemple 114	ethyl N-[4-[3-(hydroxymethyl)pyrrolidin-1-yl]-2-[4-[2-(methylamino)ethoxy]phenyl]-7-quinolyl]carbamate	465.3
115	 Exemple 115	[1-[2-(4-piperazin-1-ylphenyl)-4-quinolyl]pyrrolidin-3-yl]methanol	389.2
116	 Exemple 116	[1-[7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]azetidin-3-yl]methanol	405.2
117	 Exemple 117	[1-[7-[2-(dimethylamino)ethoxy]-2-(4-pyrrolidin-1-ylphenyl)-4-quinolyl]pyrrolidin-3-yl]methanol	461.3

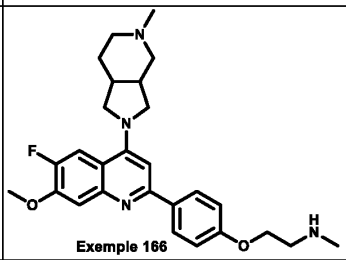
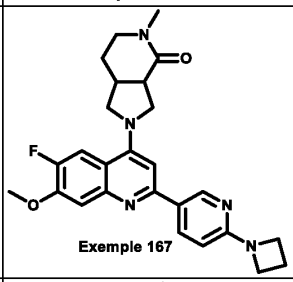
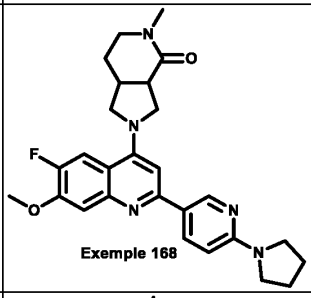
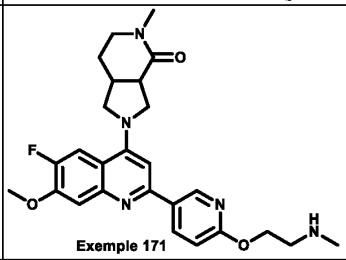
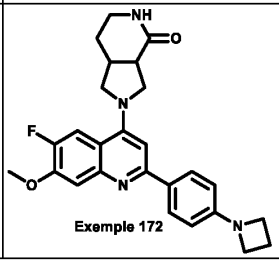
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
118	 Exemple 118	[1-[7-(dimethylamino)-2-[4-(methylamino)phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol	377.3
119	 Exemple 119	N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine	434.4
121	 Exemple 121	N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-pyrrolidin-1-yl-quinolin-7-amine	392.1
122	 Exemple 122	(R)-2-(4-(4-(3,3-difluoro-4-methoxypyrrolidin-1-yl)-7-methoxyquinolin-2-yl)phenoxy)-N-methylethan-1-amine	444.4
123	 Exemple 123	[1-[7-(dimethylamino)-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]azetidin-3-yl]methanol	408.2
124	 Exemple 124	2-[[5-[7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine	421.1

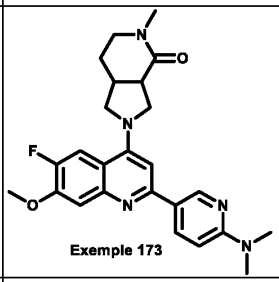
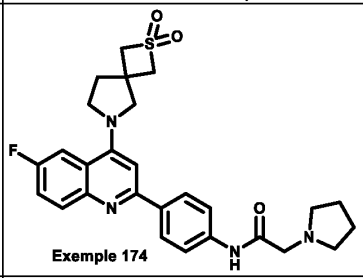
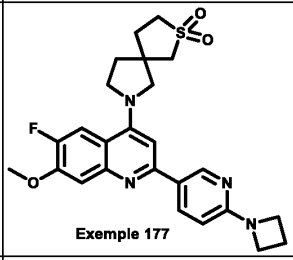
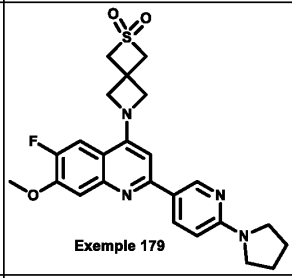
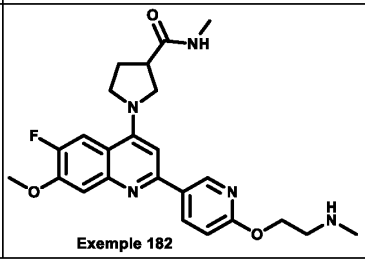
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
127	 Exemple 127	7-[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide	450.2
128	 Exemple 128	N-methyl-2-[[5-[7-morpholino-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-2-pyridyl]oxy]ethanamine	476.2
129	 Exemple 129	[1-[7-(dimethylamino)-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol	422.3
130	 Exemple 130	2-(5-methoxy-2-pyridyl)-N,N-dimethyl-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine	391.1
133	 Exemple 133	N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinolin-7-amine	461.3
134	 Exemple 134	7-methoxy-4-(3-methoxypyrrolidin-1-yl)-2-(4-piperazin-1-ylphenyl)quinoline	419.3

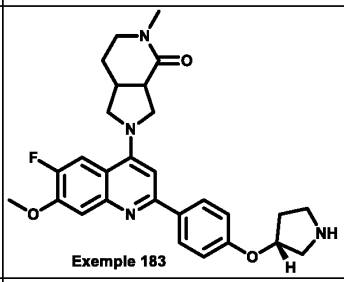
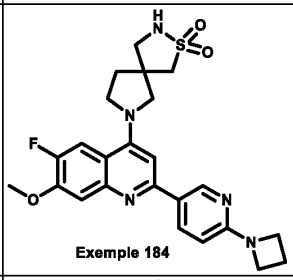
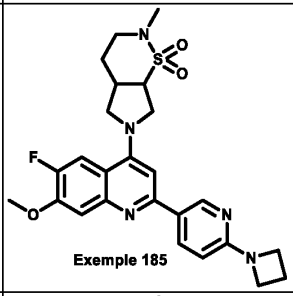
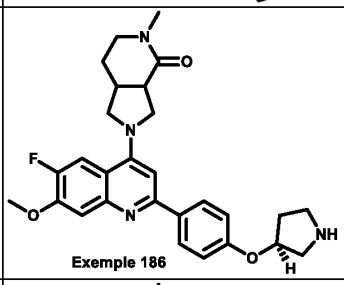
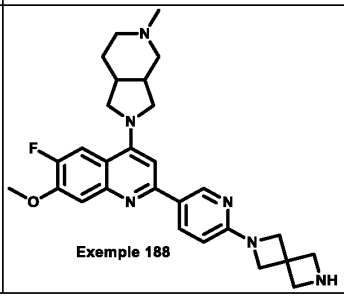
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
135	 Exemple 135	ethyl N-[4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[6-(methylamino)-3-pyridyl]-7-quinolyl]carbamate	461.3
136	 Exemple 136	4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(6-piperazin-1-yl-3-pyridyl)quinolin-7-amine	433.2
137	 Exemple 137	[1-[7-(dimethylamino)-2-(5-methoxy-2-pyridyl)-4-quinolyl]pyrrolidin-3-yl]methanol	379.2
138	 Exemple 138	N-methyl-1-[1-[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]azetidin-3-yl]methanamine	389.2
139	 Exemple 139	[1-[7-methoxy-2-(5-piperazin-1-yl-2-pyridyl)-4-quinolyl]pyrrolidin-3-yl]methanol	420.2
143	 Exemple 143	N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-[3-(trifluoromethoxy)pyrrolidin-1-yl]quinolin-7-amine	476.2

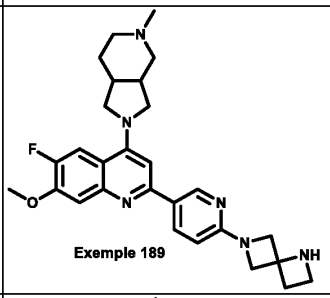
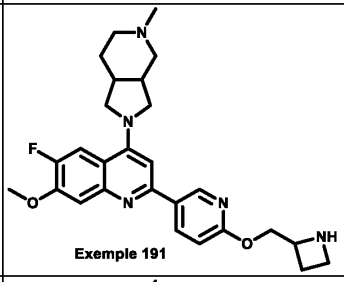
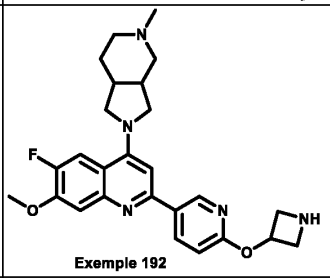
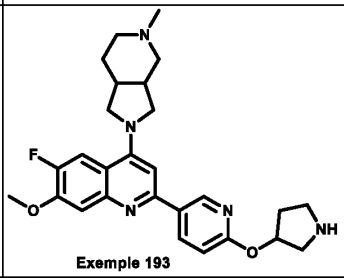
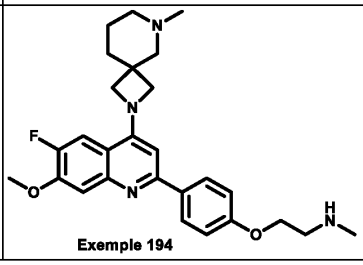
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
144	 Exemple 144	4-(3-ethoxypyrrolidin-1-yl)-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]quinolin-7-amine	436.3
145	 Exemple 145	2-[[5-[4-(3-methoxypyrrolidin-1-yl)-7-pyrrolidin-1-yl-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine	448.2
146	 Exemple 146	4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-[6-(2-pyrrolidin-1-ylethoxy)-3-pyridyl]quinolin-7-amine	462.2
147	 Exemple 147	2-[[5-[4-(3-methoxypyrrolidin-1-yl)-7-morpholino-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine	464.3
148	 Exemple 148	[1-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]pyrrolidin-3-yl]methanol	427.3
149	 Exemple 149	7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(5-pyrrolidin-1-yl-2-pyridyl)quinoline	444.3

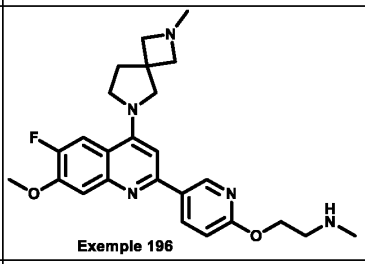
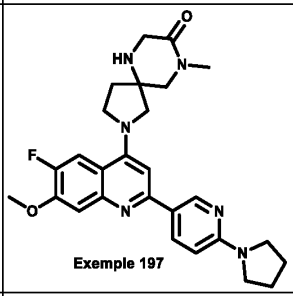
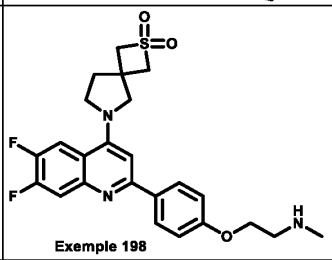
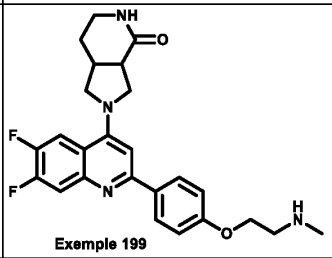
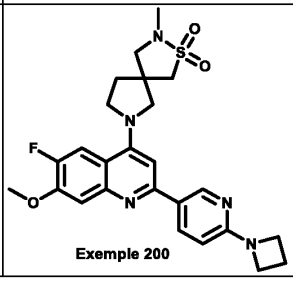
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
150	 Exemple 150	2-[[5-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine	466.2
151	 Exemple 151	4-(1,3,3a,4,5,6,7,7a-octahydropyrrolo[3,4-c]pyridin-2-yl)-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)quinoline	430.2
152	 Exemple 153	6-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)octahydropyrrolo[3,4-e][1,2]thiazine 1,1-dioxide	483.3
155	 Exemple 155	N-methyl-1-[1-[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]pyrrolidin-3-yl]methanamine	403.2
158	 Exemple 158	2-[[5-[7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine	448.3
163	 Exemple 163	2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine	486.1

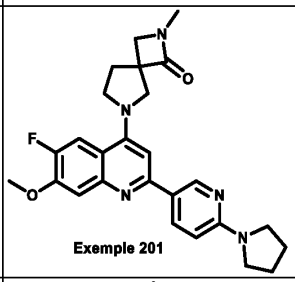
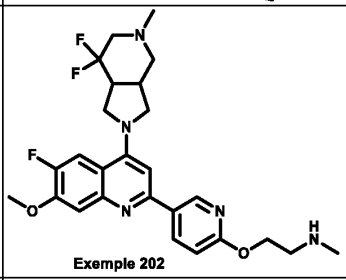
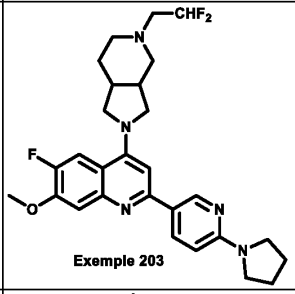
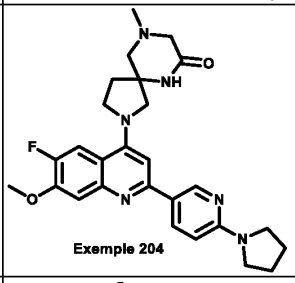
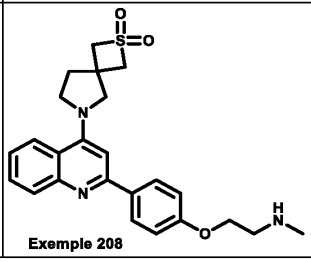
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
166	 Exemple 166	2-[4-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine	466.2
167	 Exemple 167	2-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	462.3
168	 Exemple 168	2-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	476.4
171	 Exemple 171	2-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	480.2
172	 Exemple 172	2-[2-[4-(azetidin-1-yl)phenyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	447.2

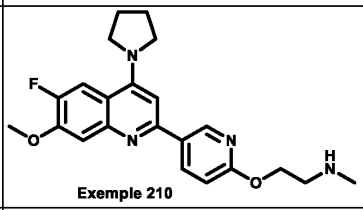
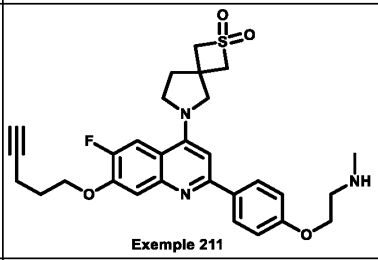
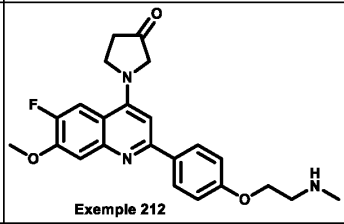
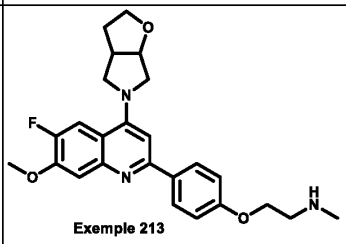
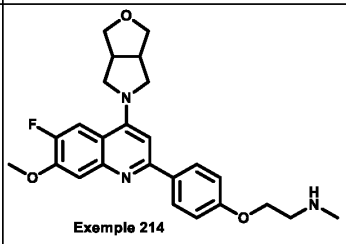
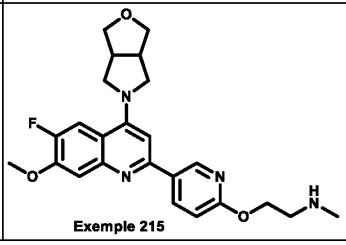
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
173	 Exemple 173	2-[2-[6-(dimethylamino)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	450.2
174	 Exemple 174	N-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-2-quinolyl]phenyl]-2-pyrrolidin-1-yl-acetamide	509.3
177	 Exemple 177	7-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2λ6-thia-7-azaspiro[4.4]nonane 2,2-dioxide	483.2
179	 Exemple 179	6-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-2λ6-thia-6-azaspiro[3.3]heptane 2,2-dioxide	469.2
182	 Exemple 182	1-[6-fluoro-7-methoxy-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	454.3

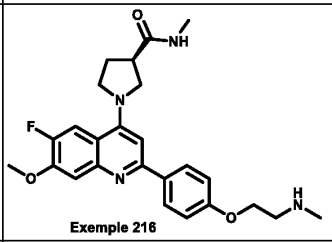
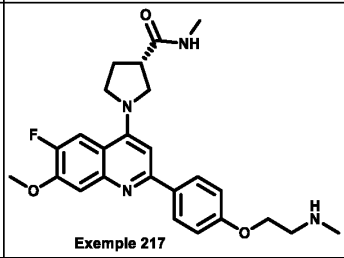
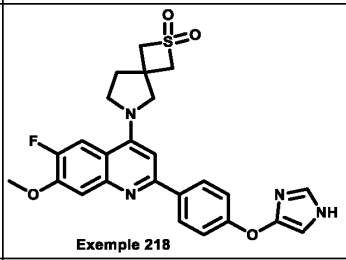
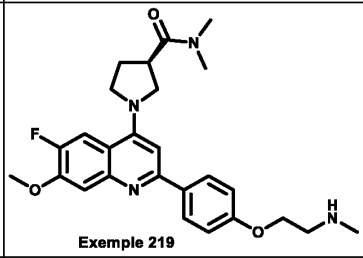
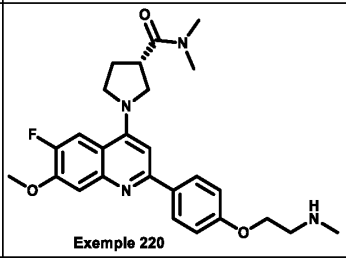
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
183	 Exemple 183	2-[6-fluoro-7-methoxy-2-[4-[(3R)-pyrrolidin-3-yl]oxyphenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	491.2
184	 Exemple 184	7-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2λ6-thia-3,7-diazaspiro[4.4]nonane 2,2-dioxide	484.1
185	 Exemple 185	6-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-2-methyl-3,4,4a,5,7,7a-hexahydropyrrolo[3,4-e]thiazine 1,1-dioxide	498.2
186	 Exemple 186	2-[6-fluoro-7-methoxy-2-[4-[(3S)-pyrrolidin-3-yl]oxyphenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	491.2
188	 Exemple 188	2-[6-(2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline	489.4

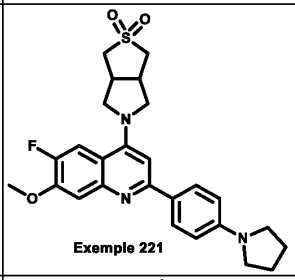
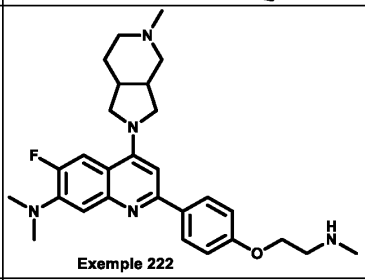
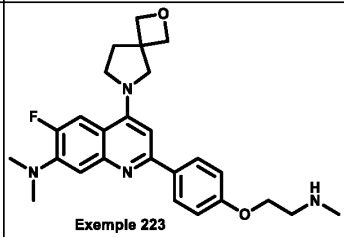
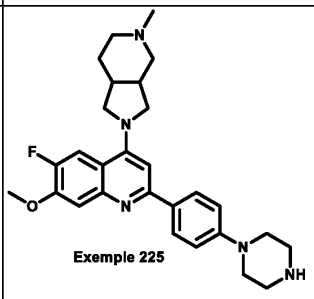
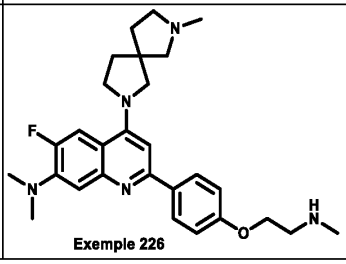
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
189	 Exemple 189	2-[6-(1,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline	489.3
191	 Exemple 191	2-[6-(azetidin-2-ylmethoxy)-3-pyridyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline	478.4
192	 Exemple 192	2-[4-(azetidin-3-yloxy)phenyl]-6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)quinoline	463.2
193	 Exemple 193	6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(4-pyrrolidin-3-yloxyphenyl)quinoline	477.2
194	 Exemple 194	2-[4-[6-fluoro-7-methoxy-4-(8-methyl-2,8-diazaspiro[3.5]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine	465.3

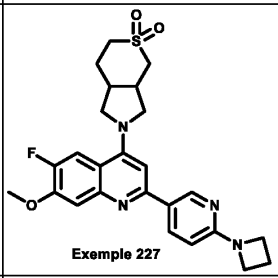
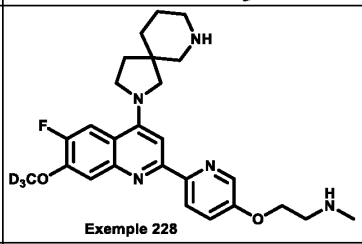
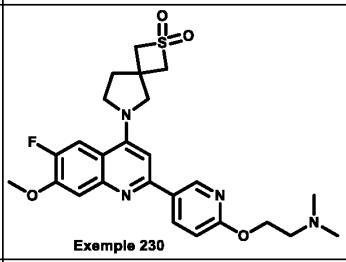
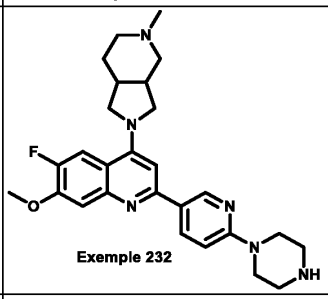
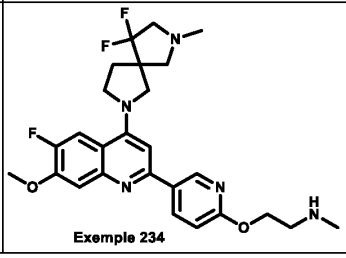
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
196	 Exemple 196	2-[[5-[6-fluoro-7-methoxy-4-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine	452.3
197	 Exemple 197	2-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-9-methyl-2,6,9-triazaspiro[4.5]decan-8-one	491.2
198	 Exemple 198	2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6,7-difluoro-2-quinolyl]phenoxy]-N-methyl-ethanamine	474.2
199	 Exemple 199	2-[6,7-difluoro-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	453.2
200	 Exemple 200	7-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-3-methyl-2λ6-thia-3,7-diazaspiro[4.4]nonane 2,2-dioxide	498.2

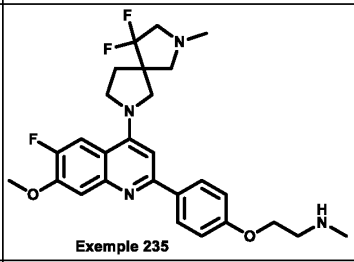
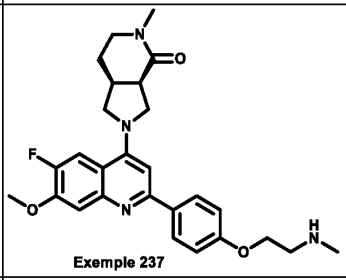
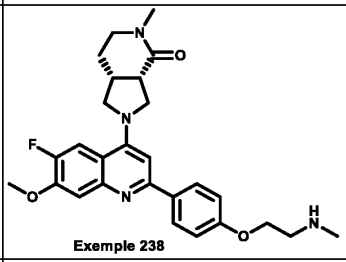
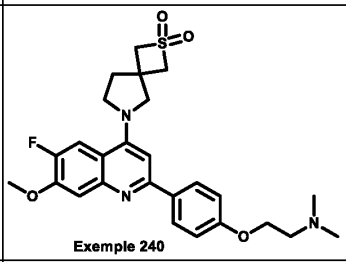
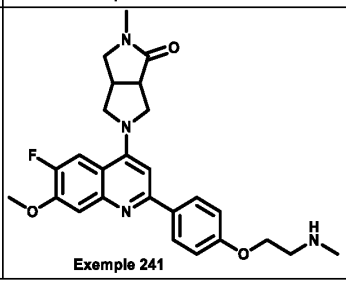
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
201	 Exemple 201	6-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-2-methyl-2,6-diazaspiro[3.4]octan-3-one	462.3
202	 Exemple 202	2-[[5-[4-(7,7-difluoro-5-methyl-1,3,3a,4,6,7a-hexahydropyrrolo[3,4-c]pyridin-2-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine	502.3
203	 Exemple 203	4-[5-(2,2-difluoroethyl)-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl]-6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)quinoline	512.2
204	 Exemple 204	2-[6-fluoro-7-methoxy-2-(6-pyrrolidin-1-yl-3-pyridyl)-4-quinolyl]-9-methyl-2,6,9-triazaspiro[4.5]decan-7-one	491.3
208	 Exemple 208	2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine	438.3

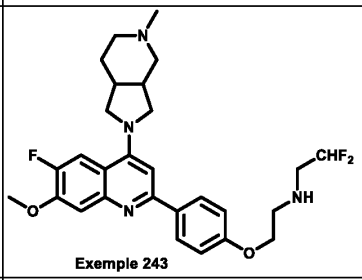
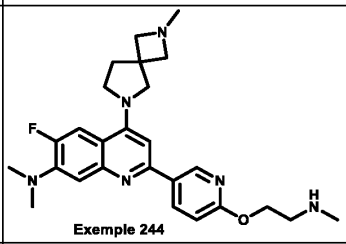
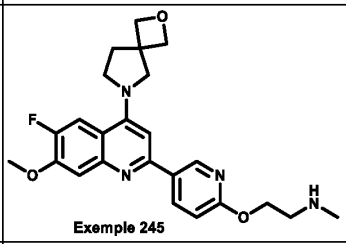
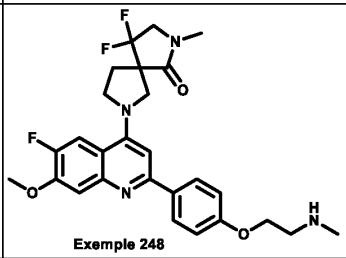
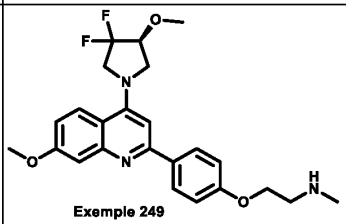
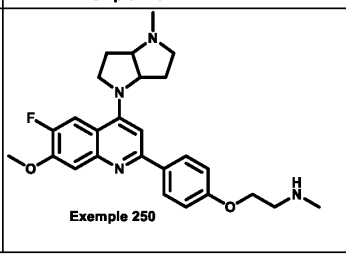
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
210	 Exemple 210	2-[[5-(6-fluoro-7-methoxy-4-pyrrolidin-1-yl-2-quinolyl)-2-pyridyl]oxy]-N-methyl-ethanamine	397.2
211	 Exemple 211	2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-pent-4-ynoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine	538.2
212	 Exemple 212	1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-one	410.3
213	 Exemple 213	2-[4-[4-(2,3,3a,4,6,6a-hexahydrofuro[2,3-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine	438.2
214	 Exemple 214	2-[4-[4-(1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine	438.3
215	 Exemple 215	2-[[5-[4-(1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine	439.2

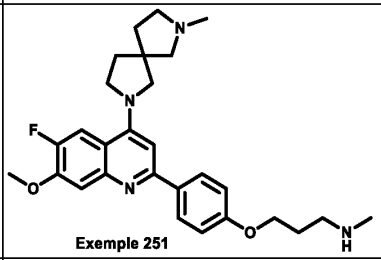
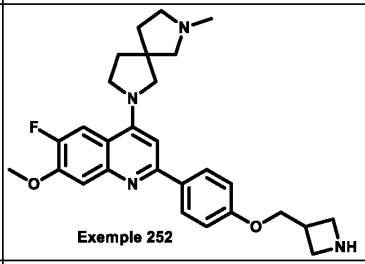
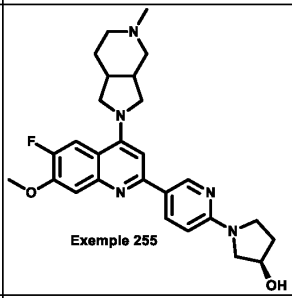
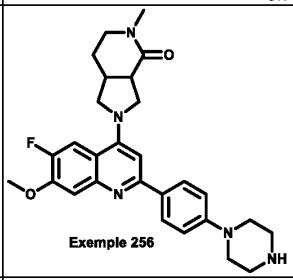
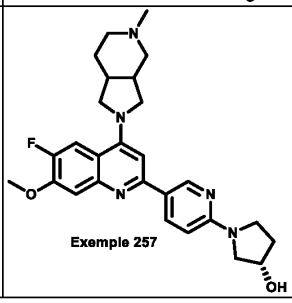
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
216	 Exemple 216	(3R)-1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	453.2
217	 Exemple 217	(3S)-1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	453.2
218	 Exemple 218	7-[6-fluoro-2-[4-(1H-imidazol-4-yloxy)phenyl]-7-methoxy-4-quinolyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide	495.1
219	 Exemple 219	(3R)-1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N,N-dimethyl-pyrrolidine-3-carboxamide	467.3
220	 Exemple 220	(3S)-1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N,N-dimethyl-pyrrolidine-3-carboxamide	467.3

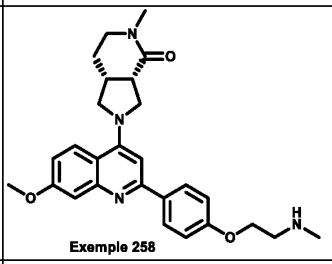
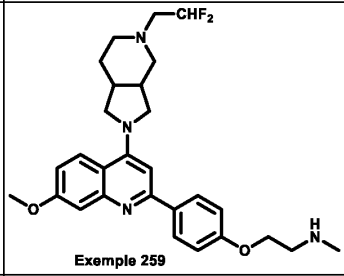
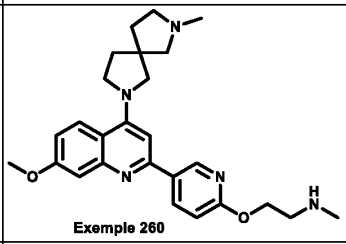
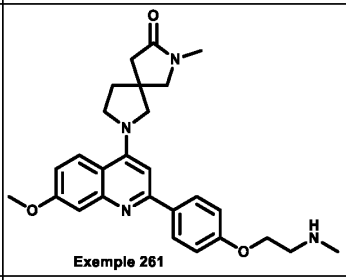
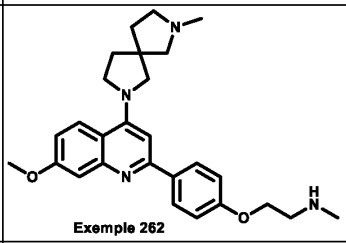
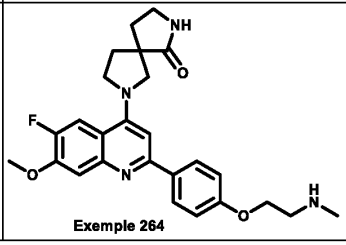
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
221	 Exemple 221	5-[6-fluoro-7-methoxy-2-(4-pyrrolidin-1-ylphenyl)-4-quinolyl]-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrole 2,2-dioxide	482.1
222	 Exemple 222	6-fluoro-N,N-dimethyl-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-[4-[2-(methylamino)ethoxy]phenyl]quinolin-7-amine	478.4
223	 Exemple 223	6-fluoro-N,N-dimethyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)quinolin-7-amine	451.2
225	 Exemple 225	6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(4-piperazin-1-ylphenyl)quinoline	476.3
226	 Exemple 226	6-fluoro-N,N-dimethyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinolin-7-amine	478.4

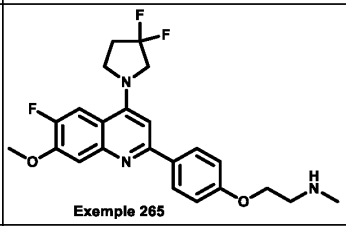
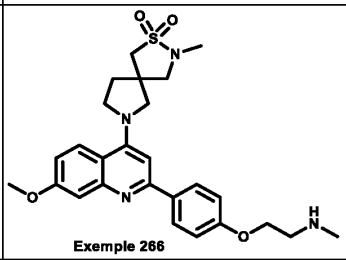
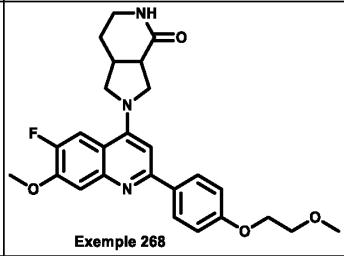
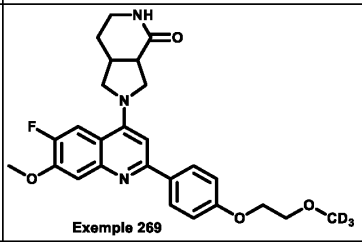
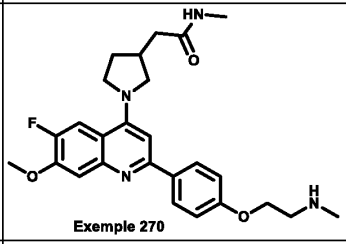
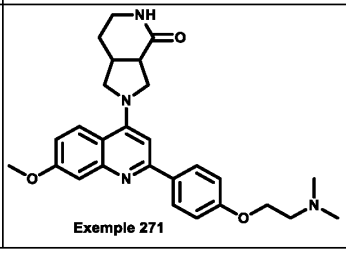
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
227	 Exemple 227	2-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-fluoro-7-methoxy-4-quinolyl]-3,3a,4,6,7,7a-hexahydro-1H-thiopyrano[3,4-c]pyrrole 5,5-dioxide	483.2
228	 Exemple 228	2-[[6-[4-(2,9-diazaspiro[4.5]decan-2-yl)-6-fluoro-7-(trideuteriomethoxy)-2-quinolyl]-3-pyridyl]oxy]-N-methyl-ethanamine	469.3
230	 Exemple 230	2-[[5-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N,N-dimethyl-ethanamine	501.1
232	 Exemple 232	6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-(6-piperazin-1-yl-3-pyridyl)quinoline	477.3
234	 Exemple 234	2-[[5-[4-(9,9-difluoro-7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine	502.3

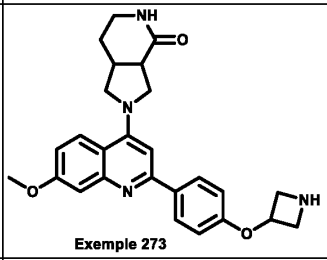
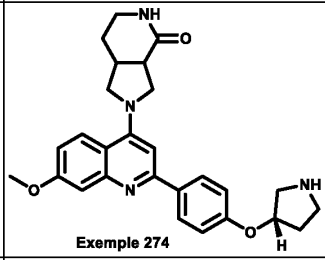
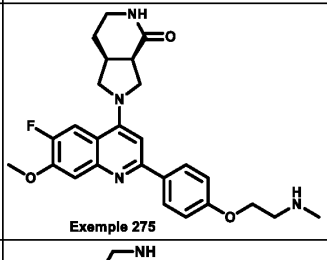
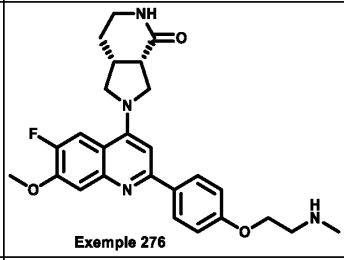
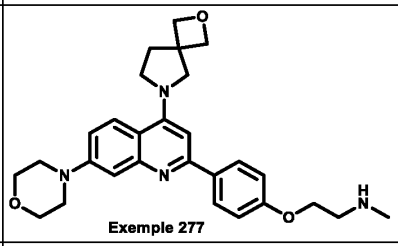
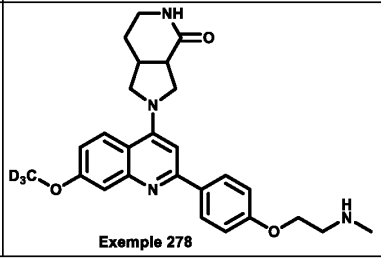
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
235	 Exemple 235	2-[4-[4-(9,9-difluoro-7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine	501.2
237	 Exemple 237	(3aR,7aS)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	479.4
238	 Exemple 238	(3aS,7aR)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	479.4
240	 Exemple 240	2-[4-[4-(2,2-dioxo-2λ6-thia-7-azaspiro[3.4]octan-7-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N,N-dimethyl-ethanamine	500.1
241	 Exemple 241	5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2-methyl-3a,4,6,6a-tetrahydro-1H-pyrrolo[3,4-c]pyrrol-3-one	465.2

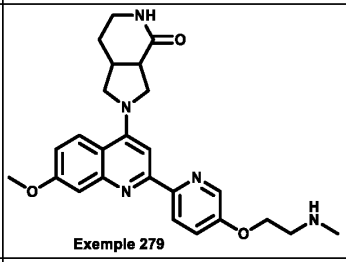
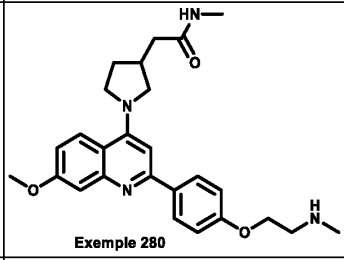
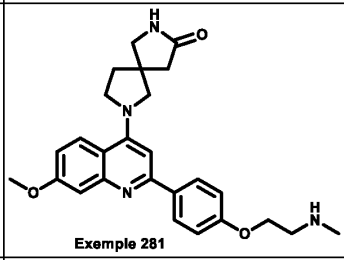
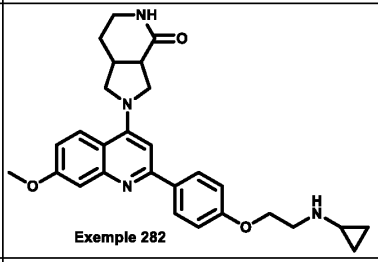
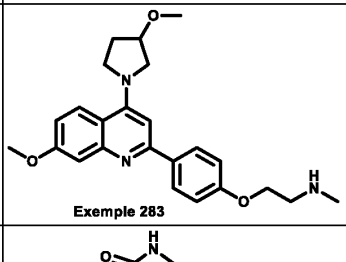
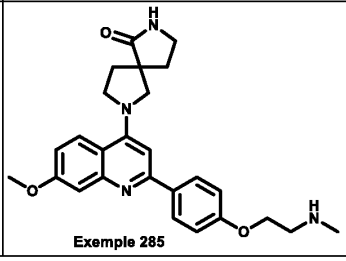
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
243	 Exemple 243	2,2-difluoro-N-[2-[4-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenoxy]ethyl]ethanamine	515.3
244	 Exemple 244	6-fluoro-N,N-dimethyl-2-[6-[2-(methylamino)ethoxy]-3-pyridyl]-4-(2-methyl-2,6-diazaspiro[3.4]octan-6-yl)quinolin-7-amine	465.4
245	 Exemple 245	2-[[5-[6-fluoro-7-methoxy-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine	439.2
248	 Exemple 248	4,4-difluoro-7-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2-methyl-2,7-diazaspiro[4.4]nonan-1-one	515.3
249	 Exemple 249	(S)-2-(4-(4-(3,3-difluoro-4-methoxypyrrolidin-1-yl)-7-methoxyquinolin-2-yl)phenoxy)-N-methylethan-1-amine	444.2
250	 Exemple 250	2-[4-[6-fluoro-7-methoxy-4-(1-methyl-2,3,3a,5,6,6a-hexahydropyrrolo[3,2-b]pyrrol-4-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine	451.3

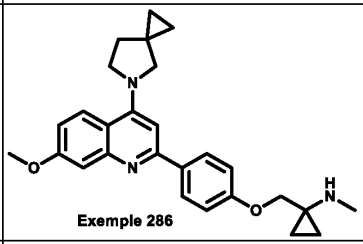
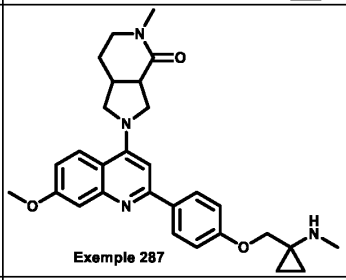
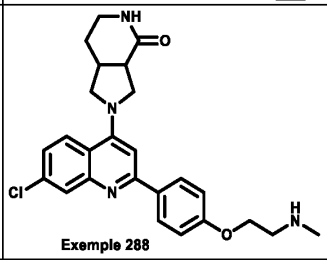
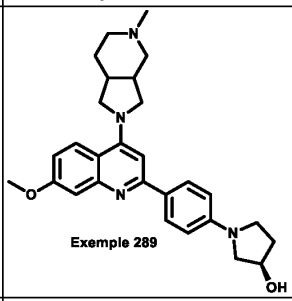
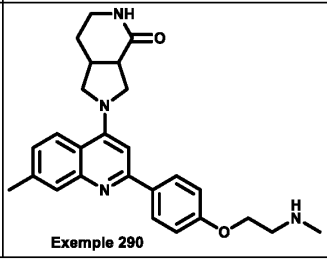
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
251	 Exemple 251	3-[4-[6-fluoro-7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-propan-1-amine	479.3
252	 Exemple 252	2-[4-(azetidin-3-ylmethoxy)phenyl]-6-fluoro-7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)quinoline	477.3
255	 Exemple 255	(3R)-1-[5-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]pyrrolidin-3-ol	478.2
256	 Exemple 256	2-[6-fluoro-7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	490.2
257	 Exemple 257	(3S)-1-[5-[6-fluoro-7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]-2-pyridyl]pyrrolidin-3-ol	478.2

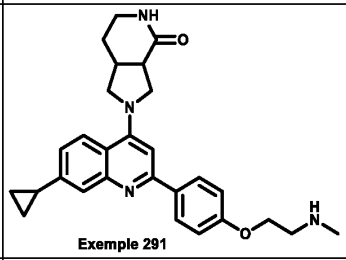
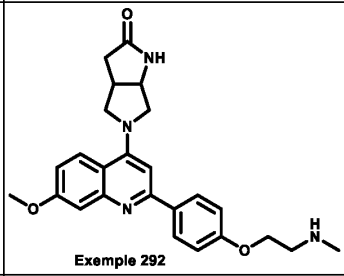
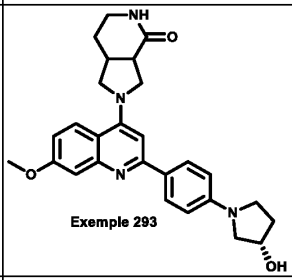
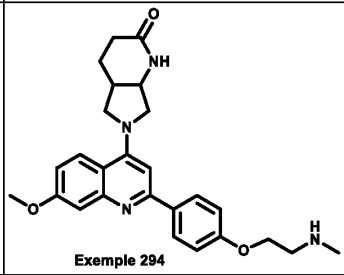
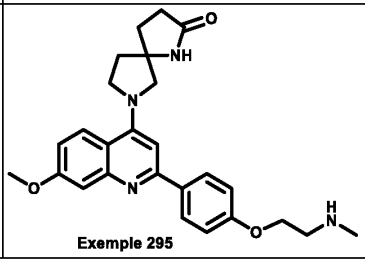
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
258	 Exemple 258	(3aS,7aR)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	461.3
259	 Exemple 259	2-[4-[4-[5-(2,2-difluoroethyl)-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl]-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine	497.3
260	 Exemple 260	2-[[5-[7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]-2-pyridyl]oxy]-N-methyl-ethanamine	448.2
261	 Exemple 261	2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-7-methyl-2,7-diazaspiro[4.4]nonan-8-one	461.3
262	 Exemple 262	2-[4-[7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine	447.3
264	 Exemple 264	7-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-1-one	465.3

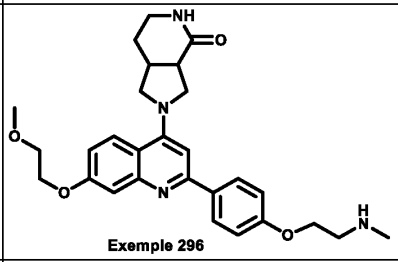
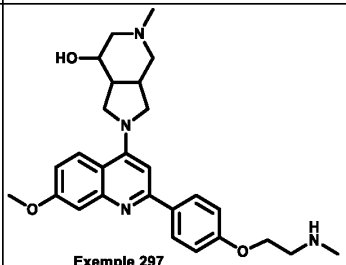
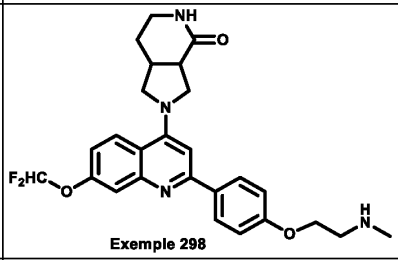
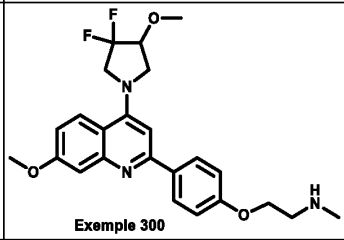
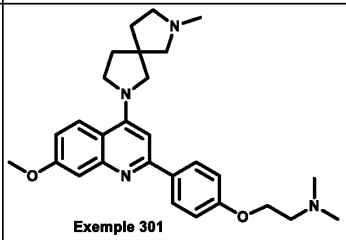
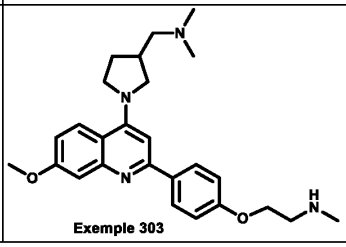
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
265	 Exemple 265	2-[4-[4-(3,3-difluoropyrrolidin-1-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine	432.2
266	 Exemple 266	2-[4-[7-methoxy-4-(3-methyl-2,2-dioxo-2λ6-thia-3,7-diazaspiro[4.4]nonan-7-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine	497.3
268	 Exemple 268	2-[6-fluoro-7-methoxy-2-[4-(2-methoxyethoxy)phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	466.3
269	 Exemple 269	2-[6-fluoro-7-methoxy-2-[4-[2-(trideuteriomethoxy)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	469.3
270	 Exemple 270	2-[1-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]-N-methyl-acetamide	467.3
271	 Exemple 271	2-[2-[4-[2-(dimethylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	461.3

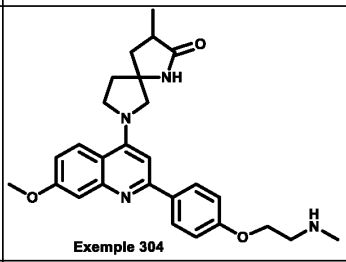
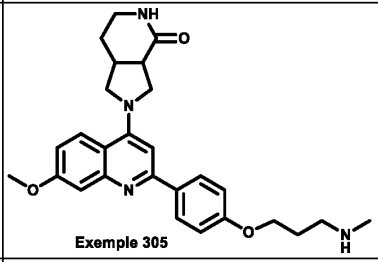
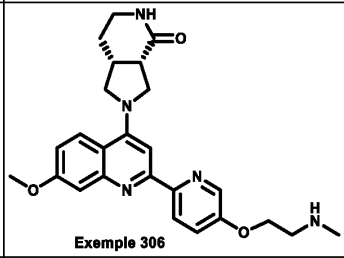
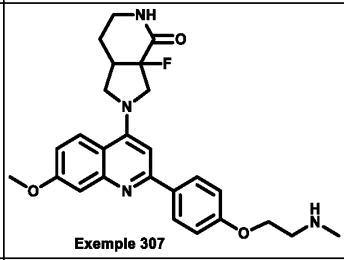
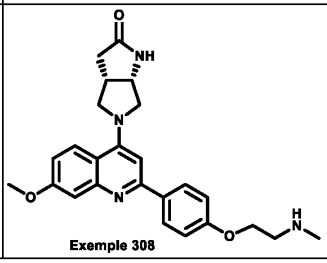
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
273	 Exemple 273	2-[2-[4-(azetidin-3-yloxy)phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	433.2
274	 Exemple 274	2-[7-methoxy-2-[4-[(3S)-pyrrolidin-3-yl]oxyphenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	459.3
275	 Exemple 275	(3aR,7aS)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	465.2
276	 Exemple 276	(3aS,7aR)-2-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	465.2
277	 Exemple 277	N-methyl-2-[4-[7-morpholino-4-(2-oxa-7-azaspiro[3.4]octan-7-yl)-2-quinolyl]phenoxy]ethanamine	475.3
278	 Exemple 278	2-[2-[4-[2-(methylamino)ethoxy]phenyl]-7-(trideuteriomethoxy)-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	450.2

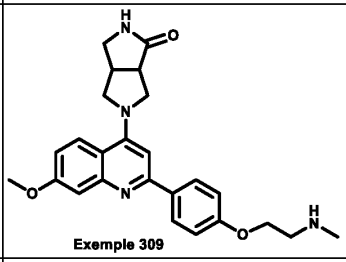
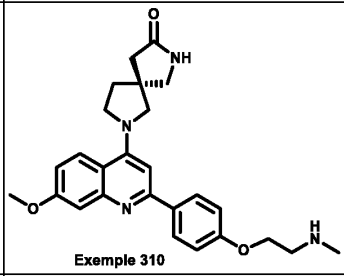
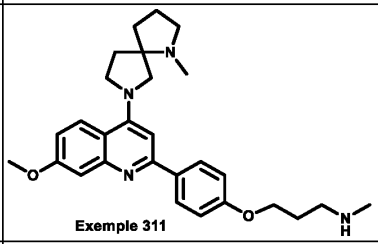
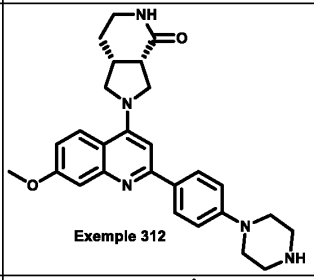
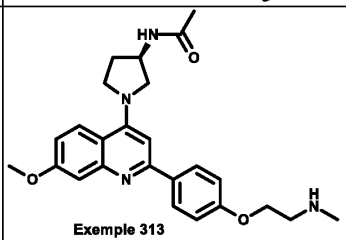
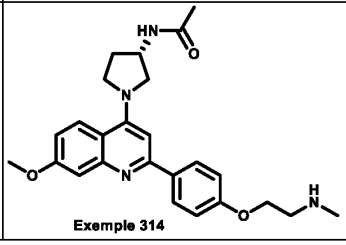
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
279	 Exemple 279	2-[7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	448.3
280	 Exemple 280	2-[1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]-N-methyl-acetamide	449.2
281	 Exemple 281	2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-8-one	447.2
282	 Exemple 282	2-[2-[4-[2-(cyclopropylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	473.3
283	 Exemple 283	2-[4-[7-methoxy-4-(3-methoxypyrrolidin-1-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine	408.2
285	 Exemple 285	7-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-1-one	447.3

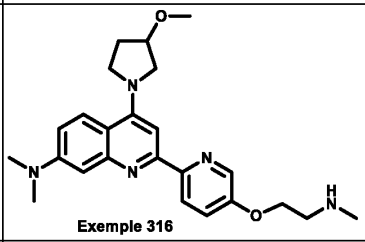
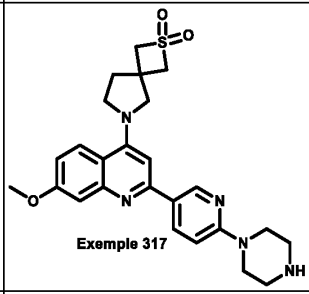
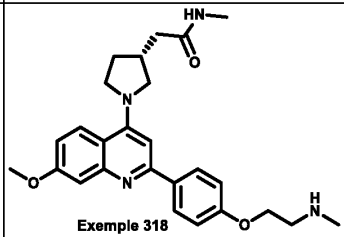
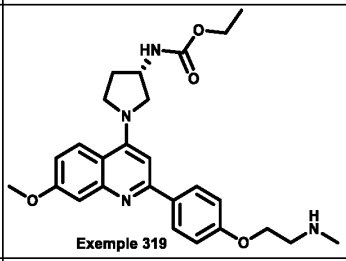
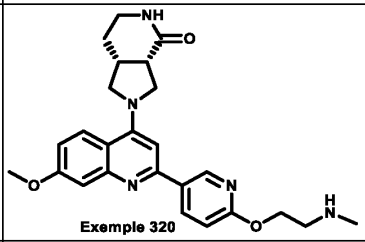
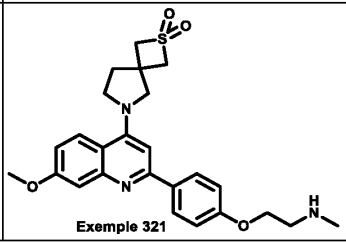
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
286	 Exemple 286	1-[[4-[4-(5-azaspiro[2.4]heptan-5-yl)-6-fluoro-7-methoxy-2-quinolyl]phenoxy]methyl]-N-methyl-cyclopropanamine	448.3
287	 Exemple 287	2-[7-methoxy-2-[4-[[1-(methylamino)cyclopropyl]methoxy]phenyl]-4-quinolyl]-5-methyl-1,3,3a,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	487.3
288	 Exemple 288	2-[7-chloro-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	451.2
289	 Exemple 289	(3R)-1-[4-[7-methoxy-4-(5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-quinolyl]phenyl]pyrrolidin-3-ol	459.3
290	 Exemple 290	2-[7-methyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	431.2

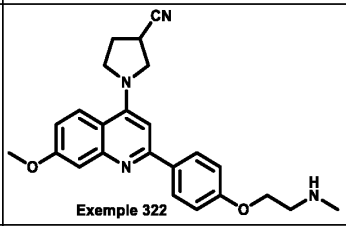
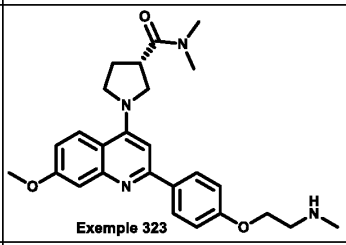
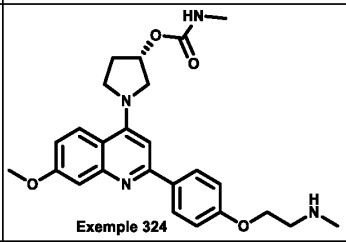
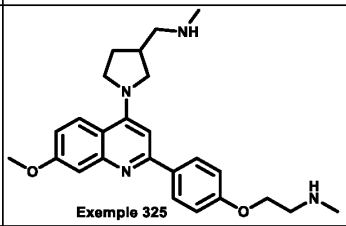
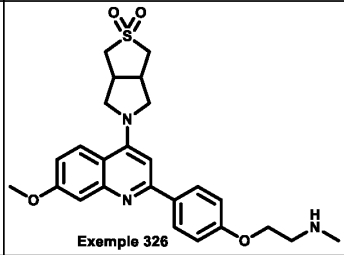
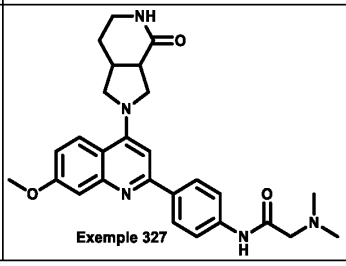
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
291	 Exemple 291	2-[7-cyclopropyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	457.3
292	 Exemple 292	5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,3a,4,6,6a-hexahydropyrrolo[2,3-c]pyrrol-2-one	433.2
293	 Exemple 293	2-[2-[4-[(3S)-3-hydroxypyrrolidin-1-yl]phenyl]-7-methoxy-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	459.3
294	 Exemple 294	6-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,4,4a,5,7,7a-hexahydro-1H-pyrrolo[3,4-b]pyridin-2-one	447.3
295	 Exemple 295	7-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,7-diazaspiro[4.4]nonan-2-one	447.3

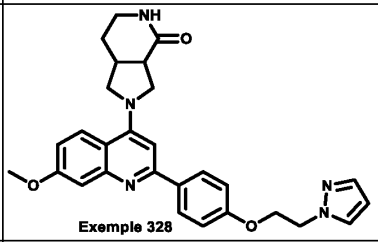
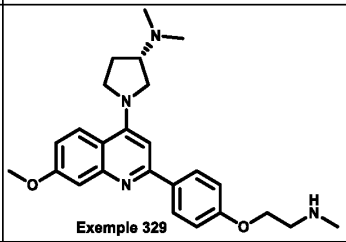
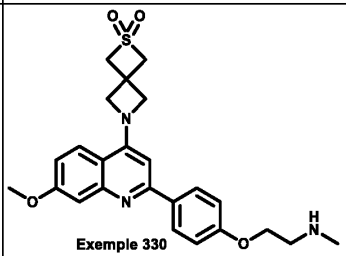
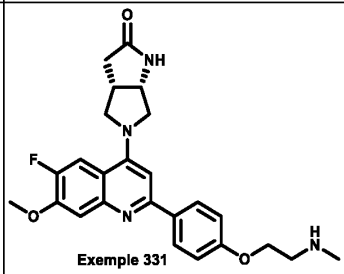
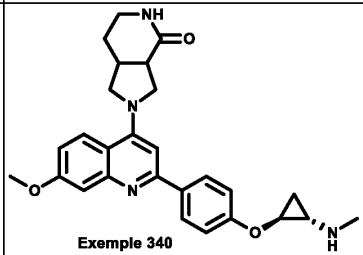
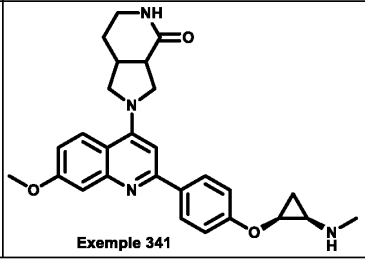
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
296	 Exemple 296	2-[7-(2-methoxyethoxy)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	491.3
297	 Exemple 297	2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-5-methyl-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-7-ol	463.3
298	 Exemple 298	2-[7-(difluoromethoxy)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	483.2
300	 Exemple 300	2-[4-[4-(3,3-difluoro-4-methoxy-pyrrolidin-1-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine	444.2
301	 Exemple 301	2-[4-[7-methoxy-4-(7-methyl-2,7-diazaspiro[4.4]nonan-2-yl)-2-quinolyl]phenoxy]-N,N-dimethyl-ethanamine	461.3
303	 Exemple 303	2-[4-[4-[3-[(dimethylamino)methyl]pyrrolidin-1-yl]-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine	435.3

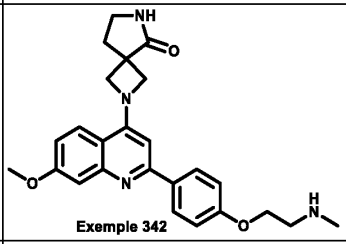
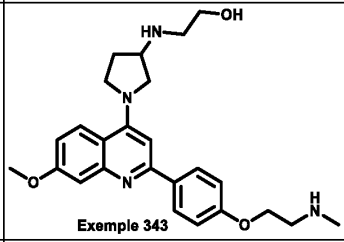
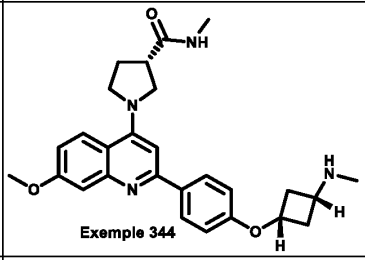
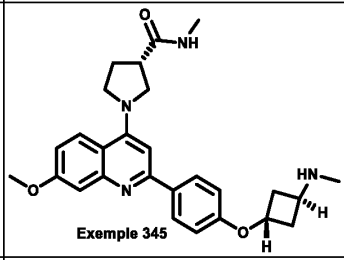
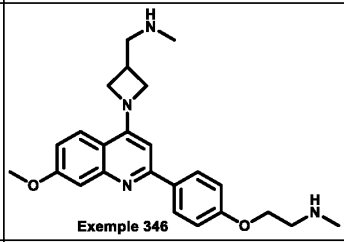
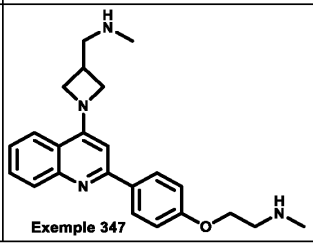
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
304	 Exemple 304	7-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3-methyl-1,7-diazaspiro[4.4]nonan-2-one	461.4
305	 Exemple 305	2-[7-methoxy-2-[4-[3-(methylamino)propoxy]phenyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	461.3
306	 Exemple 306	(3aS,7aR)-2-[7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-4-one	448.3
307	 Exemple 307	3a-fluoro-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,5,6,7,7a-hexahydropyrrolo[3,4-c]pyridin-4-one	465.4
308	 Exemple 308	(3aR,6aR)-5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-b]pyrrol-2-one	433.2

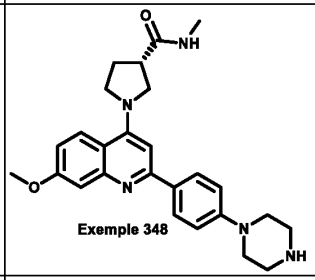
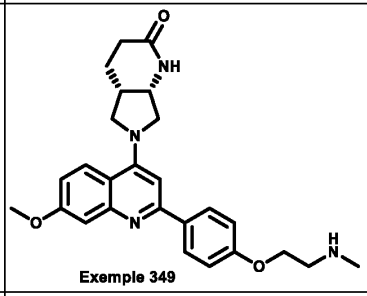
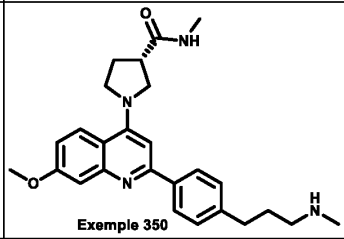
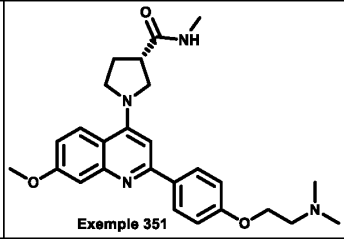
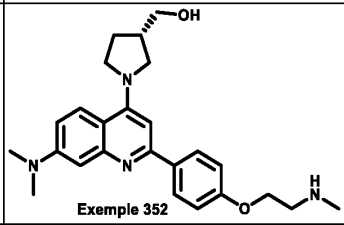
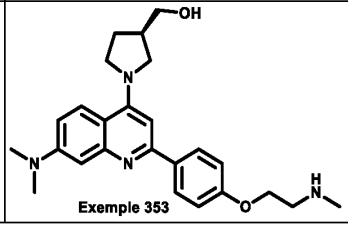
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
309	 Exemple 309	5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one	433.2
310	 Exemple 310	(5R)-2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,7-diazaspiro[4.4]nonan-8-one	447.2
311	 Exemple 311	3-[4-[7-methoxy-4-(1-methyl-1,7-diazaspiro[4.4]nonan-7-yl)-2-quinolyl]phenoxy]-N-methyl-propan-1-amine	461.5
312	 Exemple 312	(3aS,7aR)-2-(7-methoxy-2-(4-(piperazin-1-yl)phenyl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one	458.3
313	 Exemple 313	(R)-N-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)acetamide	435.3
314	 Exemple 314	(S)-N-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)acetamide	435.3

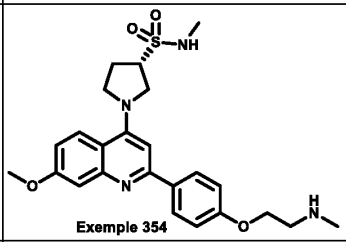
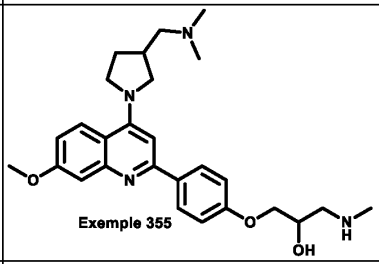
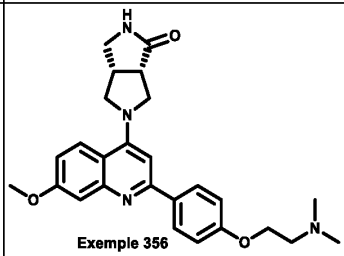
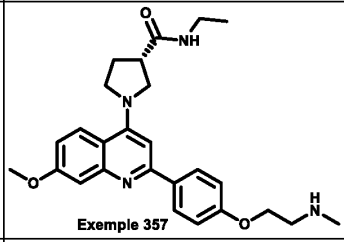
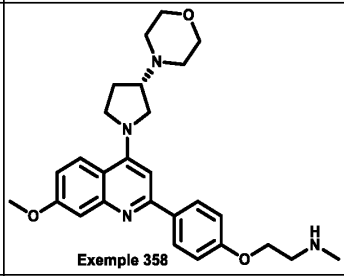
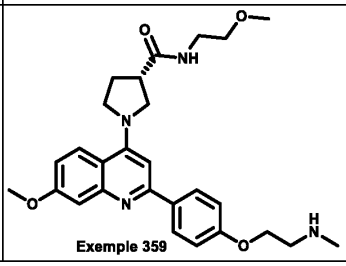
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
316	 Exemple 316	4-(3-methoxypyrrolidin-1-yl)-N,N-dimethyl-2-(5-(2-(methylamino)ethoxy)pyridin-2-yl)quinolin-7-amine	422.2
317	 Exemple 317	6-(7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)-2-thia-6-azaspiro[3.4]octane 2,2-dioxide	480.2
318	 Exemple 318	(R)-2-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)-N-methylacetamide	449.4
319	 Exemple 319	ethyl (S)-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)carbamate	465.3
320	 Exemple 320	(3aS,7aR)-2-(7-methoxy-2-(6-(2-(methylamino)ethoxy)pyridin-3-yl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one	448.4
321	 Exemple 321	6-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-2-thia-6-azaspiro[3.4]octane 2,2-dioxide	468.4

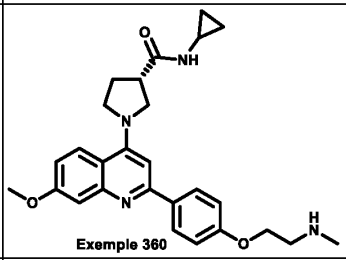
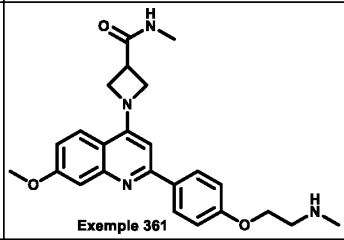
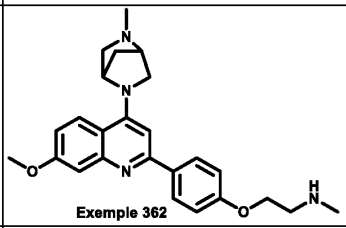
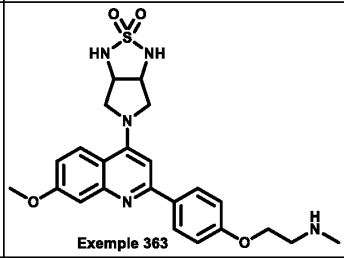
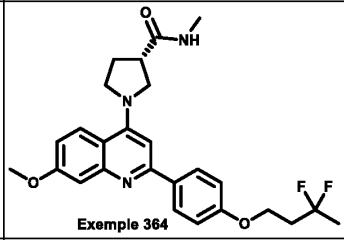
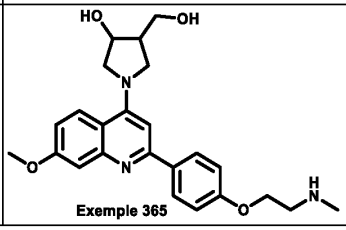
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
322	 Exemple 322	1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidine-3-carbonitrile	403.2
323	 Exemple 323	(S)-1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-N,N-dimethylpyrrolidine-3-carboxamide	449.2
324	 Exemple 324	(S)-1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl methylcarbamate	451.2
325	 Exemple 325	2-(4-(7-methoxy-4-(3-((methylamino)methyl)pyrrolidin-1-yl)quinolin-2-yl)phenoxy)-N-methylethan-1-amine	421.3
326	 Exemple 326	5-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)hexahydro-1H-thieno[3,4-c]pyrrole 2,2-dioxide	468.4
327	 Exemple 327	2-(dimethylamino)-N-(4-(7-methoxy-4-(4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)quinolin-2-yl)phenyl)acetamide	474.3

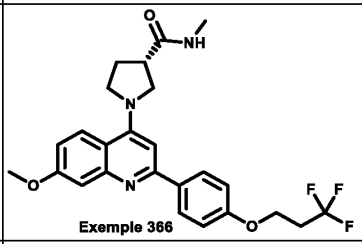
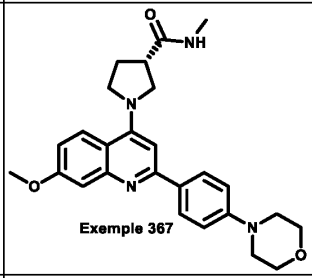
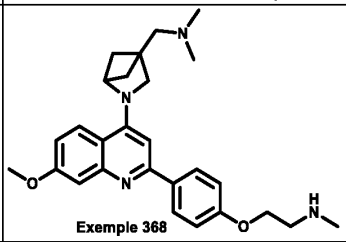
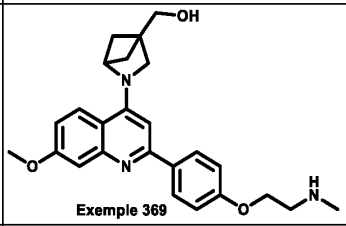
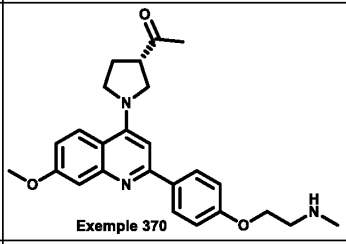
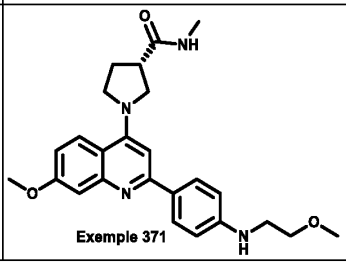
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
328	 Exemple 328	2-(2-(4-(2-(1H-pyrazol-1-yl)ethoxy)phenyl)-7-methoxyquinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one	484.2
329	 Exemple 329	(S)-1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-N,N-dimethylpyrrolidin-3-amine	421.2
330	 Exemple 330	6-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)-2-thia-6-azaspiro[3.3]heptane 2,2-dioxide	454.1
331	 Exemple 331	(3aS,6aS)-5-(6-fluoro-7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)hexahydropyrrolo[3,4-b]pyrrol-2(1H)-one	451.2
340	 Exemple 340	(cis)-2-(7-methoxy-2-(4-((1S,2S)-2-(methylamino)cyclopropoxy)phenyl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one	459.2
341	 Exemple 341	(cis)-2-(7-methoxy-2-(4-((1S,2R)-2-(methylamino)cyclopropoxy)phenyl)quinolin-4-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one	459.2

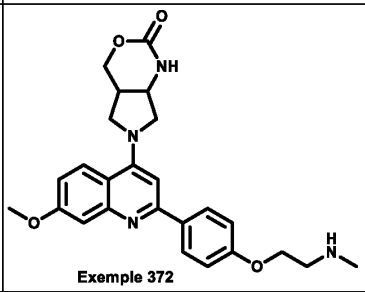
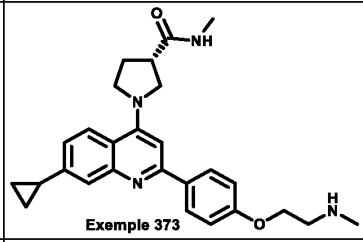
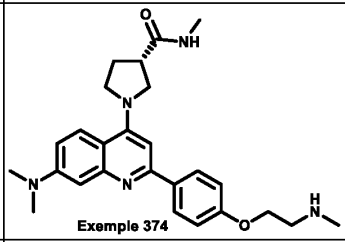
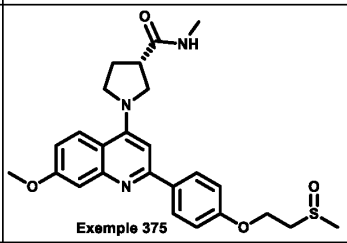
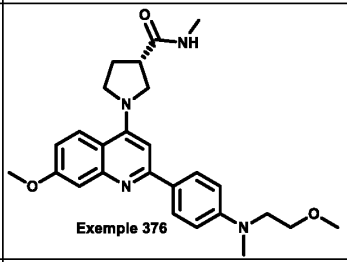
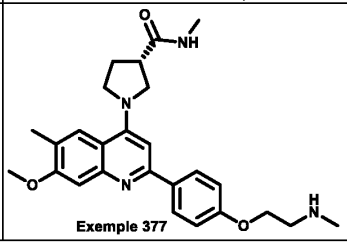
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
342	 Exemple 342	2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2,6-diazaspiro[3.4]octan-5-one	433.3
343	 Exemple 343	2-[[1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]amino]ethanol	437.3
344	 Exemple 344	(S)-1-(7-methoxy-2-(4-((1s,3R)-3-(methylamino)cyclobutoxy)phenyl)quinolin-4-yl)-N-methylpyrrolidine-3-carboxamide	461.3
345	 Exemple 345	(S)-1-(7-methoxy-2-(4-((1r,3S)-3-(methylamino)cyclobutoxy)phenyl)quinolin-4-yl)-N-methylpyrrolidine-3-carboxamide	461.3
346	 Exemple 346	2-[4-[7-methoxy-4-[3-(methylaminomethyl)azetidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine	407.3
347	 Exemple 347	N-methyl-2-[4-[4-[3-(methylaminomethyl)azetidin-1-yl]-2-quinolyl]phenoxy]ethanamine	377.3

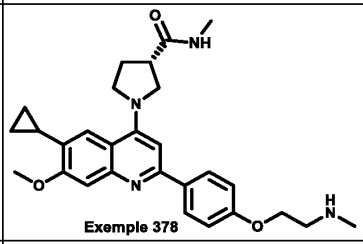
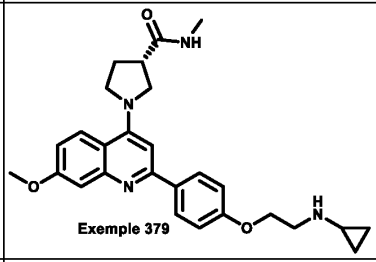
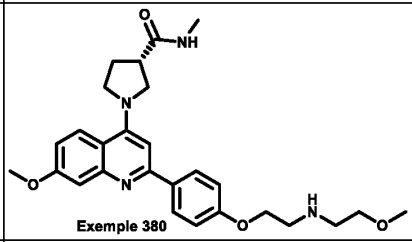
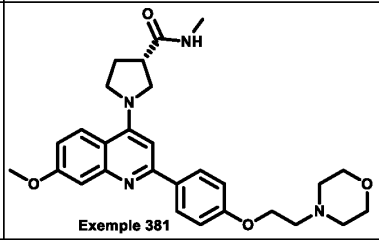
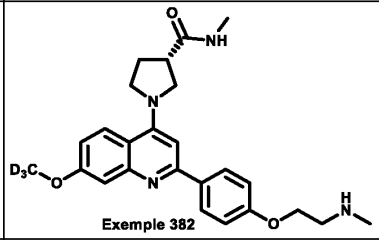
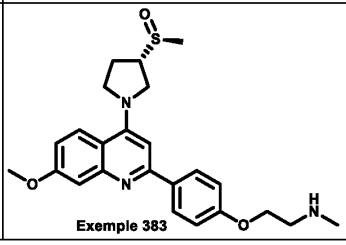
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
348	 Exemple 348	(3S)-1-[7-methoxy-2-(4-piperazin-1-ylphenyl)-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	446.3
349	 Exemple 349	(4aS,7aS)-6-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-3,4,4a,5,7,7a-hexahydro-1H-pyrrolo[3,4-b]pyridin-2-one	447.2
350	 Exemple 350	(3S)-1-[7-methoxy-2-[4-[3-(methylamino)propyl]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	433.3
351	 Exemple 351	(3S)-1-[2-[4-[2-(dimethylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	449.3
352	 Exemple 352	[(3S)-1-[7-(dimethylamino)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol	421.3
353	 Exemple 353	[(3R)-1-[7-(dimethylamino)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]methanol	421.3

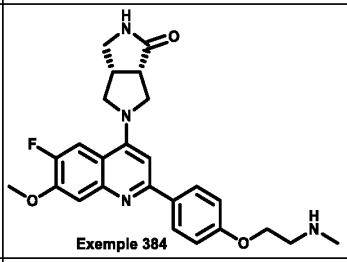
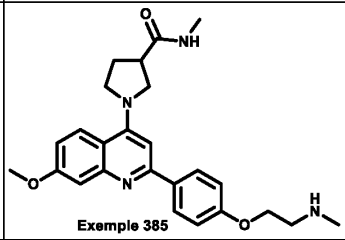
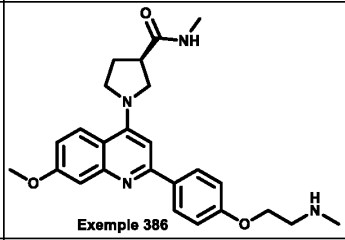
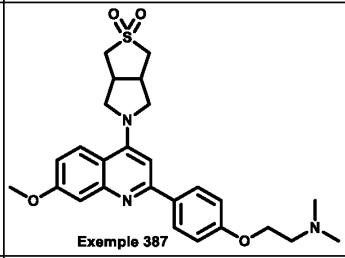
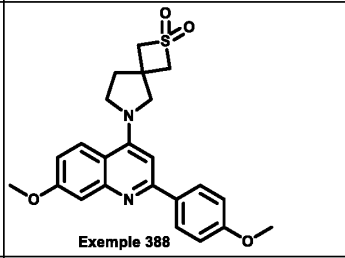
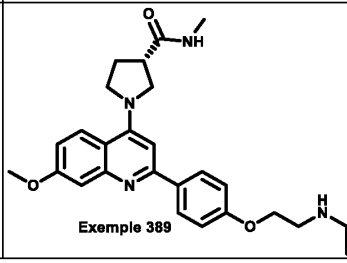
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
354	 Exemple 354	(3S)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-sulfonamide	471.2
355	 Exemple 355	1-[4-[4-[3-[(dimethylamino)methyl]pyrrolidin-1-yl]-7-methoxy-2-quinolyl]phenoxy]-3-(methylamino)propan-2-ol	465.3
356	 Exemple 356	(3aS,6aS)-5-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one	433.2
357	 Exemple 357	(3S)-N-ethyl-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidine-3-carboxamide	449.3
358	 Exemple 358	2-[4-[7-methoxy-4-[(3S)-3-morpholinopyrrolidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine	463.3
359	 Exemple 359	(3S)-N-(2-methoxyethyl)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidine-3-carboxamide	479.3

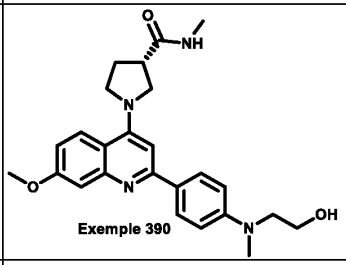
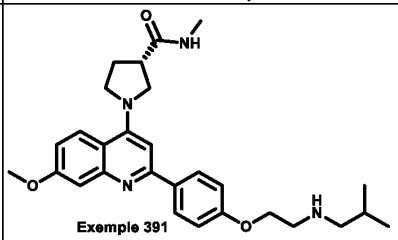
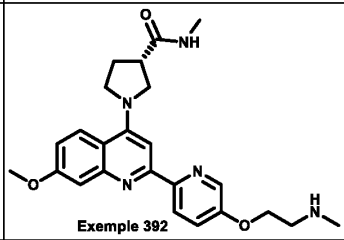
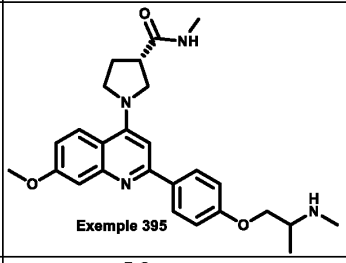
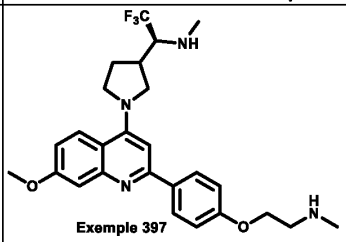
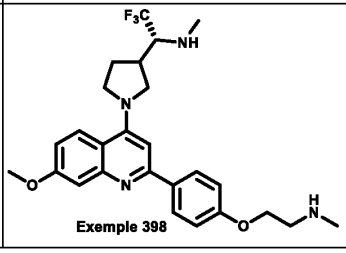
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
360	 Exemple 360	(3S)-N-cyclopropyl-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidine-3-carboxamide	461.3
361	 Exemple 361	1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-azetidine-3-carboxamide	421.2
362	 Exemple 362	2-[4-[7-methoxy-4-(5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-2-quinolyl]phenoxy]-N-methyl-ethanamine	419.3
363	 Exemple 363	2-[4-[4-(2,2-dioxo-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c][1,2,5]thiadiazol-5-yl)-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine	470.3
364	 Exemple 364	(3S)-1-[2-[4-(3,3-difluorobutoxy)phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	470.3
365	 Exemple 365	4-(hydroxymethyl)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-ol	424.2

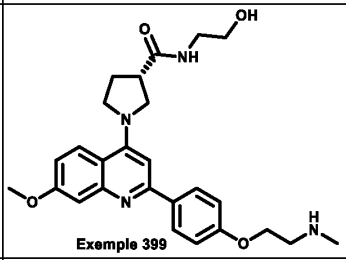
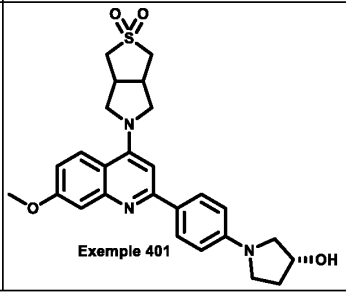
Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
366	 Exemple 366	(3S)-1-[7-methoxy-2-[4-(3,3,3-trifluoropropoxy)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	474.3
367	 Exemple 367	(3S)-1-[7-methoxy-2-(4-morpholinophenyl)-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	447.2
368	 Exemple 368	2-[4-[4-[4-[(dimethylamino)methyl]-2-azabicyclo[2.1.1]hexan-2-yl]-7-methoxy-2-quinolyl]phenoxy]-N-methyl-ethanamine	447.3
369	 Exemple 369	[2-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-2-azabicyclo[2.1.1]hexan-4-yl]methanol	420.3
370	 Exemple 370	1-[(3S)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]pyrrolidin-3-yl]ethanone	420.2
371	 Exemple 371	(3S)-1-[7-methoxy-2-[4-(2-methoxyethylamino)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	435.0

Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
372	 Exemple 372	(cis)-6-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,4,4a,5,7,7a-hexahydropyrrolo[3,4-d][1,3]oxazin-2-one	449.0
373	 Exemple 373	(3S)-1-[7-cyclopropyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	445.2
374	 Exemple 374	(3S)-1-[7-(dimethylamino)-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	448.4
375	 Exemple 375	(3S)-1-[7-methoxy-2-[4-(2-methylsulfinylethoxy)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	468.2
376	 Exemple 376	(3S)-1-[7-methoxy-2-[4-[2-methoxyethyl(methyl)amino]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	449.2
377	 Exemple 377	(3S)-1-[7-methoxy-6-methyl-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	449.3

Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
378	 Exemple 378	(3S)-1-[6-cyclopropyl-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	475.4
379	 Exemple 379	(3S)-1-[2-[4-[2-(cyclopropylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	461.4
380	 Exemple 380	(3S)-1-[7-methoxy-2-[4-[2-(2-methoxyethylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	479.4
381	 Exemple 381	(3S)-1-[7-methoxy-2-[4-(2-morpholinoethoxy)phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	491.4
382	 Exemple 382	(3S)-N-methyl-1-[2-[4-[2-(methylamino)ethoxy]phenyl]-7-(trideuteriomethoxy)-4-quinolyl]pyrrolidine-3-carboxamide	438.3
383	 Exemple 383	2-[4-[7-methoxy-4-[(3S)-3-[(S)-methylsulfinyl]pyrrolidin-1-yl]-2-quinolyl]phenoxy]-N-methyl-ethanamine	440.3

Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
384	 Exemple 384	(3aS,6aS)-5-[6-fluoro-7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one	451.3
385	 Exemple 385	1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	435.2
386	 Exemple 386	(3R)-1-[7-methoxy-2-[4-[2-(methylamino)ethoxy]phenyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	435.2
387	 Exemple 387	(cis)-2-[4-[4-(2,2-dioxo-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrol-5-yl)-7-methoxy-2-quinolyl]phenoxy]-N,N-dimethyl-ethanamine	482.3
388	 Exemple 388	7-[7-methoxy-2-(4-methoxyphenyl)-4-quinolyl]-2λ6-thia-7-azaspiro[3.4]octane 2,2-dioxide	425.2
389	 Exemple 389	(3S)-1-[2-[4-[2-(isopropylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	463.4

Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
390	 Exemple 390	(3S)-1-[2-[4-[2-hydroxyethyl(methyl)amino]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	435.3
391	 Exemple 391	(3S)-1-[2-[4-[2-(isobutylamino)ethoxy]phenyl]-7-methoxy-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	477.4
392	 Exemple 392	(3S)-1-[7-methoxy-2-[5-[2-(methylamino)ethoxy]-2-pyridyl]-4-quinolyl]-N-methyl-pyrrolidine-3-carboxamide	436.2
395	 Exemple 395	(3S)-1-(7-methoxy-2-(4-(2-(methylamino)propoxy)phenyl)quinolin-4-yl)-N-methylpyrrolidine-3-carboxamide	449.2
397	 Exemple 397	(1S)-2,2,2-trifluoro-1-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)-N-methylethan-1-amine	489.4
398	 Exemple 398	(1R)-2,2,2-trifluoro-1-(1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidin-3-yl)-N-methylethan-1-amine	489.4

Ex. No.	Structure	Name	MS m/z (ESI) $[M+H]^+$
399	 Exemple 399	(S)-N-(2-hydroxyethyl)-1-(7-methoxy-2-(4-(2-(methylamino)ethoxy)phenyl)quinolin-4-yl)pyrrolidine-3-carboxamide	465.2
401	 Exemple 401	(cis)-5-(2-(4-((R)-3-hydroxypyrrolidin-1-yl)phenyl)-7-methoxyquinolin-4-yl)hexahydro-1H-thieno[3,4-c]pyrrole 2,2-dioxide	480.2

Biological Examples

[0727] Exemplary assays for evaluating the biological activity of compounds described herein are described below.

Example B-1 - Induced Pluripotent Stem Cells (iPSCs) Culture and Differentiation

[0728] iPSCs were maintained in mTesR Plus (Stem Cell Technologies) on Geltrex-coated cell culture plates. Cells were passaged as colonies using PBS + 0.5 mM EDTA. For differentiation to spinal motor neurons, a previously described protocol was adapted (Baxi, *et al. Nature Neuroscience* 2022, hereby incorporated by reference in its entirety). iPSCs were dissociated to single cells using Accutase (Stem Cell Technologies) and plated at 50,000 cells/cm^2 in mTesR Plus with 10 uM Y-27632 (Stem Cell Technologies). The following day, cells were transitioned a basal media of 1:1 IMDM/F12 containing 1% non-essential amino acids, 1% B27, 1% N2, Anti/Anti (ThermoFisher) and the following small molecules: 0.2 µM LDN-193189, 3 µM CHIR-99021, and 10 µM SB-431542 (Cayman Chemical; Stage 1 media). After 6 days, cells were dissociated and split 1:4 in basal medium containing 0.2 µM LDN-193189, 3 µM CHIR99021, 10 µM SB-431542, 0.1 µM all-trans retinoic acid, 1 µM SAG, and 10 µM Y-27632 (Cayman Chemical; Stage 2 media). On day 12 of culture, cells were dissociated using Accutase and cryopreserved.

[0729] To mature motor neuron progenitors, cells were thawed on plates sequentially coated with PEI followed by 1% Geltrex in basal media containing 0.5 µM all-trans retinoic acid,

0.1 µM SAG, 0.1 µM Compound E, 2.5 µM DAPT, 20 ng/mL L-ascorbic acid, 0.1 µM dibutyryl cyclic-AMP, 10 ng/mL of BDNF and GDNF, and 10 µM Y-27632 (Stage 3 media). From day 14 post-thaw onwards, neurons were maintained in basal medium containing 10 ng/mL BDNF and GDNF (Stage 4 media). All treatments were performed on day 16 post-thaw.

Example B-2 - iPSC-derived Motor Neuron Condensate Assay

[0730] C-mods demonstrate dose-dependent modulation of TDP-43 cytoplasmic condensates in iPSC-derived motor neurons. Neurons (3000/well in PhenoPlate 384 well plates) were cultured in Stage 4 media (described above) for 48 h prior to stress and compound treatment. On day 16 post-thaw from the motor neuron progenitor stage, media was aspirated and replaced with 30 µL/well of Stage 4 media containing 10 µg/mL puromycin. Cells were immediately treated with compounds (2-fold dilutions beginning at 15 uM) using an Echo 650 acoustic dispenser with a consistent 0.16% DMSO across conditions. 30 µM digitonin was added to 6 wells evenly distributed across the plate to establish a 100% cytotoxicity control for normalization of a multiplexed lactate dehydrogenase (LDH) assay. Neurons were fixed by adding 30 µL of 8% PFA in PBS exactly 24 h post-treatment. Cells were subsequently washed in PBS, permeabilized for 15 min at RT with PBS + 0.1% Triton X-100 + 1% BSA, and primary antibodies (table below) were incubated overnight in permeabilization buffer. The following day, plates were washed twice in PBS + 0.05% Tween-20 and incubated with secondary antibodies (table below) for 1 h at RT. Plates were washed twice with PBS + 0.05% Tween-20, followed by once with PBS, sealed and stored at 4 °C until imaging. All images were acquired using an Opera Phenix High-Content Screening System (Perkin Elmer) with the confocal setting and 2-3 planes per field-of-view.

Table B-1. Primary Antibodies

Antigen	Manufacturer	Catalog number	Dilution
MAP2	Abcam	ab5392	1:10,000
TDP-43	ProteinTech	10782-2-AP	1:750

Table B-2. Secondary Antibodies

Antigen	Manufacturer	Catalog number	Dilution
G3BP1	Santa Cruz	sc-365338	1:500
Chicken IgG	ThermoFisher Scientific	A-11039	1:2,000

Rabbit IgG	ThermoFisher Scientific	A-21245	1:2,000
DAPI	ThermoFisher Scientific	62248	1:10,000

Example B-3 - Quantitative PCR (qPCR)

[0731] Diverse cellular stressors trigger TDP-43 to exit the nucleus and phase separate into cytoplasmic heterogeneous biomolecular condensates. A consequence of this subcellular translocation is that TDP-43-dependent functions such as pre-mRNA splicing of *STMN2* and *POLDIP3* are negatively impacted. C-mods demonstrate dose-dependent restoration of *STMN2* and *POLDIP3* splicing in iPSC-derived motor neurons.

[0732] Stress and compound treatment in iPSC-MNs were administered as described above in "iPSC-derived motor neuron condensate assay ". Following 24 h of stress and compound, media was aspirated and cells were lysed using the Cells-to-CT Lysis buffer (ThermoFisher Scientific, cat# 4391851C) using half the manufacturer's recommended volume. cDNA was generated using the Cells-to-CT Advanced RT Reagents (ThermoFisher Scientific, cat# A39110) using a quarter of the manufacturer's recommended volume. cDNA was stored at -20 °C until use. Multiplex qPCR was performed in a 10 µL 384 well format using TaqMan Fast Advanced Master Mix (ThermoFisher Scientific, cat# 4444558) according to manufacturer's protocol. Primers were ordered from Integrated DNA Technologies (IDT) and the sequences are described below.

GAPDH_CY5

Forward: GAAGATGGTGATGGGATTTC

Reverse: GAAGGTGAAGGTCGGAGTC

Probe: CAAGCTTCCCGTTCTCAGCC

(/5Cy5/CAAGCTTCC/TAO/CGTTCTCAGCC/3IAbRQSp/)

STMN2_HEX

For detection of full length *STMN2* mRNA. Amplicon spans exon 2-3 junction.

Forward: AGCTGTCCATGCTGTCACTG

Reverse: GGTGGCTTCAAGATCAGCTC

Probe: ATTTGCTTCACTTCCATATCATCGTAAGTATAGATG

(/5HEX/ATTTGCTTC/ZEN/ACTTCCATATCATCGTAAGTATAGATG/3IABkFQ/)

POLDIP3-EX3exclusion-FAM

For detection of isoform of *POLDIP3* exon3 exclusion mRNA. Amplicon spans exon 2-4 junction.

Forward: ACTGCTTAGCCCAGCCATGT

Reverse: GCTCACCAAAACCATCCAGAA

Probe: ATGGTATAGCTTCCGTTCCTACTAAAC

(/56-FAM/ATGGTATAG/ZEN/CTTCCGTTCCTACTAAAC/31ABkFQ/)

[0733] The above procedure was performed for the compounds in Table B-3, for which the results are provided. The symbol "****" indicates a EC_{50} or IC_{50} less than or equal to 0.10 μM. The symbol "***" indicates an EC_{50} or IC_{50} greater than 0.10 μM and less than or equal to 0.50 μM. The symbol "**" indicates an EC_{50} or IC_{50} greater than 0.50 μM and less than or equal to 1.0 μM. The symbol "*" indicates a EC_{50} or IC_{50} greater than 1.0 μM and less than or equal to 5.0 μM. The symbol "NA" indicates no activity. The symbol "-" indicates no data is available.

Table B-3.

Ex. No.	*POLDIP3* Puromycin Stress qPCR Assay EC_{50} (μM)	*STMN2* Puromycin Stress qPCR Assay EC_{50} (μM)	Puromycin Stress Imaging Assay IC_{50} (μM)
1	NA	>5 μM	-
2	*	> 5 μM	*
3	***	**	**
4	***	*	*
5	*	-	*
6	*	*	*
7	*	-	-
8	-	>5 μM	*
9	**	-	***
10	**	*	***
11	***	**	***
12	>5 μM	*	-
13	*	*	*
14	*	*	***
15	*	*	*
16	***	**	***
17	***	***	***
18	**	*	*
19	***	***	**
20	-	-	-
21	*	*	*
22	***	**	***

Ex. No.	*POLDIP3* Puromycin Stress qPCR Assay EC_{50} (μM)	*STMN2* Puromycin Stress qPCR Assay EC_{50} (μM)	Puromycin Stress Imaging Assay IC_{50} (μM)
23	*	*	**
24	***	**	***
25	**	**	***
26	***	**	***
27	***	***	***
28	****	***	***
29	**	*	***
30	*	-	-
31	*	*	*
32	***	**	***
33	*	*	***
34	*	*	*
35	NA	-	-
36	*	*	**
37	*	*	**
38	-	NA	>5 μM
39	*	*	**
40	NA	-	-
41	-	*	-
42	-	-	*
43	*	*	***
44	*	*	-
45	**	*	**
46	**	*	**
47	***	**	**
48	***	***	***
49	***	*	***
50	***	**	***
51	*	*	-
52	*	*	*
53	*	*	-
54	**	*	**
55	*	*	**
56	*	*	**
57	*	*	*
58	*	*	*
59	*	*	*
60	*	*	*
61	*	-	>5 μM
62	*	*	-
63	**	*	**
64	**	*	**
65	***	*	*
66	**	*	*
67	**	*	**

Ex. No.	*POLDIP3* Puromycin Stress qPCR Assay EC_{50} (μM)	*STMN2* Puromycin Stress qPCR Assay EC_{50} (μM)	Puromycin Stress Imaging Assay IC_{50} (μM)
68	***	*	***
69	**	*	**
70	**	**	**
71	**	*	**
72	**	*	**
73	****	***	****
74	**	*	**
75	***	*	***
76	**	**	****
77	**	*	***
78	***	*	***
79	**	*	**
80	**	*	***
81	**	*	***
82	**	*	**
83	**	-	***
84	***	***	***
85	***	**	***
86	***	***	***
87	****	***	****
88	***	*	***
89	***	***	***
90	**	*	**
91	***	**	***
92	***	*	***
93	**	*	**
94	***	**	***
95	***	**	**
96	***	**	***
97	***	**	***
98	***	*	***
99	***	**	****
100	***	**	****
101	****	***	****
102	***	***	***
103	**	*	***
104	***	*	***
105	***	**	****
106	**	*	***
107	**	*	**
109	**	*	***
110	***	*	***
111	**	*	**
112	**	*	***
113	***	*	***

Ex. No.	*POLDIP3* Puromycin Stress qPCR Assay EC_{50} (μM)	*STMN2* Puromycin Stress qPCR Assay EC_{50} (μM)	Puromycin Stress Imaging Assay IC_{50} (μM)
114	**	-	**
115	***	-	**
116	***	*	***
117	**	*	***
118	**	*	***
119	***	***	****
120	***	***	****
121	***	*	***
123	**	*	**
124	***	**	***
125	****	**	***
126	***	***	***
127	**	*	***
128	**	*	***
129	**	*	***
130	**	**	***
131	**	*	***
132	***	***	****
133	****	***	****
134	***	*	***
135	**	**	***
136	***	*	***
137	**	**	**
138	***	***	***
139	***	*	***
140	***	***	***
141	****	***	****
142	***	***	****
143	**	*	***
144	**	*	**
145	***	**	****
146	**	*	**
147	**	*	***
148	***	**	***
149	***	*	***
150	***	**	****
151	**	*	***
152	***	*	***
153	***	*	****
154	****	***	****
155	**	**	***
156	***	*	***
157	***	-	***
158	***	*	***
159	***	**	****

Ex. No.	*POLDIP3* Puromycin Stress qPCR Assay EC_{50} (μM)	*STMN2* Puromycin Stress qPCR Assay EC_{50} (μM)	Puromycin Stress Imaging Assay IC_{50} (μM)
160	***	***	****
161	***	*	***
162	***	**	***
163	****	***	****
164	****	***	****
165	***	*	***
166	***	***	****
167	**	*	**
168	**	*	**
169	****	***	****
170	***	**	****
171	***	*	***
172	**	*	**
173	**	*	**
174	**	*	**
175	***	**	***
176	**	*	***
177	**	*	**
178	****	***	****
179	***	*	***
180	***	-	***
181	***	*	***
182	**	*	***
183	***	*	***
184	**	*	**
185	**	*	***
186	***	*	***
187	***	**	***
188	***	*	***
189	***	*	***
190	***	*	***
191	***	*	**
192	***	*	***
193	***	**	****
194	***	***	****
195	****	***	****
196	***	*	***
197	**	*	**
198	***	**	***
199	**	*	***
200	**	*	**
201	**	*	**
202	***	*	***
203	**	*	**
204	**	*	**

Ex. No.	*POLDIP3* Puromycin Stress qPCR Assay EC_{50} (μM)	*STMN2* Puromycin Stress qPCR Assay EC_{50} (μM)	Puromycin Stress Imaging Assay IC_{50} (μM)
205	***	***	***
206	***	*	***
207	***	*	***
208	***	*	***
209	***	***	***
210	***	*	***
211	****	***	****
212	**	*	**
213	****	***	****
214	****	***	****
215	***	*	***
216	****	**	****
217	****	**	****
218	***	**	**
219	****	**	****
220	****	***	****
221	**	*	**
222	****	***	****
223	****	***	****
224	****	***	****
225	****	***	****
226	****	***	****
227	**	*	**
228	****	****	****
229	****	***	****
230	***	**	***
231	****	***	****
232	****	**	****
233	****	**	****
234	**	*	***
235	***	***	****
236	***	*	***
237	****	***	****
238	****	**	****
239	****	***	****
240	****	***	****
241	****	**	****
242	****	**	****
243	***	***	****
244	****	***	****
245	***	**	***
246	****	***	****
247	****	***	****
248	***	*	***
250	***	**	***

Ex. No.	*POLDIP3* Puromycin Stress qPCR Assay EC_{50} (μM)	*STMN2* Puromycin Stress qPCR Assay EC_{50} (μM)	Puromycin Stress Imaging Assay IC_{50} (μM)
251	****	***	****
252	****	***	****
253	****	***	****
254	***	**	***
255	***	***	****
256	***	***	****
257	****	***	****
258	***	*	***
259	***	**	***
260	***	*	***
261	***	**	***
262	****	***	****
263	***	***	***
264	***	***	****
265	**	*	***
266	****	***	****
267	****	***	****
268	**	*	***
269	**	*	**
270	****	*	***
271	***	**	***
272	***	*	****
273	**	*	***
274	**	*	**
275	***	***	****
276	***	*	****
277	***	**	****
278	***	*	***
279	***	*	***
280	***	*	***
281	***	*	**
282	***	*	****
283	***	*	***
284	***	***	***
285	***	-	***
286	**	*	***
287	***	*	***
288	***	*	***
289	***	*	***
290	***	**	***
291	***	*	****
292	***	-	***
293	**	-	***
294	**	*	****
295	***	*	***

Ex. No.	*POLDIP3* Puromycin Stress qPCR Assay EC_{50} (μM)	*STMN2* Puromycin Stress qPCR Assay EC_{50} (μM)	Puromycin Stress Imaging Assay IC_{50} (μM)
296	**	*	**
297	***	*	***
298	**	*	**
299	****	***	****
300	**	*	**
301	***	**	***
302	***	***	****
303	****	**	****
304	***	**	***
305	***	*	**
306	***	*	***
307	***	*	***
308	***	*	***
309	***	*	***
310	**	*	*
311	***	**	***
312	***	*	***
313	***	*	***
314	***	*	***
315	***	***	***
316	****	***	****
317	****	**	****
318	***	*	***
319	***	**	****
320	**	*	**
321	****	***	****
322	***	**	***
323	***	**	***
324	***	**	***
325	***	**	****
326	***	**	****
327	***	**	****
328	**	*	**
329	***	**	****
330	****	**	****
331	***	*	****
332	NA	**	***
333	***	*	****
334	***	***	****
335	**	**	**
336	**	*	***
337	****	***	****
338	**	*	**
339	**	*	***
340	**	*	***

Ex. No.	*POLDIP3* Puromycin Stress qPCR Assay EC_{50} (μM)	*STMN2* Puromycin Stress qPCR Assay EC_{50} (μM)	Puromycin Stress Imaging Assay IC_{50} (μM)
341	**	*	**
342	**	*	***
343	***	*	***
344	***	*	***
345	**	*	***
346	***	**	****
347	***	*	***
349	**	-	**
352	***	*	***
353	***	*	***
354	***	*	***
355	***	**	****
356	**	*	**
357	***	*	***
358	***	*	***
359	**	*	***
360	***	*	***
361	***	*	***
362	***	**	***

Example B-4 – Traumatic brain injury model

[0734] All animal experiments were performed according to the National Institutes of Health (Bethesda, MD, USA) guidelines for the care and use of laboratory animals. Animals were weighed upon arrival to facility, acclimated for 2 weeks, tested for portosystemic shunts, and weighed everyday throughout the in-life portion of the study.

[0735] Test articles were delivered to wild-type C57Bl/6J mice (8-12 weeks of age) by oral (p.o.) or subcutaneous (s.c.) administration 3-4h prior to surgery. Mice were anesthetized in an induction chamber at 5% isoflurane and maintained at 1.5-2.5% isoflurane via face mask throughout the surgery. Eyes were protected with Viscotears, body temperature was monitored, and animals were hydrated s.c. with warm Ringer's lactate solution.

[0736] Anesthetized mice were positioned in a stereotaxic frame where a unilateral craniotomy of 3 mm diameter was performed at bregma -2.0 mm and lateral + 2.0 mm from the midline. A single controlled cortical impact (CCI; PintPoint Precision Cortical Impactor, Hatteras Instruments, Inc.) was delivered using a 2.5 mm diameter tip traveling at 3.0 m/s to a depth of 1.0 mm, with a dwell time of 50 ms. After impact, the bone flap was replaced using dental cement, and the wound was sutured. Control sham animals underwent surgery and craniotomy, but no cortical impact. Buprenorphine (0.05 mg/kg, s.c.) was administered 30

min before surgery and for 2 days following surgery (every 8 hours). General animal welfare, body weight and wound recovery was evaluated daily.

[0737] Mice were terminally anesthetized with pentobarbital (180 mg/kg intraperitoneal) 7 days following TBI. Terminal body weights, plasma, and cerebrospinal fluid (CSF) were collected. Animals were then transcardially perfused with ice-cold heparinized saline. Brains were processed for immunohistochemistry.

[0738] NfL was measured from CSF using Quanterix Simoa NF-Light 2 Advantage assay kit (#104073) according to the manufacturer's protocol. Plasma proteomics analysis was performed by SomaLogic for 1500 target SomaScan.

[0739] The above procedure was performed for exemplary compounds of formula (II-D-2), as defined herein, for which the results are provided in **Table B-4**. * indicates P<0.05 relative to TBI alone (Row 2). ** indicates P<0.01 relative to TBI alone (Row 2). *** indicates P<0.001 relative to TBI alone (Row 2). **** indicates P<0.0001 relative to TBI alone (Row 2). No stars indicate no statistically significant changes. "a.u." represents arbitrary units.

Table B-4.

Surgery	Ex. Cmpd of formula (II-D-2).	RoA	Dose (mg/kg)	TDP-43 Mean (SEM)	CSF NfL (pg/mL) Mean (SEM)	Plasma GFAP (a.u.) Mean (SEM)
Sham	Vehicle			0 (0)	159.7 (24.8)	1829 (35.5)
TBI	Vehicle			0.95 (0.27)	6544 (950.4)	3280 (230.8)
TBI	A	p.o.	3	0.83 (0.24)	6501 (1354)	2959 (133.8)
TBI	A	p.o.	10	0.45 (0.11)	2004 (1403) **	2105 (68.72) ****
TBI	B	s.c.	3	0.27 (0.07) *	1958 (699) **	2000 (97.17) ****

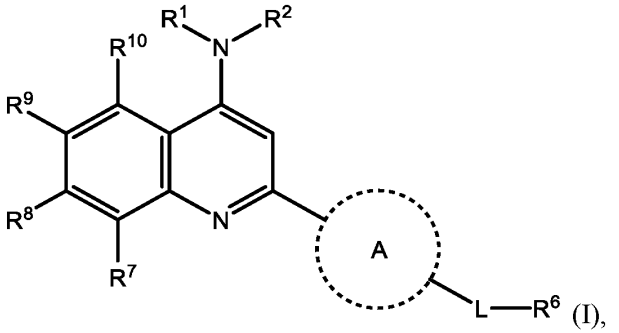
[0740] All publication, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entireties, to the same extent as if each were incorporated by reference individually.

[0741] It is to be understood that, while the disclosure has been described in conjunction with the above embodiments, the foregoing description and examples are intended to illustrate and not limit the scope of the disclosure. Other aspects, advantages and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

CLAIMS

What is claimed is:

1. A compound of formula (I)



(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein

R^1 and R^2 are taken together with the N to which they are attached to form a saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 10-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl, wherein

the saturated 4- to 5-membered monocyclic heterocyclyl, saturated 7- to 9-membered fused heterocyclyl, or saturated 7- to 10-membered spirocyclic heterocyclyl is optionally substituted with one or more R^3;

each R^3 is independently halo, C_{1-6}alkyl, oxo, $-OR^{12}$, $-N(R^x)(R^y)$, -CN, or $-C(=O)N(R^{13})(R^{14})$, wherein

the C_{1-6}alkyl of R^3 is optionally substituted with R^{3a};

Ring A is 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the 4- to 8-membered cycloalkenyl, 4- to 8-membered unsaturated heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4, and

the 4- to 8-membered unsaturated heterocyclyl or 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^4 is independently halo, C_{1-6}alkyl, or $-OR^{12}$;

L is a bond, C_{1-6}alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^5)(C_{1-6}alkyl)-$;

R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, or $-OR^{12}$, and

the C_{3-8}cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is $-OR^{12}$, -O-(3- to 12-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-C(=O)N(R^{13})(R^{14})$, $-N(R^{13})S(=O)_2R^{14}$, $-S(=O)N(R^{13})R^{14}$, $-S(=O)_2N(R^{13})(R^{14})$, $-(C_{3-8}cycloalkyl)N(R^x)(R^y)$, or 3- to 8-membered N-containing heterocyclyl, wherein

the -O-(3- to 8-membered N-containing heterocyclyl), -O-(5- to 6-membered N-containing heteroaryl), or 3- to 8-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b}, $-C(=O)R^{14}$, $-C(=O)N(R^{13})(R^{14})$, or $-C(=O)OR^{14}$, and

the 3- to 8-membered N-containing heterocyclyl of R^6 optionally further comprises 1 or 2 atoms selected from the group consisting of N, O, and S;

R^7 is H or halo;

R^8 and R^9 are each independently H, halo, C_{1-6}alkyl, $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(=O)R^{14}$, $-N(R^{13})C(=O)OR^{14}$, $-N(R^{13})C(=O)N(R^{13})R^{14}$, $-OC(=O)R^{14}$, $-OC(=O)OR^{14}$, $-OC(=O)N(R^{13})R^{14}$, $-C(=O)R^{14}$, $-C(=O)OR^{14}$, $-C(=O)N(R^{13})(R^{14})$, C_{3-8}cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^8 or R^9 is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl of R^8 is optionally substituted with one or more R^{7b}, and

the 3- to 8-membered heterocyclyl of R^8 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

R^{10} is H;

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently $-OR^{12}$, $-N(R^x)(R^y)$, $-C(=O)N(R^{13})(R^{14})$, or 3- to 8-membered heterocyclyl;

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C_{1-6}alkyl, $-OR^{11}$, or $-N(R^x)(R^y)$, wherein

the C_{1-6}alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8}cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^{11} is independently H or C_{1-6}alkyl;

each R^{12} is independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, or 5- to 10-membered heteroaryl,

wherein the C_{1-6}alkyl of R^{12} is optionally substituted with one or more halo, deuterium, -O(C_{1-6}alkyl), or -N(R^x)(R^y);

each R^{13} is independently H or C_{1-6}alkyl;

each R^{14} is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C_{1-6}alkyl of R^{14} is optionally substituted by one or more halo, -OH, -O(C_{1-6}alkyl), -N(R^x)(R^y), C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C_{3-8}cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{14} is optionally substituted with halo, C_{1-6}alkyl, or -N(R^x)(R^y);

each R^{15} is independently H or C_{1-6}alkyl; and

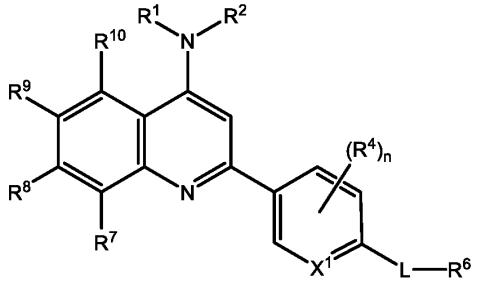
each R^x and R^y is independently H, C_{1-6}alkyl, C_{3-8}cycloalkyl, -C(=O)(C_{1-6}alkyl), or -C(=O)O(C_{1-6}alkyl), wherein

the C_{1-6}alkyl of R^x or R^y is optionally substituted with halo, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -NH_2, NH(C_{1-6}alkyl), or -N(C_{1-6}alkyl)(C_{1-6}alkyl), and

the C_{1-6}alkyl of -C(=O)(C_{1-6}alkyl) or -C(=O)O(C_{1-6}alkyl) is optionally substituted with -O(C=O)C_{1-8}alkyl), wherein

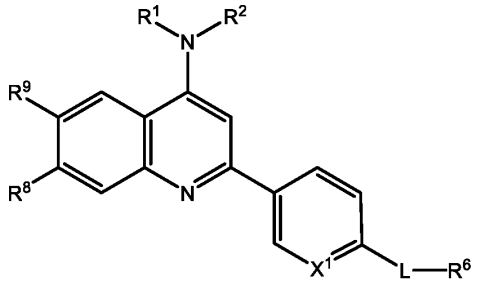
when Ring A is phenyl, then -L-R^6 is not -NH_2 or -OCH_3.

2. The compound of claim 1, wherein the compound is a compound of formula (II)



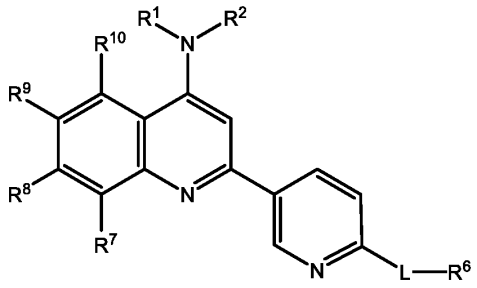
(II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1 is N or CH, and n is 0, 1, 2, or 3.

3. The compound of claim 2 wherein the compound is a compound of formula (II-A)



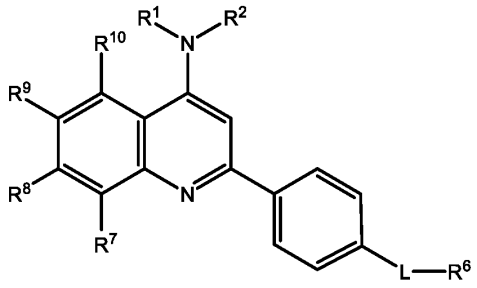
(II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

4. The compound of claim 2, wherein the compound is a compound of formula (II-B)



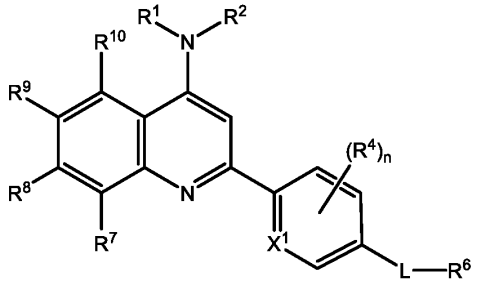
(II-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

5. The compound of claim 2, wherein the compound is a compound of formula (II-C)



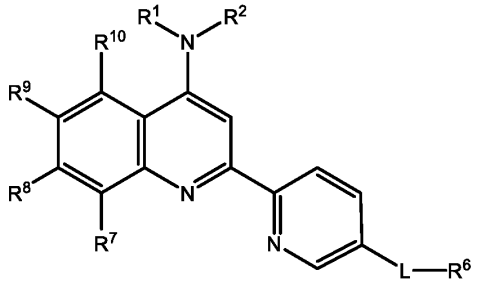
(II-C), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

6. The compound of claim 1, wherein the compound is a compound of formula (III)



(III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1 is N or CH; and n is 0, 1, 2, or 3.

7. The compound of claim 6, wherein the compound is a compound of formula (III-B)



(III-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

8. The compound of any of claims 1-7, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein

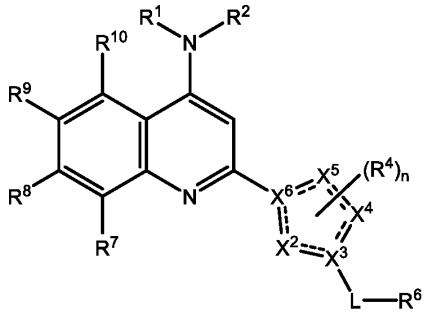
R^8 is H, halo, C_{1-6}alkyl, $-OR^{12}$, $-N(R^x)(R^y)$, $-N(R^{13})C(O)R^{14}$, $-N(R^{13})C(O)OR^{14}$, $-N(R^{13})C(O)N(R^{13})R^{14}$, $-C(O)N(R^{13})(R^{14})$, or C_{3-6}cycloalkyl, wherein

the C_{1-6}alkyl of R^8 is optionally substituted by one or more R^{7a}; and

R^9 is H, halo, C_{1-6}alkyl, $-OR^{12}$, -CN, or C_{3-6}cycloalkyl, wherein

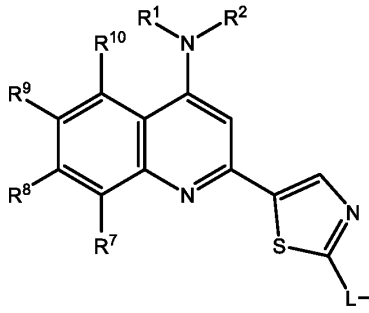
the C_{1-6}alkyl of R^9 is optionally substituted by one or more R^{7a}.

9. The compound of claim 1, wherein the compound is a compound of formula (IV):



(IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^2, X^4 and X^5 are each independently C, N, O or S; X^3 and X^6 are each independently C or N; and n is 0, 1, 2, or 3.

10. The compound of claim 9, wherein the compound is a compound of formula (IV-A):



(IV-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

11. The compound of claim 1, wherein Ring A is phenyl or 5- to 6-membered heteroaryl, wherein phenyl or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R^4.

12. The compound of claim 11, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Ring A is selected from the group consisting of phenyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, furan, thiophene, oxazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

13. The compound of claim 12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Ring A is phenyl, thiazolyl, or pyridinyl.

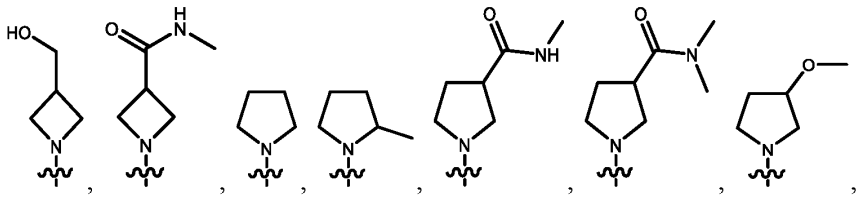
14. The compound of any of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a saturated 4- to 5-membered monocyclic heterocyclyl optionally substituted with one or more R^3.

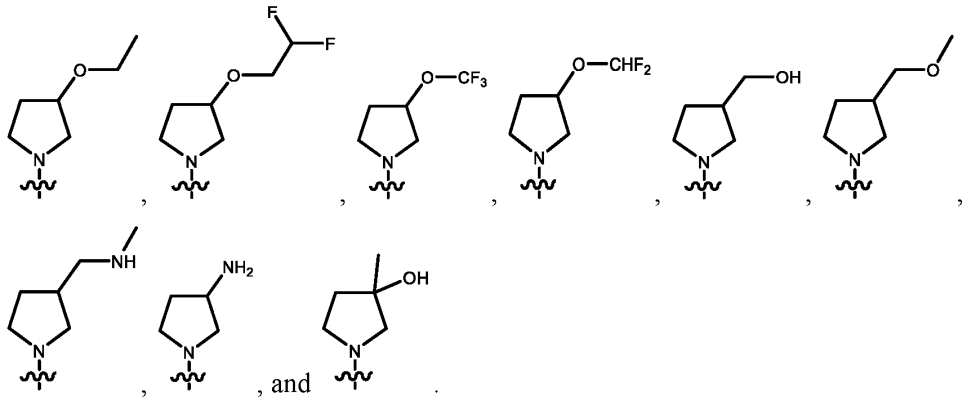
15. The compound of any of claims 1-14, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they are attached to form an azetidinyl or pyrrolidinyl, wherein the azetidinyl or pyrrolidinyl of R^1 and R^2 is optionally substituted with one or more R^3.

16. The compound of claim 14 or 15, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^3 is independently -OH, C_{1-6}alkyl, C_{1-6}alkoxy, or $-N(R^x)(R^y)$ wherein the C_{1-6}alkyl of the R^3 is optionally substituted with R^{3a}.

17. The compound of claim 16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^3 is independently -OH, C_{1-4}alkyl, C_{1-4}alkoxy, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)(C_{1-4}alkyl)$, $-NH(C_{3-6}cycloalkyl)$, or $-N(C_{1-4}alkyl)(C_{3-6}cycloalkyl)$, wherein the C_{1-4}alkyl of the R^3 is optionally substituted with R^{3a}.

18. The compound of claim 17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^3 is independently -OH, $-CH_3$, $-CH_2OH$, $-OCH_3$, or $-NH_2$.

19. The compound of claim 14 or 15, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of 

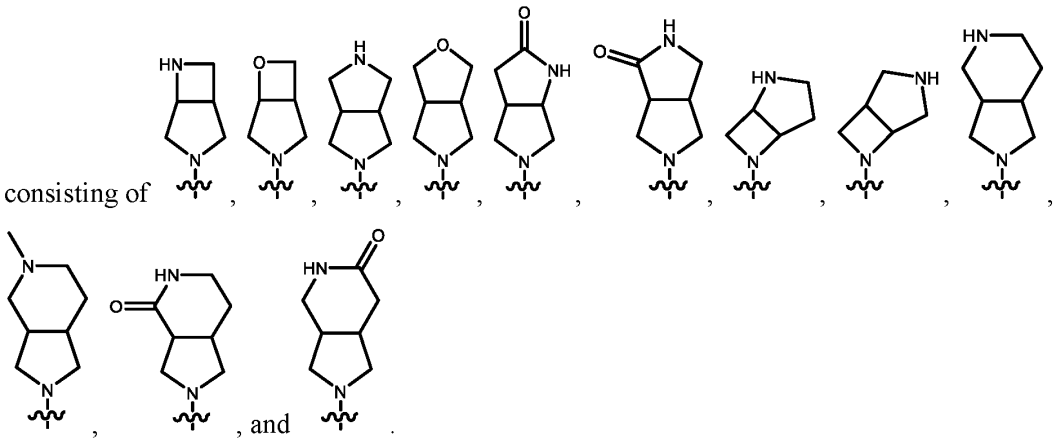


20. The compound of any of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they are attached to form a saturated 7- to 10-membered fused heterocyclyl optionally substituted with one or more R^3.

21. The compound of claim 20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^3 is independently $C_{1\text{-}6}$alkyl or oxo.

22. The compound of claim 21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^3 is independently -CH_3 or oxo.

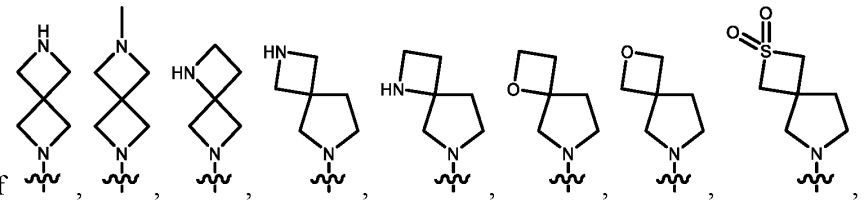
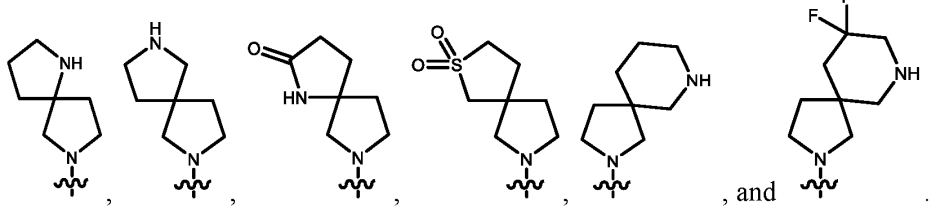
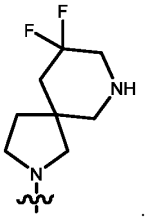
23. The compound of claim 20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of



24. The compound of any of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they are attached to form a saturated 7- to 10-membered spirocyclic heterocyclyl optionally substituted with one or more R^3.

25. The compound of claim 24, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^3 is halo.

26. The compound of claim 25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^3 is F.

27. The compound of claim 24, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group consisting of  ,  , and  .

28. The compound of any of claims 1, 2, 6, 9, or 11, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^4 is independently halo or -O-(C_{1-6}alkyl).

29. The compound of claim 28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^4 is independently halo or -OCH_3.

30. The compound of any of claims 1-29, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl, wherein

the C_{1-6}alkyl of R^5 is optionally substituted with one or more halo, -N(R^x)(R^y), -OR^{12}, and

the C_{3-8}cycloalkyl of R^5 is optionally substituted with one or more R^{5b}.

31. The compound of any of claims 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^5 is H, C_{1-6}alkyl, or C_{3-8}cycloalkyl.

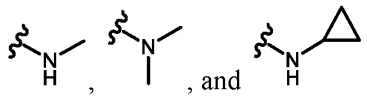
32. The compound of any of claims 1-31, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^5 is H or C_{1-6}alkyl.

33. The compound of any of claims 1-32, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^5 is H.

34. The compound of any of claims 1-29, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is a bond or -O-(C_{1-6}alkyl)-.

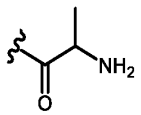
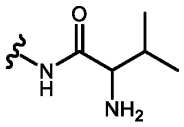
35. The compound of any of claims 1-29, or 34, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is a bond or -O-(CH_2CH_2)-.

36. The compound of any of claims 1-35, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is -N(R^x)(R^y).

37. The compound of claim 1-36, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is selected from the group consisting of  .

38. The compound of any of claims 1-35, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is -N(R^{13})C(O)R^{14}, -N(R^{13})C(O)OR^{14}, -N(R^{13})C(O)N(R^{13})R^{14}, -C(O)N(R^{13})(R^{14}), or -C(O)(C_{1-6}alkyl)N(R^{13})(R^{14}).

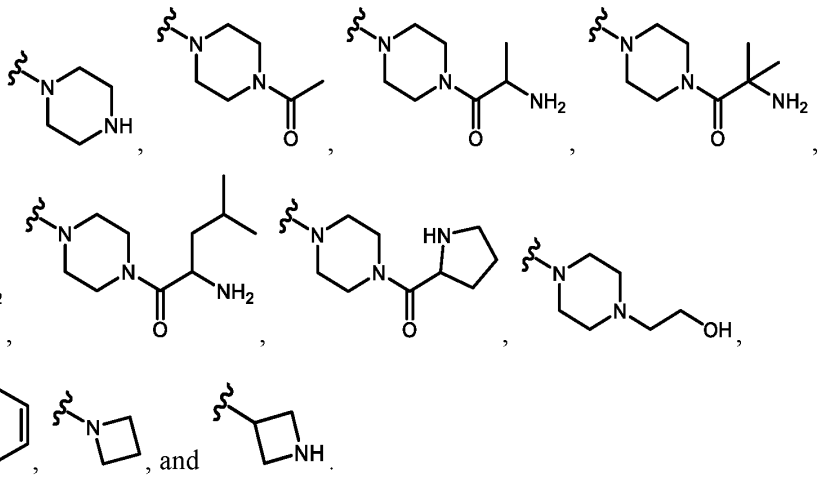
39. The compound of any of claims 1-35 or 38, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is -N(R^{13})C(O)R^{14} or -C(O)(C_{1-6}alkyl)N(R^{13})(R^{14}).

40. The compound of any of claims 1-35 or 39, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is  or  .

41. The compound of any of claims 1-35, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is 3- to 12-membered N-containing heterocyclyl optionally substituted with one or more R^{6b}.

42. The compound of any of claims 1-35 or 41, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is a bond and R^6 is 3- to 12-membered N-containing heterocyclyl optionally substituted with one or more R^{6b}.

43. The compound of any of claims 1-35, 41, or 42, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is azetidinyl, pyrrolidinyl, or piperazinyl, wherein the azetidinyl, pyrrolidinyl, or piperazinyl is optionally substituted with one or more R^{6b}.

44. The compound of any of claims 1-35 or 41-43, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is selected from the group consisting of  , and .

45. The compound of any of claims 1-44, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^8 and R^9 are each independently H, halo, $-N(R^x)(R^y)$, $-OR^{11}$, $-N(R^{13})C(O)R^{14}$, or $-N(R^{13})C(O)OR^{14}$.

46. The compound of claim 45, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^8 and R^9 are each independently H, halo, $-NH_2$, $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$, $-O(C_{1-6}alkyl)$, -NHC(O)(5- to 6-membered aryl), or $-NHC(O)O(C_{1-6}alkyl)$, wherein

the 5- to 6-membered aryl of -NHC(O)(5- to 6-membered aryl) is optionally substituted with $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$.

47. The compound of claim 46, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^8 and R^9 are each independently H, F, Cl, $-NH_2$, $-N(CH_3)(CH_3)$, $-OCH_3$, -NHC(O)(phenyl), or $-NHC(O)O(CH_2CH_3)$, wherein

the phenyl of -NHC(O)(phenyl) is substituted with $-N(CH_3)(CH_3)$.

48. The compound of any of claims 1-47, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^8 and R^9 are each H.

49. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is selected from Table 1.

50. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is selected from compounds 1 to 68 of Table 1.

51. A pharmaceutical composition comprising a compound of any of claims 1-50, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients or carriers.

52. A method for treating a disease or condition mediated by TDP-43, comprising administering to an individual in need thereof a compound of any of claims 1-50, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 51.

53. The method of claim 52, wherein said disease or condition mediated by TDP-43 is a neurological disease or condition.

54. The method of claim 53, wherein the neurological disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, traumatic brain injury (TBI), chronic traumatic encephalopathy (CTE), frontotemporal dementia (FTD),

inclusion body myositis, Perry syndrome, corticobasal degeneration, spinocerebellar ataxia type 3, and amyotrophic lateral sclerosis (ALS).

55. The method of claim 53 or 54, wherein the neurological disease or condition is traumatic brain injury (TBI).

56. The method of claim 53 or 54, wherein the neurological disease or condition is frontotemporal dementia (FTD).

57. The method of claim 53 or 54, wherein the neurological disease or condition is amyotrophic lateral sclerosis (ALS).

58. The method of any of claims 53, 54, or 57, wherein the neurological disease or condition is sporadic amyotrophic lateral sclerosis or C9ORF72 amyotrophic lateral sclerosis.

59. The method of any of claims 52-58, wherein neurodegeneration is reduced.

60. A method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of any of claims 1-50, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 51, wherein

modulating TDP-43 comprises modulating TDP-43 incorporation into condensates, modulating TDP-43 binding to RNA in condensates, modulating TDP-43 aggregation, or modulating TDP43 protein-protein interactions.

61. A method of modulating TDP-43 driven gene expression levels, comprising contacting a cell with an effective amount of a compound of any of claims 1-50, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 51.

62. The method of claim 61, wherein the gene expression levels are for *STMN2*.

63. The method of claim 61, wherein the gene expression levels are for *POLDIP3*.

64. The compound of any of claims 1-50, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 51 for use in the treatment of a disease or condition mediated by TDP-43.

65. Use of a compound of any of claims 1-50, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a disease or condition mediated by TDP-43.

66. A kit, comprising (i) a compound of any one of claims 1-50, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 51 and (ii) instructions for use in treating a TDP-43 mediated disease or condition in an individual in need thereof.