

AMINO QUINOLINE COMPOUNDS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of United States Provisional Patent Application No. 63/618,220 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.

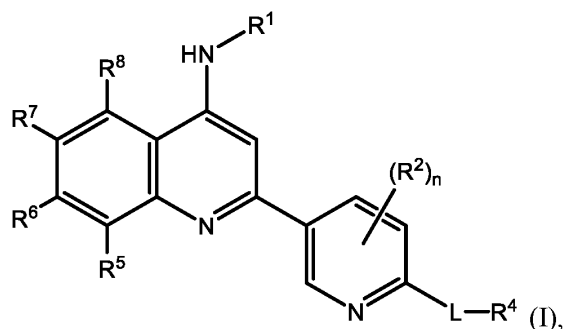
BACKGROUND OF THE INVENTION

[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 G₄C₂ 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):



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

R¹ is H, C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)N(R¹⁰)(R¹¹), -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R¹ is optionally substituted with one or more R^{1a},

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R¹ is optionally substituted with one or more R^{1b}, and optionally, two substituents of the C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)N(R¹⁰)(R¹¹), -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl group of R¹ are taken together with the atoms to which they are attached to form a C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 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};

each R² is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -SR⁹, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R² is optionally substituted by one or more R^{2a},

the C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R² is optionally substituted with one or more R^{2b}, and the 3- to 8-membered heterocyclyl of R² comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

n is 0, 1, 2, or 3;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R³)(C₁₋₆alkyl)- wherein the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R³)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -SF₅, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, C₃₋₈cycloalkyl, 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 C₃₋₈cycloalkyl or 3- to 8-membered heterocyclyl;

R³ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -SF₅, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NR¹²)OR¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, or -S(=O)₂N(R¹⁰)(R¹¹), and the C₃₋₈cycloalkyl is optionally substituted with one or more R^{3b};

R⁴ is H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -SR⁹, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NR¹²)OR¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁴ is optionally substituted by one or more R^{4a},

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁴ is optionally substituted with one or more R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹, and

the 3- to 12-membered heterocyclyl of R⁴ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R⁴ are taken together with the atoms to which they are attached form a C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹;

R⁵, R⁶, R⁷, and R⁸ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹³, -SR⁹, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁵, R⁶, R⁷, or R⁸ is optionally substituted by one or more R^{5a}, the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁵, R⁶, R⁷, or R⁸ is optionally substituted with one or more R^{5b}, and the 3- to 8-membered heterocyclyl of R⁵, R⁶, R⁷, or R⁸ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R⁵, R⁶, R⁷, or R⁸ are taken together with the atoms to which they are attached form a C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{5b};

or R⁶ and R⁷ are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl;

each R^{1a}, R^{2a}, R^{4a}, or R^{5a} is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -

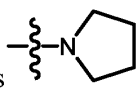
$S(=NR^{12})OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein
 the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a} , R^{2a} , R^{4a} , or R^{5a} is optionally substituted with one or more R^{1b} , and
 the 3- to 12-membered heterocyclyl of R^{1a} , R^{2a} , R^{4a} , or R^{5a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;
 each R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is independently halo, C_{1-6} alkyl, $-OR^{13}$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein
 wherein the C_{1-6} alkyl of R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is optionally substituted by $-OR^9$, $-N(R^x)(R^y)$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;
 each R^9 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, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^9 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^{10} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;
 each R^{11} 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^{11} is optionally substituted by one or more halo, $-OH$, $-O(C_{1-6}alkyl)$, $-O(phenyl)$, $-SH$, $-S(C_{1-6}alkyl)$, $-(C=O)NH_2$, $-(C=O)OH$, $-O(C=O)C_{1-8}alkyl$, $-NH(C=NH)NH_2$, $-N(R^x)(R^y)$, 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^{11} is optionally substituted with halo, C_{1-6} alkyl, $-OH$, or $-N(R^x)(R^y)$;
 each R^{12} is independently H or C_{1-6} alkyl;
 each R^{13} 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^{13} 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, C₁₋₃alkyl, C₁₋₃alkoxy, -N(R^x)(R^y), or 3- to 12-membered heterocyclyl, and

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R¹³ is optionally substituted with halo, C₁₋₃alkyl, C₁₋₃alkoxy, or -N(R^x)(R^y); and

each R^x and R^y is independently H, C₁₋₆alkyl, C₃₋₈cycloalkyl, -C(=O)(C₁₋₆alkyl), or -C(=O)O(C₁₋₆alkyl), wherein

the C₁₋₆alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or -NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆alkyl)(C₁₋₆alkyl), and the C₁₋₆alkyl of -C(=O)(C₁₋₆alkyl) or -C(=O)O(C₁₋₆alkyl) is optionally substituted with -O(C(=O)C₁₋₈alkyl), wherein

when L is -OCH₂CH₂CH₂-, R⁴ is , and R⁵ and R⁶ are each H, R¹ is not -CH₂CH₂CH₂N(CH₃)(CH₃).

[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 R¹, R², n, L, R^L, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R^{1a}, R^{2a}, R^{4a}, R^{5a}, R^{1b}, R^{2b}, R^{3b}, R^{4b}, R^{5b}, R⁹, R¹⁰, R¹¹, R¹², R¹³, R^x, and R^y, apply to formula (II) or (III), 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) or (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another 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 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) or (III), 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) or (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another 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 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) or (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate 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) or (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another 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 of any of the foregoing. This aspect in some embodiments may employ a compound of any of formulas (II) or (III), 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) or (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another 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 of any of the foregoing. This aspect in some embodiments may employ a compound of any of formulas (II) or (III), 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) or (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another aspect, 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 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) or (III), 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) or (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another aspect, 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 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) or (III), 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) or (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another aspect, 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) or (III), 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) or (III), 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.*, C₁₋₂₀alkyl), 1-16 carbons (*i.e.*, C₁₋₁₆alkyl), 1-12 carbons (*i.e.*, C₁₋₁₂alkyl), 1-10 carbons (*i.e.*, C₁₋₁₀alkyl), 1-8 carbons (*i.e.*, C₁₋₈alkyl), 1-6 carbons (*i.e.*, C₁₋₆alkyl), 1-4 carbons (*i.e.*, C₁₋₄alkyl), or 1-3 carbons (*i.e.*, C₁₋₃alkyl). 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.*, C₂₋₂₀alkenyl), 2-16 carbons (*i.e.*, C₂₋₁₆alkenyl), 2-12 carbons (*i.e.*, C₂₋₁₂alkenyl), 2-10 carbons (*i.e.*, C₂₋₁₀alkenyl), 2-8 carbons (*i.e.*, C₂₋₈alkenyl), 2-6 carbons (*i.e.*, C₂₋₆alkenyl), 2-4 carbons (*i.e.*, C₂₋₄alkenyl), or 2-3 carbons (*i.e.*, C₂₋₃alkenyl). 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.*, C₂₋₂₀alkynyl), 2-16 carbons (*i.e.*, C₂₋₁₆alkynyl), 2-12 carbons (*i.e.*, C₂₋₁₂alkynyl), 2-10 carbons (*i.e.*, C₂₋₁₀alkynyl), 2-8 carbons (*i.e.*, C₂₋₈alkynyl), 2-6 carbons (*i.e.*, C₂₋₆alkynyl), 2-4 carbons (*i.e.*, C₂₋₄alkynyl), or 2-3 carbons (*i.e.*, C₂₋₃alkynyl). 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 C₃₋₂₀cycloalkyl), 3 to 16 annular carbon atoms (*i.e.*, a C₃₋₁₆cycloalkyl), 3 to 12 annular carbon atoms (*i.e.*, a C₃₋₁₂cycloalkyl), 3 to 10 annular carbon atoms (*i.e.*, a C₃₋₁₀cycloalkyl), 3 to 8 annular carbon atoms (*i.e.*, a C₃₋₈cycloalkyl), 3 to 6 annular carbon atoms (*i.e.*, a C₃₋₆cycloalkyl), or 3 to 5 annular carbon atoms (*i.e.*, a C₃₋₅cycloalkyl). 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, norbornyl, decalanyl, 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 “C₁₋₄haloalkyl” is meant 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- to 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.*, azetidiny, piperidiny, 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 atom. 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 -CH₃, -CH₂Cl, -CHCl₂, and -CCl₃ 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 ^2H , ^3H , ^{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

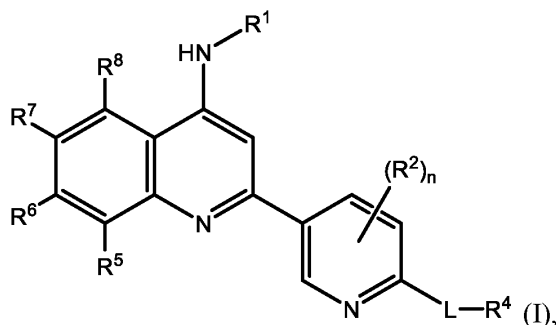
pressure liquid chromatography (HPLC), and chiral supercritical fluid chromatography (SFC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, unless specified otherwise, it is intended that the present disclosure includes both E and Z geometric 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. 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.

COMPOUNDS

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



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

R^1 is H, C_{1-6} alkyl, C_{2-6} alkenyl, $-\text{C}(=\text{O})\text{R}^{11}$, $-\text{C}(=\text{O})\text{OR}^{11}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{10})(\text{R}^{11})$, $-\text{S}(=\text{O})_2\text{R}^{11}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{10})(\text{R}^{11})$, 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 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 is optionally substituted with one or more R^{1b} , and

optionally, two substituents of the C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)N(R¹⁰)(R¹¹), -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl group of R¹ are taken together with the atoms to which they are attached to form a C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 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};

each R² is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -SR⁹, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R² is optionally substituted by one or more R^{2a},

the C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R² is optionally substituted with one or more R^{2b}, and

the 3- to 8-membered heterocyclyl of R² comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

n is 0, 1, 2, or 3;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R³)(C₁₋₆alkyl)- wherein

the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R³)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -SF₅, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, C₃₋₈cycloalkyl, 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 C₃₋₈cycloalkyl or 3- to 8-membered heterocyclyl;

R³ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -SF₅, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -

OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, or -S(=O)₂N(R¹⁰)(R¹¹), and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{3b};

R⁴ is H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -SR⁹, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁴ is optionally substituted by one or more R^{4a},

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁴ is optionally substituted with one or more R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹, and

the 3- to 12-membered heterocyclyl of R⁴ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R⁴ are taken together with the atoms to which they are attached form a C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹;

R⁵, R⁶, R⁷, and R⁸ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹³, -SR⁹, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁵, R⁶, R⁷, or R⁸ is optionally substituted by one or more R^{5a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁵, R⁶, R⁷, or R⁸ is optionally substituted with one or more R^{5b}, and

the 3- to 8-membered heterocyclyl of R^5 , R^6 , R^7 , or R^8 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and optionally, two substituents of R^5 , R^6 , R^7 , or R^8 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^{5b} ;

or R^6 and R^7 are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl;

each R^{1a} , R^{2a} , R^{4a} , or R^{5a} is independently halo, $-N(R^x)(R^y)$, $-OR^9$, $-SR^9$, $-NO_2$, $-CN$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, $-C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=NR^{12})R^{11}$, $-S(=NR^{12})N(R^{10})R^{11}$, $-S(=NR^{12})OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, 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^{2a} , R^{4a} , or R^{5a} is optionally substituted with one or more R^{1b} , and

the 3- to 12-membered heterocyclyl of R^{1a} , R^{2a} , R^{4a} , or R^{5a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is independently halo, C_{1-6} alkyl, $-OR^{13}$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6} alkyl of R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is optionally substituted by $-OR^9$, $-N(R^x)(R^y)$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;

each R^9 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, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^9 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^{10} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

each R^{11} 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^{11} is optionally substituted by one or more halo, -OH, -O(C_{1-6} alkyl), -O(phenyl), -SH, -S(C_{1-6} alkyl), -(C=O)NH₂, -(C=O)OH, -O(C=O) C_{1-8} alkyl, -NH(C=NH)NH₂, -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^{11} is optionally substituted with halo, C_{1-6} alkyl, -OH, or -N(R^x)(R^y);

each R^{12} is independently H or C_{1-6} alkyl;

each R^{13} 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^{13} 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^{13} is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, -N(R^x)(R^y), or 3- to 12-membered heterocyclyl; 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, or -NH₂, 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 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 is C_{1-6} alkyl, C_{2-6} alkenyl, -C(=O) R^{11} , -C(=O)OR¹¹, -C(=O)N(R^{10})(R^{11}), -S(=O)₂ R^{11} , -S(=O)₂N(R^{10})(R^{11}), or C_{3-8} cycloalkyl, wherein

the C₁₋₆alkyl of R¹ is optionally substituted with one or more R^{1a},
 the C₃₋₈cycloalkyl of R¹ is optionally substituted with one or more R^{1b}, and
 optionally, two substituents of the C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹¹, -C(=O)OR¹¹, -
 C(=O)N(R¹⁰)(R¹¹), -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl group of R¹ are
 taken together with the atoms to which they are attached to form a C₃₋₈cycloalkyl, 3-
 to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered
 heteroaryl, wherein

the C₃₋₈cycloalkyl, 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};

each R² is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -SR⁹, -SF₅, -
 N(R^x)(R^y), -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -
 OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -
 C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -
 N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -
 S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to
 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R² is optionally substituted by one or more R^{2a},
 the C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to
 10-membered heteroaryl of R² is optionally substituted with one or more R^{2b}, and
 the 3- to 8-membered heterocyclyl of R² comprises 1, 2, or 3 atoms selected from the
 group consisting of N, O, and S;

n is 0, 1, 2, or 3;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R³)(C₁₋₆alkyl)- wherein

the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R³)(C₁₋₆alkyl)- is optionally
 substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -SF₅, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -
 N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -
 OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, C₃₋₈cycloalkyl, 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
 C₃₋₈cycloalkyl or 3- to 8-membered heterocyclyl;

R³ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), or
 C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -SF₅, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, or -S(=O)₂N(R¹⁰)(R¹¹), and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{3b};

R⁴ is -N(R^x)(R^y), -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)N(R¹⁰)R¹¹, -C(=O)(C₁₋₆alkyl)N(R^x)(R^y), -C(=O)N(R¹⁰)(R¹¹), -N(R¹⁰)S(=O)₂R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), or 3- to 8-membered N-containing heterocyclyl, wherein

the 3- to 8-membered N-containing heterocyclyl of R⁴ is optionally substituted with one or more R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹, and

the 3- to 8-membered N-containing heterocyclyl of R⁴ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

R⁵, R⁶, R⁷, and R⁸ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹³, -SR⁹, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁵, R⁶, R⁷, or R⁸ is optionally substituted by one or more R^{5a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁵, R⁶, R⁷, or R⁸ is optionally substituted with one or more R^{5b}, and

the 3- to 8-membered heterocyclyl of R⁵, R⁶, R⁷, or R⁸ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R⁵, R⁶, R⁷, or R⁸ are taken together with the atoms to which they are attached form a C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{5b};

or R⁶ and R⁷ are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl;

each R^{1a}, R^{2a}, R^{4a}, or R^{5a} is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a}, R^{2a}, R^{4a}, or R^{5a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{2a}, R^{4a}, or R^{5a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{2b}, R^{3b}, R^{4b}, or R^{5b} is independently halo, C₁₋₆alkyl, -OR¹³, -N(R^x)(R^y), oxo, -CN, C₃₋₈cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C₁₋₆alkyl of R^{1b}, R^{2b}, R^{3b}, R^{4b}, or R^{5b} is optionally substituted by -OR⁹, -N(R^x)(R^y), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;

each R⁹ is independently H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C₁₋₆alkyl is optionally substituted with one or more halo, deuterium, C₁₋₆alkoxy, -N(R^x)(R^y), or 3- to 8-membered heterocyclyl;

each R¹⁰ is independently H, C₁₋₆alkyl, or C₃₋₈cycloalkyl;

each R¹¹ is independently H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₈cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C₁₋₆alkyl of R¹¹ is optionally substituted by one or more halo, -OH, -O(C₁₋₆alkyl), -SH, -S(C₁₋₆alkyl), -(C=O)NH₂, -(C=O)OH, -O(C=O)C₁₋₈alkyl, -NH(C=NH)NH₂, -N(R^x)(R^y), C₃₋₈cycloalkyl, 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 C₃₋₈cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R¹¹ is optionally substituted with halo, C₁₋₆alkyl, -OH, or -N(R^x)(R^y);

each R¹² is independently H or C₁₋₆alkyl;

each R¹³ is independently H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R¹³ 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, C₁₋₃alkyl, C₁₋₃alkoxy, or -N(R^x)(R^y), and

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R¹³ is optionally substituted with halo, C₁₋₃alkyl, C₁₋₃alkoxy, -N(R^x)(R^y), or 3- to 12-membered heterocyclyl; and

each R^x and R^y is independently H, C₁₋₆alkyl, C₃₋₈cycloalkyl, -C(=O)(C₁₋₆alkyl), or -C(=O)O(C₁₋₆alkyl), wherein

the C₁₋₆alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or -NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆alkyl)(C₁₋₆alkyl), and the C₁₋₆alkyl of -C(=O)(C₁₋₆alkyl) or -C(=O)O(C₁₋₆alkyl) is optionally substituted with -O(C(=O)C₁₋₈alkyl). 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.

[0047] 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:

R¹ is C₁₋₆alkyl, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R¹ is optionally substituted with one or more R^{1a},

the C₃₋₈cycloalkyl of R¹ is optionally substituted with one or more R^{1b};

optionally, two substituents of the C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl group of R¹ are taken together with the atoms to which they are attached to form a C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 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};

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

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

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

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

n is 0, 1, 2, or 3;

L is a bond, C_{1-6} alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^3)(C_{1-6}alkyl)-$ wherein

the C_{1-6} alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^3)(C_{1-6}alkyl)-$ is optionally substituted by one or more R^L ;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^9$, $-SR^9$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, 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^3 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(=O)R^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, or C_{3-8} cycloalkyl, wherein

the C_{1-6} alkyl of R^3 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^9$, $-SR^9$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, $-C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, or $-S(=O)_2N(R^{10})(R^{11})$, and

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

R^4 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^9$, $-SR^9$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, $-C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, and

$S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=NR^{12})R^{11}$, $-S(=NR^{12})N(R^{10})R^{11}$, $-S(=NR^{12})OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, 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^4 is optionally substituted by one or more R^{4a} ,
 the C_{3-8} cycloalkyl, 3- to 12-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} , $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, or $-C(=O)OR^{11}$, and
 the 3- to 12-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and
 optionally, two substituents of R^4 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^{4b} , $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, or $-C(=O)OR^{11}$;

R^5 is H;

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

the C_{1-6} alkyl of R^6 or R^7 is optionally substituted by one or more R^{5a} ,
 the 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of R^6 or R^7 is optionally substituted with one or more R^{5b} , and
 the 3- to 8-membered heterocyclyl of R^6 or R^7 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

or R^6 and R^7 are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl;

R^8 is H;

each R^{1a} , R^{2a} , R^{4a} , and R^{5a} is independently halo, $-N(R^x)(R^y)$, $-OR^9$, $-SR^9$, $-NO_2$, $-CN$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, -

$C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of R^{1a} , R^{2a} , R^{4a} , or R^{5a} is optionally substituted with one or more R^{1b} , and the 3- to 12-membered heterocyclyl of R^{1a} , R^{2a} , R^{4a} , or R^{5a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is independently halo, C_{1-6} alkyl, $-OR^{13}$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6} alkyl of R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is optionally substituted by $-OR^9$, $-N(R^x)(R^y)$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^9 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^{10} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

each R^{11} 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^{11} 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^{11} is optionally substituted with halo, C_{1-6} alkyl, $-OH$, or $-N(R^x)(R^y)$;

each R^{12} is independently H or C_{1-6} alkyl;

each R^{13} 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

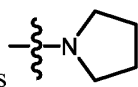
the C_{1-6} alkyl of R^{13} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

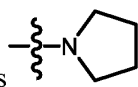
the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C₁₋₃alkyl, C₁₋₃alkoxy, -N(R^x)(R^y), or 3- to 12-membered heterocyclyl, and

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R¹³ is optionally substituted with halo, C₁₋₃alkyl, C₁₋₃alkoxy, or -N(R^x)(R^y); and

each R^x and R^y is independently H, C₁₋₆alkyl, C₃₋₈cycloalkyl, -C(=O)(C₁₋₆alkyl), or -C(=O)O(C₁₋₆alkyl), wherein

the C₁₋₆alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or -NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆alkyl)(C₁₋₆alkyl), and the C₁₋₆alkyl of -C(=O)(C₁₋₆alkyl) or -C(=O)O(C₁₋₆alkyl) is optionally substituted with -O(C(=O)C₁₋₈alkyl);



wherein when L is -OCH₂CH₂CH₂-, R⁴ is , and R⁵ and R⁶ are each H, R¹ is not -CH₂CH₂CH₂N(CH₃)(CH₃). 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.

[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:

R¹ is C₁₋₆alkyl, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R¹ is optionally substituted with one or more R^{1a},

the C₃₋₈cycloalkyl of R¹ is optionally substituted with one or more R^{1b};

optionally, two substituents of the C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl of R¹ are taken together with the atoms to which they are attached to form a C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 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}; and

each R² is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -SR⁹, -N(R^x)(R^y), -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -

$S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

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

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

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

n is 0, 1, 2, or 3;

L is a bond, C_{1-6} alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^3)(C_{1-6}alkyl)-$;

R^3 is H, C_{1-6} alkyl, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $-C(=O)R^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, or C_{3-8} cycloalkyl, wherein

the C_{1-6} alkyl of R^3 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^9$, $-SR^9$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, $-C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, or $-S(=O)_2N(R^{10})(R^{11})$, and

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

R^4 is $-N(R^x)(R^y)$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, or 3- to 8-membered N-containing heterocyclyl, wherein

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

the 3- to 8-membered N-containing heterocyclyl of R^4 is optionally substituted with one or more R^{4b} , $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, or $-C(=O)OR^{11}$, and

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

R^5 is H;

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

the C₁₋₆alkyl of R⁶ or R⁷ is optionally substituted by one or more R^{5a},
 the 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of R⁶ or R⁷ is optionally substituted with one or more R^{5b}, and
 the 3- to 8-membered heterocyclyl of R⁶ or R⁷ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

or R⁶ and R⁷ are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl;

R⁸ is H;

each R^{1a}, R^{2a}, R^{4a}, and R^{5a} is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl is optionally substituted with of R^{1a}, R^{2a}, R^{4a}, or R^{5a} is optionally substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{2a}, R^{4a}, or R^{5a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b}, R^{2b}, R^{3b}, R^{4b}, or R^{5b} is independently halo, C₁₋₆alkyl, -OR¹³, -N(R^x)(R^y), oxo, -CN, C₃₋₈cycloalkyl, or 3- to 8-membered heterocyclyl;

each R⁹ is independently H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

wherein the C₁₋₆alkyl is optionally substituted with one or more halo, deuterium, C₁₋₆alkoxy, -N(R^x)(R^y), or 3- to 8-membered heterocyclyl;

each R¹⁰ is independently H, C₁₋₆alkyl, or C₃₋₈cycloalkyl;

each R¹¹ is independently H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₈cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C₁₋₆alkyl of R¹¹ is optionally substituted by halo, -OH, -O(C₁₋₆alkyl), -O(C=O)C₁₋₈alkyl, -N(R^x)(R^y), C₃₋₈cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C₃₋₈cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R¹¹ is optionally substituted with halo, C₁₋₆alkyl, or -N(R^x)(R^y);

each R^{12} is independently H or C_{1-6} alkyl;

each R^{13} 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^{13} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

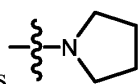
the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, or $-N(R^x)(R^y)$, and

the 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{13} is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, or $-N(R^x)(R^y)$; 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, or $-NH_2$, $NH(C_{1-6}alkyl)$, 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 L is $-OCH_2CH_2CH_2-$, R^4 is $-CH_2CH_2CH_2N(CH_3)(CH_3)$, and R^5 and R^6 are each H, R^1 is not $-CH_2CH_2CH_2N(CH_3)(CH_3)$. 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.

[0049] 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 is C_{1-6} alkyl optionally substituted with one or more R^{1a} ;

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

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

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

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

n is 0, 1, 2, or 3;

L is a bond, C_{1-6} alkyl, $-O-(C_{1-6}$ alkyl)-, $-S-(C_{1-6}$ alkyl)-, or $-N(R^3)(C_{1-6}$ alkyl)- wherein

the C_{1-6} alkyl, $-O-(C_{1-6}$ alkyl)-, $-S-(C_{1-6}$ alkyl)-, or $-N(R^3)(C_{1-6}$ alkyl)- is optionally substituted by one or more R^L ;

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^9$, $-SR^9$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, 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^3 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(=O)R^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, or C_{3-8} cycloalkyl, wherein

the C_{1-6} alkyl of R^3 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^9$, $-SR^9$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, $-C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, or $-S(=O)_2N(R^{10})(R^{11})$, and

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

R^4 is $-N(R^x)(R^y)$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-C(=O)(C_{1-6}$ alkyl) $N(R^x)(R^y)$, $-C(=O)N(R^{10})(R^{11})$, or 3- to 8-membered N-containing heterocyclyl, wherein

the 3- to 8-membered N-containing heterocyclyl of R^4 is optionally substituted with one or more R^{4b} , $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, or $-C(=O)OR^{11}$, and

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

R^5 is H;

R^6 and R^7 are each independently H, halo, C_{1-6} alkyl, $-OR^9$, $-OR^{13}$, $-N(R^x)(R^y)$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, $-C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, or $-S(=O)_2N(R^{10})(R^{11})$, wherein

the C₁₋₆alkyl of R⁶ or R⁷ is optionally substituted by one or more R^{5a};
 or R⁶ and R⁷ are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl;
 R⁸ is H;
 each R^{1a}, R^{2a}, R^{4a}, and R^{5a} is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein
 the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of R^{1a}, R^{2a}, R^{4a}, or R^{5a} is optionally substituted with one or more R^{1b}, and the 3- to 12-membered heterocyclyl of R^{1a}, R^{2a}, R^{4a}, or R^{5a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;
 each R^{1b}, R^{2b}, R^{3b}, R^{4b}, or R^{5b} is independently halo, C₁₋₆alkyl, -OR¹³, -N(R^x)(R^y), oxo, -CN, C₃₋₈cycloalkyl, or 3- to 8-membered heterocyclyl, wherein
 the C₁₋₆alkyl of R^{1b}, R^{2b}, R^{3b}, R^{4b}, or R^{5b} is optionally substituted by -OR⁹, -N(R^x)(R^y), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;
 each R⁹ is independently H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,
 wherein the C₁₋₆alkyl is optionally substituted with one or more halo, deuterium, C₁₋₆alkoxy, -N(R^x)(R^y), or 3- to 8-membered heterocyclyl;
 each R¹⁰ is independently H, C₁₋₆alkyl, or C₃₋₈cycloalkyl;
 each R¹¹ is independently H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₈cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein
 the C₁₋₆alkyl of R¹¹ is optionally substituted by one or more halo, -OH, -O(C₁₋₆alkyl), -SH, -S(C₁₋₆alkyl), -(C=O)NH₂, -(C=O)OH, -O(C=O)C₁₋₈alkyl, -NH(C=NH)NH₂, -N(R^x)(R^y), C₃₋₈cycloalkyl, 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 C₃₋₈cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R¹¹ is optionally substituted with halo, C₁₋₆alkyl, -OH, or -N(R^x)(R^y);

each R^{12} is independently H or C_{1-6} alkyl;

each R^{13} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C_{1-6} alkyl of R^{13} is optionally substituted with phenyl, or 5- to 6-membered heteroaryl, wherein

the phenyl, or 5- to 6-membered heteroaryl is optionally substituted with halo,

C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl, and

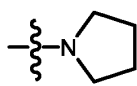
the phenyl, or 5- to 6-membered heteroaryl of R^{13} is optionally substituted with halo,

C_{1-3} alkyl, C_{1-3} alkoxy, or $-N(R^x)(R^y)$; 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, or $-NH_2$, $NH(C_{1-6}$ 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 L is $-OCH_2CH_2CH_2-$, R^4 is $CH_2CH_2CH_2N(CH_3)(CH_3)$, and R^5 and R^6 are each H, R^1 is not $-CH_2CH_2CH_2N(CH_3)(CH_3)$. 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.

[0050] 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 is C_{1-6} alkyl optionally substituted with one or more R^{1a} ;

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

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

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

the 3- to 8-membered heterocyclyl of R² comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

n is 0, 1, 2, or 3;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R³)(C₁₋₆alkyl)-;

R³ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=O)₂R¹¹, or -S(=O)₂N(R¹⁰)(R¹¹), and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{3b};

R⁴ is -N(R^x)(R^y), -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)N(R¹⁰)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or 3- to 8-membered N-containing heterocyclyl, wherein

the C₁₋₆alkyl of R⁴ is optionally substituted by one or more R^{4a},

the 3- to 8-membered N-containing heterocyclyl of R⁴ is optionally substituted with one or more R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹, and

the 3- to 8-membered N-containing heterocyclyl of R⁴ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S; and

R⁵ is H;

R⁶ and R⁷ are each independently H, halo, C₁₋₆alkyl, -OR⁹, -N(R^x)(R^y), -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, or -S(=O)₂N(R¹⁰)(R¹¹), wherein

the C₁₋₆alkyl of R⁶ or R⁷ is optionally substituted by one or more R^{5a};

or R⁶ and R⁷ are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl;

R⁸ is H;

each R^{1a}, R^{2a}, R^{4a}, and R^{5a} is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -

$C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl is optionally substituted with one or more R^{1a} , R^{2a} , R^{4a} , or R^{5a} is optionally substituted with one or more R^{1b} , and

the 3- to 12-membered heterocyclyl of R^{1a} , R^{2a} , R^{4a} , or R^{5a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is independently halo, C_{1-6} alkyl, $-OR^{13}$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl;

each R^9 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^{10} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

each R^{11} 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^{11} 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^{11} is optionally substituted with halo, C_{1-6} alkyl, or $-N(R^x)(R^y)$;

each R^{12} is independently H or C_{1-6} alkyl;

each R^{13} 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

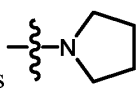
the C_{1-6} alkyl of R^{13} is optionally substituted with 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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^{13} is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, or $-N(R^x)(R^y)$; 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 C₁₋₆alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or -NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆alkyl)(C₁₋₆alkyl), and the C₁₋₆alkyl of -C(=O)(C₁₋₆alkyl) or -C(=O)O(C₁₋₆alkyl) is optionally substituted with -O(C=O)C₁₋₈alkyl, wherein

when L is -OCH₂CH₂CH₂-, R⁴ is , and R⁵ and R⁶ are each H, R¹ is not -CH₂CH₂CH₂N(CH₃)(CH₃). 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.

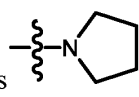
[0051] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or salt of any of the foregoing:

L is a bond or -O(C₁₋₆alkyl);

R⁴ is 3- to 12-membered N-containing heterocyclyl optionally substituted by R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹; and

R¹ is C₁₋₄alkyl optionally substituted with one or more substituents selected from the group consisting of -OH, -NH(CH₃), and -N(CH₃)(CH₃). 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.

[0052] In some embodiments 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

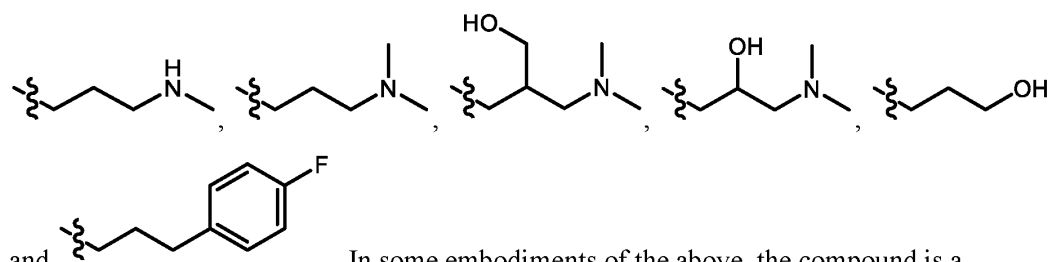
of the foregoing, when L is -OCH₂CH₂CH₂-, R⁴ is , and R⁵ and R⁶ are each H, R¹ is not -CH₂CH₂CH₂N(CH₃)(CH₃). In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0053] 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, R¹ is C₁₋₆alkyl substituted with one or more R^{1a}. 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 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, each R^{1a} is independently -OH, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)(C₁₋₆alkyl), or phenyl, wherein the phenyl is optionally substituted by halo. In some embodiments, each R^{1a} is independently -OH, -NH(CH₃), -N(CH₃)(CH₃), or fluorophenyl. 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.

[0055] 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, R^1 is selected from the group consisting of



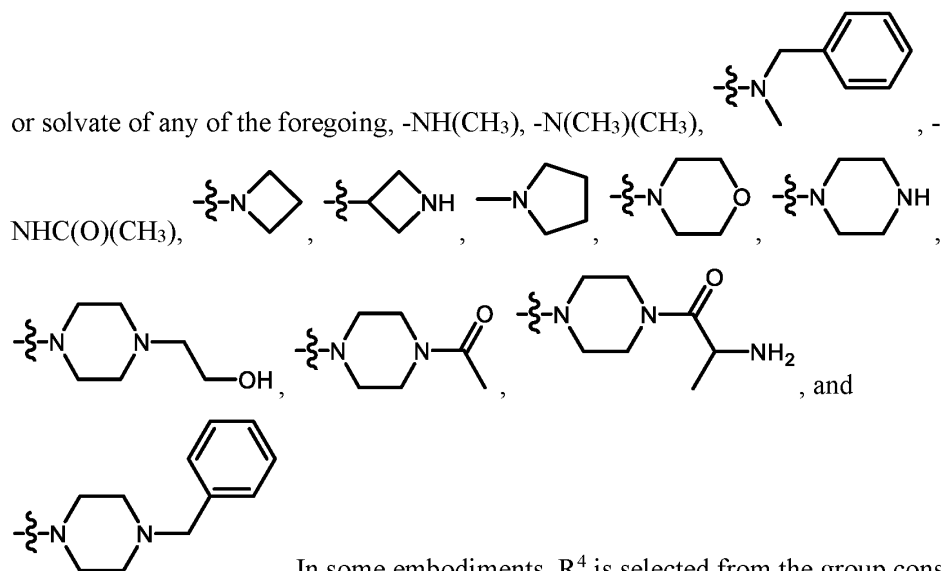
and . In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0056] 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, L is a bond or -O(C₁₋₆alkyl)-. In some embodiments, L is a bond or -O(C₁₋₄alkyl)-. In some embodiments, L is a bond or -O(CH₂CH₂)-. 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.

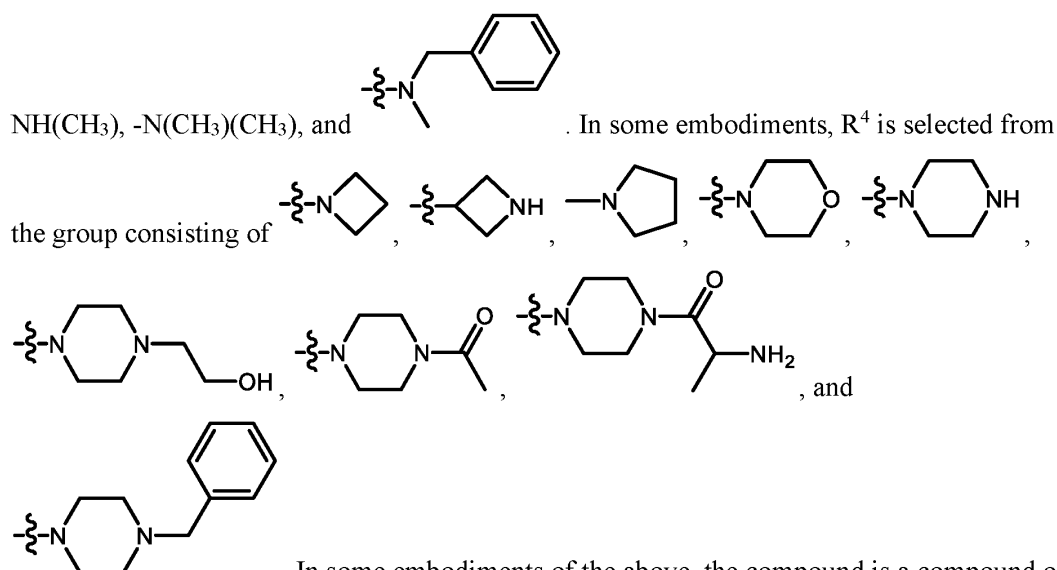
[0057] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^4 is -N(R^x)(R^y). In some embodiments, R^4 is -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)(C₁₋₆alkyl), wherein each C₁₋₆alkyl is independently optionally substituted by one or more R^{4a} . In some embodiments, R^4 is -N(R¹⁰)C(O)R¹¹. In some embodiments, R^4 is -NHC(O)(C₁₋₆alkyl). In some embodiments, R^4 is -NHC(O)(CH₃). In some embodiments, R^4 is 3- to 12-membered N-containing heterocyclyl optionally substituted by R^{4b} , -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹. In some embodiments, R^4 is azetidiny, pyrrolidinyl, morpholinyl, piperazinyl, wherein the piperazinyl is optionally substituted by R^{4b} , -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹. In some embodiments, R^4 is azetidiny, pyrrolidinyl, morpholinyl, piperazinyl, wherein the piperazinyl is optionally

substituted by R^{4b} or $-C(=O)R^{11}$. 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 a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate,



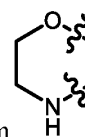
. In some embodiments, R^4 is selected from the group consisting of -



. 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.

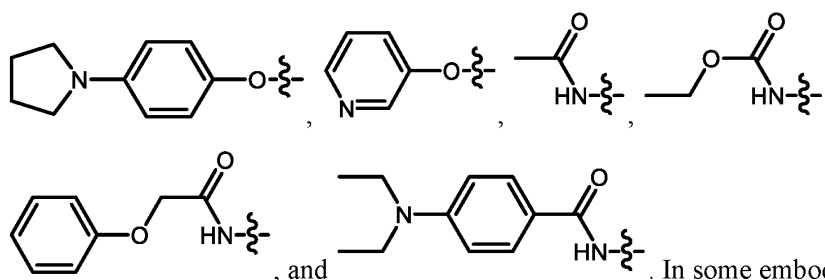
[0059] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate,

or solvate of any of the foregoing, R^6 and R^7 are each independently H, halo, C_{1-6} alkyl, $-N(R^x)(R^y)$, $-OR^9$, $-N(R^{10})C(O)R^{11}$, or $-N(R^{10})C(O)OR^{11}$. In some embodiments, R^6 and R^7 are each independently H, halo, C_{1-6} alkyl, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$, $-O(C_{1-6}alkyl)$, $-O(5- \text{ to } 6\text{-membered aryl})$, $-O(5- \text{ to } 6\text{-membered heteroaryl})$, $-NHC(O)(C_{1-6}alkyl)$, $-NHC(O)(5- \text{ to } 6\text{-membered aryl})$, or $-NHC(O)O(C_{1-6}alkyl)$, wherein the $-O(C_{1-6}alkyl)$ of R^6 or R^7 is optionally substituted with phenyl or halo; the $-O(5- \text{ to } 6\text{-membered aryl})$ of R^6 or R^7 is optionally substituted with 4- to 6-membered heterocyclyl; the $-NHC(O)(C_{1-6}alkyl)$ of R^6 or R^7 is optionally by $-O(5- \text{ to } 6\text{-membered aryl})$; and the $-NHC(O)(5- \text{ to } 6\text{-membered aryl})$ of R^6 or R^7 is optionally substituted with $-N(R^x)(R^y)$. In some embodiments, R^6 and R^7 are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl. In some embodiments, R^6 and R^7 are taken together with the carbon atoms to which they are attached to form a 5- to 6-membered heterocyclyl. In some embodiments, R^6 and R^7 are taken together with the carbon atoms to which they are attached to form a 5-membered heterocyclyl. In some embodiments, R^6 and R^7 are taken together with the carbon atoms to which they are attached to form a 6-membered heterocyclyl. In some embodiments,

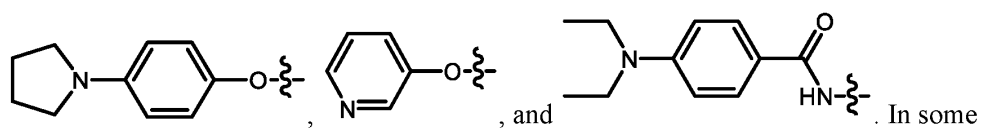


R^6 and R^7 are taken together with the carbon atoms to which they are attached to form . In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0060] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^6 and R^7 are each independently selected from the group consisting of H, $-CH_3$, F, $-NH(CH_3)$, $-N(CH_3)(CH_3)$, $-OCF_3$, $-OCH_3$,

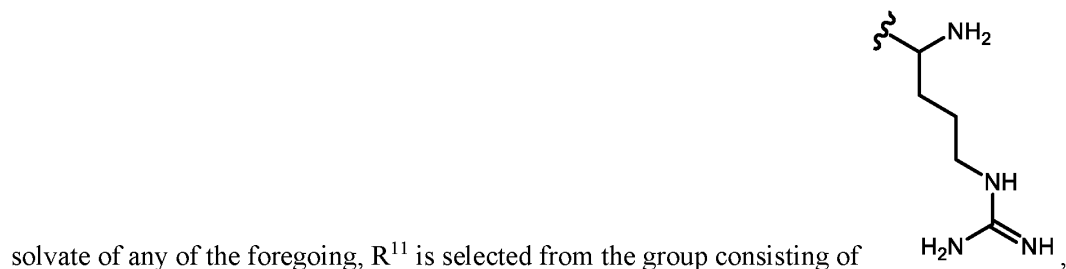


, and . In some embodiments, R^6 and R^7 are each independently selected from the group consisting of H, $-CH_3$, F, $-OCH_3$,

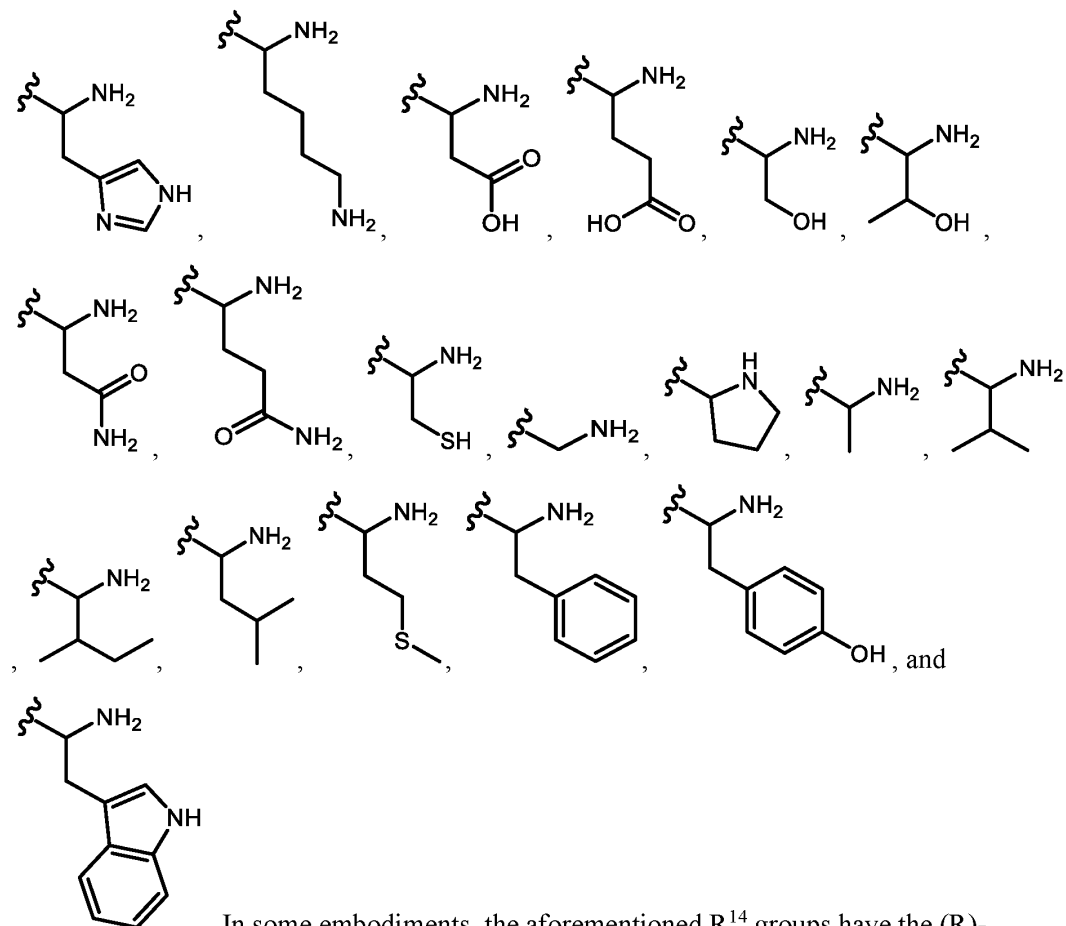


embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[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



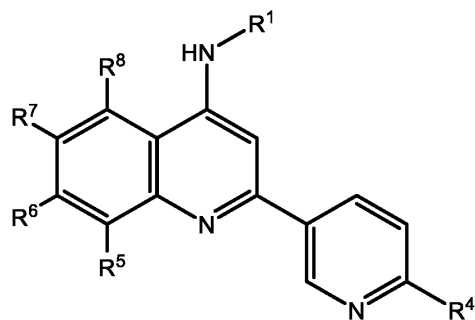
solvate of any of the foregoing, R¹¹ is selected from the group consisting of



. In some embodiments, the aforementioned R¹⁴ groups have the (R)-configuration. In some embodiments, the aforementioned R¹⁴ groups have the (S)-

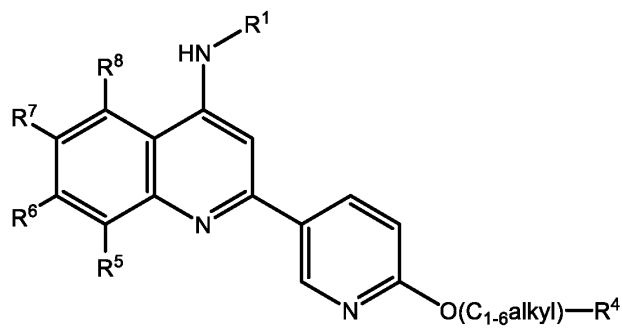
configuration. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0062] In some embodiments of a compound of formula (I), the compound is a compound of formula (II)



(II), 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 R¹, R⁴, R⁵, R⁶, R⁷, and R⁸ are as defined elsewhere herein. In another variation, R¹, R⁴, R⁵, R⁶, R⁷, and R⁸ 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.

[0063] In some embodiments of a compound of formula (I), the compound is a compound of formula (III)



thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R¹, R⁴, R⁵, R⁶, R⁷, and R⁸ are as defined elsewhere herein. In another variation, R¹, R⁴, R⁵, R⁶, R⁷, and R⁸ are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of

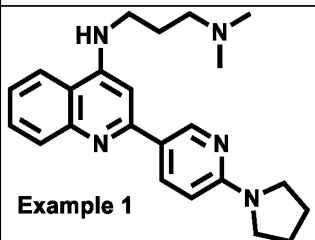
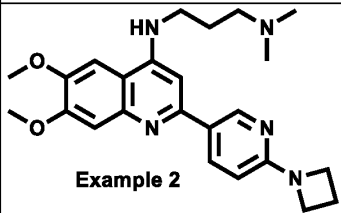
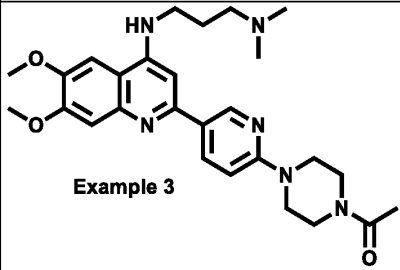
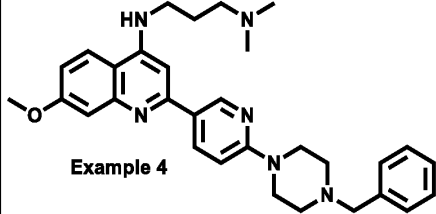
any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

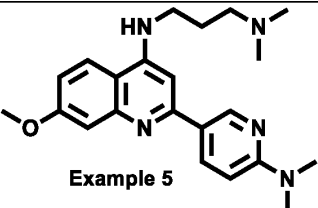
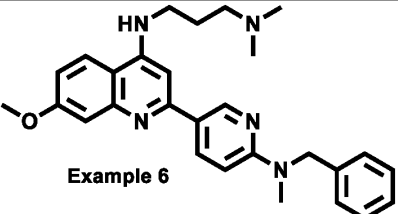
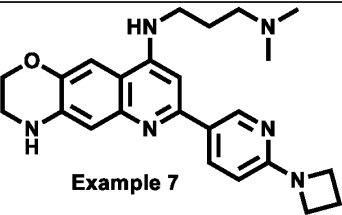
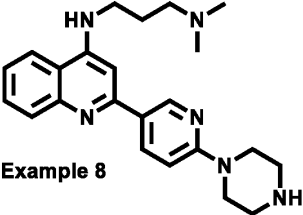
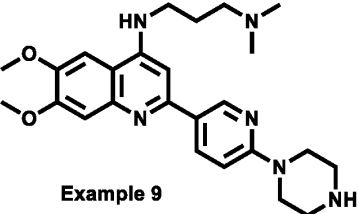
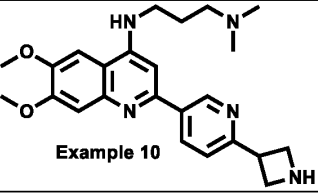
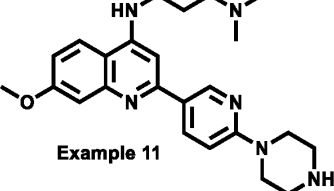
[0064] In some embodiments, the compounds of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, selectively modulate TDP-43. In some embodiments, the compounds of formula (I), or any variation or embodiment 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.

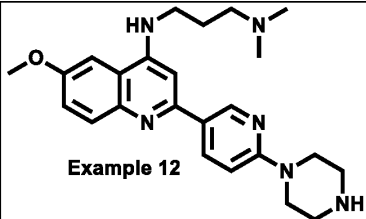
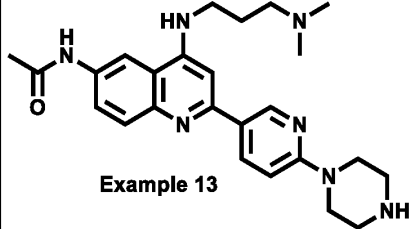
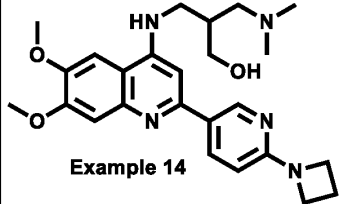
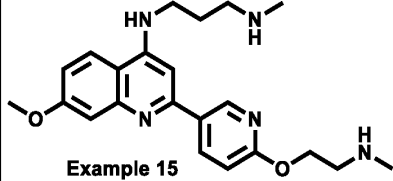
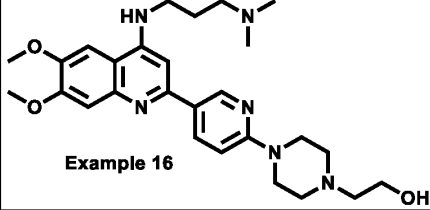
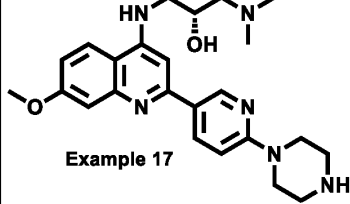
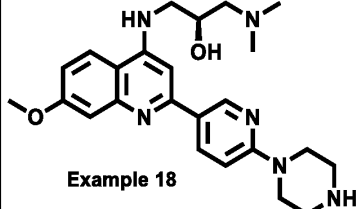
[0065] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is selected from Table 1. In some embodiments of a compound of formula (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 1-40 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),

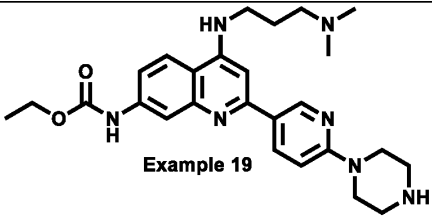
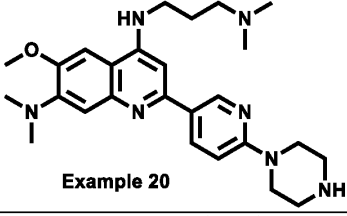
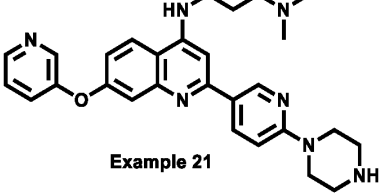
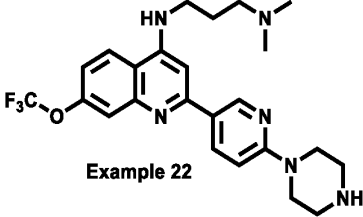
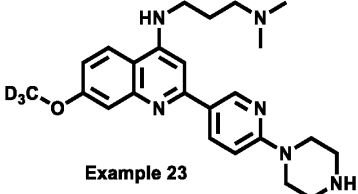
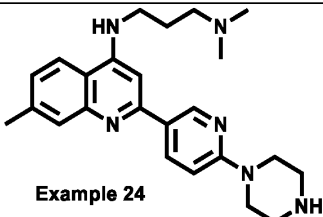
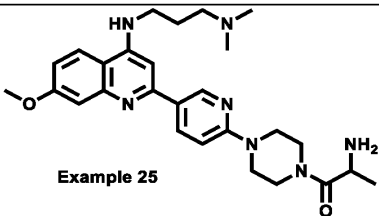
or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is selected from compounds 1-40 of Table 1, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments 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 1-28, or 30-40 of Table 1, or a pharmaceutically acceptable salt of any of the foregoing.

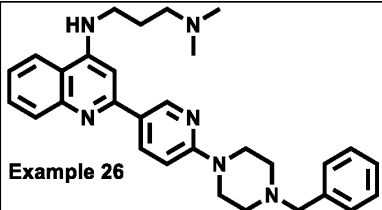
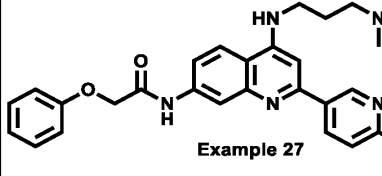
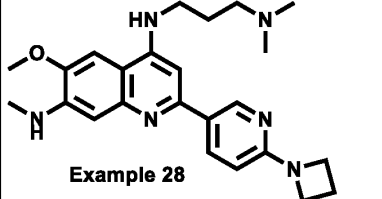
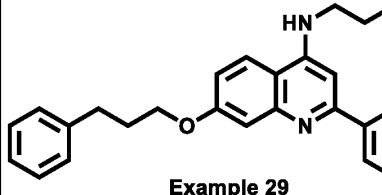
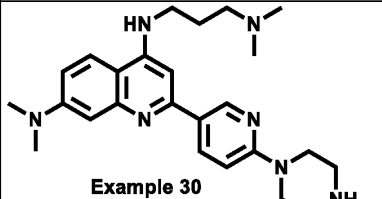
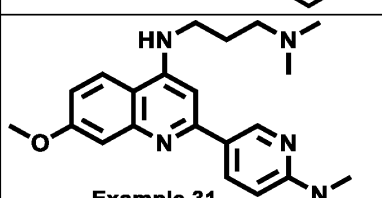
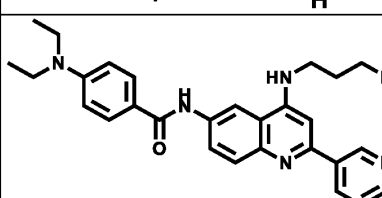
Table 1

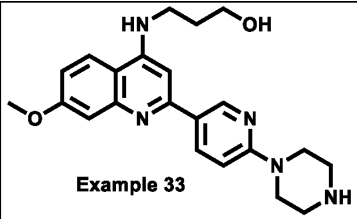
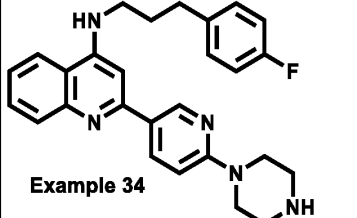
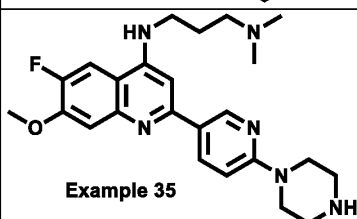
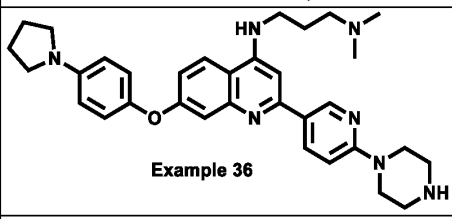
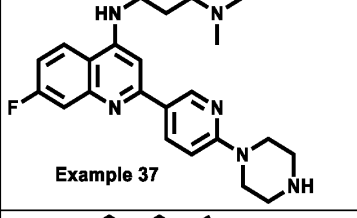
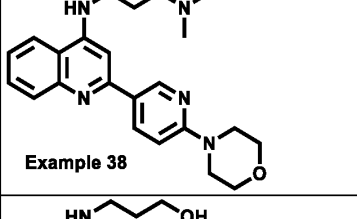
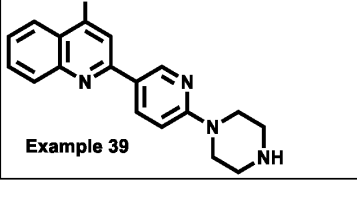
Example No.	Structure	Name
1	 Example 1	<i>N</i> ¹ , <i>N</i> ¹ -dimethyl- <i>N</i> ³ -(2-(6-(pyrrolidin-1-yl) pyridin-3-yl) quinolin-4-yl) propane-1,3-diamine
2	 Example 2	<i>N</i> ¹ -(2-(6-(azetidin-1-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine
3	 Example 3	1-(4-(5-(4-((3-(dimethylamino) propyl) amino)-6,7-dimethoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-one
4	 Example 4	<i>N</i> ¹ -(2-(6-(4-benzylpiperazin-1-yl) pyridin-3-yl)-7-methoxyquinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine

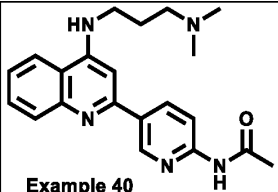
5	 Example 5	<i>N</i> ¹ -(2-(6-(dimethylamino) pyridin-3-yl)-7-methoxyquinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine
6	 Example 6	<i>N</i> ¹ -(2-(6-(benzyl(methyl)amino) pyridin-3-yl)-7-methoxyquinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine
7	 Example 7	<i>N</i> ¹ -(2-(6-(azetidin-1-yl) pyridin-3-yl)-7-fluoro-6-methoxyquinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine
8	 Example 8	<i>N</i> ¹ , <i>N</i> ¹ -dimethyl- <i>N</i> ³ -(2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)propane-1,3-diamine
9	 Example 9	<i>N</i> ¹ -(6,7-dimethoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine
10	 Example 10	<i>N</i> ¹ -(2-(6-(azetidin-3-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine
11	 Example 11	<i>N</i> ¹ -(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine

12	 Example 12	<i>N</i> ¹ -(6-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine
13	 Example 13	<i>N</i> -(4-((3-(dimethylamino) propyl) amino)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-6-yl) acetamide
14	 Example 14	3-((2-(6-(azetidin-1-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl) amino)-2-((dimethylamino)methyl) propan-1-ol
15	 Example 15	<i>N</i> ¹ -(7-methoxy-2-(6-(2-(methylamino) ethoxy) pyridin-3-yl) quinolin-4-yl)- <i>N</i> ³ -methylpropane-1,3-diamine
16	 Example 16	2-(4-(5-(4-((3-(dimethylamino) propyl) amino)-6,7-dimethoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-ol
17	 Example 17	(<i>R</i>)-1-(dimethylamino)-3-((7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) amino) propan-2-ol
18	 Example 18	(<i>S</i>)-1-(dimethylamino)-3-((7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) amino) propan-2-ol

19	 Example 19	ethyl 4-((3-(dimethylamino) propyl) amino)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-7-yl carbamate
20	 Example 20	N^4 -(3-(dimethylamino) propyl)-6-methoxy- N^7,N^7 -dimethyl-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline-4,7-diamine
21	 Example 21	N^1,N^1 -dimethyl- N^3 -(2-(6-(piperazin-1-yl) pyridin-3-yl)-7-(pyridin-3-yloxy) quinolin-4-yl) propane-1,3-diamine
22	 Example 22	N^1,N^1 -dimethyl- N^3 -(2-(6-(piperazin-1-yl) pyridin-3-yl)-7-(trifluoromethoxy) quinolin-4-yl) propane-1,3-diamine
23	 Example 23	N^1 -(7-(methoxy- d_3)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)- N^3,N^3 -dimethylpropane-1,3-diamine
24	 Example 24	N^1,N^1 -dimethyl- N^3 -(7-methyl-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) propane-1,3-diamine
25	 Example 25	2-amino-1-(4-(5-(4-((3-(dimethylamino) propyl) amino)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) propan-1-one

26	 Example 26	<i>N</i> ¹ -(2-(6-(4-benzylpiperazin-1-yl) pyridin-3-yl) quinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine
27	 Example 27	<i>N</i> -(2-(6-(azetidin-1-yl) pyridin-3-yl)-4-((3-(dimethylamino) propyl) amino) quinolin-7-yl)-2-phenoxyacetamide
28	 Example 28	2-(6-(azetidin-1-yl) pyridin-3-yl)- <i>N</i> ⁴ -(3-(dimethylamino) propyl)-6-methoxy- <i>N</i> ⁷ -methylquinoline-4,7-diamine
29	 Example 29	<i>N</i> ¹ , <i>N</i> ¹ -dimethyl- <i>N</i> ³ -(7-(3-phenylpropoxy)-2-(pyridin-3-yl)quinolin-4-yl)propane-1,3-diamine
30	 Example 30	<i>N</i> ⁴ -[3-(dimethylamino) propyl]- <i>N</i> ⁷ , <i>N</i> ⁷ -dimethyl-2-(6-piperazin-1-yl-3-pyridyl)quinoline-4,7-diamine
31	 Example 31	<i>N</i> ¹ -(7-methoxy-2-(6-(methylamino)pyridin-3-yl)quinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine
32	 Example 32	<i>N</i> -[2-[6-(azetidin-1-yl)-3-pyridyl]-4-[3-(dimethylamino) propylamino]-6-quinolyl]-4-(diethylamino) benzamide

33	 Example 33	3-((7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)amino)propan-1-ol
34	 Example 34	<i>N</i> -[3-(4-fluorophenyl)propyl]-2-(6-piperazin-1-yl-3-pyridyl)quinolin-4-amine
35	 Example 35	<i>N</i> '-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine
36	 Example 36	<i>N</i> ', <i>N</i> '-dimethyl- <i>N</i> ³ -(2-(6-(piperazin-1-yl)pyridin-3-yl)-7-(4-(pyrrolidin-1-yl)phenoxy)quinolin-4-yl)propane-1,3-diamine
37	 Example 37	<i>N</i> '-(7-fluoro-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)- <i>N</i> ³ , <i>N</i> ³ -dimethylpropane-1,3-diamine
38	 Example 38	<i>N</i> ', <i>N</i> '-dimethyl- <i>N</i> ³ -(2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)propane-1,3-diamine
39	 Example 39	3-[[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]amino]propan-1-ol

40	 Example 40	N-(5-(4-((3-(dimethylamino) propyl) amino) quinolin-2-yl) pyridin-2-yl) acetamide
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[0066] 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:

N^1, N^1 -dimethyl- N^3 -(2-(6-(pyrrolidin-1-yl) pyridin-3-yl) quinolin-4-yl) propane-1,3-diamine;
 N^1 -(2-(6-(azetidin-1-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl)- N^3, N^3 -dimethylpropane-1,3-diamine;
 1-(4-(5-(4-((3-(dimethylamino) propyl) amino)-6,7-dimethoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-one;
 N^1 -(2-(6-(4-benzylpiperazin-1-yl) pyridin-3-yl)-7-methoxyquinolin-4-yl)- N^3, N^3 -dimethylpropane-1,3-diamine;
 N^1 -(2-(6-(dimethylamino) pyridin-3-yl)-7-methoxyquinolin-4-yl)- N^3, N^3 -dimethylpropane-1,3-diamine;
 N^1 -(2-(6-(benzyl(methyl)amino) pyridin-3-yl)-7-methoxyquinolin-4-yl)- N^3, N^3 -dimethylpropane-1,3-diamine;
 N^1 -(2-(6-(azetidin-1-yl) pyridin-3-yl)-7-fluoro-6-methoxyquinolin-4-yl)- N^3, N^3 -dimethylpropane-1,3-diamine;
 N^1, N^1 -dimethyl- N^3 -(2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)propane-1,3-diamine;
 N^1 -(6,7-dimethoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)- N^3, N^3 -dimethylpropane-1,3-diamine;
 N^1 -(2-(6-(azetidin-3-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl)- N^3, N^3 -dimethylpropane-1,3-diamine;
 N^1 -(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)- N^3, N^3 -dimethylpropane-1,3-diamine;
 N^1 -(6-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)- N^3, N^3 -dimethylpropane-1,3-diamine;
 N-(4-((3-(dimethylamino) propyl) amino)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-6-yl) acetamide;

3-((2-(6-(azetidin-1-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl) amino)-2-
 ((dimethylamino)methyl) propan-1-ol;
*N*¹-(7-methoxy-2-(6-(2-(methylamino) ethoxy) pyridin-3-yl) quinolin-4-yl)-*N*³-
 methylpropane-1,3-diamine;
 2-(4-(5-(4-((3-(dimethylamino) propyl) amino)-6,7-dimethoxyquinolin-2-yl) pyridin-2-yl)
 piperazin-1-yl) ethan-1-ol;
 (R)-1-(dimethylamino)-3-((7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)
 amino) propan-2-ol;
 (S)-1-(dimethylamino)-3-((7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)
 amino) propan-2-ol;
 ethyl (4-((3-(dimethylamino) propyl) amino)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-7-
 yl) carbamate;
*N*⁴-(3-(dimethylamino) propyl)-6-methoxy-*N*⁷,*N*⁷-dimethyl-2-(6-(piperazin-1-yl) pyridin-3-yl)
 quinoline-4,7-diamine;
*N*¹,*N*¹-dimethyl-*N*³-(2-(6-(piperazin-1-yl) pyridin-3-yl)-7-(pyridin-3-yloxy) quinolin-4-yl)
 propane-1,3-diamine;
*N*¹, *N*¹-dimethyl-*N*³-(2-(6-(piperazin-1-yl) pyridin-3-yl)-7-(trifluoromethoxy) quinolin-4-yl)
 propane-1,3-diamine;
*N*¹-(7-(methoxy-d₃)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-*N*³, *N*³-
 dimethylpropane-1,3-diamine;
*N*¹,*N*¹-dimethyl-*N*³-(7-methyl-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) propane-1,3-
 diamine;
 2-amino-1-(4-(5-(4-((3-(dimethylamino) propyl) amino)-7-methoxyquinolin-2-yl) pyridin-2-
 yl) piperazin-1-yl) propan-1-one;
*N*¹-(2-(6-(4-benzylpiperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-*N*³, *N*³-dimethylpropane-1,3-
 diamine;
N-(2-(6-(azetidin-1-yl) pyridin-3-yl)-4-((3-(dimethylamino) propyl) amino) quinolin-7-yl)-2-
 phenoxyacetamide;
 2-(6-(azetidin-1-yl) pyridin-3-yl)-*N*⁴-(3-(dimethylamino) propyl)-6-methoxy-*N*⁷-
 methylquinoline-4,7-diamine;
*N*¹,*N*¹-dimethyl-*N*³-(7-(3-phenylpropoxy)-2-(pyridin-3-yl)quinolin-4-yl)propane-1,3-diamine;
*N*⁴-[3-(dimethylamino) propyl]-*N*⁷,*N*⁷-dimethyl-2-(6-piperazin-1-yl-3-pyridyl) quinoline-4,7-
 diamine;

*N*¹-(7-methoxy-2-(6-(methylamino)pyridin-3-yl)quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine;
N-[2-[6-(azetidin-1-yl)-3-pyridyl]-4-[3-(dimethylamino) propylamino]-6-quinolyl]-4-(diethylamino) benzamide;
 3-((7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) amino) propan-1-ol;
N-[3-(4-fluorophenyl) propyl]-2-(6-piperazin-1-yl-3-pyridyl) quinolin-4-amine;
*N*¹-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine;
*N*¹,*N*¹-dimethyl-*N*³-(2-(6-(piperazin-1-yl)pyridin-3-yl)-7-(4-(pyrrolidin-1-yl)phenoxy)quinolin-4-yl)propane-1,3-diamine;
*N*¹-(7-fluoro-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine;
*N*¹,*N*¹-dimethyl-*N*³-(2-(6-morpholinopyridin-3-yl)quinolin-4-yl)propane-1,3-diamine;
 3-[[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl] amino] propan-1-ol; and
N-(5-(4-((3-(dimethylamino) propyl) amino) quinolin-2-yl) pyridin-2-yl) acetamide.

[0067] 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:

*N*¹,*N*¹-dimethyl-*N*³-(2-(6-(pyrrolidin-1-yl) pyridin-3-yl) quinolin-4-yl) propane-1,3-diamine;
*N*¹-(2-(6-(azetidin-1-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine;
 1-(4-(5-(4-((3-(dimethylamino) propyl) amino)-6,7-dimethoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-one;
*N*¹-(2-(6-(4-benzylpiperazin-1-yl) pyridin-3-yl)-7-methoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine;
*N*¹-(2-(6-(dimethylamino) pyridin-3-yl)-7-methoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine;
*N*¹-(2-(6-(benzyl(methyl)amino) pyridin-3-yl)-7-methoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine;
*N*¹-(2-(6-(azetidin-1-yl) pyridin-3-yl)-7-fluoro-6-methoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine;

*N*¹,*N*¹-dimethyl-*N*³-(2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)propane-1,3-diamine;
*N*¹-(6,7-dimethoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-*N*³, *N*³-
dimethylpropane-1,3-diamine;
*N*¹-(2-(6-(azetidin-3-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-
1,3-diamine;
*N*¹-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-
diamine;
*N*¹-(6-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-
diamine;
N-(4-((3-(dimethylamino) propyl) amino)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-6-yl)
acetamide;
3-((2-(6-(azetidin-1-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl) amino)-2-
((dimethylamino)methyl) propan-1-ol;
*N*¹-(7-methoxy-2-(6-(2-(methylamino) ethoxy) pyridin-3-yl) quinolin-4-yl)-*N*³-
methylpropane-1,3-diamine;
2-(4-(5-(4-((3-(dimethylamino) propyl) amino)-6,7-dimethoxyquinolin-2-yl) pyridin-2-yl)
piperazin-1-yl) ethan-1-ol;
1-(dimethylamino)-3-((7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) amino)
propan-2-ol;
1-(dimethylamino)-3-((7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) amino)
propan-2-ol;
ethyl 4-((3-(dimethylamino) propyl) amino)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-7-
yl) carbamate;
*N*⁴-(3-(dimethylamino) propyl)-6-methoxy-*N*⁷,*N*⁷-dimethyl-2-(6-(piperazin-1-yl) pyridin-3-yl)
quinoline-4,7-diamine;
*N*¹,*N*¹-dimethyl-*N*³-(2-(6-(piperazin-1-yl) pyridin-3-yl)-7-(pyridin-3-yloxy) quinolin-4-yl)
propane-1,3-diamine;
*N*¹, *N*¹-dimethyl-*N*³-(2-(6-(piperazin-1-yl) pyridin-3-yl)-7-(trifluoromethoxy) quinolin-4-yl)
propane-1,3-diamine;
*N*¹-(7-(methoxy-d₃)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-*N*³, *N*³-
dimethylpropane-1,3-diamine;
*N*¹,*N*¹-dimethyl-*N*³-(7-methyl-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) propane-1,3-
diamine;

2-amino-1-(4-(5-(4-((3-(dimethylamino) propyl) amino)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) propan-1-one;

*N*¹-(2-(6-(4-benzylpiperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-*N*³, *N*³-dimethylpropane-1,3-diamine;

N-(2-(6-(azetidin-1-yl) pyridin-3-yl)-4-((3-(dimethylamino) propyl) amino) quinolin-7-yl)-2-phenoxyacetamide;

2-(6-(azetidin-1-yl) pyridin-3-yl)-*N*⁴-(3-(dimethylamino) propyl)-6-methoxy-*N*⁷-methylquinoline-4,7-diamine;

*N*¹,*N*¹-dimethyl-*N*³-(7-(3-phenylpropoxy)-2-(pyridin-3-yl)quinolin-4-yl)propane-1,3-diamine;

*N*⁴-[3-(dimethylamino) propyl]-*N*⁷,*N*⁷-dimethyl-2-(6-piperazin-1-yl-3-pyridyl) quinoline-4,7-diamine;

*N*¹-(7-methoxy-2-(6-(methylamino)pyridin-3-yl)quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine;

N-[2-[6-(azetidin-1-yl)-3-pyridyl]-4-[3-(dimethylamino) propylamino]-6-quinolyl]-4-(diethylamino) benzamide;

3-((7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) amino) propan-1-ol;

N-[3-(4-fluorophenyl) propyl]-2-(6-piperazin-1-yl-3-pyridyl) quinolin-4-amine;

*N*¹-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine;

*N*¹,*N*¹-dimethyl-*N*³-(2-(6-(piperazin-1-yl)pyridin-3-yl)-7-(4-(pyrrolidin-1-yl)phenoxy)quinolin-4-yl)propane-1,3-diamine;

*N*¹-(7-fluoro-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine;

*N*¹,*N*¹-dimethyl-*N*³-(2-(6-morpholinopyridin-3-yl)quinolin-4-yl)propane-1,3-diamine;

3-[[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl] amino] propan-1-ol; and

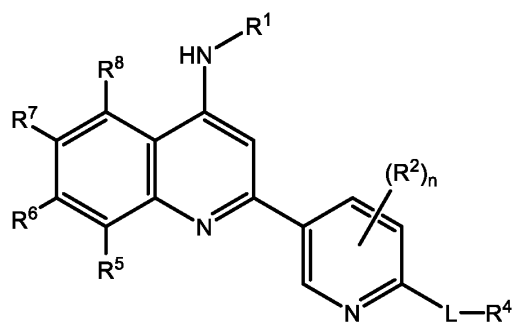
N-(5-(4-((3-(dimethylamino) propyl) amino) quinolin-2-yl) pyridin-2-yl) acetamide.

PHARMACEUTICAL COMPOSITIONS

[0068] Provided herein are pharmaceutical compositions comprising a compound of formula (I), or any variation or embodiment thereof, such as (II) or (III), or a stereoisomer or tautomer thereof, 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, such as (II) or (III), or a stereoisomer or tautomer thereof, 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) or (III), 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.

[0069] 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 is C_{1-6} alkyl optionally substituted with one or more R^{1a} ;

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

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

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

the 3- to 8-membered heterocyclyl of R² comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

n is 0, 1, 2, or 3;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R³)(C₁₋₆alkyl)-;

R³ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=O)₂R¹¹, or -S(=O)₂N(R¹⁰)(R¹¹), and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{3b};

R⁴ is -N(R^x)(R^y), -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)N(R¹⁰)R¹¹, -C(=O)(C₁₋₆alkyl)N(R^x)(R^y), -C(=O)N(R¹⁰)(R¹¹), or 3- to 8-membered N-containing heterocyclyl, wherein

the 3- to 8-membered N-containing heterocyclyl of R⁴ is optionally substituted with one or more R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹, and

the 3- to 8-membered N-containing heterocyclyl of R⁴ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

R⁵ is H;

R⁶ and R⁷ are each independently H, halo, C₁₋₆alkyl, -OR⁹, -N(R^x)(R^y), -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=O)₂R¹¹, or -S(=O)₂N(R¹⁰)(R¹¹), wherein

the C₁₋₆alkyl of R⁶ or R⁷ is optionally substituted by one or more R^{5a};

or R⁶ and R⁷ are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl;

each R^{1a}, R^{2a}, R^{4a}, and R^{5a} is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -

$S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl is optionally substituted with one or more R^{1a} , R^{2a} , R^{4a} , or R^{5a} is optionally substituted with one or more R^{1b} , and

the 3- to 12-membered heterocyclyl of R^{1a} , R^{2a} , R^{4a} , or R^{5a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is independently halo, C_{1-6} alkyl, $-OR^{13}$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6} alkyl of R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is optionally substituted by $-OR^9$, $-N(R^x)(R^y)$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^9 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, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^9 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^{10} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

each R^{11} 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^{11} is optionally substituted by halo, $-OH$, $-O(C_{1-6}alkyl)$, $-O(phenyl)$, $-O(C(=O)C_{1-8}alkyl)$, $-N(R^x)(R^y)$, 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^{11} is optionally substituted with halo, C_{1-6} alkyl, or $-N(R^x)(R^y)$;

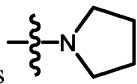
each R^{12} is independently H or C_{1-6} alkyl;

each R^{13} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C_{1-6} alkyl of R^{13} is optionally substituted with phenyl, or 5- to 6-membered heteroaryl, wherein

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

the phenyl, or 5- to 6-membered heteroaryl of R^{13} is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, or $-N(R^x)(R^y)$; 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, or $-NH_2$, $NH(C_{1-6}$ 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 L is $-OCH_2CH_2CH_2-$, R^4 is , and R^5 and R^6 are each H, R^1 is not $-CH_2CH_2CH_2N(CH_3)(CH_3)$.

[0070] 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

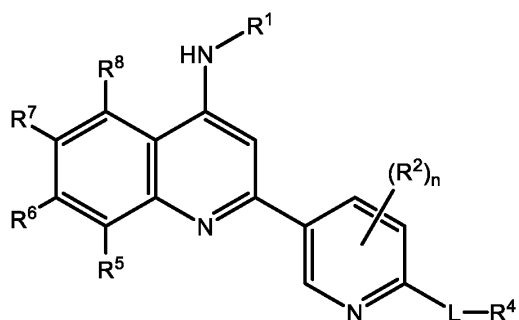
[0071] Traumatic brain injury (TBI) is a risk factor for ALS as demonstrated by the significantly higher incidence of disease in professional athletes and military veterans [See, e.g., Lehman *et al. Neurology* 79, 1970-1974 (2012); McKee *et al. J. Neuropathol. Exp. Neurol.* 69, 989-929 (2010); Chio *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].

[0072] 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) or (III), 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) or (III), 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) or (III), 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) or (III), 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) or (III), 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) or (III), 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) or (III), 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) or (III), 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.

[0073] 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 is C_{1-6} alkyl optionally substituted with one or more R^{1a} ;

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

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

the C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of R² is optionally substituted with one or more R^{2b}, and
the 3- to 8-membered heterocyclyl of R² comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

n is 0, 1, 2, or 3;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R³)(C₁₋₆alkyl)-;

R³ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=O)₂R¹¹, or -S(=O)₂N(R¹⁰)(R¹¹), and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{3b};

R⁴ is -N(R^x)(R^y), -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)N(R¹⁰)R¹¹, -C(=O)(C₁₋₆alkyl)N(R^x)(R^y), -C(=O)N(R¹⁰)(R¹¹), or 3- to 8-membered N-containing heterocyclyl, wherein

the 3- to 8-membered N-containing heterocyclyl of R⁴ is optionally substituted with one or more R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹, and

the 3- to 8-membered N-containing heterocyclyl of R⁴ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

R⁵ is H;

R⁶ and R⁷ are each independently H, halo, C₁₋₆alkyl, -OR⁹, -N(R^x)(R^y), -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=O)₂R¹¹, or -S(=O)₂N(R¹⁰)(R¹¹), wherein

the C₁₋₆alkyl of R⁶ or R⁷ is optionally substituted by one or more R^{5a};

or R⁶ and R⁷ are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl;

each R^{1a}, R^{2a}, R^{4a}, and R^{5a} is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -

$C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl is optionally substituted with one or more R^{1a} , R^{2a} , R^{4a} , or R^{5a} is optionally substituted with one or more R^{1b} , and

the 3- to 12-membered heterocyclyl of R^{1a} , R^{2a} , R^{4a} , or R^{5a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is independently halo, C_{1-6} alkyl, $-OR^{13}$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6} alkyl of R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is optionally substituted by $-OR^9$, $-N(R^x)(R^y)$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl;

each R^9 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, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^9 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^{10} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

each R^{11} 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^{11} is optionally substituted by halo, $-OH$, $-O(C_{1-6}$ alkyl), $-O(phenyl)$, $-O(C(=O)C_{1-8}$ 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^{11} is optionally substituted with halo, C_{1-6} alkyl, or $-N(R^x)(R^y)$;

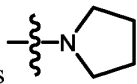
each R^{12} is independently H or C_{1-6} alkyl;

each R^{13} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C_{1-6} alkyl of R^{13} is optionally substituted with phenyl, or 5- to 6-membered heteroaryl, wherein

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

the phenyl, or 5- to 6-membered heteroaryl of R^{13} is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, or $-N(R^x)(R^y)$; 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, or $-NH_2$, $NH(C_{1-6}$ 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 L is $-OCH_2CH_2CH_2-$, R^4 is , and R^5 and R^6 are each H, R^1 is not $-CH_2CH_2CH_2N(CH_3)(CH_3)$.

[0074] 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).

[0075] In some embodiments, the disease or condition is traumatic brain injury (TBI).

[0076] In some embodiments, the disease or condition is frontotemporal dementia (FTD).

[0077] 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.

[0078] In some embodiments, the individual is a human.

[0079] 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) or (III), 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) or (III), 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) or (III), 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) or (III), 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.

[0080] 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) or (III), 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) or (III), 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) or (III), 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) or (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0081] 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) or (III), 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) or (III), 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) or (III), 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) or (III), 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 TDP-43 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 inhibiting TDP-43 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.

[0082] 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) or (III), 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) or (III), 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) or (III), 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) or (III), 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.

[0083] In one aspect, provided herein is a compound of formula (I), or any variation or embodiment thereof, such as (II) or (III), 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) or (III), 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) or (III), 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) or (III), 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. 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.

[0084] In one aspect, provided herein is the use of a compound of formula (I) or any variation or embodiment thereof, such as (II) or (III), 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) or (III), 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) or (III), 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) or (III), 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

[0085] 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.

[0086] Provided herein are kits, comprising (i) an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II) or (III), 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) or (III), 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) or (III), 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) or (III), 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) or (III), 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.

[0087] In some embodiments, the individual is a human.

[0088] 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) or (III), 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) or (III), 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) or (III), 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) or (III), 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

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] All the products generated from the following reactions can be isolated and purified employing standard techniques, such as extraction, ion exchange chromatography,

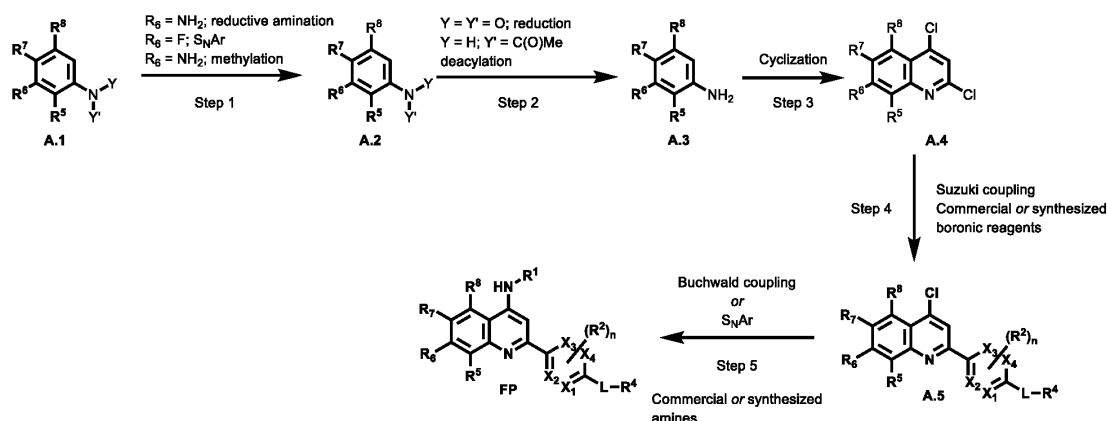
chromatography on silica gel, prep-HPLC. Specific purification steps and methods were set up and will be referred to in the text as follows.

[0095] 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.

[0096] 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, 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.

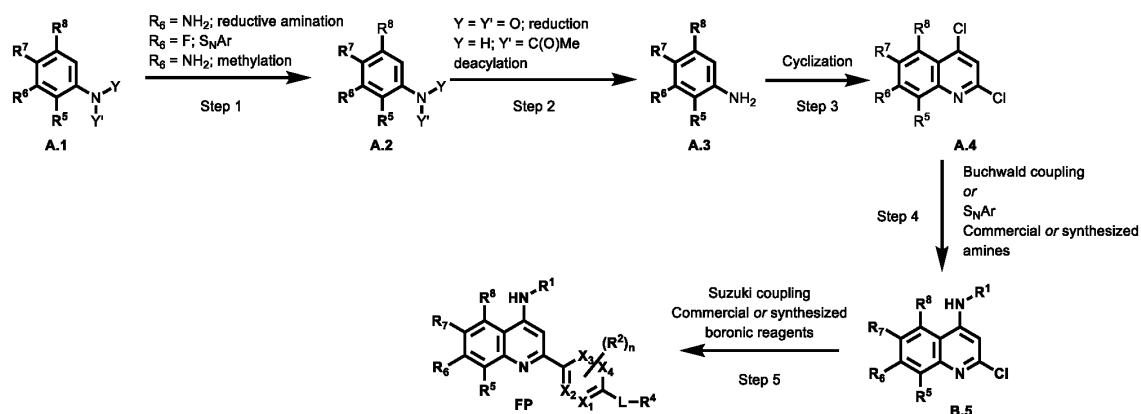
[0097] The 2,4-dichloroquinoline **A.4** underwent a Suzuki cross coupling reaction with commercially available or synthesized boronic ester or boronic acids derivatives (Scheme 1). Quinolines **A.4** were selectively substituted in position 2 to give compounds **A.5**. The substitution of position 4 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.



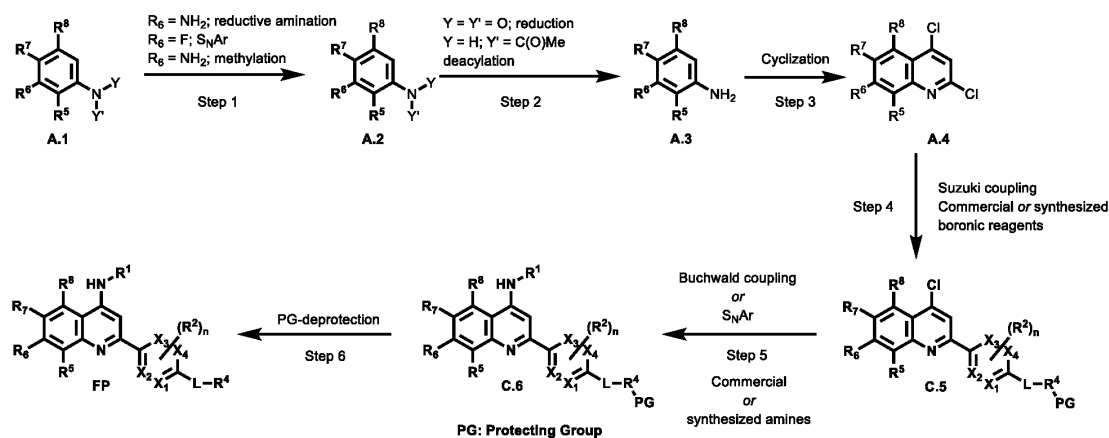
[0098] Similarly to Scheme 1, others **FP** were synthesized applying first the Buchwald coupling or the nucleophilic aromatic substitution on quinolines **A.4** to give derivatives **B.5** (Scheme 2). This step was then followed by a Suzuki coupling to give **FP**.

SCHEME 2.



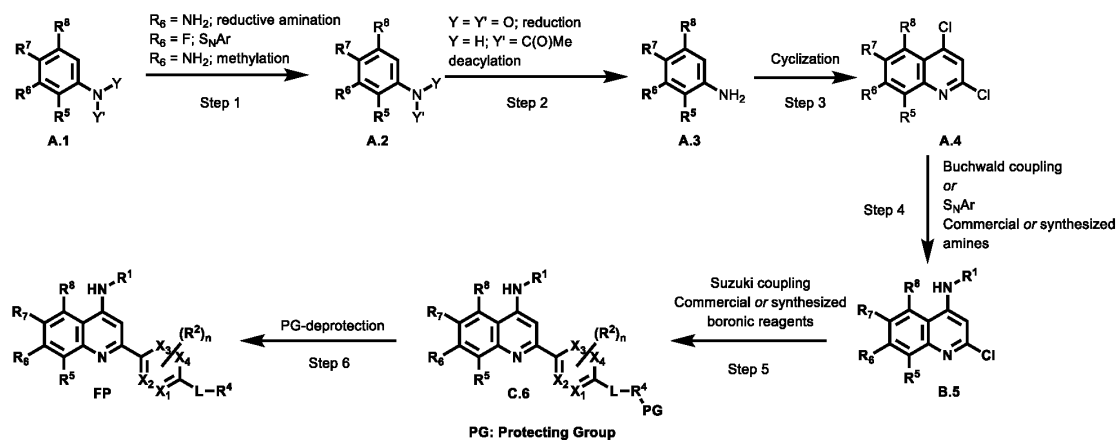
[0099] In some cases, the substituted (hetero)aromatic ring added during the Suzuki coupling on quinolines **A.4** contains a protecting group (**PG**, Schemes 3 and 4). In these cases, **FP** were obtained after an additional step of deprotection. Scheme 3 describes the synthetic sequence similar to Scheme 1, with a Suzuki cross coupling realized first on quinolines **A.4**, followed by the substitution of quinolines **C.5** using a Buchwald reaction or a nucleophilic aromatic substitution to give compounds **C.6**. Compound **C.6** underwent then a deprotection step to give **FP**.

SCHEME 3.



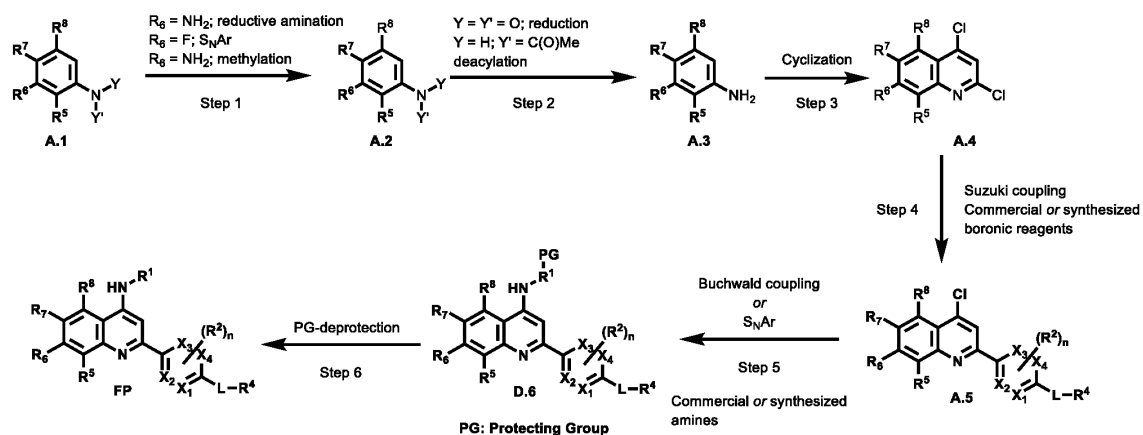
[0100] Scheme 4 describes a synthetic sequence similar to Scheme 2, with first a Buchwald or aromatic nucleophilic substitution realized on quinolines **A.4** to give derivatives **B.5** and followed by a Suzuki cross coupling to obtain **C.6** derivatives which upon a final deprotection step will afford the desired **FPs**.

SCHEME 4.



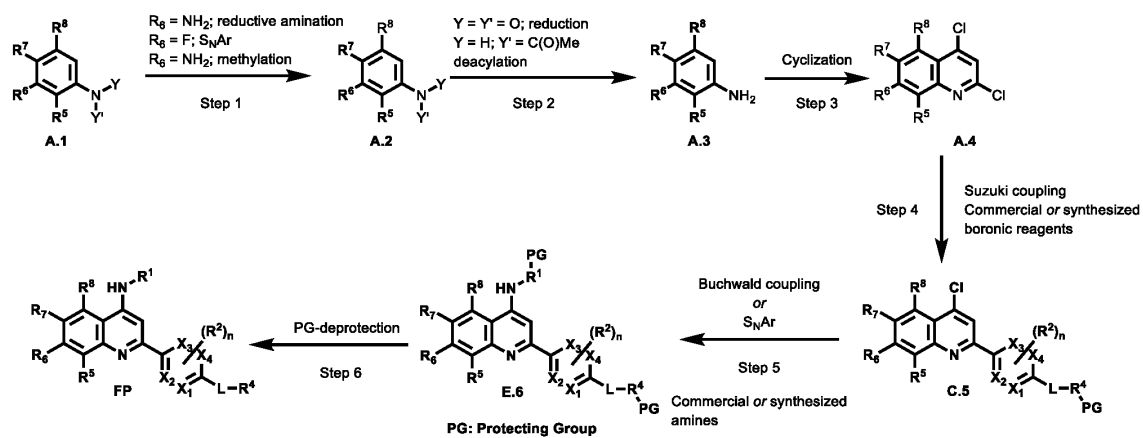
[0101] Scheme 5 describes a synthetic sequence similar to Scheme 1, with first a Suzuki cross coupling realized on position 2 of quinolines **A.4**. This step is followed by the substitution of position 4 of quinolines **A.5** using a nucleophilic aromatic substitution or a Buchwald coupling with amines bearing a protective group to obtain **D.6** intermediates. **FP** is obtained after an additional step of deprotection.

SCHEME 5.



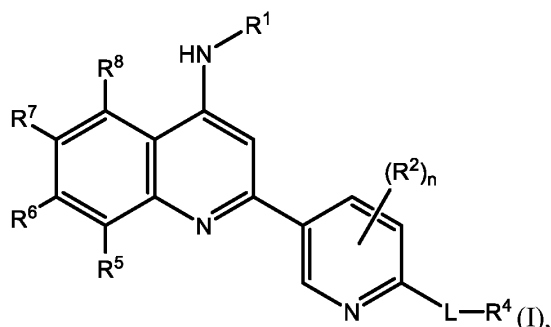
[0102] Scheme 6 describes a synthetic sequence where both boronic ester derivatives used for the Suzuki coupling and the amine used for the Buchwald coupling or aromatic substitution held a protecting group, PG and PG' respectively. Compound **E.6** is then fully deprotected to give **FP**.

SCHEME 6.



ENUMERATED EMBODIMENTS

[0103] Enumerated Embodiment 1. A compound of formula (I):



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

R^1 is H, C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, 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 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 is optionally substituted with one or more R^{1b} , and optionally, two substituents of the C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, or C_{3-8} cycloalkyl group of R^1 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} ;

each R^2 is independently halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^9$, $-SR^9$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, $-C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=NR^{12})R^{11}$, $-S(=NR^{12})N(R^{10})R^{11}$, $-S(=NR^{12})OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, 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^2 is optionally substituted by one or more R^{2a} ,

the C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R² is optionally substituted with one or more R^{2b}, and the 3- to 8-membered heterocyclyl of R² comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

n is 0, 1, 2, or 3;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R³)(C₁₋₆alkyl)- wherein the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R³)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -SF₅, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, C₃₋₈cycloalkyl, 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 C₃₋₈cycloalkyl or 3- to 8-membered heterocyclyl;

R³ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -SF₅, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, or -S(=O)₂N(R¹⁰)(R¹¹), and the C₃₋₈cycloalkyl is optionally substituted with one or more R^{3b};

R⁴ is H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -SR⁹, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁴ is optionally substituted by one or more R^{4a},

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁴ is optionally substituted with one or more R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹, and

the 3- to 12-membered heterocyclyl of R⁴ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R⁴ are taken together with the atoms to which they are attached form a C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹;

R⁵, R⁶, R⁷, and R⁸ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹³, -SR⁹, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -S(=NR¹²)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁵, R⁶, R⁷, or R⁸ is optionally substituted by one or more R^{5a}, the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁵, R⁶, R⁷, or R⁸ is optionally substituted with one or more R^{5b}, and the 3- to 8-membered heterocyclyl of R⁵, R⁶, R⁷, or R⁸ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R⁵, R⁶, R⁷, or R⁸ are taken together with the atoms to which they are attached form a C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{5b};

or R⁶ and R⁷ are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl;

each R^{1a}, R^{2a}, R^{4a}, or R^{5a} is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -NO₂, -CN, -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=NR¹²)R¹¹, -S(=NR¹²)N(R¹⁰)R¹¹, -

$S(=NR^{12})OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, 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^{2a} , R^{4a} , or R^{5a} is optionally substituted with one or more R^{1b} , and
 the 3- to 12-membered heterocyclyl of R^{1a} , R^{2a} , R^{4a} , or R^{5a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;
 each R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is independently halo, C_{1-6} alkyl, $-OR^{13}$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein
 the C_{1-6} alkyl of R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is optionally substituted by $-OR^9$, $-N(R^x)(R^y)$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;
 each R^9 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^{10} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;
 each R^{11} 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^{11} 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^{11} is optionally substituted with halo, C_{1-6} alkyl, $-OH$, or $-N(R^x)(R^y)$;
 each R^{12} is independently H or C_{1-6} alkyl;
 each R^{13} 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^{13} 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^{13} is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl; 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, or $-NH_2$, $NH(C_{1-6}$ 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).

[0104] 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 is C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, or C_{3-8} cycloalkyl, wherein

the C_{1-6} alkyl of R^1 is optionally substituted with one or more R^{1a} ,
 the C_{3-8} cycloalkyl of R^1 is optionally substituted with one or more R^{1b} , and
 optionally, two substituents of the C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, or C_{3-8} cycloalkyl group of R^1 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} ; and

R^4 is $-N(R^x)(R^y)$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-C(=O)(C_{1-6}$ alkyl) $N(R^x)(R^y)$, $-C(=O)N(R^{10})(R^{11})$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, or 3- to 8-membered N-containing heterocyclyl, wherein

the 3- to 8-membered N-containing heterocyclyl of R^4 is optionally substituted with one or more R^{4b} , $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, or $-C(=O)OR^{11}$, and
 the 3- to 8-membered N-containing heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S.

[0105] 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 is C_{1-6} alkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{10})(R^{11})$, or C_{3-8} cycloalkyl, wherein

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

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

optionally, two substituents of the C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)N(R^{10})(R^{11})$, or C_{3-8} cycloalkyl group of R^1 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} ;

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

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

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

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

R^3 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(=O)R^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, or C_{3-8} cycloalkyl, wherein

the C_{1-6} alkyl of R^3 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^9$, $-SR^9$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, $-C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, or $-S(=O)_2N(R^{10})(R^{11})$, and

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

R^5 is H;

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

the C_{1-6} alkyl of R^6 or R^7 is optionally substituted by one or more R^{5a} ,
 the 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of R^6 or R^7 is optionally substituted with one or more R^{5b} , and
 the 3- to 8-membered heterocyclyl of R^6 or R^7 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

or R^6 and R^7 are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl;

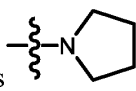
R^8 is H;

each R^{1a} , R^{2a} , R^{4a} , and R^{5a} is independently halo, $-N(R^x)(R^y)$, $-OR^9$, $-SR^9$, $-NO_2$, $-CN$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, $-C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of R^{1a} , R^{2a} , R^{4a} , or R^{5a} is optionally substituted with one or more R^{1b} , and
 the 3- to 12-membered heterocyclyl of R^{1a} , R^{2a} , R^{4a} , or R^{5a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

each R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is independently halo, C_{1-6} alkyl, $-OR^{13}$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C_{1-6} alkyl of R^{1b} , R^{2b} , R^{3b} , R^{4b} , or R^{5b} is optionally substituted by $-OR^9$, $-N(R^x)(R^y)$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;

wherein when L is $-OCH_2CH_2CH_2-$, R^2 is , and R^5 and R^6 are each H, R^1 is not $-CH_2CH_2CH_2N(CH_3)(CH_3)$.

[0106] 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 is C_{1-6} alkyl optionally substituted with one or more R^{1a} ;

R^4 is $-N(R^x)(R^y)$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-C(=O)(C_{1-6}alkyl)N(R^x)(R^y)$, $-C(=O)N(R^{10})(R^{11})$, or 3- to 8-membered N-containing heterocyclyl, wherein

the 3- to 8-membered N-containing heterocyclyl of R^4 is optionally substituted with one or more R^{4b} , $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, or $-C(=O)OR^{11}$, and

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

R^6 and R^7 are each independently H, halo, $C_{1-6}alkyl$, $-OR^9$, $-N(R^x)(R^y)$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, $-C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, or $-S(=O)_2N(R^{10})(R^{11})$, wherein

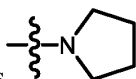
the $C_{1-6}alkyl$ of R^6 or R^7 is optionally substituted by one or more R^{5a} ;

or R^6 and R^7 are taken together with the carbon atoms to which they are attached to form a 4- to 8-membered heterocyclyl; and

each R^{13} is independently H, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{3-8}cycloalkyl$, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the $C_{1-6}alkyl$ of R^{13} is optionally substituted with phenyl, or 5- to 6-membered heteroaryl, wherein

the phenyl, or 5- to 6-membered heteroaryl is optionally substituted with halo, $C_{1-3}alkyl$, $C_{1-3}alkoxy$, $-N(R^x)(R^y)$, or 3- to 8-membered heterocyclyl, and the phenyl, or 5- to 6-membered heteroaryl of R^{13} is optionally substituted with halo, $C_{1-3}alkyl$, $C_{1-3}alkoxy$, or $-N(R^x)(R^y)$;

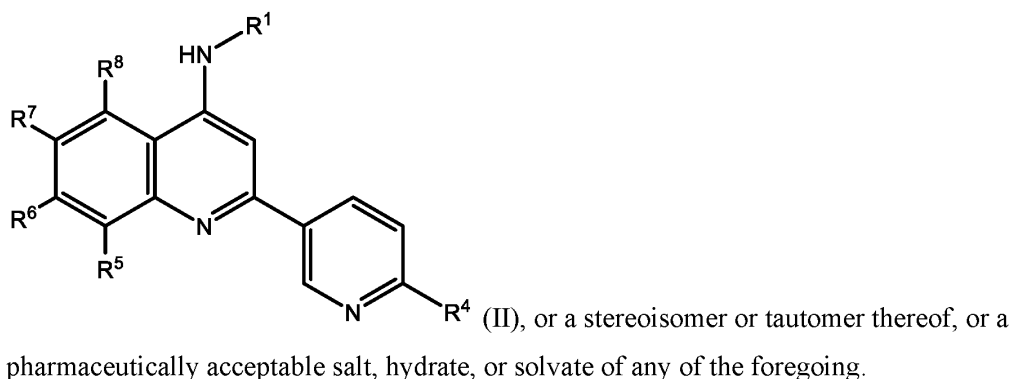
wherein when L is $-OCH_2CH_2CH_2-$, R^2 is , and R^5 and R^6 are each H, R^1 is not $-CH_2CH_2CH_2N(CH_3)(CH_3)$.

[0107] Enumerated Embodiment 5. 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 L is a bond or $-O(C_{1-6}alkyl)-$.

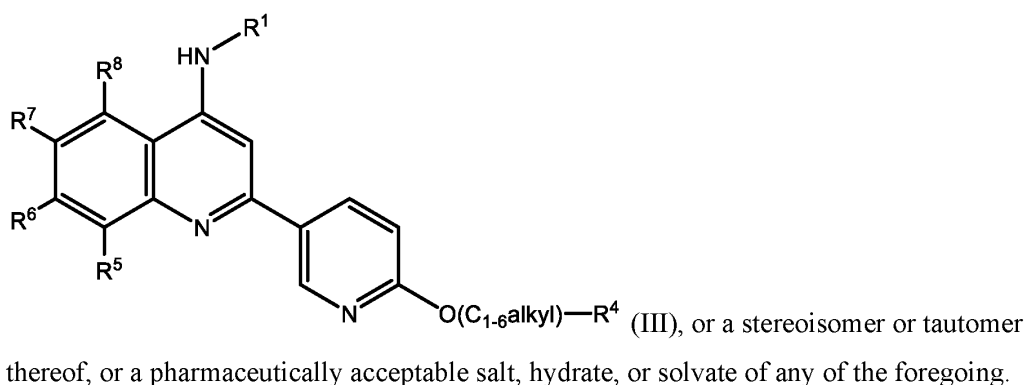
[0108] Enumerated Embodiment 6. The compound of Enumerated Embodiment 5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein L is a bond or -O(C₁₋₄alkyl)-.

[0109] Enumerated Embodiment 7. The compound of Enumerated Embodiment 6, 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(CH₂CH₂)-.

[0110] Enumerated Embodiment 8. The compound of any of Enumerated Embodiments 1-7, wherein the compound is a compound of formula (II):



[0111] Enumerated Embodiment 9. The compound of any of Enumerated Embodiments 1-7, wherein the compound is a compound of formula (III):



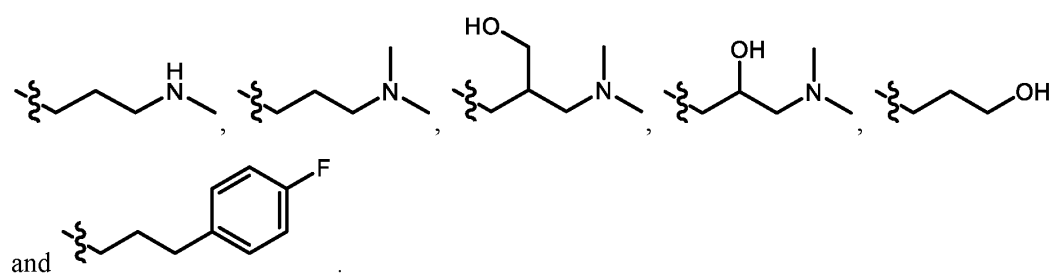
[0112] Enumerated Embodiment 10. The compound of any of Enumerated Embodiments 1-9, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R¹ is C₁₋₆alkyl substituted with one or more R^{1a}.

[0113] 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 each R^{1a} is independently -OH, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)(C₁₋₆alkyl), or phenyl, wherein the phenyl is optionally substituted by halo.

[0114] Enumerated Embodiment 12. The compound of Enumerated Embodiment 11, 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(CH₃), -N(CH₃)(CH₃), or fluorophenyl.

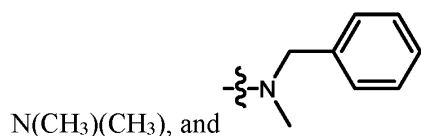
[0115] Enumerated Embodiment 13. The compound of any of Enumerated Embodiments 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 is selected from the group consisting of



[0116] Enumerated Embodiment 14. The compound of any of Enumerated Embodiments 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^4 is -N(R^x)(R^y).

[0117] 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 R^4 is -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)(C₁₋₆alkyl), wherein each C₁₋₆alkyl is independently optionally substituted by one or more R^{4a} .

[0118] 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 R^4 is selected from the group consisting of -NH(CH₃), -



[0119] Enumerated Embodiment 17. The compound of any of Enumerated Embodiments 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^4 is -N(R^{10})C(O) R^{11} .

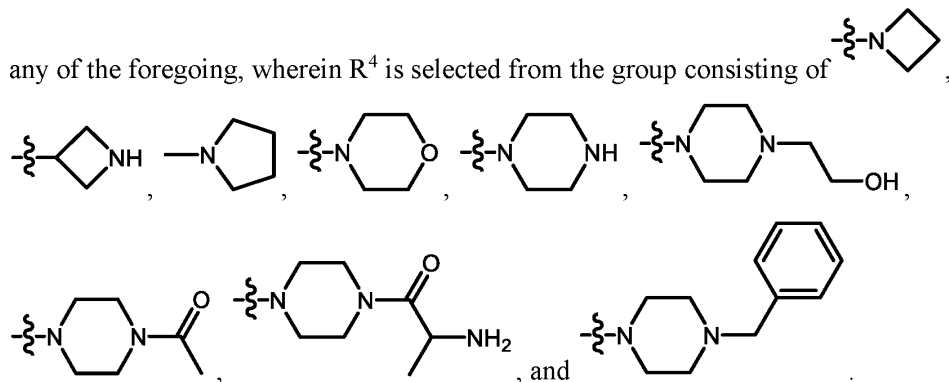
[0120] Enumerated Embodiment 18. The compound of Enumerated Embodiment 17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^4 is $-NHC(O)(C_{1-6}alkyl)$.

[0121] Enumerated Embodiment 19. The compound of Enumerated Embodiment 18, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^4 is $-NHC(O)(CH_3)$.

[0122] Enumerated Embodiment 20. The compound of any of Enumerated Embodiments 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^4 is 3- to 12-membered N-containing heterocyclyl optionally substituted by R^{4b} , $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, or $-C(=O)OR^{11}$.

[0123] Enumerated Embodiment 21. The compound of Enumerated Embodiment 20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^4 is azetidynyl, pyrrolidinyl, morpholinyl, piperazinyl, wherein the piperazinyl is optionally substituted by R^{4b} , $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, or $-C(=O)OR^{11}$.

[0124] Enumerated Embodiment 22. The compound of Enumerated Embodiment 21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of



[0125] Enumerated Embodiment 23. The compound of any of Enumerated Embodiments 1-22, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^6 and R^7 are each independently H, halo, $C_{1-6}alkyl$, $-N(R^x)(R^y)$, $-OR^9$, $-N(R^{10})C(O)R^{11}$, or $-N(R^{10})C(O)OR^{11}$.

[0126] Enumerated Embodiment 24. The compound any of Enumerated Embodiments 1-23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^6 and R^7 are each independently H, halo, $C_{1-6}alkyl$,

-NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)(C₁₋₆alkyl), -O(C₁₋₆alkyl), -O(5- to 6-membered aryl), -O(5- to 6-membered heteroaryl), -NHC(O)(C₁₋₆alkyl), -NHC(O)(5- to 6-membered aryl), or -NHC(O)O(C₁₋₆alkyl), wherein

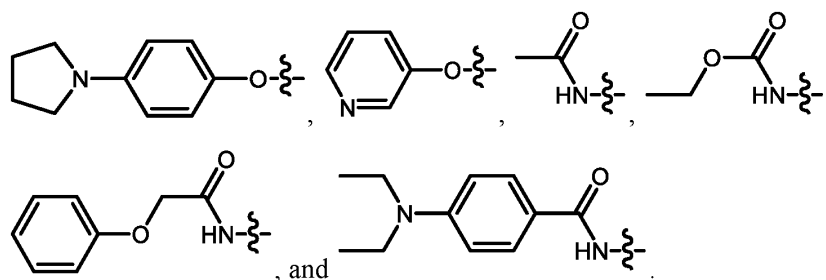
the -O(C₁₋₆alkyl) is optionally substituted with phenyl or halo;

the -O(5- to 6-membered aryl) is optionally substituted with 4- to 6-membered heterocyclyl;

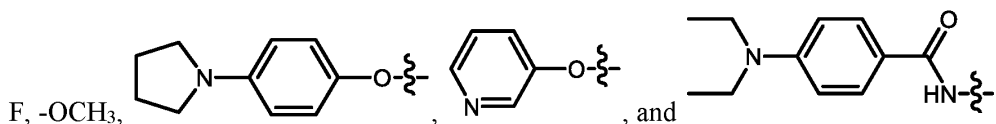
the -NHC(O)(C₁₋₆alkyl) is optionally by -O(5- to 6-membered aryl); and

the -NHC(O)(5- to 6-membered aryl) is optionally substituted with -N(R^x)(R^y).

[0127] Enumerated Embodiment 25. The compound of any of Enumerated Embodiments 1-24, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R⁶ and R⁷ are each independently selected from the group consisting of H, -CH₃, F, -NH(CH₃), -N(CH₃)(CH₃), -OCF₃, -OCH₃,



[0128] Enumerated Embodiment 26. The compound of any of Enumerated Embodiments 1-23, wherein R⁶ and R⁷ are each independently selected from the group consisting of H, -CH₃,



[0129] Enumerated Embodiment 27. 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:

L is a bond or -O(C₁₋₆alkyl);

R⁴ is 3- to 12-membered N-containing heterocyclyl optionally substituted by R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹; and

R¹ is C₁₋₄alkyl optionally substituted with one or more substituents selected from the group consisting of -OH, -NH(CH₃), and -N(CH₃)(CH₃).

[0130] Enumerated Embodiment 28. 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.

[0131] Enumerated Embodiment 29. A pharmaceutical composition comprising a compound of any of Enumerated Embodiments 1-28, 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.

[0132] Enumerated Embodiment 30. 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 1-28, 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 29.

[0133] Enumerated Embodiment 31. The method of Enumerated Embodiment 30, wherein a therapeutically effective amount of the compound is administered.

[0134] Enumerated Embodiment 32. The method of Enumerated Embodiment 30 or 31, wherein said disease or condition mediated by TDP-43 is a neurological disease or condition.

[0135] Enumerated Embodiment 33. The method of Enumerated Embodiment 32, 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).

[0136] Enumerated Embodiment 34. The method of Enumerated Embodiment 32 or 33, wherein the neurological disease or condition is traumatic brain injury (TBI).

[0137] Enumerated Embodiment 35. The method of Enumerated Embodiment 32 or 33, wherein the neurological disease or condition is frontotemporal dementia (FTD).

[0138] Enumerated Embodiment 36. The method of Enumerated Embodiment 32 or 33, wherein the neurological disease or condition is amyotrophic lateral sclerosis (ALS).

[0139] Enumerated Embodiment 37. The method of any of Enumerated Embodiments 32, 33, or 36, wherein the neurological disease or condition is sporadic amyotrophic lateral sclerosis or C9ORF72 amyotrophic lateral sclerosis.

[0140] Enumerated Embodiment 38. The method of any of Enumerated Embodiments 30-37, wherein the subject is a human.

[0141] Enumerated Embodiment 39. A method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of any of Enumerated Embodiments 1-28, 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 29, 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 TDP-43 protein-protein interactions.

[0142] Enumerated Embodiment 40. 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 1-28, 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 29.

[0143] Enumerated Embodiment 41. The method of Enumerated Embodiment 40, wherein the gene expression levels are for *STMN2*.

[0144] Enumerated Embodiment 42. The method of Enumerated Embodiment 40, wherein the gene expression levels are for *POLDIP3*.

[0145] Enumerated Embodiment 43. The compound of any of Enumerated Embodiments 1-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, or the pharmaceutical composition of Enumerated Embodiment 34 for use in the treatment of a disease or condition mediated by TDP-43.

[0146] Enumerated Embodiment 44. Use of a compound of any of Enumerated Embodiments 1-28, 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 disorder mediated by TDP-43.

[0147] Enumerated Embodiment 45. A kit, comprising (i) a compound of any one of Enumerated Embodiments 1-28, 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 29 and (ii) instructions for use in treating a TDP-43 mediated disease or condition in an individual in need thereof.

EXAMPLES

[0148] 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)
uL (microliters)	¹ H (proton)
M (molar)	rt (room temperature)
MHz (megahertz)	mmol (millimoles)
Hz (hertz)	min (minutes)
EtOAc (ethyl acetate)	PE (petroleum ether)
DCM (dichloromethane)	MeOH (methanol)
OTs (tosylate)	SCX (Strong Cation Exchange Resin)
HCl (Hydrochloric acid)	ACN (acetonitrile)
mm (millimeters)	um (micrometers)
h (hours)	% (percent)
UV (ultraviolet)	HATU (Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium)
TFA (trifluoroacetic acid)	THF (tetrahydrofuran)
FA (formic acid)	DIEA (diisopropyl ethyl amine)
prep- (preparative)	SiO ₂ (silica)
TLC (thin layer chromatography)	DMSO (dimethyl sulfoxide)
TBS (<i>tert</i> -butyl dimethyl)	DMF (dimethylformamide)
Fmoc (fluorenyl methoxycarbonyl)	KOAc (potassium acetate)
LED (light-emitting diode)	Pd (PPh ₃) ₄ (palladium tetrakis(triphenyl)phosphine)

ESI (electrospray ionization)	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 ((<i>SP</i> -4-3)-[Dicyclohexyl[2',4',6'-tris(1-methylethyl) [1,1'-biphenyl]-2-yl] phosphine) (methanesulfonato-κ <i>O</i>) [2'-(methylamino-κ <i>N</i>) [1,1'-biphenyl]-2-yl-κ <i>C</i>] palladium)	
[Pd (OAc) ₂] ₃ (palladium II acetate)	CPhos Pd G3 [(2-Dicyclohexylphosphino-2',6'-bis (<i>N,N</i> -dimethylamino)-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium (II) methansulfonate
BINAP (1,1'-binaphtyl-2,2'-diphemyl phosphine)	Pd[P(<i>t</i> -Bu) ₃] ₂ (palladium bis tri(tert-butyl)phosphine)
Na ₂ SO ₄ (Sodium sulfate)	DIAD (diisopropyl azodicarboxylate)
PPh ₃ (Triphenyl phosphine)	DME (Dimethoxyethane)
TTMSS (bis(trimethylsilyl)silyl-trimethyl-silane)	Ir[dF(CF ₃)ppy] ₂ (bpy)PF ₆ ((2,2'-Bipyridine)bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl]iridium(III) Hexafluorophosphate)
B ₂ pin ₂ (Bis(pinacolato)diboron)	NiCl ₂ ,dtbbpy (4- <i>tert</i> -butyl-2-(4- <i>tert</i> -butyl-2-pyridyl)pyridine; dichloronickel)
K ₂ CO ₃ (potassium carbonate)	Boc ₂ O (Di- <i>tert</i> -butyl dicarbonate)
AcOH (acetic acid)	TEA (Triethylamine)
NaBH ₃ CN (Sodium cyanoborohydride)	POCl ₃ (Phosphoryl chloride)

[0149] 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 neutralize 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 cleave

compound from the resin. Solvents were then concentrated and lyophilized to get the desired product.

[0150] 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 % NH₃)
- 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 C₁₈ 150 x 25 mm x 10mm; mobile phase: water (HCl)-ACN

[0151] Flash chromatography. Puri Flash XS520Plus, Interchim, PF-30SIHP-JP-F00xx, 30 µm.

[0152] NMR and LCMS. The analytical characterization of synthesized compounds was done by NMR and LCMS. ¹H 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 (CDCl₃ for deuterated chloroform, DMSO-d₆ for deuterated dimethylsulfoxide and methanol-d₄ 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.

[0153] LCMS spectra were recorded according to the following conditions:

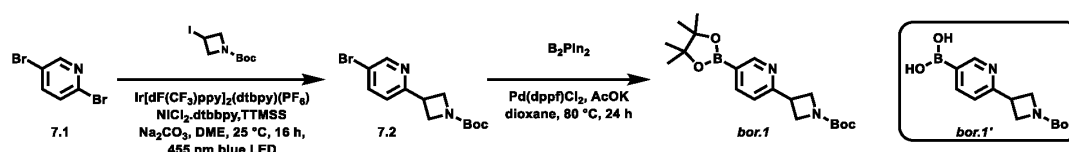
SHIMADZU LCMS-2020 using LabSolution software Version 5.89 and 5.93; HALO C18 column 3.0 x 30 mm x 5.0 µm or Kinetex EVO C18 column 2.1 x 30 mm x 5 µm; mobile

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 μ m 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% NH₃)-ACN (flow rate 0.7 mL/min) with UV detection at 220 and 254 nm; ESI for mass spectra.

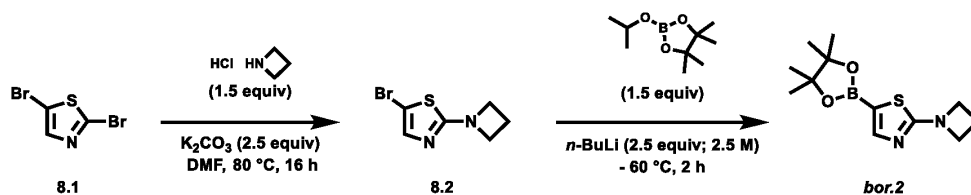
Synthesis of non-commercially available boronic ester derivative reagents

bor.1': [6-(1-*tert*-butoxycarbonylazetidin-3-yl)-3-pyridyl] boronic acid



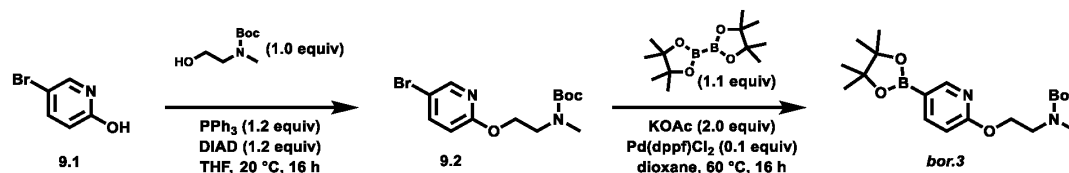
[0154] To a solution of 2,5-dibromopyridine **7.1** (3.0 g, 13 mmol, 1.0 equiv), *tert*-butyl 3-iodoazetidine-1-carboxylate (4.7 g, 16.5 mmol, 1.3 equiv) in DME (30 mL) were added Ir[dF(CF₃)ppy]₂(bpy)PF₆ (0.14 g, 0.13 mmol, 0.01 equiv), NiCl₂·dtbbpy (25 mg, 0.06 mmol, 0.005 equiv), TTMSS (3.15 g, 13 mmol, 1.0 equiv) and Na₂CO₃ (2.7 g, 25 mmol, 2.0 equiv) at 25 °C. After stirring at 25 °C for 16 h irradiated with a 455 nm blue LED, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue 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.

[0155] To a solution of **7.2** (1.0 g, 2.75 mmol, 1.0 equiv), B₂Pin₂ (0.91 g, 3.6 mmol, 1.3 equiv) in dioxane (25 mL) was added Pd(dppf)Cl₂ (0.20 g, 0.28 mmol, 0.10 equiv) and KOAc (1.1 g, 11 mmol, 4.0 equiv) 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 Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue 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

[0156] To a solution of 2,5-dibromothiazole **8.1** (1.0 g, 4.1 mmol, 1.0 equiv) in *N,N*-dimethylformamide (10 mL) was added K_2CO_3 (1.1 g, 8.2 mmol, 2.0 equiv) and azetidine (0.60 g, 6.4 mmol, 0.71 mL, 1.6 equiv, 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 Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue 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) $[M+H]^+ = 221.0$.

[0157] To a solution of **8.2** (0.25 g, 1.1 mmol, 1.0 equiv) in THF (10 mL) was added $n-BuLi$ (2.5 M, 1.0 mL, 2.2 equiv) at -60 °C under stirring, after 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 equiv) was added into the mixture at -60 °C. Then, the mixture was stirred at -60 °C for 2 h. The reaction mixture was added into saturated aqueous solution of ammonium chloride (20 mL) and extracted with EtOAc (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 boronic ester **bor.2** (0.20 g, 0.38 mmol, 33% yield, 50% purity) as a brown solid. MS m/z (ESI) $[M+H]^+ = 267.1$.

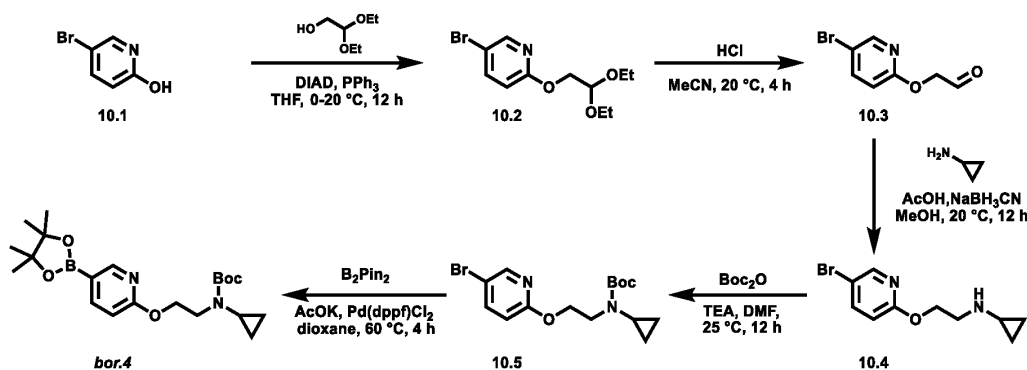
bor.3: *tert*-butyl *N*-methyl-*N*-[2-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy] ethyl] carbamate

[0158] To a solution of 5-bromopyridin-2-ol **9.1** (1.0 g, 5.8 mmol, 1.0 equiv), *tert*-butyl *N*-(2-hydroxyethyl)-*N*-methylcarbamate (1.2 g, 6.9 mmol, 1.2 equiv) in THF (20 mL) was added PPh_3 (1.8 g, 6.9 mmol, 1.2 equiv) and DIAD (1.4 g, 6.9 mmol, 1.3 mL, 1.2 equiv) at 25 °C.

After stirring at 25 °C for 16 h, the reaction mixture was concentrated under reduced pressure. The residue 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) $[M-55]^+ = 241.0$.

[0159] A mixture of **9.2** (0.50 g, 1.5 mmol, 1.0 equiv), 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 equiv), Pd(dppf)Cl₂ (0.11 g, 0.15 mmol, 0.10 equiv), KOAc (0.30 g, 3.0 mmol, 2.0 equiv) in dioxane (10 mL, degassed and purged with nitrogen for 3 times at 25 °C) was heated at 80 °C for 16 h under nitrogen atmosphere and stirring. Then, the reaction mixture was concentrated under reduced pressure. The residue 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



[0160] To a solution of 5-bromopyridin-2-ol **10.1** (2.0 g, 11.5 mmol, 1.0 equiv), 2,2-diethoxyethanol (1.9 g, 14 mmol, 1.2 equiv) in THF (20 mL) were added PPh₃ (3.6 g, 14 mmol, 1.2 equiv) and diisopropyl azodiformate (2.8 g, 14 mmol, 1.2 equiv) at 0 °C. After stirring at 20 °C for 12 h, the reaction mixture was concentrated under reduced pressure. The residue 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. ¹H NMR (400 MHz, DMSO-d₆) δ (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).

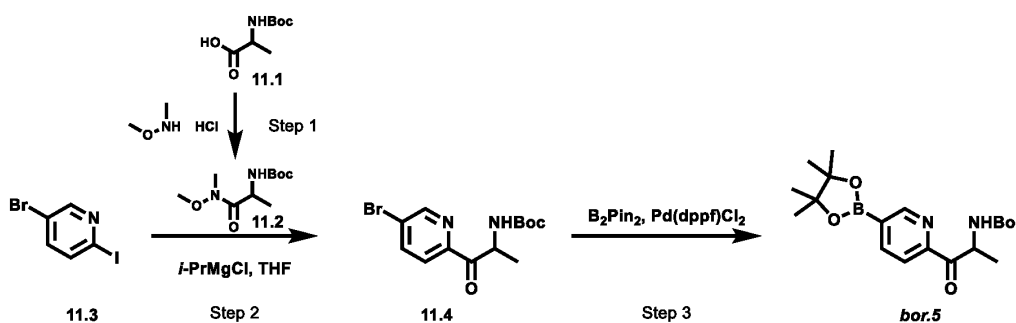
[0161] To a solution of **10.2** (2.8 g, 10 mmol, 1.0 equiv) in ACN (20 mL) was added HCl (4 M, 6.0 mL, 2.5 equiv) at 20 °C. The mixture was stirred at 20 °C for 4 h. The reaction mixture was diluted with water (20 mL) and then extracted with EtOAc (30.0 mL, three times), the combined organic phase was washed with brine (10 mL, three times), dried over Na₂SO₄, 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.

[0162] To a solution of **10.3** (1.1 g, 5.1 mmol, 1.0 equiv) and cyclopropanamine (0.26 g, 4.6 mmol, 0.90 equiv) in MeOH (15 mL) were added AcOH (0.92 g, 15 mmol, 3.0 equiv) and NaBH₃CN (0.48 g, 7.6 mmol, 1.5 equiv) at 20 °C. After stirring at 20 °C for 12 h, the reaction mixture was concentrated under reduce presser, the residue was diluted with water (15 mL) and then extracted with EtOAc (15 mL, three times), the combined organic phase was washed with brine (5.0 mL, three times), dried over Na₂SO₄, 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.

[0163] To a solution of **10.4** (0.80 g, 2.4 mmol, 1.0 equiv) in DMF (10 mL) were added TEA (0.73 g, 7.2 mmol, 1.0 mL, 3.0 equiv) and Boc₂O (1.1 g, 4.8 mmol, 1.1 mL, 2.0 equiv) 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 EtOAc (20.0 mL, three times), the combined organic phase was washed with brine (10 mL, three times), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue 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.

[0164] To a mixture of **10.5** (0.60 g, 1.4 mmol, 1.0 equiv) and B₂pin₂ (0.44 g, 1.7 mmol, 1.2 equiv) in dioxane (10 mL) were added Pd(dppf)Cl₂ (53 mg, 0.07 mmol, 0.05 equiv) and KOAc (0.28 g, 2.9 mmol, 2.0 equiv) 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 EtOAc (10 mL), then the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue 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

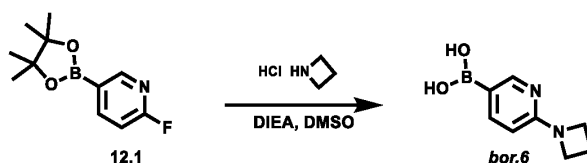


[0165] To a solution of 2-(*tert*-butoxycarbonylamino) propanoic acid **11.1** (10 g, 53 mmol, 1.0 equiv) in DMF (100 mL) was added HATU (25 g, 66 mmol, 1.2 equiv), the reaction mixture was stirred at 25 °C for 10 min. Then the mixture was added DIEA (19 g, 0.14 mol, 25 mL, 2.7 equiv) and *N*-methoxymethanamine (6.0 g, 62 mmol, 1.2 equiv, HCl). The mixture was stirred at 25 °C for another 5 h. The reaction mixture was extracted with EtOAc (400 mL) and H₂O (300 mL). The combined organic layers were washed with *saturated* aqueous NH₄Cl (300 mL), *saturated* aqueous NaHCO₃ (300 mL) and brine (300 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue 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.

[0166] To a solution of 5-bromo-2-iodo-pyridine **11.3** (9.7 g, 34 mmol, 1.0 equiv) in THF (150 mL) was added **11.2** (8.0 g, 34 mmol, 1.0 equiv), the reaction mixture was degassed and purged with N₂ for three times, then *i*-PrMgCl (2 M, 35 mL, 2.0 equiv) was added to the reaction mixture at 0 °C, the reaction mixture was stirred at 25 °C for 1 h under N₂ atmosphere. The reaction mixture was quenched with *saturated* aqueous NH₄Cl (300 mL) and extracted with EtOAc (500 mL, twice). The combined organic layers were washed with brine (400 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (80 g column, Eluent of 0~9% EtOAc/PE gradient at 100 mL/min) to give 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.

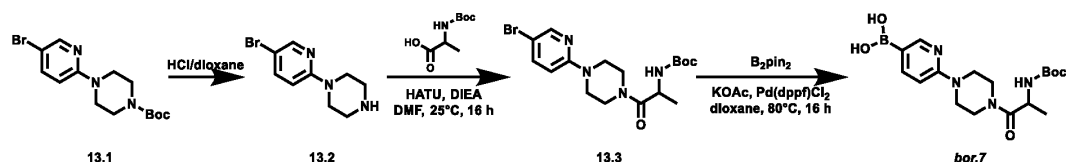
[0167] To a solution of **11.4** (0.36 g, 1.1 mmol, 1.0 equiv) and B₂pin₂ (0.44 g, 1.7 mmol, 1.6 equiv) in dioxane (5.0 mL) was added Pd(dppf)Cl₂ (72 mg, 98 μmol, 0.09 equiv) and KOAc (0.33 g, 3.3 mmol, 3.0 equiv), the reaction mixture was degassed and purged with N₂ for three times. The mixture was stirred at 80 °C for 5 h under N₂ atmosphere. 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



[0168] 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 equiv) and azetidine (2.3 g, 24 mmol, 2.7 mL, 1.2 equiv, HCl) in DMSO (40 mL) was added K₂CO₃ (8.4 g, 61 mmol, 3.0 equiv) at 25 °C. The mixture was stirred at 100 °C for 16 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (60 mL, three times). The organic phase was washed with brine (150 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by prep-HPLC 3' (gradient: 0%-30% ACN over 10 min) to give [6-(azetidin-1-yl)-3-pyridyl] boronic acid **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



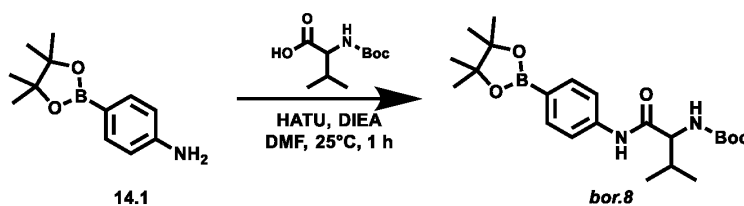
[0169] To a solution of tert-butyl 4-(5-bromo-2-pyridyl) piperazine-1-carboxylate **13.1** (1.0 g, 2.9 mmol, 1.0 equiv) in dioxane (0.5 mL) was added HCl/dioxane (2.0 M, 2.0 mL) at 25 °C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give 1-(5-bromo-2-pyridyl) piperazine **13.2** (0.80 g, 2.8 mmol, 96% yield, 98% purity, HCl). MS m/z (ESI) [M+H]⁺ = 242.0.

[0170] To a solution of **13.2** (0.80 g, 2.9 mmol, 1.0 eq, HCl) in DMF (3.0 mL) was added Boc-DL-Ala-OH (0.65 g, 3.4 mmol, 1.2 equiv), HATU (2.2 g, 5.7 mmol, 2.0 equiv) and DIEA (1.5 g, 11 mmol, 2.0 mL, 4 equiv). The mixture was stirred at 25 °C for 16 h. The

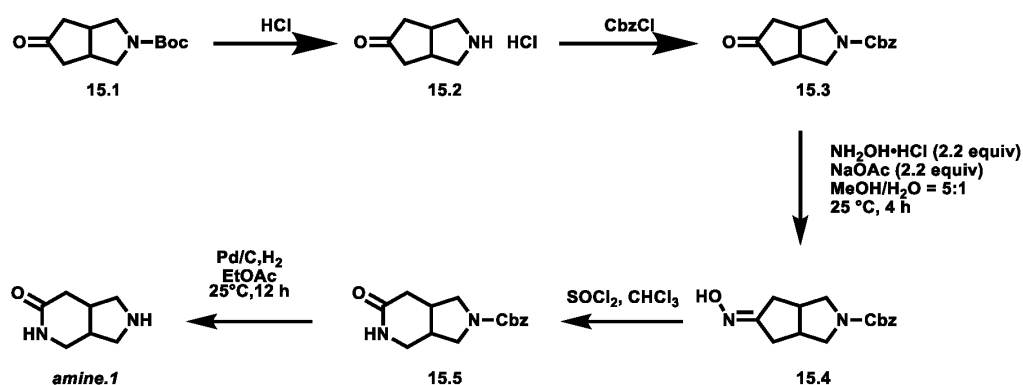
reaction mixture was filtered and concentrated under reduced pressure to give *tert*-butyl *N*-[2-[4-(5-bromo-2-pyridyl) piperazin-1-yl]-1-methyl-2-oxo-ethyl] carbamate **13.3** (1.1 g, 2.6 mmol, 92% yield, 99% purity). MS *m/z* (ESI) $[M+H]^+ = 413.1$.

[0171] A mixture of **13.3** (1.1 g, 2.7 mmol, 1 equiv), B₂pin₂ (1.0 g, 4.0 mmol, 1.5 equiv), Pd(dppf)Cl₂ (0.20 g, 0.27 mmol, 0.10 equiv), AcOK (0.79 g, 8.0 mmol, 3.0 equiv) in dioxane (3.0 mL) was degassed and purged with N₂ three times at 25 °C, and then the mixture was stirred at 80 °C for 16 h under N₂ 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 Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC 2 (gradient: 10%-40% 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



[0172] 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 equiv) and Boc-DL-Val (1.0 g, 4.6 mmol, 1.0 equiv) in DMF (20 mL) was added HATU (2.6 g, 6.9 mmol, 1.5 equiv) and DIEA (2.0 g, 15 mmol, 2.7 mL, 3.4 equiv) 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.* NH₄Cl (50 mL, twice), *sat.* NaHCO₃ (50 mL, twice), brine (50 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to give crude material. The residue was purified by flash chromatography 2 (40 g Column, Eluent of 0 to 40% EtOAc/PE gradient at 40 mL/min) to give product **bor. 8** (1.2 g, 2.2 mmol, 48% yield, 76% purity) as white solid. MS *m/z* (ESI) $[M+H]^+ = 419.3$.

*Synthesis of amine intermediates***amine.1:** 1, 2, 3, 3a, 4, 5, 7, 7a-octahydropyrrolo [3, 4-c] pyridin-6-one

[0173] Tert-butyl 5-oxo-1,3,3a,4,6,6a-hexahydrocyclopenta[c]pyrrole-2-carboxylate **15.1** (5.0 g, 22 mmol, 1.0 equiv) was added to HCl/dioxane (2 M, 40 mL, 3.6 equiv). The reaction solution was stirred at 25 °C for 1 h. The reaction 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.

[0174] To a solution of **15.2** (3.6 g, 22 mmol, 1.0 equiv, HCl) and TEA (7.3 g, 72 mmol, 10 mL, 3.2 equiv) in DCM (40 mL) was added CbzCl (4.6 g, 27 mmol, 3.8 mL, 1.2 equiv) 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 organic phase was washed by sat. NaCl (50 mL). The combined organic layers were dried over Na₂SO₄ and evaporated to give a crude material. The residue 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.

[0175] To a solution of **15.3** (1.2 g, 4.6 mmol, 1.0 equiv) in MeOH (20 mL) /H₂O (5 mL) was added NH₂OH.HCl (0.72 g, 10 mmol, 2.2 equiv) and NaOAc (1.1 g, 13 mmol, 2.8 equiv), The reaction solution was stirred at 25 °C for 1 h. The residue was partitioned between EtOAc (500 mL) and water (500 mL). The organic phase was washed by sat. NaCl (500 mL). The combined organic layers were dried over Na₂SO₄ and evaporated. The residue was purified by flash silica gel 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-

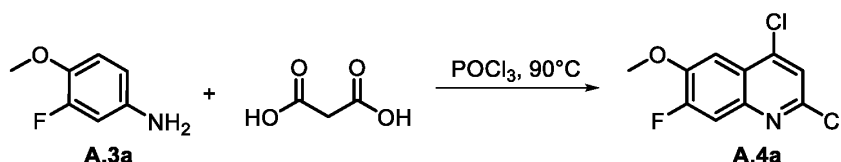
yellow oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.38 - 7.33 (m, 5H), 5.14 (d, $J = 4.9$ Hz, 2H), 3.71 - 3.63 (m, 2H), 3.33 - 3.18 (m, 2H), 2.83 - 2.65 (m, 4H), 2.44 - 2.34 (m, 2H).

[0176] To a solution of **15.4** (1.2 g, 4.4 mmol, 1.0 equiv) in THF (10 mL) was added SOCl_2 (1.6 g, 14 mmol, 1.0 mL, 3.2 equiv) at 0°C , the reaction solution was stirred at 25°C for 2 h. The residue was partitioned between EtOAc (500 mL) and water (500 mL). The organic phase was washed by sat. NaCl (500 mL). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue 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) δ (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) $[\text{M}+\text{H}]^+ = 275.2$.

[0177] To a solution of Pd/C (20 mg, 10% purity) in EtOAc (5.0 mL) was added **15.5** (0.10 g, 0.36 mmol, 1.0 equiv) 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 filtrate was concentrated under vacuum to give *amine.1* (50 mg, crude) as a yellow oil was used for next step without purification.

Synthesis of dichloroquinoline intermediates

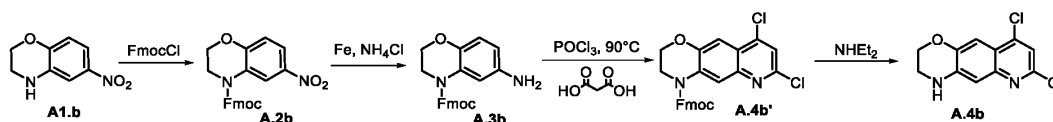
A.4a ($\text{R}_6 = \text{F}$; $\text{R}_7 = \text{OMe}$): 2, 4-dichloro-7-fluoro-6-methoxy-quinoline



[0178] To a solution of 3-fluoro-4-methoxy-aniline **A.3a** (2.0 g, 14 mmol, 1.0 equiv) and malonic acid (1.6 g, 15 mmol, 1.6 mL, 1.1 equiv) in POCl_3 (33 g, 215 mmol, 20 mL, 15 equiv) 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 $20^\circ\text{C} \sim 30^\circ\text{C}$, washed with aq. NaHCO_3 then was partitioned between EtOAc (30 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (30 mL) twice. The combined organic layers were dried over Na_2SO_4 and evaporated to give a crude material. The water phase was added aq. NaOH and adjusted to pH = 7 then put into waste liquid tank. The residue was purified by flash

chromatography (40 g column, Eluent of 0~10% EtOAc/PE gradient at 40 mL/min) to afford 2, 4-dichloro-7-fluoro-6-methoxy-quinoline **A.4a** (1.9 g, 7.7 mmol, 54% yield, 100% purity) as white solid. ^1H 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) $[\text{M}+\text{H}]^+ = 246.0$.

A.4b ($\text{R}_6\text{-R}_7 = \text{NHCH}_2\text{CH}_2\text{O}$): 7,9-dichloro-3,4-dihydro-2H-pyrido[2,3-g] [1,4] benzoxazine



[0179] To a solution of 6-nitro-3,4-dihydro-2H-1,4-benzoxazine **A.1b** (4.2 g, 23 mmol, 1.0 equiv) and NaOH (2.8 g, 70 mmol, 1.3 mL, 3.0 equiv) in THF (40 mL) was added Fmoc-Cl (7.2 g, 28 mmol, 1.2 equiv) at 0 °C. The mixture was stirred at 25 °C for 1 h. The mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL, three times). The organic phase was washed with brine (300 mL), dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated. The residue was purified by flash chromatography (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) $[\text{M}+\text{Na}]^+ = 425.1$.

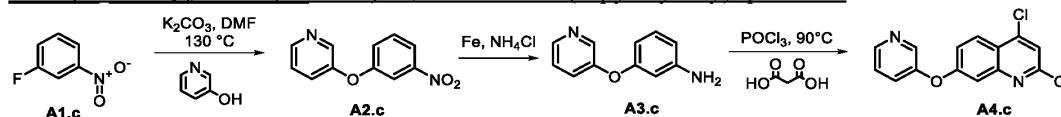
[0180] To a solution of **A.2b** (7.6 g, 19 mmol, 1.0 equiv) and NH_4Cl (6.1 g, 113 mmol, 6.0 eq) in EtOH (60 mL) / H_2O (60 mL) was added Fe (5.3 g, 94 mmol, 5.0 equiv) at 60 °C, the mixture was stirred at 60 °C for 16 h. The mixture was diluted with water (200 mL) and extracted with EtOAc (200 mL, three times). The organic phase was washed with brine (300 mL), dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated. The residue 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) $[\text{M}+\text{H}]^+ = 373.2$.

[0181] 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 EtOAc (200 mL, three times). The organic phase was 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. The residue 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) $[M+H]^+ = 477.1$.

[0182] *Intermediate A.4b' underwent an additional step of deprotection.* To a solution of **A.4b'** (0.90 g, 1.9 mmol, 1.0 equiv) in DCM (5.0 mL) was added diethylamine (3.2 g, 44 mmol, 4.5 mL, 23 equiv) at 25 °C. The mixture was stirred at 60 °C for 2 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL, three times). The organic phase was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by flash chromatography (20 g column, Eluent of 0~50% EtOAc/PE gradient at 40 mL/min) to give quinoline **A.4b** (0.15 g, 0.59 mmol, 31% yield) was obtained as yellow oil. ¹H NMR (400 MHz, DMSO-d₆) 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 (R₆ = O-pyridine; R₇ = H): 2,4-dichloro-7-(3-pyridyloxy) quinoline

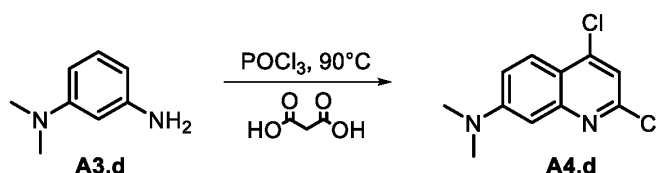


[0183] To a mixture of 1-fluoro-3-nitrobenzene **A.1c** (10 g, 71 mmol, 7.6 mL, 1.0 equiv) and pyridin-3-ol (8.1 g, 85 mmol, 1.2 equiv) in DMF (100 mL) was added potassium carbonate (20 g, 0.14 mol, 2.0 equiv) at 20 °C. The reaction mixture was stirred at 130 °C for 48 h. The reaction mixture was quenched with water (500 mL) and extracted with EtOAc (500 mL, twice). The combined organic phase was washed with brine (500 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (SiO₂, PE/EtOAc = 10:1 to 3:1) to give 3-(3-nitrophenoxy)pyridine **A.2c** (7.0 g, 45% yield) as a yellow oil. MS m/z (ESI) $[M+H]^+ = 216.9$.

[0184] To a mixture of **A.2c** (7.0 g, 32 mmol, 1.0 equiv) in a mixed solution of EtOH (80 mL) and water (10 mL) was added NH₄Cl (14 g, 0.26 mol, 8.0 equiv) at 20 °C. The reaction mixture was stirred at 80 °C and Fe (9.0 g, 0.16 mol, 5.0 equiv) 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 flash chromatography (SiO₂, PE/EtOAc = 5:1 to 1:1) to give 3-(3-pyridyloxy)aniline **A.3c** (4.0 g, 66% yield) as yellow oil.

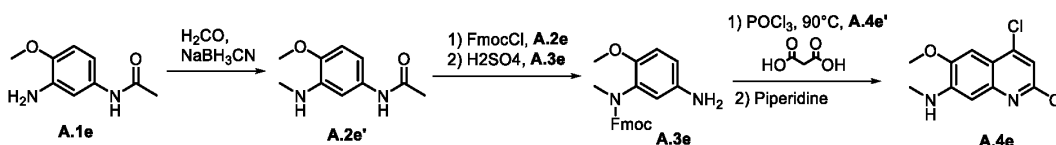
[0185] A mixture of **A.3c** (4.0 g, 22 mmol, 1.0 eq) and malonic acid (2.5 g, 24 mmol, 2.5 mL, 1.1 equiv) in POCl₃ (40 mL) as stirred at 110 °C for 16 h. The reaction mixture was cooled to room temperature and most of the POCl₃ was removed by decompress distillation to give a residue. The residue was quenched with saturated NaHCO₃ solution (500 mL) and extracted with EtOAc (500 mL, twice). The combined organic phase was washed with brine (500 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated *in vacuo* to. The crude product was purified by column chromatography (SiO₂, PE/EtOAc = 10:1 to 3:1) and preparative TLC (SiO₂, PE/EtOAc = 3:1) quinoline **A.4c** (0.20 g, 3% yield) as a yellow solid. MS *m/z* (ESI) [M+H]⁺ = 290.9.

A.4d (R₆ = Me₂N; R₇ = H): 2,4-dichloro-*N,N*-dimethyl-quinolin-7-amine



[0186] To a solution of *N,N*-dimethylbenzene-1,3-diamine **A.3d** (10 g, 73 mmol, 1.0 equiv) in POCl₃ (90 mL) was added malonic acid (10 g, 96 mmol, 10 mL, 1.3 equiv) at 25 °C. After stirring at 110 °C for 16 h, the reaction mixture was added into saturated NaHCO₃ solution (200 mL) and extracted with EtOAc 300 mL (3 x 100 mL). The combined organic layers were washed with brine 300 mL (3 x 100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (80 g column, Eluent of 0~7% EtOAc/PE gradient at 30 mL/min) to give quinoline **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 (R₆ = MeNH; R₇ = OMe): 2,4-dichloro-6-methoxy-*N*-methyl-quinolin-7-amine



[0187] To a solution of *N*-(3-amino-4-methoxy-phenyl) acetamide **A.1e** (12 g, 67 mmol, 1.0 equiv) in MeOH (100 mL)/acetic acid (10 mL) was added formaldehyde (2.0 g, 67 mmol, 1.8 mL, 1.0 equiv) and NaBH₃CN (13 g, 0.20 mol, 3.0 equiv) 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 then, extracted with EtOAc 300 mL (3 x 100 mL). The combined organic layers were washed with brine 300 mL (3 x 100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue 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-(methylanino) phenyl] acetamide **A.2e'** (7.0 g, 24 mmol, 36% yield, 66% purity) as a yellow solid. MS *m/z* (ESI) $[M+H]^+ = 195.0$.

[0188] *Intermediate A.2e'* underwent an additional step of protection. To a solution of *N*-[4-methoxy-3-(methylanino) phenyl] acetamide **A.2e'** (6.5 g, 22 mmol, 1.0 equiv) in dioxane (100 mL) was added NaHCO₃ (5.6 g, 66 mmol, 2.6 mL, 3.0 equiv) and Fmoc-Cl (6.3 g, 24 mmol, 1.1 equiv) 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 Na₂SO₄, filtered, and concentrated under reduced pressure. The residue 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) $[M+H]^+ = 417.2$.

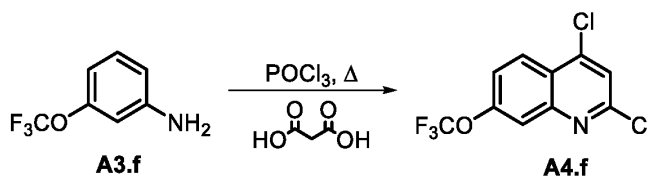
[0189] To a solution **A.2e** (9.9 g, 24 mmol, 1.0 equiv) in methanol (100 mL) was added sulfuric acid (12 M, 20 mL, 10 equiv) at 25 °C. After stirring at 60 °C for 16 h, the reaction mixture was added into water and adjusted the pH to 7-8, extracted with ethyl acetate 120 mL (3 x 40 mL). The combined organic layers were washed with brine 120 mL (3 x 40 mL), dried over Na₂SO₄, 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) $[M+H]^+ = 375.1$.

[0190] To a solution of **A.3e** (10 g, 27 mmol, 1.0 equiv) in POCl₃ (90 mL) was added malonic acid (3.5 g, 34 mmol, 3.5 mL, 1.3 equiv) at 25 °C. After stirring at 110°C for 16 h, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was added into saturated NaHCO₃ solution (200 mL) and extracted with EtOAc 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 Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue 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) $[M+H]^+ = 479.1$.

[0191] *Intermediate A.4e'* underwent an additional step of deprotection. To a solution of **A.4e'** (2.0 g, 4.2 mmol, 1.0 equiv) in DCM (20 mL) was added piperidine (8.6 g, 0.10 mol, 10 mL, 24 equiv) at 25 °C. After stirring at 60 °C for 2 h, the reaction mixture was added into water and extracted with EtOAc 60 mL (3 x 20 mL). The combined organic layers were

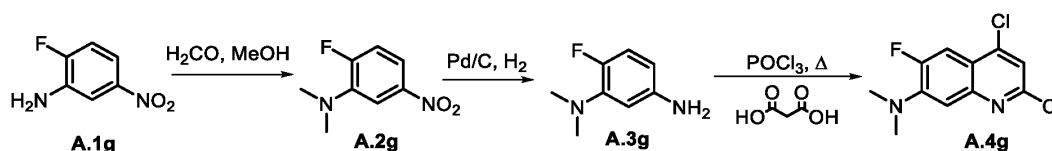
washed with brine 60 mL (3 x 20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (12 g column, Eluent of 0~30% EtOAc/PE gradient at 45 mL/min) to give quinoline **A.4e** (0.60 g, 1.6 mmol, 39% yield, 70% purity) as a yellow solid. MS m/z (ESI) [M+H]⁺ = 256.9.

A.4f (R₆ = OCF₃; R₇ = H): 2,4-dichloro-7-(trifluoromethoxy) quinoline



[0192] To a solution of 3-(trifluoromethoxy) aniline **A.3f** (10 g, 56 mmol, 7.6 mL, 1.0 equiv) in POCl₃ (90 mL) was added malonic acid (7.5 g, 72 mmol, 7.5 mL, 1.3 equiv) 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* NaHCO₃ (500 mL). The mixture was then extracted with EtOAc (1000 mL, three times), the combined organic phase was washed with brine (1000 mL, three times), dried with anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (80g column, Eluent of 0~10% EtOAc/PE gradient at 40 mL/min) to afford quinoline **A.4f** (5.2 g, 18 mmol, 33% yield) as colorless oil. ¹H NMR (400 MHz, CDCl₃) *d* (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 (R₆ = F; R₇ = Me): 2,4-dichloro-6-fluoro-*N,N*-dimethyl-quinolin-7-amine



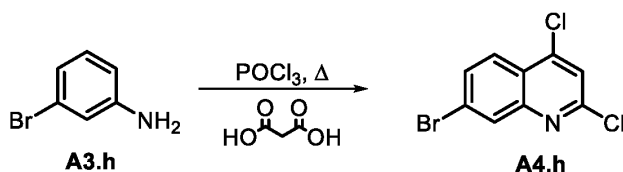
[0193] To a solution of 2-fluoro-5-nitro-aniline **A.1g** (10 g, 64 mmol, 1.0 equiv) in MeOH (100 mL) /AcOH (10 mL) was added HCHO (5.8 g, 192 mmol, 5.3 mL, 3.0 equiv) at 25 °C. After stirring at 25 °C for 48 h. The reaction mixture was added into saturated aqueous solution of NH₄Cl (200 mL) and extracted with EtOAc 300 mL (100 mL, three times). The combined organic layers were washed with brine 300 mL (100 mL, three times), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue 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) $[M+H]^+ = 185.1$.

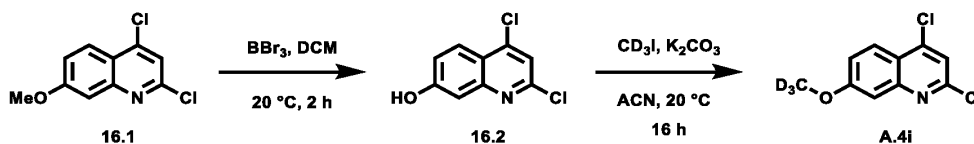
[0194] To a solution of Pd/C (0.10 g, 10% purity) in EtOAc (20 mL) was added **A.2g** (1.0 g, 5.4 mmol, 1.0 equiv) under N₂ atmosphere at 25 °C. The suspension was degassed and purged with H₂ three times at 25 °C. After stirring under H₂ (15 Psi) at 25 °C for 16 h, the reaction mixture was filtered and concentrated under reduced pressure to give 4-fluoro-*N,N*-dimethyl-benzene-1,3-diamine **A.3g** (0.70 g, 4.1 mmol, 75% yield, 90% purity) as brown oil. MS *m/z* (ESI) $[M+H]^+ = 155.1$.

[0195] To a solution of **A.3g** (0.70 g, 4.5 mmol, 1.0 equiv), malonic acid (0.5 g, 4.8 mmol, 0.50 mL, 1.1 equiv) in POCl₃ (7.0 mL) at 25 °C. After stirring at 100 °C for 16 h, the reaction mixture was added into *saturated* NaHCO₃ aqueous solution (100 mL) and extracted with EtOAc 60 mL (20 mL, three times). The combined organic layers were washed with brine 60 mL (20 mL, three times), dried over Na₂SO₄ filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (40 g column, Eluent of 0~5% EtOAc/PE gradient at 45 mL/min) to give quinoline **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 (R₆ = Br; R₇ = H): 7-bromo-2,4-dichloro-quinoline

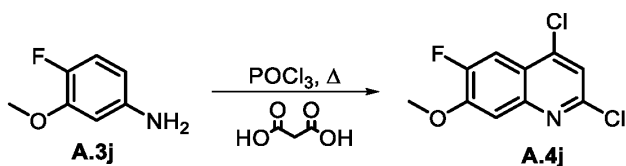


[0196] To a solution of 3-bromoaniline **A.3h** (10 g, 58 mmol, 6.3 mL, 1 equiv) and malonic acid (6.7 g, 64 mmol, 6.7 mL, 1.1 equiv) in POCl₃ (100 mL) at 25 °C. The mixture was stirred at 25 °C for 1 h. Then the mixture was stirred at 100 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove POCl₃. The reaction mixture was quenched with water (200 mL) at 25 °C, the mixture was adjusted to pH=7~8 with NaHCO₃. The mixture was diluted with water (200 mL) and extracted with EtOAc (200 mL, three times). The organic phase was washed with brine (600 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated to give a residue. The mixture was concentrated. The residue was purified by column chromatography (SiO₂, PE/EtOAc). Quinoline **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 (R₆ = OCD₃; R₇ = H): 2,4-dichloro-7-(trideuteriomethoxy) quinoline

[0197] To a solution of 2,4-dichloro-7-methoxy-quinoline (1.0 g, 4.4 mmol, 1.0 equiv) in DCM (15 mL) was added BBr₃ (2.6 g, 10 mmol, 2.4 equiv) at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by MeOH (20 mL), the mixture was diluted with water (50 mL) and then to the mixture was added NaHCO₃ 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 Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (20 g column, Eluent of 0~30% EtOAc/PE gradient at 40 mL/min) to give 2,4-dichloroquinolin-7-ol **16.2** (0.85 g, 3.7 mmol, 84% yield, 93% purity) as a white solid. MS m/z (ESI) [M+H]⁺ = 214.1.

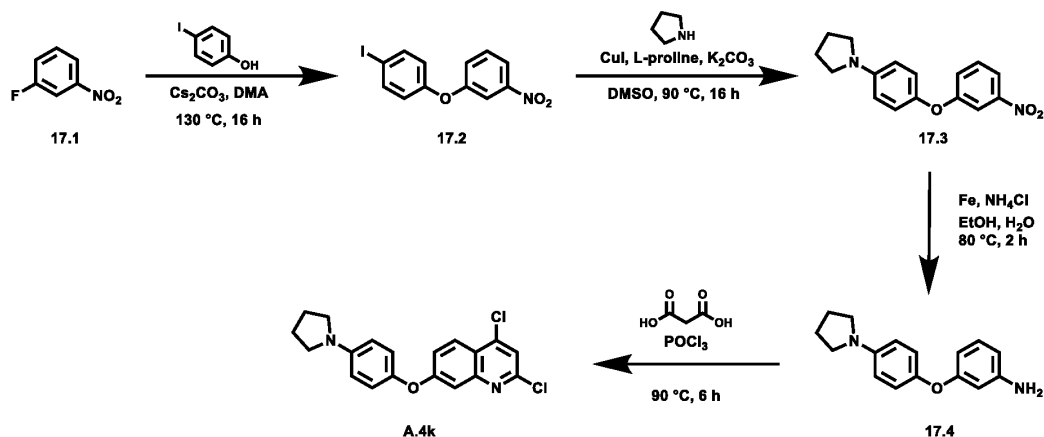
[0198] To a solution of **16.2** (0.40 g, 1.9 mmol, 1.0 equiv) in ACN (8.0 mL) was added K₂CO₃ (0.52 g, 3.7 mmol, 2.0 equiv) and CD₃I (0.35 g, 2.4 mmol, 1.3 equiv) at 20 °C. The mixture was stirred at 20 °C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (12 g column, Eluent of 0~20% EtOAc/PE gradient at 30 mL/min) to give quinoline **A.4i** (0.30 g, 1.3 mmol, 70% yield, 100% purity) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) 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.4j (R₆ = OMe; R₇ = F): 2,4-dichloro-6-fluoro-7-methoxy-quinoline

[0199] To a solution of 4-fluoro-3-methoxy-aniline (10 g, 71 mmol, 1.0 equiv) in POCl₃ (165 g, 1.1 mol, 0.10 L, 15 equiv) was added malonic acid (7.4 g, 71 mmol, 7.4 mL, 1.0 equiv). The reaction solution was stirred at 105 °C for 12 h. The reaction solution was quenched by H₂O (0.10 L). The pH of the residue was adjusted to 8 by adding sat. NaHCO₃. The residue was extracted by EtOAc (0.30 L, twice), The organic phase was washed by sat. NaHCO₃ (0.20 L, three times). The combined organic layers were dried over Na₂SO₄ and evaporated. The residue was purified by flash chromatography **2** (12 g column, Eluent of

0~20% EtOAc/PE gradient at 40 mL/min) to afford **A.4j** (13 g, 52 mmol, 74% yield, 99% purity) as a light green solid. MS m/z (ESI) $[M+H]^+ = 246.0$. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.79 (d, $J = 11.4$ Hz, 1H), 7.44 (d, $J = 7.9$ Hz, 1H), 7.41 (s, 1H), 4.03 (s, 3H).

A.4k (R₆ = O-Ph-pyrrolidine; R₇ = H): 2, 4-dichloro-7-(4-pyrrolidin-1-ylphenoxy) quinoline



[0200] To a solution of 4-iodophenol **17.1** (19 g, 86 mmol, 1.2 equiv) in DMA (0.15 L) was added Cs_2CO_3 (47 g, 0.14 mol, 2.0 equiv) and 1-fluoro-3-nitrobenzene (10 g, 71 mmol, 7.6 mL, 1.0 equiv). The mixture was stirred at 130 °C for 16 h. The reaction mixture was quenched by water (0.15 L), and then the resulting organic phase was extracted with EtOAc (0.10 L, three times). The combined organic layers were washed with brine (0.10 L), dried over Na_2SO_4 , filtered and the filtrate was concentrated in vacuum. The residue was purified by flash chromatography (120 g, PE/EtOAc) to afford 1-(4-iodophenoxy)-3-nitrobenzene **17.2** (15 g, 44 mmol, 62% yield) as yellow solid. ^1H NMR (400 MHz, methanol- d_4) δ (ppm): 7.99 (ddd, $J = 0.9, 2.1, 8.2$ Hz, 1H), 7.80 - 7.71 (m, 3H), 7.60 (t, $J = 8.3$ Hz, 1H), 7.40 (ddd, $J = 0.8, 2.4, 8.3$ Hz, 1H), 6.93 - 6.87 (m, 2H).

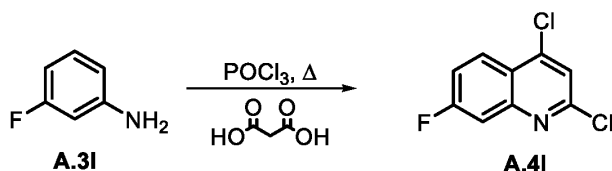
[0201] To a solution of **17.2** (13 g, 38 mmol, 1.0 equiv) in DMSO (0.15 L) was added pyrrolidine (3.9 g, 55 mmol, 1.4 equiv), L-Proline (0.88 g, 7.6 mmol, 0.20 equiv), K_2CO_3 (12 g, 87 mmol, 2.3 equiv) and CuI (0.78 g, 4.1 mmol, 0.10 equiv). The mixture was degassed and purged with N_2 three times, and then the mixture was stirred at 90 °C for 16 h under N_2 atmosphere. The reaction mixture was quenched by water (0.20 L), and then the resulting organic phase was extracted with EtOAc (0.20 L, twice). The combined organic layers were washed with brine (0.10 L, twice), dried over Na_2SO_4 , filtered and the filtrate was concentrated in vacuum. The residue was purified by flash chromatography (80 g, PE/EtOAc) to afford 1-[4-(3-nitrophenoxy)phenyl]pyrrolidine **17.3** (6.7 g, 24 mmol, 62% yield) as

orange solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.83 (dd, $J = 1.6, 8.1$ Hz, 1H), 7.69 (t, $J = 2.3$ Hz, 1H), 7.41 (t, $J = 8.3$ Hz, 1H), 7.25 (d, $J = 2.4$ Hz, 1H), 7.00 - 6.93 (m, 2H), 6.57 (d, $J = 8.9$ Hz, 2H), 3.30 (br t, $J = 6.5$ Hz, 4H), 2.08 - 2.01 (m, 4H).

[0202] To a solution of (6.7 g, 24 mmol, 1.0 equiv) in EtOH (70 mL) and H_2O (30 mL) was added NH_4Cl (8.0 g, 0.15 mol, 6.3 equiv). Then mixture was added Fe (7.0 g, 0.13 mol, 5.3 equiv) in batches at 50 °C. Then the mixture was stirred at 80 °C for 2 h. The reaction mixture was filtered through celite, and the filtrate was concentrated *in vacuum*. The residue was extracted with EtOAc (0.10 L, twice). The combined organic layers were washed with brine (0.10 L), dried over Na_2SO_4 , filtered and the filtrate was concentrated *in vacuum*. The residue was purified by flash chromatography (PE/EtOAc) to afford 3-(4-pyrrolidin-1-ylphenoxy) aniline **17.4** (5.1 g, 20 mmol, 86% yield) as off-white solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.03 (t, $J = 8.0$ Hz, 1H), 6.99 - 6.94 (m, 2H), 6.57 - 6.52 (m, 2H), 6.32 (dd, $J = 2.2, 8.1$ Hz, 2H), 6.26 - 6.21 (m, 1H), 3.63 (br s, 2H), 3.28 (br t, $J = 6.6$ Hz, 4H), 2.01 (td, $J = 3.3, 6.6$ Hz, 4H).

[0203] To a solution of POCl_3 (50 mL) was added malonic acid (2 g, 19.2 mmol, 1.2 eq) and **17.4** (4.1 g, 16 mmol, 1.0 equiv) carefully at 20 °C. The mixture was stirred at 20~90 °C for 15 min and 90 °C for 6 h. The reaction mixture was concentrated *in vacuum*, then the residue was diluted with EtOAc (0.10 L), then quenched by water (0.10 L) and adjusted pH to 8 with NaHCO_3 solution, and then the resulting organic phase was extracted with EtOAc (0.10 L, three times), the un-dissolved solid was abandoned. The combined organic layers were washed with brine (0.10 L), dried over Na_2SO_4 , filtered and the filtrate was concentrated *in vacuum* to give a residue. The residue was purified by flash chromatography (PE/EtOAc) to afford **A.4k** (0.80 g, 2.2 mmol, 14% yield) as yellow solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.11 (d, $J = 9.2$ Hz, 1H), 7.42 (dd, $J = 2.6, 9.2$ Hz, 1H), 7.34 (s, 1H), 7.24 (d, $J = 2.4$ Hz, 1H), 7.04 - 6.96 (m, 2H), 6.62 - 6.52 (m, 2H), 3.30 (br t, $J = 6.5$ Hz, 4H), 2.04 (td, $J = 3.3, 6.5$ Hz, 4H).

A.4l (R₆ = F; R₇ = H): 2,4-dichloro-7-fluoro-quinoline



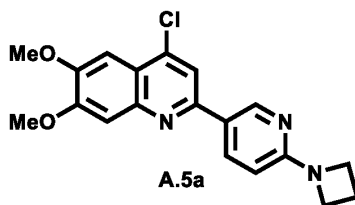
[0204] To a solution of 3-fluoroaniline **A.3l** (25 g, 0.22 mol, 22 mL, 1.0 equiv) in POCl_3 (0.20 L) was added malonic acid (28 g, 0.27 mol, 28 mL, 1.2 equiv) at 25 °C. The mixture

was stirred at 110 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove POCl₃. The residue was diluted with NaHCO₃ solution (0.10 L) and extracted with EtOAc 0.60 L (0.20 L, three times). The combined organic layers were washed with brine (0.30 L), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography **2** (120 g column, Eluent of 0~10% EtOAc/PE gradient at 40 mL/min) to give **A.4I** (12 g, 57 mmol, 25% yield, 100% purity) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.23 (dd, J = 6.0, 9.3 Hz, 1H), 7.90 (s, 1H), 7.80 (dd, J = 2.6, 9.9 Hz, 1H), 7.70 (dt, J = 2.6, 8.8 Hz, 1H). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.19 - 8.10 (m, 1H), 7.61 (dd, J = 2.1, 9.4 Hz, 1H), 7.46 - 7.34 (m, 2H). MS m/z (ESI) $[M+H]^+ = 215.9$.

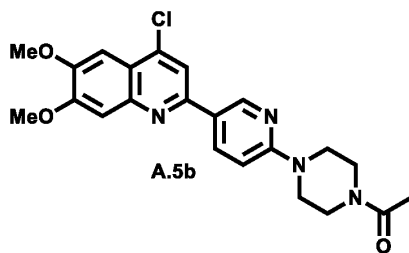
Synthesis of Suzuki Coupling Products A.5 and C.5 – (Schemes 1, 3, 5 and 6; step 4), (Scheme 4; step 5)

[0205] General conditions for Suzuki Coupling. A mixture of 2,4-dichloroquinoline derivative **A.4** (1.0 equiv), boronic ester derivatives (**bor.** When not commercially available) (1.2 equiv), Na₂CO₃ (3.0 equiv), Pd(PPh₃)₄ (0.10 equiv) in **S1**: dioxane/H₂O (0.85:0.15; 0.16M) or **S2**: EtOH/toluene/H₂O (0.45:0.45:0.10; 0.17M) was degassed and purged with N₂ for three times at 25 °C, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was diluted with water and extracted with EtOAc (three times). The organic phase was washed with brine (three times), dried over *anhydrous* Na₂SO₄, filtered and the filtrate was concentrated.

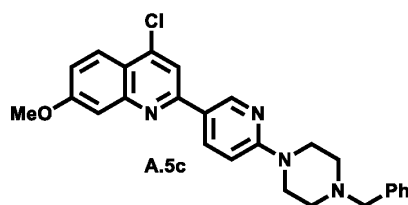
A.5a: 2-[6-(azetidine-1-yl)-3-pyridyl]-4-chloro-6,7-dimethoxy-quinoline



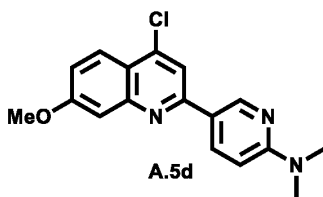
[0206] According to scheme 1 and 5, step 4, 2,4-Dichloro-6,7-dimethoxy-quinoline (0.40 g, 1.6 mmol, 1.0 equiv) and boronic acid **bor.6** (0.33 g, 1.9 mmol, 1.2 equiv) reacted under the general conditions for Suzuki coupling. The residue was purified by flash silica gel chromatography (20g column, Eluent of 0~100% EtOAc/PE gradient at 40mL/min) to give compound **A.5a** (0.22 g, 0.42 mmol, 27% yield, 68% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 356.0$.

A.5b: 1-[4-[5-(4-chloro-6,7-dimethoxy-2-quinolyl)-2-pyridyl] piperazin-1-yl] ethanone

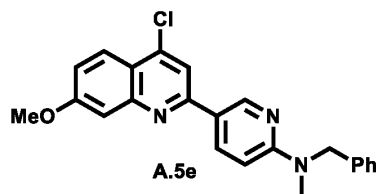
[0207] According to scheme 1 and 5, step 4, 2,4-Dichloro-6,7-dimethoxy-quinoline (0.25 g, 0.97 mmol, 1.0 equiv). The residue was purified by prep-TLC (SiO₂, PE/EtOAc = 1:1) to give compound **A.5b** (0.27 g, 0.59 mmol, 61% yield, 94% purity) was obtained as a brown solid. MS m/z (ESI) [M+H]⁺ = 427.1.

A.5c: 2-[6-(4-benzylpiperazin-1-yl)-3-pyridyl]-4-chloro-7-methoxy-quinoline

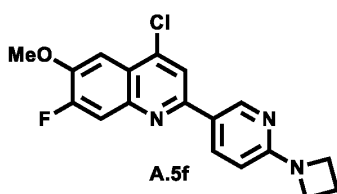
[0208] According to scheme 1 and 5, step 4, 2,4-Dichloro-7-methoxy-quinoline (0.20 g, 0.88 mmol, 1.0 equiv). The crude product was triturated with MeOH (25 mL) at 25 °C for 30 min to give compound **A.5c** (0.35 g, 0.61 mmol, 69% yield, 77% purity) was obtained as a white solid. MS m/z (ESI) [M+H]⁺ = 445.2.

A.5d: 5-(4-chloro-7-methoxy-2-quinolyl)-N,N-dimethyl-pyridin-2-amine

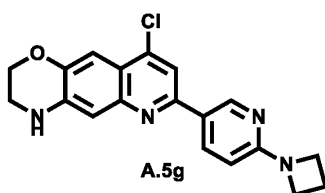
[0209] According to scheme 1 and 5, step 4, 2,4-Dichloro-7-methoxy-quinoline (0.30 g, 1.3 mmol, 1.0 equiv). The residue was purified by prep-TLC (SiO₂, DCM/MeOH = 10:1) to give compound **A.5d** (0.15 g, 0.45 mmol, 35% yield, 95% purity) as a yellow solid. MS m/z (ESI) [M+H]⁺ = 314.1.

A.5e: *N*-benzyl-5-(4-chloro-7-methoxy-2-quinolyl) -*N*-methyl-pyridin-2-amine

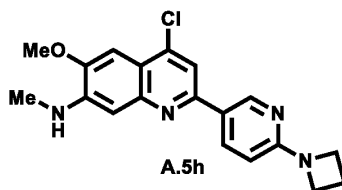
[0210] According to scheme 1 and 5, step 4, 2, 4-Dichloro-7-methoxy-quinoline (0.20 g, 0.88 mmol, 1.0 equiv). The residue was purified by prep-TLC (Plate 1: PE/EtOAc = 3:1) to give compound **1.5l** (0.13 g, 0.30 mmol, 34% yield, 90% purity) as a white solid.

A.5f: 2-[6-(azetidin-1-yl) -3-pyridyl]-4-chloro-7-fluoro-6-methoxy-quinoline

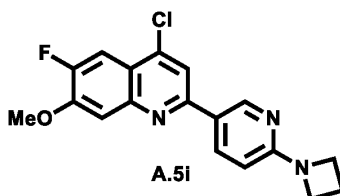
[0211] According to scheme 1 and 5, step 4, 2, 4-Dichloro-7-fluoro-6-methoxy-quinoline **A.4a** (0.30 g, 1.2 mmol, 1.0 equiv), boronic acid **bor. 6**. The residue was purified by flash silica gel chromatography (40 g column, Eluent of 0~30% EtOAc/PE gradient at 40 mL/min) to afford compound **A.5f** (0.28 g, 0.63 mmol, 51% yield, 77% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.82 (d, J = 2.1 Hz, 1H), 8.28 (dd, J = 2.4, 8.8 Hz, 1H), 7.80 (s, 1H), 7.74 (d, J = 12.0 Hz, 1H), 7.51 - 7.48 (m, 1H), 6.37 (d, J = 8.8 Hz, 1H), 4.16 (t, J = 7.4 Hz, 4H), 4.07 (s, 3H), 2.51 - 2.41 (m, 2H). MS m/z (ESI) $[M+H]^+ = 344.1$.

A.5g: 7-[6-(azetidin-1-yl)-3-pyridyl]-9-chloro-3,4-dihydro-2H-pyrido[2,3-g][1,4]benzoxazine

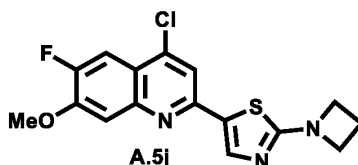
[0212] According to scheme 1 and 5, step 4, 7,9-Dichloro-3,4-dihydro-2H-pyrido[2,3-g][1,4]benzoxazine **A.4b** (0.13 g, 0.51 mmol, 1.0 equiv), boronic acid **bor. 6**. The residue was purified by prep-TLC (SiO₂, PE/EtOAc = 0:1) to give compound **A.5g** (70 mg, 0.18 mmol, 36% yield, 92% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 353.2$.

A.5h: 2-[6-(azetidin-1-yl)-3-pyridyl]-4-chloro-6-methoxy-*N*-methyl-quinolin-7-amine

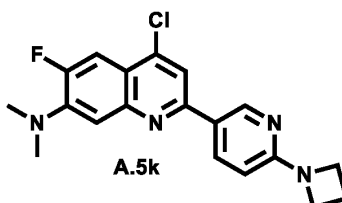
[0213] According to scheme 1 and 5, step 4, 2,4-Dichloro-6-methoxy-*N*-methyl-quinolin-7-amine **A.4e** (0.60 g, 1.9 mmol, 1.0 equiv), boronic acid **bor. 6**. The residue was triturated with ethyl acetate at 25 °C for 25 minutes to give compound **A.5h** (0.35 g, 0.59 mmol, 32% yield, 60% purity) was obtained as a yellow solid. MS *m/z* (ESI) $[M+H]^+ = 355.1$.

A.5i: 2-[6-(azetidin-1-yl)-3-pyridyl]-4-chloro-6-fluoro-7-methoxy-quinoline

[0214] According to scheme 1 and 5, step 4, 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.20 g, 0.81 mmol, 1.0 equiv), boronic acid **bor. 6**. The crude product was triturated with ethyl acetate (5.0 mL) at 25 °C for 10 min to give compound **A.5i** (0.15 g, 0.41 mmol, 50% yield, 93% purity) as a yellow solid. MS *m/z* (ESI) $[M+H]^+ = 344.0$.

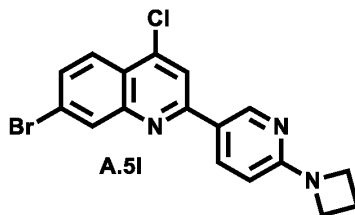
A.5j: 2-(azetidin-1-yl)-5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) thiazole

[0215] According to scheme 1 and 5, step 4, 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.30 g, 1.2 mmol, 1.0 equiv), boronic ester **bor. 2**. The residue was purified by prep-TLC (SiO₂, PE/EtOAc = 3:1) to give compound **A.5j** (50 mg, 0.10 mmol, 8.2% yield, 70% purity) as yellow oil. MS *m/z* (ESI) $[M+H]^+ = 350.0$.

A.5k: 2-[6-(azetidin-1-yl)-3-pyridyl]-4-chloro-6-fluoro-*N,N*-dimethyl-quinolin-7-amine

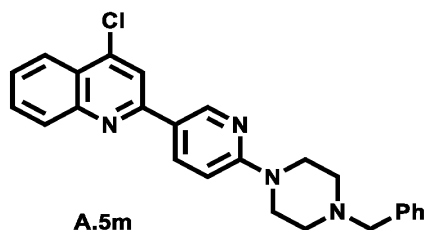
[0216] According to scheme 1 and 5, step 4, 2,4-Dichloro-6-fluoro-*N,N*-dimethyl-quinolin-7-amine (0.17 g, 0.66 mmol, 1.0 equiv), boronic acid **bor.6**. The residue was purified by flash silica gel chromatography (12 g column, Eluent of 0~20% EtOAc/PE gradient at 45 mL/min) to give compound **A.5k** (0.12 g, 0.30 mmol, 46% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 357.1$.

A.5l: 2-[6-(azetidin-1-yl)-3-pyridyl]-7-bromo-4-chloro-quinoline



[0217] According to scheme 1 and 5, step 4, 2,4-Dichloro-7-bromo-quinoline **A4.h** (1.0 g, 3.6 mmol, 1.0 equiv). Boronic acid **bor.6**. The crude product was triturated with EtOAc (10 mL) 25 °C for 10 min. Product **A.5l** (1.0 g, 2.4 mmol, 67% yield, 91% purity) was obtained as a white solid. MS (ESI) m/z . 374.0 $[M+H]^+$.

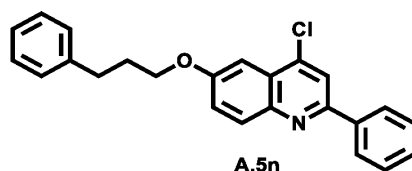
A.5m: 2-(6-(4-benzylpiperazin-1-yl) 114zetidin-3-yl)-4-chloroquinoline



[0218] A solution of substrate **C.5b** (33 g, 78 mmol, 1.0 equiv) in EtOAc (0.10 L) was degassed and purged with N_2 three times. HCl/EtOAc (2.0 M, 0.50 mL, 13 equiv) 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 (40.0 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 (1V) at room temperature for 12 h. The free amine (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, $CDCl_3$) δ (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).

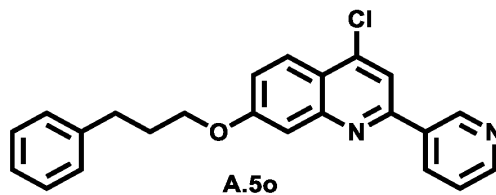
[0219] Free amine (1.5 g, 4.6 mmol, 1.0 equiv) was mixed with cesium carbonate (3.0 g, 9.2 mmol, 2.0 equiv) and (chloromethyl)benzene (0.64 mL, 5.5 mmol, 1.2 equiv) in 100 mL flask. DMF (37 mL) was added, and the reaction was stirred at room temperature for 3 days. The reaction mixture was transferred 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.5m** (0.71 g, 1.7 mmol, 37% yield) was obtained as yellow solid. ¹H NMR (400 MHz, CDCl₃) *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.5n: 4-chloro-2-phenyl-6-(3-phenylpropoxy) quinoline

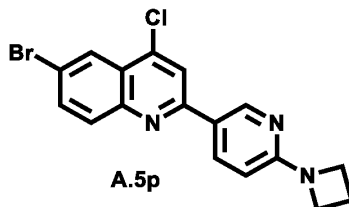


[0220] 2,4-dichloroquinolin-6-ol (0.18 g, 0.84 mmol, 1.0 equiv), Cs₂CO₃ (0.55 g, 1.7 mmol, 2.0 equiv) were transferred to a Schlenk tube, 5 A/V cycles were performed and DMF (3.8 mL, 5.2 mL/mmol) were added in counter flow, 3-(chloropropyl)benzene (0.16 g, 0.144 μL, 1.2 Eq, 1.01 mmol) was added taken up in DMF (0.8 mL), the mixture was heated to reflux for 2.5 h. 2,4-dichloroquinolin-6-ol (0.18 g, 0.84 mmol, 1.0 equiv), Cs₂CO₃ (0.55 g, 1.7 mmol, 2.0 equiv) were transferred to a Schlenk tube, 5 A/V cycles were performed. DMF (3.8 mL, 5.2 mL / mmol) were added in counter flow and (3-chloropropyl)benzene (0.16 g, 0.14 mL, 1.0 mmol, 1.2 equiv) was added taken up in DMF (0.8 mL). The mixture was heated to reflux for 2.5 h. After work-up, residue was purified by flash chromatography using DCM/MeOH to give 2,4-dichloro-6-(3-phenylpropoxy)quinoline (0.10 g, 0.84 mmol, 37%).

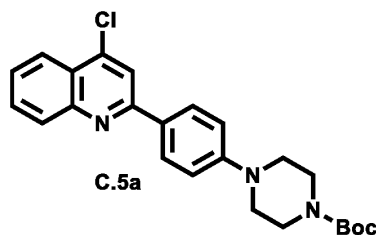
[0221] According to scheme 1 and 5, 2,4-dichloro-6-(3-phenylpropoxy) quinoline (69 mg, 0.21 mmol, 1.0 equiv), phenylboronic acid (20 mg, 0.17 mmol, 0.80 equiv), Na₂CO₃ (66 mg, 0.62 mmol, 3.0 equiv) were transferred to a Schlenk tube, 5 A/V cycles were performed, degassed Toluene (3.4 mL, 1.6 mL/mmol) EtOH (3.4 mL) water (1.0 mL) were added in counter flow. Pd(PPh₃)₄ (24 mg, 21 μmol, 0.10 equiv) was added in counterflow, the mixture was heated to 65 °C (external temp), the mixture was filtered through a syringe filter, diluted with H₂O and DCM (25 mL), phases were separated and evaporated to dryness. The sample was purified using flash chromatography to give **A.5n** (52 mg, 0.14 mmol, 67 %) as a yellow solid.

A.5o: 4-chloro-7-(3-phenylpropoxy)-2-(3-pyridyl) quinoline

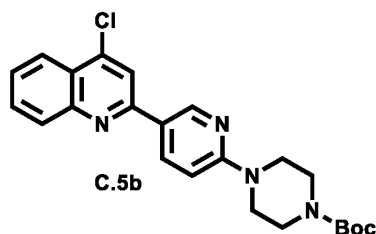
[0222] According to scheme 1 and 5, a mixture of 2,4-dichloro-7-(3-phenylpropoxy)quinoline (0.20 g, 0.60 mmol, 1.0 equiv), 3-pyridylboronic acid (59 mg, 0.48 mmol, 0.80 equiv), Pd(PPh₃)₄ (70 mg, 60 μmol, 0.10 equiv), Na₂CO₃ (0.19 g, 1.8 mmol, 3.0 equiv) in toluene (2.0 mL) / EtOH (2.0 mL) / H₂O (0.40 mL) was degassed and purged with N₂ three times at 25 °C, and then the mixture was stirred at 60 °C for 16 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (30 mL) and extracted with EtOAc (40 mL, three times). The combined organic layers were washed with brine (35 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography **2** (12 g column, Eluent of 0~30% EtOAc/PE gradient at 60 mL/min) to give **A.5o** (0.16 g, 0.41 mmol, 68% yield, 96% purity) was obtained as a yellow solid. MS m/z (ESI) [M+H]⁺ = 375.1.

A.5p: 2-[6-(116zetidine-1-yl)-3-pyridyl]-6-bromo-4-chloro-quinoline

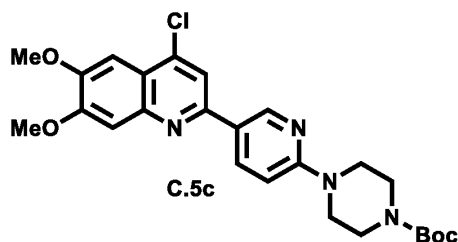
[0223] According to scheme 1 and 5, step 4, to a solution 6-bromo-2,4-dichloro-quinoline (1.0 g, 3.6 mmol, 1.0 equiv) in dioxane (50 mL) / H₂O (5.0 mL) was added **bor. 6** (0.80 g, 4.5 mmol, 1.2 equiv), Na₂CO₃ (1.2 g, 11 mmol, 3.0 equiv) and Pd(PPh₃)₂Cl₂ (0.26 g, 0.37 mmol, 0.10 equiv). The reaction solution was degassed and purged under N₂ three times; the reaction mixture was stirred at 60 °C for 12 h. The reaction mixture was concentrated to give a residue. The crude product was triturated with EtOAc (20 mL) at 25 °C for 20 min and the resulting solid was filtered and washed with EtOAc (2.0 mL), the filter cake was concentrated to give **A.5p** (1.8 g, crude) as yellow solid.

C.5a: *tert*-butyl 4-[4-(4-chloro-2-quinolyl) phenyl] piperazine-1-carboxylate

[0224] According to scheme 3 and 6, step 4, 2,4-Dichloroquinoline (2.0 g, 10 mmol, 1.0 equiv). The residue was purified by flash chromatography (SiO₂, **PE**/**EtOAc** = **20/1** to **3/1**) to afford compound **C.5a** (3.0 g, 7.1 mmol, 70% yield) as a yellow solid. MS m/z (ESI) [M+H]⁺ = 424.2.

C.5b: *tert*-butyl 4-[5-(4-chloro-2-quinolyl) -2-pyridyl] piperazine-1-carboxylate

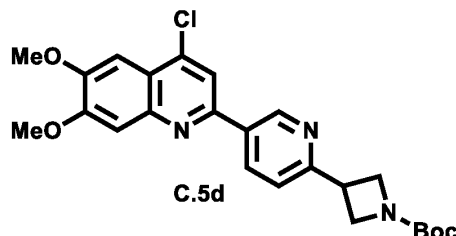
[0225] According to scheme 3 and 6, step 4, 2,4-Dichloroquinoline (0.35 g, 1.8 mmol, 1.0 equiv). The crude product was purified by flash silica gel chromatography (40 g column, Eluent of 0-21% EtOAc/PE gradient at 40 mL/min) to give compound **C.5b** (0.65 g, 1.5 mmol, 87% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) *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.5c: *tert*-butyl 4- [5-(4-chloro-6, 7-dimethoxy-2-quinolyl) -2-pyridyl] piperazine-1-carboxylate

[0226] According to scheme 3 and 6, step 4, 2, 4-Dichloro-6, 7-dimethoxy-quinoline (0.20 g, 0.77 mmol, 1.0 equiv) The residue was purified by flash silica gel chromatography (20 g

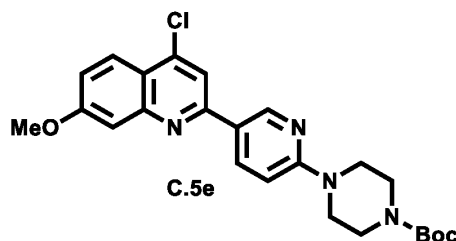
column, Eluent of 0~50% EtOAc/PE gradient at 30 mL/min) to afford compound **C.5c** (0.35 g, 0.59 mmol, 76% yield, 82% purity) as yellow gum. MS m/z (ESI) $[M+H]^+ = 485.2$.

C.5d: 3-[5-(4-chloro-6,7-dimethoxy-2-quinolyl)-2-pyridyl] azetidine-1-carboxylate



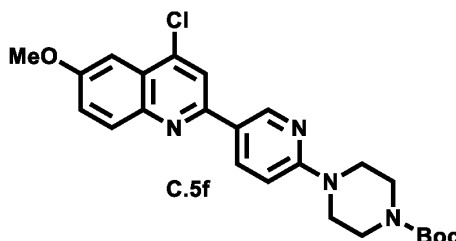
[0227] According to scheme 3 and 6, step 4, 2,4-Dichloro-6,7-dimethoxy-quinoline (0.20 g, 0.78 mmol, 1.0 equiv), boronic acid *bor.a'* (0.28 g, 0.93 mmol, 1.2 equiv). The residue was purified by flash silica gel chromatography (12 g column, Eluent of 0~60% EtOAc/PE gradient at 30 mL/min) to give compound **C.5d** (0.20 g, 0.39 mmol, 50% yield, 88% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 456.3$.

C.5e: *tert*-butyl 4-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate



[0228] According to scheme 3 and 6, step 4, 2,4-Dichloro-7-methoxy-quinoline (0.30 g, 1.3 mmol, 1.0 equiv). The residue was purified by prep-TLC (SiO₂, PE/EtOAc = 2:1) to give compound **C.5e** (0.50 g, 1.0 mmol, 77% yield, 92% purity) was obtained as yellow oil. MS m/z (ESI) $[M+H]^+ = 455.2$.

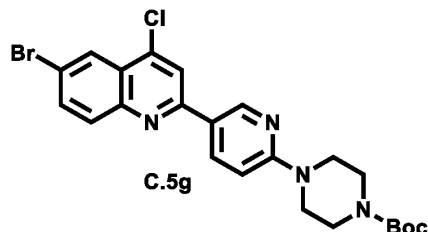
C.5f: *tert*-butyl 4-[5-(4-chloro-6-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate



[0229] According to scheme 3 and 6, step 4, 2,4-Dichloro-6-methoxy-quinoline (0.30 g, 1.3 mmol, 1.0 equiv). The crude was used next step without purification. Compound **C.5f** (0.60

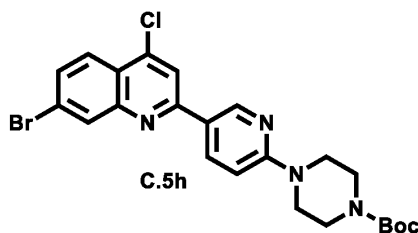
g, 1.1 mmol, 82% yield, 82% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+ = 455.2$.

C.5g: *tert*-butyl 4-[5-(6-bromo-4-chloro-2-quinoly)-2-pyridyl] piperazine-1-carboxylate



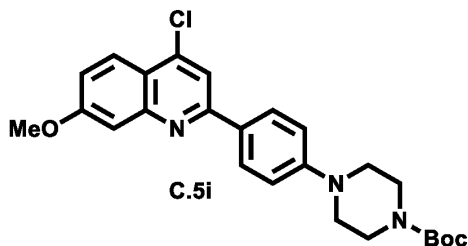
[0230] According to scheme 3 and 6, step 4, 6-Bromo-2,4-dichloro-quinoline (2.0 g, 7.2 mmol, 1.0 equiv). The residue was purified by flash silica gel chromatography (25 g column, Eluent of 0~35% EtOAc/PE gradient at 55 mL/min) to give compound **C.5g** (2.0 g, 3.6 mmol, 49% yield, 90% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 505.1$.

C.5h: *tert*-butyl 4-[5-(7-bromo-4-chloro-2-quinoly)-2-pyridyl] piperazine-1-carboxylate



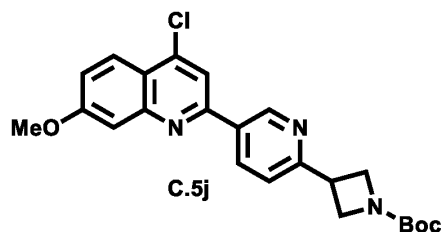
[0231] According to scheme 3 and 6, step 4, 7-Bromo-2,4-dichloro-quinoline **A.4h** (0.60 g, 2.2 mmol, 1.0 equiv). The residue was purified by flash silica gel chromatography (20 g column, Eluent of 0~40% EtOAc/PE gradient at 80 mL/min) to give compound **C.5h** (0.76 g, 1.2 mmol, 54% yield, 78% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+ = 505.1$.

C.5i: *tert*-butyl 4-[4-(4-chloro-7-methoxy-2-quinoly) phenyl] piperazine-1-carboxylate



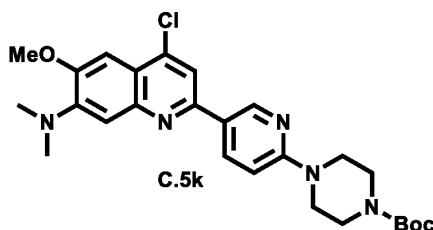
[0232] According to scheme 3 and 6, step 4, 2,4-Dichloro-7-methoxy-quinoline (0.40 g, 1.8 mmol, 1.0 equiv). The residue was purified by flash silica gel chromatography (12 g column, Eluent of 20~30% EtOAc/PE gradient at 40 mL/min) to afford compound **C.5i** (0.60 g, 1.3 mmol, 75% yield, 99% purity) as yellow oil. MS m/z (ESI) $[M+H]^+ = 454.2$.

C.5j: *tert*-butyl 3-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl] azetidine-1-carboxylate



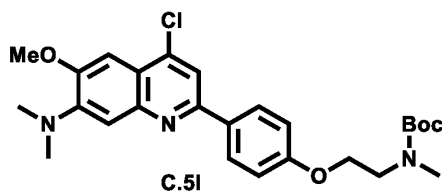
[0233] According to scheme 3 and 6, step 4, 2,4-Dichloro-7-methoxy-quinoline (0.40 g, 1.8 mmol, 1.0 equiv), boronic acid *bor.1'*. The residue was purified by flash silica gel chromatography (40g column, Eluent of 0~10% EtOAc/PE gradient at 40 mL/min) to afford compound **C.5j** (0.36 g, 0.74 mmol, 42% yield, 88% purity) as yellow oil. MS m/z (ESI) $[M+H]^+ = 426.1$.

C.5k: *tert*-butyl 4-[5-[4-chloro-7-(dimethylamino)-6-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



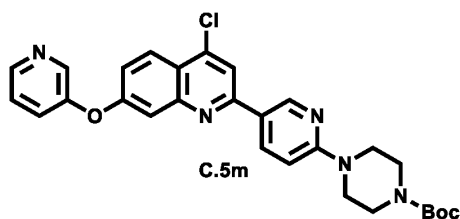
[0234] According to scheme 3 and 6, step 4, 2,4-Dichloro-6-methoxy-*N,N*-dimethyl-quinolin-7-amine (0.15 g, 0.55 mmol, 1.0 equiv). The residue was purified by prep-TLC (SiO₂, PE/EtOAc = 2:1) to give compound **C.5k** (0.20 g, 0.40 mmol, 73% yield, 100% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 498.3$.

C.5l: *tert*-butyl *N*-[2-[4-[4-chloro-7-(dimethylamino)-6-methoxy-2-quinolyl] phenoxy] ethyl]-*N*-methylcarbamate



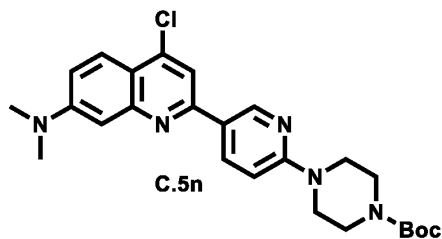
[0235] According to scheme 3 and 6, step 4, 2,4-Dichloro-6-methoxy-*N,N*-dimethyl-quinolin-7-amine (0.15 g, 0.55 mmol, 1.0 equiv), boronic ester *bor.3*. The residue was purified by prep-TLC (SiO₂, PE/EtOAc = 2:1) to give compound **C.5l** (0.16 g, 0.33 mmol, 60% yield, 100% purity) as a yellow oil. MS m/z (ESI) $[M+H]^+ = 486.3$.

C.5m: tert-butyl 4-[4-chloro-7-(3-pyridyloxy)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



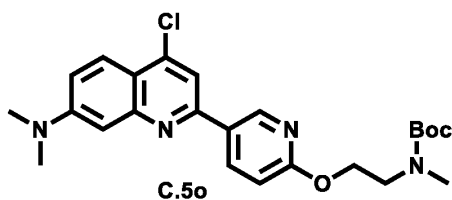
[0236] According to scheme 3 and 6, step 4, 2,4-Dichloro-7-(3-pyridyloxy) quinoline **A.4c** (0.20 g, 0.69 mmol, 1.0 equiv). The residue was purified by preparative TLC (SiO₂, PE/EtOAc = 3:1) to give compound **C.5m** (0.18 g, 0.35 mmol, 35% yield) as a white solid. MS m/z (ESI) [M+H]⁺ = 518.3.

C.5n: tert-butyl 4-[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



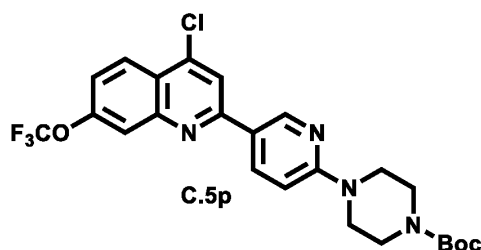
[0237] According to scheme 3 and 6, step 4, 2,4-Dichloro-*N,N*-dimethyl-quinolin-7-amine **A.4d** (0.50 g, 2.1 mmol, 1.0 equiv). The crude was not purified. Compound **C.5n** (0.80 g, 1.2 mmol, 58% yield, 70% purity) was obtained as a yellow solid. MS m/z (ESI) [M+H]⁺ = 468.2.

C.5o: tert-butyl *N*-[2-[[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl] oxy] ethyl]-*N*-methylcarbamate



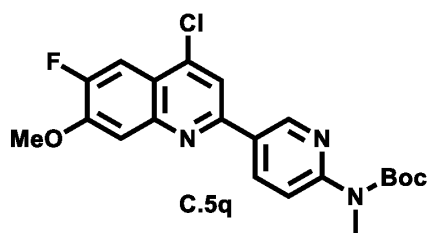
[0238] According to scheme 3 and 6, step 4, 2,4-Dichloro-*N,N*-dimethyl-quinolin-7-amine **A.4d** (0.30 g, 1.2 mmol, 1.0 equiv), boronic ester **bor.3**. The crude was not purified. Compound **C.5o** (0.80 g, 1.2 mmol, 98% yield, 70% purity) as a yellow solid. MS m/z (ESI) [M+H]⁺ = 457.2.

C.5p: *tert*-butyl 4-[5-[4-chloro-7-(trifluoromethoxy)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



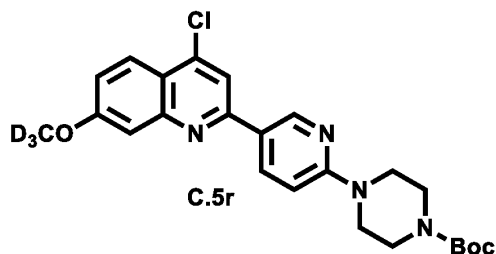
[0239] According to scheme 3 and 6, step 4, 2,4-Dichloro-7-(trifluoromethoxy) quinoline **A.4f** (0.20 g, 0.71 mmol, 1.0 equiv). The residue was purified by flash chromatography (12 g column, Eluent of 0~30% EtOAc/PE gradient at 40 mL/min) to afford compound **C.5p** (0.41 g, 0.55 mmol, 78% yield, 69% purity) as yellow solid. MS *m/z* (ESI) $[M+H]^+ = 509.1$.

C.5q: *tert*-butyl *N*-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]-*N*-methylcarbamate



[0240] According to scheme 3 and 6, step 4, 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.45 g, 1.8 mmol, 1.0 equiv). The residue was purified by flash silica gel chromatography (12 g column, Eluent of 0~20% EtOAc/PE gradient at 40 mL/min) to afford compound **C.5q** (0.60 g, 1.2 mmol, 64% yield, 82% purity) as a light green solid. MS *m/z* (ESI) $[M+H]^+ = 418.1$.

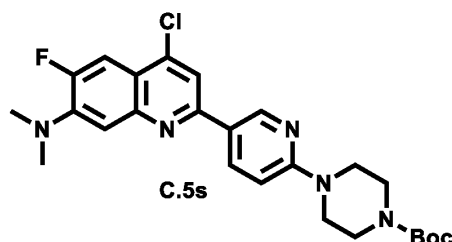
C.5r: *tert*-butyl 4-[5-[4-chloro-7-(trideuteriomethoxy)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



[0241] According to scheme 3 and 6, step 4, 2,4-Dichloro-7-(trideuteriomethoxy) quinoline **A.4i** (0.30 g, 1.3 mmol, 1.0 equiv). The residue was purified by flash silica gel

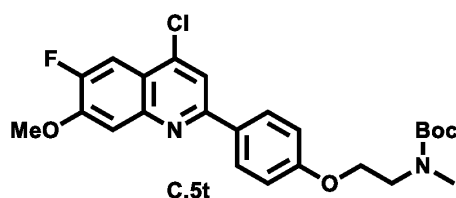
chromatography (12 g column, Eluent of 0 to 30% EtOAc/PE gradient at 30 mL/min) to give compound **C.5r** (0.45 g, 0.91 mmol, 70% yield, 93% purity) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 9.08 - 8.98 (m, 1H), 8.44 (dd, $J = 9.00, 2.40$ Hz, 1H), 8.15 (s, 1H), 8.04 (d, $J = 9.12$ Hz, 1H), 7.44 (d, $J = 2.52$ Hz, 1H), 7.30 (dd, $J = 9.12, 2.52$ Hz, 1H), 6.98 (d, $J = 9.12$ Hz, 1H), 3.70 - 3.60 (m, 4H), 3.45 (s, 4H), 1.43 (s, 9H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 458.3$.

C.5s: *tert*-butyl 4-[5-[4-chloro-7-(dimethylamino)-6-fluoro-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate



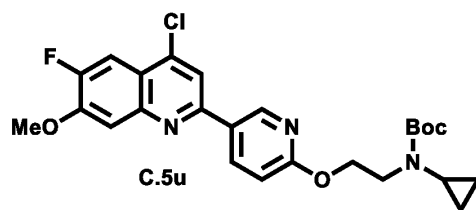
[0242] According to scheme 3, step 4, 2,4-Dichloro-6-fluoro-*N,N*-dimethyl-quinolin-7-amine (0.30 g, 1.2 mmol, 1.0 equiv) and 6. The residue was purified by flash silica gel chromatography (12 g column, Eluent of 0 to 15% EtOAc/PE gradient at 45 mL/min) to give compound **C.5s** (0.50 g, 0.84 mmol, 73% yield, 82% purity) as a yellow solid. MS m/z (ESI) $[\text{M}+\text{H}]^+ = 486.2$.

C.5t: *tert*-butyl *N*-[2-[4-(4-chloro-6-fluoro-7-methoxy-2-quinolyl) phenoxy] ethyl]-*N*-methylcarbamate



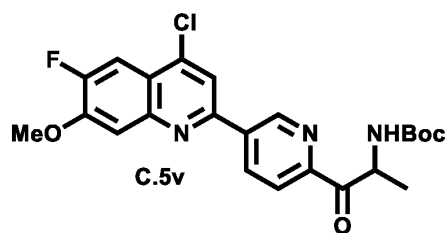
[0243] According to scheme 3 and 6, step 4, 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.30 g, 1.2 mmol, 1.0 equiv), boronic ester **bor.3**. The residue was purified by silica gel chromatography (Biotage, 100-200 mesh silica gel, product came out at B = 25% EtOAc/PE) to afford product compound **C.5t** (0.50 g, 1.1 mmol, 89% yield) as off-white solid.

C.5u: *tert*-butyl *N*-[2-[[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl] oxy] ethyl]-*N*-cyclopropyl-carbamate



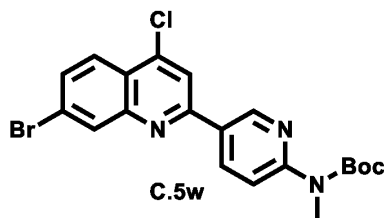
[0244] According to scheme 3 and 6, step 4, 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.18 g, 0.73 mol, 1.0 equiv), boronic ester **bor.4**. The residue was purified by flash silica gel chromatography (20 g column, Eluent of 0~30% EtOAc/PE gradient at 30 mL/min) to give compound **C.5u** (0.12 g, 0.17 mmol, 23% yield, 69% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 488.2$.

C.5v: *tert*-butyl *N*-[2-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]- 1-methyl-2-oxo-ethyl] carbamate



[0245] According to scheme 3 and 6, step 4, 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.30 g, 1.2 mmol, 1.0 equiv), boronic ester **bor.5**. The residue was purified by flash silica gel 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 compound **C.5v** (0.30 g, 0.65 mmol, 53% yield, 99% purity) as an off-white solid.

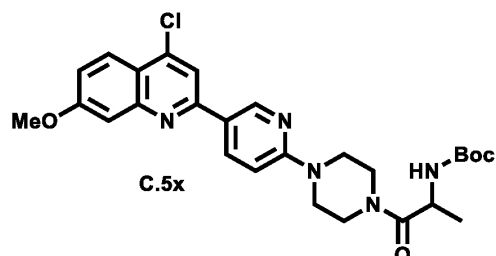
C.5w: *tert*-butyl *N*-[5-(7-bromo-4-chloro-2-quinolyl) -2-pyridyl]-*N*-methylcarbamate



[0246] According to scheme 3 and 6, step 4, 7-Bromo-2,4-dichloro-quinoline **A.4h** (0.30 g, 1.1 mmol, 1.0 equiv). The residue was purified by flash silica gel chromatography (12 g

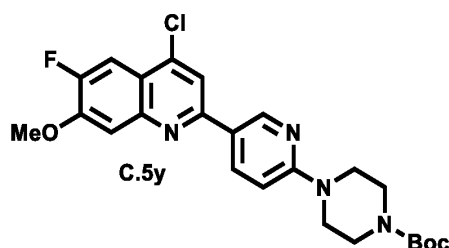
column, Eluent of 0~10% EtOAc/PE gradient at 40 mL/min) to afford compound **C.5w** (0.30 g, 0.66 mmol, 60% yield, 98% purity) as a white solid. MS m/z (ESI) $[M+H]^+ = 450.0$.

C.5x: *tert*-butyl *N*-[2-[4-[5-(4-chloro-7-methoxy-2-quinoly)]-2-pyridyl] piperazin-1-yl]-1-methyl-2-oxo-ethyl] carbamate



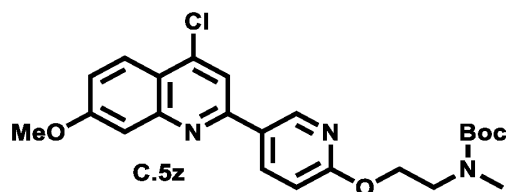
[0247] According to scheme 3 and 6, step 4, 2,4-Dichloro-7-methoxy-quinoline (0.25 g, 1.1 mmol, 1.0 equiv), boronic acid **bor. 7** (0.48 g, 1.3 mmol, 1.2 equiv). The crude product was triturated with EtOAc (30 mL) at 25 °C for 30 min to give compound **C.5x** (0.23 g, 0.41 mmol, 37% yield, 94% purity). MS m/z (ESI) $[M+H]^+ = 526.2$.

C.5y: *tert*-butyl 4-[5-(4-chloro-6-fluoro-7-methoxy-2-quinoly)]-2-pyridyl] piperazine-1-carboxylate



[0248] According to scheme 3 and 6, step 4, 2,4-Dichloro-6-fluoro-7-methoxy-quinoline (0.30 g, 1.2 mmol, 1.0 equiv). The residue was purified by flash silica gel chromatography (40g column, Eluent of 0~25% EtOAc/PE gradient at 40 mL/min) to afford compound **C.5y** (0.55 g, 0.95 mmol, 78% yield, 82% purity) as yellow oil. MS m/z (ESI) $[M+H]^+ = 473.2$.

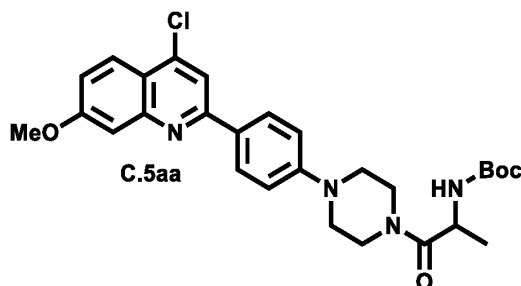
C.5z: *tert*-butyl (2-((5-(4-chloro-7-methoxyquinolin-2-yl) pyridin-2-yl) oxy) ethyl) (methyl)carbamate



[0249] According to scheme 3 and 6, step 4, 2,4-Dichloro-7-methoxy-quinoline (0.30 g, 1.3 mmol, 1.0 equiv). The residue was purified by flash silica gel chromatography (20 g column,

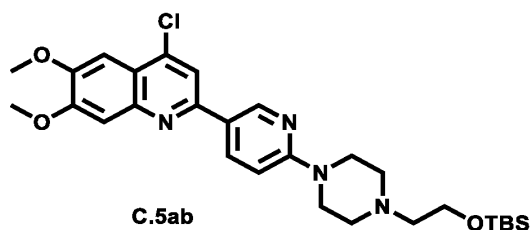
EtOAc/PE 0 to 21% at 60 mL/min) to give product **C.5z** (0.60 g, 0.81 mmol, 62% yield, 60% purity) as a colourless gum.

C.5aa: tert-butyl (1-(4-(4-(4-chloro-7-methoxyquinolin-2-yl) phenyl) piperazin-1-yl)-1-oxopropan-2-yl) carbamate



[0250] According to scheme 3 and 6, step 4, 2,4-Dichloro-7-methoxy-quinoline (0.10 mg, 0.44 mmol, 1.0 equiv eq), boronic acid *bor. 7*. The crude product was triturated with Ethyl acetate (20 mL) at 25 °C for 20 min to give tert-butyl N-[2-[4-[4-(4-chloro-7-methoxy-2-quinolyl) phenyl] piperazin-1-yl]-1-methyl-2-oxo-ethyl] carbamate **C.5aa** (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.5ab: tert-butyl-[2-[4-[5-(4-chloro-6,7-dimethoxy-2-quinolyl)-2-pyridyl] piperazin-1-yl] ethoxy]-dimethyl-silane

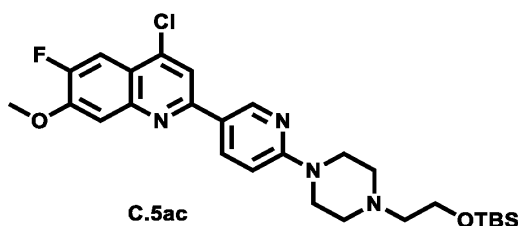


[0251] To a solution of compound **C.5c** (0.70 g, 1.4 mmol, 1.0 equiv) in dioxane (2.0 mL) was added HCl/dioxane (4.0 M, 5.0 mL) at 25 °C. The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give 4-chloro-6,7-dimethoxy-2-(6-piperazin-1-yl-3-pyridyl) quinoline (0.17 g, 0.44 mmol, 77% yield, 100% purity) was obtained as a light-yellow solid. ¹H NMR (400 MHz, DMSO-d₆) 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.

[0252] 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 equiv) in DMF (2.0 mL) was added 2-bromoethoxy-tert-butyl-dimethyl-silane (0.14 g, 0.59 mmol, 1.6 equiv) and K₂CO₃ (0.21 g, 1.5 mmol, 4.2 equiv) at 25

°C. The mixture was stirred at 60 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. 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 was purified by prep-TLC (SiO₂, PE/EtOAc = 1:1) to give compound **C.5ab** (0.14 g, 0.25 mmol, 69% yield, 98% purity) was obtained as a yellow oil. MS m/z (ESI) [M+H]⁺ = 543.3.

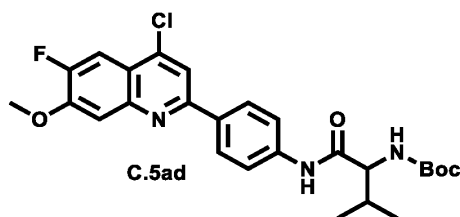
C.5ac: *tert*-butyl-[2-[4-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl] piperazin-1-yl] ethoxy]-dimethyl-silane



[0253] To a solution of *tert*-butyl 4-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate **C.5y** (0.19 g, 0.40 mmol, 1.0 equiv) in dioxane (2.0 mL) was added HCl/dioxane (2.0 M, 5.0 mL, 25 equiv). 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 was used next step without purification. MS m/z (ESI) [M+H]⁺ = 373.1.

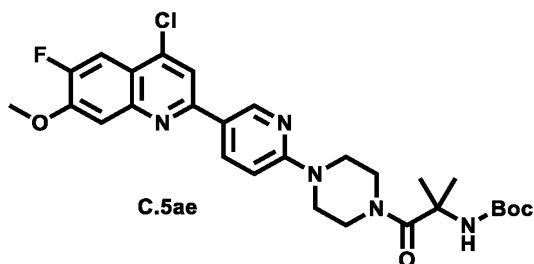
[0254] To a solution of 4-chloro-6-fluoro-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl) quinoline (0.13 g, 0.35 mmol, 1.0 equiv) and 2-bromoethoxy-*tert*-butyl-dimethyl-silane (0.17 g, 0.71 mmol, 2.0 equiv) in DMF (5.0 mL) was added K₂CO₃ (0.10 g, 0.75 mmol, 2.2 equiv) at 25 °C. The mixture was stirred at 60 °C for 5 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL, three times). The organic phase was washed with brine (50 mL, three times), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC 2 (gradient: 34%–64% B over 10 min) to give compound **C.5ac** (0.15 g, 0.19 mmol, 55% yield, 68% purity) as a white solid. MS m/z (ESI) [M+H]⁺ = 531.3.

C.5ad: tert-butyl (1-((4-(4-chloro-6-fluoro-7-methoxyquinolin-2-yl) phenyl) amino)-3-methyl-1-oxobutan-2-yl) carbamate



[0255] According to scheme 3 and 6, step 4, **A.4j** (0.20 g, 0.81 mmol, 1.0 equiv), **bor. 8** (1.0 equiv), **S1**, Pd (PPh₃)₄ (0.10 equiv), Na₂CO₃ (2.3 equiv). Purification was done by flash chromatography 2 (4.0 g Column, Eluent of 0 to 100% EtOAc/PE gradient at 20 mL/min) to give **C.5ad** (0.29 g, 0.56 mmol, 69% yield, 97% purity) as colorless gum. MS m/z (ESI) [M+H]⁺ = 502.4.

C.5ae: tert-butyl (1-(4-(5-(4-chloro-6-fluoro-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl)-2-methyl-1-oxopropan-2-yl) carbamate

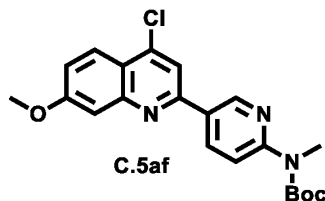


[0256] To a solution of tert-butyl 4-[5-(4-chloro-6-fluoro-7-methoxy-2-quinoly)l-2-pyridyl] piperazine-1-carboxylate **C.5y** (0.19 g, 0.40 mmol, 1.0 equiv) in dioxane (2.0 mL) was added HCl/dioxane (2 M, 5.0 mL, 25 equiv). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated to give 4-chloro-6-fluoro-7-methoxy-2-(6-piperazin-1-yl-3-pyridyl) quinoline (0.14 g, 0.38 mmol, 93%) as a white solid. The crude was used next step without purification. MS m/z (ESI) [M+H]⁺ = 373.1.

[0257] 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 equiv) in DMF (10 mL) was added 2-(tert-butoxycarbonylamino)-2-methyl-propanoic acid (0.17 g, 0.84 mmol, 1.6 equiv), HATU (0.32 g, 0.84 mmol, 1.6 equiv) and DIEA (0.22 g, 1.7 mmol, 0.30 mL, 3.2 equiv), the reaction mixture was stirred at 25 °C for 12 h. The reaction was poured into water (100 mL), extracted with EtOAc (50 mL, three times). The combined organic phase was washed with saturated brine (50 mL, twice), dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel chromatography 2 (40 g column, Eluent of 0 to 10% EtOAc/PE gradient at

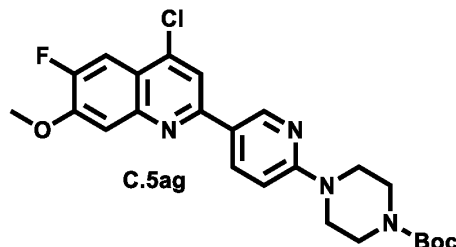
40 mL/min) to afford **C.5ae** (0.20 g, 0.34 mmol, 63% yield, 94% purity) as red oil. MS m/z (ESI) $[M+H]^+ = 558.2$.

C.5af: tert-butyl N-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl]-N-methyl-carbamate



[0258] According to scheme 3 and 6, step 4, to a solution of 2, 4-dichloro-7-methoxy-quinoline (0.30 g, 1.3 mmol, 1.0 equiv), tert-butyl N-methyl-N-[5-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-2-pyridyl]carbamate (0.39 g, 1.2 mmol, 0.90 equiv) in EtOH (0.50 mL), toluene (0.50 mL), H₂O (0.10 mL) were added Pd(PPh₃)₄ (0.15 g, 0.13 mmol, 0.10 equiv) and sodium carbonate (0.28 g, 2.6 mmol, 2.0 equiv) at 20 °C. The mixture was degassed and purged with N₂ three times, and then the mixture was stirred at 60 °C for 12 h under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE/EtOAc = 3:1) to give **C.5af** (0.30 g, 0.68 mmol, 51% yield, 90% purity) as a white solid.

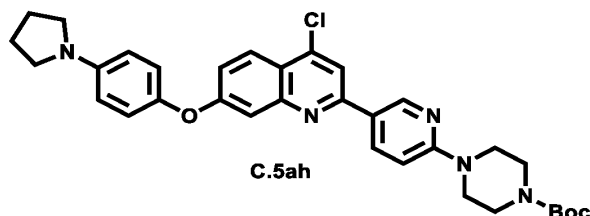
C.5ag: tert-butyl 4-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate



[0259] According to scheme 3 and 6, step 4, To a solution of **A.4j** (1.0 g, 4.1 mmol, 1.0 equiv) in the mixture solvent of H₂O (1.0 mL), EtOH (5.0 mL) and toluene (5.0 mL) was added tert-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]piperazine-1-carboxylate (1.4 g, 3.6 mmol, 0.90 equiv), Pd(PPh₃)₄ (0.50 g, 0.43 mmol, 0.10 equiv) and Na₂CO₃ (0.86 g, 8.1 mmol, 2.0 equiv). The mixture was degassed and purged with N₂ three times, then the resulting mixture was stirred at 80 °C for 12 h. The reaction solution was concentrated under *vacuum*. The residue was purified by flash silica gel chromatography **2** (12 g column, Eluent of 0~20% EtOAc/PE gradient at 40 mL/min) to afford **C.5ag** (1.5 g, 2.6 mmol, 64% yield, 82% purity) as a light green solid. MS m/z (ESI) $[M+H]^+ = 473.2$. ¹H

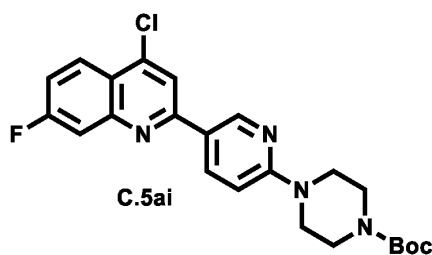
NMR (400 MHz, CDCl₃) δ (ppm): 8.88 (d, J = 2.3 Hz, 1H), 8.30 (dd, J = 2.4, 9.0 Hz, 1H), 7.80 (d, J = 11.6 Hz, 1H), 7.76 (s, 1H), 7.52 (d, J = 8.1 Hz, 1H), 6.76 (d, J = 9.0 Hz, 1H), 4.06 (s, 3H), 3.71 - 3.63 (m, 4H), 3.63 - 3.53 (m, 4H), 1.51 (s, 9H).

C.5ah: tert-butyl 4-[5-[4-chloro-7-(4-pyrrolidin-1-ylphenoxy)-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate



[0260] According to scheme 3 and 6, step 4, To a screw-cap vial equipped with a magnetic stir bar was added 2, 4-dichloro-7-(4-pyrrolidin-1-ylphenoxy) quinoline **A.4k** (0.30 g, 0.84 mmol, 1.0 equiv) and tert-butyl 4-[5-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) -2-pyridyl]piperazine-1-carboxylate (0.33 g, 0.83 mmol, 1.0 equiv), Na₂CO₃ (0.27 g, 2.6 mmol, 3.0 equiv), dioxane (5.0 mL), H₂O (1.0 mL) and Pd(PPh₃)₄ (0.10 g, 87 μ mol, 0.10 equiv) 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 h under nitrogen atmosphere. The reaction mixture was quenched by water (10 mL), and then the resulting organic phase was extracted with ethyl acetate (10 mL, three times). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered and the filtrate was concentrated *in vacuum* to give a residue. The residue was purified by silica gel chromatography (PE/EtOAc) to afford **C.5ah** (0.50 g, crude) as yellow solid.

C.5ai: tert-butyl 4-[5-(4-chloro-7-fluoro-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate



[0261] According to scheme 3 and 6, step 4, a mixture of 2,4-dichloro-7-fluoro-quinoline **A.4l** (0.30 g, 1.4 mmol, 1.0 equiv), tert-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]piperazine-1-carboxylate (0.49 g, 1.3 mmol, 0.90 equiv), Na₂CO₃ (0.30 g, 2.8 mmol, 2.0 equiv), Pd(*t*-Bu₃P)₂ (0.16 g, 0.14 mmol, 0.10 equiv) in toluene (3.0 mL) / ethanol (3.0 mL) / H₂O (0.60 mL) was degassed and purged with N₂ three times at 25 °C, and then

the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (25 mL) and extracted with ethyl acetate (30 mL, three times). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography 2 (40 g column, Eluent of 0~50% EtOAc/PE gradient at 80 mL/min) to give **C.5ai** (0.33 g, 0.74 mmol, 53% yield, 99% purity) was obtained as a yellow solid. MS m/z (ESI) [M+H]⁺ = 443.1.

Synthesis of Buchwald coupling and S_NAr products – Intermediates B.5 (Schemes 2 and 4; step 4), C.6 (Scheme 3; step 5), D.6 (Scheme 5; step 5), E.6 (Scheme 6; step 5) & Suzuki coupling products – Intermediates C.6 (Scheme 4; step 5)

[0262] Conditions 1 Buchwald: A mixture of derivative **A.5** or **C.5** (1.0 equiv), amine (2.0 equiv), BrettPhos Pd G3 (0.10 equiv), *t*-BuONa (3.0 equiv) in dioxane (0.10 M) was degassed and purged with N₂ for three times at 25 °C, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was diluted with water and extracted with EtOAc (three times). The organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to give a residue.

[0263] Conditions 2 Buchwald: A mixture of derivative **A.5** or **C.5** (1.0 equiv), amine (1.3 equiv), PdP(*t*-Bu)₃ (0.10 equiv), *t*-BuONa (3.0 equiv) in dioxane (0.15 M) was degassed and purged with N₂ for three times at 25 °C, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was diluted with water and extracted with EtOAc (three times). The organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to give a residue.

[0264] Conditions 3 Buchwald: A mixture of derivative **A.5** or **C.5** (1.0 equiv), amine (3.0 equiv), CPhos Pd G3 (0.10 equiv), CsCO₃ (2.0 equiv) in dioxane (0.10 M) was degassed and purged with N₂ for three times at 25 °C, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The mixture was diluted with water and extracted with EtOAc (three times). The organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to give a residue.

[0265] Conditions 4 Buchwald: A mixture of derivative **A.5** or **C.5** (1.0 equiv), amine (1.2 equiv), SPhos Pd G₃ (0.10 equiv), Cs₂CO₃ (3.0 equiv) in dioxane was degassed and purged with N₂ for three times, and then the mixture was stirred at 80 °C for 16 hours under N₂

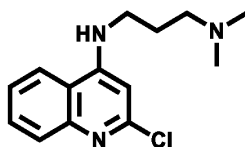
atmosphere. The mixture was diluted with water and extracted with ethyl acetate (three times). The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to give a residue.

[0266] Conditions 1 S_NAr : To a solution of quinoline **A.4** or **C.5** (1.0 equiv), amine (1.5 equiv) in dimethyl sulfoxide (0.40 M) was added cesium fluoride (2.0 equiv) at 25 °C. After stirring at 130 °C for 16 h, the reaction mixture was added into water (0.08 M) and extracted with ethyl acetate (three times). The combined organic layers were washed with brine (three times), dried over sodium sulfate, filtered, and concentrated under reduced pressure.

[0267] Conditions 2 S_NAr : To a screw-cap vial equipped with a magnetic stir bar was added **A.4** or **C.5** (1.0 equiv), and amine (> 10 equiv) 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 (three 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.

[0268] Conditions 3 S_NAr : To a solution of **A.4** or **C.5** (1.0 equiv) in DMSO (0.40 M) was added amine (3.0 equiv) and DIEA (1.7 equiv) at 25 °C. The mixture was stirred at 100 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. 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 to give a residue.

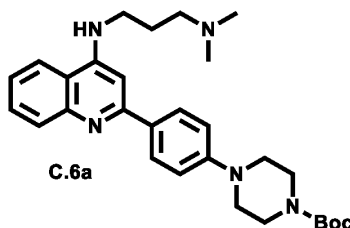
B.5a: *N*1-(2-chloroquinolin-4-yl)-*N*3, *N*3-dimethylpropane-1,3-diamine



B.5a

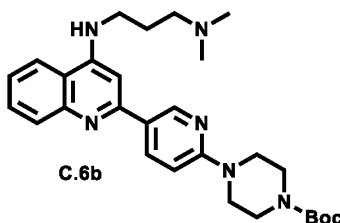
[0269] According to schemes 2 and 4, step4, conditions 2 S_NAr . 2,4-Dichloroquinoline (2.0 g, 0.01 mol, 1.0 equiv) was treated with *N*1, *N*1-dimethylpropane-1,3-diamine (9.7 g, 12 mL, 95 mmol, 9.0 equiv). The reaction was stirred at room temperature overnight. The crude material was divided in multiple fractions and purified by PuriFlash XS520Plus reversed phase (H₂O/ACN):0.1% FA = (97.5:2.5 to 90:10), PF-C18HP, 15 μm, 80g). Product **B.5a** (1.3 g, 4.9 mmol, 50 %) was isolated as a white solid and the regioisomer (0.86 g, 3.3 mmol, 30 %) was isolated as a yellow oil.

C.6a: *tert*-butyl 4-(4-(4-((3-(dimethylamino) propyl) amino) quinolin-2-yl) phenyl) piperazine-1-carboxylate



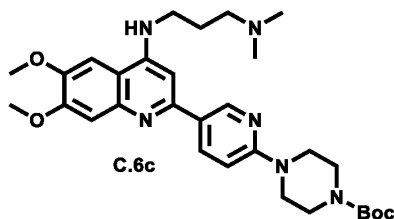
[0270] According to scheme 3, step 5, to a solution of C.5a (3.0 g, 7.1 mmol, 1.0 equiv), *N,N'*-dimethylpropane-1,3-diamine (2.2 g, 21 mmol, 2.7 mL, 3.0 equiv), [Pd(OAc)₂]₃ (0.16 g, 0.71 mmol, 0.10 equiv), BINAP (0.88 g, 1.4 mmol, 0.20 equiv) in 1,4-dioxane (30 mL) was added K₃PO₄ (3.0 g, 14 mmol, 2.0 equiv) at 20 °C. The reaction mixture was degassed and purged with nitrogen atmosphere three times. After stirring at 100 °C for 16 h under nitrogen atmosphere, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, PE/EtOAc = 10:1 to 1:1) to afford product C.6a (3.0 g, 4.6 mmol, 65% yield, 75% purity) as a yellow solid. MS *m/z* (ESI) [M+H]⁺ = 490.1.

C.6b: *tert*-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



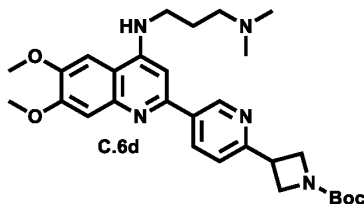
[0271] According to scheme 3, step 5, conditions 2 Buchwald. *Tert*-butyl 4-[5-(4-chloro-2-quinolyl) -2-pyridyl] piperazine-1-carboxylate **C.5b** (0.20 g, 0.47 mmol, 1.0 equiv). The crude product was purified by prep-HPLC 1 (B%: 18%-48%, 10 min) After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give compound **C.6b** (0.12 g, 0.24 mmol, 52% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) *d* (ppm): 8.42 (s, 1H) 8.06 (d, *J* = 9.2 Hz, 1H) 7.59 (s, 1H) 7.26 - 7.31 (m, 2H) 6.31 (br s, 1H) 4.13 (t, *J* = 6.4 Hz, 2H) 3.24 (br t, *J* = 6.8 Hz, 2H) 2.59 (t, *J* = 7.2 Hz, 2H) 2.49 (br d, *J* = 4 Hz, 4H) 2.39 (t, *J* = 6.8 Hz, 2H) 2.19 (s, 6H) 1.95 (br t, *J* = 6.8 Hz, 2H) 1.82 (quin, *J* = 6.8 Hz, 2H) 1.69 (dt, *J* = 6.4, 3.13 Hz, 4H).

C.6c: tert-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-6, 7-dimethoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



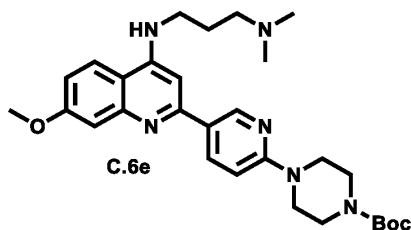
[0272] According to scheme 3, step 5, conditions 1 Buchwald. *Tert*-butyl 4-[5-(4-chloro-6, 7-dimethoxy-2-quinolyl) -2-pyridyl]piperazine-1-carboxylate **C.5c** (0.10 g, 0.21 mmol, 1.0 equiv). The reaction mixture was concentrated to give a residue. The filter liquor was purified by Prep-HPLC 4 (gradient: 1%-30%, 10 min). The elute was directly lyophilized to give compound **C.6c** (30 mg, 54 μ mol, 26% yield, N/A purity) as yellow solid. MS m/z (ESI) $[M+H]^+ = 551.4$.

C.6d: tert-butyl 3-[5-[4-[3-(dimethylamino) propylamino]-6,7-dimethoxy-2-quinolyl]-2-pyridyl] azetidine-1-carboxylate



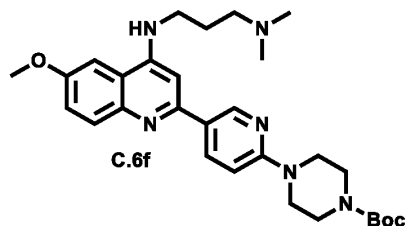
[0273] According to scheme 3, step 5, conditions 3 Buchwald. *Tert*-butyl 3-[5-(4-chloro-6,7-dimethoxy-2-quinolyl)-2-pyridyl] azetidine-1- carboxylate **C.5d** (0.18 g, 0.35 mmol, 1.0 equiv). The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC 1 (gradient: 11%-31% over 9 min) to give compound **C.6d** (0.11 g, 0.21 mmol, 64% yield, 100% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 522.3$.

C.6e: tert-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



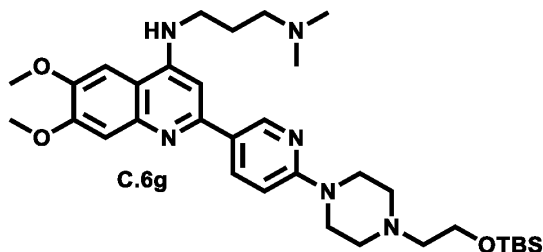
[0274] According to scheme 3, step 5, conditions 2 Buchwald. *Tert*-butyl 4-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate **C.5e** (0.15 g, 0.33 mmol, 1.0 equiv). The residue was purified by prep-HPLC 1 (gradient: 11%-41% over 10 min) to give compound **C.6e** (75 mg, 0.14 mmol, 43% yield, 98% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+ = 521.3$.

C.6f: *tert*-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-6-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



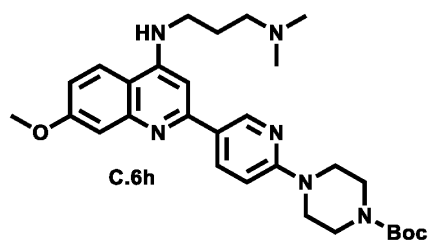
[0275] According to scheme 3, step 5, conditions 2 Buchwald. *Tert*-butyl 4-[5-(4-chloro-6-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate **C.5f** (0.30 g, 0.66 mmol, 1.0 equiv). Amine 1.0 equiv. The residue was purified by prep-HPLC 2 (gradient: 10%-40% over 10 min). Compound **C.6f** (0.21 g, 0.40 mmol, 60% yield, 98% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+ = 521.5$.

C.6g: *N*-[2-[6-[4-[2-[*tert*-butyl(dimethyl)silyl] oxyethyl] piperazin-1-yl]-3-pyridyl]-6,7-dimethoxy-4-quinolyl]-*N*', *N*'-dimethyl-propane-1,3-diamine



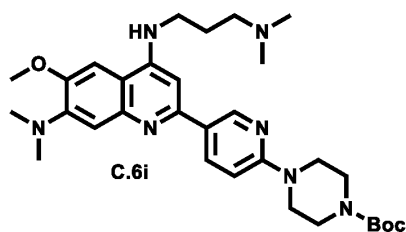
[0276] According to scheme 3, step 5, conditions 2 Buchwald. *Tert*-butyl-[2-[4-[5-(4-chloro-6,7-dimethoxy-2-quinolyl)-2-pyridyl] piperazin-1-yl] ethoxy]-dimethyl-silane **C.5ab** (0.18 g, 0.33 mmol, 1.0 equiv). The residue was purified by prep-HPLC 2 (gradient: 8%-38% over 10 min) to give compound **C.6g** (40 mg, 43 μ mol, 13% yield, 65% purity) was obtained as a yellow oil. MS m/z (ESI) $[M+H]^+ = 609.4$.

C.6h: *tert*-butyl 4-[5-[4-[3-(dimethylamino) propyl amino]-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



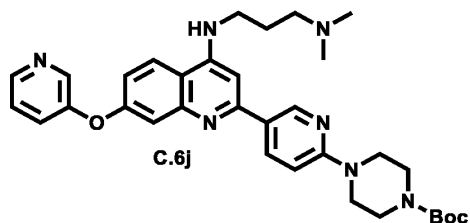
[0277] According to scheme 3, step 5, conditions 2 Buchwald. *Tert*-butyl 4-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate **C.5e** (0.30 g, 0.66 mmol, 1.0 equiv). The residue was purified by prep-HPLC 2 (gradient: 5%-35% over 10 min) to give compound **C.6h** (0.21 g, 0.40 mmol, 61% yield, 99% purity) was obtained as a yellow solid. MS *m/z* (ESI) $[M+H]^+ = 521.3$.

C.6i: *tert*-butyl 4-[5-[7-(dimethylamino)-4-[3-(dimethylamino) propylamino]-6-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



[0278] According to scheme 3, step 5, conditions 1 Buchwald. *Tert*-butyl 4-[5-[4-chloro-7-(dimethylamino)-6-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **C.5k** (0.16 g, 0.32 mmol, 1.0 equiv). The residue was purified by prep-HPLC 2 (gradient: 11%-41% over 10 min) to give compound **C.6i** (0.10 g, 0.18 mmol, 55% yield, 100% purity) as a yellow solid. MS (ESI) *m/z*. 564.4.

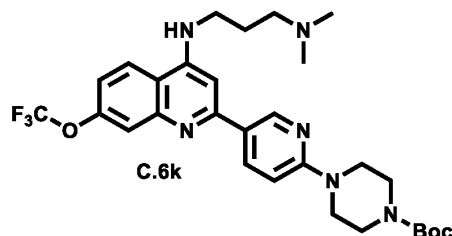
C.6j: *tert*-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-7-(3-pyridyloxy)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



[0279] According to scheme 3, step 5, conditions 2 Buchwald. *Tert*-butyl 4-[5-[4-chloro-7-(3-pyridyloxy)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **C.5m** (0.15 g, 0.29 mmol, 1.0

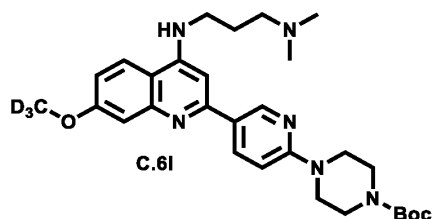
equiv). The filtrate was concentrated *in vacuo* to give compound **C.6j** (0.15 g, 0.26 mmol, 59% yield) as a white solid. MS *m/z* (ESI) $[M+H]^+ = 584.3$.

C.6k: *tert*-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-7-(trifluoromethoxy)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



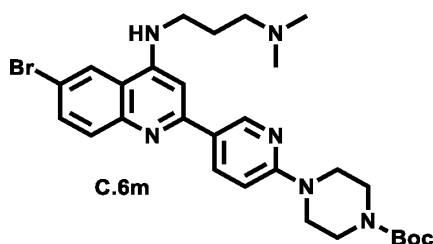
[0280] According to scheme 3, step 5, conditions 1 Buchwald. 4-[5-[4-chloro-7-(trifluoromethoxy)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **C.5p** (0.41 g, 0.81 mmol, 1.0 equiv). The residue was purified by flash silica gel chromatography (40 g, Eluent of 0~10% EtOAc/PE gradient at 40 mL/min) to afford compound **C.6k** (0.23 g, 0.38 mmol, 47% yield, 95% purity) as yellow oil. MS *m/z* (ESI) $[M+H]^+ = 575.3$.

C.6l: *tert*-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-7-(trideuteriomethoxy)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



[0281] According to scheme 3, step 5, conditions 1 Buchwald. *tert*-butyl 4-[5-[4-chloro-7-(trideuteriomethoxy)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **C.5r** (0.22 g, 0.45 mmol, 1.0 equiv). BrettPhos Pd G4 (0.10 equiv). No work-up, only filtration. The reaction mixture was diluted with methanol (5.0 mL) and then the reaction mixture was filtered, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (PE/EtOAc = 0:1) to give compound **C.6l** (0.18 g, 0.27 mmol, 61% yield, 79% purity) as a yellow solid. MS *m/z* (ESI) $[M+H]^+ = 524.3$.

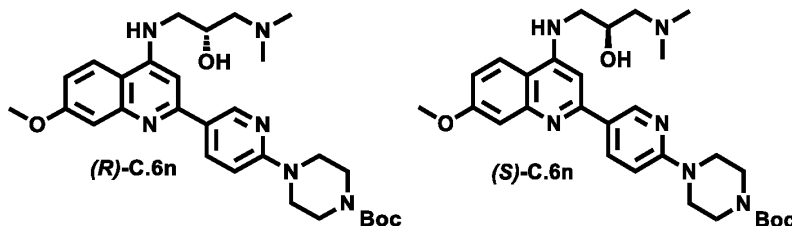
C.6m: *tert*-butyl 4-[5-[6-bromo-4-[3-(dimethylamino) propylamino]-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



[0282] According to scheme 3, step 5, conditions 1 S_NAr . *tert*-butyl 4-[5-(6-bromo-4-chloro-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate **C.5g** (1.9 g, 3.8 mmol, 1.0 equiv). Compound **C.6m** (1.9 g, 3.0 mmol, 80% yield, 90% purity) as a white solid. MS m/z (ESI) $[M+H]^+ = 571.2$.

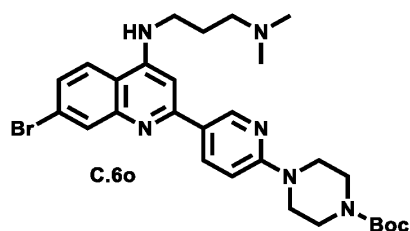
(R)-C.6n: *tert*-butyl 4-[5-[4-[(2*S*)-3-(dimethylamino)-2-hydroxy-propyl] amino]-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate AND

(S)-C.6n: *tert*-butyl (S)-4-(5-(4-((3-(dimethylamino)-2-hydroxypropyl) amino)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazine-1-carboxylate



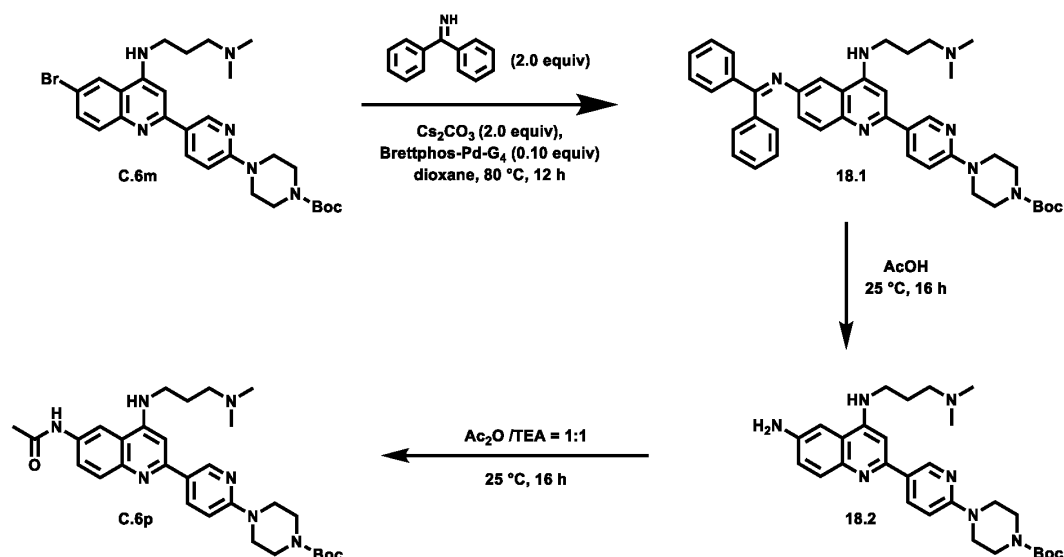
[0283] According to scheme 3, step 5, conditions 1 S_NAr . *tert*-butyl 4-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate **C.5e** (0.40 g, 0.62 mmol, 1.0 equiv). The residue was purified by prep-HPLC 2 (gradient: 10%-40% over 10 min). The residue was further separated by SFC (B: 60%, isocratic elution mode) to give **(S)-C.6n** (40 mg, 75 μ mol, 12% yield, 100% purity) as a yellow gum and give **(R)-C.6n** (60 mg, 0.11 mmol, 18% yield, 100% purity) as a yellow gum. **(S)-C.6n:** MS m/z (ESI) $[M+H]^+ = 537.5$. **(R)-C.6n:** MS m/z (ESI) $[M+H]^+ = 537.5$.

C.6o: *tert*-butyl 4-[5-[7-bromo-4-[3-(dimethylamino) propylamino]-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



[0284] According to scheme 3, step 5, conditions 2 S_NAr . *tert*-butyl 4-[5-(7-bromo-4-chloro-2-quinolyl)-2-pyridyl] piperazine-1-carboxylate **C.5w** (0.92 g, 1.5 mmol, 1.0 equiv). N' , N' -dimethylpropane-1,3-diamine (31 equiv). The residue was purified by prep-HPLC 2 (gradient: 6%-36% over 10 min) to give compound **C.6o** (0.45 g, 0.74 mmol, 51% yield, 94% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+ = 571.0$.

C.6p: *tert*-butyl 4-[5-[6-acetamido-4-[3-(dimethylamino) propylamino]-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



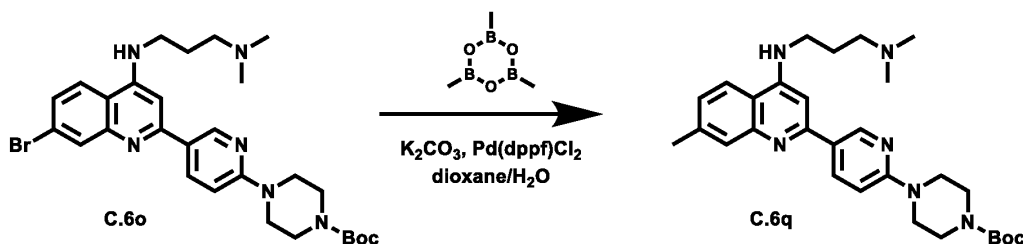
[0285] To a solution of *tert*-butyl 4-[5-[6-bromo-4-[3-(dimethylamino)propylamino]-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate **C.6m** (1.7 g, 3.0 mmol, 1.0 equiv), diphenylmethanimine (2.7 g, 15 mmol, 2.5 mL, 5.0 equiv) in dioxane (20 mL) was added cesium carbonate (2.0 g, 6.0 mmol, 2.0 equiv) and [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;(5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenylphosphane (0.28 g, 0.30 mmol, 0.10 equiv) at 25 °C. After stirring at 80 °C for 16 h, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , PE/EtOAc = 0:1, then EtOAc/MeOH = 10:1) to

give *tert*-butyl 4-[5-[6-(benzhydrylideneamino)-4-[3-(dimethylamino) propylamino]-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **18.1** (1.5 g, 1.6 mmol, 53% yield, 70% purity) as a yellow solid. MS *m/z* (ESI) $[M+H]^+ = 670.4$.

[0286] A solution of **18.1** (0.20 g, 0.30 mmol, 1.0 equiv) in AcOH (0.52 g, 8.7 mmol, 0.50 mL, 29 equiv) was stirred at 25 °C for 16 h, the mixture was used as such for the next step (no work-up). MS *m/z* (ESI) $[M+H]^+ = 506.3$ (**18.2**).

[0287] To a solution of *tert*-butyl 4-[5-[6-amino-4-[3-(dimethylamino) propylamino]-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **18.2** (0.10 g, 0.20 mmol, 1.0 equiv) in acetic acid (0.50 mL) was added acetic anhydride (0.54 g, 5.3 mmol, 0.50 mL, 27 equiv) and triethylamine (0.36 g, 3.6 mmol, 0.50 mL, 18 equiv) at 25 °C. After stirring at 25 °C for 1.5 h, the reaction mixture was filtered to give a solution. The solution was purified by prep-HPLC (FA condition) to give *tert*-butyl 4-[5-[6-acetamido-4-[3-(dimethylamino) propylamino]-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **C.6p** (80 mg, 0.13 mmol, 66% yield, 90% purity) as a yellow solid. MS *m/z* (ESI) $[M+H]^+ = 548.3$.

C.6q: *tert*-butyl 4-(5-(4-((3-(dimethylamino) propyl) amino)-7-methylquinolin-2-yl) pyridin-2-yl) piperazine-1-carboxylate

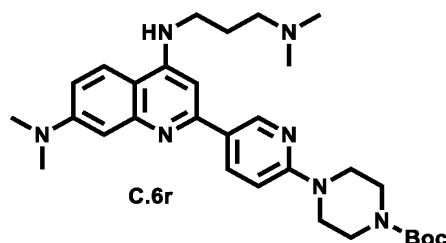


[0288] To a solution of *tert*-butyl 4-[5-[7-bromo-4-[3-(dimethylamino)propylamino]-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate **C.6o** (0.30 g, 0.53 mmol, 1.0 equiv) in dioxane (5.0 mL) /H₂O (1.0 mL) was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (3.5 M, 0.34 mL, 2.3 equiv), Pd(dppf)Cl₂ (40 mg, 55 μmol, 0.10 equiv) and K₂CO₃ (0.22 g, 1.6 mmol, 3.0 equiv) at 20 °C. The mixture was degassed and purged with N₂ three times, and then the mixture was stirred at 90 °C for 4 h under N₂ atmosphere. The reaction was poured into water (100 mL), extracted with EtOAc (50 mL, three times). The combined organic phase was washed with saturated brine (50 mL, twice), dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by prep-HPLC 2 (gradient: 8%-38% B over 10 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give *tert*-butyl 4-[5-[4-[3-

(dimethylamino) propylamino]-7-methyl-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate

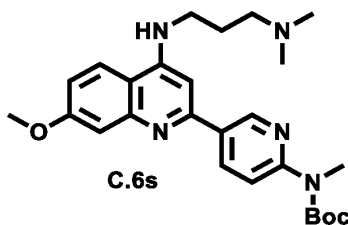
C.6q (0.11 g, 0.22 mmol, 41% yield, 99% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 505.3$.

C.6r: tert-butyl 4-[5-[7-(dimethylamino)-4-[3-(dimethylamino) propylamino]-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



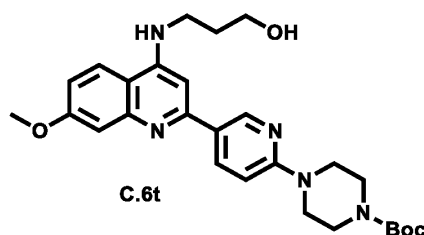
[0289] According to scheme 3, step 5, to a solution of tert-butyl 4-[5-[4-chloro-7-(dimethylamino)-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate **C.5n** (0.27 g, 0.58 mmol, 1.0 equiv) in DMSO (2.0 mL) was added CsF (0.18 g, 1.2 mmol, 43 μ L, 2.0 equiv) and N',N'-dimethylpropane-1,3-diamine (1.6 g, 16 mmol, 2.0 mL, 28 equiv) at 25 °C. After stirring at 130 °C for 16 h, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (gradient: 12%-42% over 10 min) to give **C.6r** (0.15 g, 0.27 mmol, 46% yield, 95% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 534.3$.

C.6s: tert-butyl N-[5-[4-[3-(dimethylamino) propylamino]-7-methoxy-2-quinolyl]-2-pyridyl]-N-methylcarbamate



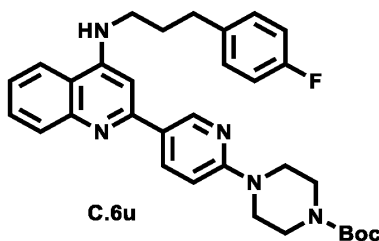
[0290] According to scheme 3, step 5, to a solution of tert-butyl N-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl]-N-methyl-carbamate **C.5g** (0.30 g, 0.75 mmol, 1.0 equiv), N', N'-dimethylpropane-1, 3-diamine (0.10 g, 0.98 mmol, 0.12 mL, 1.3 equiv) in dioxane (4.0 mL) was added Pd(*t*-Bu₃P)₂ (40 mg, 78 μ mol, 0.10 equiv) and *t*-BuONa (0.15 g, 1.6 mmol, 2.1 equiv). The mixture was degassed and purged with N₂ three times, and then the mixture was stirred at 80 °C for 12 h under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give **C.6s** (0.30 g, crude) as a yellow solid.

C.6t: tert-butyl 4-[5-[4-(3-hydroxypropylamino)-7-methoxy-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate



[0291] According to scheme 3, step 5, to a solution of tert-butyl 4-[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl]piperazine-1-carboxylate (0.20 g, 0.44 mmol, 1.0 equiv) in dioxane (6.0 mL) was added 3-aminopropan-1-ol (0.10 g, 1.3 mmol, 0.10 mL, 3.0 equiv), Pd(*t*-Bu₃P)₂ (30 mg, 59 μmol, 0.10 equiv), *t*-BuONa (0.15 g, 1.6 mmol, 3.6 equiv), then the resulting mixture was purged with N₂ for three times and stirred at 80 °C for 12 h. The reaction mixture was partitioned between EtOAc (0.15 L) and water (80 mL), washed with brine (70 mL), dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography **2** (20 g column, Eluent of 0~30% EtOAc/PE gradient at 40 mL/min) to give **C.6t** (0.17 g, 0.31 mmol, 71% yield, 90% purity) as a yellow solid. MS *m/z* (ESI) [M+H]⁺ = 494.3.

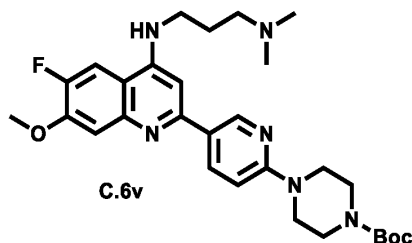
C.6u: tert-butyl 4-[5-[4-[3-(4-fluorophenyl)propylamino]-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate



[0292] According to scheme 3, step 5, a mixture of tert-butyl 4-[5-(4-chloro-2-quinolyl)-2-pyridyl]piperazine-1-carboxylate (0.10 g, 0.19 mmol, 1.0 equiv), 3-(4-fluorophenyl)propan-1-amine (29 mg, 0.19 mmol, 1.0 equiv), *t*-BuONa (54 mg, 0.56 mmol, 3.0 equiv), BrettPhos-Pd-G3 (17 mg, 19 μmol, 0.10 equiv) in dioxane (0.10 mL) was degassed and purged with N₂ three times at 25 °C, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The reaction mixture was extracted with ethyl acetate (30 mL, three times). The combined organic layer was washed with saturated salt water (30 mL), dried on anhydrous Na₂SO₄, filtered, and reduced pressure concentrated. The residue was purified by prep-TLC (SiO₂,

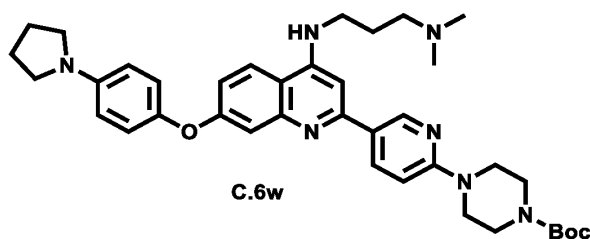
PE/EtOAc = 0:1). The residue was purified by prep-TLC (SiO₂, PE/EA = 0:1) to give **C.6u** (80 mg, 0.15 mmol, 78% yield) as a yellow solid. MS *m/z* (ESI) [M+H]⁺ = 542.3.

C.6v: tert-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



[0293] According to scheme 3, step 5, to a solution of tert-butyl 4-[5-(4-chloro-6-fluoro-7-methoxy-2-quinolyl)-2-pyridyl]piperazine-1-carboxylate **C.5g** (0.40 g, 0.85 mmol, 1.0 equiv) in DMSO (5.0 mL) was added N',N'-dimethylpropane-1,3-diamine (0.12 g, 1.2 mmol, 0.15 mL, 1.4 equiv) and TEA (0.29 g, 2.9 mmol, 0.40 mL, 3.4 equiv). The reaction mixture was stirred at 120 °C for 12 h. The residue was partitioned between EtOAc (50 mL) and water (50 mL). The organic phase was washed by sat. NaCl (50 mL). The combined organic layers were dried over (Na₂SO₄) and evaporated to give **C.6v** (0.90 g, 0.82 mmol, 97% yield) which was used for next step without further purification.

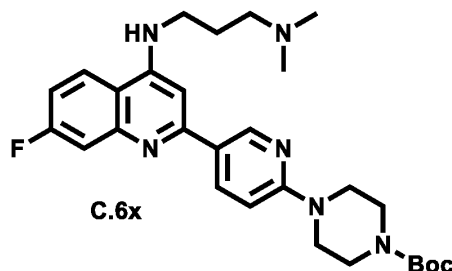
C.6w: tert-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-7-(4-pyrrolidin-1-ylphenoxy)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



[0294] According to scheme 3, step 5, to a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 4-[5-[4-chloro-7-(4-pyrrolidin-1-ylphenoxy)-2-quinolyl]-2-pyridyl]piperazine-1-carboxylate **C.5h** (0.46 g, 0.78 mmol, 1.0 equiv) and dioxane (10 mL) and N', N'-dimethylpropane-1, 3-diamine (0.12 g, 1.2 mmol, 1.5 equiv) and *t*-BuONa (0.23 g, 2.4 mmol, 3.0 equiv) and Pd(*t*-Bu₃P)₂ (40 mg, 78 μmol, 0.10 equiv) 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 h under nitrogen atmosphere. The reaction mixture was quenched by water (20 mL), and then the resulting organic phase was extracted with ethyl acetate (20 mL, twice). The combined organic layers were washed with brine (20 mL), dried

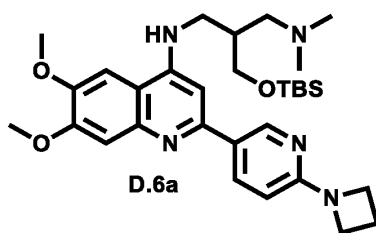
over Na₂SO₄, filtered and the filtrate was concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (EtOAc/MeOH) to afford **C.6w** (0.26 g, 0.40 mmol, 51% yield) as yellow solid.

C.6x: tert-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-7-fluoro-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate



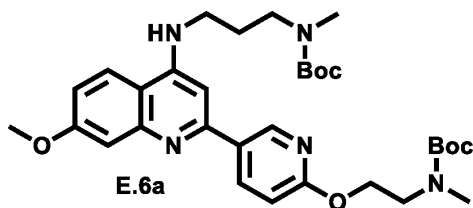
[0295] According to scheme 3, step 5, a mixture of **C.5I** (0.33 g, 0.75 mmol, 1.0 equiv), N',N'-dimethylpropane-1,3-diamine (90 mg, 0.88 mmol, 0.11 mL, 1.2 equiv), Pd(*t*-Bu₃P)₂ (38 mg, 74 μmol, 0.10 equiv), sodium 2-methylpropan-2-olate (0.22 g, 2.2 mmol, 3.0 equiv) in dioxane (3.0 mL) was degassed and purged with N₂ three times at 25 °C, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with water (30 mL) and extracted with ethyl acetate (40 mL, three times). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give **C.6x** (0.45 g, crude) as yellow gum. MS *m/z* (ESI) [M+H]⁺ = 509.3.

D.6a: N-[2-[6-(azetidin-1-yl)-3-pyridyl]-6,7-dimethoxy-4-quinolyl]-2-[tert-butyl (dimethyl)silyl]oxymethyl]-N',N'-dimethyl-propane-1,3-diamine



[0296] According to scheme 5, step 5, conditions 1 Buchwald. 2-[[*Tert*-butyl (dimethyl)silyl]oxymethyl]-N',N'-dimethyl-propane-1,3-diamine **C.5c** (50 mg, 0.20 mmol, 1.0 equiv). The residue was purified by prep-HPLC 3 (gradient: 3-10 min 21-51%). Compound **D.6a** (80 mg, 0.14 mmol, 70% yield) was obtained as a yellow solid. MS *m/z* (ESI) [M+H]⁺ = 566.4.

E.6a: *tert*-butyl *N*-[3-[[2-[6-[2-[*tert*-butoxycarbonyl(methyl)amino] ethoxy]-3-pyridyl]-7-methoxy-4-quinolyl] amino] propyl]-*N*-methylcarbamate



[0297] According to scheme 6, step 5, conditions 2 Buchwald. *Tert*-butyl *N*-[2-[[5-(4-chloro-7-methoxy-2-quinolyl)-2-pyridyl] oxy] ethyl]-*N*-methyl-carbamate **C.5aa** (0.20 g, 0.45 mmol, 1.0 equiv). The reaction mixture was filtered and concentrated under reduced pressure to give the residue. The residue was purified by prep-HPLC 2 (gradient: 25%-55% over 10 min). The eluent was lyophilized to give compound **E.6a** (0.13 g, 0.20 mmol, 44% yield, 90% purity) as a brown gum.

Synthesis of Final Products

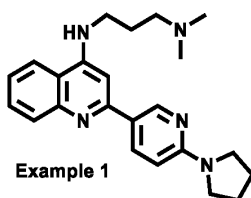
[0298] Final products from Suzuki coupling (Scheme 2; step 5), Buchwald coupling or SNAr (Scheme 1; step 5) – See above protocols.

[0299] Final products from deprotection step (Schemes 3, 4, 5 and 6; step 6) – Protocols below

[0300] Conditions 1 HCl. To a solution of substrate **C.6** or **D.6** or **E.6** (1.0 equiv) in dioxane (0.06M) was added HCl/dioxane (> 20 equiv). The mixture was stirred at 25 °C for 2 h. The mixture was concentrated to give a residue.

[0301] Conditions 2 TFA. To a solution of substrate **C.6** or **D.6** or **E.6** (1.0 equiv) in DCM (0.15M) was added TFA (> 10 equiv) at 25 °C. After stirring at 25 °C for 4 h, the reaction mixture was filtered and concentrated under reduced pressure to give a residue.

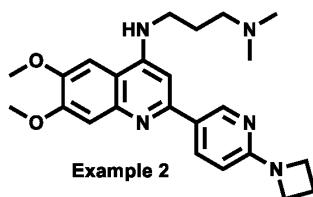
Example 1: *N*¹,*N*¹-dimethyl-*N*³-(2-(6-(pyrrolidin-1-yl) pyridin-3-yl) quinolin-4-yl) propane-1,3-diamine



[0302] According to scheme 2, step 5, quinoline **B.5a** (70 mg, 0.27 mmol, 1.0 equiv), 2-(pyrrolidin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (87 mg, 0.32

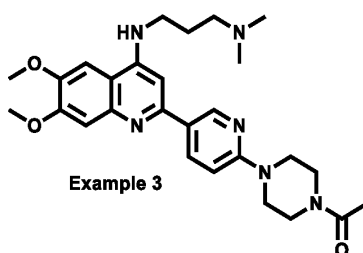
mmol, 1.2 equiv), XPhos Pd G2 (10 mg, 13 μ mol, 0.05 equiv), and K_2CO_3 (73 mg, 0.53 mmol, 2.0 equiv) were suspended in MeOH (2.7 mL) and heated to 65 °C for two days, not fully converted. XPhos Pd G2 (10 mg, 13 μ mol, 0.05 equiv) and potassium carbonate (73 mg, 0.53 mmol, 2.0 equiv) were added and the reaction was stirred for another day. The crude was concentrated and purified by prep-HPLC 6 and then 7 to give **Example 1** (35 mg, 93 μ mol, 35 %) as a yellow solid.

Example 2: *N*¹-(2-(6-(azetidin-1-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine



[0303] According to scheme 1, step 5, conditions 2 Buchwald. Substrate **A.5a** (80 mg, 0.22 mmol, 1.0 equiv) *N*¹, *N*¹-dimethylpropane-1,3-diamine (28 mg, 0.27 mmol, 34 μ L, 1.2 equiv). The residue was purified by prep-HPLC 2 (gradient: 1%-30% over 10 min) to give **Example 2** (40 mg, 86 μ mol, 38% yield, 100% purity, FA) was obtained as a yellow solid. Then the crude product was purified with SCX (see general protocol). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.83 (d, *J* = 2.0 Hz, 1H), 8.26 (dd, *J* = 2.3, 8.7 Hz, 1H), 7.41 (s, 1H), 7.19 (s, 1H), 7.10 (d, *J* = 4.5 Hz, 1H), 6.78 (s, 1H), 6.43 (d, *J* = 8.6 Hz, 1H), 4.00 (t, *J* = 7.4 Hz, 4H), 3.89 (d, *J* = 1.3 Hz, 6H), 3.43 - 3.38 (m, 2H), 2.43 (t, *J* = 6.8 Hz, 2H), 2.38 - 2.31 (m, 2H), 2.23 (s, 6H), 1.85 (q, *J* = 6.8 Hz, 2H). MS *m/z* (ESI) [*M*+*H*]⁺ = 422.2.

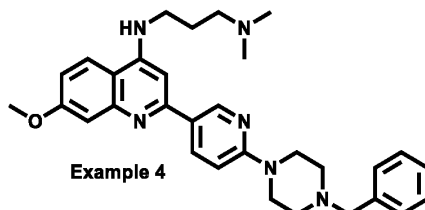
Example 3: 1-(4-(5-(4-((3-(dimethylamino) propyl) amino)-6,7-dimethoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-one



[0304] According to scheme 1, step 5, conditions 2 Buchwald. Substrate **A.5b** (0.10 g, 0.23 mmol, 1.0 equiv). The residue was purified by prep-HPLC 2 (gradient: 1%-30% over 10 min) to give **Example 3** (40 mg, 74 μ mol, 32% yield, 100% purity, FA) was obtained as a yellow solid. Then the salt was neutralized with SCX (see general protocol). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.90 (d, *J* = 2.2 Hz, 1H), 8.32 (dd, *J* = 2.3, 8.9 Hz, 1H), 7.43 (s, 1H),

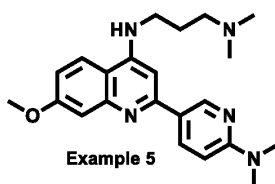
7.20 (s, 1H), 7.11 (s, 1H), 6.94 (d, $J = 8.9$ Hz, 1H), 6.82 (s, 1H), 3.89 (d, $J = 1.1$ Hz, 6H), 3.64 (d, $J = 3.1$ Hz, 2H), 3.57 (s, 6H), 3.41 (s, 2H), 2.46 (t, $J = 6.8$ Hz, 2H), 2.25 (s, 6H), 2.06 (s, 3H), 1.86 (q, $J = 7.0$ Hz, 2H). MS m/z (ESI) $[M+H]^+ = 493.3$.

Example 4: *N*¹-(2-(6-(4-benzylpiperazin-1-yl) pyridin-3-yl)-7-methoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine



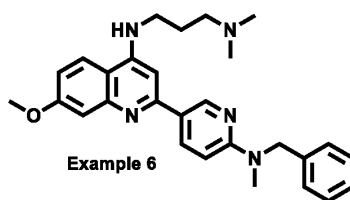
[0305] According to scheme 1, step 5, conditions 2 Buchwald. Substrate **A.5c** (0.10 g, 0.17 mmol, 1.0 equiv). The crude product was triturated with MeOH (20 mL) at 25 °C for 40 min to give **Example 4** (69 mg, 0.13 mmol, 76% yield, 98% purity) was obtained as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.91 (d, $J = 2.1$ Hz, 1H), 8.31 (dd, $J = 2.3$, 8.9 Hz, 1H), 8.01 (d, $J = 9.1$ Hz, 1H), 7.35 (d, $J = 4.3$ Hz, 4H), 7.30 - 7.24 (m, 1H), 7.23 - 7.16 (m, 2H), 6.98 (dd, $J = 2.6$, 9.1 Hz, 1H), 6.90 (d, $J = 9.0$ Hz, 1H), 6.79 (s, 1H), 3.88 (s, 3H), 3.62 - 3.56 (m, 4H), 3.53 (s, 2H), 3.41 - 3.36 (m, 2H), 2.49 - 2.46 (m, 4H), 2.37 (t, $J = 6.8$ Hz, 2H), 2.18 (s, 6H), 1.82 (t, $J = 6.8$ Hz, 2H). MS m/z (ESI) $[M+H]^+ = 511.3$.

Example 5: *N*¹-(2-(6-(4-benzylpiperazin-1-yl) pyridin-3-yl)-7-methoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine



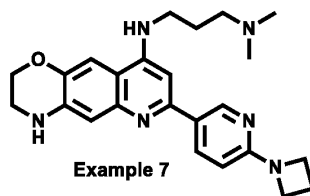
[0306] According to scheme 1, step 5, conditions 2 Buchwald. Substrate **A.5d** (0.15 g, 0.48 mmol, 1.0 equiv). The residue was purified by prep-TLC (SiO₂, DCM/MeOH = 10:1 (NH₃·H₂O), then, DCM/MeOH = 5:1 (NH₃·H₂O) to give **Example 5** (0.11 g, 0.28 mmol, 59% yield, 99% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.90 (d, $J = 2.4$ Hz, 1H), 8.30 (dd, $J = 8.9$, 2.4 Hz, 1H), 8.02 (d, $J = 9.1$ Hz, 1H), 7.24 (s, 1H), 7.18 (d, $J = 2.6$ Hz, 1H), 6.99 (dd, $J = 9.1$, 2.6 Hz, 1H), 6.80 (s, 1H), 6.73 (d, $J = 9.0$ Hz, 1H), 3.88 (s, 3H), 3.41 (d, $J = 5.6$ Hz, 2H), 3.10 (s, 6H), 2.45 (t, $J = 6.8$ Hz, 2H), 2.24 (s, 6H), 1.84 (q, $J = 6.9$ Hz, 2H). MS m/z (ESI) $[M+H]^+ = 380.2$.

Example 6: *N*¹-(2-(6-(benzyl(methyl)amino) pyridin-3-yl)-7-methoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine

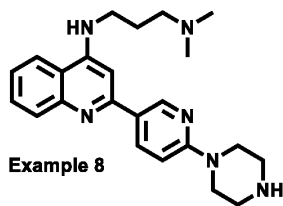


[0307] According to scheme 1, step 5, conditions 2 Buchwald. Substrate **A.5e** (0.10 g, 0.26 mmol, 1.0 equiv); Amine (16 equiv). The reaction mixture was filtered and concentrated under reduced pressure to give residue. The residue was purified by prep-TLC (Plate 1 DCM/MeOH = 10:1) to give **Example 6** (25 mg, 54 μ mol, 21% yield, 99% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.91 (d, *J* = 2 Hz, 1H), 8.30 (dd, *J* = 2.4, 8.8 Hz, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.35 - 7.30 (m, 2H), 7.27 - 7.21 (m, 3H), 7.20 - 7.15 (m, 2H), 6.97 (dd, *J* = 2.6, 9.2 Hz, 1H), 6.81 - 6.73 (m, 2H), 4.88 (s, 2H), 3.87 (s, 3H), 3.43 - 3.37 (m, 2H), 3.10 (s, 3H), 2.36 (t, *J* = 6.8 Hz, 2H), 2.17 (s, 6H), 1.81 (t, *J* = 6.8 Hz, 2H). MS *m/z* (ESI) [*M*+*H*]⁺ = 456.3.

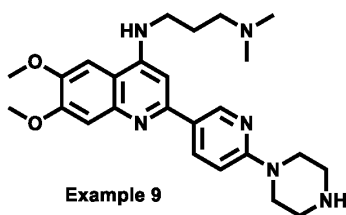
Example 7: *N*¹-(2-(6-(azetidin-1-yl) pyridin-3-yl)-7-fluoro-6-methoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine



[0308] According to scheme 1, step 5, conditions 1 Buchwald. Substrate **A.5g** (60 mg, 0.17 mmol, 1.0 equiv). The residue was purified by prep-HPLC 2 (gradient: 2%-32% over 10 min). The residue was purified by strong cation exchange resin SCX (see general protocol) to give **Example 7** (38 mg, 91 μ mol, 54% yield, 100% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.74 (d, *J* = 2.4 Hz, 1H), 8.15 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.41 (s, 1H), 7.25 - 7.12 (m, 1H), 6.87 (s, 1H), 6.70 (s, 1H), 6.59 (s, 1H), 6.43 (d, *J* = 8.8 Hz, 1H), 4.20 (t, *J* = 4.0 Hz, 2H), 4.01 (t, *J* = 7.6 Hz, 4H), 3.38 (d, *J* = 4.4 Hz, 4H), 2.36 (q, *J* = 6.8 Hz, 4H), 2.18 (s, 6H), 1.82- 1.75 (m, 2H). MS *m/z* (ESI) [*M*+*H*]⁺ = 419.2.

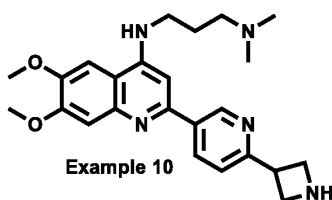
Example 8: *N*¹,*N*¹-dimethyl-*N*³-(2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)propane-1,3-diamine

[0309] According to scheme 3, step 6, conditions 1 HCl. Substrate **C.6b** (0.10 g, 0.20 mmol, 1.0 equiv) in EtOH (2.0 mL). Neutralization was done using SCX (see general protocol). After Lyophilization, **Example 8** (25 mg, 64 μ mol, 31% yield, 100% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, methanol-*d*₄) δ (ppm): 8.66 - 8.63 (m, 1H), 8.11 - 8.06 (m, 1H), 7.96 - 7.91 (m, 1H), 7.81 - 7.76 (m, 1H), 7.57 - 7.50 (m, 1H), 7.34 - 7.28 (m, 1H), 6.85 - 6.80 (m, 1H), 6.72 - 6.68 (m, 1H), 3.56 - 3.49 (m, 4H), 3.44 - 3.37 (m, 2H), 3.25 - 3.17 (m, 6H), 2.89 - 2.82 (m, 4H), 2.46 - 2.40 (m, 2H), 1.93 - 1.84 (m, 2H). MS *m/z* (ESI) [M+H]⁺ = 391.3.

Example 9: *N*¹-(6,7-dimethoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine

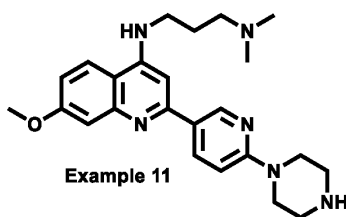
[0310] According to scheme 3, step 6, conditions 1 HCl. Substrate **C.6c** (30 mg, 54 μ mol, 1.0 equiv) in MeOH (0.50 mL). The filter liquor was purified by Prep-HPLC 2 (gradient: 8%-38% B over 9 min). The elute was directly lyophilized to give Example 9 (20 mg, 45 μ mol, 82% yield, 100% purity) as off-white solid. ¹H NMR (400 MHz, methanol-*d*₄) δ (ppm) : 8.84 (d, *J* = 2.4 Hz, 1H), 8.52 (dd, *J* = 2.4, 9.4 Hz, 1H), 7.84 (s, 1H), 7.48 - 7.43 (m, 2H), 7.09 (s, 1H), 4.13 - 4.10 (m, 4H), 4.07 (s, 3H), 4.05 (s, 3H), 3.83 (t, *J* = 7.1 Hz, 2H), 3.49 - 3.46 (m, 4H), 3.40 - 3.36 (m, 2H), 2.94 (s, 6H), 2.34 - 2.27 (m, 2H). MS *m/z* (ESI) [M+H]⁺ = 451.3.

Example 10: *N*¹-(2-(6-(azetidin-3-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine



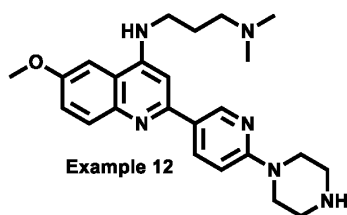
[0311] According to scheme 3, step 6, conditions 1 HCl. Substrate **C.6d** (0.10 g, 0.19 mmol, 1.0 equiv) in HCl/MeOH (4.0 M, 10 mL). After lyophilization, **Example 10** (70 mg, 0.16 mmol, 86% yield, 99% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) : 14.32 (s, 1H), 10.96 (s, 1H), 9.96 (d, *J* = 6.1 Hz, 1H), 9.75 - 9.64 (m, 1H), 9.62 - 9.49 (m, 1H), 9.40 (d, *J* = 2.0 Hz, 1H), 8.75 - 8.65 (m, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.08 (s, 1H), 4.47 - 4.35 (m, 1H), 4.32 - 4.18 (m, 4H), 3.98 (s, 3H), 3.89 (s, 3H), 3.75 (d, *J* = 5.6 Hz, 2H), 3.30 - 3.15 (m, 2H), 2.76 (d, *J* = 4.8 Hz, 6H), 2.26 - 2.11 (m, 2H). MS *m/z* (ESI) [M+H]⁺ = 422.2.

Example 11: *N*¹-(7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine



[0312] According to scheme 3, step 6, conditions 1 HCl. Substrate **C.6e** (75 mg, 0.14 mmol, 1.0 equiv). The residue was purified by prep-HPLC 1 (gradient: 8%-38% over 10 min) to give **Example 11** (23 mg, 54 μmol, 38% yield, 100% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) : 13.76 (s, 1H), 10.94 (s, 1H), 9.71 (s, 2H), 9.49 - 9.41 (m, 1H), 8.99 (s, 1H), 8.63 (d, *J* = 9.4 Hz, 1H), 8.50 (d, *J* = 9.3 Hz, 1H), 7.92 (s, 1H), 7.30 - 7.22 (m, 1H), 7.16 (d, *J* = 9.3 Hz, 1H), 7.01 (s, 1H), 3.98 (s, 4H), 3.92 (s, 3H), 3.75 (d, *J* = 5.8 Hz, 2H), 3.19 (s, 6H), 2.74 (d, *J* = 4.8 Hz, 6H), 2.20 - 2.10 (m, 2H). MS *m/z* (ESI) [M+H]⁺ = 421.2.

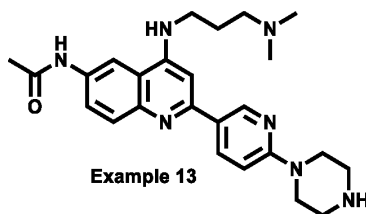
Example 12: *N*¹-(6-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine



[0313] According to scheme 3, step 6, conditions 1 HCl. Substrate **C.6f** (0.20 g, 0.38 mmol, 1.0 equiv). The residue was purified by prep-HPLC 1 (gradient: 9%-39% over 10 min).

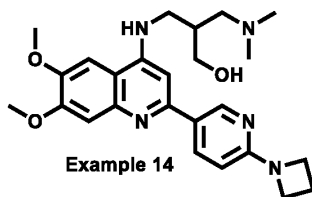
Example 12 (0.13 g, 0.32 mmol, 83% yield, 100% purity) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) : 13.97 (s, 1H), 10.91 (br s, 1H), 9.73 (br s, 2H), 9.60 (br t, *J* = 5.6 Hz, 1H), 8.98 (d, *J* = 2.8 Hz, 1H), 8.49 (dd, *J* = 9.2, 2.5 Hz, 1H), 8.35 (d, *J* = 9.6 Hz, 1H), 8.20 (d, *J* = 2.4 Hz, 1H), 7.56 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.15 (d, *J* = 9.2 Hz, 1H), 7.05 (s, 1H), 3.99 - 3.94 (m, 7H), 3.78 (q, *J* = 6.4 Hz, 2H), 3.25 - 3.21 (m, 2H), 3.21 - 3.15 (m, 4H), 2.76 (d, *J* = 5.2 Hz, 6H), 2.18 (quin, *J* = 7.6 Hz, 2H). MS *m/z* (ESI) [*M*+*H*]⁺ = 421.3.

Example 13: *N*-(4-((3-(dimethylamino) propyl) amino)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-6-yl) acetamide



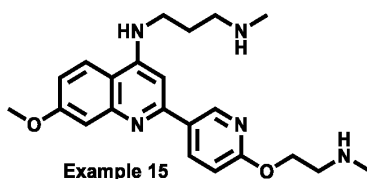
[0314] According to schemes 3 and 4, step 6, conditions 2 TFA. Substrate **C.6p** (50 mg, 91 mmol, 1.0 equiv). The residue was purified by prep-HPLC 2 to give **Example 13** (29 mg, 63 μ mol, 69% yield, 97% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) : 10.16 (s, 1H), 8.97 (d, *J* = 1.9 Hz, 1H), 8.30 - 8.48 (m, 2H), 8.20 (s, 2H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.61 (br d, *J* = 8.9 Hz, 1H), 7.34 - 7.50 (m, 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 6.91 (s, 1H), 3.79 (s, 4H), 3.48 (s, 2H), 3.19 (s, 4H), 2.87 (t, *J* = 6.5 Hz, 2H), 2.56 (s, 6H), 2.11 (s, 3H), 1.90 - 2.02 (m, 2H). MS *m/z* (ESI) [*M*+*H*]⁺ = 448.2.

Example 14: 3-((2-(6-(azetidin-1-yl) pyridin-3-yl)-6,7-dimethoxyquinolin-4-yl) amino)-2-((dimethylamino)methyl) propan-1-ol



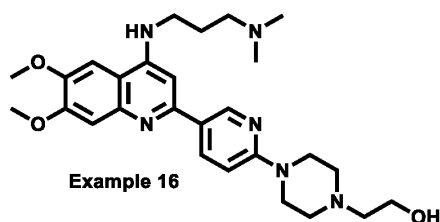
[0315] According to scheme 5, step 6, conditions 1 HCl. Substrate **D.6a** (75 mg, 0.13 mmol, 1.0 equiv) in EtOAc (1.0 mL). At 0 °C for 1 h. The residue was purified by prep-HPLC 8 (gradient: 2-9 min 0-30% ACN). Then the product was purified with SCX (see general protocol). **Example 14** (24 mg, 53 μmol, 65% yield, 99% purity) was obtained as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) : 8.83 - 8.82 (m, 1H), 8.25 - 8.25 (m, 1H), 7.43 - 7.42 (m, 1H), 7.38 (s, 1H), 7.19 (s, 1H), 6.87 (s, 1H), 6.44 - 6.42 (m, 1H), 4.02 - 4.01 (m, 4H), 3.90 (s, 6H), 3.50 - 3.47 (m, 4H), 2.33 - 2.31 (m, 4H), 2.23 (s, 6H), 2.05 - 2.03 (m, 1H). MS *m/z* (ESI) [M+H]⁺ = 452.2.

Example 15: *N*¹-(7-methoxy-2-(6-(2-(methylamino) ethoxy) pyridin-3-yl) quinolin-4-yl)-*N*³-methylpropane-1,3-diamine



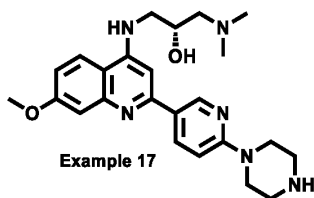
[0316] According to scheme 6, step 6, conditions 1 HCl. Substrate **E.6a** (0.12 g, 0.20 mmol, 1.0 equiv) in MeOH (1.0 mL). The residue was purified by prep-HPLC 8 (gradient: 1%-25% ACN over 8 min). The eluent was lyophilized to give **Example 15** (27 mg, 69 μmol, 34% yield, 99% purity) as a yellow gum. Then the crude product was purified with SCX (see general protocol). ¹H NMR (400 MHz, methanol-*d*₄) δ (ppm): 8.72 (d, *J* = 2.3 Hz, 1H), 8.27 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 2.6, 9.3 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.73 (s, 1H), 4.49 (t, *J* = 5.3 Hz, 2H), 3.93 (s, 3H), 3.50 (t, *J* = 7.0 Hz, 2H), 3.03 (t, *J* = 5.3 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.49 (s, 3H), 2.46 (s, 3H), 2.04 - 1.95 (m, 2H). MS *m/z* (ESI) [M+H]⁺ = 396.3.

Example 16: 2-(4-(5-(4-((3-(dimethylamino) propyl) amino)-6,7-dimethoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) ethan-1-ol



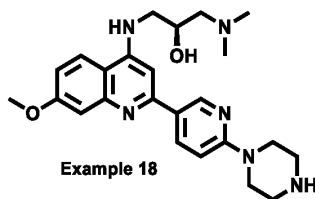
[0317] According to schemes 3 and 4, step 6, conditions 1 HCl. Substrate **C.6g** (40 mg, 66 μ mol, 1.0 equiv) in dioxane (1.0 mL). Then the residue was purified with SCX (see general protocol) to give **Example 16** (14 mg, 27 μ mol, 41% yield, 99% purity) was obtained as a yellow solid. Then the crude product was purified with SCX (see general protocol). ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.88 (d, J = 2.3 Hz, 1H), 8.28 (dd, J = 2.4, 8.9 Hz, 1H), 7.42 (s, 1H), 7.20 (s, 1H), 7.11 (s, 1H), 6.90 (d, J = 9.0 Hz, 1H), 6.81 (s, 1H), 3.89 (d, J = 1.5 Hz, 6H), 3.58 - 3.53 (m, 6H), 3.44 - 3.39 (m, 2H), 2.53 (d, J = 4.9 Hz, 4H), 2.47 - 2.42 (m, 4H), 2.24 (s, 6H), 1.85 (q, J = 6.8 Hz, 2H). MS m/z (ESI) $[M+H]^+ = 495.3$.

Example 17: (R)-1-(dimethylamino)-3-((7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) amino) propan-2-ol



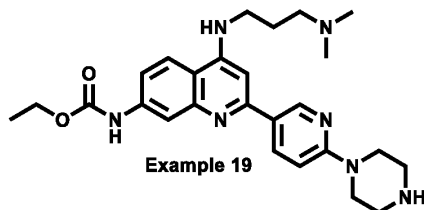
[0318] According to schemes 3 and 4, step 6, conditions 1 HCl. Substrate **R-C.6n** (60 mg, 0.11 mmol, 1.0 equiv). The residue was purified by prep-HPLC 8 (gradient: 2%-30% over 9 min). Then the residue was purified with SCX (see general protocol) to give **Example 17** (7.8 mg, 18 μ mol, 16% yield, 99% purity) was obtained as a white solid. ^1H NMR (400 MHz, methanol- d_4) δ (ppm): 8.73 (d, J = 2.4 Hz, 1H), 8.16 (dd, J = 8.8, 2.4 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.07 (dd, J = 9.2, 2.8 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.82 (s, 1H), 4.17 - 4.07 (m, 1H), 3.94 (s, 3H), 3.68 - 3.60 (m, 4H), 3.58 - 3.41 (m, 2H), 3.00 - 2.92 (m, 4H), 2.63 - 2.48 (m, 2H), 2.35 (s, 6H). MS m/z (ESI) $[M+H]^+ = 437.3$.

Example 18: (S)-1-(dimethylamino)-3-((7-methoxy-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) amino) propan-2-ol



[0319] According to schemes 3 and 4, step 6, conditions 1 HCl. Substrate **S-C.6n** (40 mg, 75 μ mol, 1.0 equiv). The residue was purified by prep-HPLC 8 (gradient: 1%-25% ACN over 9 min). Then the residue was purified with SCX (see general protocol) to give **Example 18** (13 mg, 30 μ mol, 40% yield, 98% purity) was obtained as a white solid. ^1H NMR (400 MHz, methanol- d_4) δ (ppm): 8.71 (d, $J = 2.4$ Hz, 1H) 8.13 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.92 (d, $J = 9.2$ Hz, 1H), 7.27 (d, $J = 2.4$ Hz, 1H), 7.04 (dd, $J = 9.2, 2.4$ Hz, 1H), 6.92 - 6.85 (m, 1H), 6.77 (s, 1H), 4.14 - 4.05 (m, 1H), 3.92 (s, 3H), 3.66 - 3.56 (m, 4H), 3.55 - 3.38 (m, 2H), 2.98 - 2.90 (m, 4H), 2.60 - 2.45 (m, 2H), 2.37 - 2.28 (m, 6H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 437.3$.

Example 19: ethyl 4-((3-(dimethylamino) propyl) amino)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-7-yl) carbamate

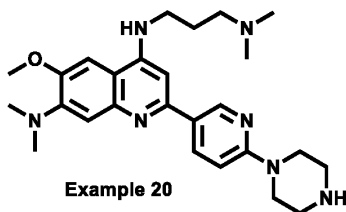


[0320] Conditions 1 Buchwald. Substrate **C.6o** (0.20 g, 0.35 mmol, 1.0 equiv), ethyl carbamate (1.60 equiv). The residue was purified by prep-HPLC 2 (gradient: 13%-43% over 10 min) to give *tert*-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-7-(ethoxycarbonylamino)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate (0.10 g, 0.17 mmol, 49% yield, 99% purity) was obtained as a yellow solid. MS m/z (ESI) $[\text{M}+\text{H}]^+ = 578.4$.

[0321] According to scheme 3, step 6, conditions 1 HCl. *tert*-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-7-(ethoxycarbonylamino)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate (50 mg, 86 μ mol, 1.0 equiv). The residue was purified with SCX (see general protocol) to give **Example 19** (20 mg, 41 μ mol, 48% yield, 98% purity) was obtained as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 9.84 (s, 1H), 8.90 (d, $J = 2.0$ Hz, 1H), 8.33 - 8.27 (m, 1H), 8.02 - 7.90 (m, 2H), 7.48 - 7.40 (m, 1H), 7.21 (s, 1H), 6.90 (d, $J = 8.9$ Hz, 1H), 6.80 (s, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.55 (s, 4H), 3.40 (d, $J = 5.5$ Hz, 2H), 2.86 (s,

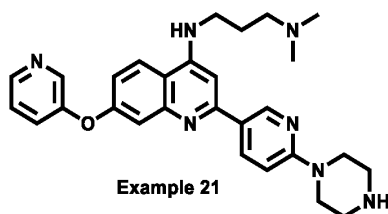
4H), 2.40 (t, $J = 6.8$ Hz, 2H), 2.20 (s, 6H), 1.86 - 1.79 (m, 2H), 1.28 (t, $J = 7.1$ Hz, 3H). MS m/z (ESI) $[M+H]^+ = 478.3$.

Example 20: *N*⁴-(3-(dimethylamino) propyl)-6-methoxy-*N*⁷,*N*⁷-dimethyl-2-(6-(piperazin-1-yl) pyridin-3-yl) quinoline-4,7-diamine



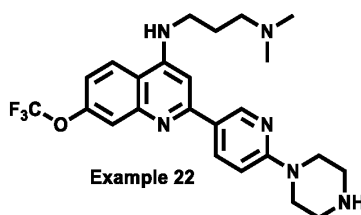
[0322] According to schemes 3 and 4, step 6, conditions 1 HCl. Substrate **C.6i** (80 mg, 0.14 mmol, 1.0 equiv). The residue was purified by prep-HPLC 8 (gradient: 1%-30% CAN over 9 min) to give pure product. Then the residue was purified with SCX (see general protocol) to give **Example 20** (31 mg, 67 μ mol, 47% yield, 99% purity) as yellow gum. ¹H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.87 (d, $J = 2.0$ Hz, 1H), 8.28 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.37 (s, 1H), 7.16 (d, $J = 3.6$ Hz, 1H), 7.12 (s, 1H), 6.91 (d, $J = 4.4$ Hz, 1H), 6.78 (s, 1H), 3.93 (s, 3H), 3.57 - 3.54 (m, 4H), 3.48 - 3.45 (m, 2H), 2.91 - 2.86 (m, 4H), 2.83 (s, 6H), 2.42 (t, $J = 6.8$ Hz, 2H), 2.22 (s, 6H), 1.84 (t, $J = 6.8$ Hz, 2H). MS m/z (ESI) $[M+H]^+ = 464.3$.

Example 21: *N*¹,*N*¹-dimethyl-*N*³-(2-(6-(piperazin-1-yl) 155uinolin-3-yl)-7-(155uinolin-3-yloxy) 155uinoline-4-yl) propane-1,3-diamine



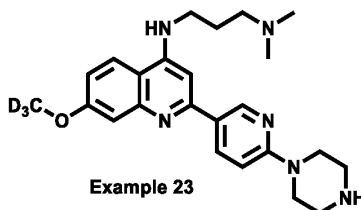
[0323] According to schemes 3 and 4, step 6, conditions 1 HCl. Substrate **C.6j** (0.14 g, 0.24 mmol, 1.0 equiv). The residue was purified by prep-HPLC 8 (gradient: 1%-27% ACN over 9 min) and purified with SCX (see general protocol) to give **Example 21** (36 mg, 30% yield) as a white solid. ¹H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.72 (s, 1H), 8.47-8.35 (m, 2H), 8.16-8.10 (m, 2H), 7.64-7.60 (m, 1H), 7.51-7.48 (m, 1H), 7.22 (s, 1H), 7.20 (d, $J = 8.8$ Hz, 1H), 6.91 (d, $J = 8.8$ Hz, 1H), 6.79 (s, 1H), 3.63 (t, $J = 4.4$ Hz, 4H), 3.51 (t, $J = 6.8$ Hz, 2H), 2.96 (t, $J = 4.4$ Hz, 4H), 2.55 (t, $J = 6.8$ Hz, 2H), 2.32 (s, 6H), 1.97 (t, $J = 6.8$ Hz, 2H). MS m/z (ESI) $[M+H]^+ = 484.4$.

Example 22: *N*¹,*N*¹-dimethyl-*N*³-(2-(6-(piperazin-1-yl) pyridin-3-yl)-7-(trifluoromethoxy) quinolin-4-yl) propane-1,3-diamine



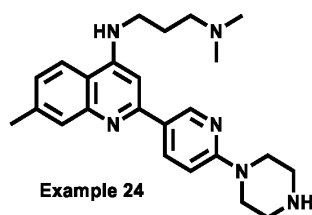
[0324] According to scheme s 3 and 4, step 6, conditions 1 HCl. Substrate **C.6h** (0.23 g, 0.40 mmol, 1.0 equiv). The residue was purified by prep-HPLC 8 (gradient: 0%-30% over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 22** (66 mg, 0.14 mmol, 35% yield, 100% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.96 (d, *J* = 2.3 Hz, 1H), 8.35 (dd, *J* = 2.4, 8.9 Hz, 1H), 8.27 (d, *J* = 9.3 Hz, 1H), 7.64 (d, *J* = 1.1 Hz, 1H), 7.50 (br t, *J* = 5.2 Hz, 1H), 7.35 (dd, *J* = 1.9, 8.9 Hz, 1H), 7.02 - 6.87 (m, 2H), 3.60 - 3.53 (m, 4H), 3.45 (br s, 2H), 2.92 - 2.80 (m, 4H), 2.41 (br t, *J* = 6.8 Hz, 2H), 2.21 (s, 6H), 1.84 (quin, *J* = 6.7 Hz, 2H). MS *m/z* (ESI) [M+H]⁺ = 475.3.

Example 23: *N*¹-(7-(methoxy-*d*₃)-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-*N*³, *N*³-dimethylpropane-1,3-diamine



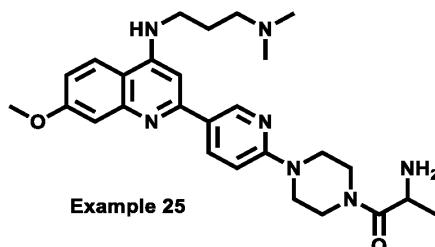
[0325] According to schemes 3 and 4, step 6, conditions 1 HCl. Substrate **C.6l** (0.18 g, 0.27 mmol, 1.0 equiv) in MeOH (2.0 mL). The residue was purified by prep-HPLC 8 (gradient: 0%-28% ACN over 9 min) to give product (chlorine hydride salt) as a yellow solid. The HCl salt product was purified SCX (see general protocol) to give **Example 23** (60 mg, 0.14 mmol, 52% yield, 100% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.91 (d, *J* = 2.2 Hz, 1H), 8.31 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.14 - 7.23 (m, 2H), 6.98 (dd, *J* = 9.1, 2.7 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.79 (s, 1H), 3.46 - 3.57 (m, 4H), 3.42 - 3.38 (m, 2H), 2.85 - 2.75 (m, 4H), 2.42 - 2.33 (m, 2H), 2.18 (s, 6H), 1.82 (q, *J* = 6.8 Hz, 2H). MS *m/z* (ESI) [M+H]⁺ = 424.3.

Example 24: *N*¹,*N*¹-dimethyl-*N*³-(7-methyl-2-(6-(piperazin-1-yl) pyridin-3-yl) quinolin-4-yl) propane-1,3-diamine



[0326] According to schemes 3 and 4, step 6, conditions 1 HCl. Substrate **C.6q** (0.10 g, 0.20 mmol, 1.0 equiv). The residue was purified by prep-HPLC 8 (gradient: 1%-28% over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 24** (20 mg, 49 μ mol, 25% yield, 100% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 1.78 - 1.88 (m, 2H) 2.20 (s, 6H) 2.40 (s, 2H) 2.45 (s, 3H) 2.79 - 2.86 (m, 4H) 3.41 - 3.44 (m, 2H) 3.50 - 3.58 (m, 4H) 6.84 (s, 1H) 6.90 (d, *J* = 9.0 Hz, 1H) 7.15 - 7.25 (m, 2H) 7.59 (s, 1H) 7.99 (d, *J* = 8.5 Hz, 1H) 8.31 (dd, *J* = 8.9, 2.3 Hz, 1H) 8.91 (d, *J* = 2.1 Hz, 1H). MS *m/z* (ESI) [*M*+*H*]⁺ = 405.3.

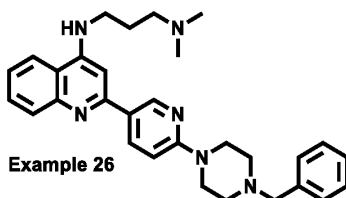
Example 25: 2-amino-1-(4-(5-(4-((3-(dimethylamino) propyl) amino)-7-methoxyquinolin-2-yl) pyridin-2-yl) piperazin-1-yl) propan-1-one



[0327] To a solution of *N*-[7-methoxy-2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]-*N*¹,*N*¹-dimethyl-propane-1,3-diamine **Example 11** (0.18 g, 0.43 mmol, 1.0 equiv) in DMF (2.0 mL) was added Boc-Ala-OH (0.10 g, 0.53 mmol, 1.2 equiv), HATU (0.41 g, 1.1 mmol, 2.5 equiv) and DIEA (0.23 g, 1.7 mmol, 0.30 mL, 4.1 equiv) at 25 °C. The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC 2 (gradient: 7%-37% B over 10 min) to give *tert*-butyl *N*-[2-[4-[5-[4-[3-(dimethylamino)propylamino]-7-methoxy-2-quinolyl]-2-pyridyl]piperazin-1-yl]-1-methyl-2-oxo-ethyl]carbamate (0.10 g, 0.17 mmol, 39% yield, 98% purity) was obtained as a yellow solid. MS *m/z* (ESI) [*M*+*H*]⁺ = 592.4.

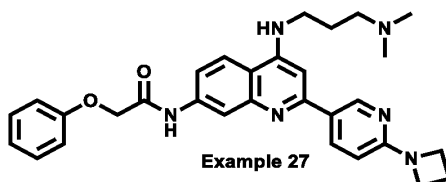
[0328] According to schemes 3 and 4, step 6, conditions 1 HCl. Substrate (0.10 g, 0.17 mmol, 1.0 equiv). The residue was purified by prep-HPLC 8 (gradient: 1%-30% over 9 min) to give a residue. Then the residue was purified with SCX (see general protocol) to give **Example 25** (20 mg, 40 μ mol, 24% yield, 98% purity) was obtained as yellow gum. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.94 (d, $J = 2.2$ Hz, 1H), 8.35 (dd, $J = 2.4, 9.0$ Hz, 1H), 8.02 (d, $J = 9.2$ Hz, 1H), 7.22 (t, $J = 5.1$ Hz, 1H), 7.18 (d, $J = 2.6$ Hz, 1H), 7.01 - 6.94 (m, 2H), 6.81 (s, 1H), 3.95 (q, $J = 7.0$ Hz, 1H), 3.88 (s, 3H), 3.68 - 3.55 (m, 8H), 3.44 - 3.35 (m, 4H), 2.38 (t, $J = 6.7$ Hz, 2H), 2.19 (s, 6H), 1.82 (q, $J = 6.7$ Hz, 2H), 1.16 (d, $J = 6.7$ Hz, 3H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 492.3$.

Example 26: *N*¹-(2-(6-(4-benzylpiperazin-1-yl) pyridin-3-yl) quinolin-4-yl)-*N*³, *N*³-dimethylpropane-1,3-diamine



[0329] To a solution of **Example 8** (0.20 g, 0.51 mmol, 1.0 equiv), benzaldehyde (54 mg, 0.51 mmol, 52 μ L, 1.0 equiv) in MeOH (3.0 mL) was added acetic acid (3.1 mg, 51 μ mol, 2.9 μ L, 0.10 equiv) at 20 °C. The mixture was stirred at 20 °C for 5 min, then to the mixture was added sodium cyanoborohydride (64 mg, 1.0 mmol, 2.0 equiv) at 20 °C. The mixture was stirred at 60 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC 2 (gradient: 0%-30% over 2 min) to give **Example 26** (50 mg, 0.10 mmol, 20% yield, 99% purity) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 8.94 (d, $J = 2.4$ Hz, 1H), 8.34 (dd, $J = 2.4, 8.8$ Hz, 1H), 8.22 (s, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 7.6$ Hz, 1H), 7.60 (t, $J = 7.6$ Hz, 1H), 7.41 - 7.31 (m, 6H), 7.30 - 7.23 (m, 1H), 6.92 (t, $J = 4.4$ Hz, 2H), 3.64 - 3.57 (m, 4H), 3.53 (s, 2H), 3.46 (d, $J = 2.4$ Hz, 2H), 2.68 (t, $J = 6.8$ Hz, 2H), 2.47 (s, 4H), 2.40 (s, 6H), 1.93 (q, $J = 6.8$ Hz, 2H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 481.3$.

Example 27: *N*-(2-(6-(azetidin-1-yl) pyridin-3-yl)-4-((3-(dimethylamino) propyl) amino) quinolin-7-yl)-2-phenoxyacetamide

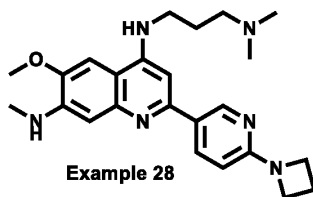


[0330] According to scheme 1, step 5, conditions 1 S_NAr: **A.5I** (1.0 g, 2.7 mmol, 1.0 equiv), *N,N'*-dimethylpropane-1,3-diamine (409 mg, 4.0 mmol, 1.5 equiv). CsF (2.03 g, 13.3 mmol, 5.0 equiv). The crude was used next step without purification. N1-(2-(6-(azetidin-1-yl)pyridin-3-yl)-7-bromoquinolin-4-yl)-N3, N3-dimethylpropane-1,3-diamine (1.0 g, 2.3 mmol, 74% yield, 87% purity) was obtained as a white solid. MS m/z (ESI) [M+H]⁺ = 440.2.

[0331] A mixture of N1-[2-[6-(azetidin-1-yl)-3-pyridyl]-7-bromo-4-quinolyl]-*N,N'*-dimethyl-propane-1,3-diamine (1.0 g, 2.3 mmol, 1.0 equiv), diphenylmethanimine (0.45 g, 2.5 mmol, 0.42 mL, 1.1 equiv), Xantphos Pd G4 (0.22 g, 0.23 mmol, 0.10 equiv), *t*-BuONa (2.0 M, 3.4 mL, 3.0 equiv) in dioxane (10 mL) was degassed and purged with N₂ three times at 25 °C, and then the mixture was stirred at 100 °C for 16 h under N₂ atmosphere. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL, three times). The organic phase was washed with brine (40 mL, three times), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC 2 (gradient: 10%-40% over 15 min). Compound 2-[6-(azetidin-1-yl)-3-pyridyl]-N4-[3-(dimethylamino) propyl] quinoline-4,7-diamine (0.8 g, 2.1 mmol, 92% yield, 98% purity) was obtained as a white solid. MS (ESI) m/z. 377.2 [M+H]⁺.

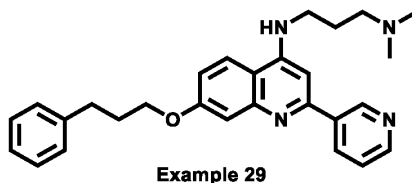
[0332] To a solution of 2-[6-(azetidin-1-yl)-3-pyridyl]-N4-[3-(dimethylamino)propyl]quinoline-4,7-diamine (0.20 g, 0.53 mmol, 1.0 equiv) and 2-phenoxyacetic acid (81 mg, 0.53 mmol, 1.0 equiv) in DMF (5.0 mL) was added HATU (0.24 g, 0.63 mmol, 1.2 equiv) and DIEA (0.21 g, 1.6 mmol, 0.28 mL, 3.0 equiv). The mixture was stirred at 25 °C for 16 h. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL, three times). The organic phase was washed with brine (100 mL, three times), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated to give a residue. The residue was purified by prep-HPLC 2 (gradient: 16%-46% B over 10 min). The residue was then purified with SCX (see general protocol). **Example 27** (34 mg, 65 μmol, 12% yield, 98% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 10.27 (s, 1H), 8.87 (d, *J* = 2.0 Hz, 1H), 8.29 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.19 (d, *J* = 1.6 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.58 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 2H), 7.26 (br s, 1H), 7.11 - 6.94 (m, 3H), 6.81 (s, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 4.77 (s, 2H), 4.02 (t, *J* = 7.6 Hz, 4H), 3.48 - 3.43 (m, 2H), 2.42 (br t, *J* = 6.8 Hz, 2H), 2.38 - 2.29 (m, 2H), 2.22 (s, 6H), 1.84 (quin, *J* = 6.8 Hz, 2H).

Example 28: 2-(6-(azetidin-1-yl) pyridin-3-yl)-*N*⁴-(3-(dimethylamino) propyl)-6-methoxy-*N*⁷-methylquinoline-4,7-diamine



[0333] According to scheme 1, step 5, conditions 1 Buchwald. Substrate **A.5h** (0.20 g, 564 μ mol, 1 equiv), *N*, *N*'-dimethylpropane-1,3-diamine (0.17 g, 1.7 mmol, 0.21 mL, 3.0 equiv). The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC 2 (gradient: 0%-30% ACN over 10 min) and purified with SCX (see general protocol) to give after lyophilization **Example 28** (53 mg, 0.13 mmol, 23% yield, 100% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.78 (d, *J* = 1.9 Hz, 1H), 8.22 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.26 (s, 1H), 6.90 - 7.06 (m, 1H), 6.65 (d, *J* = 3.1 Hz, 2H), 6.42 (d, *J* = 8.6 Hz, 1H), 5.64 (d, *J* = 4.4 Hz, 1H), 4.00 (t, *J* = 7.4 Hz, 4 H), 3.93 (s, 3H), 3.38 - 3.45 (m, 2H), 2.81 (d, *J* = 5.0 Hz, 3H), 2.30 - 2.41 (m, 4H), 2.20 (s, 6H), 1.83 (q, *J* = 6.9 Hz, 2H). MS *m/z* (ESI) [*M*+*H*]⁺ = 421.2.

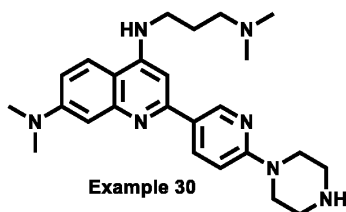
Example 29: *N*¹,*N*¹-dimethyl-*N*³-(7-(3-phenylpropoxy)-2-(pyridin-3-yl)quinolin-4-yl)propane-1,3-diamine



[0334] According to scheme 1, step 5, a mixture of 4-chloro-7-(3-phenylpropoxy)-2-(3-pyridyl)quinoline (50 mg, 0.13 mmol, 1.0 equiv), *N*,*N*'-dimethylpropane-1,3-diamine **A.5o** (16 mg, 0.16 mmol, 20 μ L, 1.2 equiv), Pd(*t*-Bu₃P)₂ (6.8 mg, 13 μ mol, 0.10 equiv), *t*-BuONa (38 mg, 0.40 mmol, 3.0 equiv) in dioxane (3.0 mL) was degassed and purged with N₂ three times at 25 °C, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with ethyl acetate (30 mL, three times). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC 1 (gradient: 21%-51% over 10 min) to give **Example 29** (25 mg, 58 μ mol, 43% yield, 100% purity) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 14.01 (s, 1H), 10.81 -

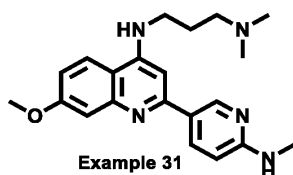
10.70 (m, 1H), 9.62 (t, $J = 5.1$ Hz, 1H), 9.34 (s, 1H), 8.90 (d, $J = 4.9$ Hz, 1H), 8.69 - 8.62 (m, 2H), 7.83 - 7.77 (m, 1H), 7.72 (s, 1H), 7.37 (d, $J = 9.1$ Hz, 1H), 7.34 - 7.23 (m, 4H), 7.23 - 7.15 (m, 2H), 4.15 (t, $J = 6.1$ Hz, 2H), 3.77 (d, $J = 6.6$ Hz, 2H), 3.22 - 3.15 (m, 2H), 2.83 - 2.73 (m, 8H), 2.18 - 2.10 (m, 4H). MS m/z (ESI) $[M+H]^+ = 441.3$.

Example 30: *N*⁴-[3-(dimethylamino) propyl]-*N*⁷,*N*⁷-dimethyl-2-(6-piperazin-1-yl-3-pyridyl)quinoline-4,7-diamine



[0335] According to schemes 3 and 4, step 6, to a solution of tert-butyl 4-[5-[7-(dimethylamino)-4-[3-(dimethylamino) propylamino]-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **C.6r** (0.10 g, 0.19 mmol, 1.0 equiv) in methanol (1.0 mL) was added HCl/MeOH(4.0 M, 47 μ L, 1.0 equiv) at 25 °C. After stirring at 25 °C for 4 h, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC 8 (gradient: 0%-30% over 10 min) to give **Example 30** (58 mg, 0.12 mmol, 66% yield, 100% purity, HCl) as an orange solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 13.18 (s, 1 H), 10.91 (s, 1 H), 9.70 (s, 2 H), 9.11 (t, $J = 5.4$ Hz, 1 H), 8.93 (d, $J = 2.5$ Hz, 1 H), 8.34 - 8.52 (m, 2 H), 7.32 (d, $J = 2.3$ Hz, 1 H), 7.10 - 7.24 (m, 2 H), 6.83 (s, 1 H), 3.93 - 4.02 (m, 4 H), 3.70 (q, $J = 6.2$ Hz, 2 H), 3.15 - 3.28 (m, 6 H), 3.09 (s, 6 H), 2.74 (d, $J = 4.9$ Hz, 6 H), 2.12 (q, $J = 7.1$ Hz, 2 H). MS m/z (ESI) $[M+H]^+ = 434.3$.

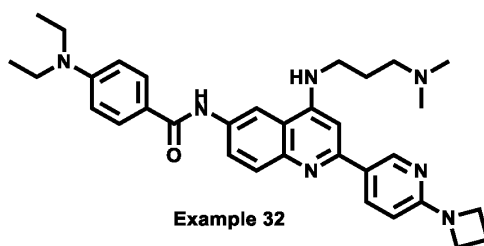
Example 31: *N*¹-(7-methoxy-2-(6-(methylamino)pyridin-3-yl)quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine



[0336] According to schemes 3 and 4, step 6, to a solution of tert-butyl N-[5-[4-[3-(dimethylamino) propylamino]-7-methoxy-2-quinolyl]-2-pyridyl]-N-methyl-carbamate **C.6s** (0.30 g, 0.64 mmol, 1.0 equiv) in dioxane (5.0 mL) was added HCl/dioxane (4 M, 3.0 mL) at 25 °C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC 8 (gradient: 3%-33% ACN over 8

min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give a yellow solid. Then the solid was purified with SCX (see general protocol) to give **Example 31** (60 mg, 0.16 mmol, 25% yield, 99% purity) as a light yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.81 (d, J = 2.4 Hz, 1H), 8.19 (dd, J = 2.4, 8.8 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.23 - 7.10 (m, 2H), 6.96 (dd, J = 2.8, 9.2 Hz, 1H), 6.82 - 6.69 (m, 2H), 6.53 (d, J = 8.8 Hz, 1H), 3.87 (s, 3H), 3.38 (d, J = 5.6 Hz, 2H), 2.84 (d, J = 4.8 Hz, 3H), 2.37 (t, J = 6.8 Hz, 2H), 2.18 (s, 6H), 1.85 - 1.75 (m, 2H). MS m/z (ESI) $[M+H]^+ = 366.2$.

Example 32: *N*-[2-[6-(azetidin-1-yl)-3-pyridyl]-4-[3-(dimethylamino) propylamino]-6-quinolyl]-4-(diethylamino) benzamide



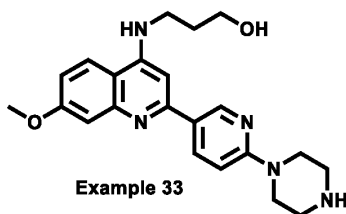
[0337] To a solution of 2-[6-(azetidin-1-yl)-3-pyridyl]-6-bromo-4-chloro-quinoline **A.5p** (1.8 g, 4.80 mmol, 1.0 equiv) in DMSO (30 mL) was added N,N' -dimethylpropane-1,3-diamine (1.0 g, 9.8 mmol, 1.2 mL, 2.0 equiv) and TEA (1.5 g, 14 mmol, 2.0 mL, 3.0 equiv), the reaction mixture was stirred at 100 °C for 12 h. The reaction was poured into water (0.20 L), extracted with EtOAc (0.30 L, three times). The combined organic phase was washed with saturated brine (0.30 L, twice), dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by prep-HPLC 2 (gradient: 1%-15% over 15 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give *N*-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-bromo-4-quinolyl]- N,N' -dimethyl-propane-1,3-diamine (0.27 g, 0.53 mmol, 11% yield, 86% purity) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.90 (d, J = 1.9 Hz, 1H), 8.42 (d, J = 1.6 Hz, 1H), 8.31 (dd, J = 2.3, 8.8 Hz, 1H), 7.74 - 7.67 (m, 2H), 7.40 - 7.30 (m, 1H), 6.44 (d, J = 8.8 Hz, 1H), 4.02 (d, J = 7.4 Hz, 4H), 3.41 (br d, J = 5.5 Hz, 2H), 2.48 - 2.43 (m, 2H), 2.36 (br d, J = 7.6 Hz, 2H), 2.26 (s, 6H), 1.90 - 1.84 (m, 2H). MS m/z (ESI) $[M+H]^+ = 440.2$.

[0338] To a solution of *N*-[2-[6-(azetidin-1-yl)-3-pyridyl]-6-bromo-4-quinolyl]- N,N' -dimethyl-propane-1,3-diamine (0.27 g, 0.61 mmol, 1.0 equiv) in dioxane (5.0 mL) was added diphenylmethanimine (0.23 g, 1.3 mmol, 0.21 mL, 2.1 equiv), Xantphos Pd G4 (60

mg, 62 μ mol, 0.10 equiv) and *t*-BuONa (2.0 M, 0.94 mL, 3.1 equiv) at 20 °C. The mixture was degassed and purged with N₂ three times, and then the mixture was stirred at 100 °C for 2 h under N₂ atmosphere. The reaction mixture was concentrated to give a residue. The residue was purified by prep-HPLC 2 (gradient: 10%-40% over 10 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give 2-[6-(azetidin-1-yl)-3-pyridyl]-N4-[3-(dimethylamino)propyl] quinoline-4,6-diamine (50 mg, 0.13 mmol, 22% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.77 (d, *J* = 2.2 Hz, 1H), 8.20 (br d, *J* = 2.4 Hz, 1H), 7.57 (d, *J* = 8.9 Hz, 1H), 7.06 (br d, *J* = 9.4 Hz, 1H), 6.95 (br s, 1H), 6.73 (s, 1H), 6.44 (d, *J* = 8.6 Hz, 1H), 4.01 (t, *J* = 7.3 Hz, 6H), 2.35 (br d, *J* = 7.1 Hz, 2H), 2.28 (br s, 8H), 1.86 (br t, *J* = 6.4 Hz, 2H).

[0339] To a solution of 2-[6-(azetidin-1-yl)-3-pyridyl]-N4-[3-(dimethylamino)propyl]quinoline-4,6-diamine (40 mg, 0.11 mmol, 1.0 equiv) in DMF (1.0 mL) was added 4-(diethylamino)benzoic acid (26 mg, 0.13 mmol, 1.3 equiv), HATU (50 mg, 0.13 mmol, 1.2 equiv) and DIEA (22 mg, 0.17 mmol, 30 μ L, 1.6 equiv), the reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated to give a residue, the pH of the residue was adjusted to 6 by adding AcOH. The residue 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 32** (4.8 mg, 8.7 μ mol, 48% yield, 100% purity) as a yellow solid. ¹H NMR (400 MHz, methanol-*d*₄) δ (ppm): 8.69 - 8.60 (m, 2H), 8.54 (br s, 1H), 8.12 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.97 - 7.85 (m, 4H), 6.88 (s, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.53 (d, *J* = 8.9 Hz, 1H), 4.19 (t, *J* = 7.5 Hz, 4H), 3.71 (br t, *J* = 6.4 Hz, 2H), 3.51 (q, *J* = 7.0 Hz, 4H), 2.99 (br t, *J* = 7.3 Hz, 2H), 2.68 (s, 6H), 2.50 (br t, *J* = 7.6 Hz, 2H), 2.22 - 2.06 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 6H). MS *m/z* (ESI) [M+H]⁺ = 552.3.

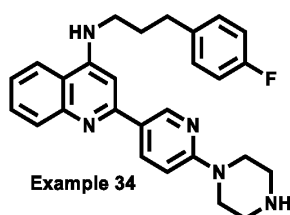
Example 33: 3-((7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)amino)propan-1-ol



[0340] According to schemes 3 and 4, step 6, to a solution of tert-butyl 4-[5-[4-(3-hydroxypropylamino)-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **C.6t** (50

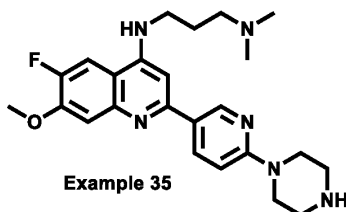
mg, 0.10 mmol, 1.0 equiv) in dioxane (2.0 mL) was added HCl/dioxane (2 M, 1.0 mL, 20 equiv), then the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was adjusted to pH = 8 by adding NH₃.H₂O. The crude product was purified by prep-HPLC 2 (gradient: 0%-30% ACN over 10 min) to give **Example 33** (13 mg, 32 μmol, 31% yield, 100% purity) as a white solid. ¹H NMR (400 MHz, methanol-d₄) δ (ppm): 8.51 (s, 2H), 8.19 (d, *J* = 9.3 Hz, 2H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.25 (d, *J* = 2.2, 9.3 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 6.93 (s, 1H), 4.02 - 3.99 (m, 3H), 3.96 (s, 4H), 3.77 - 3.70 (m, 4H), 3.29 (s, 4H), 2.01 (quin, *J* = 6.3 Hz, 2H). MS *m/z* (ESI) [M+H]⁺ = 394.2.

Example 34: *N*-[3-(4-fluorophenyl) propyl]-2-(6-piperazin-1-yl-3-pyridyl) quinolin-4-amine



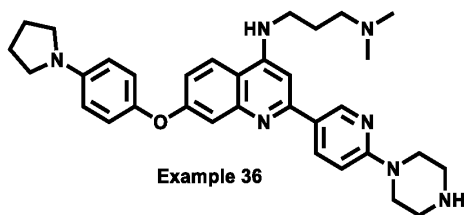
[0341] According to schemes 3 and 4, step 6, to a solution of tert-butyl 4-[5-[4-[3-(4-fluorophenyl) propylamino]-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **C.6u** (80 mg, 0.15 mmol, 1.0 equiv) in dioxane (0.50 mL) was added HCl/dioxane (4 M, 0.50 mL, 14 equiv) at 25 °C. The mixture was stirred at 25 °C for 4 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC 2 (gradient: 5%-35% over 10 min). The residue was purified by prep-HPLC 2 (gradient: 5%-35% over 10 min) to give **Example 34** (50 mg, 113.24 μmol, 76.67% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.92 (d, *J* = 2.3 Hz, 1H), 8.34 (dd, *J* = 2.4, 8.9 Hz, 1H), 8.24 (br d, *J* = 8.3 Hz, 1H), 8.13 (s, 1H), 7.83 (br d, *J* = 8.1 Hz, 1H), 7.63 (br t, *J* = 7.1 Hz, 1H), 7.40 (br t, *J* = 7.3 Hz, 1H), 7.30 (dd, *J* = 5.7, 8.4 Hz, 2H), 7.16 - 7.01 (m, 3H), 6.83 (s, 1H), 3.92 - 3.74 (m, 4H), 3.48 - 3.41 (m, 2H), 3.23 - 3.16 (m, 4H), 2.74 (br t, *J* = 7.4 Hz, 2H), 2.05 - 1.95 (m, 2H). MS *m/z* (ESI) [M+H]⁺ = 442.3.

Example 35: *N*¹-(6-fluoro-7-methoxy-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine



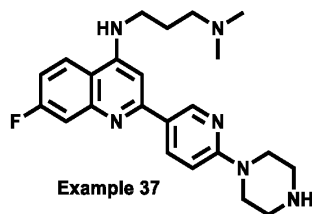
[0342] According to schemes 3 and 4, step 6, tert-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-6-fluoro-7-methoxy-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate- **C.6v** (0.50 g, 0.46 mmol, 1.0 equiv) was added to HCl/dioxane (4.0 M, 4.0 mL, 35 equiv). The reaction solution was stirred at 25 °C for 1 h. The reaction solution was concentrated under *vacuum*. The residue was purified by prep-HPLC 7 (gradient: 28%-58% over 10 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The compound was neutralized by SCX (see general protocol) to give **Example 35** (0.10 g, 0.22 mmol, 48% yield, 96% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.91 (d, *J* = 2.3 Hz, 1H), 8.30 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.98 (d, *J* = 13.4 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.01 (br t, *J* = 4.9 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 1H), 6.84 (s, 1H), 3.97 (s, 3H), 3.55 - 3.50 (m, 4H), 3.39 (br s, 2H), 2.88 - 2.78 (m, 4H), 2.37 (t, *J* = 6.9 Hz, 2H), 2.18 (s, 6H), 1.82 (br t, *J* = 6.9 Hz, 2H). MS *m/z* (ESI) [*M*+*H*]⁺ = 439.2.

Example 36: *N*¹,*N*¹-dimethyl-*N*³-(2-(6-(piperazin-1-yl)pyridin-3-yl)-7-(4-(pyrrolidin-1-yl)phenoxy)quinolin-4-yl)propane-1,3-diamine



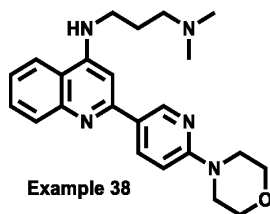
[0343] According to schemes 3 and 4, step 6, to a screw-cap vial equipped with a magnetic stir bar was added tert-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-7-(4-pyrrolidin-1-ylphenoxy)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **C.6w** (0.25 g, 0.38 mmol, 1.0 equiv) and dioxane (2.0 mL) and HCl/dioxane (2.0 M, 3.0 mL) sequentially. The vial was sealed with a Teflon-lined septum. Then the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C₁₈ 150*25 mm* 10um; mobile phase: [water (HCl) -ACN]; gradient: 5%-35% over 9 min), followed by lyophilization to give product (HCl salt). The product (HCl salt) was neutralized by SCX (see general protocol) to give **Example 36** (41 mg, 75 μmol, 19% yield, 100% purity) as yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.85 (d, *J* = 2.4 Hz, 1H), 8.25 (dd, *J* = 2.4, 8.9 Hz, 1H), 8.07 (d, *J* = 9.4 Hz, 1H), 7.27 (br t, *J* = 5.1 Hz, 1H), 7.08 (dd, *J* = 2.7, 9.1 Hz, 1H), 7.04 - 6.99 (m, 2H), 6.88 (d, *J* = 2.6 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 6.80 (s, 1H), 6.62 (d, *J* = 8.9 Hz, 2H), 3.53 - 3.47 (m, 4H), 3.43 - 3.38 (m, 2H), 3.25 (br t, *J* = 6.4 Hz, 4H), 2.85 - 2.77 (m, 4H), 2.38 (t, *J* = 6.8 Hz, 2H), 2.19 (s, 6H), 2.00 - 1.94 (m, 4H), 1.86 - 1.78 (m, 2H). MS *m/z* (ESI) [*M*+*H*]⁺ = 552.4.

Example 37: *N*¹-(7-fluoro-2-(6-(piperazin-1-yl)pyridin-3-yl)quinolin-4-yl)-*N*³,*N*³-dimethylpropane-1,3-diamine



[0344] According to schemes 3 and 4, step 6, to a solution of tert-butyl 4-[5-[4-[3-(dimethylamino) propylamino]-7-fluoro-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate **C.6x** (0.45 g, 0.88 mmol, 1.0 equiv) in dioxane (1.0 mL) was added HCl/dioxane (4.0 M, 3.0 mL) at 25 °C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC 8 (gradient: 0%-30% over 9 min) to give *N*-[7-fluoro-2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl]-*N*¹, *N*¹-dimethyl-propane-1,3-diamine (HCl salt) which was neutralized with SCX (see general protocol) to give **Example 37** (0.12 g, 0.29 mmol, 32% yield, 100% purity) as a yellow gum. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 8.93 (d, *J* = 2.4 Hz, 1H), 8.31 (dd, *J* = 2.4, 8.9 Hz, 1H), 8.19 (dd, *J* = 6.3, 9.2 Hz, 1H), 7.46 (dd, *J* = 2.6, 10.9 Hz, 1H), 7.39 (t, *J* = 5.2 Hz, 1H), 7.25 (dt, *J* = 2.8, 8.7 Hz, 1H), 6.89 (t, *J* = 4.5 Hz, 2H), 3.56 - 3.49 (m, 4H), 3.42 (d, *J* = 5.5 Hz, 2H), 2.86 - 2.76 (m, 4H), 2.38 (t, *J* = 6.8 Hz, 2H), 2.18 (s, 6H), 1.82 (q, *J* = 6.8 Hz, 2H). MS *m/z* (ESI) [*M*+*H*]⁺ = 409.2.

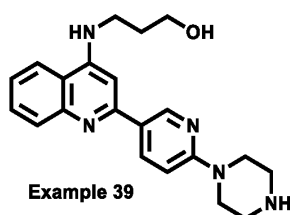
Example 38: *N*¹,*N*¹-dimethyl-*N*³-(2-(6-morpholinopyridin-3-yl)quinolin-4-yl)propane-1,3-diamine



[0345] According to scheme 2, step 5, a mixture of *N*-(2-chloro-4-quinolyl)-*N*¹,*N*¹-dimethylpropane-1,3-diamine **B.5a** (70 mg, 0.27 mmol, 1.0 equiv), *N*-(2-chloro-4-quinolyl)-*N*¹,*N*¹-dimethylpropane-1,3-diamine (70 mg, 0.27 mmol, 1.0 equiv), K₂CO₃ (73 mg, 0.53 mmol, 2.0 equiv) and XPhos-Pd-G2 (10 mg, 0.01 mmol, 0.05 equiv) in MeOH (2.7 mL) was stirred under inert atmosphere at 65 °C overnight. DEAM (0.60 g) was added and the reaction was stirred for 1 h. The crude was filtrated, and the solvent removed under reduced pressure. The mixture was dissolved in DCM and re-purified on aluminum oxide (90 neutral, 25 g)

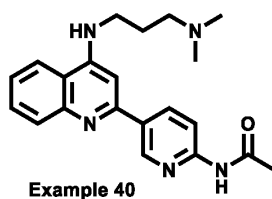
DCM/MeOH 100:0 to 99:1. The fractions containing the product were combined and the solvent was removed under reduced pressure. The residue was dissolved in ACN and purified by prep-HPLC 7 to afford **Example 38** (40 mg, 0.10 mmol, 38%) as a yellow solid. ^1H NMR (400 MHz, methanol- d_4) δ (ppm): 8.73 (d, $J = 2.5$ Hz, 1H), 8.18 (dd, $J = 8.9, 2.5$ Hz, 1H), 8.01 (dd, $J = 8.5, 1.3$ Hz, 1H), 7.90 – 7.82 (m, 1H), 7.61 (ddd, $J = 8.4, 6.9, 1.4$ Hz, 1H), 7.39 (ddd, $J = 8.2, 6.8, 1.3$ Hz, 1H), 6.91 (d, $J = 8.9$ Hz, 1H), 6.79 (s, 1H), 3.85 – 3.76 (m, 4H), 3.61 – 3.54 (m, 4H), 3.48 (t, $J = 6.9$ Hz, 2H), 2.51 (t, $J = 7.3$ Hz, 2H), 2.28 (s, 7H), 1.96 (p, $J = 7.1$ Hz, 2H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 392.2$.

Example 39: 3-[[2-(6-piperazin-1-yl-3-pyridyl)-4-quinolyl] amino] propan-1-ol



[0346] According to schemes 3 and 4, step 6, tert-butyl 4-[5-[4-(3-hydroxypropylamino)-2-quinolyl]-2-pyridyl] piperazine-1-carboxylate (0.34 mg, 0.72 mmol, 1.0 equiv) was dissolved in DCM (6.0 mL) and TFA (1.0 mL, 0.72 mmol, 1.0 equiv) was added. The reaction was stirred at rt overnight. The reaction mixture was evaporated and worked-up with DCM/aq. Na_2CO_3 (pH 12) and dried over Na_2SO_4 . Purification was done by prep-HPLC 6. After lyophilization, **Example 39** was obtained as a yellow powder. MS m/z (ESI) $[\text{M}+\text{H}]^+ = 364.2$.

Example 40: *N*-(5-(4-((3-(dimethylamino) propyl) amino) quinolin-2-yl) pyridin-2-yl) acetamide



[0347] According to scheme 2, step 5, N1-(2-chloroquinolin-4-yl)-N3,N3-dimethylpropane-1,3-diamine **B.5a** (50 mg, 0.19 mmol, 1.0 equiv), (6-acetamidopyridin-3-yl)boronic acid (41 mg, 0.23 mmol, 1.2 equiv), XPhos-Pd-G2 (7.5 mg, 9.5 μmol , 0.05 equiv), and K_2CO_3 (52 mg, 0.38 mmol, 2.0 equiv) were suspended in MeOH (1.5 mL) under inert atmosphere and heated to 65 $^\circ\text{C}$ overnight. The reaction mixture was concentrated and purified by prep-HPLC 5 to give **Example 40** (35 mg, 96 μmol , 51%) was isolated as an orange solid. ^1H

NMR (METHANOL- D_4) δ : 8.90 (d, J = 2.5 Hz, 1H), 8.46 (s, 1H), 8.34 (dd, J = 8.7, 2.4 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.16 – 8.11 (m, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.75 (tt, J = 8.0, 1.1 Hz, 1H), 7.53 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H), 6.95 (s, 1H), 3.62 (t, J = 6.9 Hz, 2H), 2.94 (t, J = 7.8 Hz, 2H), 2.62 (s, 6H), 2.20 (s, 3H), 2.10 (dt, J = 14.4, 6.9 Hz, 2H). MS m/z (ESI) $[M+H]^+ = 364.0$.

Biological Examples

[0348] 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

[0349] 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/cm² in mTesR Plus with 10 μ M 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 μ M LDN-193189, 3 μ M CHIR-99021, and 10 μ M SB-431542 (Cayman Chemical; Stage 1 media). After 6 days, cells were dissociated and split 1:4 in basal medium containing 0.2 μ M LDN-193189, 3 μ M CHIR99021, 10 μ M SB-431542, 0.1 μ M all-trans retinoic acid, 1 μ M SAG, and 10 μ M Y-27632 (Cayman Chemical; Stage 2 media). On day 12 of culture, cells were dissociated using Accutase and cryopreserved.

[0350] To mature motor neuron progenitors, cells were thawed on plates sequentially coated with PEI followed by 1% Geltrex in basal media containing 0.5 μ M all-trans retinoic acid, 0.1 μ M SAG, 0.1 μ M Compound E, 2.5 μ M DAPT, 20 ng/mL L-ascorbic acid, 0.1 μ M dibutyryl cyclic-AMP, 10 ng/mL of BDNF and GDNF, and 10 μ M 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

[0351] 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 μ L/well of Stage 4 media containing 10 μ g/mL puromycin. Cells were immediately treated with compounds (2-fold dilutions beginning at 15 μ M) using an Echo 650 acoustic dispenser with a consistent 0.16% DMSO across conditions. 30 μ M 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 μ L 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)

[0352] 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.

[0353] 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: ATGGTATAGCTTCCGTTCTACTAAAC

(/56-FAM/ATGGTATAG/ZEN/CTTCCGTTCTACTAAAC/31ABkFQ/)

[0354] 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.

Example No.	<i>POLDIP3</i> Puromycin Stress qPCR Assay EC_{50} (μM)	<i>STMN2</i> Puromycin Stress qPCR Assay EC_{50} (μM)	Puromycin Stress Imaging Assay IC_{50} (μM)
1	*	*	*
2	-	-	*
3	*	>5 mM	*
4	-	*	*
5	*	*	*
6	*	*	**
7	*	*	**
8	**	*	*
9	**	*	**
10	*	*	*
11	***	*	*
12	**	> 5 mM	*
13	-	-	*
14	-	-	*
15	*	*	***
16	**	*	**
17	*	*	**
18	**	*	***
19	*	*	*
20	*	*	*
21	**	*	***
22	*	*	*
23	***	**	**
24	**	**	***
25	*	*	**
26	*	*	**
27	-	-	**
28	*	*	*
29	*	*	*
30	*	-	-
31	*	*	***
32	*	*	***
33	*	*	
34	**	**	***
35	**	*	***
36	**	*	***
37	**	*	**
38	-	-	*

Example No.	<i>POLDIP3</i> Puromycin Stress qPCR Assay EC ₅₀ (μM)	<i>STMN2</i> Puromycin Stress qPCR Assay EC ₅₀ (μM)	Puromycin Stress Imaging Assay IC ₅₀ (μM)
39	*	-	-
40	-	-	-

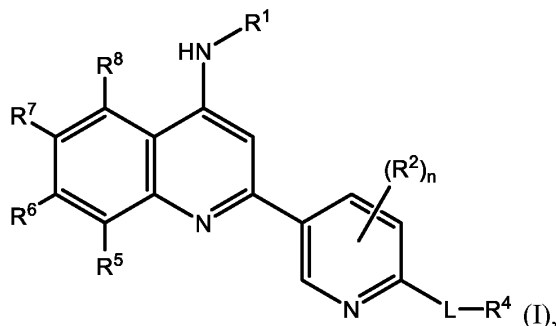
[0355] All publication, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entireties, to the same extent as if each were incorporated by reference individually.

[0356] 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)



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

R^1 is C_{1-6} alkyl optionally substituted with one or more R^{1a} ;

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

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

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

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

n is 0, 1, 2, or 3;

L is a bond, C_{1-6} alkyl, $-O-(C_{1-6}alkyl)-$, $-S-(C_{1-6}alkyl)-$, or $-N(R^3)(C_{1-6}alkyl)-$;

R^3 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(=O)R^{11}$, $-S(=O)_2R^{11}$, $-S(=O)_2N(R^{10})(R^{11})$, or C_{3-8} cycloalkyl, wherein

the C_{1-6} alkyl of R^3 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^9$, $-SR^9$, $-N(R^{10})C(=O)R^{11}$, $-N(R^{10})C(=O)N(R^{10})R^{11}$, $-N(R^{10})C(=O)OR^{11}$, $-OC(=O)R^{11}$, $-OC(=O)N(R^{10})R^{11}$, $-OC(=O)OR^{11}$, $-C(=O)R^{11}$, $-C(=O)N(R^{10})(R^{11})$, $-C(=O)OR^{11}$, $-C(=NR^{12})R^{11}$, $-C(=NOR^{11})R^{11}$, $-C(=NR^{12})N(R^{10})R^{11}$, $-C(=NR^{12})OR^{11}$, $-N(R^{10})S(=O)_2R^{11}$, $-S(=O)R^{11}$, $-S(=O)N(R^{10})R^{11}$, $-S(=O)OR^{11}$, $-S(=O)_2R^{11}$, or $-S(=O)_2N(R^{10})(R^{11})$, and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{3b};
 R⁴ is -N(R^x)(R^y), -N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -
 OC(=O)N(R¹⁰)R¹¹, -C(=O)(C₁₋₆alkyl)N(R^x)(R^y), -C(=O)N(R¹⁰)(R¹¹), or 3- to 8-membered N-
 containing heterocyclyl, wherein

the 3- to 8-membered N-containing heterocyclyl of R⁴ is optionally substituted with
 one or more R^{4b}, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), or -C(=O)OR¹¹, and

the 3- to 8-membered N-containing heterocyclyl of R⁴ comprises 1, 2, or 3 atoms
 selected from the group consisting of N, O, and S;

R⁵ is H;

R⁶ and R⁷ are each independently H, halo, C₁₋₆alkyl, -OR⁹, -N(R^x)(R^y), -N(R¹⁰)C(=O)R¹¹, -
 N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -OC(=O)N(R¹⁰)R¹¹, -
 OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹,
 -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -
 S(=O)OR¹¹, -S(=O)₂R¹¹, or -S(=O)₂N(R¹⁰)(R¹¹), wherein

the C₁₋₆alkyl of R⁶ or R⁷ is optionally substituted by one or more R^{5a};
 or R⁶ and R⁷ are taken together with the carbon atoms to which they are attached to form a 4-
 to 8-membered heterocyclyl;

each R^{1a}, R^{2a}, R^{4a}, and R^{5a} is independently halo, -N(R^x)(R^y), -OR⁹, -SR⁹, -NO₂, -CN, -
 N(R¹⁰)C(=O)R¹¹, -N(R¹⁰)C(=O)N(R¹⁰)R¹¹, -N(R¹⁰)C(=O)OR¹¹, -OC(=O)R¹¹, -
 OC(=O)N(R¹⁰)R¹¹, -OC(=O)OR¹¹, -C(=O)R¹¹, -C(=O)N(R¹⁰)(R¹¹), -C(=O)OR¹¹, -
 C(=NR¹²)R¹¹, -C(=NOR¹¹)R¹¹, -C(=NR¹²)N(R¹⁰)R¹¹, -C(=NR¹²)OR¹¹, -N(R¹⁰)S(=O)₂R¹¹, -
 S(=O)R¹¹, -S(=O)N(R¹⁰)R¹¹, -S(=O)OR¹¹, -S(=O)₂R¹¹, -S(=O)₂N(R¹⁰)(R¹¹), C₃₋₈cycloalkyl, 3-
 to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, phenyl, or 5- to 6-membered
 heteroaryl is optionally substituted with of R^{1a}, R^{2a}, R^{4a}, or R^{5a} is optionally
 substituted with one or more R^{1b}, and

the 3- to 12-membered heterocyclyl of R^{1a}, R^{2a}, R^{4a}, or R^{5a} comprises 1, 2, or 3 atoms
 selected from the group consisting of N, O, and S;

each R^{1b}, R^{2b}, R^{3b}, R^{4b}, or R^{5b} is independently halo, C₁₋₆alkyl, -OR¹³, -N(R^x)(R^y), oxo, -CN,
 C₃₋₈cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C₁₋₆alkyl of R^{1b}, R^{2b}, R^{3b}, R^{4b}, or R^{5b} is optionally substituted by -OR⁹, -
 N(R^x)(R^y), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-
 membered heteroaryl;

each R^9 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, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^9 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^{10} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

each R^{11} 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^{11} is optionally substituted by halo, -OH, $-O(C_{1-6}$ alkyl), $-O(\text{phenyl})$, $-O(C=O)C_{1-8}$ 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^{11} is optionally substituted with halo, C_{1-6} alkyl, or $-N(R^x)(R^y)$;

each R^{12} is independently H or C_{1-6} alkyl;

each R^{13} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

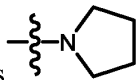
the C_{1-6} alkyl of R^{13} is optionally substituted with phenyl, or 5- to 6-membered heteroaryl, wherein

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

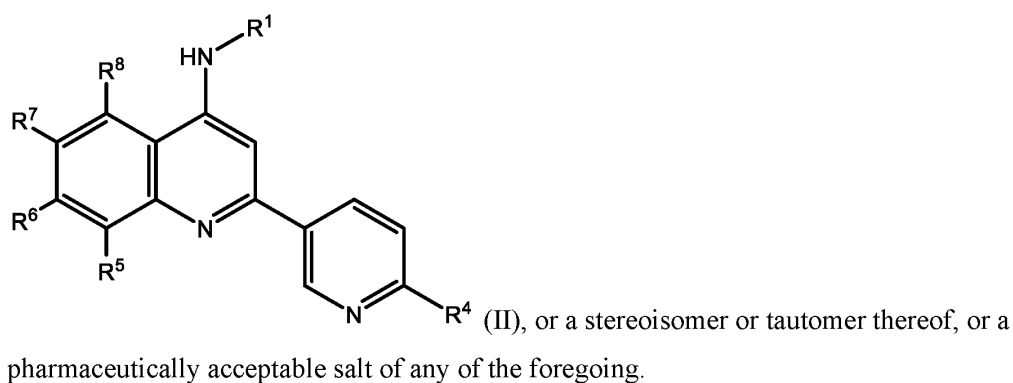
the phenyl, or 5- to 6-membered heteroaryl of R^{13} is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, or $-N(R^x)(R^y)$; and

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

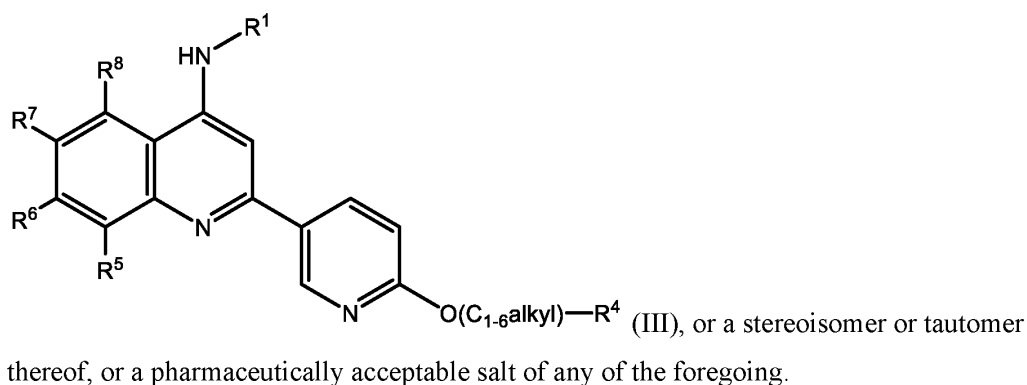
the C_{1-6} alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, -OH, $-NH_2$, $NH(C_{1-6}$ alkyl), or $-N(C_{1-6}$ alkyl)(C_{1-6} alkyl), and the C_{1-6} alkyl of $-C(=O)(C_{1-6}$ alkyl) or $-C(=O)O(C_{1-6}$ alkyl) is optionally substituted with $-O(C=O)C_{1-8}$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

when L is $-OCH_2CH_2CH_2-$, R^4 is , and R^5 and R^6 are each H, R^1 is not $-CH_2CH_2CH_2N(CH_3)(CH_3)$.

2. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is a bond or -O(C₁₋₆alkyl)-.
3. The compound of claim 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is a bond or -O(C₁₋₄alkyl)-.
4. The compound of claim 3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L is a bond or -O(CH₂CH₂)-.
5. The compound of any of claims 1-4, wherein the compound is a compound of formula (II)



6. The compound of any of claims 1-4, wherein the compound is a compound of formula (III)

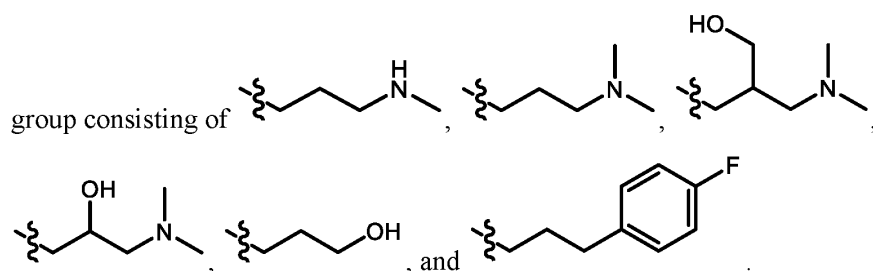


7. The compound of any of claims 1-6, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is C_{1-6} alkyl substituted with one or more R^{1a} .

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 each R^{1a} is independently -OH, - $NH(C_{1-6}alkyl)$, - $N(C_{1-6}alkyl)(C_{1-6}alkyl)$, or phenyl, wherein the phenyl is optionally substituted by halo.

9. The compound of claim 8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^{1a} is independently -OH, - $NH(CH_3)$, - $N(CH_3)(CH_3)$, or fluorophenyl.

10. 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^1 is selected from the

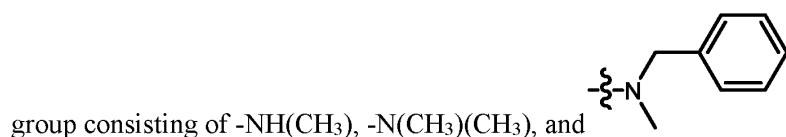


11. The compound of any of claims 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is - $N(R^x)(R^y)$.

12. The compound of claim 11, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is - $NH(C_{1-6}alkyl)$, - $N(C_{1-6}alkyl)(C_{1-6}alkyl)$,

wherein each $C_{1-6}alkyl$ is independently optionally substituted by one or more R^{4a} .

13. The compound of claim 12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is selected from the



14. The compound of any of claims 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is $-\text{N}(\text{R}^{10})\text{C}(\text{O})\text{R}^{11}$.

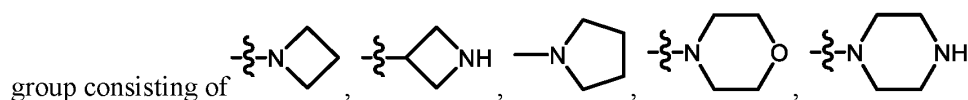
15. The compound of claim 14, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is $-\text{NHC}(\text{O})(\text{C}_{1-6}\text{alkyl})$.

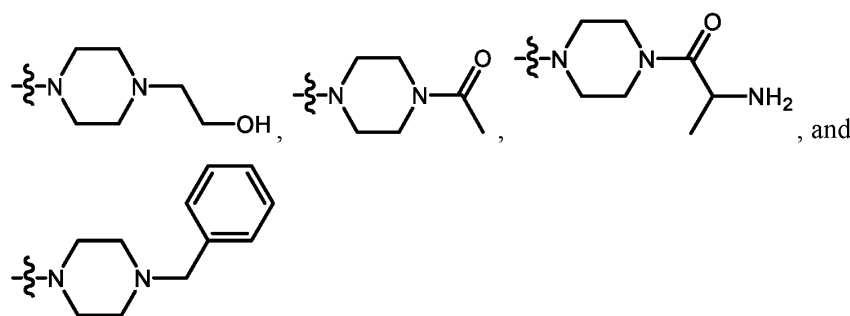
16. The compound of claim 15, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is $-\text{NHC}(\text{O})(\text{CH}_3)$.

17. The compound of any of claims 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is 3- to 12-membered N-containing heterocyclyl optionally substituted by R^{4b} , $-\text{C}(=\text{O})\text{R}^{11}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{10})(\text{R}^{11})$, or $-\text{C}(=\text{O})\text{OR}^{11}$.

18. The compound of claim 17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is azetidiny, pyrrolidinyl, morpholinyl, piperazinyl, wherein the piperazinyl is optionally substituted by R^{4b} , $-\text{C}(=\text{O})\text{R}^{11}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{10})(\text{R}^{11})$, or $-\text{C}(=\text{O})\text{OR}^{11}$.

19. The compound of claim 18, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 is selected from the





20. The compound of any of claims 1-19, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 and R^7 are each independently H, halo, C_{1-6} alkyl, $-N(R^x)(R^y)$, $-OR^9$, $-N(R^{10})C(O)R^{11}$, or $-N(R^{10})C(O)OR^{11}$.

21. The compound any of claims 1-20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 and R^7 are each independently H, halo, C_{1-6} alkyl, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$, $-O(C_{1-6}alkyl)$, $-O(5- to 6-membered aryl)$, $-O(5- to 6-membered heteroaryl)$, $-NHC(O)(C_{1-6}alkyl)$, $-NHC(O)(5- to 6-membered aryl)$, or $-NHC(O)O(C_{1-6}alkyl)$, wherein

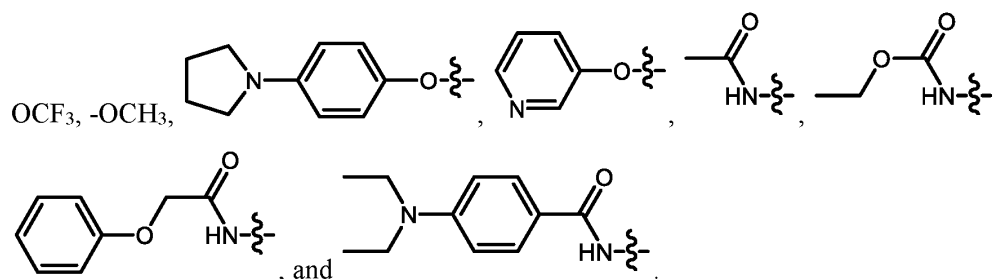
the $-O(C_{1-6}alkyl)$ is optionally substituted with phenyl or halo;

the $-O(5- to 6-membered aryl)$ is optionally substituted with 4- to 6-membered heterocyclyl;

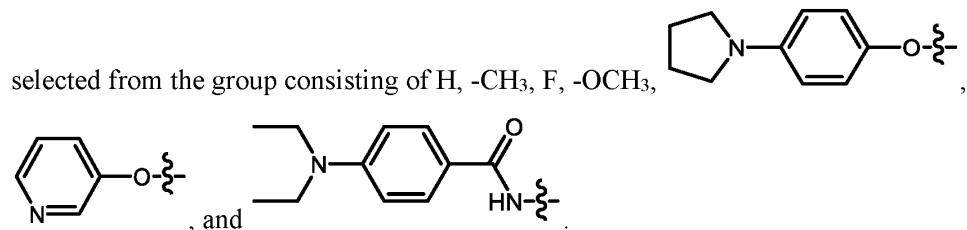
the $-NHC(O)(C_{1-6}alkyl)$ is optionally by $-O(5- to 6-membered aryl)$; and

the $-NHC(O)(5- to 6-membered aryl)$ is optionally substituted with $-N(R^x)(R^y)$.

22. The compound of any of claims 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 and R^7 are each independently selected from the group consisting of H, $-CH_3$, F, $-NH(CH_3)$, $-N(CH_3)(CH_3)$, -



23. The compound of any of claims 1-20, wherein R^6 and R^7 are each independently



24. The compound of any of claims 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

L is a bond or -O(C₁₋₆alkyl);

R^4 is 3- to 12-membered N-containing heterocyclyl optionally substituted by R^{4b} , -C(=O) R^{11} , -C(=O)N(R^{10})(R^{11}), or -C(=O)OR¹¹; and

R^1 is C₁₋₄alkyl optionally substituted with one or more substituents selected from the group consisting of -OH, -NH(CH₃), and -N(CH₃)(CH₃).

25. 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.

26. A compound selected from compounds 1 to 40 of Table 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

27. A pharmaceutical composition comprising a compound of any of claims 1-26, 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.

28. 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 1-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 27.

29. The method of claim 28, wherein said disease or condition mediated by TDP-43 is a neurological disease or condition.

30. The method of claim 29, 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).

31. The method of claim 29 or 30, wherein the neurological disease or condition is traumatic brain injury (TBI).

32. The method of claim 29 or 30, wherein the neurological disease or condition is frontotemporal dementia (FTD).

33. The method of claim 29 or 30, wherein the neurological disease or condition is amyotrophic lateral sclerosis (ALS).

34. The method of any of claims 29, 30, or 33, wherein the neurological disease or condition is sporadic amyotrophic lateral sclerosis or C9ORF72 amyotrophic lateral sclerosis.

35. The method of any of claims 28-34, wherein the individual is a human.

36. A method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of any of claims 1-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 27, 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 TDP-43 protein-protein interactions.

37. 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 1-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 27.

38. The method of claim 37, wherein the gene expression levels are for *STMN2*.
39. The method of claim 37, wherein the gene expression levels are for *POLDIP3*.
40. The compound of any of claims 1-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 27 for use in the treatment of a disease or condition mediated by TDP-43.
41. Use of a compound of any of claims 1-26, 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 disorder mediated by TDP-43.
42. A kit, comprising (i) a compound of any one of claims 1-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 27 and (ii) instructions for use in treating a TDP-43 mediated disease or condition in an individual in need thereof.