

THIENOPYRIDINE COMPOUNDS AND USES THEREOF**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority benefit of United States Provisional Patent Application No. 63/618,195 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 thienopyridine 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.

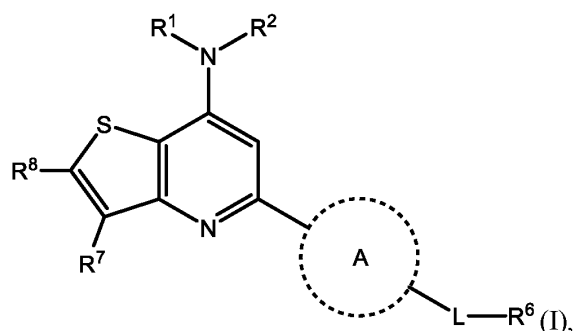
BACKGROUND OF THE INVENTION

[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 solvate of any of the foregoing, wherein

R¹ and R² are each independently H, C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R¹ or R² 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 or R² is optionally substituted with one or more R^{1b},

and

optionally, two substituents of the C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl group of R¹ or R² 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};

or R¹ and R² are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein

3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of R¹ and R² is

optionally substituted with one or more R³;

each R³ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -

$C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{11})R^{12}$, $-S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein
 the C_{1-6} alkyl of R^3 is optionally substituted with one or more R^{3a} ;
 the C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{3b} ; and
 optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl,

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

Ring A is C_{3-8} cycloalkyl, 4- to 12-membered cycloalkenyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C_{3-8} cycloalkyl, 4- to 12-membered cycloalkenyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R^4 , and

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

each R^4 is independently halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{11})R^{12}$, $-S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein
 the C_{1-6} alkyl of R^4 is optionally substituted by one or more R^{4a} ,

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

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

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

the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 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;

R⁵ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R⁵ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², or -S(=O)₂N(R¹¹)(R¹²), and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{5b};

R⁶ is H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁶ is optionally substituted with one or more R^{6b}, -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), or -C(=O)OR¹², and

the 3- to 12-membered heterocyclyl of R⁶ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R⁶ 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^{6b};

R⁷ and R⁸ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹³)R¹², -S(=NR¹³)OR¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁷ or R⁸ is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁷ or R⁸ is optionally substituted with one or more R^{7b}, and

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

optionally, two substituents of 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^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹³)R¹², -S(=NR¹³)OR¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), 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^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

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

each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, -CN, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

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

each R^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 of R^9 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^9 is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

each R^{10} 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, $-N(R^x)(R^y)$, 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 8-membered heterocyclyl, 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 $-N(R^x)(R^y)$;

each R^{11} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

each R^{12} 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^{12} 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

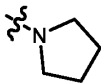
the C_{3-8} cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{12} is optionally substituted with halo, C_{1-6} alkyl, or $-N(R^x)(R^y)$;

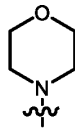
each R^{13} is independently H or C_{1-6} alkyl; and

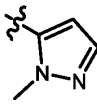
each R^x and R^y is independently H, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-C(=O)(C_{1-6}$ alkyl), or $-C(=O)O(C_{1-6}$ alkyl), wherein

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

(i) when $-(\text{Ring A})-L-R^6$ are taken together to form , and R^1 is H, R^8 is not optionally substituted pyrazolyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form , and Ring A is 5-membered N-containing heteroaryl, then $L-R^6$ are not taken together to form halo, pyridyl substituted by methyl, or substituted phenyl; and

(iii) when $-(\text{Ring A})-L-R^6$ are taken together to form , R^1 is H, and R^2 is $-CH_3$, R^8 is not $-CH_3$.

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

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

if each and every embodiment were specifically and individually listed. It is also understood and described that all such embodiments may be used in any of the pharmaceutical compositions, methods, kits, uses, or other aspects detailed herein.

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

[0009] In one aspect, provided is a method for treating a disease or condition mediated by TDP-43, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another variation, provided is a method for treating a disease or condition mediated by TDP-43, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt 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 (I), (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

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

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

(III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

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

[0013] In one aspect, provided herein is the use of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients, in the manufacture a medicament for the treatment of a disease or condition mediated by TDP-43. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another variation, provided is the use of 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, 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 (I), (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0014] In one aspect, provided herein is a kit, comprising (i) a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and (ii) instructions for use in treating a TDP-43 mediated disease or

condition in an individual in need thereof. This aspect in some embodiments may employ a compound of any of formulas (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing. In another variation, provided is a kit, comprising (i) 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 (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 (I), (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0015] All pharmaceutical compositions, methods, kits, uses, or other aspects described herein with reference to formula (I), or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, are also hereby described and embraced for any one of the other formulas detailed herein such as formula (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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 mean to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, difluoromethyl, and the like.

[0030] The term “heteroaryl”, as used herein, refers to an aromatic (fully unsaturated) ring moiety that comprises one or more annular heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The term “heteroaryl” includes both monocyclic and polycyclic fused-ring moieties. As used herein, a heteroaryl comprises, for example, 5 to 20 annular atoms (*i.e.*, a 5- to 20-membered heteroaryl), 5 to 16 annular atoms (*i.e.*, a 5- to 16-membered heteroaryl), 5 to 12 annular atoms (*i.e.*, a 5- to 12-membered heteroaryl), 5 to 10 annular atoms (*i.e.*, a 5- to 10-membered heteroaryl), 5 to 8 annular atoms (*i.e.*, a 5- to 8-membered heteroaryl), or 5 to 6 annular atoms (*i.e.*, a 5- to 6-membered heteroaryl). Any monocyclic or polycyclic aromatic ring moiety comprising one or more

annular heteroatoms is considered a heteroaryl, regardless of the point of attachment to the remainder of the molecule (*i.e.*, the heteroaryl moiety may be attached to the remainder of the molecule through any annular carbon or any annular heteroatom of the heteroaryl moiety). Examples of heteroaryl groups include, but are not limited to, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, and pyridazinyl.

[0031] The term “heterocyclyl”, as used herein, refers to a saturated or partially unsaturated cyclic moiety that encompasses one or more annular heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The term “heterocyclyl” includes both monocyclic and polycyclic ring moieties, wherein the polycyclic ring moieties may be fused, bridged, or spiro. Any non-aromatic monocyclic or polycyclic ring moiety comprising at least one annular heteroatom is considered a heterocyclyl, regardless of the point of attachment to the remainder of the molecule (*i.e.*, the heterocyclyl moiety may be attached to the remainder of the molecule through any annular carbon or any annular heteroatom of the heterocyclyl moiety). Further, the term heterocyclyl is intended to encompass any polycyclic ring moiety comprising at least one annular heteroatom wherein the polycyclic ring moiety comprises at least one non-aromatic ring, regardless of the point of attachment to the remainder of the molecule. As used herein, a heterocyclyl comprises, for example, 3 to 20 annular atoms (*i.e.*, a 3- to 20-membered heterocyclyl), 3 to 16 annular atoms (*i.e.*, a 3- to 16-membered heterocyclyl), 3 to 12 annular atoms (*i.e.*, a 3- to 12-membered heterocyclyl), 3 to 10 annular atoms (*i.e.*, a 3- to 10-membered heterocyclyl), 3 to 8 annular atoms (*i.e.*, a 3- to 8-membered heterocyclyl), 3 to 6 annular atoms (*i.e.*, a 3- 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, piperaziny, pyrrolidiny, pyrazolidiny, thiazolidiny, tetrahydrofuryl, or tetrahydropyrany. Examples of spiro heterocyclyl rings include, but are not limited to, bicyclic and tricyclic ring systems, such as 2-oxa-7-azaspiro[3.5]nonany, 2-oxa-6-azaspiro[3.4]octany, and 6-oxa-1-azaspiro[3.3]heptany. Examples of fused heterocyclyl rings include, but are not limited to, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidinyl, 6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidinyl, 5,7-dihydrofuro[3,4-d]pyrimidinyl, and 5,7-dihydrothieno[3,4-d]pyrimidinyl, where the heterocyclyl can be bound via either ring of the fused system.

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

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

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

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

[0036] The terms “optional” and “optionally”, as used herein, mean that the subsequently described event or circumstance may or may not occur and that the description includes instances where the event or circumstance occurs and instances where it does not.

Accordingly, the term “optionally substituted” infers that any one or more (*e.g.*, 1, 2, 1 to 5, 1 to 3, 1 to 2, etc.) hydrogen atoms on the designated atom or moiety or group may be replaced or not replaced by an atom or moiety or group other than hydrogen. By way of illustration and not limitation, the phrase “methyl optionally substituted with one or more chloro” encompasses -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.

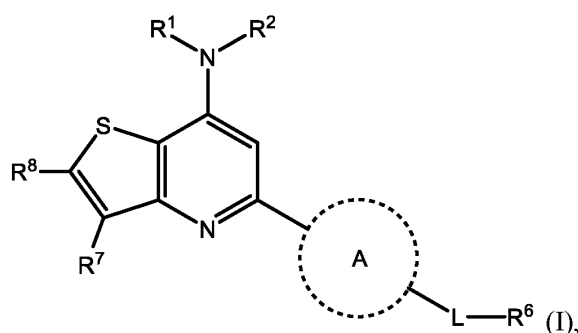
[0042] The compounds of the present disclosure, or their pharmaceutically acceptable salts, hydrates, or solvates may include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- 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 solvate of any of the foregoing, wherein

R^1 and R^2 are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{12}$, $-C(=O)OR^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

and

optionally, two substituents of the C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{12}$, $-C(=O)OR^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, or C_{3-8} cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

or R¹ and R² are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein

3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of R¹ and R² is optionally substituted with one or more R³;

each R³ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more R^{3a};

the C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{3b}; and optionally, two substituents of R³ 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 one or more R^{3b};

Ring A is C₃₋₈cycloalkyl, 4- to 12-membered cycloalkenyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 4- to 12-membered cycloalkenyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R⁴, and

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

each R⁴ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -

$S(=NR^{13})N(R^{11})R^{12}$, $-S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

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

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

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

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, -

$OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, C_{3-8} cycloalkyl, 3- to 8-

membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

two R^L are taken together along with the atoms to which they are attached to form a

C_{3-8} cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(=O)R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, or C_{3-8} cycloalkyl, wherein

the C_{1-6} alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{10}$,

$-SR^{10}$, $-SF_5$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, -

$OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, -

$C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, -

$N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, -

$S(=NR^{13})N(R^{11})R^{12}$, $-S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, or $-S(=O)_2N(R^{11})(R^{12})$, and

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

R^6 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^9$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, -

NO_2 , $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, -

$OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, -

$C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, -

$S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{11})R^{12}$, -

$S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, 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^6 is optionally substituted by one or more R^{6a} ,

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁶ is optionally substituted with one or more R^{6b}, -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), or -C(=O)OR¹², and the 3- to 12-membered heterocyclyl of R⁶ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and optionally, two substituents of R⁶ 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^{6b};

R⁷ and R⁸ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹³)R¹², -S(=NR¹³)OR¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁷ or R⁸ is optionally substituted by one or more R^{7a}, the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁷ or R⁸ is optionally substituted with one or more R^{7b}, and the 3- to 8-membered heterocyclyl of R⁷ or R⁸ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and optionally, two substituents of 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^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -

$S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{13})R^{12}$, $-S(=NR^{13})OR^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein
 the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^{1a} , R^{3a} , R^{4a} , R^{6a} , or R^{7a} is optionally substituted with one or more R^{1b} , and
 the 3- to 12-membered heterocyclyl of R^{1a} , R^{3a} , R^{4a} , R^{6a} , or R^{7a} comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;
 each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein
 the C_{1-6} alkyl of R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is optionally substituted by $-OR^{12}$, $-N(R^x)(R^y)$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl;
 each R^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 of R^9 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^9 is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;
 each R^{10} 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, $-N(R^x)(R^y)$, 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 8-membered heterocyclyl, 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 $-N(R^x)(R^y)$;
 each R^{11} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;
 each R^{12} 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 C₁₋₆alkyl of R¹² 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

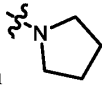
the C₃₋₈cycloalkyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or 3- to 12-membered heterocyclyl of R¹² is optionally substituted with halo, C₁₋₆alkyl, or -N(R^x)(R^y);

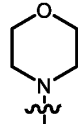
each R¹³ is independently H or C₁₋₆alkyl; and

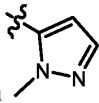
each R^x and R^y is independently H, C₁₋₆alkyl, C₃₋₈cycloalkyl, -C(=O)(C₁₋₆alkyl), or -C(=O)O(C₁₋₆alkyl), wherein

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;

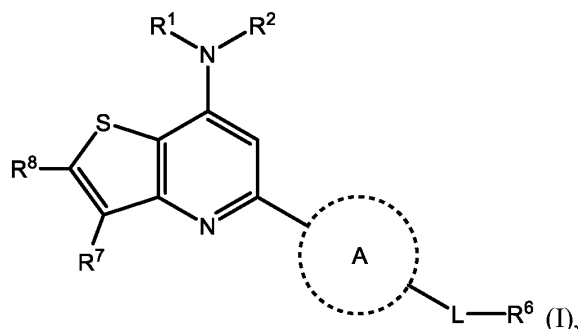
wherein

(i) when -(Ring A)-L-R⁶ are taken together to form , and R¹ is H, R⁸ is not optionally substituted pyrazolyl;

(ii) when R¹ and R² are taken together with the N to which they are attached to form , and Ring A is 5-membered N-containing heteroaryl, then L-R⁶ are not taken together to form halo, pyridyl substituted by methyl, or substituted phenyl; and

(iii) when -(Ring A)-L-R⁶ are taken together to form , R¹ is H, and R² is -CH₃, R⁸ is not -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.

[0046] 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, wherein

R^1 and R^2 are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{12}$, $-C(=O)OR^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

optionally, two substituents of the C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{12}$, $-C(=O)OR^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, or C_{3-8} cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

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

each R^3 is independently halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, -

$N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{11})R^{12}$, $-S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein the C_{1-6} alkyl of R^3 is optionally substituted with one or more R^{3a} , and optionally, two substituents of R^3 are taken together with the atoms to which they are attached form a C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted one or more R^{3b} ;

Ring A is C_{3-8} cycloalkyl, 4- to 12-membered cycloalkenyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl, 4- to 12-membered cycloalkenyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R^4 , and the 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S; each R^4 is independently halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{11})R^{12}$, $-S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein the C_{1-6} alkyl of R^4 is optionally substituted by one or more R^{4a} , the C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^4 is optionally substituted with one or more R^{4b} , and the 3- to 8-membered heterocyclyl of R^4 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S;

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

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

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

R^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(=O)R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, or C_{3-8} cycloalkyl, wherein

the C_{1-6} alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{11})R^{12}$, $-S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, or $-S(=O)_2N(R^{11})(R^{12})$, and

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

R^6 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^9$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{11})R^{12}$, $-S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, 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^6 is optionally substituted by one or more R^{6a} ,

the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^6 is optionally substituted with one or more R^{6b} , $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$, and

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

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

the 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^{6b};

R⁷ and R⁸ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹³)R¹², -S(=NR¹³)OR¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁷ or R⁸ is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁷ or R⁸ is optionally substituted with one or more R^{7b}, and

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

optionally, two substituents of 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^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹³)R¹², -S(=NR¹³)OR¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), 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^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

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

each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, -CN, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

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

each R^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 of R^9 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^9 is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

each R^{10} 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^{11} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

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

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

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

the 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)C₁₋₆alkyl). 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 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 solvate of any of the foregoing,

R¹ is H, C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), 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)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), 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};

R² is C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R² 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 R² is optionally substituted with one or more R^{1b}, and optionally, two substituents of the C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl group of R² 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};

or R¹ and R² are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein

3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of R¹ and R² is optionally substituted with one or more R³;

each R³ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more R^{3a}, and optionally, two substituents of R³ 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 one or more R^{3b};

Ring A is C₃₋₈cycloalkyl, 4- to 12-membered cycloalkenyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 4- to 12-membered cycloalkenyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R⁴, and

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

each R⁴ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -

C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-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 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁴ is optionally substituted with one or more R^{4b}, and

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

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)-, wherein

the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 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;

R⁵ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R⁵ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², or -S(=O)₂N(R¹¹)(R¹²), and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{5b};

R⁶ is H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -

$S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, 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^6 is optionally substituted by one or more R^{6a} ,
 the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^6 is optionally substituted with one or more R^{6b} , -
 $C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$, and
 the 3- to 12-membered heterocyclyl of R^6 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and
 optionally, two substituents of R^6 are taken together with the atoms to which they are attached form a C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein
 the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{6b} ,
 R^7 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^9$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{13})R^{12}$, $-S(=NR^{13})OR^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein
 the C_{1-6} alkyl of R^7 is optionally substituted by one or more R^{7a} ,
 the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^7 is optionally substituted with one or more R^{7b} , and
 the 3- to 8-membered heterocyclyl of R^7 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and
 optionally, two substituents of R^7 are taken together with the atoms to which they are attached form a C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein
 the C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b} ; and

R^8 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^9$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{13})R^{12}$, $-S(=NR^{13})OR^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, 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^8 is optionally substituted by one or more R^{7a} ,

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

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

optionally, two substituents of 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^{7b} ,

each R^{1a} , R^{3a} , R^{4a} , R^{6a} , or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{13})R^{12}$, $-S(=NR^{13})OR^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C₁₋₆alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by -OR¹², -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 of R⁹ 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 R⁹ is optionally substituted with halo, C₁₋₃alkyl, C₁₋₃alkoxy, -N(R^x)(R^y), or 3- to 12-membered heterocyclyl;

each R¹⁰ 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 R¹¹ is independently H, C₁₋₆alkyl, or C₃₋₈cycloalkyl;

each R¹² 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 R¹² 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 R¹² is optionally substituted with halo, C₁₋₆alkyl, or -N(R^x)(R^y);

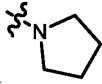
each R¹³ is independently H or C₁₋₆alkyl; and

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

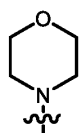
the C₁₋₆alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or -NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆alkyl)(C₁₋₆alkyl), and

the C₁₋₆alkyl of -C(=O)(C₁₋₆alkyl) or -C(=O)O(C₁₋₆alkyl) is optionally substituted with -O(C(=O)C₁₋₈alkyl);

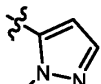
wherein

(i) when -(Ring A)-L-R⁶ are taken together to form , and R¹ is H, R⁸ is not optionally substituted pyrazolyl;

(ii) when R¹ and R² are taken together with the N to which they are attached to form



, -(Ring A)-L-R⁶ are not taken together to form a pyrazolyl substituted by 3-methylphenyl; and

(iii) when -(Ring A)-L-R⁶ are taken together to form , R¹ is H, and R² is -CH₃, R⁸ is not -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 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 solvate of any of the foregoing,

R¹ is H, C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), 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}, and

optionally, two substituents of the C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), 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};

R² is C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R² is optionally substituted with one or more R^{1a},
 the C₃₋₈cycloalkyl of R² is optionally substituted with one or more R^{1b}, and
 optionally, two substituents of the C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -
 C(=O)N(R¹¹)(R¹²), or C₃₋₈cycloalkyl group of R² 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};

or R¹ and R² are taken together with the N to which they are attached to form a 3- to 12-
 membered heterocyclyl or 5- to 10-membered heteroaryl, wherein

3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of R¹ and R² is
 optionally substituted with one or more R³;

each R³ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -
 N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -
 OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -
 C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -
 N(R¹¹)S(=O)₂R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered
 heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more R^{3a}, and
 optionally, two substituents of R³ 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 one
 or more R^{3b};

Ring A is C₃₋₈cycloalkyl, 4- to 8-membered cycloalkenyl, 3- to 8-membered heterocyclyl,
 phenyl, or 5- to 6-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 4- to 8-membered cycloalkenyl, 3- to 8-membered heterocyclyl,
 phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or
 more R⁴, and

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

each R^4 is independently halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

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

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

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

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

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

R^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(=O)R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, or C_{3-8} cycloalkyl, wherein

the C_{1-6} alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)_2R^{12}$, or $-S(=O)_2N(R^{11})(R^{12})$, and

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

R^6 is H, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^9$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)_2R^{12}$, or $-S(=O)_2N(R^{11})(R^{12})$, or

$S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

$C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$, and

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

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

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

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

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

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

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

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

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

R^8 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^9$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, -

$C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, 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^8 is optionally substituted by one or more R^{7a} ,

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

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

optionally, two substituents of 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^{7b} ;

each R^{1a} , R^{3a} , R^{4a} , R^{6a} , or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

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

each R^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 C₁₋₆alkyl of R⁹ 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 R⁹ is optionally substituted with halo, C₁₋₃alkyl, C₁₋₃alkoxy, -N(R^x)(R^y), or 3- to 12-membered heterocyclyl;

each R¹⁰ 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 R¹¹ is independently H, C₁₋₆alkyl, or C₃₋₈cycloalkyl;

each R¹² is independently H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, wherein

the C₁₋₆alkyl of R¹² is optionally substituted by one or more halo, -OH, -O(C₁₋₆alkyl), -N(R^x)(R^y), C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R¹² is optionally substituted with halo, C₁₋₆alkyl, or -N(R^x)(R^y);

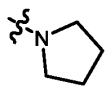
each R¹³ is independently H or C₁₋₆alkyl; and

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

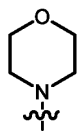
the C₁₋₆alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or -NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆alkyl)(C₁₋₆alkyl), and

the C₁₋₆alkyl of -C(=O)(C₁₋₆alkyl) or -C(=O)O(C₁₋₆alkyl) is optionally substituted with -O(C(=O)C₁₋₈alkyl);

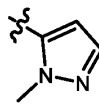
wherein

(i) when -(Ring A)-L-R⁶ are taken together to form , and R¹ is H, R⁸ is not optionally substituted pyrazolyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form



, -(Ring A)-L- R^6 are not taken together to form a pyrazolyl substituted by 3-methylphenyl; and



(iii) when -(Ring A)-L- R^6 are taken together to form , R^1 is H, and R^2 is - CH_3 , R^8 is not - 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 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 solvate of any of the foregoing,

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

R^2 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein

the C_{1-6} alkyl or C_{3-6} cycloalkyl of R^2 is optionally substituted with one or more -OH or -N(R^x)(R^y),

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

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

each R^3 is independently halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R^{11})C(=O) R^{12} , -N(R^{11})C(=O)N(R^{11}) R^{12} , -N(R^{11})C(=O)OR¹², -OC(=O) R^{12} , -OC(=O)N(R^{11}) R^{12} , -OC(=O)OR¹², -C(=O) R^{12} , -C(=O)N(R^{11})(R^{12}), -C(=O)OR¹², -C(=NR¹³) R^{12} , -C(=NOR¹²) R^{12} , -C(=NR¹³)N(R^{11}) R^{12} , -C(=NR¹³)OR¹², -N(R^{11})S(=O)₂ R^{12} , -S(=O) R^{12} , -S(=O)N(R^{11}) R^{12} , -S(=O)OR¹², -S(=NR¹³) R^{12} , -S(=NR¹³)N(R^{11}) R^{12} , -S(=NR¹³)OR¹³, -S(=O)₂ R^{12} , -S(=O)₂N(R^{11})(R^{12}), C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein the C_{1-6} alkyl of R^3 is optionally substituted with one or more R^{3a} , and

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

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

Ring A is phenyl or 5- to 6-membered heteroaryl, wherein

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

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

each R^4 is independently halo or $-OR^{10}$;

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

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

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

R^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(=O)R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, or C_{3-8} cycloalkyl, wherein

the C_{1-6} alkyl of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{11})R^{12}$, $-S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, or $-S(=O)_2N(R^{11})(R^{12})$, and the C_{3-8} cycloalkyl is optionally substituted with one or more R^{5b} ;

R^6 is H, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, -

$C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b} , - $C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$;

R^7 is H;

R^8 is C_{1-6} alkyl, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, or $-C(=O)R^{12}$;

each R^{1a} , R^{3a} , R^{4a} , R^{6a} , or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{13})R^{12}$, $-S(=NR^{13})OR^{14}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

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

each R^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 of R^9 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^9 is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

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

wherein the C₁₋₆alkyl is optionally substituted with one or more halo, deuterium, 3- to 8-membered heterocyclyl;

each R¹¹ is independently H, C₁₋₆alkyl, or C₃₋₈cycloalkyl;

each R¹² is independently H, C₁₋₆alkyl, C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the C₁₋₆alkyl of R¹² is optionally substituted by one or more halo, -OH, -O(C₁₋₆alkyl), -N(R^x)(R^y), C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R¹² is optionally substituted with halo, C₁₋₆alkyl, or -N(R^x)(R^y);

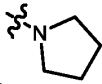
each R¹³ is independently H or C₁₋₆alkyl; and

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

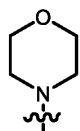
the C₁₋₆alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or -NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆alkyl)(C₁₋₆alkyl), and

the C₁₋₆alkyl of -C(=O)(C₁₋₆alkyl) or -C(=O)O(C₁₋₆alkyl) is optionally substituted with -O(C(=O)C₁₋₈alkyl);

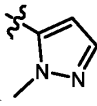
wherein

(i) when -(Ring A)-L-R⁶ are taken together to form , and R¹ is H, R⁸ is not optionally substituted pyrazolyl;

(ii) when R¹ and R² are taken together with the N to which they are attached to form



, -(Ring A)-L-R⁶ are not taken together to form a pyrazolyl substituted by 3-methylphenyl; and

(iii) when -(Ring A)-L-R⁶ are taken together to form , R¹ is H, and R² is -CH₃, R⁸ is not -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 any of the foregoing.

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

R¹ is H or C₁₋₆alkyl;

R² is C₁₋₆alkyl or C₃₋₆cycloalkyl, wherein

the C₁₋₆alkyl or C₃₋₆cycloalkyl of R² is optionally substituted with one or more -OH or -N(R^x)(R^y),

or R¹ and R² are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl, wherein

3- to 12-membered heterocyclyl of R¹ and R² is optionally substituted with one or more R³;

each R³ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more R^{3a};

the C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{3b}; and optionally, two substituents of R³ 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 one or more R^{3b};

Ring A is phenyl or 5- to 6-membered heteroaryl, wherein

the phenyl or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R⁴, and

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

each R⁴ is independently halo, C₁₋₆alkyl, or -OR¹⁰;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)-, wherein

the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 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;

R⁵ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R⁵ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², or -S(=O)₂N(R¹¹)(R¹²), and the C₃₋₈cycloalkyl is optionally substituted with one or more R^{5b};

R⁶ is H, -OR⁹, -OR¹⁰, -N(R^x)(R^y), -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b}, -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), or -C(=O)OR¹²;

R⁷ is H;

R⁸ is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR⁹, -OR¹⁰, -N(R^x)(R^y), -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl of R⁸ is optionally substituted with one or more R^{7b}, and

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

each R^{1a} , R^{3a} , R^{4a} , R^{6a} , or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{13})R^{12}$, $-S(=NR^{13})OR^{14}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

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

each R^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 of R^9 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^9 is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

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

wherein the C_{1-6} alkyl is optionally substituted with one or more halo, deuterium, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

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

each R^{11} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

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

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

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

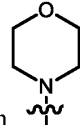
each R^{13} is independently H or C_{1-6} alkyl; and

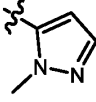
each R^x and R^y is independently H, C_{1-6} alkyl, C_{3-8} cycloalkyl, -C(=O)(C_{1-6} alkyl), or -C(=O)O(C_{1-6} alkyl), wherein

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

wherein

(i) when R^1 and R^2 are taken together with the N to which they are attached to form , - (Ring A)-L- R^6 are not taken together to form a pyrazolyl substituted by Br; and

(ii) when -(Ring A)-L- R^6 are taken together to form , R^1 is H, and R^2 is -CH₃, R^8 is not -CH₃.

[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 solvate of any of the foregoing,

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

R^2 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein

the C_{1-6} alkyl or C_{3-6} cycloalkyl of R^2 is optionally substituted with one or more -OH or -N(R^x)(R^y),

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

3- to 12-membered heterocyclyl of R¹ and R² is optionally substituted with one or more R³;

each R³ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NR¹³)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more R^{3a}, and optionally, two substituents of R³ 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 one or more R^{3b};

Ring A is phenyl or 5- to 6-membered heteroaryl, wherein

the phenyl or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R⁴, and

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

each R⁴ is independently halo or -OR¹⁰;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)-, wherein

the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 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;

R⁵ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R⁵ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)₂R¹², or -S(=O)₂N(R¹¹)(R¹²), and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{5b};

R⁶ is H, -OR⁹, -OR¹⁰, -N(R^x)(R^y), -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b}, -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), or -C(=O)OR¹²;

R⁷ is H;

R⁸ is C₁₋₆alkyl, -OR⁹, -OR¹⁰, -N(R^x)(R^y), or -C(=O)R¹²;

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), 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^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

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

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C₁₋₆alkyl, -OR⁹, -N(R^x)(R^y), oxo, -CN, C₃₋₈cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C₁₋₆alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by -OR¹², -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 of R⁹ 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 R⁹ is optionally substituted with halo, C₁₋₃alkyl, C₁₋₃alkoxy, -N(R^x)(R^y), or 3- to 12-membered heterocyclyl;

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

wherein the C₁₋₆alkyl is optionally substituted with one or more halo, deuterium, 3- to 8-membered heterocyclyl;

each R¹¹ is independently H, C₁₋₆alkyl, or C₃₋₈cycloalkyl;

each R¹² is independently H, C₁₋₆alkyl, C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the C₁₋₆alkyl of R¹² is optionally substituted by one or more halo, -OH, -O(C₁₋₆alkyl), -N(R^x)(R^y), C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R¹² is optionally substituted with halo, C₁₋₆alkyl, or -N(R^x)(R^y);

each R¹³ is independently H or C₁₋₆alkyl; and

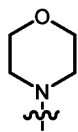
each R^x and R^y is independently H, C₁₋₆alkyl, C₃₋₈cycloalkyl, -C(=O)(C₁₋₆alkyl), or -C(=O)O(C₁₋₆alkyl), wherein

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);

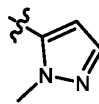
wherein

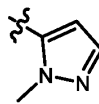
(i) when -(Ring A)-L-R⁶ are taken together to form , and R¹ is H, R⁸ is not optionally substituted pyrazolyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form



, -(Ring A)-L- R^6 are not taken together to form a pyrazolyl substituted by 3-methylphenyl; and



(iii) when -(Ring A)-L- R^6 are taken together to form , R^1 is H, and R^2 is -CH₃, R^8 is not -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 any of the foregoing.

[0052] 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 of any of the foregoing,

R^1 is H or C₁₋₆alkyl;

R^2 is C₁₋₆alkyl or C₃₋₆cycloalkyl, wherein

the C₁₋₆alkyl or C₃₋₆cycloalkyl of R^2 is optionally substituted with one or more -OH or -N(R^x)(R^y),

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

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

each R^3 is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R^{11})C(=O) R^{12} , -N(R^{11})C(=O)N(R^{11}) R^{12} , -N(R^{11})C(=O)OR¹², -OC(=O) R^{12} , -OC(=O)N(R^{11}) R^{12} , -OC(=O)OR¹², -C(=O) R^{12} , -C(=O)N(R^{11})(R^{12}), -C(=O)OR¹², -C(=NR¹³) R^{12} , -C(=NOR¹²) R^{12} , -C(=NR¹³)N(R^{11}) R^{12} , -C(=NR¹³)OR¹², -N(R^{11})S(=O)₂ R^{12} , -S(=O)₂ R^{12} , -S(=O)₂N(R^{11})(R^{12}), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R^3 is optionally substituted with one or more R^{3a} ;

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

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

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

Ring A is phenyl or 5- to 6-membered heteroaryl, wherein

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

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

each R^4 is independently halo, C_{1-6} alkyl, or $-OR^{10}$;

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

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

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or

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

R^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(=O)R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, or C_{3-8} cycloalkyl, wherein

the $C_{1-6}alkyl$ of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)_2R^{12}$, or $-S(=O)_2N(R^{11})(R^{12})$, and

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

R^6 is H, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b} , $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$;

R^7 is H;

R^8 is halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, 3- to 8-membered heterocyclyl, wherein

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

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

each R^{1a} , R^{3a} , R^{4a} , R^{6a} , or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

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

each R^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 of R^9 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^9 is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

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

wherein the C_{1-6} alkyl is optionally substituted with one or more halo, deuterium, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

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

each R^{11} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

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

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

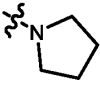
the C_{3-8} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{12} is optionally substituted with halo, C_{1-6} alkyl, or $-N(R^x)(R^y)$;

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

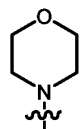
each R^x and R^y is independently H, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-C(=O)(C_{1-6}$ alkyl), or $-C(=O)O(C_{1-6}$ alkyl), wherein

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

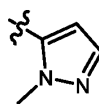
wherein

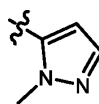
(i) when $-(\text{Ring A})-L-R^6$ are taken together to form , and R^1 is H, R^8 is not optionally substituted pyrazolyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form



, $-(\text{Ring A})-L-R^6$ are not taken together to form a pyrazolyl substituted by 3-methylphenyl; and



(iii) when $-(\text{Ring A})-\text{L}-\text{R}^6$ are taken together to form , R^1 is H, and R^2 is $-\text{CH}_3$, R^8 is not $-\text{CH}_3$.

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

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

R^2 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein

the C_{1-6} alkyl or C_{3-6} cycloalkyl of R^2 is optionally substituted with one or more $-\text{OH}$ or $-\text{N}(\text{R}^x)(\text{R}^y)$,

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

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

each R^3 is independently halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, $-\text{OR}^{10}$, $-\text{SR}^{10}$, $-\text{SF}_5$, $-\text{N}(\text{R}^x)(\text{R}^y)$, $-\text{NO}_2$, $-\text{CN}$, $-\text{N}(\text{R}^{11})\text{C}(=\text{O})\text{R}^{12}$, $-\text{N}(\text{R}^{11})\text{C}(=\text{O})\text{N}(\text{R}^{11})\text{R}^{12}$, $-\text{N}(\text{R}^{11})\text{C}(=\text{O})\text{OR}^{12}$, $-\text{OC}(=\text{O})\text{R}^{12}$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{11})\text{R}^{12}$, $-\text{OC}(=\text{O})\text{OR}^{12}$, $-\text{C}(=\text{O})\text{R}^{12}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{11})(\text{R}^{12})$, $-\text{C}(=\text{O})\text{OR}^{12}$, $-\text{C}(=\text{NR}^{13})\text{R}^{12}$, $-\text{C}(=\text{NOR}^{12})\text{R}^{12}$, $-\text{C}(=\text{NR}^{13})\text{N}(\text{R}^{11})\text{R}^{12}$, $-\text{C}(=\text{NR}^{13})\text{OR}^{12}$, $-\text{N}(\text{R}^{11})\text{S}(=\text{O})_2\text{R}^{12}$, $-\text{S}(=\text{O})\text{R}^{12}$, $-\text{S}(=\text{O})\text{N}(\text{R}^{11})\text{R}^{12}$, $-\text{S}(=\text{O})\text{OR}^{12}$, $-\text{S}(=\text{NR}^{13})\text{R}^{12}$, $-\text{S}(=\text{NR}^{13})\text{N}(\text{R}^{11})\text{R}^{12}$, $-\text{S}(=\text{NR}^{13})\text{OR}^{13}$, $-\text{S}(=\text{O})_2\text{R}^{12}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{11})(\text{R}^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

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

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

Ring A is phenyl or 5- to 6-membered heteroaryl, wherein

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

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

each R^4 is independently halo, C_{1-6} alkyl, or $-OR^{10}$;

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

each R^L is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, or two R^L are taken together along with the atoms to which they are attached to form a C_{3-8} cycloalkyl or 3- to 8-membered heterocyclyl;

R^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-C(=O)R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, or C_{3-8} cycloalkyl, wherein the $C_{1-6}alkyl$ of R^5 is optionally substituted with one or more halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{11})R^{12}$, $-S(=NR^{13})OR^{13}$, $-S(=O)_2R^{12}$, or $-S(=O)_2N(R^{11})(R^{12})$, and the C_{3-8} cycloalkyl is optionally substituted with one or more R^{5b} ;

R^6 is H, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b} , $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$;

R^7 is H;

R^8 is halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl of R⁸ is optionally substituted with one or more R^{7b}, and

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

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹³)R¹², -S(=NR¹³)OR¹⁴, -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), 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^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

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

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C₁₋₆alkyl, -OR⁹, -N(R^x)(R^y), oxo, -CN, C₃₋₈cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C₁₋₆alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by -OR¹², -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 of R⁹ 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 R⁹ is optionally substituted with halo, C₁₋₃alkyl, C₁₋₃alkoxy, -N(R^x)(R^y), or 3- to 12-membered heterocyclyl;

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

wherein the C₁₋₆alkyl is optionally substituted with one or more halo, deuterium, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, phenyl, or 5- to 6-membered heteroaryl is optionally substituted with halo, C₁₋₃alkyl, C₁₋₃alkoxy, or -N(R^x)(R^y);

each R¹¹ is independently H, C₁₋₆alkyl, or C₃₋₈cycloalkyl;

each R¹² is independently H, C₁₋₆alkyl, C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the C₁₋₆alkyl of R¹² is optionally substituted by one or more halo, -OH, -O(C₁₋₆alkyl), -N(R^x)(R^y), C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R¹² is optionally substituted with halo, C₁₋₆alkyl, or -N(R^x)(R^y);

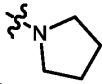
each R¹³ is independently H or C₁₋₆alkyl; and

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

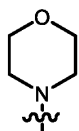
the C₁₋₆alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or -NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆alkyl)(C₁₋₆alkyl), and

the C₁₋₆alkyl of -C(=O)(C₁₋₆alkyl) or -C(=O)O(C₁₋₆alkyl) is optionally substituted with -O(C(=O)C₁₋₈alkyl);

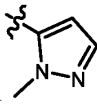
wherein

(i) when -(Ring A)-L-R⁶ are taken together to form , and R¹ is H, R⁸ is not optionally substituted pyrazolyl;

(ii) when R¹ and R² are taken together with the N to which they are attached to form



, -(Ring A)-L-R⁶ are not taken together to form a pyrazolyl substituted by 3-methylphenyl; and

(iii) when -(Ring A)-L-R⁶ are taken together to form , R¹ is H, and R² is -CH₃, R⁸ is not -CH₃. In some embodiments of the above, the compound of formula (I) is a compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0054] 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 of any of the foregoing,

R¹ is H or C₁₋₆alkyl;

R² is C₁₋₆alkyl or C₃₋₆cycloalkyl, wherein

the C₁₋₆alkyl or C₃₋₆cycloalkyl of R² is optionally substituted with one or more -OH or -N(R^x)(R^y),

or R¹ and R² are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl, wherein

3- to 12-membered heterocyclyl of R¹ and R² is optionally substituted with one or more R³;

each R³ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more R^{3a};

the C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{3b}; and optionally, two substituents of R³ 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 one or more R^{3b};

Ring A is phenyl or 5- to 6-membered heteroaryl, wherein

the phenyl or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R⁴, and

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

each R⁴ is independently halo, C₁₋₆alkyl, or -OR¹⁰;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)-, wherein

the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 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;

R⁵ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R⁵ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)₂R¹², or -S(=O)₂N(R¹¹)(R¹²), and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{5b};

R⁶ is H, -OR⁹, -OR¹⁰, -N(R^x)(R^y), -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b}, -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), or -C(=O)OR¹²;

R⁷ is H;

R⁸ is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR⁹, -OR¹⁰, -N(R^x)(R^y), -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl of R⁸ is optionally substituted with one or more R^{7b}, and

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

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -

OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), 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^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

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

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C₁₋₆alkyl, -OR⁹, -N(R^x)(R^y), oxo, -CN, C₃₋₈cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C₁₋₆alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by -OR¹², -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 of R⁹ 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 R⁹ is optionally substituted with halo, C₁₋₃alkyl, C₁₋₃alkoxy, -N(R^x)(R^y), or 3- to 12-membered heterocyclyl;

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

wherein the C₁₋₆alkyl is optionally substituted with one or more halo, deuterium, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, phenyl, or 5- to 6-membered heteroaryl is optionally substituted with halo, C₁₋₃alkyl, C₁₋₃alkoxy, or -N(R^x)(R^y);

each R¹¹ is independently H, C₁₋₆alkyl, or C₃₋₈cycloalkyl;

each R¹² is independently H, C₁₋₆alkyl, C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the C₁₋₆alkyl of R¹² is optionally substituted by one or more halo, -OH, -O(C₁₋₆alkyl), -N(R^x)(R^y), C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R¹² is optionally substituted with halo, C₁₋₆alkyl, or -N(R^x)(R^y);

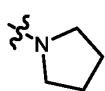
each R¹³ is independently H or C₁₋₆alkyl; and

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

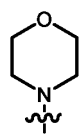
the C₁₋₆alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or -NH₂, NH(C₁₋₆alkyl), or -N(C₁₋₆alkyl)(C₁₋₆alkyl), and

the C₁₋₆alkyl of -C(=O)(C₁₋₆alkyl) or -C(=O)O(C₁₋₆alkyl) is optionally substituted with -O(C=O)C₁₋₈alkyl);

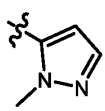
wherein

(i) when -(Ring A)-L-R⁶ are taken together to form , and R¹ is H, R⁸ is not optionally substituted pyrazolyl;

(ii) when R¹ and R² are taken together with the N to which they are attached to form



, -(Ring A)-L-R⁶ are not taken together to form a pyrazolyl substituted by 3-methylphenyl; and

(iii) when -(Ring A)-L-R⁶ are taken together to form , R¹ is H, and R² is -CH₃, R⁸ is not -CH₃.

[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,

L is a bond or -O(C₁₋₆alkyl)-; and

R³ is H, -N(R^x)(R^y), or 4- to 12-membered heterocyclyl optionally substituted with one or more R^{3a}. 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 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,

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

L is a bond; and

R^6 is 4- to 12-membered heterocyclyl optionally substituted with one or more R^{6b} , -C(=O) R^{12} , -C(=O)N(R^{11})(R^{12}), or -C(=O)OR¹². 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 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^1 and R^2 are taken together with the N to which they are attached to form a 4- to 12-membered heterocyclyl optionally substituted with one or more R^3 ;

L is a bond; and

R^6 is piperazinyl optionally substituted with one or more R^{6b} , -C(=O) R^{12} , -C(=O)N(R^{11})(R^{12}), or -C(=O)OR¹². 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 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, or solvate of any of the foregoing,

L is -O(C₁₋₆alkyl)-; and

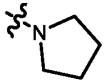
R^6 is H or -N(R^x)(R^y). In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

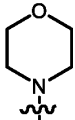
[0059] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing,

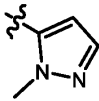
Ring A is phenyl; and

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

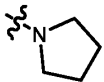
[0060] In some embodiments of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing

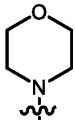
(i) when $-(\text{Ring A})-L-R^6$ are taken together to form , and R^1 is H, R^8 is not optionally substituted pyrazolyl;

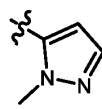
(ii) when R^1 and R^2 are taken together with the N to which they are attached to form , $-(\text{Ring A})-L-R^6$ are not taken together to form a pyrazolyl substituted by 3-methylphenyl; and

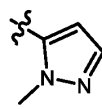
(iii) when $-(\text{Ring A})-L-R^6$ are taken together to form , R^1 is H, and R^2 is $-\text{CH}_3$, R^8 is not $-\text{CH}_3$. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0061] 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 solvate of any of the foregoing

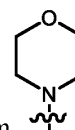
(i) when $-(\text{Ring A})-L-R^6$ are taken together to form , and R^1 is H, R^8 is not optionally substituted pyrazolyl;

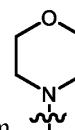
(ii) when R^1 and R^2 are taken together with the N to which they are attached to form , and Ring A is 5-membered N-containing heteroaryl, then $L-R^6$ are not taken together to form halo, pyridyl substituted by methyl, or substituted phenyl; and

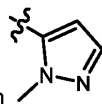


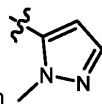
(iii) when $-(\text{Ring A})-\text{L}-\text{R}^6$ are taken together to form , R^1 is H, and R^2 is $-\text{CH}_3$, R^8 is not $-\text{CH}_3$. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0062] 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 solvate of any of the foregoing



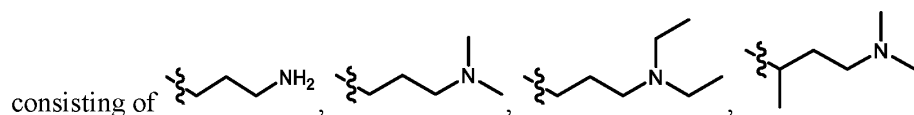
(i) when R^1 and R^2 are taken together with the N to which they are attached to form , $-(\text{Ring A})-\text{L}-\text{R}^6$ are not taken together to form a pyrazolyl substituted by Br; and

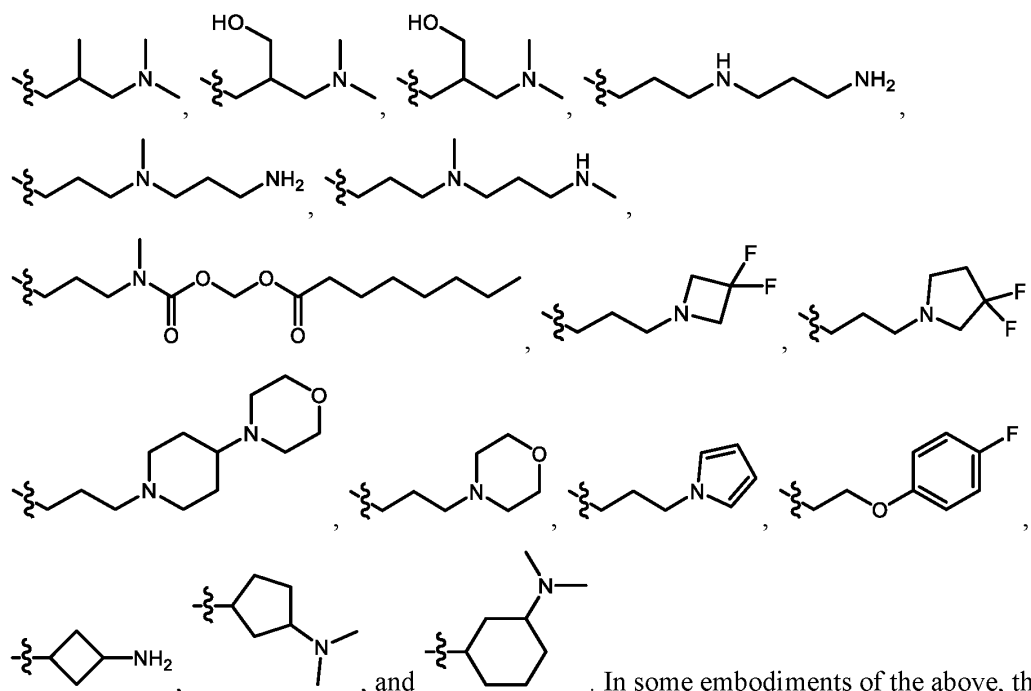


(ii) when $-(\text{Ring A})-\text{L}-\text{R}^6$ are taken together to form , R^1 is H, and R^2 is $-\text{CH}_3$, R^8 is not $-\text{CH}_3$. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0063] 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 H or C_{1-6} alkyl. In some embodiments, R^1 is H. 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 any of the foregoing.

[0064] 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^2 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein the C_{1-6} alkyl or C_{3-6} cycloalkyl of R^2 is optionally substituted with one or more $-\text{OH}$ or $-\text{N}(\text{R}^x)(\text{R}^y)$. In some embodiments, R^2 is $-(\text{C}_{1-6}\text{alkyl})\text{NH}_2$, $-(\text{C}_{1-6}\text{alkyl})\text{N}(\text{C}_{1-6}\text{alkyl})(\text{C}_{1-6}\text{alkyl})$, $-(\text{C}_{1-6}\text{alkyl})\text{NH}(\text{C}_{1-6}\text{alkyl}-\text{NH}_2)$, or $-(\text{C}_{3-6}\text{cycloalkyl})\text{NH}_2$. In some embodiments, R^2 is selected from the group



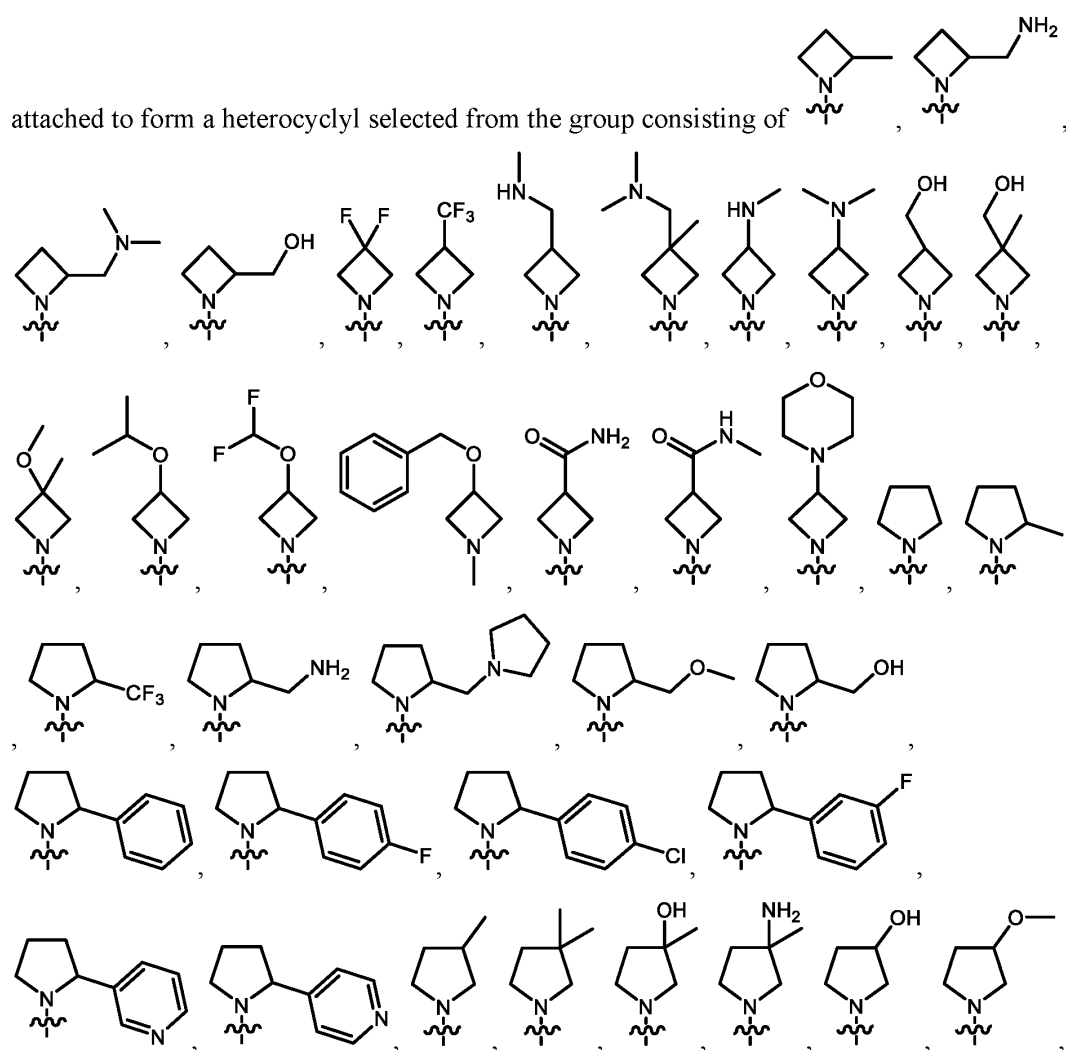


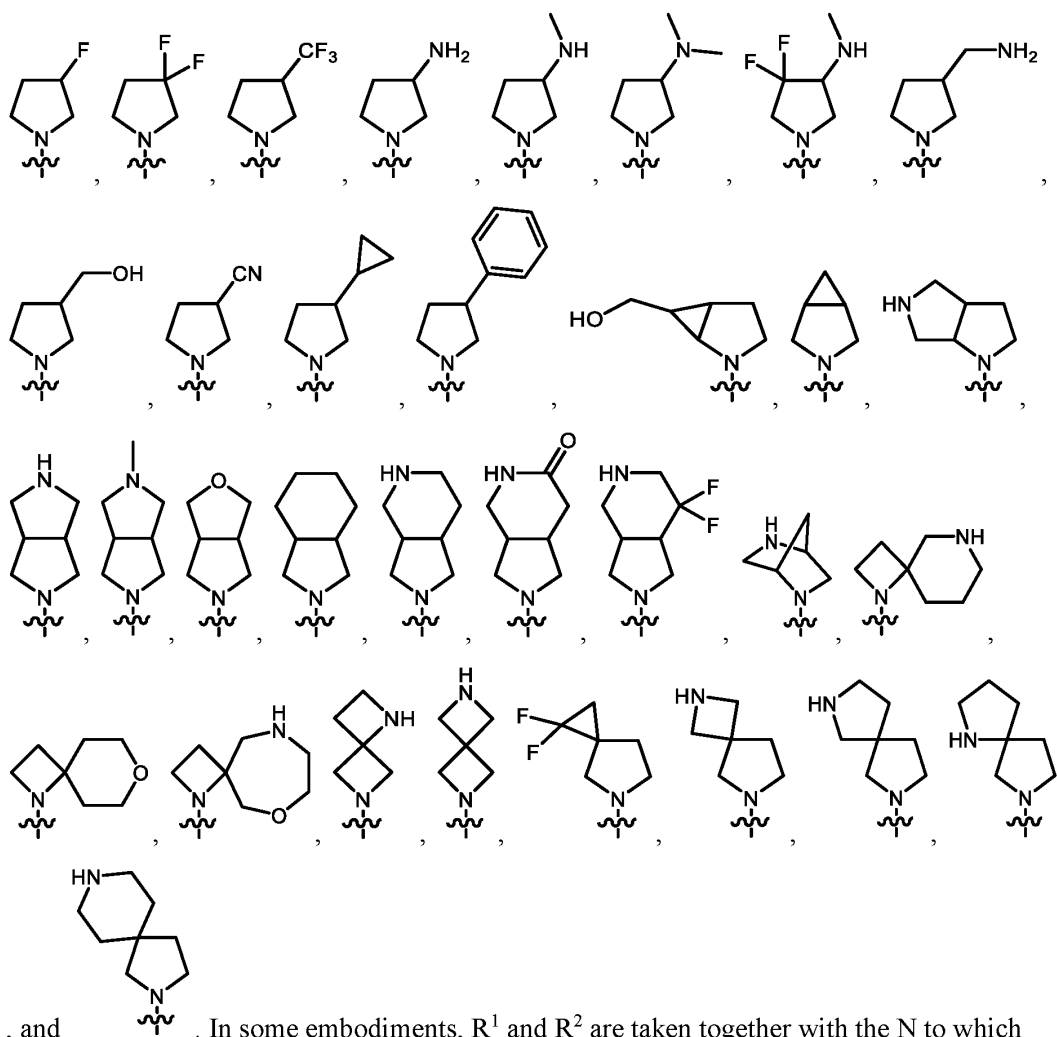
In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[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, R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3 . In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3 , wherein the 3- to 12-membered heterocyclyl comprises a 3- to 8-membered monocyclic heterocyclyl, a 5- to 12-membered fused heterocyclyl, or a 6- to 12-membered spirocyclic heterocyclyl. In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a saturated 3- to 10-membered heterocyclyl optionally substituted with one or more R^3 . In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a saturated 4- to 6-membered monocyclic heterocyclyl optionally substituted with one or more R^3 . In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form an azetidiny or pyrrolidinyl, wherein the azetidiny or pyrrolidinyl is optionally substituted with one or more R^3 . In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a saturated 6- to 10-membered fused or bridged heterocyclyl optionally substituted with one or more R^3 . In some

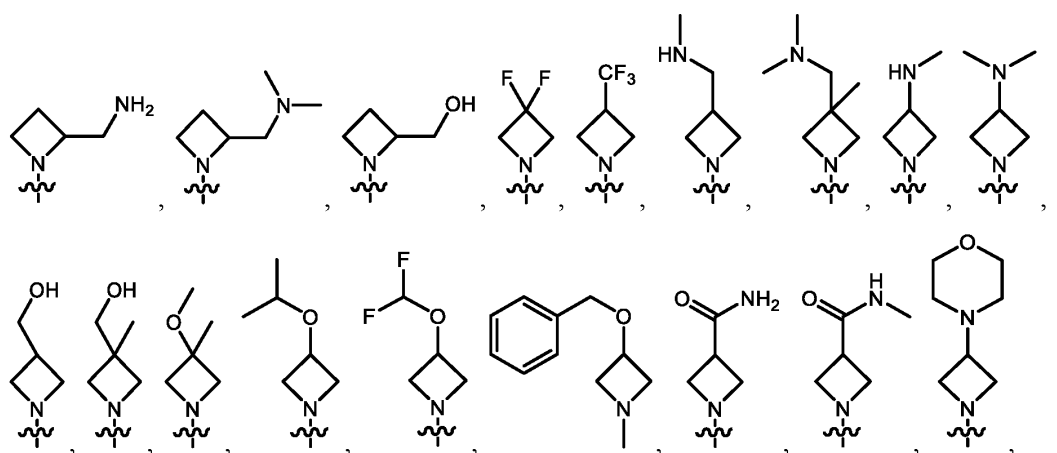
embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a saturated 6- to 10-membered fused heterocyclyl optionally substituted with one or more R^3 . In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a saturated 7- to 10-membered spirocyclic heterocyclyl optionally substituted with one or more R^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 any of the foregoing.

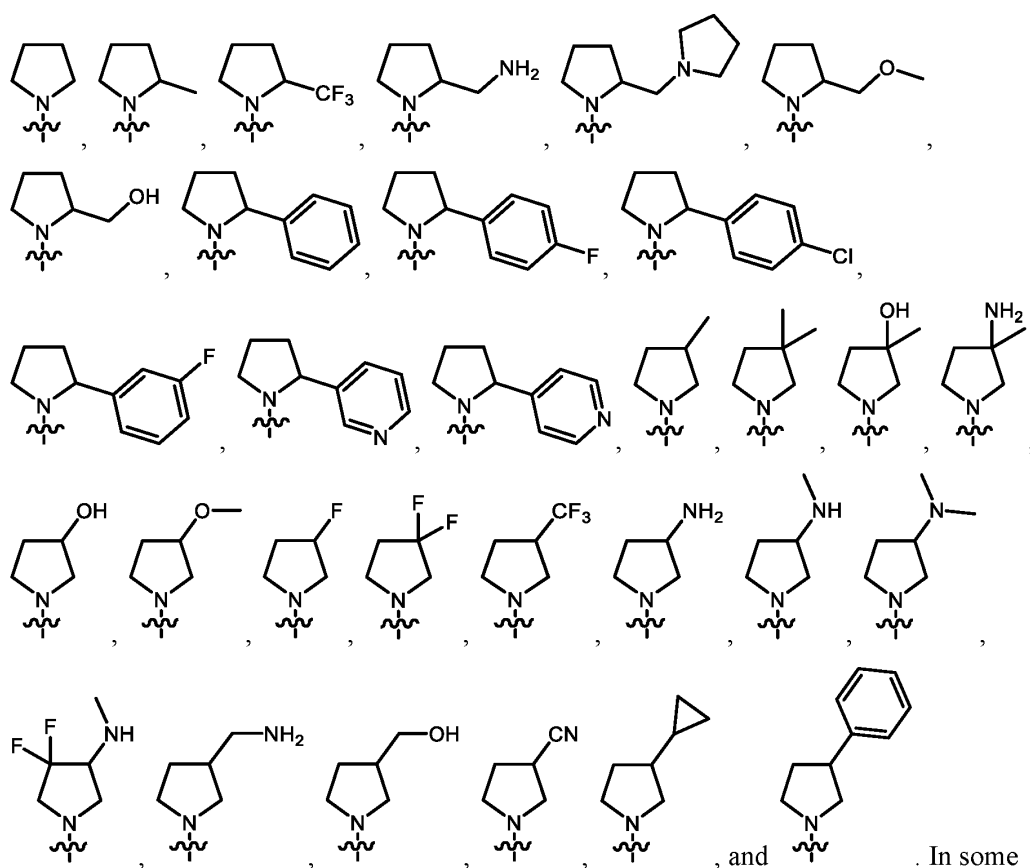
[0066] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, R^1 and R^2 are taken together with the N to which they are





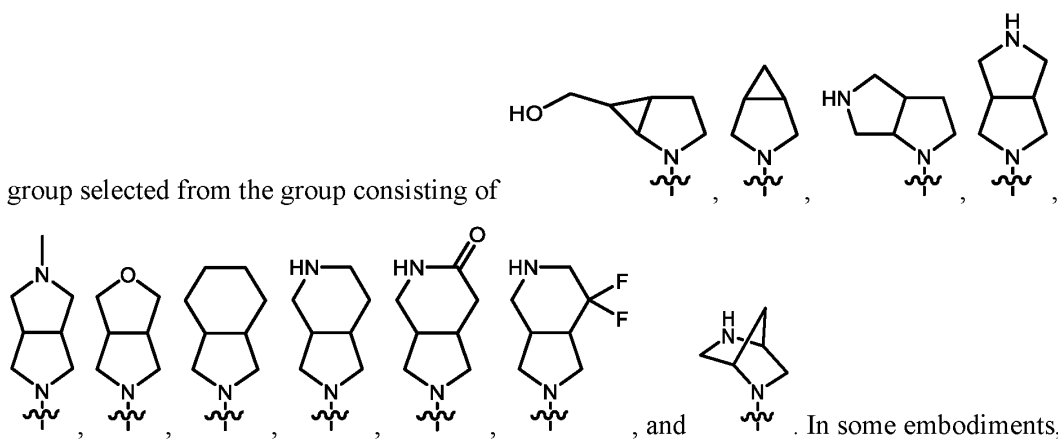
they are attached to form a heterocyclyl selected from the group consisting of ,



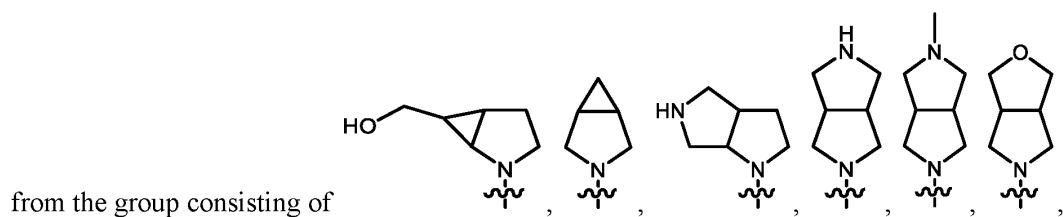


In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a

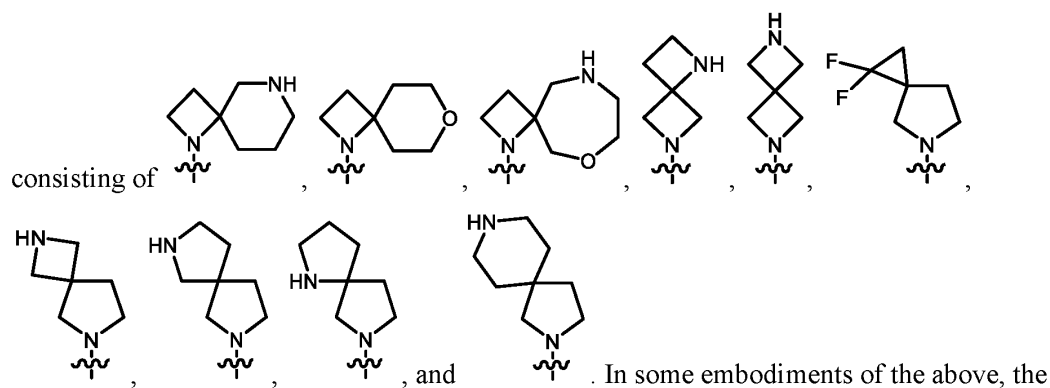
group selected from the group consisting of



R^1 and R^2 are taken together with the N to which they are attached to form a group selected

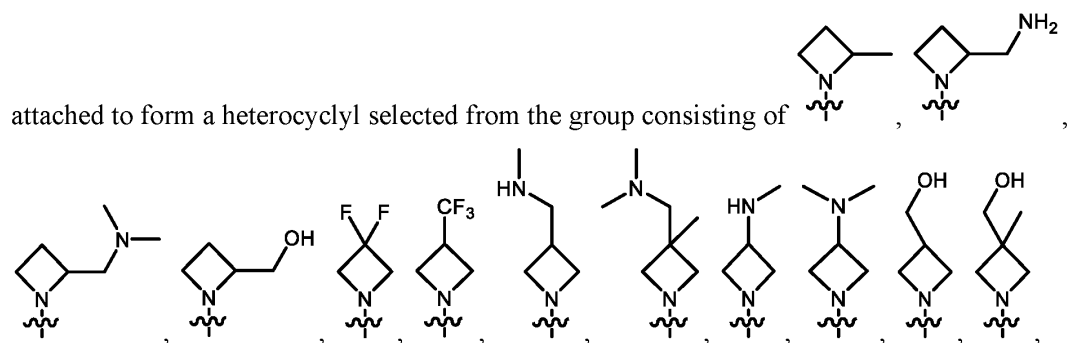


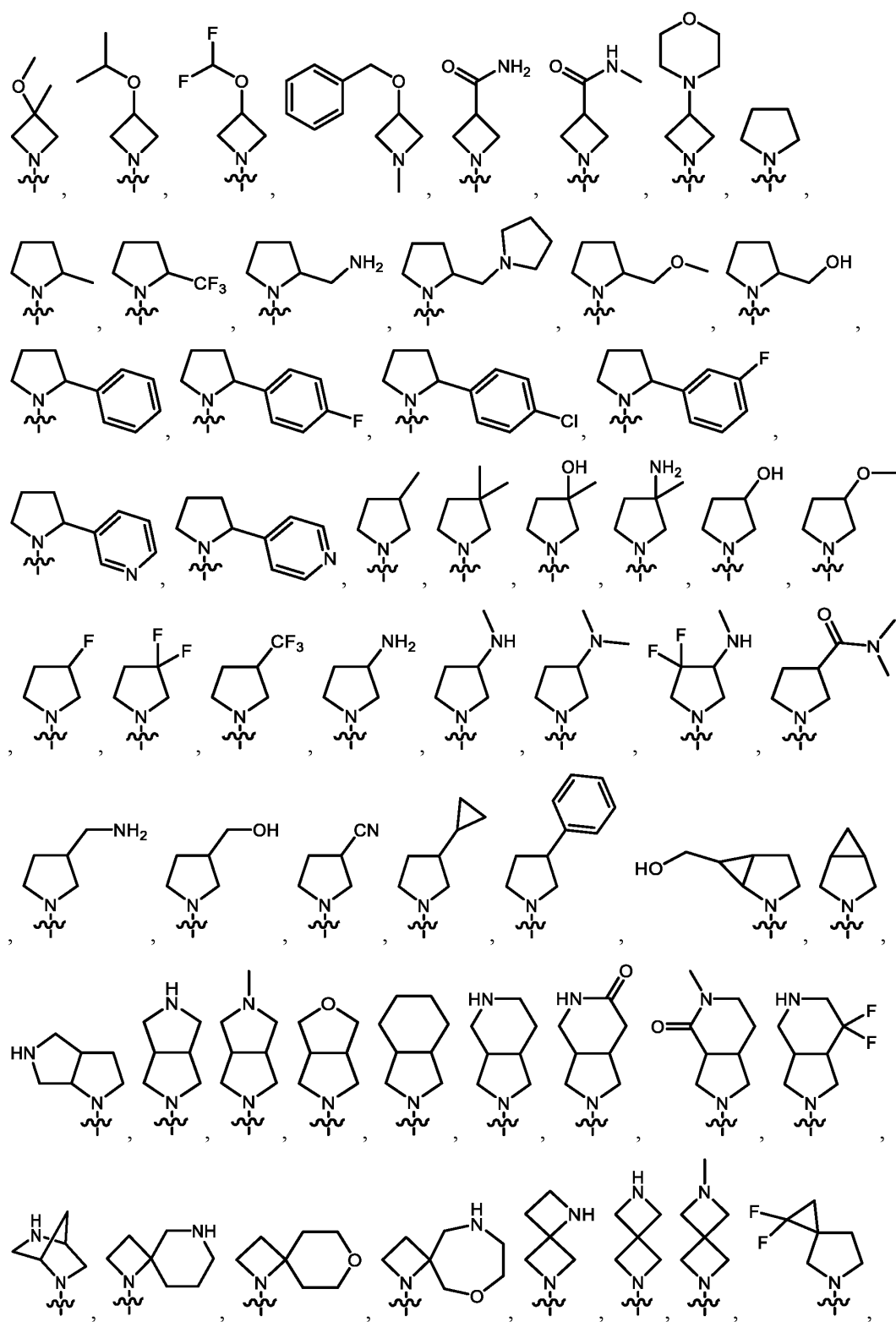
, and . In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a group selected from the group

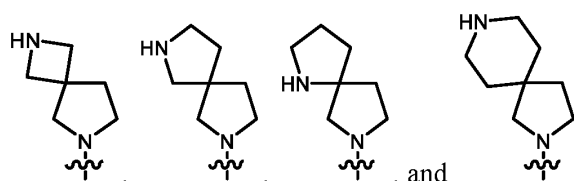


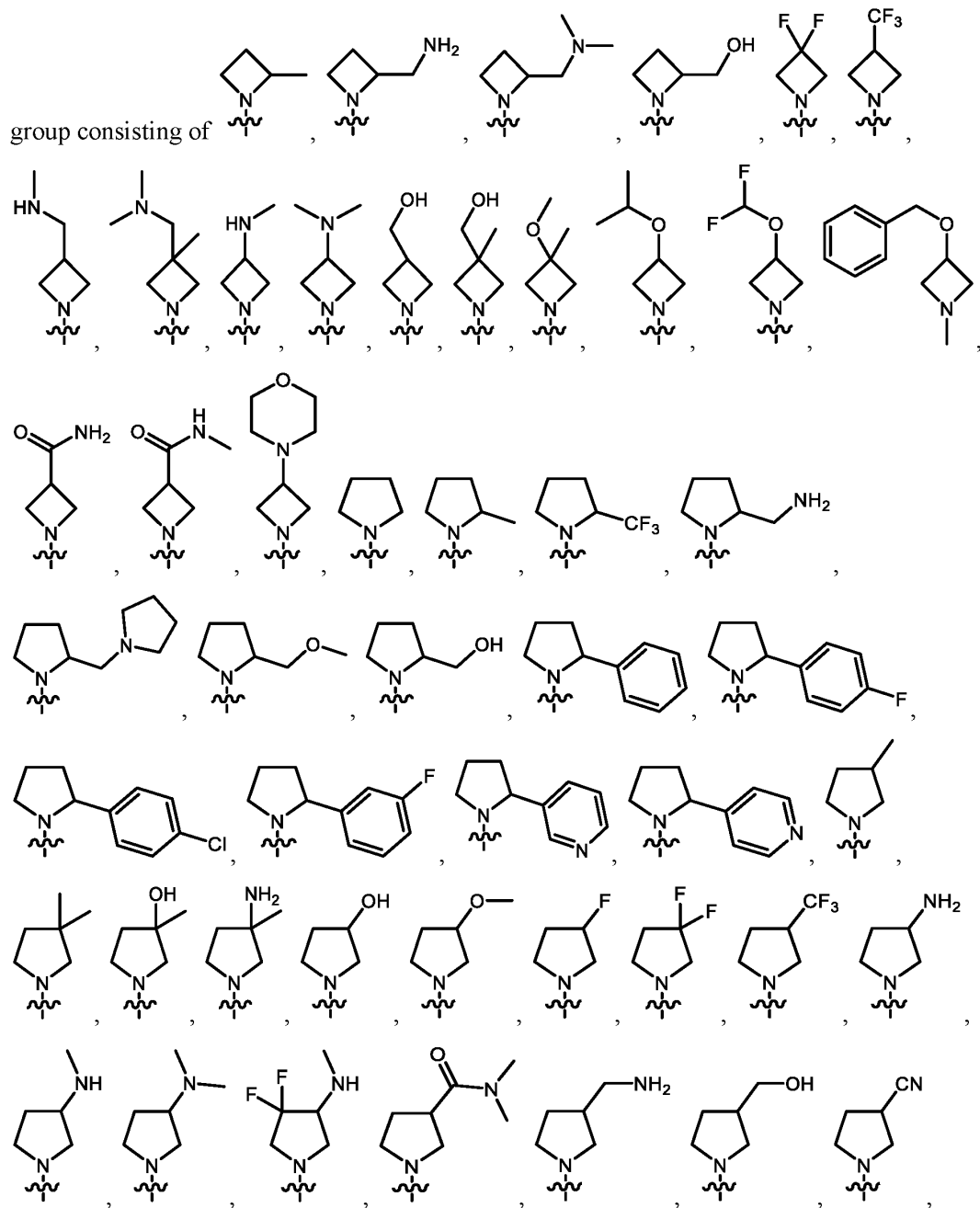
compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

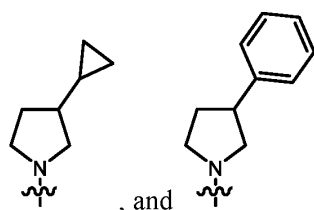
[0067] In some embodiments, R^1 and R^2 are taken together with the N to which they are



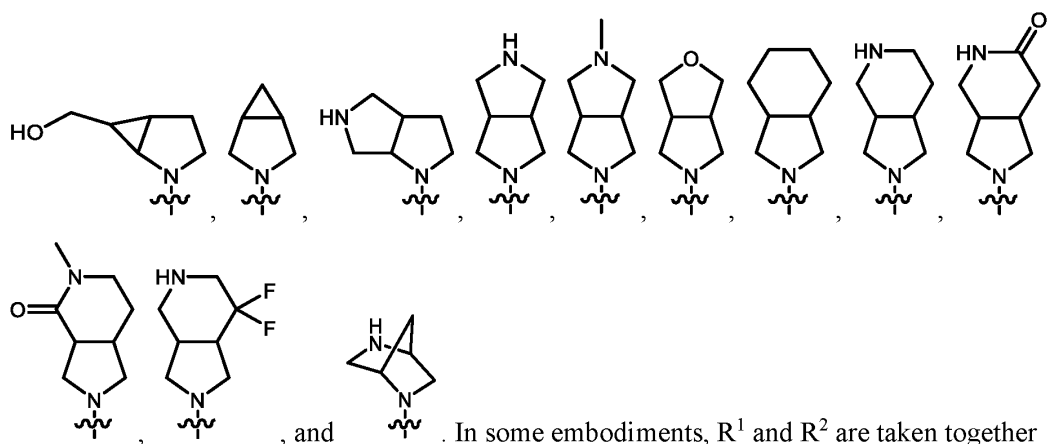



 , and . In some embodiments, R¹ and R² are taken together with the N to which they are attached to form a heterocyclyl selected from the

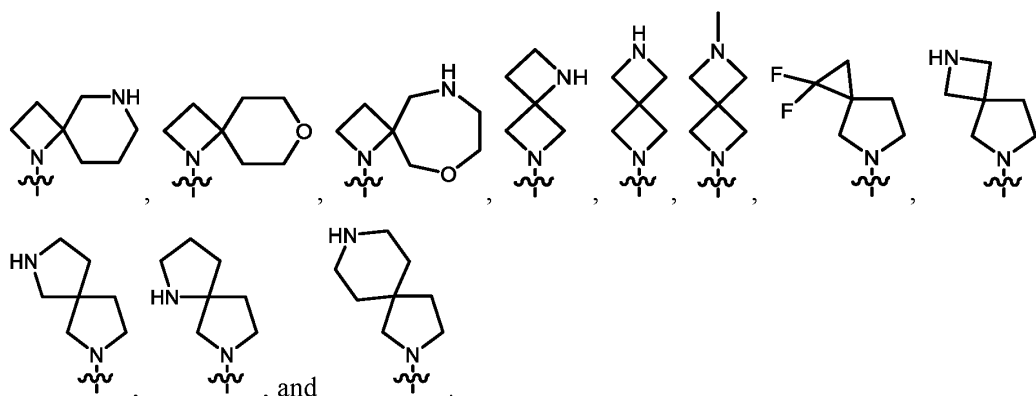




, and . In some embodiments, R^1 and R^2 are taken together with the N to which they are attached to form a group selected from the group consisting of



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

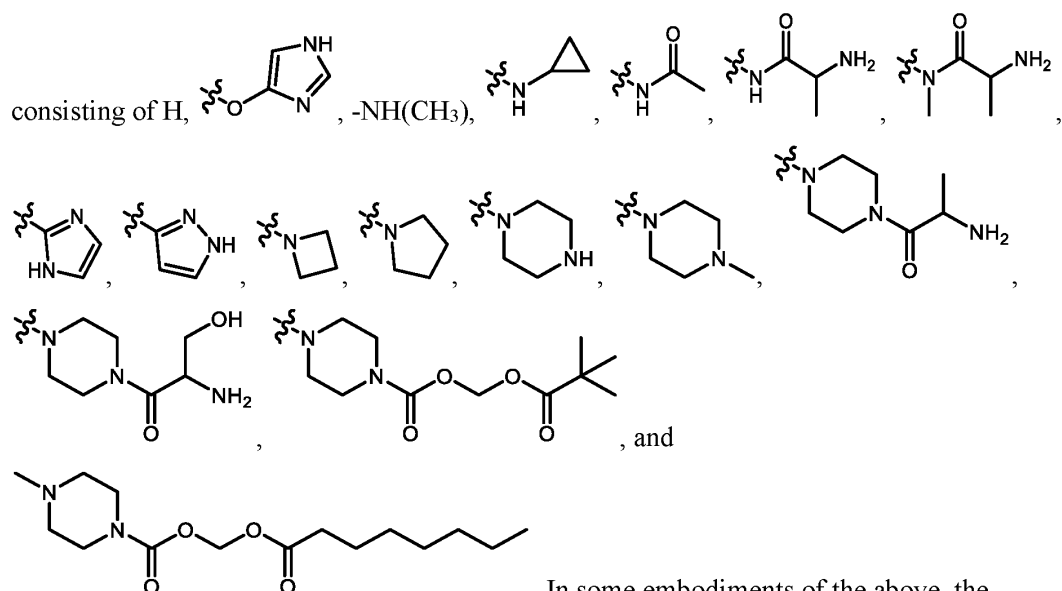


[0068] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, Ring A is phenyl or 6-membered heteroaryl, wherein the phenyl or 6-membered heteroaryl is optionally substituted by one or more R^4 , and the 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S. In some embodiments, Ring A is phenyl or 6-membered heteroaryl, wherein the phenyl or 6-membered heteroaryl is substituted by 0 or 1 R^4 , and the 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S. In some embodiments, Ring A is phenyl substituted by 0 or 1 R^4 . 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 any of the foregoing.

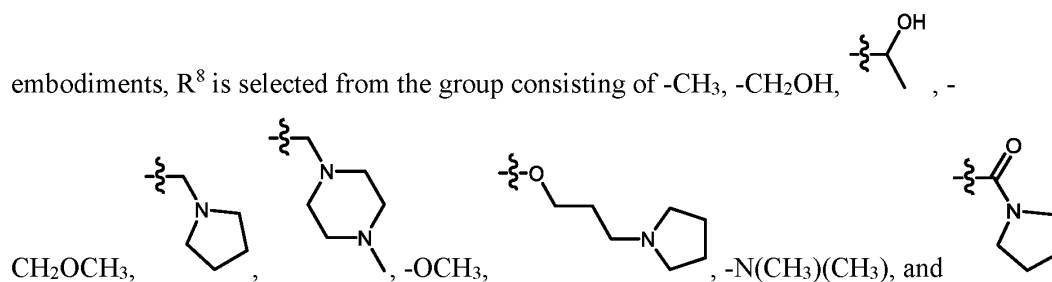
[0069] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, each R^4 is independently halo, C_{1-6} alkyl, or $-OR^{10}$. In some embodiments, each R^4 is independently chloro, or $-OCH_3$. In some embodiments, R^4 is chloro, or $-OCH_3$. In some embodiments, R^4 is chloro. In some embodiments, R^4 is $-OCH_3$. 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 any of the foregoing.

[0070] 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 is H, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein the 3- to 8-membered heterocyclyl of R^6 is optionally substituted with one or more R^{6b} . In some embodiments, R^6 is H, $-O(5\text{- to }6\text{-membered heteroaryl})$, $-NH(C_{1-6}\text{alkyl})$, $-NH(C_{3-6}\text{cycloalkyl})$, $-NHC(O)(C_{1-6}\text{alkyl})$, $-NHC(O)(C_{1-6}\text{alkyl})NH_2$, $-N(C_{1-6}\text{alkyl})C(O)(C_{1-6}\text{alkyl})NH_2$, 5-membered heteroaryl, or 4- to 6-membered N-containing heterocyclyl, wherein the 4- to 6-membered N-containing heterocyclyl of R^6 is optionally substituted with one or more R^{6b} , $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$. In some embodiments, R^6 is selected from the group



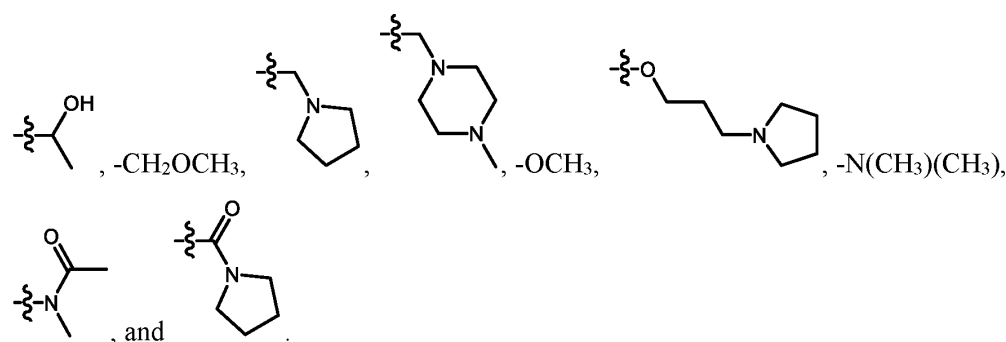
. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0071] 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^8 is C_{1-6} alkyl, $-(C_{1-6}alkyl)OH$, $-C_{1-6}alkyl-O(C_{1-6}alkyl)$, $-(C_{1-6}alkyl)(4- \text{ to } 7\text{-membered heterocyclyl})$, $-O(C_{1-6}alkyl)$, $-O(C_{1-6}alkyl)(4- \text{ to } 7\text{-membered heterocyclyl})$, $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$, or $-C(O)(4- \text{ to } 7\text{-membered heterocyclyl})$, wherein each 4- to 7-membered heterocyclyl is optionally substituted by $C_{1-6}alkyl$. In some

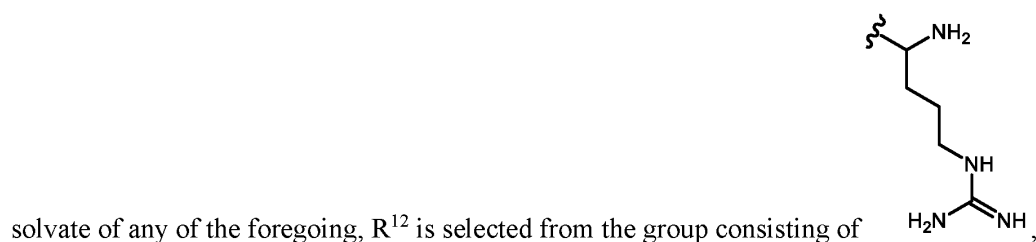


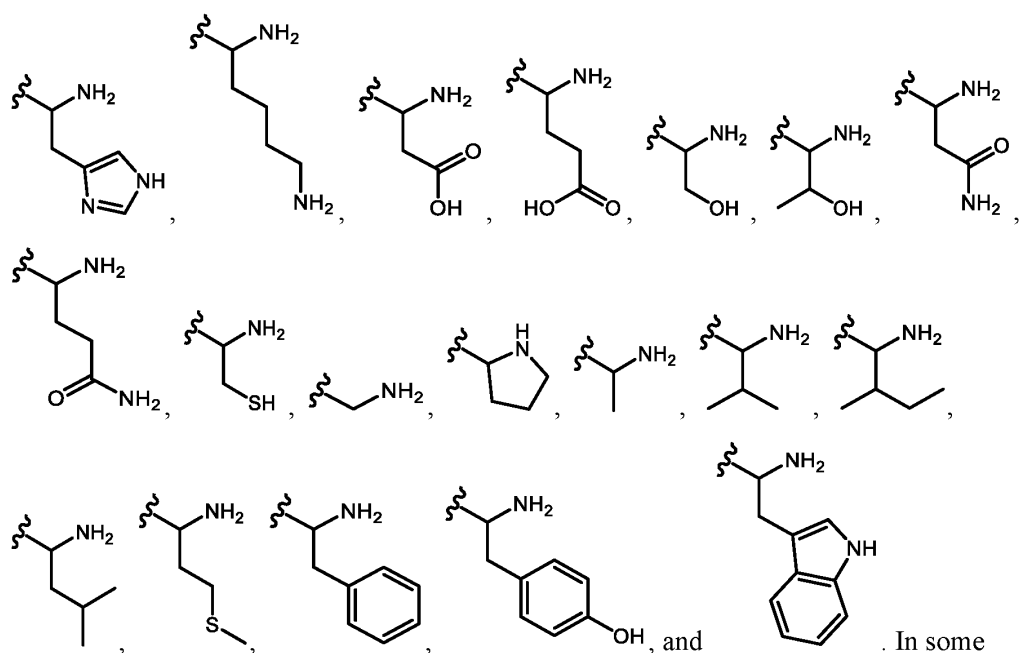
. In some embodiments of the above, the compound is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0072] In some embodiments, R^8 is selected from the group consisting of $-CH_3$, $-CH_2OH$,



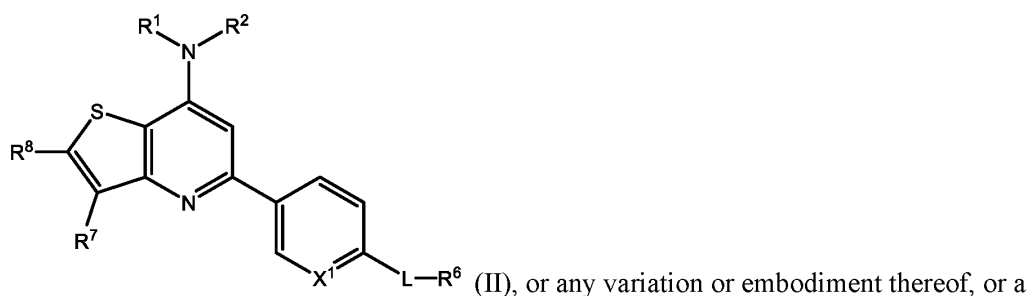
[0073] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or





In some embodiments, the aforementioned R^{12} groups have the (R)- configuration. In some embodiments, the aforementioned R^{12} 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 any of the foregoing.

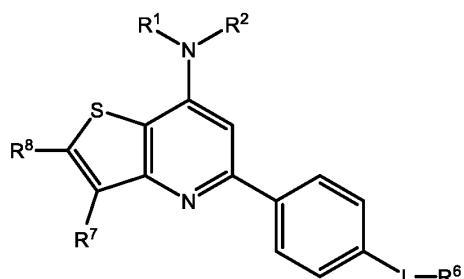
[0074] In some embodiments of a compound of formula (I), the compound is a compound of Formula (II):



(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 X^1 is CH or N, and R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined elsewhere herein. In another variation, X^1 is CH or N, and R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the

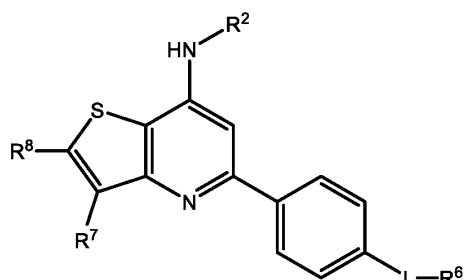
compound is a compound of formula (II), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0075] In some embodiments of a compound of formula (I), the compound is a compound of Formula (II-A):



(II-A), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined elsewhere herein. In another variation, R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (II-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

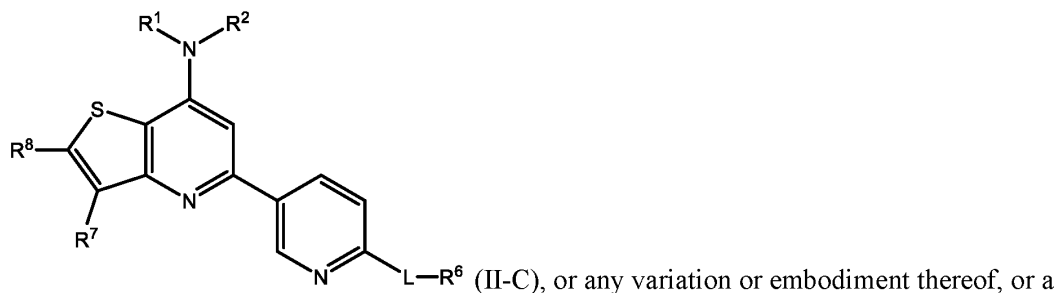
[0076] In some embodiments of a compound of formula (I), the compound is a compound of Formula (II-B):



(II-B), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^2 , R^6 , R^7 , R^8 and L are as defined elsewhere herein. In another variation, R^2 , R^6 , R^7 , R^8 and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (II-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt,

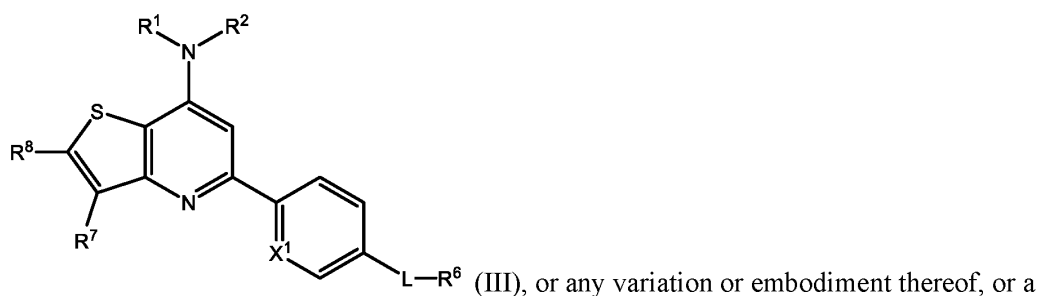
hydrate, or solvate of any of the foregoing, the compound is a compound of formula (II-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0077] In some embodiments of a compound of formula (I), the compound is a compound of Formula (II-C):



stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined elsewhere herein. In another variation, R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (II-C), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (II-C), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

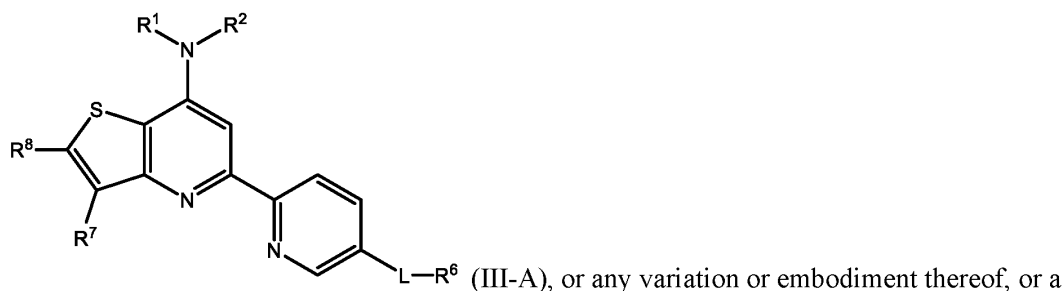
[0078] In some embodiments of a compound of formula (I), the compound is a compound of Formula (III):



stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^1 is CH or N, and R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined elsewhere herein. In another variation, X^1 is CH or N, and R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment

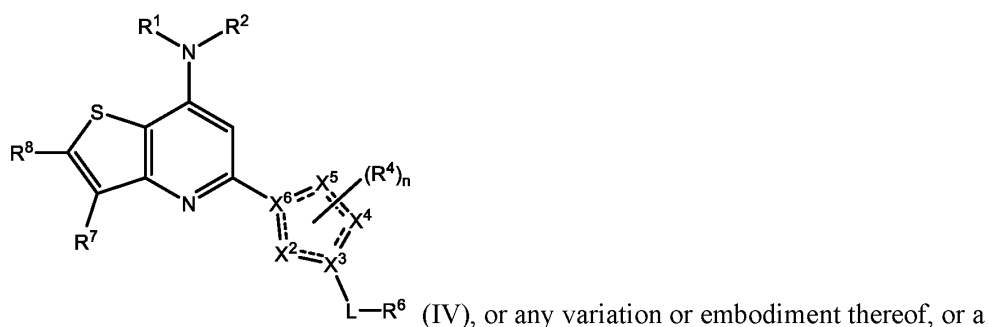
thereof. In some embodiments of a compound of formula (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (III), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable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

[0079] In some embodiments of a compound of formula (I), the compound is a compound of Formula (III-A):



stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined elsewhere herein. In another variation, R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (III-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (III-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

[0080] In some embodiments of a compound of formula (I), the compound is a compound of Formula (IV):



stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^2 , X^4 and X^5 are each independently C, N, O or S; X^3 and X^6 are each independently C or N; n is 0, 1, 2, or 3; and R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined

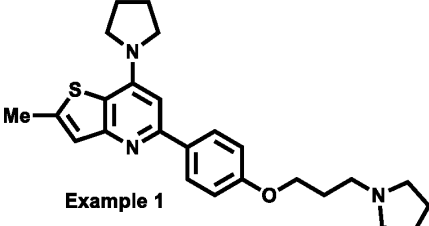
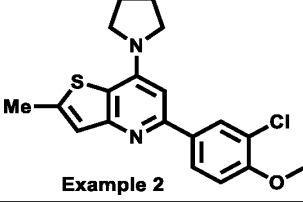
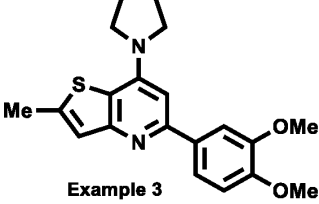
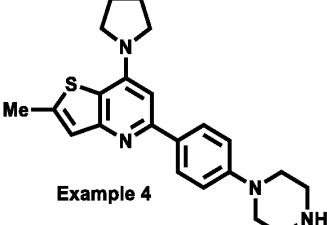
elsewhere herein. In another variation, X^2 , X^4 and X^5 are each independently C, N, O or S; X^3 and X^6 are each independently C or N; n is 0, 1, 2, or 3; and R^1 , R^2 , R^6 , R^7 , R^8 and L are as defined for a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is a compound of formula (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt any of the foregoing.

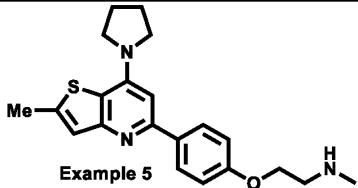
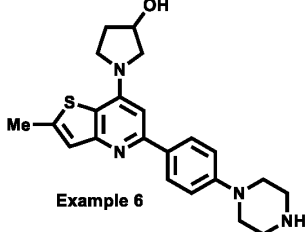
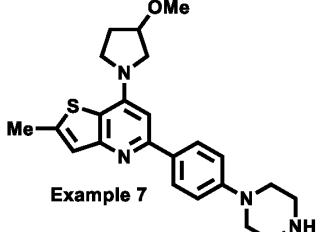
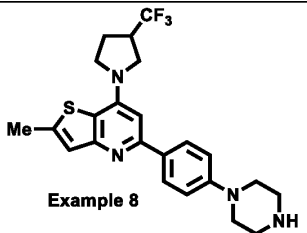
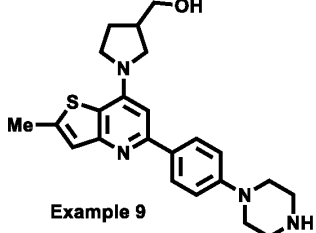
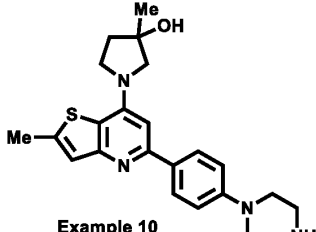
[0081] In some embodiments, the compounds of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, selectively modulate TDP-43. In some embodiments, the compounds of formula (I), or any variation or embodiment 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.

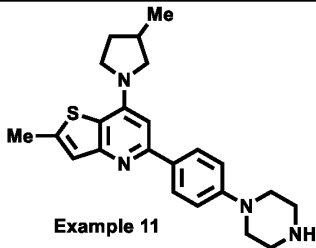
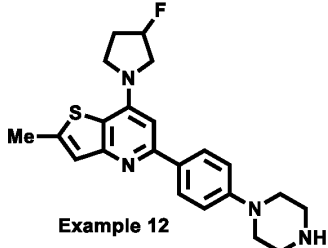
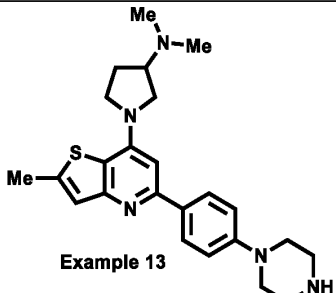
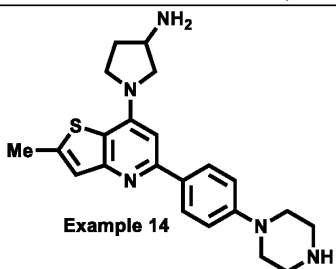
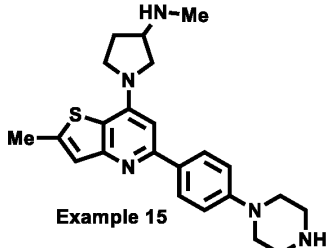
[0082] In some embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is selected from Table 1. In some embodiments of a compound of formula (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 1-65 of Table 1. In some

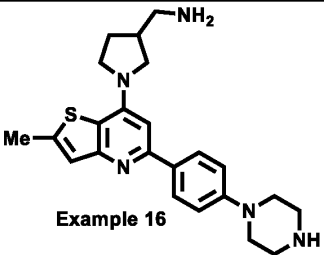
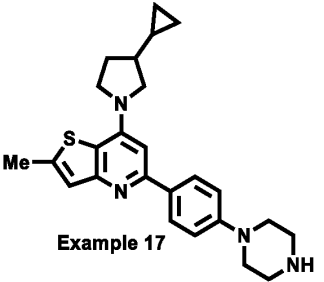
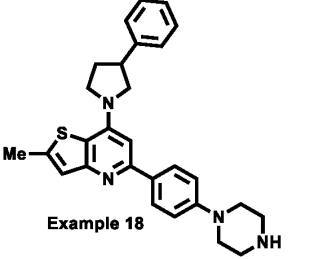
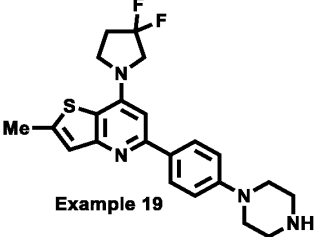
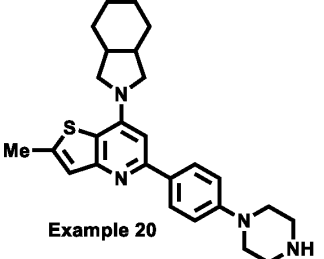
embodiments of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, the compound is selected from Table 1, or a pharmaceutically acceptable salt of any of the foregoing. 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 1-65 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 1-70 of Table 1, or a pharmaceutically acceptable salt of any of the foregoing.

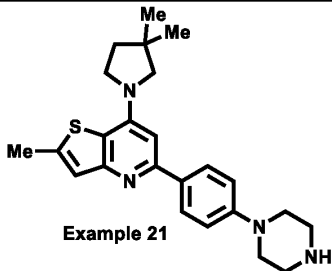
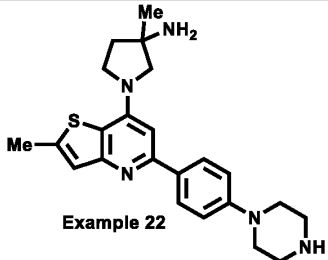
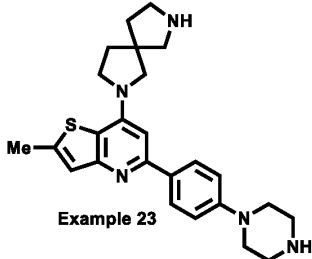
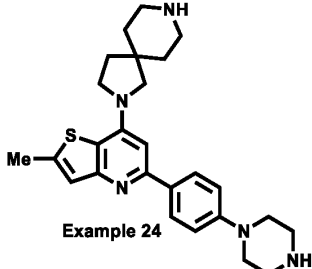
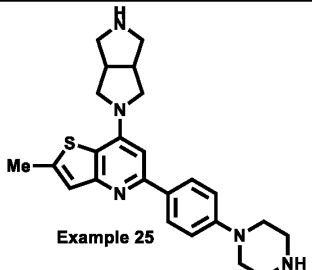
Table 1.

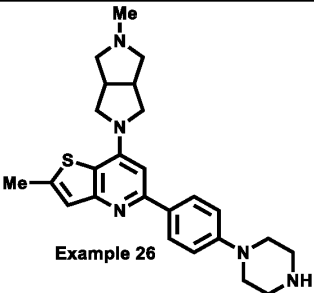
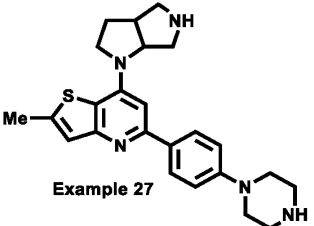
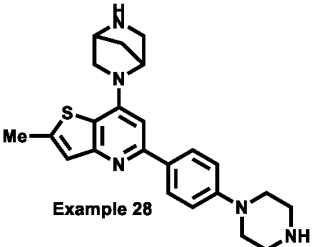
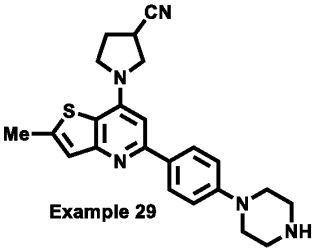
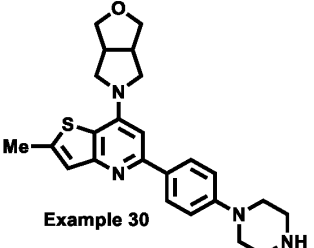
Ex. No.	Structure	Name
1	 Example 1	2-methyl-7-(pyrrolidin-1-yl)-5-(4-(3-(pyrrolidin-1-yl) propoxy) phenyl) thieno[3,2-b] pyridine
2	 Example 2	5-(3-chloro-4-methoxyphenyl)-2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine
3	 Example 3	5-(3,4-dimethoxyphenyl)-2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine
4	 Example 4	2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine

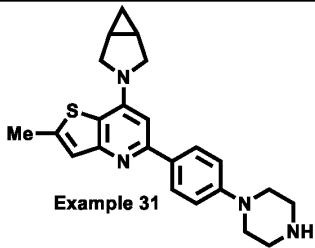
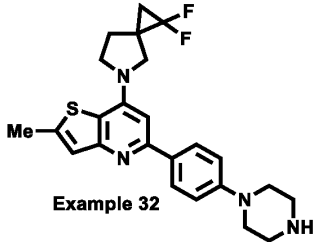
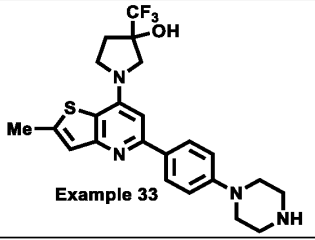
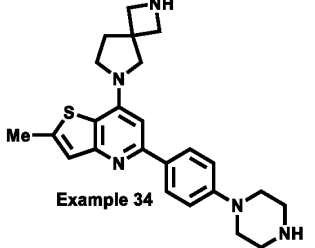
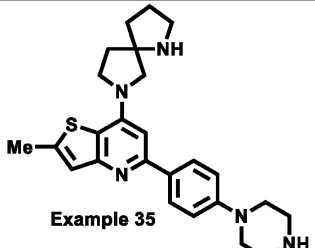
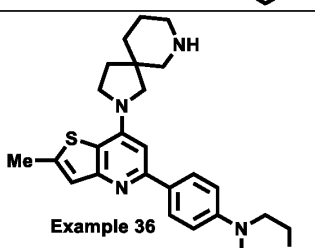
Ex. No.	Structure	Name
5	 Example 5	<i>N</i> -methyl-2-(4-(2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridin-5-yl) phenoxy) ethan-1-amine
6	 Example 6	1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-ol
7	 Example 7	7-(3-methoxypyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
8	 Example 8	2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(3-(trifluoromethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine
9	 Example 9	(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol
10	 Example 10	3-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-ol

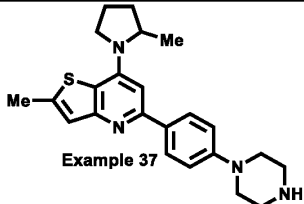
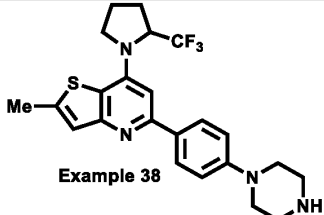
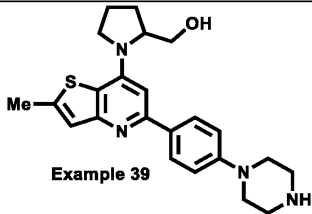
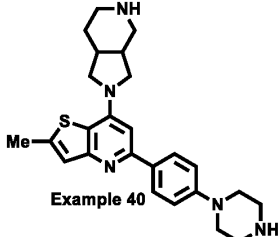
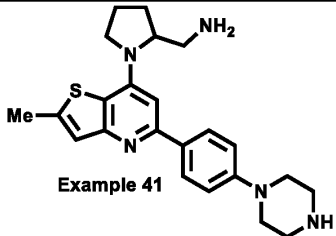
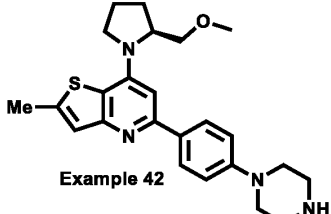
Ex. No.	Structure	Name
11	 Example 11	2-methyl-7-(3-methylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
12	 Example 12	7-(3-fluoropyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
13	 Example 13	<i>N,N</i> -dimethyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine
14	 Example 14	1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine
15	 Example 15	<i>N</i> -methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine

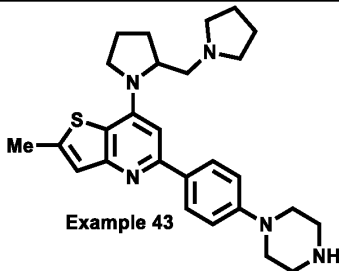
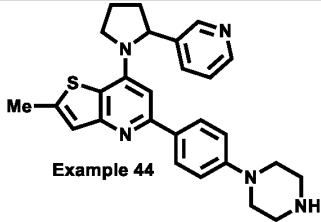
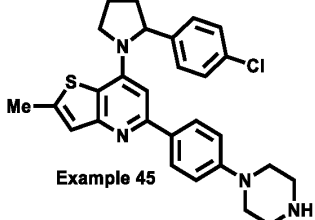
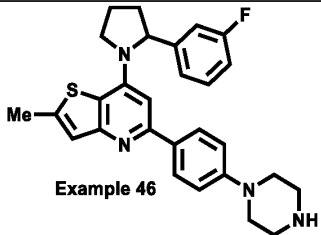
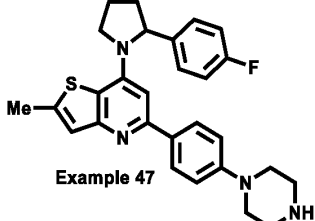
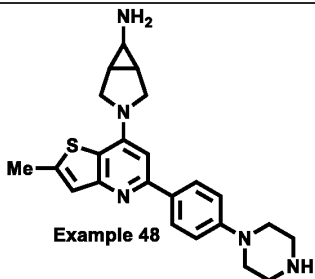
Ex. No.	Structure	Name
16	 Example 16	(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanamine
17	 Example 17	7-(3-cyclopropylpyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
18	 Example 18	2-methyl-7-(3-phenylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
19	 Example 19	7-(3,3-difluoropyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
20	 Example 20	2-methyl-7-((cis)-octahydro-2H-isoindol-2-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine

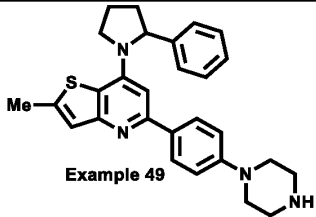
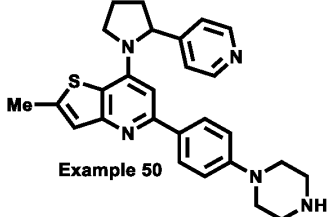
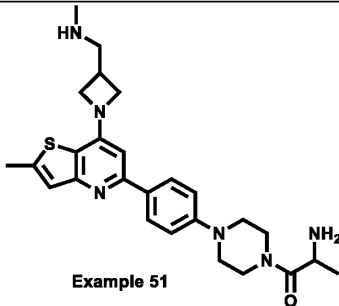
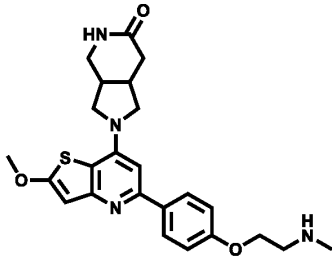
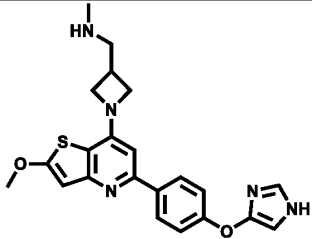
Ex. No.	Structure	Name
21	 Example 21	7-(3,3-dimethylpyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
22	 Example 22	3-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine
23	 Example 23	2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,7-diazaspiro [4.4] nonan-2-yl) thieno[3,2-b] pyridine
24	 Example 24	2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,8-diazaspiro [4.5] decan-2-yl) thieno[3,2-b] pyridine
25	 Example 25	7-((cis)-hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine

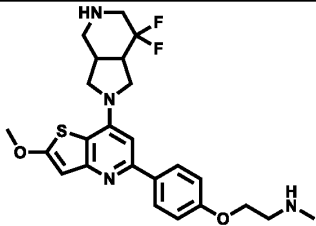
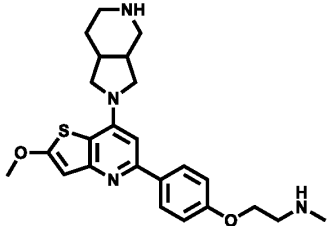
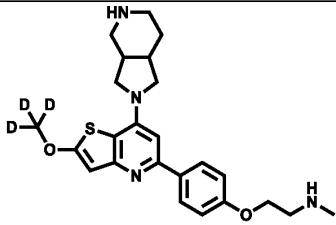
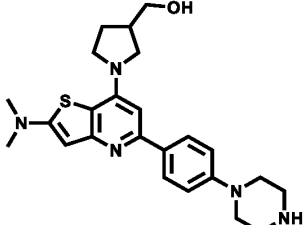
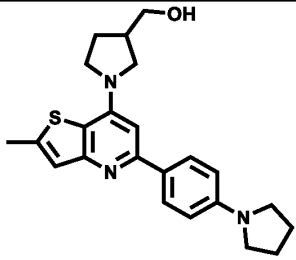
Ex. No.	Structure	Name
26	 Example 26	2-methyl-7-((cis)-5-methylhexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
27	 Example 27	7-((cis)-hexahydropyrrolo[3,4-b] pyrrol-1(2H)-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
28	 Example 28	7-(2,5-diazabicyclo [2.2.1] heptan-2-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
29	 Example 29	1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidine-3-carbonitrile
30	 Example 30	(cis)-5-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) hexahydro-1H-furo[3,4-c] pyrrole

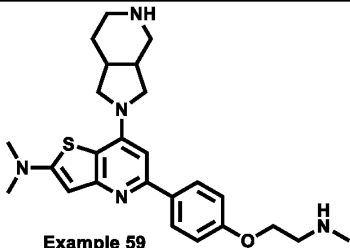
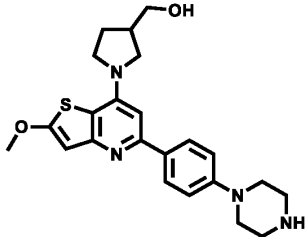
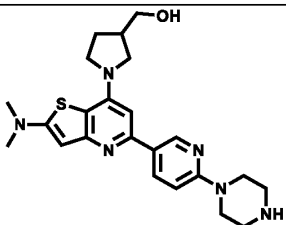
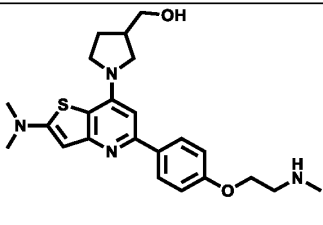
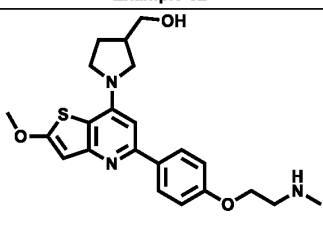
Ex. No.	Structure	Name
31	 Example 31	7-((cis)-3-azabicyclo [3.1.0] hexan-3-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
32	 Example 32	7-(1,1-difluoro-5-azaspiro [2.4] heptan-5-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
33	 Example 33	1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl)-3-(trifluoromethyl) pyrrolidin-3-ol
34	 Example 34	2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,6-diazaspiro [3.4] octan-6-yl) thieno[3,2-b] pyridine
35	 Example 35	2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(1,7-diazaspiro [4.4] nonan-7-yl) thieno[3,2-b] pyridine
36	 Example 36	2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,7-diazaspiro [4.5] decan-2-yl) thieno[3,2-b] pyridine

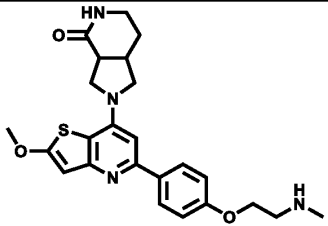
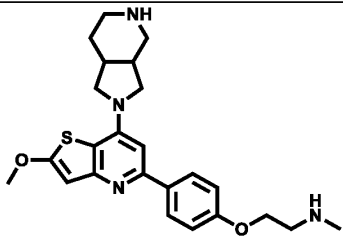
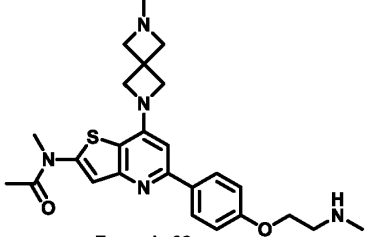
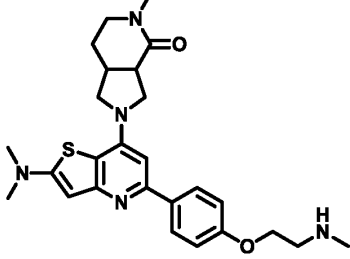
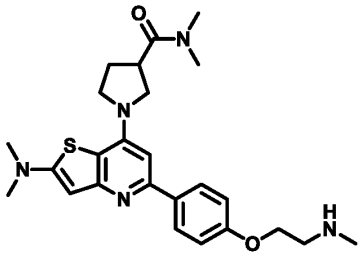
Ex. No.	Structure	Name
37	 Example 37	2-methyl-7-(2-methylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
38	 Example 38	2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(trifluoromethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine
39	 Example 39	(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-2-yl) methanol
40	 Example 40	2-methyl-7-((cis)-octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
41	 Example 41	(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-2-yl) methanamine
42	 Example 42	(S)-7-(2-(methoxymethyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine

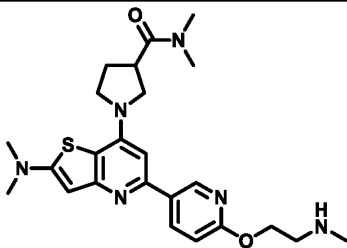
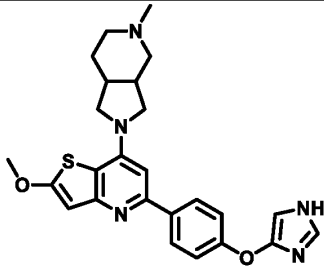
Ex. No.	Structure	Name
43	 Example 43	2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyrrolidin-1-ylmethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine
44	 Example 44	2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyridin-3-yl) pyrrolidin-1-yl) thieno[3,2-b] pyridine
45	 Example 45	7-(2-(4-chlorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
46	 Example 46	7-(2-(3-fluorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
47	 Example 47	7-(2-(4-fluorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
48	 Example 48	(cis)-3-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl)-3-azabicyclo [3.1.0] hexan-6-amine

Ex. No.	Structure	Name
49	 Example 49	2-methyl-7-(2-phenylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine
50	 Example 50	2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyridin-4-yl) pyrrolidin-1-yl) thieno[3,2-b] pyridine
51	 Example 51	2-amino-1-[4-[4-[2-methyl-7-[3-(methylaminomethyl) vazetidin-1-yl] thieno[3,2-b] pyridin-5-yl] phenyl] piperazin-1-yl] propan-1-one
52	 Example 52	(cis)-2-[2-methoxy-5-[4-[2-(methylamino) ethoxy] phenyl] thieno[3,2-b] pyridin-7-yl]-3,3a,4,5,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridin-6-one
53	 Example 53	1-[1-[5-[4-(1H-imidazol-4-yloxy) phenyl]-2-methoxy-thieno[3,2-b] pyridin-7-yl] azetidin-3-yl]-N-methyl-methanamine

Ex. No.	Structure	Name
54	 Example 54	2-[4-[7-((cis)-7,7-difluoro-3,3a,4,5,6,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl)-2-methoxy-thieno[3,2-b]pyridin-5-yl]phenoxy]-N-methyl-ethanamine
55	 Example 55	2-(4-(2-methoxy-7-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-5-yl)phenoxy)-N-methylethan-1-amine
56	 Example 56	2-(4-(2-(methoxy-d ₃)-7-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-5-yl)phenoxy)-N-methylethan-1-amine
57	 Example 57	[1-[2-(dimethylamino)-5-(4-piperazin-1-yl)phenyl]thieno[3,2-b]pyridin-7-yl]pyrrolidin-3-yl]methanol
58	 Example 58	(1-(2-methyl-5-(4-(pyrrolidin-1-yl)phenyl)thieno[3,2-b]pyridin-7-yl)pyrrolidin-3-yl)methanol

Ex. No.	Structure	Name
59	 Example 59	<i>N,N</i> -dimethyl-5-(4-(2-(methylamino)ethoxy)phenyl)-7-((trans)-octahydro-2 <i>H</i> -pyrrolo[3,4- <i>c</i>]pyridin-2-yl)thieno[3,2- <i>b</i>]pyridin-2-amine
60	 Example 60	(1-(2-methoxy-5-(4-(piperazin-1-yl)phenyl)thieno[3,2- <i>b</i>]pyridin-7-yl)pyrrolidin-3-yl)methanol
61	 Example 61	(1-(2-(dimethylamino)-5-(6-(piperazin-1-yl)pyridin-3-yl)thieno[3,2- <i>b</i>]pyridin-7-yl)pyrrolidin-3-yl)methanol
62	 Example 62	(1-(2-(dimethylamino)-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2- <i>b</i>]pyridin-7-yl)pyrrolidin-3-yl)methanol
63	 Example 63	[1-(2-methoxy-5-[4-[2-(methylamino)ethoxy]phenyl]thieno[3,2- <i>b</i>]pyridin-7-yl)pyrrolidin-3-yl)methanol

Ex. No.	Structure	Name
64	 Example 64	(cis)-2-(2-methoxy-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one
65	 Example 65	2-[4-[7-[(trans)-1,3,3a,4,5,6,7,7a-octahydropyrrolo[3,4-c]pyridin-2-yl]-2-methoxy-thieno[3,2-b]pyridin-5-yl]phenoxy]-N-methyl-ethanamine
66	 Example 66	N-methyl-N-(7-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-2-yl)acetamide
67	 Example 67	(cis)-2-(2-(dimethylamino)-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yl)-5-methyloctahydro-4H-pyrrolo[3,4-c]pyridin-4-one
68	 Example 68	1-(2-(dimethylamino)-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yl)-N,N-dimethylpyrrolidine-3-carboxamide

Ex. No.	Structure	Name
69	 Example 69	1-(2-(dimethylamino)-5-(6-(2-(methylamino)ethoxy)pyridin-3-yl)thieno[3,2-b]pyridin-7-yl)-N,N-dimethylpyrrolidine-3-carboxamide
70	 Example 70	(cis)-5-(4-((1H-imidazol-4-yl)oxy)phenyl)-2-methoxy-7-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridine

[0083] In some embodiments, the compound is selected from the group consisting of

2-methyl-7-(pyrrolidin-1-yl)-5-(4-(3-(pyrrolidin-1-yl) propoxy) phenyl) thieno[3,2-b] pyridine;

5-(3-chloro-4-methoxyphenyl)-2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine;

5-(3,4-dimethoxyphenyl)-2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine;

N-methyl-2-(4-(2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridin-5-yl) phenoxy) ethan-1-amine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-ol;

7-(3-methoxypyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(3-(trifluoromethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

3-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-ol;

2-methyl-7-(3-methylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(3-fluoropyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

N, N-dimethyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

N-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanamine;

7-(3-cyclopropylpyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-7-(3-phenylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(3,3-difluoropyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-7-(octahydro-2H-isoindol-2-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(3,3-dimethylpyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

3-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,7-diazaspiro [4.4] nonan-2-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,8-diazaspiro [4.5] decan-2-yl) thieno[3,2-b] pyridine;

7-(hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-7-(5-methylhexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(hexahydropyrrolo[3,4-b] pyrrol-1(2H)-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(2,5-diazabicyclo [2.2.1] heptan-2-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidine-3-carbonitrile

5-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) hexahydro-1H-furo[3,4-c] pyrrole;

7-(3-azabicyclo [3.1.0] hexan-3-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(1,1-difluoro-5-azaspiro [2.4] heptan-5-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl)-3-(trifluoromethyl) pyrrolidin-3-ol;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,6-diazaspiro [3.4] octan-6-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(1,7-diazaspiro [4.4] nonan-7-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,7-diazaspiro [4.5] decan-2-yl) thieno[3,2-b] pyridine;

2-methyl-7-(2-methylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(trifluoromethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-2-yl) methanol;

2-methyl-7-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-2-yl) methanamine;

7-(2-(methoxymethyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyrrolidin-1-yl)methyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyridin-3-yl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

7-(2-(4-chlorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(2-(3-fluorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(2-(4-fluorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

3-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl)-3-azabicyclo[3.1.0] hexan-6-amine;

2-methyl-7-(2-phenylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyridin-4-yl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

2-amino-1-[4-[4-[2-methyl-7-[3-(methylaminomethyl) vazetidin-1-yl] thieno[3,2-b] pyridin-5-yl] phenyl] piperazin-1-yl] propan-1-one;

2-[2-methoxy-5-[4-[2-(methylamino) ethoxy] phenyl] thieno[3,2-b] pyridin-7-yl]-3,3a,4,5,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridin-6-one;

1-[1-[5-[4-(1H-imidazol-4-yloxy) phenyl]-2-methoxy-thieno[3,2-b] pyridin-7-yl] azetidin-3-yl]-N-methyl-methanamine;

2-[4-[7-(7,7-difluoro-3,3a,4,5,6,7a-hexahydro-1H-pyrrolo[3,4-c] pyridin-2-yl)-2-methoxy-thieno[3,2-b] pyridin-5-yl] phenoxy]-N-methyl-ethanamine;

2-(4-(2-methoxy-7-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-5-yl)phenoxy)-N-methylethan-1-amine;

2-(4-(2-(methoxy-d₃)-7-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-5-yl)phenoxy)-N-methylethan-1-amine;

[1-[2-(dimethylamino)-5-(4-piperazin-1-ylphenyl) thieno[3,2-b] pyridin-7-yl] pyrrolidin-3-yl] methanol;

(1-(2-methyl-5-(4-(pyrrolidin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

N,N-dimethyl-5-(4-(2-(methylamino)ethoxy)phenyl)-7-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-2-amine;

(1-(2-methoxy-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

(1-(2-(dimethylamino)-5-(6-(piperazin-1-yl) pyridin-3-yl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

(1-(2-(dimethylamino)-5-(4-(2-(methylamino) ethoxy) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

[1-[2-methoxy-5-[4-[2-(methylamino) ethoxy] phenyl] thieno[3,2-b] pyridin-7-yl] pyrrolidin-3-yl] methanol;

2-(2-methoxy-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one;

2-[4-[7-[1,3,3a,4,5,6,7,7a-octahydropyrrolo[3,4-c] pyridin-2-yl]-2-methoxy-thieno[3,2-b]pyridin-5-yl] phenoxy]-N-methyl-ethanamine;

N-methyl-N-(7-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-2-yl)acetamide;

2-(2-(dimethylamino)-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yl)-5-methyloctahydro-4H-pyrrolo[3,4-c]pyridin-4-one;

1-(2-(dimethylamino)-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yl)-N,N-dimethylpyrrolidine-3-carboxamide;

1-(2-(dimethylamino)-5-(6-(2-(methylamino)ethoxy)pyridin-3-yl)thieno[3,2-b]pyridin-7-yl)-N,N-dimethylpyrrolidine-3-carboxamide; and

5-(4-((1H-imidazol-4-yl)oxy)phenyl)-2-methoxy-7-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridine.

[0084] 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

2-methyl-7-(pyrrolidin-1-yl)-5-(4-(3-(pyrrolidin-1-yl) propoxy) phenyl) thieno[3,2-b] pyridine;

5-(3-chloro-4-methoxyphenyl)-2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine;

5-(3,4-dimethoxyphenyl)-2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine;

N-methyl-2-(4-(2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridin-5-yl) phenoxy) ethan-1-amine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-ol;

7-(3-methoxypyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b]pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(3-(trifluoromethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

3-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-ol;

2-methyl-7-(3-methylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(3-fluoropyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

N, N-dimethyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

N-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanamine;

7-(3-cyclopropylpyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-7-(3-phenylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(3,3-difluoropyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-7-((*cis*)-octahydro-2H-isoindol-2-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(3,3-dimethylpyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

3-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,7-diazaspiro [4.4] nonan-2-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,8-diazaspiro [4.5] decan-2-yl) thieno[3,2-b] pyridine;

7-((cis)-hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-7-((cis)-5-methylhexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-((cis)-hexahydropyrrolo[3,4-b] pyrrol-1(2H)-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(2,5-diazabicyclo [2.2.1] heptan-2-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidine-3-carbonitrile

(cis)-5-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) hexahydro-1H-furo[3,4-c] pyrrole;

7-((cis)-3-azabicyclo [3.1.0] hexan-3-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(1,1-difluoro-5-azaspiro [2.4] heptan-5-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl)-3-(trifluoromethyl) pyrrolidin-3-ol;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,6-diazaspiro [3.4] octan-6-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(1,7-diazaspiro [4.4] nonan-7-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,7-diazaspiro [4.5] decan-2-yl) thieno[3,2-b] pyridine;

2-methyl-7-(2-methylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(trifluoromethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-2-yl) methanol;

2-methyl-7-((cis)-octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-2-yl) methanamine;

(S)-7-(2-(methoxymethyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyrrolidin-1-ylmethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyridin-3-yl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

7-(2-(4-chlorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(2-(3-fluorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(2-(4-fluorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

(cis)-3-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl)-3-azabicyclo [3.1.0] hexan-6-amine;

2-methyl-7-(2-phenylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyridin-4-yl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

2-amino-1-[4-[4-[2-methyl-7-[3-(methylaminomethyl) vazetidin-1-yl] thieno[3,2-b] pyridin-5-yl] phenyl] piperazin-1-yl] propan-1-one;

(cis)-2-[2-methoxy-5-[4-[2-(methylamino) ethoxy] phenyl] thieno[3,2-b] pyridin-7-yl]-3,3a,4,5,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridin-6-one;

1-[1-[5-[4-(1H-imidazol-4-yloxy) phenyl]-2-methoxy-thieno[3,2-b] pyridin-7-yl] azetidin-3-yl]-N-methyl-methanamine;

2-[4-[7-((cis)-7,7-difluoro-3,3a,4,5,6,7a-hexahydro-1H-pyrrolo[3,4-c] pyridin-2-yl)-2-methoxy-thieno[3,2-b] pyridin-5-yl] phenoxy]-N-methyl-ethanamine;

2-(4-(2-methoxy-7-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-5-yl)phenoxy)-N-methylethan-1-amine;

2-(4-(2-(methoxy-d₃)-7-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-5-yl)phenoxy)-N-methylethan-1-amine;

[1-[2-(dimethylamino)-5-(4-piperazin-1-ylphenyl) thieno[3,2-b] pyridin-7-yl] pyrrolidin-3-yl] methanol;

(1-(2-methyl-5-(4-(pyrrolidin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

N,N-dimethyl-5-(4-(2-(methylamino)ethoxy)phenyl)-7-((trans)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-2-amine;

(1-(2-methoxy-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

(1-(2-(dimethylamino)-5-(6-(piperazin-1-yl) pyridin-3-yl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

(1-(2-(dimethylamino)-5-(4-(2-(methylamino) ethoxy) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

[1-[2-methoxy-5-[4-[2-(methylamino) ethoxy] phenyl] thieno[3,2-b] pyridin-7-yl] pyrrolidin-3-yl] methanol;

(cis)-2-(2-methoxy-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one; and

2-[4-[7-[(trans)-1,3,3a,4,5,6,7,7a-octahydropyrrolo[3,4-c] pyridin-2-yl]-2-methoxy-thieno[3,2-b] pyridin-5-yl] phenoxy]-N-methyl-ethanamine.

[0085] 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

2-methyl-7-(pyrrolidin-1-yl)-5-(4-(3-(pyrrolidin-1-yl) propoxy) phenyl) thieno[3,2-b] pyridine;

5-(3-chloro-4-methoxyphenyl)-2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine;

5-(3,4-dimethoxyphenyl)-2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine;

N-methyl-2-(4-(2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridin-5-yl) phenoxy) ethan-1-amine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-ol;

7-(3-methoxypyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(3-(trifluoromethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

3-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-ol;

2-methyl-7-(3-methylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(3-fluoropyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

N, N-dimethyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

N-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanamine;

7-(3-cyclopropylpyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-7-(3-phenylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(3,3-difluoropyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-7-(octahydro-2H-isindol-2-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(3,3-dimethylpyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

3-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,7-diazaspiro [4.4] nonan-2-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,8-diazaspiro [4.5] decan-2-yl) thieno[3,2-b] pyridine;

7-(hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-7-(5-methylhexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(hexahydropyrrolo[3,4-b] pyrrol-1(2H)-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(2,5-diazabicyclo [2.2.1] heptan-2-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidine-3-carbonitrile

5-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) hexahydro-1H-furo[3,4-c] pyrrole;

7-(3-azabicyclo [3.1.0] hexan-3-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(1,1-difluoro-5-azaspiro [2.4] heptan-5-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl)-3-(trifluoromethyl) pyrrolidin-3-ol;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,6-diazaspiro [3.4] octan-6-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(1,7-diazaspiro [4.4] nonan-7-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,7-diazaspiro [4.5] decan-2-yl) thieno[3,2-b] pyridine;

2-methyl-7-(2-methylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(trifluoromethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-2-yl) methanol;

2-methyl-7-(octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

(1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-2-yl) methanamine;

7-(2-(methoxymethyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyrrolidin-1-ylmethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyridin-3-yl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

7-(2-(4-chlorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(2-(3-fluorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

7-(2-(4-fluorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

3-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl)-3-azabicyclo [3.1.0] hexan-6-amine;

2-methyl-7-(2-phenylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine;

2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyridin-4-yl) pyrrolidin-1-yl) thieno[3,2-b] pyridine;

2-amino-1-[4-[4-[2-methyl-7-[3-(methylaminomethyl) vazetidin-1-yl] thieno[3,2-b] pyridin-5-yl] phenyl] piperazin-1-yl] propan-1-one;

2-[2-methoxy-5-[4-[2-(methylamino) ethoxy] phenyl] thieno[3,2-b] pyridin-7-yl]-3,3a,4,5,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridin-6-one;

1-[1-[5-[4-(1H-imidazol-4-yloxy) phenyl]-2-methoxy-thieno[3,2-b] pyridin-7-yl] azetidin-3-yl]-N-methyl-methanamine;

2-[4-[7-(7,7-difluoro-3,3a,4,5,6,7a-hexahydro-1H-pyrrolo[3,4-c] pyridin-2-yl)-2-methoxy-thieno[3,2-b] pyridin-5-yl] phenoxy]-N-methyl-ethanamine;

2-(4-(2-methoxy-7-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-5-yl)phenoxy)-N-methylethan-1-amine;

2-(4-(2-(methoxy-d₃)-7-(octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-5-yl)phenoxy)-*N*-methylethan-1-amine;

[1-[2-(dimethylamino)-5-(4-piperazin-1-ylphenyl) thieno[3,2-b] pyridin-7-yl] pyrrolidin-3-yl] methanol;

(1-(2-methyl-5-(4-(pyrrolidin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

N,N-dimethyl-5-(4-(2-(methylamino)ethoxy)phenyl)-7-(octahydro-2*H*-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-*b*]pyridin-2-amine;

(1-(2-methoxy-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

(1-(2-(dimethylamino)-5-(6-(piperazin-1-yl) pyridin-3-yl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

(1-(2-(dimethylamino)-5-(4-(2-(methylamino) ethoxy) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol;

[1-[2-methoxy-5-[4-[2-(methylamino) ethoxy] phenyl] thieno[3,2-b] pyridin-7-yl] pyrrolidin-3-yl] methanol;

2-(2-methoxy-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yl)octahydro-4*H*-pyrrolo[3,4-c]pyridin-4-one; and

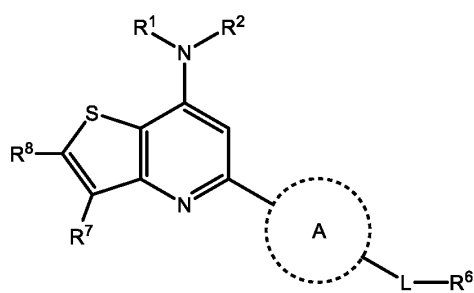
2-[4-[7-[1,3,3a,4,5,6,7,7a-octahydropyrrolo[3,4-c] pyridin-2-yl]-2-methoxy-thieno[3,2-b] pyridin-5-yl] phenoxy]-*N*-methyl-ethanamine.

PHARMACEUTICAL COMPOSITIONS

[0086] Provided herein are pharmaceutical compositions comprising a compound of formula (I), or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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 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 (I), (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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, 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.

[0087] In some embodiments, provided herein are pharmaceutical compositions comprising (i) a compound of formula (I),



pharmaceutically acceptable salt thereof, and (ii) one or more pharmaceutically acceptable excipients, wherein

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

R^2 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein

the C_{1-6} alkyl or C_{3-6} cycloalkyl of R^2 is optionally substituted with one or more -OH or -N(R^x)(R^y),

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

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

each R^3 is independently halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R^{11})C(=O)R¹², -N(R^{11})C(=O)N(R^{11})R¹², -N(R^{11})C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R^{11})R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R^{11})(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R^{11})R¹², -C(=NR¹³)OR¹², -N(R^{11})S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R^{11})R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R^{11})R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², -S(=O)₂N(R^{11})(R¹²), C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more R^{3a};
 the C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{3b}; and
 optionally, two substituents of R³ 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 one or more R^{3b};

Ring A is phenyl or 5- to 6-membered heteroaryl, wherein

the phenyl or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R⁴, and

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

each R⁴ is independently halo, C₁₋₆alkyl, or -OR¹⁰;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)-, wherein

the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 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;

R⁵ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R⁵ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², or -S(=O)₂N(R¹¹)(R¹²), and
 the C₃₋₈cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is H, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b} , $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$;

R^7 is H;

R^8 is halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, 3- to 8-membered heterocyclyl, wherein

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

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

each R^{1a} , R^{3a} , R^{4a} , R^{6a} , or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{13})R^{12}$, $-S(=NR^{13})OR^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

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

each R^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 of R^9 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^9 is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

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

wherein the C_{1-6} alkyl is optionally substituted with one or more halo, deuterium, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

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

each R^{11} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

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

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

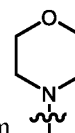
the C_{3-8} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{12} is optionally substituted with halo, C_{1-6} alkyl, or $-N(R^x)(R^y)$;

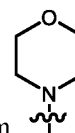
each R^{13} is independently H or C_{1-6} alkyl; and

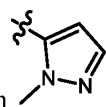
each R^x and R^y is independently H, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-C(=O)(C_{1-6}alkyl)$, or $-C(=O)O(C_{1-6}alkyl)$, wherein

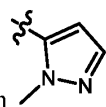
the C_{1-6} alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or $-NH_2$, $NH(C_{1-6}alkyl)$, or $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$, and

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



(i) when R^1 and R^2 are taken together with the N to which they are attached to form , - (Ring A)-L- R^6 are not taken together to form a pyrazolyl substituted by Br; and



(ii) when -(Ring A)-L-R⁶ are taken together to form , R¹ is H, and R² is -CH₃, R⁸ is not -CH₃.

[0088] 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

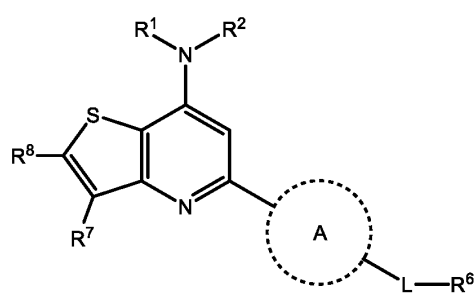
[0089] Traumatic brain injury (TBI) is a risk factor for ALS as demonstrated by the significantly higher incidence of disease in professional athletes and military veterans [See, *e.g.*, Lehman *et al. Neurology* 79, 1970-1974 (2012); McKee *et al. J. Neuropathol. Exp. Neurol.* 69, 989-929 (2010); Chio *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].

[0090] In one aspect, provided is a method for treating a disease or condition mediated by TDP-43, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, provided is a method for treating a disease or condition mediated by TDP-43, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, a therapeutically effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients is administered. In some embodiments, a therapeutically effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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.

[0091] 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, and (ii) one or more pharmaceutically acceptable excipients, wherein

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

R^2 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein

the C_{1-6} alkyl or C_{3-6} cycloalkyl of R^2 is optionally substituted with one or more -OH or -N(R^x)(R^y),

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

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

each R^3 is independently halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R^{11})C(=O)R¹², -N(R^{11})C(=O)N(R^{11})R¹², -N(R^{11})C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R^{11})R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R^{11})(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R^{11})R¹², -C(=NR¹³)OR¹², -N(R^{11})S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R^{11})R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R^{11})R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², -S(=O)₂N(R^{11})(R¹²), C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more R^{3a};
 the C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{3b}; and
 optionally, two substituents of R³ 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 one or more R^{3b};

Ring A is phenyl or 5- to 6-membered heteroaryl, wherein

the phenyl or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R⁴, and

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

each R⁴ is independently halo, C₁₋₆alkyl, or -OR¹⁰;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)-, wherein

the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 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;

R⁵ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R⁵ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², or -S(=O)₂N(R¹¹)(R¹²), and
 the C₃₋₈cycloalkyl is optionally substituted with one or more R^{5b};

R^6 is H, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b} , $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$;

R^7 is H;

R^8 is halo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, 3- to 8-membered heterocyclyl, wherein

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

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

each R^{1a} , R^{3a} , R^{4a} , R^{6a} , or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)R^{12}$, $-S(=O)N(R^{11})R^{12}$, $-S(=O)OR^{12}$, $-S(=NR^{13})R^{12}$, $-S(=NR^{13})N(R^{13})R^{12}$, $-S(=NR^{13})OR^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

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

each R^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 of R^9 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^9 is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

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

wherein the C_{1-6} alkyl is optionally substituted with one or more halo, deuterium, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

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

each R^{11} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

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

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

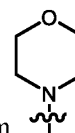
the C_{3-8} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{12} is optionally substituted with halo, C_{1-6} alkyl, or $-N(R^x)(R^y)$;

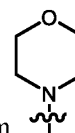
each R^{13} is independently H or C_{1-6} alkyl; and

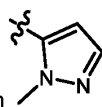
each R^x and R^y is independently H, C_{1-6} alkyl, C_{3-8} cycloalkyl, $-C(=O)(C_{1-6}alkyl)$, or $-C(=O)O(C_{1-6}alkyl)$, wherein

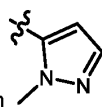
the C_{1-6} alkyl of R^x or R^y is optionally substituted with 6- to 10-membered aryl, 5- to 10-membered heteroaryl, or $-NH_2$, $NH(C_{1-6}alkyl)$, or $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$, and

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



(i) when R^1 and R^2 are taken together with the N to which they are attached to form , - (Ring A)-L- R^6 are not taken together to form a pyrazolyl substituted by Br; and



(ii) when -(Ring A)-L-R⁶ are taken together to form , R¹ is H, and R² is -CH₃, R⁸ is not -CH₃.

[0092] 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).

[0093] In some embodiments, the disease or condition is traumatic brain injury (TBI).

[0094] In some embodiments, the disease or condition is frontotemporal dementia (FTD).

[0095] 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.

[0096] In some embodiments, the individual is a human.

[0097] In one aspect, provided herein is a method of reducing neurodegeneration, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, provided herein is a method of reducing neurodegeneration, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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.

[0098] In one aspect, provided herein is a method of reducing neurodegeneration from traumatic brain injury, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, provided herein is a method of reducing neurodegeneration from traumatic brain injury, comprising administering to an individual in need thereof a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0099] In one aspect, provided herein is a method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. In

some embodiments, provided herein is a method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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 aggregation. 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 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. 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.

[0100] In one aspect, provided herein is a method of modulating TDP-43 driven gene expression levels, comprising contacting a cell with an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt,

hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, provided herein is a method of modulating TDP-43 driven gene expression levels, comprising contacting a cell with an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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.

[0101] In one aspect, provided herein is a compound of formula (I), or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients, for use in the treatment of a disease or condition mediated by TDP-43. In some embodiments, provided herein is a compound of formula (I), or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a

pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I), or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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.

[0102] In one aspect, provided herein is the use of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, or a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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

[0103] 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.

[0104] Provided herein are kits, comprising (i) an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III),

(III-A), or (IV), 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) an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) instructions for use in treating a TDP-43 mediated disease, disorder, or condition in an individual in need thereof. Also provided herein are kits, comprising (i) a pharmaceutical composition comprising an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, and one or more pharmaceutically acceptable excipients; and (ii) instructions for use in treating a TDP-43 mediated disease, disorder, or condition in an individual in need thereof. In some embodiments, the kits comprise (i) a pharmaceutical composition comprising an effective amount of a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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.

[0105] In some embodiments, the individual is a human.

[0106] Articles of manufacture are also provided, wherein the article of manufacture comprises a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, in a suitable container. In some embodiments, the article of manufacture comprises a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in a suitable container. Also provided herein are articles of manufacture, comprising a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, in a suitable container. In some embodiments, the articles of

manufacture comprise a pharmaceutical composition comprising a compound of formula (I) or any variation or embodiment thereof, such as (II), (II-A), (II-B), (II-C), (III), (III-A), or (IV), 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

[0107] 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.

[0108] 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.

[0109] 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.

[0110] 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.

[0111] Although certain exemplary embodiments are depicted and described herein, the compounds of the present disclosure, or any variation or embodiment thereof, may be

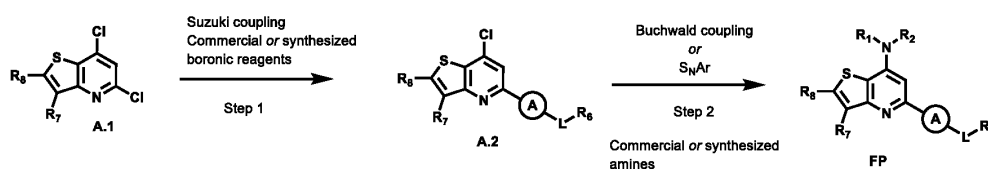
prepared using appropriate starting materials according to the methods described generally herein and/or by methods available to one of ordinary skill in the art.

[0112] 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.

[0113] 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.

[0114] The substituted 2,4-dichloro (methyl)thienopyridine **A.1** were used as starting material of **FP** (Final Product) synthetic sequence (Schemes 1 to 3). 2,4-Dichlorothienopyridine **A.1** underwent a Suzuki cross coupling (Scheme 1) with commercially available or synthesized boronic acid or ester derivatives *bor.* (see section *Synthesis of non-commercially available reagents*). Thienopyridine **A.1** were selectively substituted in position 2 to give compounds **A.2**. The substitution of position 4 of compound **A.2** was realized by Buchwald cross coupling or by aromatic nucleophilic substitution (S_NAr) with amines to afford **FP**.

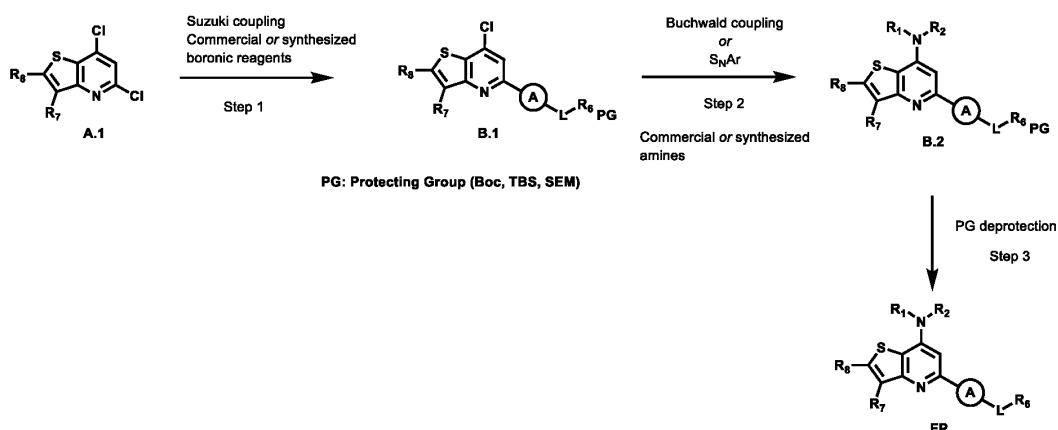
SCHEME 1.



[0115] In some cases, the substituted (hetero)aromatic ring added during the Suzuki coupling on thienopyridines **A.1** contained a **PG** (Protecting Group, Scheme 2). In these cases, **FP** was obtained after an additional step of deprotection. Scheme 2 describes the synthetic sequence

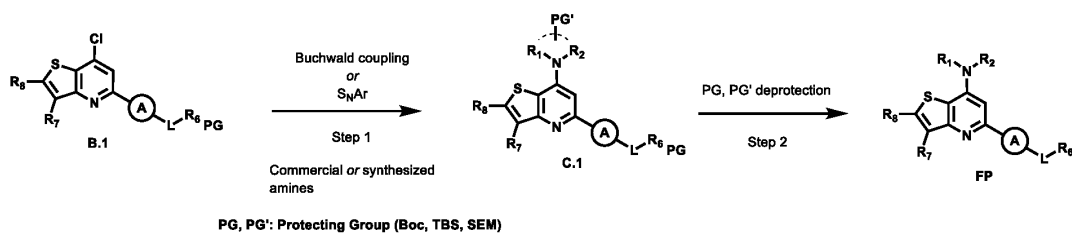
similar to Scheme 1, with a Suzuki cross coupling realized first on thienopyridines **A.1**, followed by the substitution of thienopyridine **B.1** using a Buchwald reaction or a S_NAr to afford compounds **B.2**. Compound **B.2** underwent then a deprotection step to give **FP**.

SCHEME 2.



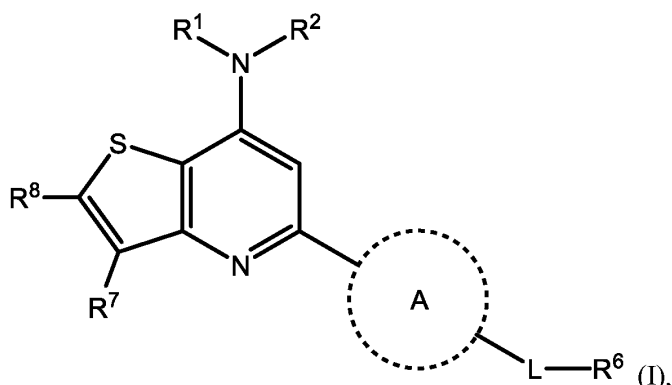
[0116] Scheme 3 describes a synthetic sequence where both boronic ester derivatives used for the Suzuki coupling and the amine used for the Buchwald coupling or aromatic substitution held a protecting group, **PG** and **PG'** respectively. Compound **C.1** was then fully deprotected to give **FP**.

SCHEME 3.



Enumerated Embodiments

[0117] Enumerated Embodiment 1. A compound of Formula (I):



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

R^1 and R^2 are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{12}$, $-C(=O)OR^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

optionally, two substituents of the C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{12}$, $-C(=O)OR^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, or C_{3-8} cycloalkyl group of R^1 or R^2 are taken together with the atoms to which they are attached to form a C_{3-8} cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

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

each R^3 is independently halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, -

OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein the C₁₋₆alkyl of R³ is optionally substituted with one or more R^{3a}, and optionally, two substituents of R³ 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 one or more R^{3b};

Ring A is C₃₋₈cycloalkyl, 4- to 12-membered cycloalkenyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 4- to 12-membered cycloalkenyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of Ring A is optionally substituted by one or more R⁴, and

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

each R⁴ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-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 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁴ is optionally substituted with one or more R^{4b}, and

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

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)-, wherein

the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 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;

R⁵ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R⁵ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², or -S(=O)₂N(R¹¹)(R¹²), and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{5b};

R⁶ is H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁶ is optionally substituted with one or more R^{6b}, -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), or -C(=O)OR¹², and

the 3- to 12-membered heterocyclyl of R⁶ comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and

optionally, two substituents of R⁶ 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^{6b};

R⁷ and R⁸ are each independently H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹³)R¹², -S(=NR¹³)OR¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁷ or R⁸ is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁷ or R⁸ is optionally substituted with one or more R^{7b}, and

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

optionally, two substituents of 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^{7b};

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹³)R¹², -S(=NR¹³)OR¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), 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^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

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

each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, -CN, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

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

each R^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 of R^9 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^9 is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

each R^{10} 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^{11} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

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

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

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

the 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).

[0118] 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:

R¹ is H, C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), 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)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), 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},

R² is C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R² 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 R² is optionally substituted with one or more R^{1b}, and
optionally, two substituents of the C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl group of R² 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};

or R¹ and R² are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein

the 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of R¹ and R² is optionally substituted with one or more R³;

R⁷ is H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹³)R¹², -S(=NR¹³)OR¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R⁷ is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁷ is optionally substituted with one or more R^{7b}, and

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

optionally, two substituents of R⁷ 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

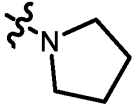
the C₃₋₈cycloalkyl, 3- to 12-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{7b}; and

R⁸ is halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)₂R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹³)R¹², -S(=NR¹³)OR¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

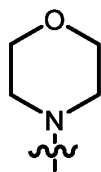
the C₁₋₆alkyl of R⁸ is optionally substituted by one or more R^{7a},

the 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R^8 is optionally substituted with one or more R^{7b} , and the 3- to 8-membered heterocyclyl of R^8 comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S, and optionally, two substituents of 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^{7b} ;

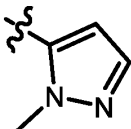
wherein

(i) when $-(\text{Ring A})-L-R^6$ are taken together to form , and R^1 is H, R^8 is not optionally substituted pyrazolyl;

(ii) when R^1 and R^2 are taken together with the N to which they are attached to form



, $-(\text{Ring A})-L-R^6$ are not taken together to form a pyrazolyl substituted by 3-methylphenyl; and

(iii) when $-(\text{Ring A})-L-R^6$ are taken together to form , R^1 is H, and R^2 is $-CH_3$, R^6 is not $-CH_3$.

[0119] 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 H, C_{1-6} alkyl, C_{2-6} alkenyl, $-C(=O)R^{12}$, $-C(=O)OR^{12}$, $-C(=O)N(R^{11})(R^{12})$, 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 C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), 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};

R² is C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R² is optionally substituted with one or more R^{1a},

the C₃₋₈cycloalkyl of R² is optionally substituted with one or more R^{1b}, and

optionally, two substituents of the C₁₋₆alkyl, C₂₋₆alkenyl, -C(=O)R¹², -C(=O)OR¹², -C(=O)N(R¹¹)(R¹²), or C₃₋₈cycloalkyl group of R² 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};

or R¹ and R² are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein

the 3- to 12-membered heterocyclyl or 5- to 10-membered heteroaryl of R¹ and R² is optionally substituted with one or more R³;

each R³ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

the C₁₋₆alkyl of R³ is optionally substituted with one or more R^{3a}, and

optionally, two substituents of R³ 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 one or more R^{3b};

Ring A is C₃₋₈cycloalkyl, 4- to 8-membered cycloalkenyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl, wherein

the C₃₋₈cycloalkyl, 4- to 8-membered cycloalkenyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R⁴, and

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

each R⁴ is independently halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), C₃₋₈cycloalkyl, 3- to 8-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 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl of R⁴ is optionally substituted with one or more R^{4b}, and

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

R⁵ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R⁵ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)₂R¹², or -S(=O)₂N(R¹¹)(R¹²), and

the C₃₋₈cycloalkyl is optionally substituted with one or more R^{5b};

R⁶ is H, halo, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -OR⁹, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -

$S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

$C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$, and

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

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

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

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

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

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

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

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

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

R^8 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-OR^9$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-N(R^x)(R^y)$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, -

$C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, 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^8 is optionally substituted by one or more R^{7a} ,

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

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

optionally, two substituents of 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^{7b} ,

each R^{1a} , R^{3a} , R^{4a} , R^{6a} , or R^{7a} is independently halo, $-N(R^x)(R^y)$, $-OR^{10}$, $-SR^{10}$, $-SF_5$, $-NO_2$, $-CN$, $-N(R^{11})C(=O)R^{12}$, $-N(R^{11})C(=O)N(R^{11})R^{12}$, $-N(R^{11})C(=O)OR^{12}$, $-OC(=O)R^{12}$, $-OC(=O)N(R^{11})R^{12}$, $-OC(=O)OR^{12}$, $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, $-C(=O)OR^{12}$, $-C(=NR^{13})R^{12}$, $-C(=NOR^{12})R^{12}$, $-C(=NR^{13})N(R^{11})R^{12}$, $-C(=NR^{13})OR^{12}$, $-N(R^{11})S(=O)_2R^{12}$, $-S(=O)_2R^{12}$, $-S(=O)_2N(R^{11})(R^{12})$, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

each R^{1b} , R^{3b} , R^{4b} , R^{5b} , R^{6b} , or R^{7b} is independently halo, C_{1-6} alkyl, $-OR^9$, $-N(R^x)(R^y)$, oxo, $-CN$, C_{3-8} cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

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

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

the C₁₋₆alkyl of R¹² is optionally substituted by one or more halo, -OH, -O(C₁₋₆alkyl), -N(R^x)(R^y), C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

the C₃₋₈cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R¹² is optionally substituted with halo, C₁₋₆alkyl, or -N(R^x)(R^y).

[0120] 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:

R¹ is H or C₁₋₆alkyl;

R² is C₁₋₆alkyl or C₃₋₆cycloalkyl, wherein

the C₁₋₆alkyl or C₃₋₆cycloalkyl of R² is optionally substituted with one or more -OH or -N(R^x)(R^y),

or R¹ and R² are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl, wherein

the 3- to 12-membered heterocyclyl of R¹ and R² is optionally substituted with one or more R³;

Ring A is phenyl or 5- to 6-membered heteroaryl, wherein

the phenyl or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R⁴, and

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

each R⁴ is independently halo or -OR¹⁰;

R⁶ is H, -OR⁹, -OR¹⁰, -N(R^x)(R^y), -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b}, -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), or -C(=O)OR¹²;

R⁷ is H;

R⁸ is C₁₋₆alkyl, -OR⁹, -OR¹⁰, -N(R^x)(R^y), or -C(=O)R¹²;

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

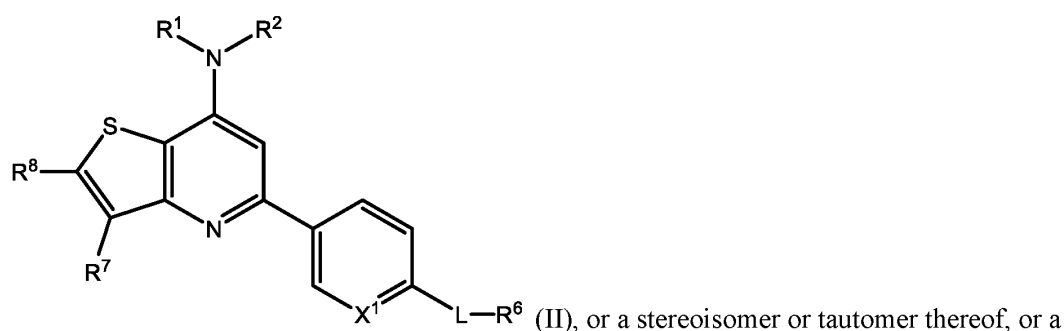
the C₁₋₆alkyl is optionally substituted with one or more halo, deuterium, or 3- to 8-membered heterocyclyl; and

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

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

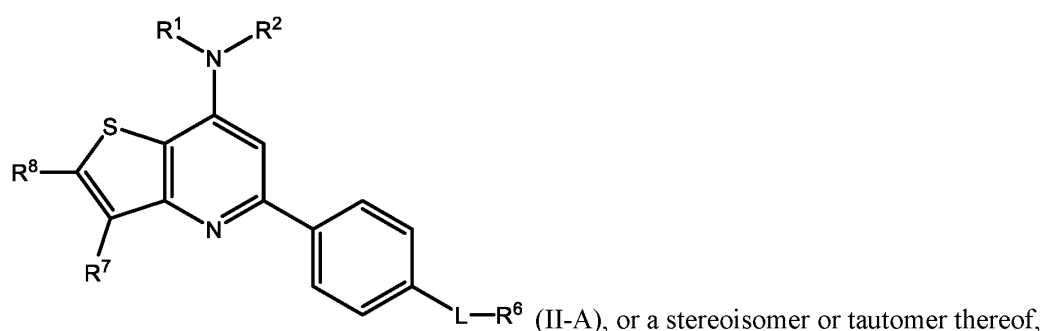
the C_{3-8} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{12} is optionally substituted with halo, C_{1-6} alkyl, or -N(R^x)(R^y).

[0121] Enumerated Embodiment 5. The compound of any of Enumerated Embodiments 1-4, wherein the compound is a compound of Formula (II):



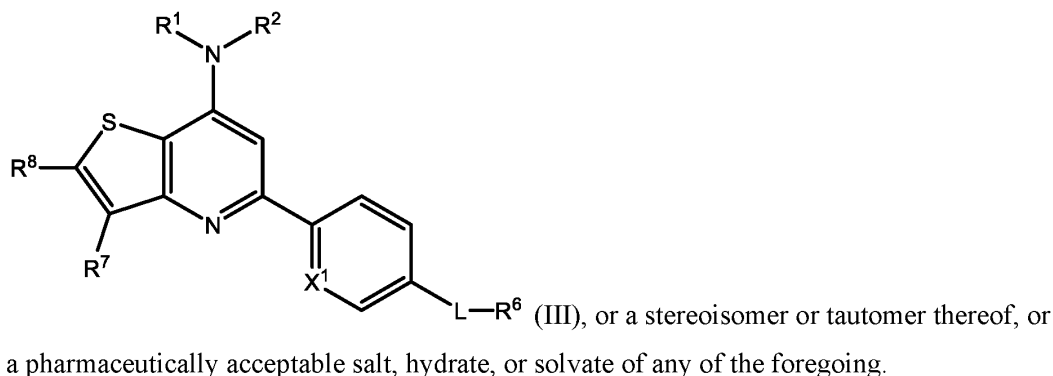
pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein X^1 is CH or N.

[0122] Enumerated Embodiment 6. The compound of any of Enumerated Embodiments 1-5, wherein the compound is a compound of Formula (II-A):



or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing.

[0123] Enumerated Embodiment 7. The compound of any of Enumerated Embodiments 1-4, wherein the compound is a compound of Formula (III):



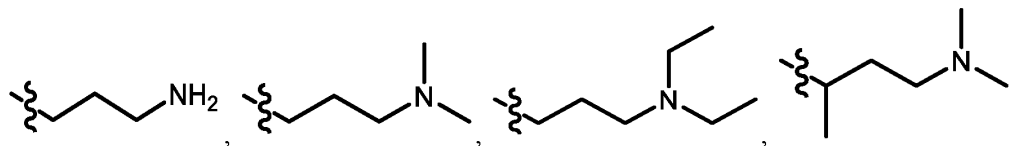
[0124] Enumerated Embodiment 8. The compound of any of Enumerated Embodiments 1-7, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 is H or C_{1-6} alkyl.

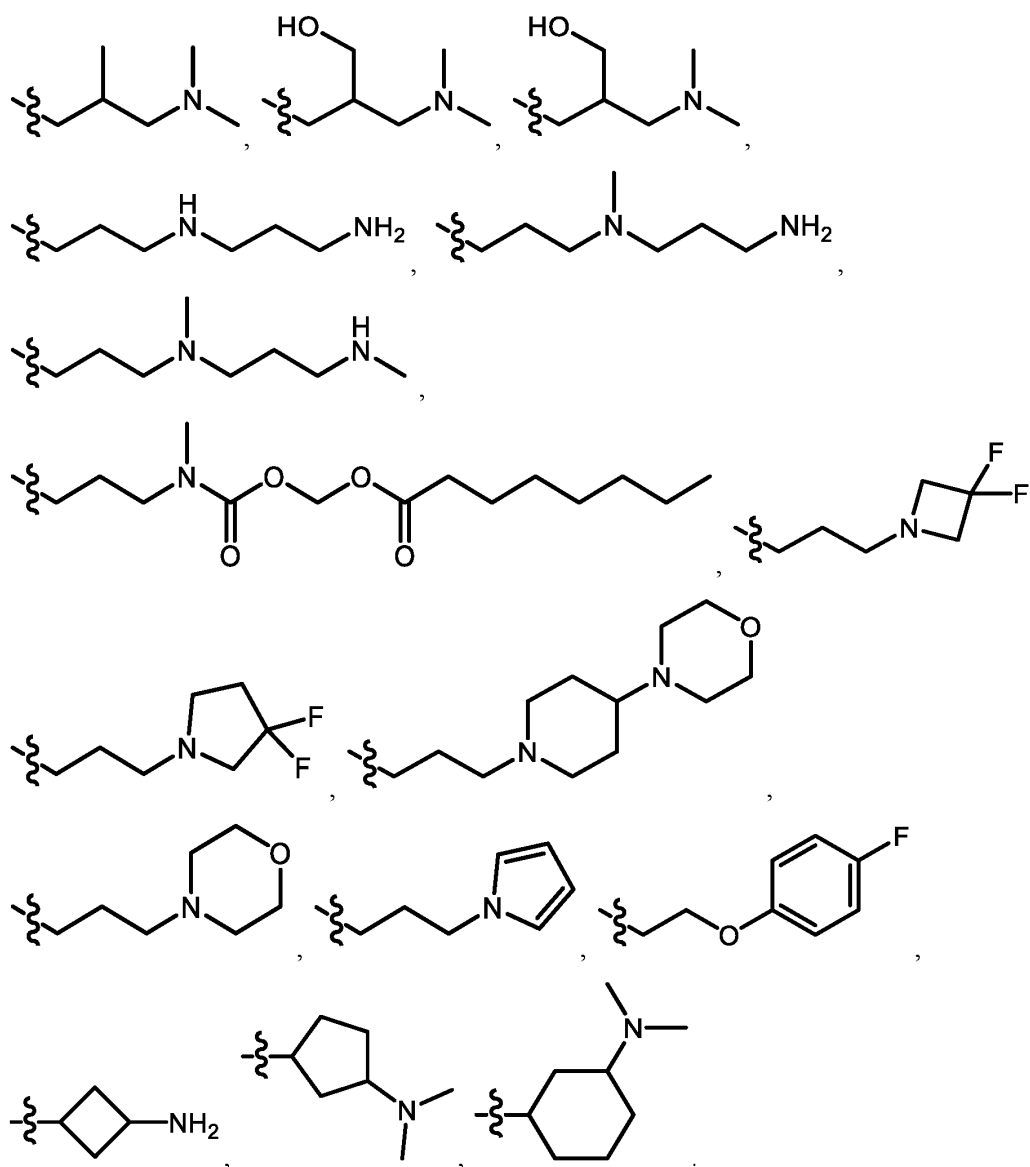
[0125] Enumerated Embodiment 9. The compound of any of Enumerated Embodiments 1-8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 is H.

[0126] 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 R^2 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein the C_{1-6} alkyl or C_{3-6} cycloalkyl of R^2 is optionally substituted with one or more -OH or $-N(R^x)(R^y)$.

[0127] Enumerated Embodiment 11. The compound of any of Enumerated Embodiments 1-10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^2 is $-(C_{1-6}alkyl)NH_2$, $-(C_{1-6}alkyl)N(C_{1-6}alkyl)(C_{1-6}alkyl)$, $-(C_{1-6}alkyl)NH(C_{1-6}alkyl-NH_2)$, or $-(C_{3-6}cycloalkyl)NH_2$.

[0128] Enumerated Embodiment 12. The compound of any of Enumerated Embodiments 1-11, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^2 is selected from the group consisting of





[0129] Enumerated Embodiment 13. The compound of any of Enumerated Embodiments 1-7, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

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

[0130] Enumerated Embodiment 14. The compound of any of Enumerated Embodiments 1-7 or 13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which

they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3 , wherein

the 3- to 12-membered heterocyclyl comprises a 3- to 8-membered monocyclic heterocyclyl, a 5- to 12-membered fused heterocyclyl, or a 6- to 12-membered spirocyclic heterocyclyl.

[0131] Enumerated Embodiment 15. The compound of Enumerated Embodiment 13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a 4- to 12-membered heterocyclyl optionally substituted with one or more R^3 .

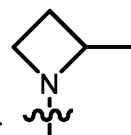
[0132] Enumerated Embodiment 16. The compound of Enumerated Embodiment 15, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a saturated 3- to 10-membered heterocyclyl optionally substituted with one or more R^3 .

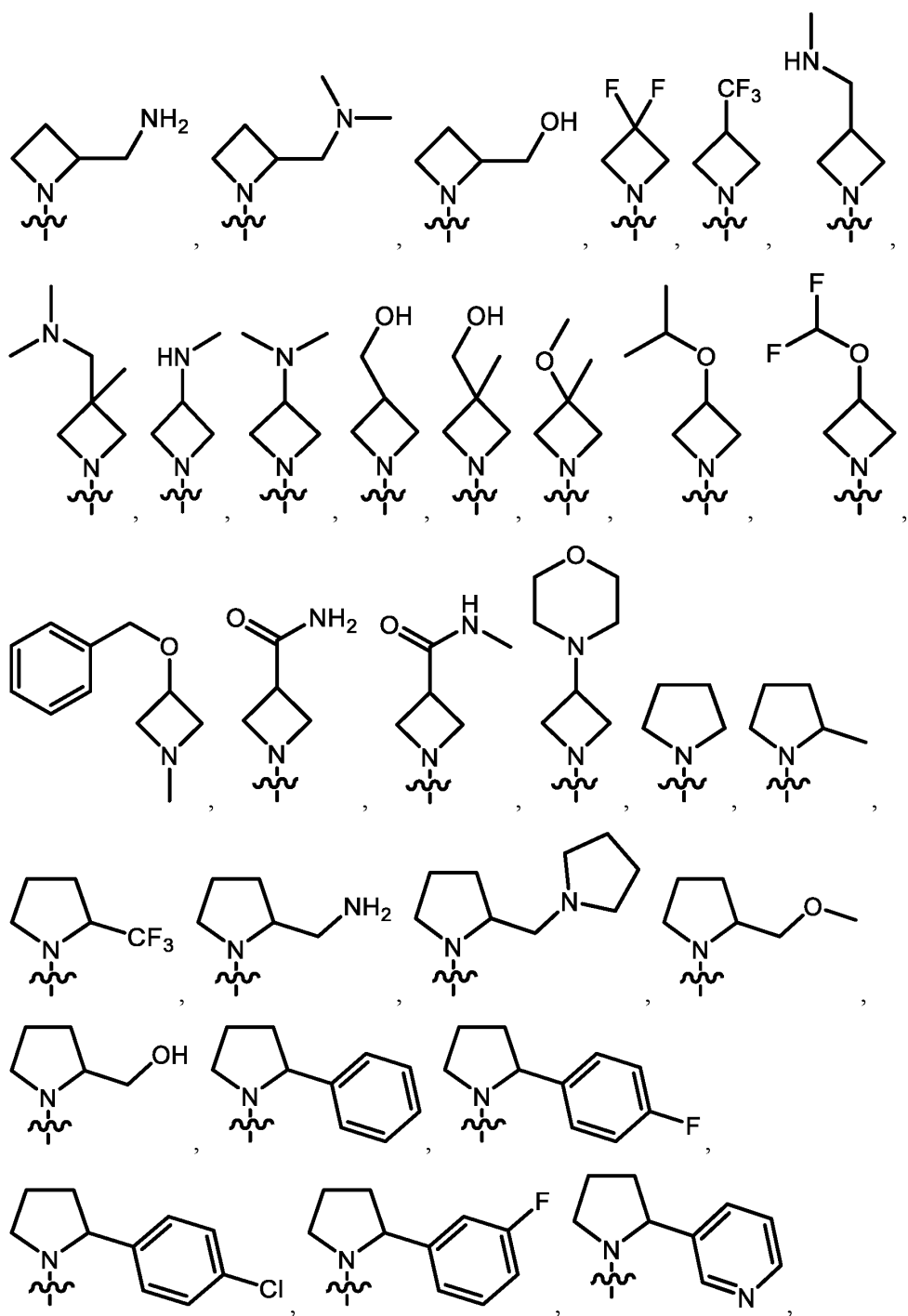
[0133] Enumerated Embodiment 17. The compound of Enumerated Embodiment 16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a saturated 4- to 6-membered monocyclic heterocyclyl optionally substituted with one or more R^3 .

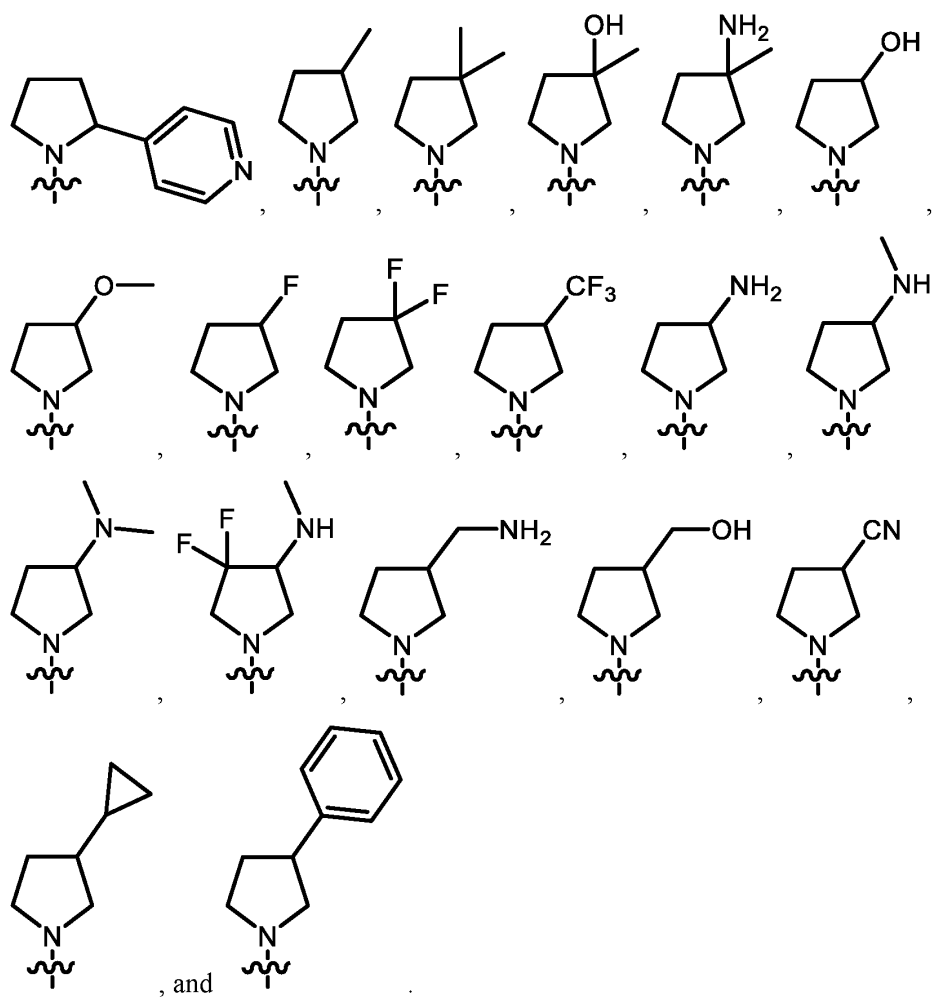
[0134] Enumerated Embodiment 18. The compound of Enumerated Embodiment 17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form an azetidiny or pyrrolidinyl, wherein the azetidiny or pyrrolidinyl is optionally substituted with one or more R^3 .

[0135] Enumerated Embodiment 19. The compound of any of Enumerated Embodiments 15-18, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which

they are attached to form a heterocyclyl selected from the group consisting of

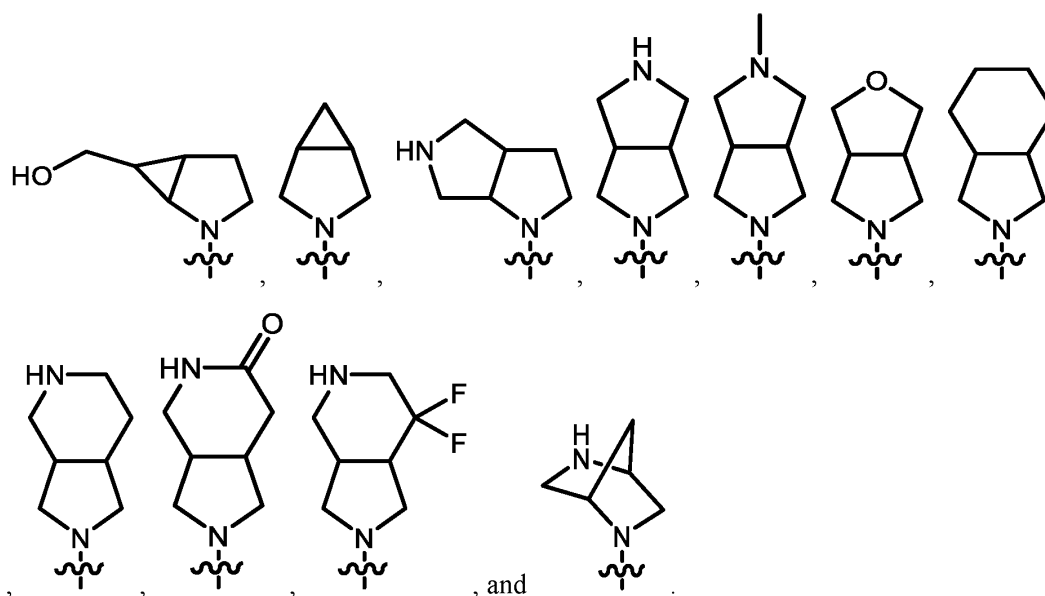






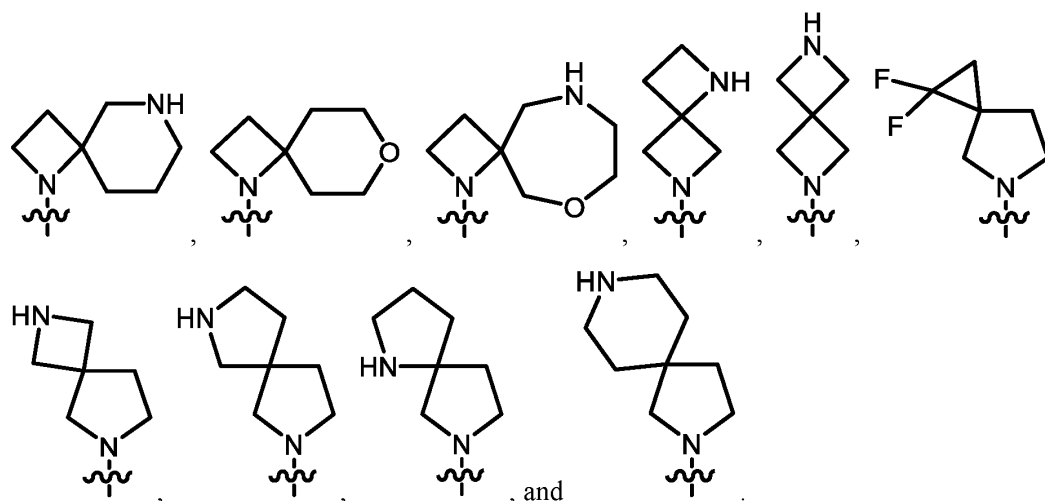
[0136] Enumerated Embodiment 20. The compound of Enumerated Embodiment 16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a saturated 6- to 10-membered fused or bridged heterocyclyl optionally substituted with one or more R^3 .

[0137] Enumerated Embodiment 21. The compound Enumerated Embodiment 20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a group selected from the group consisting of



[0138] Enumerated Embodiment 22. The compound of Enumerated Embodiment 16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a saturated 7- to 10-membered spirocyclic heterocyclyl optionally substituted with one or more R^3 .

[0139] Enumerated Embodiment 23. The compound of Enumerated Embodiment 22, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a group selected from the group consisting of



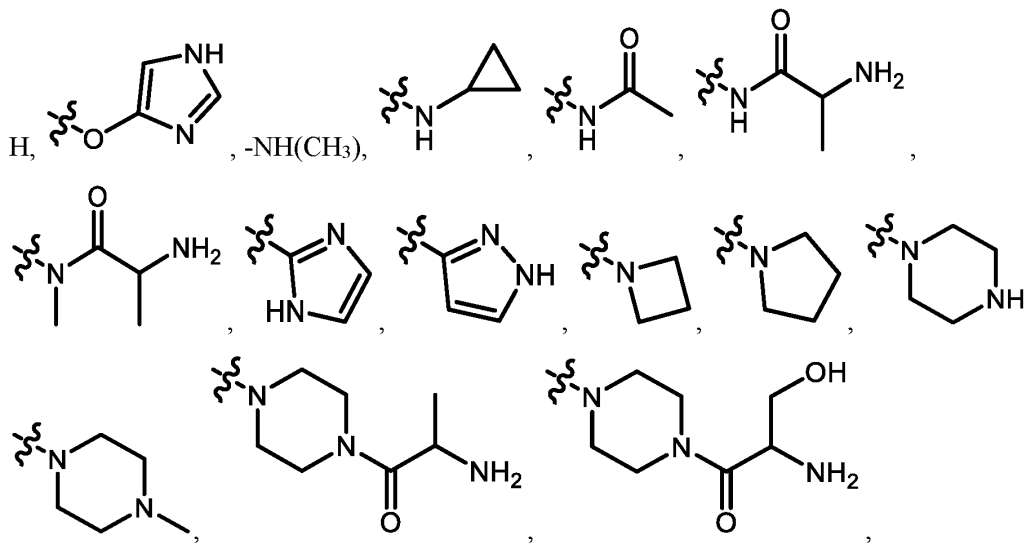
[0140] Enumerated Embodiment 24. The compound of any of Enumerated Embodiments 1-23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^6 is H, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

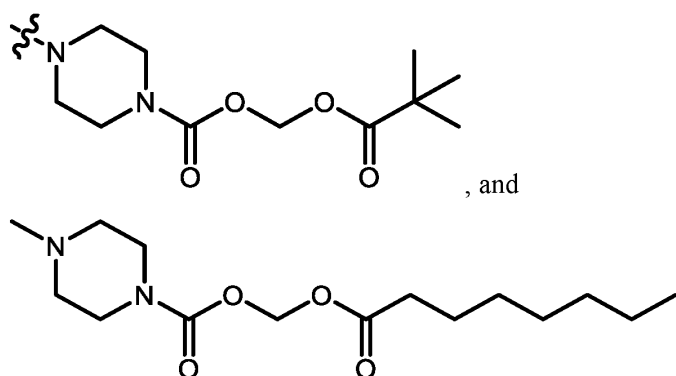
the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b} .

[0141] 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 R^6 is H, $-O(5\text{- to }6\text{-membered heteroaryl})$, $-NH(C_{1-6}\text{alkyl})$, $-NH(C_{3-6}\text{cycloalkyl})$, $-NHC(O)(C_{1-6}\text{alkyl})$, $-NHC(O)(C_{1-6}\text{alkyl})NH_2$, $-N(C_{1-6}\text{alkyl})C(O)(C_{1-6}\text{alkyl})NH_2$, 5-membered heteroaryl, or 4- to 6-membered N-containing heterocyclyl, wherein

the 4- to 6-membered N-containing heterocyclyl is optionally substituted with one or more R^{6b} , $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$.

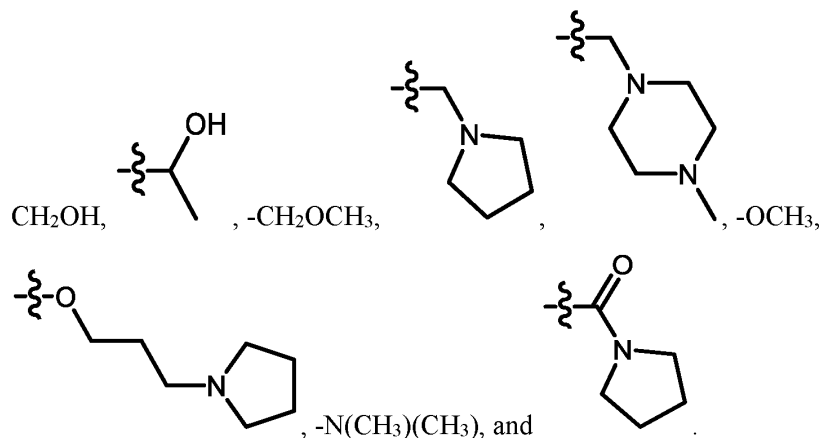
[0142] Enumerated Embodiment 26. The compound of any of Enumerated Embodiments 1-25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^6 is selected from the group consisting of





[0143] Enumerated Embodiment 27. The compound of any of Enumerated Embodiments 1-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^8 is C_{1-6} alkyl, $-(C_{1-6}alkyl)OH$, $-C_{1-6}alkyl-O(C_{1-6}alkyl)$, $-(C_{1-6}alkyl)(4- \text{ to } 7\text{-membered heterocyclyl})$, $-O(C_{1-6}alkyl)$, $-O(C_{1-6}alkyl)(4- \text{ to } 7\text{-membered heterocyclyl})$, $-N(C_{1-6}alkyl)(C_{1-6}alkyl)$, or $-C(O)(4- \text{ to } 7\text{-membered heterocyclyl})$, wherein each 4- to 7-membered heterocyclyl is optionally substituted by C_{1-6} alkyl.

[0144] Enumerated Embodiment 28. The compound of any of Enumerated Embodiments 1-27, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein R^8 is selected from the group consisting of $-CH_3$, -



[0145] Enumerated Embodiment 29. 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 $-O(C_{1-6}alkyl)-$; and

R^3 is H, $-N(R^x)(R^y)$, or 4- to 12-membered heterocyclyl optionally substituted with one or more R^{3a} .

[0146] Enumerated Embodiment 30. The compound of any of Enumerated Embodiments 1-4, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

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

L is a bond; and

R^6 is 4- to 12-membered heterocyclyl optionally substituted with one or more R^{6b} , -C(=O) R^{12} , -C(=O)N(R^{11})(R^{12}), or -C(=O)OR¹².

[0147] Enumerated Embodiment 31. The compound of Enumerated Embodiment 30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

R^6 is piperazinyl optionally substituted with one or more R^{6b} , -C(=O) R^{12} , -C(=O)N(R^{11})(R^{12}), or -C(=O)OR¹².

[0148] Enumerated Embodiment 32. The compound of any of Enumerated Embodiments 1-4, or 29, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate of any of the foregoing, wherein:

L is -O(C₁₋₆alkyl)-; and

R^6 is H or -N(R^x)(R^y).

[0149] Enumerated Embodiment 33. 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, or 31, wherein:

Ring A is phenyl; and

R^6 is C₁₋₆alkyl.

[0150] Enumerated Embodiment 34. 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.

[0151] Enumerated Embodiment 35. A pharmaceutical composition comprising a compound of any of Enumerated Embodiments 1-34, 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.

[0152] Enumerated Embodiment 36. 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 1-34, 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 35.

[0153] Enumerated Embodiment 37. The method of Enumerated Embodiment 36, wherein a therapeutically effective amount of the compound is administered.

[0154] Enumerated Embodiment 38. The method of Enumerated Embodiment 36 or 37, wherein said disease or condition mediated by TDP-43 is a neurological disease or condition.

[0155] Enumerated Embodiment 39. The method of Enumerated Embodiment 38, 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).

[0156] Enumerated Embodiment 40. The method of Enumerated Embodiment 38 or 39, wherein the neurological disease or condition is traumatic brain injury (TBI).

[0157] Enumerated Embodiment 41. The method of Enumerated Embodiment 38 or 39, wherein the neurological disease or condition is frontotemporal dementia (FTD).

[0158] Enumerated Embodiment 42. The method of Enumerated Embodiment 38 or 39, wherein the neurological disease or condition is amyotrophic lateral sclerosis (ALS).

[0159] Enumerated Embodiment 43. The method of any of Enumerated Embodiments 38, 39, or 42, wherein the neurological disease or condition is sporadic amyotrophic lateral sclerosis or C9ORF72 amyotrophic lateral sclerosis.

[0160] Enumerated Embodiment 44. The method of any of Enumerated Embodiments 36-43, wherein the subject is a human.

[0161] Enumerated Embodiment 45. A method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of any of Enumerated Embodiments 1-34, 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 35, 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.

[0162] Enumerated Embodiment 46. 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 1-34, 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 35.

[0163] Enumerated Embodiment 47. The method of Enumerated Embodiment 46, wherein the gene expression levels are for *STMN2*.

[0164] Enumerated Embodiment 48. The method of Enumerated Embodiment 46, wherein the gene expression levels are for *POLDIP3*.

[0165] Enumerated Embodiment 49. The compound of any of Enumerated Embodiments 1-34, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, or the pharmaceutical composition of Enumerated Embodiment 35 for use in the treatment of a TDP-43 mediated disease or disorder.

[0166] Enumerated Embodiment 50. Use of a compound of any of Enumerated Embodiments 1-34, 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.

[0167] Enumerated Embodiment 51. A kit, comprising (i) a compound of any one of Enumerated Embodiments 1-34, 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 35 and (ii) instructions for use in treating a TDP-43 mediated disease or condition in a subject in need thereof.

EXAMPLES

[0168] 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)
mL (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)	mm (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'-biphenyl]-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- κO) [2'-(methylamino- κN) [1,1'-biphenyl]-2-yl- κC] palladium)	
[Pd (OAc) ₂] ₃ (palladium II acetate)	CPhos Pd G3 [(2-Dicyclohexylphosphino-2',6'-bis (<i>N</i> , <i>N</i> -dimethylamino)-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium (II) methansulfonate
BINAP (1,1'-binaphthyl-2,2'-diphemyl phosphine)	Pd[P(<i>t</i> -Bu) ₃] ₂ (palladium bis tri(<i>tert</i> -butyl)phosphine)

[0169] SCX general protocol. The hydrochloride salt product was neutralized by *Strong Cation Exchange Resin*. The resin was first washed with two volumes of deionized water. The compound to neutralized was absorbed to the resin by washing the resin with a solution of the compound in methanol. The resin was then washed with deionized water until the pH of the solution is neutral. A solution of ammonium hydroxide and methanol was used to cleave compound from the resin. Solvents were then concentrated and lyophilized to get the desired product.

[0170] 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

[0171] Flash chromatography.

1: Puri Flash XS520Plus, Interchim, PF-30SIHP-JP-F00xx, 30 μ m

2: ISCO®, SepaFlash® Silica Flash column

[0172] 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 = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances, integration, br = broad singlet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, dq = doublet of quintuplet). Coupling constants *J* were measured in Hertz.

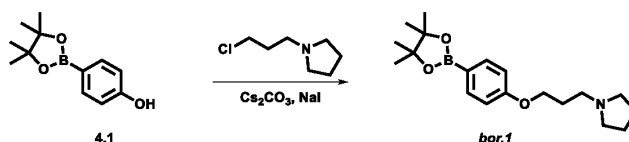
[0173] LCMS spectra were recorded according to the following conditions.

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

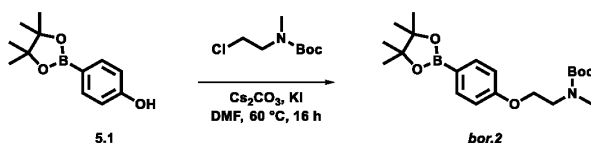
bor.1: 1-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenoxy) propyl) pyrrolidine



[0174] To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenol **4.1** (0.50 g, 2.3 mmol, 1.0 equiv) and 1-(3-chloropropyl)pyrrolidine (0.30 g, 2.0 mmol, 0.90 equiv) in

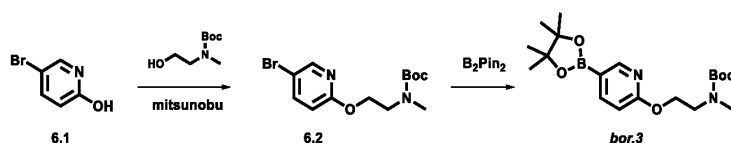
DMF (5.0 mL) was added KI (0.10 g, 0.60 mmol, 0.27 equiv) and Cs₂CO₃ (2.2 g, 6.8 mmol, 3.0 equiv) at 25 °C. The mixture was stirred at 65 °C for 16 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC **3** (gradient: 25%-55% over 10 min) to give 1-[3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenoxy] propyl] pyrrolidine **bor.1** (0.12 g, 0.36 mmol, 16% yield) as a white solid. MS m/z (ESI) [M+H]⁺ = 332.2.

bor.2: tert-butyl methyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenoxy) ethyl) carbamate



[0175] To a solution of 4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) phenol **5.1** (0.50 g, 2.3 mmol, 1.0 equiv) and *tert*-butyl *N*-(2-chloroethyl) -*N*-methyl-carbamate (0.40 g, 2.0 mmol, 0.90 equiv) in DMF (5.0 mL) were added Cs₂CO₃ (1.5 g, 4.5 mmol, 2.0 equiv) and KI (75 mg, 0.45 mmol, 0.2 equiv) at 25 °C. The mixture was stirred at 60 °C for 12 hours. The mixture was diluted with water (10 mL) and then extracted with ethyl acetate (10 mL, three times). The combined organic layers were washed with brine (10 mL, three times), dried over Na₂SO₃, filtered, and concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC **3** (gradient: 55%-85% over 10 min) to give *tert*-butyl *N*-methyl-*N*-[2-[4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) phenoxy] ethyl] carbamate **bor.2** (0.15 g, 0.36 mmol, 16% yield, 90% purity) as a white solid.

bor.3: tert-butyl methyl(2-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyridin-2-yl) oxy) ethyl) carbamate

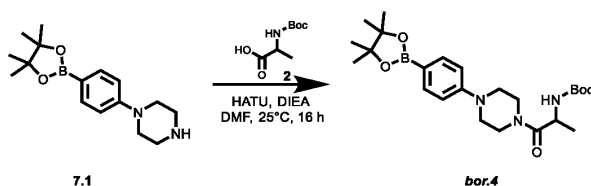


[0176] Step1: To a mixture of *tert*-butyl *N*-(2-hydroxyethyl)-*N*-methylcarbamate **6.1** (1.0 g, 5.7 mmol, 1.0 equiv) and 5-bromopyridin-2-ol (1.0 g, 5.8 mmol, 1.0 equiv) in THF (10 mL) were added PPh₃ (1.8 g, 6.9 mmol, 1.2 equiv) and diisopropyl azodiformate (1.4 g, 6.9 mmol, 1.2 equiv) at 25 °C. After stirring at 20 °C for 16 h, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a crude product. The crude product was purified by

column chromatography (SiO₂, PE/EtOAc 10:1 to 3:1) to give tert-butyl *N*-[2-[(5-bromo-2-pyridyl) oxy] ethyl]-*N*-methylcarbamate **6.2** (1.5 g, 4.5 mmol, 79% yield, 99% purity) as colorless oil. MS *m/z* (ESI) [M+H]⁺ = 333.3.

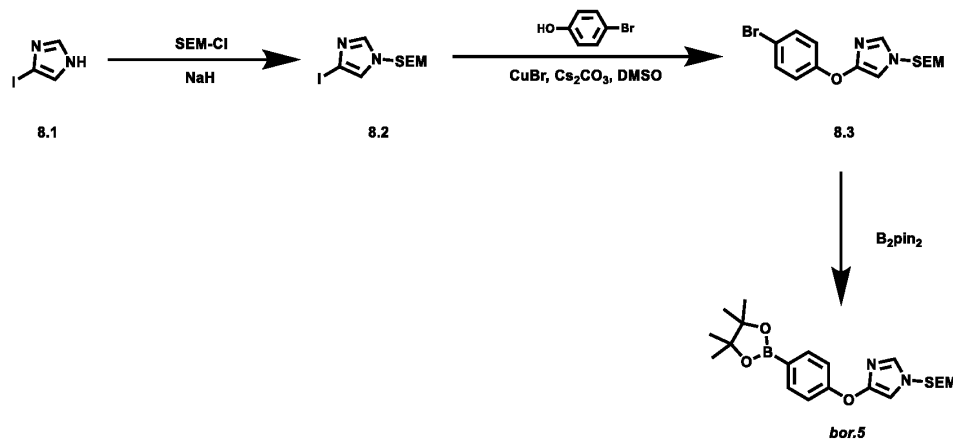
[0177] Step 2: To a mixture of tert-butyl *N*-[2-[(5-bromo-2-pyridyl)oxy]ethyl]-*N*-methylcarbamate **6.2** (1.0 g, 3.0 mmol, 1.0 equiv) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3, 2-dioxaborolane (0.81 g, 3.2 mmol, 1.1 equiv) in dioxane (15 mL) were added KOAc (0.59 g, 6.0 mmol, 2.0 equiv) and Pd(dppf)Cl₂ (0.25 g, 0.30 mmol, 0.10 equiv) at 25 °C. After stirring at 80 °C for 3 h, the reaction mixture was filtered. The filtrate was concentrated *in vacuo* to give a crude product. The crude product was purified by column chromatography (SiO₂, PE/EtOAc 10:1 to 1:1) to give tert-butyl *N*-methyl-*N*- [2- [[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan- 2-yl)-2-pyridyl] oxy] ethyl] carbamate **bor.3** (1.1 g, 2.5 mmol, 82% yield, 85% purity) as yellow oil. MS *m/z* (ESI) [M-80]⁺ = 297.2 .

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



[0178] To a solution of 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazine **7.1** (2.0 g, 6.9 mmol, 1.0 equiv) in DMF (5.0 mL) was added HATU (4.0 g, 10 mmol, 1.5 equiv), 2-(tert-butoxycarbonylamino)propanoic acid (1.6 g, 8.3 mmol, 1.2 equiv) and DIEA (2.7 g, 20.8 mmol, 3.6 mL, 3.0 equiv) at 25 °C. The mixture was stirred at 25 °C for 16 hours. 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 Na₂SO₃, filtered, and concentrated under reduced pressure to give a residue. The crude product was triturated with MeOH (30 mL) at 25 °C for 20 min to give tert-butyl *N*-[1-methyl-2-oxo-2-[4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazin-1-yl]ethyl]carbamate **bor.4** (1.7 g, 3.5 mmol, 51% yield, 95% purity) was obtained as a white solid. MS *m/z* (ESI) [M+H]⁺ = 460.3. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.52 (d, *J* = 8.6 Hz, 2H), 6.99 (r d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.47 (quin, *J* = 7.2 Hz, 1H), 3.68 - 3.54 (m, 4H), 3.26 - 3.16 (m, 4H), 1.37 (s, 9H), 1.26 (s, 12H), 1.15 (d, *J* = 6.8 Hz, 3H).

bor.5: trimethyl-[2-[[4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenoxy] imidazol-1-yl] methoxy] ethyl] silane



[0179] Step 1: To a solution of 4-iodo-1H-imidazole **8.1** (10 g, 52 mmol, 1.0 equiv) in DMF (0.10 L) was added NaH (2.5 g, 62 mmol, 60% purity, 1.2 equiv) at 0 °C, the mixture was stirred at 0 °C for 0.5 h, then SEM-Cl (9.5 g, 57 mmol, 10 mL, 1.1 equiv) was added. The mixture was stirred at 25 °C for 2 hours. The reaction mixture was quenched by saturated ammonium chloride aqueous solution (0.20 L) at 0 °C, and then extracted with ethyl acetate (0.10 L, three times). The combined organic layers were washed with saturated brine (0.30 L), dried over anhydrous Na₂SO₃, filtered, and concentrated under reduced pressure to give a residue. The residue obtained was purified by Flash chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~50% EtOAc/PE, gradient: 50 mL/min) to give 2-[(4-iodoimidazol-1-yl) methoxy] ethyl-trimethyl-silane **8.2** (13 g, 30 mmol, 58% yield, 74% purity) as colourless oil. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.01 (s, 1H), 7.77 (d, *J* = 0.9 Hz, 1H), 7.48 (d, *J* = 1.0 Hz, 1H), 7.05 (s, 1H), 5.29 (d, *J* = 11.3 Hz, 4H), 3.50 - 3.45 (m, 4H), 0.86 - 0.82 (m, 4H), -0.04 (s, 18H).

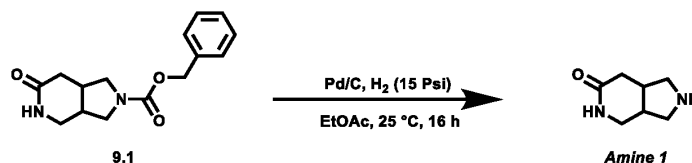
[0180] Step 2: A mixture of 2-[(4-iodoimidazol-1-yl)methoxy]ethyl-trimethyl-silane **8.2** (5.0 g, 15 mmol, 1.0 equiv), 4-bromophenol (4.0 g, 23 mmol, 1.5 equiv), bis[(*Z*)-1-methyl-3-oxo-but-1-en-2-yl]copper (0.81 g, 3.1 mmol, 0.20 equiv), Cs₂CO₃ (15 g, 46 mmol, 3.0 equiv) in dioxane (50 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 120 °C for 16 hours under N₂ atmosphere. The mixture was diluted with water (0.10 L) and extracted with ethyl acetate (0.10 L, three times). The organic phase was washed with brine (0.20 L), dried over anhydrous Na₂SO₃, filtered and the filtrate was concentrated. The residue obtained was purified by Flash chromatography (ISCO®; 80 g SepaFlash® Silica

Flash Column, Eluent of 0~100% EtOAc/PE, gradient: 50 mL/min) and prep-HPLC 7 (gradient: 62%-82% over 8 min) to give 2-[[4-(4-bromophenoxy)imidazol-1-yl]methoxy]ethyl-trimethyl-silane **8.3** (0.16 g, 0.42 mmol, 2.7% yield, 97% purity) as pink oil. MS m/z (ESI) $[M+H]^+ = 369.0$.

[0181] Step 3: A mixture of 2-[[4-(4-bromophenoxy)imidazol-1-yl]methoxy]ethyl-trimethyl-silane **8.3** (0.16 g, 0.43 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 (0.17 g, 0.65 mmol, 1.5 equiv), KOAc (0.13 g, 1.3 mmol, 3.0 equiv), Pd(dppf)Cl₂ (32 mg, 43 μ mol, 0.10 equiv) in dioxane (2.0 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 100 °C for 16 hours under N₂ atmosphere. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL, three times). The organic phase was washed with brine (20 mL), dried over anhydrous Na₂SO₃, filtered and the filtrate was concentrated. The residue obtained was purified by prep-TLC (SiO₂, PE/EtOAc = 3:1) to give trimethyl-[2-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenoxy] imidazol-1-yl] methoxy] ethyl] silane **bor.5** (0.12 g, 0.20 mmol, 47% yield, 70% purity) as colourless oil. MS m/z (ESI) $[M+H]^+ = 417.2$.

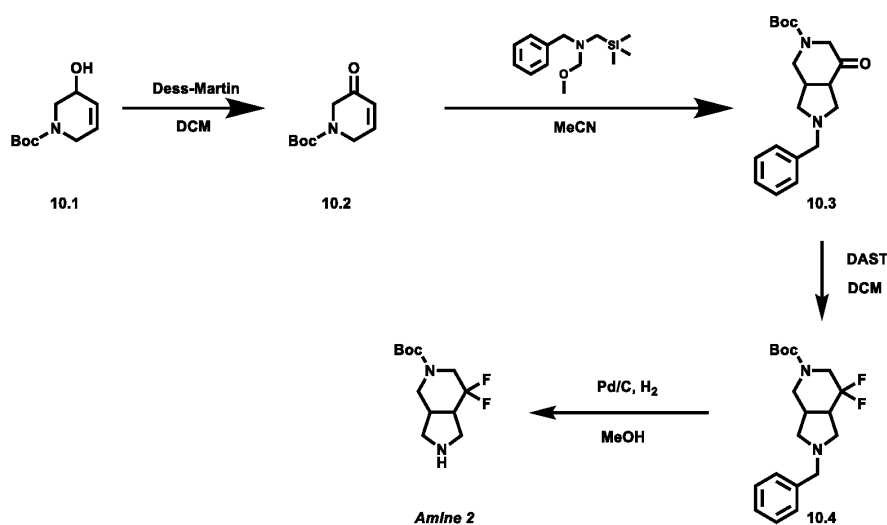
Synthesis of amine intermediates

Amine 1: cis-1,2,3,3a,4,5,7,7a-octahydropyrrolo[3,4-c] pyridin-6-one



[0182] To a solution of Pd/C (20 mg, 10% purity) in EtOAc (5.0 mL) / THF (5.0 mL) was added benzyl 6-oxo-3,3a,4,5,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridine-2-carboxylate (0.10 g, 0.36 mmol, 1.0 equiv) under N₂ atmosphere at 25 °C. The suspension was degassed and purged with H₂ three times. After stirring under H₂ (50 Psi) at 25 °C for 16 h, the reaction mixture was filtered and concentrated under reduced pressure to give **Amine 1** (0.12 mg, crude) as a yellow solid.

Amine 2: cis-tert-butyl 7,7-difluoro-2,3,3a,4,6,7a-hexahydro-1H-pyrrolo[3,4-c] pyridine-5-carboxylate



[0183] Step 1: To a solution of tert-butyl 3-hydroxy-3,6-dihydro-2H-pyridine-1-carboxylate **10.1** (3.0 g, 15 mmol, 1.0 equiv) in DCM (30 mL) was added (1,1-diacetoxy-3-oxo-1,2-benziodoxol-1-yl) acetate (13 g, 30 mmol, 9.3 mL, 2.0 equiv) at 25 °C. The mixture was stirred at 25 °C for 2 hours. The mixture was filtered, and the filtrate was concentrated. The residue obtained was purified by Flash chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~50% EtOAc/PE, gradient: 40 mL/min) to give tert-butyl 3-oxo-2,6-dihydropyridine-1-carboxylate **10.2** (2.0 g, 10 mmol, 67% yield, 99% purity) as colourless oil. MS (ESI) m/z $[M+H]^{+} = 142.1$.

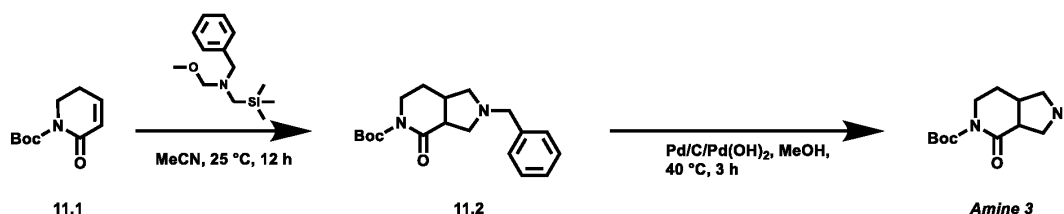
[0184] Step 2: A mixture of **10.2** (0.50 g, 2.5 mmol, 1.0 equiv) and N-(methoxymethyl)-1-phenyl-N-(trimethylsilyl)methanamine (1.2 g, 5.1 mmol, 2.0 equiv) in CH₃CN (5.0 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 25 °C for 2 hours under N₂ atmosphere. The reaction mixture was purified by prep-HPLC 7 (gradient: 39%-69% over 10 min) to give **10.3** (0.47 g, 1.4 mmol, 54% yield, 96% purity) as yellow oil. MS (ESI) m/z $[M+H]^{+} = 331.1$.

[0185] Step 3: To a solution of **10.3** (0.32 g, 0.97 mmol, 1.0 equiv) in DCM (5.0 mL) was added DAST (0.47 g, 2.9 mmol, 0.38 mL, 3.0 equiv) at -78 °C. The mixture was stirred at 20 °C for 2 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL, three times). The organic phase was washed with brine (50 mL), dried over anhydrous Na₂SO₃, filtered and the filtrate was concentrated. The residue obtained was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column,

Eluent of 0~100% EtOAc/PE, gradient: 20 mL/min) to give **10.4** (0.10 g, 0.28 mmol, 29% yield, 100% purity) as yellow oil. MS (ESI) m/z $[M+H]^+ = 353.1$.

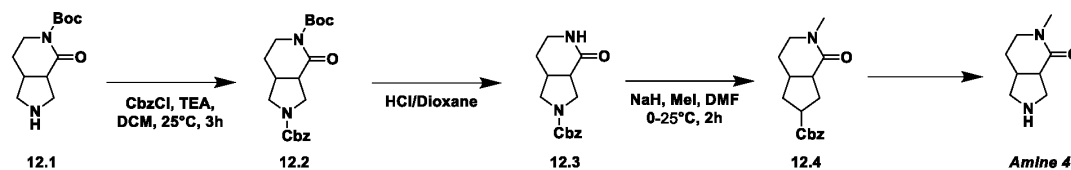
[0186] Step 4: To a solution of Pd/C (10 mg, 9.4 μ mol, 10% purity) and Pd(OH)₂ (10 mg, 36 μ mol, 20% purity) in MeOH (5.0 mL) was added **10.4** (0.10 g, 0.28 mmol, 1.0 equiv) under N₂. The suspension was degassed under vacuum and purged with H₂ three times. The mixture was stirred under H₂ (50 psi) at 50 °C for 16 hours. The reaction mixture was diluted with MeOH (10 mL), the mixture was filtered through a pad of celite, and the filtrate was concentrated to give **Amine 2** (50 mg, crude) as yellow oil. The crude was used next step without purification.

Amine 3: cis-tert-butyl 4-oxo-2,3,3a,6,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridine-5-carboxylate



[0187] Step 1: To a solution of tert-butyl 6-oxo-2,3-dihydropyridine-1-carboxylate **11.1** (0.85 g, 4.3 mmol, 1.0 equiv) in MeCN (10 mL) was added N-(methoxymethyl)-1-phenyl-N-(trimethylsilylmethyl) methanamine (1.7 g, 7.2 mmol, 1.7 equiv), then the resulting mixture was stirred at 25 °C for 12 hours. The reaction mixture was filtered and evaporated under reduced pressure to give the crude product. The crude product was purified by prep-HPLC **2** (gradient: 13%-43% over 15 min) to give **11.2** (0.56 g, 1.7 mmol, 39% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.38 - 7.35 (m, 5H), 4.19 - 4.04 (m, 1H), 3.91 - 3.81 (m, 2H), 3.45 (d, $J = 2.4, 11.2, 13.4$ Hz, 1H), 3.35 (s, 2H), 3.18 (d, $J = 3.5$ Hz, 2H), 3.15 - 2.77 (m, 2H), 2.37 - 2.27 (m, 1H), 2.09 (d, $J = 2.3, 4.9, 7.0, 14.0$ Hz, 1H), 1.54 (s, 9H).

[0188] Step 2: To a solution of **11.2** (0.15 g, 0.45 mmol, 1.0 equiv) in MeOH (5.0 mL) was added Pd/C (15 mg, 14 μ mol, 10% purity, 0.03 equiv), Pd(OH)₂ (15 mg, 21 μ mol, 20% purity, 0.05 equiv), The suspension was degassed and purged with H₂ three times. The mixture was stirred under H₂ (50 Psi) at 40 °C for 3 hours. The reaction mixture was filtered and evaporated under reduced pressure to give the **Amine 3** (0.11 g, crude) as the yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 3.24 - 3.12 (m, 4H), 3.05 - 2.88 (m, 2H), 2.58 (d, $J = 6.1, 11.2$ Hz, 1H), 2.52 - 2.41 (m, 1H), 2.05 - 1.90 (m, 1H), 1.85 (d, $J = 4.1, 13.5$ Hz, 1H), 1.46 (s, 9H).

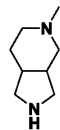
Amine 4: cis-5-methyloctahydro-4H-pyrrolo[3,4-c]pyridin-4-one

[0189] Step 1: To a solution of **12.1** (13.6 g, 56.60 mmol, 1 eq) in DCM (150 mL) was added CbzCl (9.80 g, 57.44 mmol, 8.2 mL, 1.01 eq) and TEA (14.54 g, 143.69 mmol, 20 mL, 2.54 eq). The reaction solution was stirred at 25 °C for 1 hour. The mixture was diluted with water (60 mL), and then extracted with EtOAc (50 mL, twice). The combined organic phase was washed with brine (50 mL, three times), dried over Na₂SO₄, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~3% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give **12.2** (6 g, 14.74 mmol, 26.05% yield, 92% purity) as a colorless oil. MS m/z (ESI) [M+Na]⁺ = 397.1.

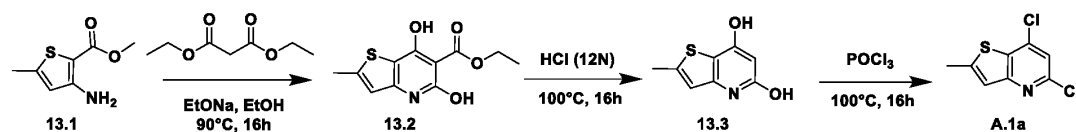
[0190] Step 2: **12.2** (5 g, 13.35 mmol, 1 eq) was added to HCl/dioxane (2 M, 100 mL). The reaction solution was stirred at 25°C for 1 hour. The reaction solution was concentrated under vacuum to give **12.3** (4 g, crude) as a yellow oil which was used for next step without further purification.

[0191] Step 3: To a solution of **12.3** (3.5 g, 12.76 mmol, 1 eq) in DMF (40 mL) was added NaH (1.5 g, 37.50 mmol, 60% purity, 2.94 eq) at 0 °C under N₂. The reaction solution was stirred at 25 °C for 1 hour. MeI (2.28 g, 16.06 mmol, 1 mL, 1.26 eq) was added to the solution at 0°C and stirred at 25 °C for another 1 hour. The mixture was quenched by H₂O (100 mL), then the aqueous phase was extracted with EtOAc (100 mL, three times). The combined organic layers were dried over Na₂SO₄, filtrated and evaporated. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~70% THF/Petroleum ether gradient @ 100 mL/min) to give **12.4** (2.6 g, 8.66 mmol, 67.85% yield, 96% purity) as a colorless oil. MS m/z (ESI) [M+H]⁺ = 289.1.

[0192] Step 4: To a solution of **12.4** (2.5 g, 8.67 mmol, 1 eq) in MeOH (200 mL) was added Pd/C (300 mg, 10% purity) and Pd(OH)₂ (300 mg, 20% purity) under N₂. The reaction solution was degassed and purged under H₂ for three times. The reaction solution was stirred at 40 °C for 3 hours. The reaction solution was filtered and the filtrate was concentrated under vacuum to give **Amine 4** (1.5 g, crude) as a colorless oil which was used for next step without further purification.

Amine 5: cis-5-methyloctahydro-1H-pyrrolo[3,4-c]pyridine**Amine 5**

[0193] To a solution of tert-butyl cis-octahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate (1.5 g, 5.71 mmol, 1 eq, HCl salt) in THF (30 mL) was added dropwise LiAlH₄ (2.5 M, 7 mL, 3 eq) at 0 °C over 1 min. After addition, the mixture was stirred at 50 °C for 16 hours under N₂ atmosphere. The reaction mixture was added Na₂SO₄ (2 g) and water (0.5 mL) at 20 °C, and then diluted with EtOAc (20 mL) filtered and concentrated under reduced pressure to give **Amine 5** (800 mg, crude) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 3.06 - 2.52 (m, 8H), 2.24 - 2.22 (m, 3H), 1.81 - 1.60 (m, 4H).

*Synthesis of dichlorothienopyridines intermediates***A.1a (R₈ = -CH₃, R₇ = -H): 5,7-dichloro-2-methylthieno [3,2-b] pyridine**

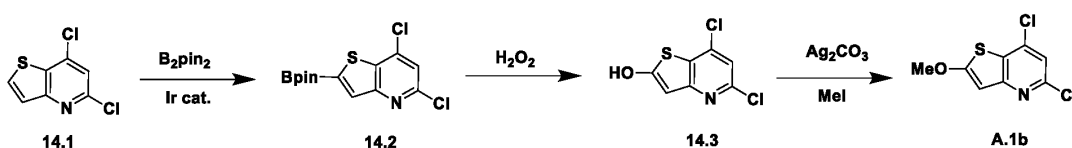
[0194] Step1: To a solution of methyl 3-amino-5-methylthiophene-2-carboxylate **13.1** (12 g, 70 mmol, 1.0 equiv) and diethyl propanedioate (34 g, 0.21 mol, 32 mL, 3.0 equiv) in EtOH (0.15 L) was added EtONa (14 g, 0.21 mol, 3.0 equiv) at 25 °C. The mixture was stirred at 90 °C for 16 hours. The mixture was adjusted to pH = 7 with HCl (2M) and filtered. The filter cake was triturated with petroleum ether (0.10 L) at 25 °C for 15 min. The title compound ethyl 5, 7-dihydroxy-2-methyl-thieno [3, 2-b] pyridine-6-carboxylate **13.2** (17 g, 67.12 mmol, 95.77% yield) as a brown solid was collected by filtration. The crude was used next step without purification. MS (ESI) m/z. [M+H]⁺ = 254.0.

[0195] Step 2: **13.2** (34 g, 0.13 mol, 1.0 equiv) was added in concentrated solution of HCl 12N (0.20 L) at 25 °C and then the mixture was stirred at 100 °C for 16 hours. The mixture was concentrated to give crude 2-methylthieno [3, 2-b] pyridine-5, 7-diol **13.3** (20 g, 0.11 mol, 82% yield) as black, brown solid which was used in the next step without purification. MS (ESI) m/z. [M+H]⁺ = 182.0.

[0196] Step 3: A solution of **13.3** (20 g, 110.37 mmol, 1 eq) and POCl₃ (0.20 L) was stirred at 100 °C for 16 hours. The reaction mixture was concentrated under reduced pressure to

remove POCl_3 and the residue was quenched with water (0.20 L) at 25 °C. The pH was adjusted to 7~8 with NaHCO_3 . The mixture was diluted with water (0.20 L) and extracted with EtOAc (0.20 L, three times). The combined organic layers were washed with brine (0.60 L), dried over anhydrous Na_2SO_3 , filtered and the filtrate was concentrated. The residue obtained was purified by column chromatography (SiO_2 , PE/EtOAc = 5:1 to 1:1) to give 5, 7-dichloro-2-methyl-thieno [3, 2-b] pyridine **A.1a** (14 g, 62 mmol, 56% yield, 96% purity) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.68 (s, 1H), 7.35 (d, J = 1.2 Hz, 1H), 2.65 (s, 3H). MS (ESI) m/z . $[\text{M}+\text{H}]^+ = 217.9$.

A.1b ($\text{R}_8 = -\text{OCH}_3$, $\text{R}_7 = -\text{H}$): 5,7-dichloro-2-methoxythieno[3,2-b] pyridine



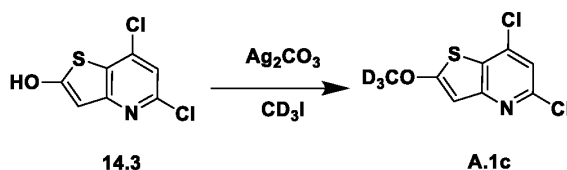
[0197] Step1: To a solution of **14.1** (1.6 g, 7.8 mmol, 1.0 equiv) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.1 g, 8.2 mmol, 1.0 equiv) in THF (15 mL) was added (1Z,5Z)-cycloocta-1,5-diene;2,4-dimethyl-BLAHbicyclo[1.1.0]butane (5.3 g, 8.0 mmol, 1.0 equiv) and 3,4,7,8-tetramethyl-1,10-phenanthroline (1.9 g, 8.1 mmol, 1.0 equiv). The mixture was stirred at 80 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give residue. The crude product **14.2** (3.6 g, crude) was directly used into the next step without further purification as brown gum.

[0198] Step 2: To a solution of **14.2** (3.6 g, 11 mmol, 1.0 equiv) in MeOH (25 mL) was added H_2O_2 (2.3 g, 20 mmol, 2.0 mL, 30% purity, 1.9 equiv) at 0 °C under N_2 atmosphere. The mixture was stirred and allowed to reach 25 °C for 2 hours. The reaction mixture was extracted with EtOAc (0.10 L) and H_2O (80 mL). The combined organic layers were washed with *saturated* aqueous Na_2SO_3 (80 mL, twice) and *saturated* aqueous NaHCO_3 (80 mL, twice), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue. The residue obtained was purified by flash silica gel chromatography (EtOAc/PE gradient 0 to 14% at 60 mL/min) to give 5,7-dichlorothieno[3,2-b] pyridin-2-ol **14.3** as a brown solid.

[0199] Step 3: To a solution of **14.3** (0.40 g, 1.8 mmol, 1.0 equiv) in MeCN (10 mL) was added Ag_2CO_3 (1.5 g, 5.5 mmol, 0.25 mL, 3.0 equiv). Then iodomethane (0.40 g, 2.8 mmol, 0.18 mL, 1.6 equiv) was added to the mixture at 0 °C under N_2 atmosphere. The mixture was

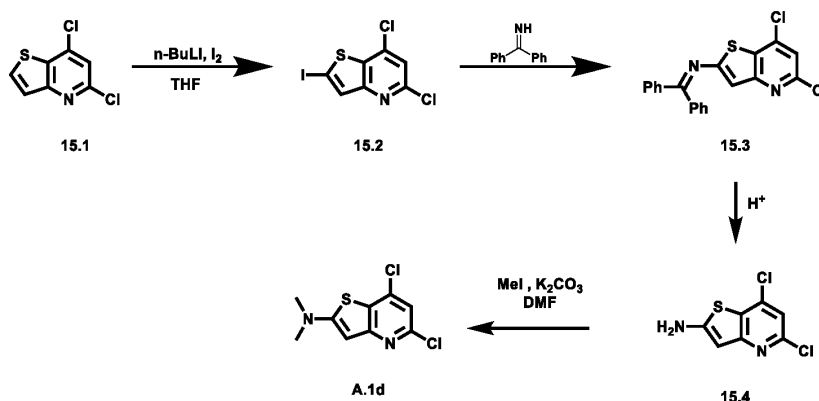
stirred and allowed to reach 25 °C for 2 hours. The reaction mixture was quenched with *saturated* aqueous NH₄Cl (10 mL), then the reaction mixture was extracted with EtOAc (60 mL) and *saturated* aqueous NaCl (20 mL). The organic layer was washed with *saturated* aqueous NaCl (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-TLC (SiO₂, PE/EtOAc 4:1) to give 5,7-dichloro-2-methoxythieno[3,2-b] pyridine **A.1b** as a yellow solid.

A.1c (R₈ = -OCD₃, R₇ = -H): 5,7-dichloro-2-(trideuteriomethoxy) thieno[3,2-b] pyridine



[0200] To a solution of **14.3** (0.38 g, 1.7 mmol, 1.0 equiv) in acetonitrile (8.0 mL) was added trideuterio(iodo)methane (0.49 g, 3.5 mmol, 2.0 equiv) and silver carbonate (0.95 g, 3.5 mmol, 2.0 equiv) at 25°C. After stirring at 25 °C for 2 hours, the reaction mixture was diluted with ethyl acetate (10 mL), then filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue obtained was purified by Flash chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0–5% EtOAc/PE, gradient: 20mL/min) to give 5,7-dichloro-2-(trideuteriomethoxy) thieno[3,2-b] pyridine **A.1c** (0.17 g, 0.61 mmol, 35% yield, 85% purity) as a yellow solid. MS (ESI) *m/z* [M+H]⁺ = 237.0.

A.1d (R_n = 2-NMe₂): 5,7-dichloro-N,N-dimethyl-thieno[3,2-b]pyridin-2-amine



[0201] Step 1: To a solution of 5,7-dichlorothieno[3,2-b]pyridine **15.1** (5.0 g, 23 mmol, 1.0 equiv) in THF (50 mL) was added n-butyllithium (2.5 M, 15 mL, 1.6 equiv) at -70 °C. The mixture was stirred at -70 °C for 0.5 hours and to the mixture was added iodine (11 g, 43

mmol, 1.9 equiv) in THF (30 mL) at -70 °C. The mixture was allowed to reach 25 °C and stirred at 25 °C for another 1.5 hours. The reaction mixture was quenched by saturated ammonium chloride aqueous solution (0.10 L) and saturated sodium sulfite solution (50 mL). Then the mixture was then extracted with ethyl acetate (50 mL, three times). The combined organic phases were 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 triturated in acetonitrile (0.10 L) and then filtered, the filtrate was concentrated under reduced pressure to give 5,7-dichloro-2-iodo-thieno[3,2-b] pyridine **15.2** (4.6 g, 12 mmol, 51% yield, 85% purity) as a gray solid. MS (ESI) m/z [M+H]⁺ = 329.9.

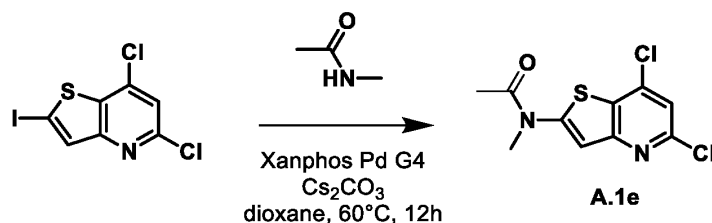
[0202] Step 2: To a mixture of 5,7-dichloro-2-iodo-thieno[3,2-b]pyridine **15.2** (4.6 g, 12 mmol, 1.0 equiv) and diphenylmethanimine (2.2 g, 12 mmol, 1.0 equiv) in dioxane (40 mL) were added Xantphos Pd G4 (0.57 g, 0.59 mmol, 0.05 equiv) and cesium carbonate (7.7 g, 24 mmol, 2.0 equiv) at 25 °C, the mixture was degassed and purged with nitrogen three times, then the mixture was stirred at 70 °C for 6 hours under nitrogen atmosphere. The reaction mixture was diluted with water (50 mL) and then extracted with ethyl acetate (40 mL, three times), the combined organic phase was 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 obtained was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~8% EtOAc/PE, gradient: 40 mL/min) to give N-(5,7-dichlorothieno[3,2-b] pyridin-2-yl)-1,1-diphenyl- methanamine **15.3** (4.8 g, 9.5 mmol, 80% yield, 76% purity) as a yellow solid. MS (ESI) m/z [M+H]⁺ = 383.0.

[0203] Step 3: To a mixture of N-(5,7-dichlorothieno[3,2-b] pyridin-2-yl)-1,1-diphenyl-methanimine **15.3** (3.8 g, 7.5 mmol, 1.0 equiv) in dioxane (30 mL) were added chlorine hydride / dioxane (2 M, 20 mL) at 25 °C, the mixture was stirred at 25 °C for 2 hours. The reaction mixture was filtered, the filter cake was added into saturated sodium bicarbonate solution (50 mL), the mixture was then extracted with ethyl acetate (30 mL, three times), the combined organic phase was washed with brine (10 mL, three times), dried with anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to give 5,7-dichlorothieno[3,2-b]pyridin-2-amine **15.4** (1.5 g, 6.4 mmol, 85% yield, 94% purity) as a yellow solid. MS (ESI) m/z [M+H]⁺ = 219.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.24 (s, 2 H), 7.12 (s, 1 H), 6.08 (s, 1 H).

[0204] Step 4: To a solution of **15.4** (1.5 g, 6.4 mmol, 1.0 equiv) in dimethylformamide (15 mL) were added methyl iodide (2.3 g, 16 mmol, 2.5 equiv) and potassium carbonate (2.7 g,

19 mmol, 3.0 equiv) at 25 °C. The mixture was stirred at 25 °C for 16 hours. The reaction mixture was then diluted with saturated sodium bicarbonate solution (50 mL), and then extracted with ethyl acetate (30 mL, three times) and the combined organic phases were washed with brine (10 mL, three times), dried with anhydrous Na₂SO₄, filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue obtained was purified by Flash chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~15% EtOAc/PE, gradient: 30 mL/min) to give 5,7-dichloro-N, N-dimethyl-thieno[3,2-b] pyridin-2-amine **A.1d** (0.20 g, 0.78 mmol, 12% yield, 96% purity) as a yellow solid. MS (ESI) m/z [M-100]⁺ = 247.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.19 (s, 1 H), 6.19 (s, 1 H), 3.09 (s, 6 H).

A.1e (R₈ = -NCH₃COCH₃, R₇ = -H): 5,7-dichloro-2-(trideuteriomethoxy) thieno[3,2-b] pyridine



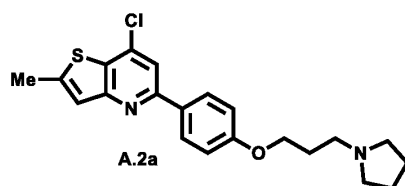
[0205] To a solution of 5,7-dichloro-2-iodo-thieno[3,2-b]pyridine (800 mg, 2.42 mmol, 1.00 eq), N-methylacetamide (177 mg, 2.42 mmol, 1.00 eq) in dioxane (10.0 mL) were added Methanesulfonato[9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene](2-methylamino-1,1-biphenyl-2-yl)palladium(II) (233 mg, 0.242 mmol, 0.100 eq), cesium carbonate (1.58 g, 4.85 mmol, 2.00 eq) at 20 °C, the mixture was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 60 °C for 12 hours under nitrogen atmosphere. The reaction mixture was diluted with water (30.0 ml) and then extracted with ethyl acetate (3 × 30.0 ml), the combined organic phase was washed with brine (3 × 10.0 ml), dried with anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~60% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give N-(5,7-dichlorothieno[3,2-b] pyridin-2-yl)-N-methyl-acetamide (700 mg, 1.63 mmol, 67.2% yield, 64% purity) as a yellow solid. MS (ESI) m/z [M+H]⁺ = 275.0.

General procedure for Suzuki coupling reaction:

Intermediates A.2 (Schemes 1; Step 1) and B.1(Scheme 2; step 1) have been obtained following the synthetic conditions described below:

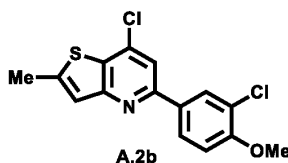
[0206] A mixture of **A.1** (1.0 equiv), boronic acid or ester derivatives (1.2 equiv), Na_2CO_3 (3.0 equiv) and $\text{Pd}(\text{PPh}_3)_4$ (0.10 equiv) in EtOH/toluene/ H_2O (0.45:0.45:0.10; 0.17M) was degassed and purged with N_2 for three times at 25 °C. Then the mixture was stirred at 60 °C or 80 °C for 16 hours under N_2 atmosphere. After cooling at 25 °C the mixture was diluted with water and extracted with ethyl acetate (three times). The organic phase was washed with brine (three times), dried over *anhydrous* Na_2SO_4 , filtered and the filtrate was concentrated. The residue obtained was purified by prep-TLC (SiO_2 , PE/EtOAc 2:1 or 3:1) or by Flash chromatography (12 g, EtOAc/PE 0 to 30% gradient at 30 mL/min).

A.2a: 7-chloro-2-methyl-5-[4-(3-pyrrolidin-1-ylpropoxy) phenyl] thieno[3,2-b] pyridine

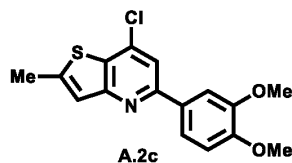


[0207] According to Scheme 1 Step 1: Substrate **A.1a** (80 mg, 366.80 μmol , 1 eq) and boronic ester **bor.1** (0.11 g, 0.33 mmol, 0.90 equiv) were used. After work-up and purification by Flash chromatography, Product **A.2a** (0.10 g, 0.25 mmol, 68% yield, 97% purity) was obtained as a white solid. MS m/z (ESI) $[\text{M}+\text{H}]^+ = 387.1$.

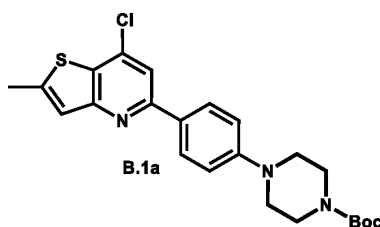
A.2b: 7-chloro-5-(3-chloro-4-methoxy-phenyl)-2-methyl-thieno[3,2-b] pyridine



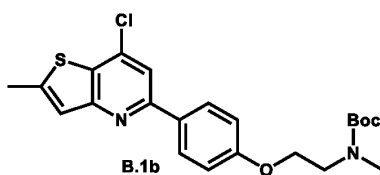
[0208] According to Scheme 1 Step 1: Substrate **A.1a** (0.30 g, 1.4 mmol, 1.0 equiv), (3-chloro-4-methoxy-phenyl) boronic acid (0.26 g, 1.4 mmol, 1.0 equiv) were used in dioxane/ H_2O (4:1). After work-up the residue obtained was triturated with EtOAc. The solid was filtrated to get Product **A.2b** (0.30 g, 0.91 mmol, 66% yield, 98% purity) as a white solid. MS m/z (ESI) $[\text{M}+\text{H}]^+ = 323.9$.

A.2c: 7-chloro-5-(3,4-dimethoxyphenyl)-2-methyl-thieno[3,2-*b*] pyridine

[0209] According to Scheme 1 Step 1: Substrate **A.1a** (0.20 g, 0.92 mmol, 1.0 equiv), Pd(PPh₃)₄ (50 mg, 43 μmol, 0.50 equiv) were used in dioxane/H₂O (4:1). After work-up Product **A.2c** (0.27 g, 0.55 mmol, 60% yield, 65% purity) was obtained as a yellow solid. No further purification was done and the product was used as a crude for the next step.

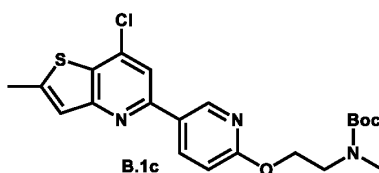
B.1a: tert-butyl 4-(4-(7-chloro-2-methylthieno[3,2-*b*] pyridin-5-yl) phenyl) piperazine-1-carboxylate

[0210] According to Scheme 2 Step 1: Substrate **A.1a** (10 g, 44 mmol, 1.0 equiv), tert-butyl 4-[4-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl) phenyl]piperazine-1-carboxylate (15 g, 39 mmol, 0.90 equiv) and Na₂CO₃ (2.0 equiv) were used. After work-up the residue obtained was purified by Flash chromatography. Product **B.1a** (14.5 g, 31.03 mmol, 71.23% yield, 95% purity) was obtained as a yellow solid. MS m/z (ESI) [M+H]⁺ = 444.1.

B.1b: *N*-[2-[4-(7-chloro-2-methyl-thieno [3, 2-*b*] pyridin-5-yl) phenoxy] ethyl]-*N*-methylcarbamate

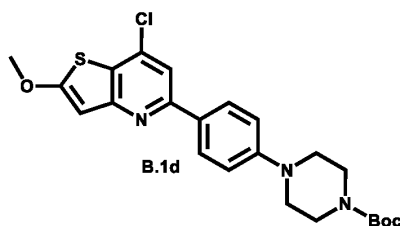
[0211] According to Scheme 2 Step 1: Substrate **A.1a** (84 mg, 0.38 mmol, 1.0 equiv) and boronic ester **bor.2** (0.13 g, 0.34 mmol, 0.90 equiv) were used. No workup was done and the crude mixture was filtered. Product **B.1b** (0.15 g, 0.31 mmol, 81% yield, 90% purity) was obtained as a white solid.

B.1c: tert-butyl N-[2-[5-(7-chloro-2-methyl-thieno[3,2-b] pyridin-5-yl)-2-pyridyl] oxy] ethyl]-N-methyl- carbamate



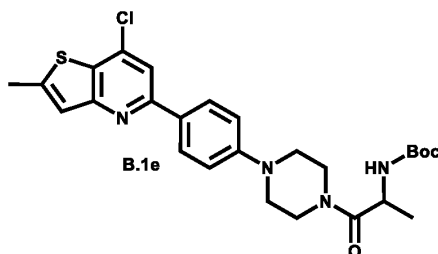
[0212] According to Scheme 2 Step 1: Substrate **A.1a** (0.20 g, 0.92 mmol, 1.0 equiv), boronic ester **bor.1** (0.41 g, 0.92 mmol, 1.0 equiv) and Na_2CO_3 (2.0 equiv) were used. After work-up Product **B.1c** (0.12 g, 0.25 mmol, 27% yield, 90% purity) was obtained as a yellow solid. MS m/z (ESI) $[\text{M}+\text{H}]^+ = 434.1$. No further purification was done and the product was used as a crude for the next step.

B.1d: tert-butyl 4-[4-(7-chloro-2-methoxy-thieno[3,2-b] pyridin-5-yl) phenyl] piperazine-1-carboxylate



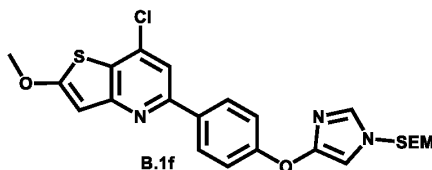
[0213] According to Scheme 2 Step 1: Substrate **A.1b** (50 mg, 0.21 mmol, 1.0 equiv) and tert-butyl 4- [4- (4,4,5,5- tetramethyl- 1,3,2 -dioxaborolan -2 -yl) phenyl] piperazine-1-carboxylate (45 mg, 0.12 mmol, 0.50 equiv) were used. After work-up Product **B.1d** (35 mg, 57 μmol , 27% yield, 75% purity) was obtained as a red solid. No further purification was done and the product was used as a crude for the next step.

B.1e: tert-butyl N-[2-[4-[4-(7-chloro-2-methyl-thieno[3,2-b] pyridin-5-yl) phenyl] piperazin-1-yl]-1-methyl-2-oxo-ethyl] carbamate



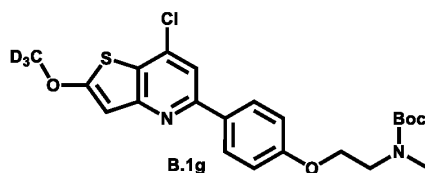
[0214] According to Scheme 2 Step 1: Substrate **A.1a** (0.10 g, 0.46 mmol, 1.0 equiv) and **bor.4** (0.25 g, 0.54 mmol, 1.2 equiv) were used. After work-up Product **B.1e** (0.20 g, 0.35 mmol, 77% yield, 91% purity) was obtained as a yellow solid. MS (ESI) m/z $[M+H]^+ = 515.2$. No further purification was done and the product was used as a crude for the next step.

B.1f: 2-[[4-[4-(7-chloro-2-methoxy-thieno[3,2-b] pyridin-5-yl) phenoxy] imidazol-1-yl] methoxy] ethyl-trimethyl-silane



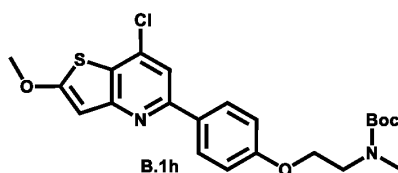
[0215] According to Scheme 2 Step 1: Substrate **A.1b** (80 mg, 0.34 mmol, 1.0 equiv), **bor.5** (0.11 g, 0.26 mmol, 0.77 equiv) in dioxane (1.0 mL) / H₂O (0.10 mL), at 80 °C for 16 hours under N₂ atmosphere. After work-up Product **B.1f** (0.11 g, crude) was obtained as a yellow oil. MS (ESI) m/z $[M+H]^+ = 488.1$. No further purification was done and the product was used as a crude for the next step.

B.1g: tert-butyl N-[2-[4-[7-chloro-2-(trideuteriomethoxy)thieno[3,2-b]pyridin-5-yl]phenoxy]ethyl]-N-methyl-carbamate



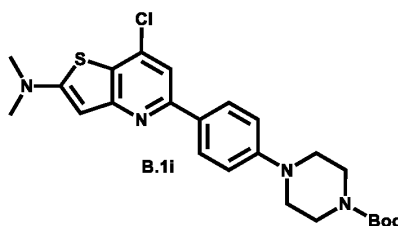
[0216] According to Scheme 2 Step 1: Substrate **A.1c** (0.17 g, 0.61 mmol, 1.0 equiv), **bor.2** (0.23 g, 0.61 mmol, 1.0 equiv) and Na₂CO₃ (0.13 g, 1.2 mmol, 2.0 equiv) were stirred at 80 °C for 5 hours. After work-up Product **B.1g** (0.18 g, 0.32 mmol, 52% yield, 80% purity) was obtained as a yellow solid. No further purification was done and the product was used as a crude for the next step. MS (ESI) m/z $[M+H]^+ = 452.2$. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.10 (d, $J = 8.8$ Hz, 2H), 7.89 (s, 1H), 7.06 (d, $J = 8.8$ Hz, 2H), 6.86 (s, 1H), 4.24 - 4.06 (m, 2H), 3.56 (t, $J = 5.2$ Hz, 2H), 2.91 - 2.84 (m, 3H), 1.36 (s, 9H), 1.07 (s, 2H). No further purification was done and the product was used as a crude for the next step.

B.1h: tert-butyl N-[2-[4-(7-chloro-2-methoxy-thieno[3,2-b] pyridin-5-yl) phenoxy] ethyl]-N-methylcarbamate



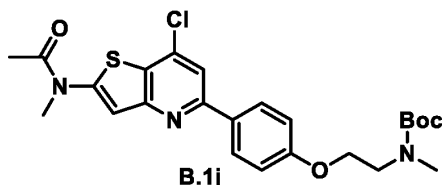
[0217] According to Scheme 2 Step 1: Substrate **A.1b** (6.0 g, 26 mmol, 1.0 equiv), **bor.2** (9.0 g, 24 mmol, 0.93 equiv) in dioxane (80 mL) and H₂O (8.0 mL), Pd(dppf)Cl₂ (1.8 g, 2.5 mmol, 0.10 equiv) and K₃PO₄ (17 g, 78 mmol, 3.0 equiv) were stirred at 80 °C for 12 hours under N₂ atmosphere. After work-up Product **B.1h** (8.1 g, 17 mmol, 68% yield, 97% purity) was obtained as a yellow gum.

B.1i: tert-butyl 4-[4-[7-chloro-2-(dimethylamino) thieno [3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



[0218] According to Scheme 2 Step 1: Substrate **A.1d** (0.20 mg, 0.78 mmol, 1.0 equiv), tert-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl] piperazine- 1-carboxylate (0.30 g, 0.78 mmol, 1.0 equiv), Na₂CO₃ (0.17 mg, 1.6 mmol, 2.0 equiv) were stirred at 80 °C for 5 hours. After work-up Product **B.1i** (0.23 g, 0.40 mmol, 51% yield, 82% purity) was obtained as a yellow solid. MS (ESI) m/z [M+H]⁺ = 473.3. No further purification was done and the product was used as a crude for the next step.

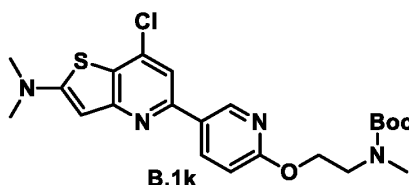
B.1j: tert-butyl (2-(4-(7-chloro-2-(N-methylacetamido)thieno[3,2-b]pyridin-5-yl)phenoxy)ethyl)(methyl)carbamate



[0219] According to Scheme 2 Step 1: Substrate **A.1e** (600 mg, 1.40 mmol, 1.00 eq), **bor.2** (527 mg, 1.40 mmol, 1.00 eq) in dioxane (15.0 mL), water (1.00 mL), Pd(PPh₃)₄ (161 mg,

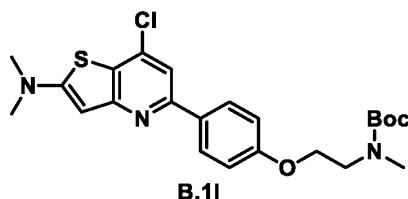
0.140 mmol, 0.100 eq), potassium carbonate (579 mg, 4.19 mmol, 3.00 eq) were stirred at 80 °C for 12 hours under N₂ atmosphere. After work-up the residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~60% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give Product **B.1j** (450 mg, 0.450 mmol, 32.2% yield, 49% purity) as a yellow solid. MS (ESI) m/z [M-81]⁺ = 490.2.

B.1k: tert-butyl (2-((5-(7-chloro-2-(dimethylamino)thieno[3,2-b]pyridin-5-yl)pyridin-2-yl)oxy)ethyl)(methyl)carbamate



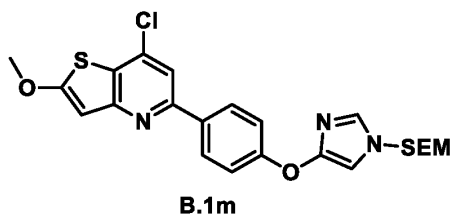
[0220] According to Scheme 2 Step 1: Substrate **A.1d** (1.2 g, 4.86 mmol, 1 eq), Na₂CO₃ (1.03 g, 9.71 mmol, 2.0 eq) and tert-butyl N-methyl-N-[2-[[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy]ethyl]carbamate (1.84 g, 4.86 mmol, 1 eq) in toluene (10 mL)/EtOH (10 mL)/Water (2 mL), Pd(PPh₃)₄ (561.08 mg, 485.55 μmol, 0.1 eq) were stirred at 80°C for 16 hours under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue purified by column chromatography (SiO₂, PE/EtOAc= 5/1 to 0/1). **B.1k** (1.5 g, 3.24 mmol, 66.72% yield) was obtained as yellow oil. MS (ESI) m/z [M+H]⁺ = 463.2.

B.1l: tert-butyl (2-(4-(7-chloro-2-(dimethylamino)thieno[3,2-b]pyridin-5-yl)phenoxy)ethyl)(methyl)carbamate



[0221] According to Scheme 2 Step 1: A solution of **A.1d** (200 mg, 809.25 μmol, 1 eq), **bor.2** (300 mg, 795.16 μmol, 9.83e-1 eq), Pd(PPh₃)₄ (100 mg, 86.54 μmol, 1.07e-1 eq) and Na₂CO₃ (200 mg, 1.89 mmol, 2.33 eq) in toluene (4 mL), EtOH (4 mL), H₂O (1 mL) were stirred at 80°C for 12 hours under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure and residue was purified by prep-TLC (PE/AcOEt 3/1) to give **B.1l** (200 mg, 367.96 μmol, 45.47% yield, 85% purity) as a yellow solid.

B.1m: 7-chloro-2-methoxy-5-(4-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)oxy)phenyl)thieno[3,2-b]pyridine



[0222] According to Scheme 2 Step 1: A mixture of **bor.5** (445 mg, 1.07 mmol, 1 eq), **A.1b** (250 mg, 1.07 mmol, 1 eq), Pd(PPh₃)₄ (123 mg, 106.44 μmol, 9.97e-2 eq) and Na₂CO₃ (340 mg, 3.21 mmol, 3 eq) in toluene (2.5 mL), EtOH (2.5 mL) and Water (0.5 mL) was stirred at 80 °C for 12h under N₂. After work-up the residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~35% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) to give **B.1m** (370 mg, 633.76 μmol, 59.35% yield, 83.6% purity) as yellow oil. MS (ESI) m/z [M + H]⁺ = 488.1.

General procedure for Buchwald coupling and S_NAr products:

Intermediates B.2 (Schemes 2; Step 2), C.1 (Scheme 3; step 1)) have been obtained following the synthetic conditions described below:

[0223] Conditions 1 Buchwald: A mixture of derivative **B.1** (1.0 equiv), amine (1.0 equiv), PdP₂(*t*-Bu)₆ (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 4-16 hours under N₂ atmosphere. The mixture was diluted with water and extracted with EtOAc (three times). The organic phase was washed two to three times with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo* to give a residue.

[0224] Conditions 2 Buchwald: A mixture of derivative **B.1** (1.0 equiv), amine (5.0 equiv), Cphos Pd G3 (0.10 equiv), Cs₂CO₃ (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 100 °C for 16 hours under N₂ atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue.

[0225] Conditions 3 Buchwald: To a solution of derivative **B.1** (1.0 equiv) and *t*-BuONa (2.0 equiv) in 1,4-dioxane or toluene (0.17 M) was added amine (1.5 equiv) and BrettPhos Pd G₃ (0.10 equiv) at 20 °C. The reaction mixture was degassed and purged with N₂ for three times,

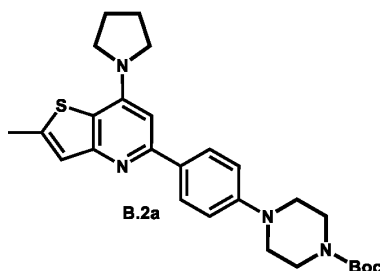
and then the mixture was stirred at 70 °C for 16 hours under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give residue purified by prep-TLC (SiO₂, PE/ EtOAc 1:1) or flash silica gel chromatography (40 g, Eluent of 0 to 60% EtOAc/PE gradient at 40 mL/min)

[0226] Conditions 1 S_NAr: To a solution of derivative **B.1** (1.0 equiv) and amine (large excess) at 25 °C. The mixture was stirred at 100-130 °C for 16 hours. The mixture was diluted with water and extracted with EtOAc (three times). The organic phase was washed with brine (three times), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated.

[0227] Conditions 2 S_NAr: To a solution of derivative **B.1** (1.0 equiv) and amine (1.0 equiv) in DMF (0.45 M) was added K₂CO₃ (3.0 equiv) at 25 °C. The mixture was stirred at 100 °C for 16 hours. 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. The crude was used next step without purification.

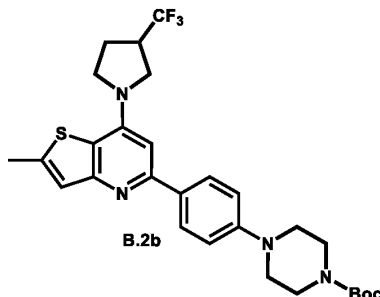
[0228] Conditions 3 S_NAr: To a solution of derivative **B.1** (1.0 equiv) and amine (1.2 equiv) in DMF or DMSO (0.10 M) was added DIEA (2.0 equiv) at 25 °C. The mixture was stirred at 130 °C for 16 hours. The mixture was diluted with water and extracted with ethyl acetate (three times). The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated.

B.2a: tert-butyl 4-[4-(2-methyl-7-pyrrolidin-1-yl-thieno[3,2-b] pyridin-5-yl) phenyl] piperazine-1-carboxylate



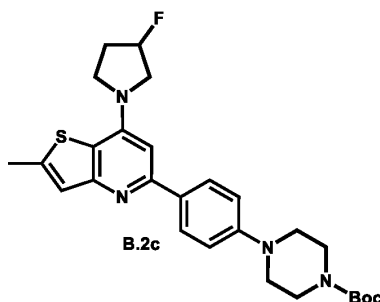
[0229] According to Scheme 3 Step 1: Conditions 1 Buchwald: Substrate **B.1a** (0.20 g, 0.45 mmol, 1.0 equiv) in dioxane (0.05 M) were used. After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 26%-56% over 10 min). Compound **B.2a** (30 mg, 62 μmol, 14% yield, 99% purity) was obtained as a brown solid. MS m/z (ESI) [M+H]⁺ = 479.2.

B.2b: *tert*-butyl 4-[4-[2-methyl-7-[3-(trifluoromethyl) pyrrolidin-1-yl] thieno [3, 2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



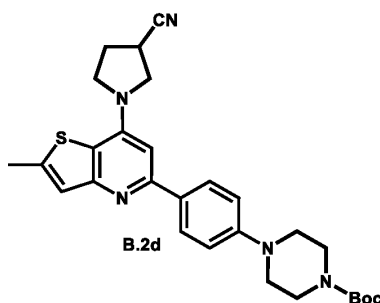
[0230] According to Scheme 3 Step 1: Conditions 3 Buchwald: Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv) in dioxane. After work-up the residue obtained was purified by prep-TLC. Product **B.2b** (0.23 g, 0.42 mmol, 62% yield) was obtained as yellow oil. MS m/z (ESI) $[M+H]^+ = 547.4$.

B.2c: *tert*-butyl 4-[4-[7-(3-fluoropyrrolidin-1-yl)-2-methyl-thieno[3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



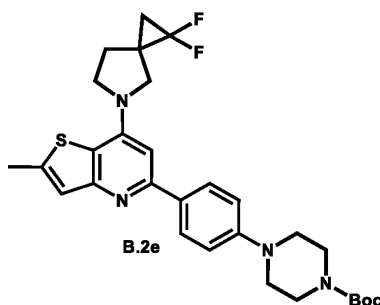
[0231] According to Scheme 3 Step 1: Conditions 1 Buchwald: Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 3-fluoropyrrolidine.HCl (0.12 g, 0.96 mmol, 1.4 equiv) in dioxane (0.07 M). After work-up the crude product was purified by prep-TLC with (DCM/MeOH = 10:1) to give product **B.2c** (0.30 g, 0.57 mmol, 85% yield, 95% purity) as green oil. MS m/z (ESI) $[M+H]^+ = 497.3$.

B.2d: *tert*-butyl 4-[4-[7-(3-cyanopyrrolidin-1-yl)-2-methyl-thieno[3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



[0232] According to Scheme 3 Step 1: Conditions 1 Buchwald: To a substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv) in dioxane (0.06 M) was added pyrrolidine-3-carbonitrile; HCl (0.14 g, 1.0 mmol, 1.5 equiv). The mixture was stirred at 80 °C for 12 hours. After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 22%-52% over 10 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give product **B.2d** (0.15 g, 0.30 mmol, 44% yield, 100% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.99 (d, *J* = 8.5 Hz, 2H), 7.14 (s, 1H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.72 (s, 1H), 4.06 - 4.00 (m, 1H), 3.97 - 3.88 (m, 2H), 3.87 - 3.79 (m, 1H), 3.67 - 3.59 (m, 1H), 3.48 (br d, *J* = 4.1 Hz, 4H), 3.23 - 3.15 (m, 4H), 2.57 (s, 3H), 1.51 (br d, *J* = 14.4 Hz, 2H), 1.44 (s, 9H). MS *m/z* (ESI) [*M*+*H*]⁺ = 504.3.

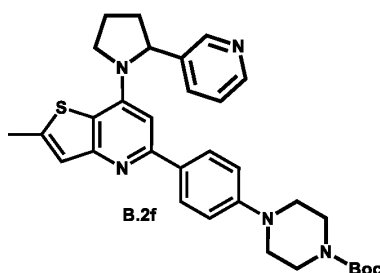
B.2e: *tert*-butyl 4-[4-[7-(2,2-difluoro-5-azaspiro [2.4] heptan-5-yl) -2-methyl-thieno [3, 2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



[0233] According to Scheme 3 Step 1: Conditions 3 Buchwald: Substrate **B.1a** (0.20 g, 0.45 mmol, 1.0 equiv), 2, 2-difluoro-5-azaspiro [2.4] heptane (0.10 g, 0.77 mmol, 1.7 equiv), *t*-BuONa (2.0 equiv), BrettPhos Pd G₃ (0.1 equiv) were added in 1, 4-dioxane (0.23 M). After work-up the residue obtained was purified by prep-HPLC **3** (gradient: 4-10 min 40-70%).

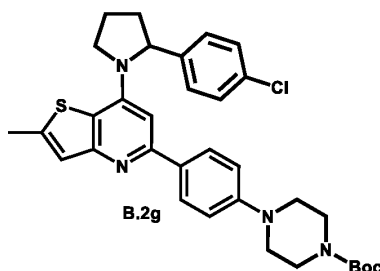
Compound **B.2e** (0.11 g, 0.20 mmol, 45% yield) was obtained as a brown solid. MS m/z (ESI) $[M+H]^+ = 541.3$.

B.2f: *tert*-butyl 4-[4-[2-methyl-7-[2-(3-pyridyl) pyrrolidin-1-yl] thieno [3, 2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



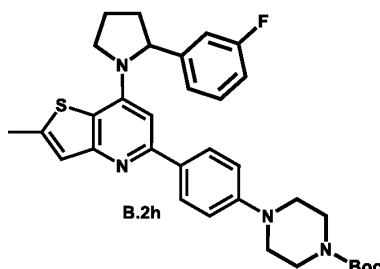
[0234] According to Scheme 3 Step 1: Conditions 2 Buchwald: Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 3-pyrrolidin-2-ylpyridine (0.12 g, 0.81 mmol, 0.11 mL, 1.2 equiv), Cs_2CO_3 (2.0 equiv), CPHOS PD G₃ (0.10 equiv) were added in 1,4-dioxane (0.23M). The reaction mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °C for 16 hours under N_2 atmosphere. After work-up the residue obtained was purified by prep-HPLC **3** (gradient: 2-10 min 25-55%). Compound **B.2f** (0.20 g, 0.36 mmol, 53% yield) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+ = 556.4$.

B.2g: *tert*-butyl 4-[4-[7-[2-(4-chlorophenyl) pyrrolidin-1-yl]-2-methyl-thieno [3, 2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



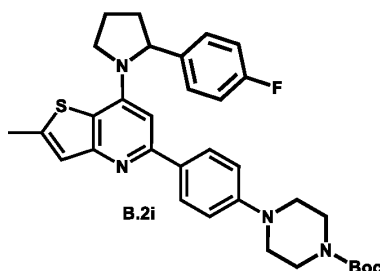
[0235] According to Scheme 3 Step 1: Conditions 2 Buchwald: Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 2-(4-chlorophenyl) pyrrolidine (0.15 g, 0.83 mmol, 1.2 equiv), CPHOS PD G₃ (60 mg, 74 μmol , 0.11 equiv) and Cs_2CO_3 (2.0 equiv) were added in dioxane (0.14 M) and stirred at 60 °C for 12 hours. After work-up the residue obtained was purified by prep-TLC (PE/EtOAc = 2:1) to give compound **B.2g** (0.20 g, 0.25 mmol, 38% yield, 75% purity) as a yellow solid.

B.2h: *tert*-butyl 4-[4-[7-[2-(3-fluorophenyl) pyrrolidin-1-yl]-2-methyl-thieno [3, 2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



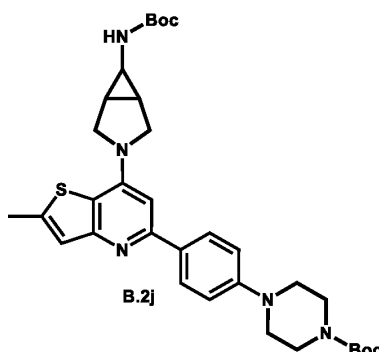
[0236] According to Scheme 3 Step 1: Conditions 2 Buchwald: Substrate Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 2-(3-fluorophenyl) pyrrolidine (0.14 g, 0.85 mmol, 1.3 equiv), CPHOS PD G₃ (0.10 equiv) and Cs₂CO₃ (2.0 equiv) was added in dioxane (1.4 M) and stirred at 60°C for 12 hours. After work-up the residue obtained was purified by prep-TLC (PE/EtOAc = 2:1) to give product **B.2h** (0.20 g, 0.25 mmol, 38% yield, 73% purity) as a yellow solid.

B.2i: *tert*-butyl 4-[4-[7-[2-(4-fluorophenyl) pyrrolidin-1-yl]-2-methyl-thieno[3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



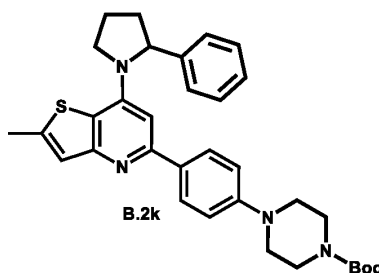
[0237] According to Scheme 3 Step 1: Conditions 2 Buchwald: **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), in dioxane (0.14 M), 2-(4-fluorophenyl) pyrrolidine (0.17 g, 1.0 mmol, 1.5 equiv), CPHOS PD G₃ (0.11 equiv) and Cs₂CO₃ (2.7 equiv). The mixture was stirred at 60 °C for 12 hours. The residue was partitioned between EtOAc (30 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (30 mL) twice. The combined organic layers were dried over (Na₂SO₄) and evaporated to give a crude material. The residue obtained was purified by flash silica gel chromatography (12 g, Eluent of 40~60% EtOAc/PE gradient at 20 mL/min) to afford product **B.2i** (0.30 g, 0.47 mmol, 70% yield, 90% purity) as yellow oil. MS m/z (ESI) [M+H]⁺ = 573.4.

B.2j: *tert*-butyl 4-[4-[7-[6-(*tert*-butoxycarbonylamino)-3-azabicyclo [3.1.0] hexan-3-yl]-2-methyl-thieno[3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate (cis mixture)



[0238] According to Scheme 3 Step 1: Conditions 2 Buchwald: Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), dioxane (0.68 M), *tert*-butyl N-(3-azabicyclo [3.1.0] hexan-6-yl) carbamate (0.16 g, 0.81 mmol, 1.2 equiv), CPHOS PD G3 (0.10 equiv) and Cs₂CO₃ (3.0 equiv). The mixture was stirred at 60 °C for 16 hours. 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 (35 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-TLC (SiO₂, PE/EtOAc = 3:1) to give product **B.2j** (60 mg, 97 μmol, 14% yield, 98% purity) was obtained as a yellow solid. MS m/z (ESI) [M+H]⁺ = 606.4.

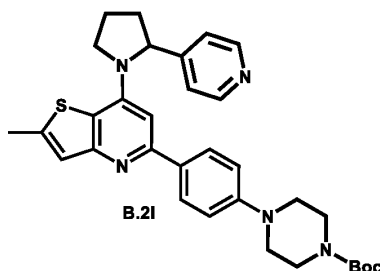
B.2k: *tert*-butyl 4-[4-[2-methyl-7-(2-phenylpyrrolidin-1-yl) thieno [3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



[0239] According to Scheme 3 Step 1: Conditions 2 Buchwald: Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 2-phenylpyrrolidine (0.12 g, 0.81 mmol, 1.2 equiv) in dioxane (0.68M), CPHOS PD G3 (0.10 equiv) and Cs₂CO₃ (3.0 equiv). The mixture was stirred at 60 °C for 16 hours. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL, three times). The organic phases were washed with brine (40 mL, three times), dried over

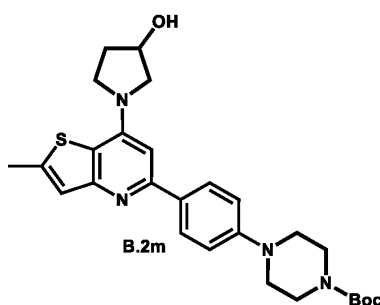
anhydrous sodium sulfate, filtered and the filtrate was concentrated. The residue obtained was purified by prep-HPLC **2** (gradient: 37%-67% over 10 min). Compound **B.2k** (0.20 g, 0.32 mmol, 47% yield, 88% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+ = 555.5$.

B.2l: *tert*-butyl 4-(4-(2-methyl-7-(2-(pyridin-4-yl) pyrrolidin-1-yl) thieno [3,2-b] pyridin-5-yl) phenyl) piperazine-1-carboxylate



[0240] According to Scheme 3 Step 1: Conditions 2 Buchwald: Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 4-pyrrolidin-2-ylpyridine (0.15 g, 1.0 mmol, 1.5 equiv), CPHOS PD G3 (0.11 equiv) and Cs_2CO_3 (2.7 equiv) were added in dioxane (0.14M). The mixture was stirred at 60 °C for 16 hours. After work-up the residue was partitioned between ethyl acetate (20 mL) and water (30 mL). The aqueous layer was extracted with ethyl acetate (30 mL) twice. The combined organic layers were dried over (Na_2SO_4) and evaporated to give a crude material. The residue obtained was purified by flash silica gel chromatography (12 g, Eluent of 40~60% EtOAc/PE gradient at 20 mL/min) to afford **B.2l** (0.20 g, 0.26 mmol, 38% yield, 71% purity) as yellow oil. MS m/z (ESI) $[M+H]^+ = 556.2$.

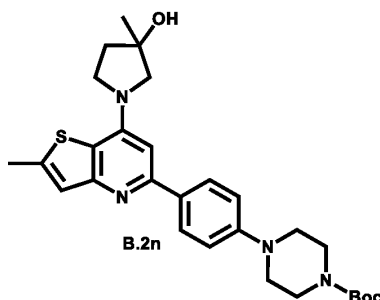
B.2m: *tert*-butyl 4-[4-[7-(3-hydroxypyrrolidin-1-yl)-2-methyl-thieno [3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



[0241] According to Scheme 2 Step 2: Conditions 2 $\text{S}_{\text{N}}\text{Ar}$: Substrate **B.1a** (0.20 g, 0.45 mmol, 1.0 eq) in DMSO (1.4 M). The mixture was stirred at 130 °C for 72 hours. After

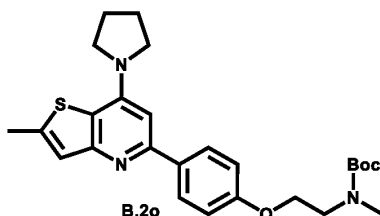
work-up Product **B.2m** (0.20 g, 0.36 mmol, 79% yield, 88% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+ = 495.3$.

B.2n: *tert*-butyl 4-[4-[7-(3-hydroxy-3-methyl-pyrrolidin-1-yl)-2-methyl-thieno [3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



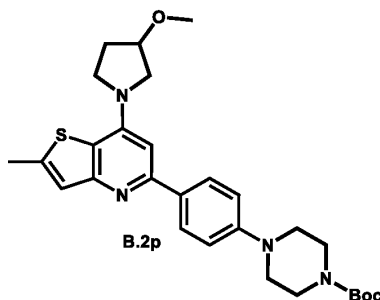
[0242] According to Scheme 2 Step 2: Conditions 3 S_NAr : Substrate **B.1a** (0.20 g, 0.45 mmol, 1.0 equiv), (0.09 M), 3-methylpyrrolidin-3-ol (455.63 mg, 4.50 mmol, 10 eq) in DMSO (1.4 M). The mixture was stirred at 120 °C for 16 hours. After work-up, no further purification was done. Product **B.2n** (0.18 g, 0.32 mmol, 71% yield, 91% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+ = 509.2$.

B.2o: *tert*-butyl *N*-methyl-*N*- [2- [4-(2-methyl-7-pyrrolidin-1-yl-thieno [3, 2-b] pyridin-5-yl) phenoxy] ethyl] carbamate



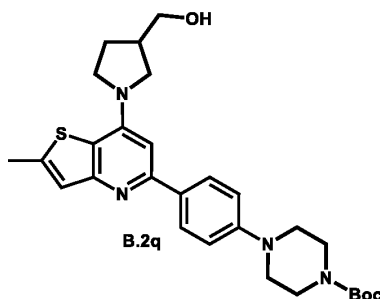
[0243] According to Scheme 2 Step 2: Conditions 1 S_NAr : Substrate **B.1b** (0.10 g, 0.23 mmol, 1.0 equiv), pyrrolidine (259 equiv) in DMSO (1.4 M). The mixture was stirred at 130 °C for 72 hours. Product **B.2o** was obtained after work-up (50 mg, 96 μ mol, 42% yield, 90% purity) as a yellow solid.

B.2p: *tert*-butyl 4-[4-[7-(3-methoxypyrrolidin-1-yl)-2-methyl-thieno[3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



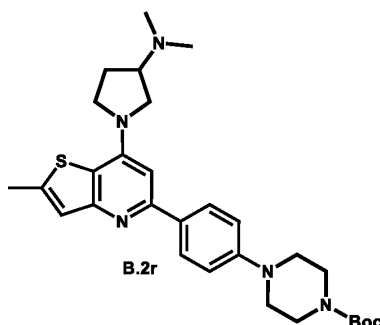
[0244] According to Scheme 2 Step 2: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 3-methoxypyrrolidine (0.30 g, 3.0 mmol, 4.4 equiv) in DMSO (1.4 M). The mixture was stirred at 120 °C for 12 hours. After work-up the crude product **B.2p** (400 mg, crude) was directly used into the next step without further purification as a yellow gum.

B.2q: *tert*-butyl 4-[4-[7-[3-(hydroxymethyl) pyrrolidin-1-yl]-2-methyl-thieno [3, 2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



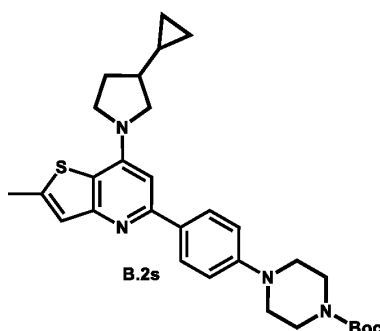
[0245] According to Scheme 2 Step 2: Conditions 3 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), (0.68 M) in DMF (1.4 M). The mixture was stirred at 130 °C for 72 hours. After work-up the residue obtained was purified by prep-HPLC **3** (gradient: 3-9 min 25-55%). Compound **B.2q** (0.18 g, 0.35 mmol, 52% yield) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+ = 509.4$.

B.2r: *tert*-butyl 4-[4-[7-[3-(dimethylamino) pyrrolidin-1-yl]-2-methyl-thieno [3, 2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



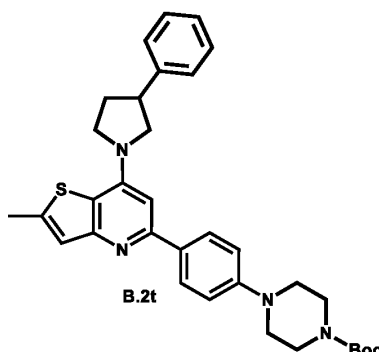
[0246] According to Scheme 2 Step 2: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv) *N,N*-dimethylpyrrolidin-3-amine (0.77 g, 6.8 mmol, 10 equiv) in DMSO (0.07 M). The mixture was stirred at 130 °C for 72 hours. After work-up product **B.2r** (0.22 g, 0.34 mmol, 50% yield, 80% purity) was obtained as a yellow solid.

B.2s: *tert*-butyl 4-[4-[7-(3-cyclopropylpyrrolidin-1-yl)-2-methyl-thieno [3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



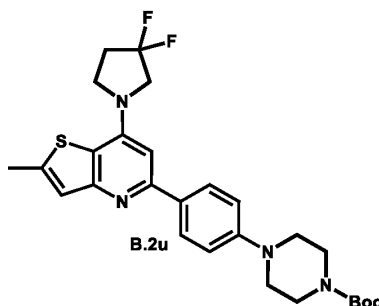
[0247] According to Scheme 2 Step 2: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv) and 3-cyclopropylpyrrolidine (0.23 g, 2.0 mmol, 3.0 equiv) in DMSO (1.4 M). The mixture was stirred at 130 °C for 72 hours. After work-up the residue obtained was triturated with MeOH, and the solution was purified by prep-HPLC **2** (gradient: 33%-63% over 10 min) to give product **B.2s** (0.25 g, 0.47 mmol, 69% yield, 97% purity) as an off-white solid. MS m/z (ESI) $[M+H]^+ = 519.3$.

B.2t: *tert*-butyl 4-[4-[2-methyl-7-(3-phenylpyrrolidin-1-yl)thieno [3,2-b] pyridin-5-yl]phenyl] piperazine-1-carboxylate



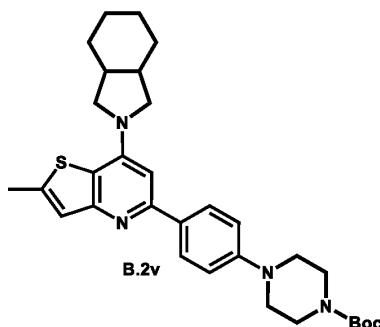
[0248] According to Scheme 2 Step 2: Conditions 1 S_NAr . Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv) and 3-phenylpyrrolidine (0.50 g, 3.4 mmol, 5.0 equiv) in DMSO (1.4 M). The mixture was stirred at 130 °C for 72 hours. After work-up the residue obtained was purified was triturated with DMF (10 mL) to give product **B.2t** (0.10 g, 0.18 mmol, 26% yield, 98% purity) as an off-white solid. MS m/z (ESI) $[M+H]^+ = 555.3$.

B.2u: *tert*-butyl 4-[4-[7-(3,3-difluoropyrrolidin-1-yl)-2-methyl-thieno [3,2-b] pyridin-5-yl]phenyl] piperazine-1-carboxylate



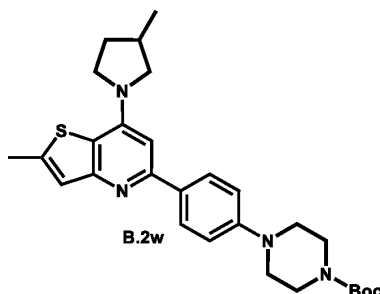
[0249] According to Scheme 2 Step 2: Conditions 2 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 3,3-difluoropyrrolidine (0.49 g, 3.4 mmol, 5.0 equiv, HCl), DMSO (0.14 mL), Et_3N (0.34 g, 3.4 mmol, 0.47 mL, 5.0 equiv). The mixture was stirred at 130 °C for 72 hours. After work-up the residue obtained was concentrated *in vacuo* to give product **B.2u** (0.31 g, 62% yield, 69% purity) as a brown solid. MS m/z (ESI) $[M+H]^+ = 515.2$.

B.2v: *tert*-butyl 4-[4-[7-(1,3,3a,4,5,6,7,7a-octahydroisoindol-2-yl)-2-methyl-thieno [3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate (cis mixture)



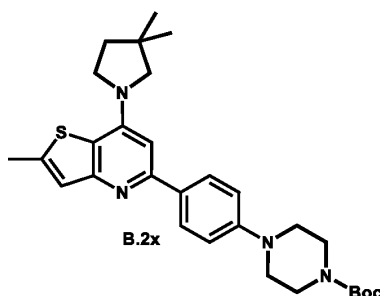
[0250] According to Scheme 2 Step 2: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 2,3,3a,4,5,6,7,7a-octahydro-1H-isoindole (0.85 g, 6.8 mmol, 10 equiv) in DMSO (1.4 M). The mixture was stirred at 130 °C for 72 hours. After work-up the residue obtained was purified by prep-HPLC 2 (gradient: 37%-67% over 10 min) to give product **B.2v** (0.12 g, 0.23 mmol, 33% yield, 100% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+ = 533.3$.

B.2w: *tert*-butyl 4-(4-(2-methyl-7-(3-methylpyrrolidin-1-yl) thieno [3,2-b] pyridin-5-yl) phenyl) piperazine-1-carboxylate



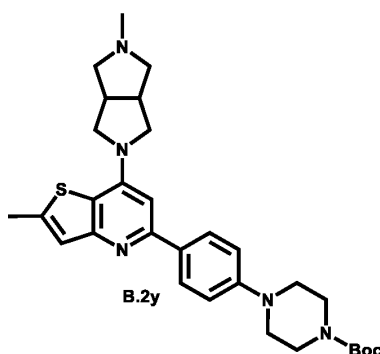
[0251] According to Scheme 2 Step 2: Conditions 3 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 3-methylpyrrolidine.HCl (0.18 g, 1.5 mmol, 2.2 equiv) and DIEA (0.90 g, 7.0 mmol, 1.2 mL, 10 equiv) in DMSO (1.4 M). The mixture was stirred at 100 °C for 12 hours. No work-up, mixture was filtered and concentrated under reduced pressure. The residue obtained was purified by prep-HPLC (SiO₂, DCM/MeOH = 10:1) to give **B.2w** (0.18 g, 0.33 mmol, 49% yield, 90% purity) as a yellow oil.

B.2x: *tert*-butyl 4-[4-[7-[3-(*tert*-butoxycarbonylamino) -3-methyl-pyrrolidin-1-yl]-2-methyl-thieno [3, 2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



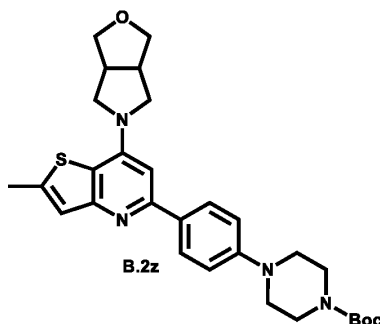
[0252] According to Scheme 2 Step 2: Conditions 3 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 3, 3-dimethylpyrrolidine; HCl (0.92 g, 6.8 mmol, 10 equiv) , DIEA (0.87 g, 6.8 mmol, 1.2 mL, 10 equiv) in DMSO (3.4 M). The mixture was stirred at 100 °C for 12 hours. Product **B.2x** (0.20 g, 0.31 mmol, 46% yield, 95% purity) was obtained after work-up as a yellow solid.

B.2y: *tert*-butyl 2-[5-[4-(4-*tert*-butoxycarbonylpiperazin-1-yl) phenyl]-2-methyl-thieno [3,2-b] pyridin-7-yl]-1,3,3a,4,6,6a-hexahydropyrrolo [3,4-c] pyrrole-5-carboxylate (cis mixture)



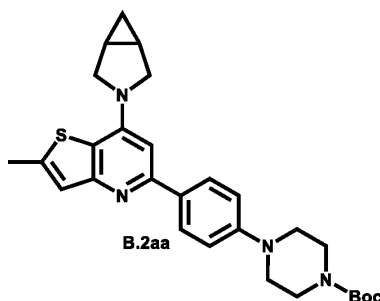
[0253] According to Scheme 2 Step 2: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), in DMSO (1.4 M), *tert*-butyl 2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c] pyrrole-5-carboxylate (0.90 g, 4.2 mmol, 6.3 equiv). The mixture was stirred at 130 °C for 72 hours. After work-up the residue obtained was purified by prep-TLC (DCM/MeOH 10:1) to give product **B.2y** (0.40 g, 0.57 mmol, 84% yield, 88% purity) as a yellow solid.

B.2z: *tert*-butyl 4-[4-[7-(1,3,3a,4,6,6a-hexahydrofuro [3,4-c] pyrrol-5-yl)-2-methyl-thieno [3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate (cis mixture)



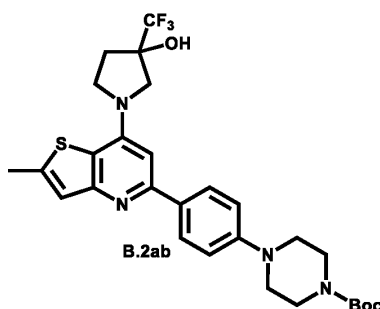
[0254] According to Scheme 2 Step 2: Conditions 3 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), in DMSO (0.07 M), 3,3a,4,5,6,6a-hexahydro-1H-furo[3,4-c] pyrrole (0.12 g, 1.1 mmol, 1.6 equiv) and DIEA (3.1 equiv). The mixture was stirred at 130 °C for 72 hours. After work-up the residue obtained was purified by Flash chromatography (10 g, Eluent of 0 to 40% EtOAc/PE gradient at 25 mL/min) to afford product **B.2z** (0.26 g, 0.47 mmol, 70% yield, 95% purity) as red oil. MS m/z (ESI) $[M+H]^+ = 521.3$.

B.2aa: *tert*-butyl 4-[4-[7-(3-azabicyclo [3.1.0]hexan-3-yl)-2-methyl-thieno [3,2-b]pyridin-5-yl] phenyl]piperazine-1-carboxylate (cis mixture)



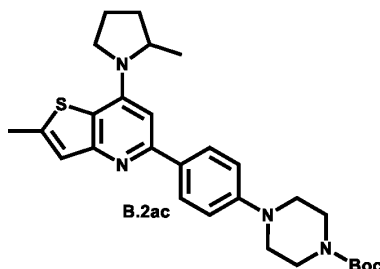
[0255] According to Scheme 2 Step 2: Conditions 3 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), in DMSO (0.07 M), 3-azabicyclo [3.1.0] hexane; HCl (0.13 g, 1.1 mmol, 1.6 equiv) and DIEA (3.1 equiv). The mixture was stirred at 130 °C for 72 hours. After work-up the residue obtained was purified by Flash chromatography (10 g, Eluent of 0 to 40% EtOAc/PE gradient at 25 mL/min) to afford product **B.2aa** (0.26 g, 0.38 mmol, 56% yield, 72% purity) as red oil. MS m/z (ESI) $[M+H]^+ = 491.3$.

B.2ab: *tert*-butyl 4-[4-[7-[3-hydroxy-3-(trifluoromethyl) pyrrolidin-1-yl]-2-methyl-thieno [3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



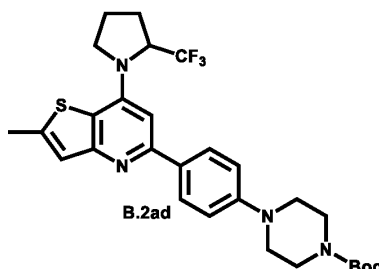
[0256] According to Scheme 2 Step 2: Conditions 2 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), 3-(trifluoromethyl) pyrrolidin-3-ol (0.31 g, 2.0 mmol, 3.0 equiv) in DMSO (0.7 M), DIPEA (3.0 equiv). The mixture was stirred at 130 °C for 16 hours. After work-up the residue obtained was purified by prep-HPLC **3** (gradient: 3-10 min 38 - 58%). Compound **B.2ab** (0.13 g, 0.23 mmol, 34% yield) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+ = 563.2$.

B.2ac: *tert*-butyl 4-[4-[2-methyl-7-(2-methylpyrrolidin-1-yl) thieno [3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



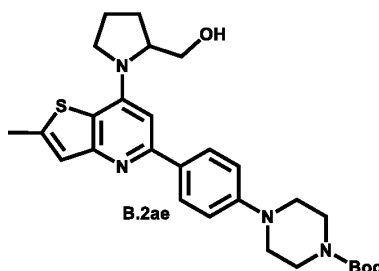
[0257] According to Scheme 2 Step 2: Conditions 1 S_NAr : Substrate **B.1a** (0.20 g, 0.45 mmol, 1.0 equiv), 2-methylpyrrolidine (0.40 g, 4.7 mmol, 0.48 mL, 10 equiv) were added in DMSO (0.45 M). After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 32% - 62% over 10 min). Compound **B.2ac** (0.10 g, 0.20 mmol, 44% yield, 98% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+ = 493.2$.

B.2ad: *tert*-butyl 4-[4-[2-methyl-7-[2-(trifluoromethyl) pyrrolidin-1-yl] thieno [3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



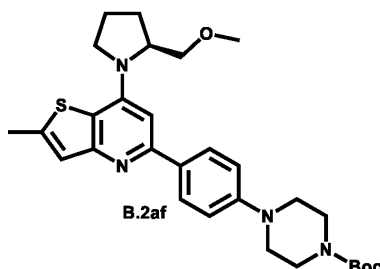
[0258] According to Scheme 2 Step 2: Conditions 1 S_NAr : Substrate **B.1a** (0.20 g, 0.45 mmol, 1.0 equiv) and 2-(trifluoromethyl) pyrrolidine (0.60 g, 4.3 mmol, 9.6 equiv) were added in DMSO (0.45 M). After work-up the residue obtained was purified by prep-HPLC 2 (gradient: 32%-62% over 10 min). Compound **B.2ad** (0.10 g, 0.18 mmol, 39% yield, 96% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+ = 547.3$.

B.2ae: *tert*-butyl 4-[4-[7-[2-(hydroxymethyl) pyrrolidin-1-yl]-2-methyl-thieno [3,2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



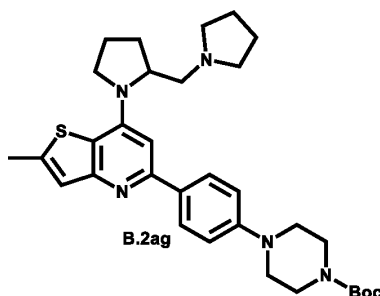
[0259] According to Scheme 2 Step 2: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv) and pyrrolidin-2-ylmethanol (68 mg, 0.68 mmol, 1.0 equiv) were stirred at 120 °C for 12 hours. After work-up the residue obtained was purified by prep-TLC (SiO_2 , DCM/MeOH 10:1) to give product **B.2ae** (0.30 g, 0.58 mmol, 86% yield, 98% purity) as a yellow gum.

B.2af: *tert*-butyl 4-[4-[7-[(2*S*)-2-(methoxymethyl) pyrrolidin-1-yl]- 2-methyl-thieno [3,2-*b*] pyridin-5-yl] phenyl] piperazine-1-carboxylate



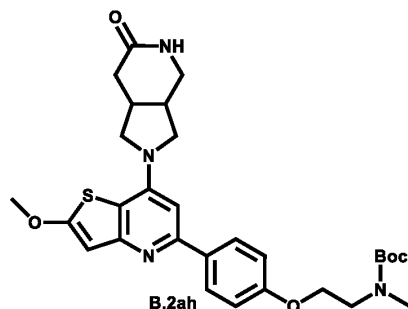
[0260] According to Scheme 2 Step 2: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv) in DMSO (1.4 M) and (2*S*)-2-(methoxymethyl) pyrrolidine (0.78 g, 6.8 mmol, 10 equiv) were stirred at 130°C for 96 hours. After work-up the residue obtained was purified by prep-HPLC 2 (gradient: 25%-55% over 10 min) to give product **B.2af** (0.23 g, 0.43 mmol, 81% yield, 97% purity) as a yellow solid. MS *m/z* (ESI) $[M+H]^+ = 523.3$.

B.2ag: *tert*-butyl 4-(4-(2-methyl-7-(2-(pyrrolidin-1-ylmethyl) pyrrolidin-1-yl) thieno [3,2-*b*] pyridin-5-yl) phenyl) piperazine-1-carboxylate



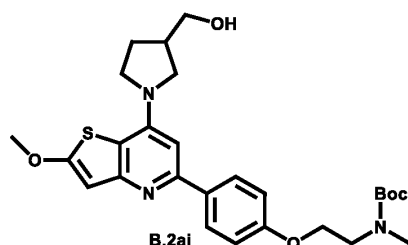
[0261] According to Scheme 2 Step 2: Conditions 3 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv) in DMSO (1.4 M) and 1-(pyrrolidin-2-ylmethyl) pyrrolidine (0.94 g, 6.1 mmol, 9.0 equiv) were stirred at 130 °C for 72 h, no DIEA. After work-up the residue obtained was purified by prep-HPLC 2 (gradient: 12%-32% over 10 min). Product **B.2ag** (0.20 g, 0.35 mmol, 52% yield, 100% purity) was obtained as a yellow solid. MS *m/z* (ESI) $[M+H]^+ = 562.4$.

B.2ah: tert-butyl N-[2-[4-[2-methoxy-7-(6-oxo-3,3a,4,5,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl) thieno[3,2-b] pyridin-5-yl] phenoxy] ethyl]-N-methylcarbamate (cis mixture)



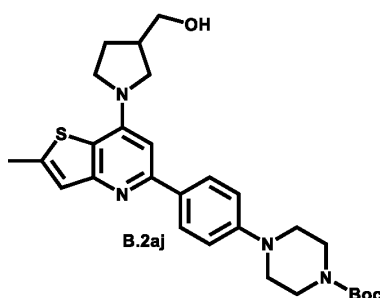
[0262] According to Scheme 2 Step 2: Conditions 2 Buchwald: To a solution of substrate **B.1a** (0.10 g, 0.22 mmol, 1.0 equiv), *Amine 1* (47 mg, 0.33 mmol, 1.5 equiv), SPhos Pd G3 (17 mg, 22 μ mol, 0.10 equiv), and Cs_2CO_3 (0.18 g, 0.56 mmol, 2.5 equiv) in dioxane (4.0 mL) was degassed and purged with N_2 three times at 25 °C. After stirring at 80 °C for 16h under inert atmosphere, the reaction mixture filtered and concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 2 (gradient: 18%-48% over 10 min) to give **B.2ah** (25 mg, 43 μ mol, 19% yield, 95% purity) as a white solid. MS m/z (ESI) $[\text{M}+\text{H}]^+ = 553.2$.

B.2ai: tert-butyl N-[2-[4-[7-[3-(hydroxymethyl) pyrrolidin-1-yl]-2-methoxy-thieno[3,2-b]pyridin-5-yl] phenoxy] ethyl]-N-methylcarbamate



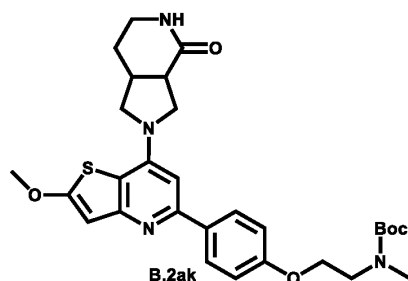
[0263] According to Scheme 2 Step 2: Conditions 2 Buchwald: To the substrate **B.1h** (70 mg, 0.16 mmol, 1.0 equiv) and pyrrolidin-3-ylmethanol (20 mg, 0.20 mmol, 1.3 equiv) in dioxane (3.0 mL) was added SPhos Pd G3 (14 mg, 18 μ mol, 0.12 equiv) and Cs_2CO_3 (0.15 g, 0.46 mmol, 3.0 equiv). The reaction mixture was degassed and purged with N_2 three times. The mixture was stirred at 80 °C for 12 hours under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give the residue. The residue obtained was purified by prep-TLC (SiO_2 , PE/EtOAc = 2:1) to give **B.2ai** (75 mg, 0.12 mmol, 78% yield, 83% purity) as a yellow gum.

B.2aj: tert-butyl 4-[4-[2-(dimethylamino)-7-[3-(hydroxymethyl)pyrrolidin-1-yl]thieno[3,2-b]pyridin-5-yl]phenyl]piperazine-1-carboxylate



[0264] According to Scheme 2 Step 2: Conditions 3 S_NAr : To the substrate **B.1i** (0.20 g, 0.35 μ mol, 1.0 equiv) in dimethyl sulfoxide (2.0 mL) was added CsF (0.16 mg, 1.0 mmol, 3.0 equiv) and pyrrolidin-3-ylmethanol (0.17 g, 1.7 mmol, 5.0 equiv) at 25 °C. The mixture was stirred at 100 °C for 12 hours. The reaction mixture was diluted with water (10 mL), yellow solid was precipitated out, the mixture was filtered and the filtrate cake was dried under reduced pressure to give **B.2aj** (0.22 g, 0.30 mmol, 86% yield, 73% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 538.4$.

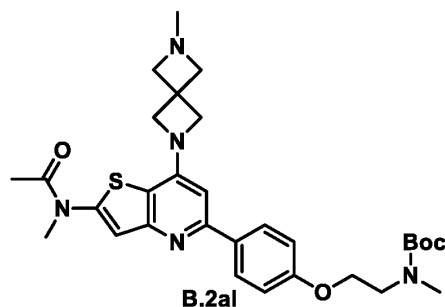
B.2ak: tert-butyl N-[2-[4-[2-methoxy-7-[rac-(3aS,7aR)-4-oxo-3,3a,5,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-2-yl]thieno[3,2-b]pyridin-5-yl]phenoxy]ethyl]-N-methylcarbamate (cis mixture)



[0265] According to Scheme 2 Step 2: Conditions 2 Buchwald: To the substrate **B.1h** (0.15 g, 0.33 mmol, 1.0 equiv) in dioxane (3.0 mL) was added *Amine 3* (90 mg, 0.37 mmol, 1.1 equiv), Cs_2CO_3 (0.30 g, 0.92 mmol, 2.8 equiv) and SPhos Pd G₃ (30 mg, 38 μ mol, 0.12 equiv). Then the resulting mixture was purged with N_2 three times and stirred at 80 °C for 12 hours. The reaction mixture was partitioned between EtOAc (0.15 L) and water (80 mL), washed with brine (70 mL), dried over Na_2SO_4 , filtered, and evaporated under reduced pressure to give the crude product. The reaction mixture was purified by prep-TLC (SiO_2 ,

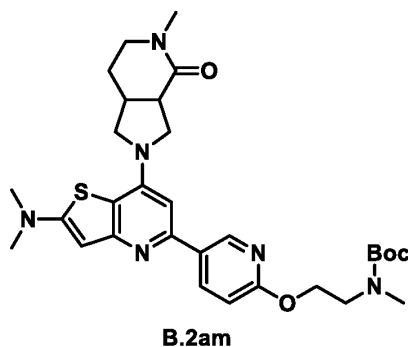
PE/EtOAc = 1:1, R_f = 0.1) to give **B.2ak** (95 mg, 84 μ mol, 25% yield, 49% purity) as a white solid. MS m/z (ESI) $[M+H]^+ = 553.3$.

B.2al: tert-butyl methyl(2-(4-(7-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-2-(N-methylacetamido)thieno[3,2-b]pyridin-5-yl)phenoxy)ethyl)carbamate



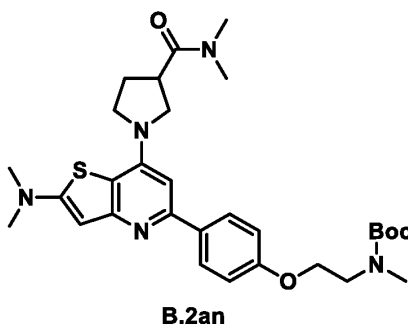
[0266] According to Scheme 2 Step 2: Conditions 2 Buchwald: To a mixture of tert-butylN-[2-[4-[2-[acetyl(methyl)amino]-7-chloro-thieno[3,2-b]pyridin-5-yl] phenoxy]ethyl]-N-methyl-carbamate (400 mg, 0.400 mmol, 1.00 eq), 2-methyl-2,6-diazaspiro[3.3] heptane (71.3 mg, 0.480 mmol, 1.20 eq, HCl) in dioxane (3.00 mL) were added Methanesulfonato(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (31.2 mg, 0.0400 mmol, 0.100 eq), cesium carbonate (391 mg, 1.20 mmol, 3.00 eq) at 20 °C, the mixture was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 80 °C for 16 hours under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (10.0 ml), then the mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/methanol gradient @ 30 mL/min) to give tert-butylN-[2-[4-[2-[acetyl(methyl)amino]- 7-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)thieno[3,2-b]pyridin-5-yl]phenoxy]ethyl]-N-methyl-carbamate (250 mg, 0.301 mmol, 75.1% yield, 68% purity) as a yellow solid. MS (ESI) m/z $[M+H]^+ = 566.3$.

B.2am: tert-butyl (2-((5-(2-(dimethylamino)-7-(5-methyl-4-oxooctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-5-yl)pyridin-2-yl)oxy)ethyl)(methyl)carbamate



[0267] According to Scheme 2 Step 2: Conditions 2 Buchwald: To a solution of **B.1k** (200 mg, 431.97 μmol , 1 *eq*) and Cs_2CO_3 (430 mg, 1.32 mmol, 3.06 *eq*) in dioxane (2 mL) was added SPhos Pd G3 (70 mg, 89.71 μmol , 2.08e-1 *eq*) and *Amine 5* (100 mg, 648.47 μmol , 1.50 *eq*). The reaction solution was stirred at 80 °C for 12 hours. The reaction solution was concentrated under vacuum and the residue was purified by flash silica gel chromatography (ISCO®, 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to **B.2am** (250 mg, 378.83 μmol , 87.70% yield, 88% purity) as a yellow oil. MS (ESI) m/z $[\text{M}+\text{H}]^+ = 581.6$.

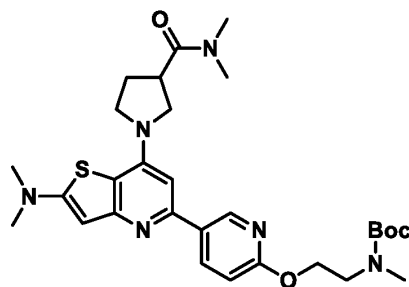
B.2an: tert-butyl (2-(4-(2-(dimethylamino)-7-(3-(dimethylcarbamoyl)pyrrolidin-1-yl)thieno[3,2-b]pyridin-5-yl)phenoxy)ethyl)(methyl)carbamate



[0268] According to Scheme 2 Step 2: Conditions 2 Buchwald: To a solution of **B.1l** (200.00 mg, 432.90 μmol , 1 *eq*), N,N-dimethylpyrrolidine-3-carboxamide (66.52 mg, 467.83 μmol , 1.08 *eq*) in dioxane (5 mL) were added SPhos Pd G3 (39.91 mg, 51.16 μmol , 1.18e-1 *eq*), Cs_2CO_3 (299.36 mg, 918.79 μmol , 2.12 *eq*) and then the mixture was stirred at 80°C for 12hr under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure and the

residue was purified by prep-TLC (PE/EtOAc 0/1) to give **B.2an** (200 mg, 317.05 μ mol, 73.24% yield, 90% purity) as a yellow solid.

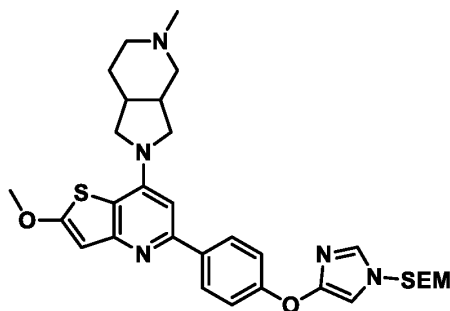
B.2ao: tert-butyl (2-((5-(2-(dimethylamino)-7-(3-(dimethylcarbamoyl)pyrrolidin-1-yl)thieno[3,2-b]pyridin-5-yl)pyridin-2-yl)oxy)ethyl)(methyl)carbamate



B.2ao

[0269] According to Scheme 2 Step 2: Conditions 2 Buchwald: A solution of **B.1k** (330 mg, 712.76 μ mol, 1 eq), N,N-dimethylpyrrolidine-3-carboxamide (191 mg, 1.07 mmol, 1.5 eq, HCl), SPhos Pd G3 (56 mg, 71.77 μ mol, 1.01e-1 eq) and Cs_2CO_3 (1.16 g, 3.56 mmol, 5 eq) in dioxane (5 mL) was stirred at 80 °C for 12 hours under N_2 . The mixture was concentrated and the residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~85% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) to give **B.2ao** (240 mg, 405.96 μ mol, 56.96% yield, 96.2% purity) as yellow oil. MS (ESI) m/z $[\text{M} + \text{H}]^+ = 569.3$.

B.2ap: 2-methoxy-7-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)-5-(4-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)oxy)phenyl)thieno[3,2-b]pyridine

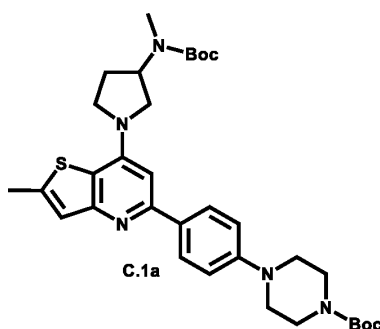


B.2ap

[0270] According to Scheme 2 Step 2: Conditions 2 Buchwald: A solution of **B.1m** (370 mg, 758.08 μ mol, 1 eq), **Amine 5** (160 mg, 1.14 mmol, 1.51 eq), SPhos Pd G3 (59 mg, 75.62 μ mol, 9.97e-2 eq) and Cs_2CO_3 (1.23 g, 3.79 mmol, 5 eq) in dioxane (10 mL) was stirred at 80

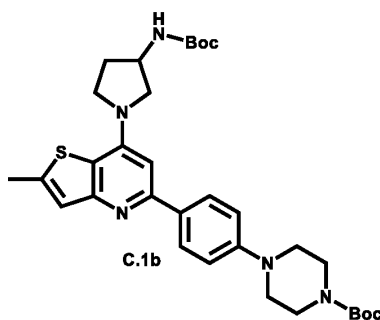
°C for 12 hours under N₂. The mixture was concentrated and the residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether, then 0~20% MeOH/Ethyl acetate gradient @ 18 mL/min) to **B.2ap** (260 mg, 355.84 μmol, 46.94% yield, 81% purity) as yellow oil. MS (ESI) m/z [M + H]⁺ = 592.3.

C.1a: tert-butyl 4-[4-[7-[3-[tert-butoxycarbonyl (methyl) amino] pyrrolidin-1-yl]-2-methyl-thieno [3, 2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



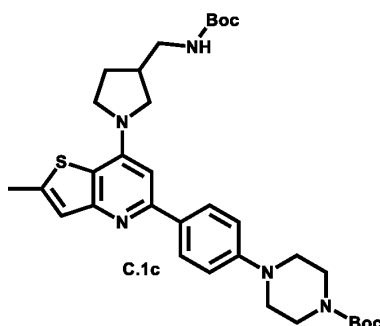
[0271] According to Scheme 3 Step 1: Conditions 3 Buchwald: Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv) (0.07 M), tert-butyl *N*-methyl-*N*-pyrrolidin-3-yl-carbamate (1.1 equiv) and *t*-BuONa (3.1 equiv) were added in toluene and stirred at 60 °C for 12 hours. After work-up the residue obtained was purified by Flash chromatography (40 g column, gradient: 0 to 60% EtOAc/PE at 40 mL/min) to afford product **C.1a** (0.29 g, 0.42 mmol, 63% yield, 89% purity) as yellow solid. ¹H NMR (400 MHz, CDCl₃) *d* (ppm): 8.06 - 7.94 (m, 2H), 7.43 - 7.32 (m, 1H), 7.13 - 7.05 (m, 2H), 6.72 - 6.57 (m, 1H), 5.15 - 4.92 (m, 1H), 4.31 - 3.98 (m, 4H), 3.71 (br s, 4H), 3.36 - 3.29 (m, 4H), 2.96 (br s, 3H), 2.68 (br s, 3H), 2.35 - 2.29 (m, 1H), 2.04 - 1.98 (m, 1H), 1.59 (br s, 18H). MS m/z (ESI) [M+H]⁺ = 608.3.

C.1b: tert-butyl 4-[4-[7-[3-(tert-butoxycarbonylamino) pyrrolidin-1-yl]-2-methyl-thieno [3, 2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



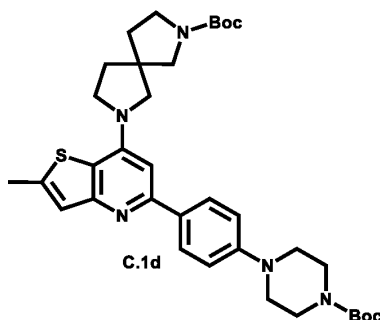
[0272] According to Scheme 3 Step 1: Conditions 3 S_NAr. Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), tert-butyl N-pyrrolidin-3-ylcarbamate (0.50g, 2.7 mmol, 4.0 equiv), DIEA (0.74 g, 5.7 mmol, 1.0 mL, 8.5 equiv) were added in DMSO(0.07 M) and stirred at 120 °C for 12 hours. After work-up the residue was triturated with EtOAc to give product **C.1b** (0.18 g, 0.27 mmol, 39% yield, 88% purity) as a white solid.

C.1c: tert-butyl 4-[4-[7-[3-[(tert-butoxycarbonylamino) methyl] pyrrolidin-1-yl]-2-methyl-thieno [3, 2-b] pyridin-5-yl] phenyl] piperazine-1-carboxylate



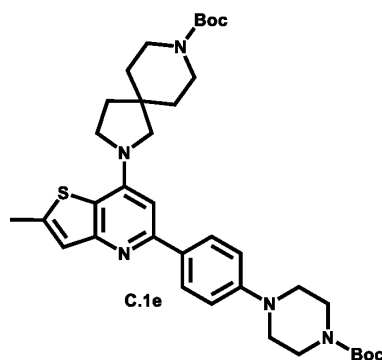
[0273] According to Scheme 3 Step 1: Conditions 3 S_NAr. Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), tert-butyl N-(pyrrolidin-3-ylmethyl) carbamate (5.0 equiv) and DIEA (8.5 equiv) were added in DMSO (1.4 M) and stirred at 120 °C for 12 hours. After work-up the residue obtained was purified by Flash chromatography (40 g column, gradient 0 to 60% EtOAc/PE at 40 mL/min) to afford product **C.1c** (0.23 g, 0.28 mmol, 41% yield, 74% purity) as yellow solid. MS m/z (ESI) [M+H]⁺ = 608.4.

C.1d: tert-butyl 7-[5-[4-(4-tert-butoxycarbonylpiperazin-1-yl) phenyl]-2-methyl-thieno [3,2-b] pyridin-7-yl]-2,7-diazaspiro [4.4] nonane-2-carboxylate



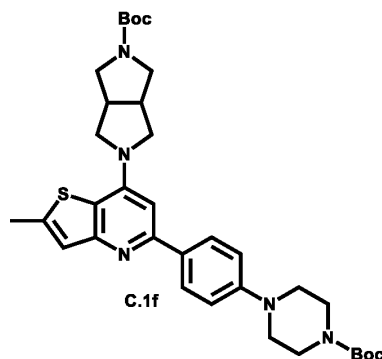
[0274] According to Scheme 3 Step 1: Conditions 3 S_NAr : Substrate **B.1a** (0.20 g, 0.45 mmol, 1.0 equiv) and tert-butyl 2,7-diazaspiro [4.4] nonane-2-carboxylate (1.0 g, 4.5 mmol, 10 equiv), DIEA (3.0 equiv) were added in DMSO (1.4 M) and stirred at 120 °C for 12 hours. After work-up the residue obtained was purified by prep-HPLC 2 (gradient: 33%-63% over 10 min). Compound **C.1d** (0.12 g, 0.19 mmol, 42% yield, 100% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+ = 634.4$.

C.1e: tert-butyl 2-[5-[4-(4-tert-butoxycarbonylpiperazin-1-yl) phenyl]-2-methyl-thieno [3,2-b] pyridin-7-yl]-2,8-diazaspiro [4.5] decane-8-carboxylate



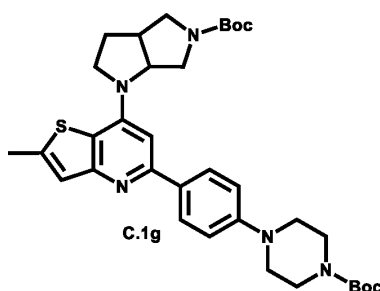
[0275] According to Scheme 3 Step 1: Conditions 3 S_NAr : Substrate **B.1a** (0.20 g, 0.45 mmol, 1.0 equiv), tert-butyl 2,8-diazaspiro [4.5] decane-8-carboxylate (1.1 g, 4.5 mmol, 10 equiv) and DIEA (3.0 equiv) were added in DMSO (1.4 M) and stirred at 130 °C for 16 hours. After work-up the residue obtained was purified by prep-HPLC 2 (gradient: 37%-67% over 10 min). Compound **C.1e** (0.10 g, 0.15 mmol, 33% yield, 95% purity) was obtained as a white solid. MS m/z (ESI) $[M+H]^+ = 648.4$.

C.1f: tert-butyl 2-[5-[4-(4-tert-butoxycarbonylpiperazin-1-yl) phenyl]-2-methyl-thieno [3,2-b] pyridin-7-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c] pyrrole-5-carboxylate (cis mixture)



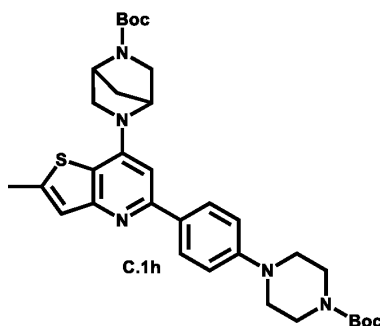
[0276] According to Scheme 3 Step 1: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv) and tert-butyl 2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c] pyrrole-5-carboxylate (0.90 g, 4.2 mmol, 6.3 equiv) were added in DMSO (1.4 M) and stirred at 130 °C for 16 hours. After work-up the residue obtained was purified by prep-TLC (DCM/MeOH 10:1) to give product **C.1f** (0.40 g, 0.57 mmol, 84% yield, 88% purity) as a yellow solid.

C.1g: tert-butyl 1-[5-[4-(4-tert-butoxycarbonylpiperazin-1-yl) phenyl]-2-methyl-thieno [3,2-b] pyridin-7-yl]-2,3,3a,4,6,6a-hexahydropyrrolo [3,4-b] pyrrole-5-carboxylate (cis mixture)



[0277] According to Scheme 3 Step 1: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), tert-butyl 2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-b] pyrrole-5-carboxylate (0.72 g, 3.4 mmol, 5.0 equiv) in DMSO (2.7 M) and stirred at 130 °C for 16 hours. After work-up the residue obtained was purified by prep-HPLC 2 (gradient: 35%-65% over 9 min) to give product **C.1g** (0.25 g, 0.38 mmol, 57% yield, 95% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 620.3$.

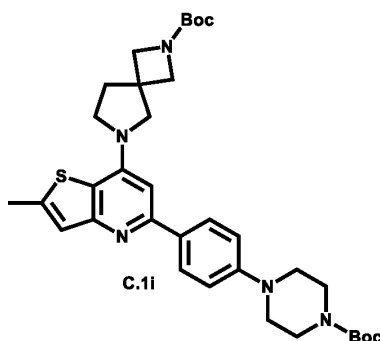
C.1h: tert-butyl 5-[5-[4-(4-tert-butoxycarbonylpiperazin-1-yl) phenyl]-2-methyl-thieno [3,2-b] pyridin-7-yl]-2,5 diazabicyclo [2.2.1] heptane-2-carboxylate



[0278] According to Scheme 3 Step 1: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), tert-butyl 2,5-diazabicyclo [2.2.1] heptane-2-carboxylate (0.75 g, 3.8

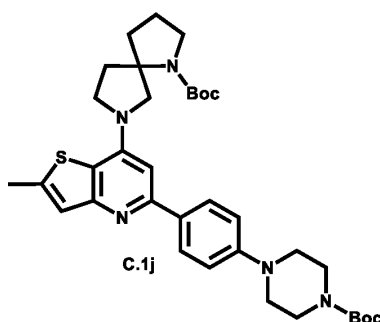
mmol, 5.6 equiv) in DMSO (1.4 M) and stirred at 130 °C for 16 hours. After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 32%-60% over 9 min) to give product **C.1h** (0.25 g, 0.39 mmol, 58% yield, 95% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+ = 606.2$.

C.1i: *tert*-butyl 7-[5-[4-(4-*tert*-butoxycarbonylpiperazin-1-yl) phenyl]-2-methyl-thieno [3,2-b] pyridin-7-yl]-2,7-diazaspiro [3.4] octane-2-carboxylate



[0279] According to Scheme 3 Step 1: Conditions 3 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), *tert*-butyl 2,7-diazaspiro [3.4] octane-2-carboxylate (0.72 g, 3.4 mmol, 5.0 equiv), DIEA (10 equiv) in DMSO (0.34 M) and stirred at 100 °C for 16 hours. After work-up the residue obtained was purified by Flash chromatography (25 g, Eluent of 0~100% EtOAc/PE gradient at 40mL/min) to give product **C.1i** (0.27 g, 0.37 mmol, 55% yield, 86% purity) as a yellow solid. MS m/z (ESI) $[M+H]^+ = 620.3$.

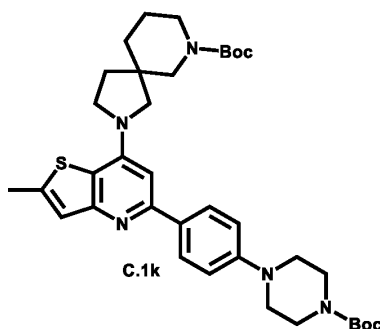
C.1j: *tert*-butyl 7-[5-[4-(4-*tert*-butoxycarbonylpiperazin-1-yl) phenyl]-2-methyl-thieno [3,2-b] pyridin-7-yl]-1,7-diazaspiro [4.4] nonane-1-carboxylate



[0280] According to Scheme 3 Step 1: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), *tert*-butyl 1,7-diazaspiro [4.4] nonane-1-carboxylate (0.76 g, 3.4 mmol, 5.0 equiv) in DMSO (1.4 M) and stirred at 130 °C for 16 hours. After work-up the residue

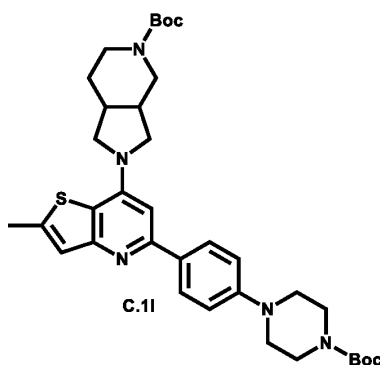
obtained was purified by prep-HPLC **2** (gradient: 37%-67% over 9 min) to give product **C.1j** (0.30 g, 0.47 mmol, 70% yield, 100% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+ = 634.4$.

C.1k: tert-butyl 2-[5-[4-(4-tert-butoxycarbonylpiperazin-1-yl) phenyl]-2-methyl-thieno[3,2-b] pyridin-7-yl]-2,7-diazaspiro [4.5] decane-7-carboxylate



[0281] According to Scheme 3 Step 1: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), tert-butyl 2,7-diazaspiro [4.5] decane-7-carboxylate (0.81 g, 3.4 mmol, 5.0 equiv) in DMSO (1.4 M) and stirred at 130 °C for 16 hours. After work-up the residue obtained was purified by prep-HPLC **2** (gradient: 37%-67% over 10 min) to give product **C.1k** (0.22 g, 0.34 mmol, 50% yield, 100% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+ = 648.3$.

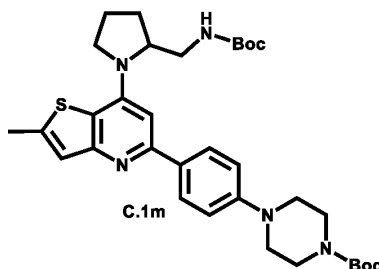
C.1l: tert-butyl 2-[5-[4-(4-tert-butoxycarbonylpiperazin-1-yl) phenyl]-2-methyl-thieno[3,2-b] pyridin-7-yl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c] pyridine-5-carboxylate (cis mixture)



[0282] According to Scheme 3 Step 1: Conditions 3 S_NAr : Substrate **B.1a** (0.25 g, 0.56 mmol, 1.0 equiv), tert-butyl 1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,4-c] pyridine-5-carboxylate (0.38 g, 1.7 mmol, 3.0 equiv) and DIEA (64 equiv) in DMSO (1.0 M) and stirred at 130 °C for 16 hours. After work-up the residue obtained was purified by prep-HPLC **2** (gradient:

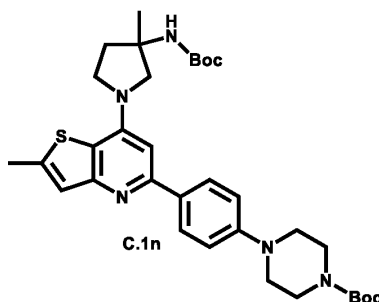
30%-60% over 10 min) to give product **C.1l** (0.10 g, 0.16 mmol, 28% yield, 100% purity) was obtained as a yellow solid. MS m/z (ESI) $[M+H]^+ = 634.4$.

C.1m: *tert*-butyl 4-[4-[7-[2-[(*tert*-butoxycarbonylamino) methyl] pyrrolidin-1-yl]-2-methyl-thieno[3,2-*b*] pyridin-5-yl] phenyl] piperazine-1-carboxylate



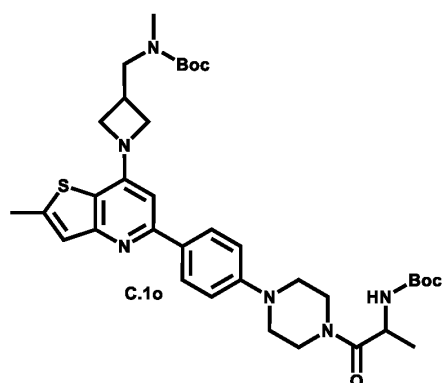
[0283] According to Scheme 3 Step 1: Conditions 1 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), *tert*-butyl *N*-(pyrrolidin-2-ylmethyl) carbamate (1.0 g, 5.0 mmol, 7.4 equiv) in DMSO (1.4 M) and stirred at 130 °C for 16 hours. After work-up the residue obtained was purified by prep-TLC (SiO_2 , EtOAc/MeOH 10:1) to give product **C.1m** (0.21 g, 0.31 mmol, 46% yield, 90% purity) as a yellow gum.

C.1n: 3-methyl-1-[2-methyl-5-(4-piperazin-1-ylphenyl) thieno [3, 2-*b*] pyridin-7-yl] pyrrolidin-3-amine



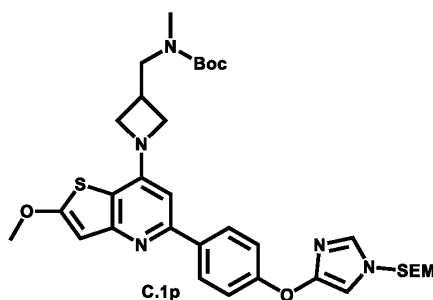
[0284] According to Scheme 3 Step 1: Conditions 3 S_NAr : Substrate **B.1a** (0.30 g, 0.68 mmol, 1.0 equiv), *tert*-butyl *N*-(3-methylpyrrolidin-3-yl) carbamate (1.35 g, 6.76 mmol, 10 eq) and DIEA (1.70 equiv) in DMSO (3.4 M) at 20 °C for 16 hours. After work-up Product **C.1n** (0.20 g, 0.31 mmol, 46% yield, 95% purity) was obtained as a yellow solid.

C.1o: tert-butyl N-[[1-[5-[4-[4-[2-(tert-butoxycarbonylamino) propanoyl] piperazin-1-yl] phenyl]-2-methyl-thieno[3,2-b] pyridin-7-yl] azetidin-3-yl] methyl]-N-methylcarbamate



[0285] According to Scheme 3 Step 1: Conditions 1 Buchwald: Substrate **B.1e** (0.20 g, 0.39 mmol, 1.0 equiv), tert-butyl N-(azetidin-3-ylmethyl)-N-methyl-carbamate (0.11 g, 0.46 mmol, 1.2 eq, HCl), Cs₂CO₃ (0.38 g, 1.2 mmol, 3.0 equiv), SPhos Pd G3 (30 mg, 38 μmol, 0.10 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 hours 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 a residue. The residue obtained was purified by prep-HPLC **2** (gradient: 25%-55% over 10 min) to give **C.1o** (0.15 g, 0.21 mmol, 53% yield, 93% purity) was obtained as a light yellow solid. MS m/z (ESI) [M+H]⁺ = 679.3.

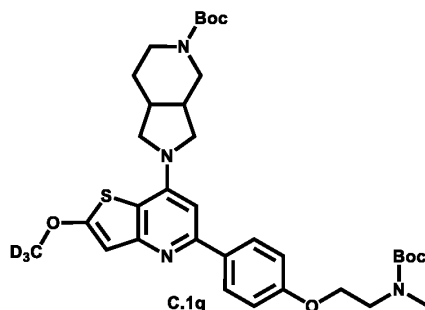
C.1p: tert-butyl N-[[1-[2-methoxy-5-[4-[1-(2-trimethylsilylethoxymethyl) imidazol-4-yl] oxyphenyl] thieno[3,2-b] pyridin-7-yl] azetidin-3-yl] methyl]-N-methylcarbamate



[0286] According to Scheme 3 Step 1: Conditions 1 Buchwald: Substrate **B.1f** (0.10 g, 0.20 mmol, 1.0 eq), tert-butyl N-(azetidin-3-ylmethyl)-N-methyl-carbamate (62 mg, 0.31 mmol, 1.5 equiv), SPhos Pd G3 (16 mg, 20 μmol, 0.10 equiv), Cs₂CO₃ (0.27 g, 0.82 mmol, 4.0

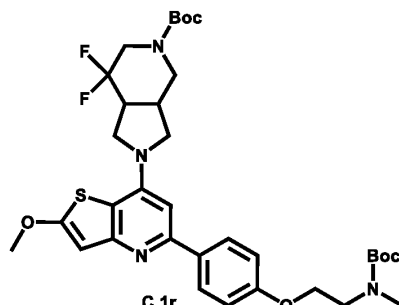
equiv) in dioxane (1.0 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 90 °C for 3 hours under N₂ atmosphere. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL, three times). The organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated. The residue obtained was purified by prep-HPLC **2** (gradient: 35%-65% over 10 min) to give **C.1p** (80 mg, 0.12 mmol, 60% yield, 100% purity) as a yellow solid. MS m/z (ESI) [M+H]⁺ = 652.3.

C.1q: tert-butyl 2-[5-[4-[2-[tert-butoxycarbonyl (methyl)amino]ethoxy]phenyl]-2-(trideuteriomethoxy)thieno[3,2-b]pyridin-7-yl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridine-5-carboxylate (cis mixture)



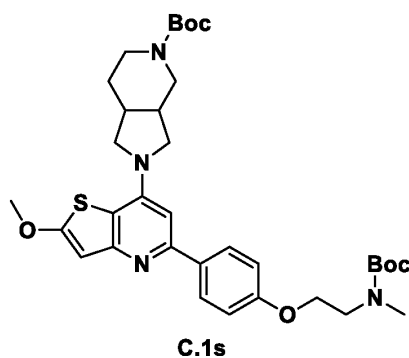
[0287] According to Scheme 3 Step 1: Conditions 1 Buchwald: Substrate **B.1g** (0.18 g, 0.32 μmol, 1.0 equiv), tert-butyl 1,2,3,3a,4,6,7,7a- octahydropyrrolo[3,4-c] pyridine-5-carboxylate (90 mg, 0.40 mmol, 1.3 equiv) in dioxane (2.0 mL) were added RuPhos Pd G3 (27 mg, 0.03 mmol, 0.10 equiv) and Cs₂CO₃ (0.21 g, 0.64 mmol, 2.0 equiv) at 25 °C. The mixture was degassed and purged with nitrogen three times, then the mixture was stirred at 80 °C for 4 hours. The reaction mixture was diluted with ethyl acetate (10 mL), then the mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-TLC (PE/EtOAc = 1:2) to give **C.1q** (0.12 g, 0.18 mmol, 56% yield, 95% purity) as a yellow solid. MS m/z (ESI) [M+H]⁺ = 642.4.

C.1r: tert-butyl 2-[5-[4-[2-[tert-butoxycarbonyl(methyl)amino] ethoxy] phenyl]-2-methoxy-thieno[3,2-b] pyridin-7-yl]-7,7-difluoro-1,3,3a,4,6,7a-hexahydropyrrolo[3,4-c] pyridine-5-carboxylate (cis mixture)



[0288] According to Scheme 3 Step 1: Conditions 1 Buchwald: Substrate **B.1h** (50 mg, 0.11 mmol, 1.0 equiv), **Amine 2** (35 mg, 0.13 mmol, 1.2 equiv), SPhos Pd G₃ (8.7 mg, 11 μ mol, 0.10 equiv), Cs₂CO₃ (0.11 g, 0.33 mmol, 3.0 equiv) in dioxane (1.0 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 80 °C for 16 hours under N₂ atmosphere. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL, three times). The organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated. The residue obtained was purified by prep-HPLC **2** (gradient: 33%-63% over 10 min) to give **C.1r** (30 mg, 38 μ mol, 34% yield, 85% purity) as a white solid. MS m/z (ESI) [M+H]⁺ = 675.3.

C.1s: tert-butyl 2-[5-[4-[2-[tert-butoxycarbonyl (methyl)amino]ethoxy]phenyl]-2-(trideuteriomethoxy)thieno[3,2-b]pyridin-7-yl]-3,3a,4,6,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridine-5-carboxylate (cis mixture)



[0289] According to Scheme 3 Step 1: To a solution of tert-butyl N-[2-[4-(7-chloro-2-methoxy-thieno[3,2-b]pyridin-5-yl)phenoxy]ethyl]-N-methyl-carbamate (200 mg, 445.47 μ mol, 1 eq) and tert-butyl 1,2,3,3a,4,6,7,7a-octahydropyrrolo[3,4-c]pyridine-5-carboxylate (250 mg, 1.10 mmol, 2.48 eq) in dioxane (4 mL) was added Pd(t-Bu₃P)₂ (20 mg, 39.13 μ mol,

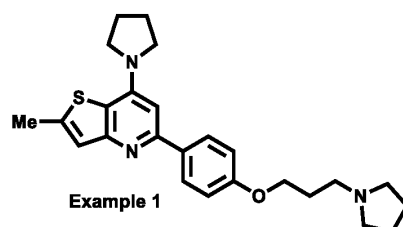
8.79e-2 eq) and t-BuONa (130 mg, 1.35 mmol, 3.04 eq). The mixture was stirred at 80 °C for 12 hours under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN]; gradient: 35%-55% B over 10 min). The eluent was lyophilized to give **C.1s** (88 mg, 132.24 μmol, 29.69% yield, 96% purity) as a white solid.

Synthesis of final products

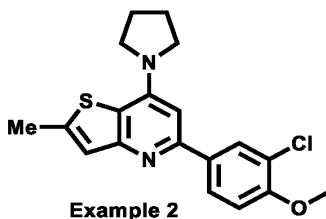
[0290] Conditions 1 HCl. To a solution of substrate **B.2** or **C.1** (1.0 equiv) in dioxane was added HCl/dioxane (*large excess*). The mixture was stirred at 25 °C for 2 hours. The mixture was concentrated. Purification detailed in protocols below.

[0291] Conditions 2 TFA. To a solution of substrate **B.2** or **C.1** (1.0 equiv) in DCM was added TFA (*large excess*) 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. Purification detailed in protocols below.

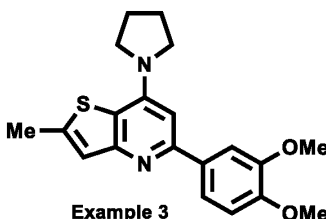
Example 1: 2-methyl-7-(pyrrolidin-1-yl)-5-(4-(3-(pyrrolidin-1-yl) propoxy) phenyl) thieno[3,2-b] pyridine



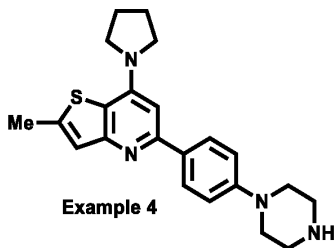
[0292] According to Scheme 1 Step 2: Conditions 1 S_NAr: To a solution of **A.2a** (0.10 g, 0.26 mmol, 1.0 equiv) and pyrrolidine (4.3 g, 60 mmol, 5.0 mL, 232 equiv) in DMF (1.0 mL) at 25 °C. The mixture was stirred at 100 °C for 16 hours. After work-up, the residue obtained was purified by prep-HPLC **1** (gradient: 21%-51% over 10 min). **Example 1** (37 mg, 85 μmol, 33% yield, 98% purity) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-d₆) *d* (ppm): 7.89 - 7.82 (m, 2H), 7.29 (d, *J* = 1.2 Hz, 1H), 7.23 - 7.16 (m, 2H), 6.67 (s, 1H), 4.30 - 4.15 (m, 4H), 3.79 - 3.68 (m, 4H), 3.51 - 3.41 (m, 2H), 3.22 - 3.08 (m, 2H), 2.70 (d, *J* = 0.80 Hz, 3H), 2.36 - 2.26 (m, 2H), 2.22 - 2.15 (m, 6H), 2.11 - 2.03 (m, 2H). MS *m/z* (ESI) [M+H]⁺ = 422.2.

Example 2: 5-(3-chloro-4-methoxyphenyl)-2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b]pyridine

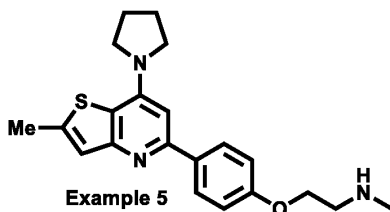
[0293] According to Scheme 1 Step 2: Conditions 1 S_NAr : To a solution of **A.2b** (0.30 g, 0.93 mmol, 1.0 equiv) and pyrrolidine (66 mg, 0.93 mmol, 77 μ L, 1.0 equiv) in pyrrolidine (2.0 mL) at 25 °C. The mixture was stirred at 60 °C for 16 hours. After work-up, the crude product was triturated with EtOAc (10 mL) at 25 °C for 30 min. **Example 2** (19 mg, 51 μ mol, 5.5% yield, 96% purity) was obtained as a white solid. 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.15 (d, J = 3.2 Hz, 1H), 8.03 (dd, J = 8.40, 2.0 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 0.80 Hz, 1H), 6.67 (s, 1H), 3.92 (s, 3H), 3.72 (br s, 4H), 2.55 (s, 3H), 2.08 - 1.94 (m, 4H). MS m/z (ESI) $[M+H]^+ = 359.0$.

Example 3: 5-(3,4-dimethoxyphenyl)-2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b]pyridine

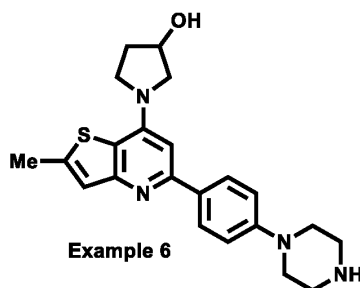
[0294] According to Scheme 1 Step 2: Conditions 3 S_NAr . To a mixture of **A.2c** (0.25 g, 0.78 mmol, 1.0 equiv) and pyrrolidine (0.25 g, 3.5 mmol, 0.29 mL, 4.5 equiv) was added DIEA (0.50 g, 3.9 mmol, 0.67 mL, 5.0 equiv). The mixture was stirred at 130 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give the residue. The residue obtained was purified by prep-HPLC **1** (gradient: 31%-61% over 10 min). The eluent was lyophilized to give **Example 3** as a yellow solid. The residue was neutralized with SCX (see general protocol). 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.68 - 7.56 (m, 2H), 7.12 (d, J = 1.1 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.65 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.72 (br t, J = 6.4 Hz, 4H), 2.55 (s, 3H), 2.00 (s, 4H). MS m/z (ESI) $[M+H]^+ = 355.1$.

Example 4: 2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridine

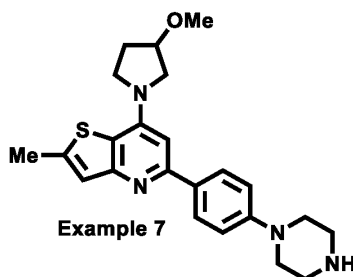
[0295] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2a** (20 mg, 0.04 mmol, 1.0 equiv), HCl/dioxane (4.0 M, 1.0 mL, 96 equiv). The mixture was concentrated. The residue obtained was purified by prep-HPLC (gradient: 18%-48% over 10 min). **Example 4** (10 mg, 0.03 mmol, 66% yield, 100% purity) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.84 (d, $J = 8.8$ Hz, 2H), 7.30 (s, 1H), 7.24 (d, $J = 8.8$ Hz, 2H), 6.66 (s, 1H), 4.34 - 4.04 (m, 2H), 3.90 - 3.68 (m, 2H), 3.67 - 3.60 (m, 4H), 3.45 - 3.39 (m, 4H), 2.69 (s, 3H), 2.17 (br s, 4H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 379.1$.

Example 5: *N*-methyl-2-(4-(2-methyl-7-(pyrrolidin-1-yl) thieno[3,2-b] pyridin-5-yl) phenoxy) ethan-1-amine

[0296] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2o** (50 mg, 0.11 mmol, 1.0 equiv), HCl/dioxane (4 M, 1.0 mL), for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC **2** (gradient: 1%-30% over 10 min) and then by prep-HPLC **1** (gradient: 19%-49% over 10 min) to give **Example 5** (26 mg, 0.07 mmol, 88% yield, 99% purity) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 14.19 (s, 1H), 9.40 - 9.17 (m, 2H), 8.05 (d, $J = 8.8$ Hz, 2H), 7.55 (s, 1H), 7.23 (d, $J = 8.8$ Hz, 2H), 6.73 (s, 1H), 4.40 (t, $J = 5.2$ Hz, 2H), 4.24 - 3.62 (m, 4H), 3.43 - 3.36 (m, 2H), 2.68 (s, 3H), 2.63 (s, 3H), 2.06 (s, 4H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 368.1$.

Example 6: 1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-ol

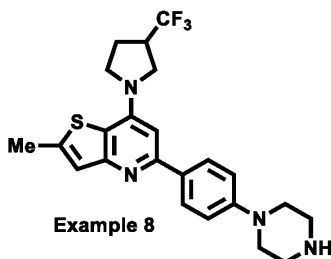
[0297] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2m** (0.20 g, 0.40 mmol, 1.0 equiv), HCl/dioxane (4 M, 2.0 mL, 20 equiv), for 1 hour. The mixture was concentrated. The residue obtained was purified by prep-HPLC **1** (gradient: 6%-36% over 10 min). The residue obtained was purified with SCX (see general protocol). **Example 6** (39 mg, 98 μ mol, 24% yield, 100% purity) was obtained as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.93 (d, J = 8.4 Hz, 2H), 7.09 (s, 1H), 6.97 (br d, J = 8.8 Hz, 2H), 6.60 (s, 1H), 5.09 (br s, 1H), 4.44 (br s, 1H), 3.85 (br dd, J = 10, 4.8 Hz, 1H), 3.82 - 3.67 (m, 2H), 3.60 (br d, J = 10 Hz, 1H), 3.21 - 3.05 (m, 4H), 2.94 - 2.80 (m, 4H), 2.54 (s, 3H), 2.15 - 2.00 (m, 1H), 2.00 - 1.84 (m, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 395.2$.

Example 7: 7-(3-methoxypyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine

[0298] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2p** (0.40 g, 0.79 mmol, 1.0 equiv) in MeOH (0.5 mL), HCl/MeOH (4 M, 1.0 mL, 5.1 equiv). The reaction mixture was filtered and concentrated under reduced pressure to give the residue. The residue obtained was purified by prep-HPLC **1** (gradient: 17%-47% over 10 min). The eluent was lyophilized, and residue was neutralized with SCX (see general protocol). **Example 7** (39 mg, 98 μ mol, 24% yield, 100% purity) was obtained as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.97 - 7.90 (m, 2H), 7.12 - 7.07 (m, 1H), 7.00 - 6.93 (m, 2H), 6.65

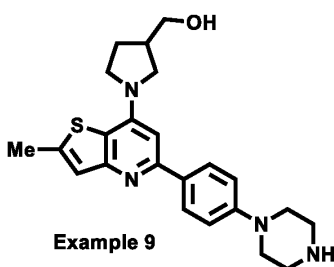
- 6.60 (m, 1H), 4.16 - 4.10 (m, 1H), 3.87 - 3.67 (m, 4H), 3.30 - 3.29 (m, 3H), 3.15 - 3.09 (m, 4H), 2.89 - 2.83 (m, 4H), 2.56 - 2.53 (m, 3H), 2.17 - 2.06 (m, 2H). MS m/z (ESI) $[M+H]^+ = 409.2$.

Example 8: 2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(3-(trifluoromethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine



[0299] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2b** (0.23 g, 0.42 mmol, 1.0 equiv) in EtOAc (1.0 mL), HCl/EtOAc (4 M, 5.0 mL, 48 equiv), for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC **3** (gradient: 3-9 min 25-55%). Compound was neutralized with SCX (see general protocol). **Example 8** (41 mg, 90 μ mol, 31% yield, 98% purity) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.98-7.97 (m, 2H), 7.13 (s, 1H), 6.97-6.96 (m, 2H), 6.72 (s, 1H), 3.97 - 3.96 (m, 1H), 3.91-3.90 (m, 1H), 3.80 - 3.79 (m, 2H), 3.33-3.32 (m, 1H), 3.12 - 3.10 (m, 4H), 2.86 - 2.84 (m, 4H), 2.56 (s, 3H), 2.33 - 2.31 (m, 1H), 2.16 - 2.14 (m, 1H). MS m/z (ESI) $[M+H]^+ = 447.1$.

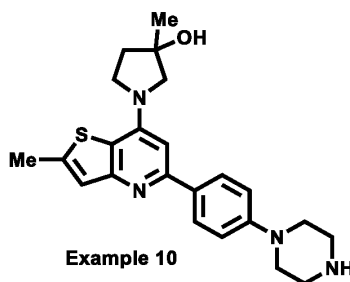
Example 9: (1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-yl) methanol



[0300] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2q** (0.18 g, 0.35 mmol, 1.0 equiv) in EtOAc (1.0 mL), HCl/EtOAc (4 M, 5.0 mL, 57 equiv), for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was neutralized with SCX (see general protocol). **Example 9** (76 mg, 0.19 mmol, 64% yield) was

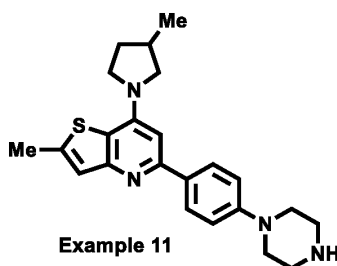
obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.94-7.92 (m, 2H), 7.09 (s, 1H), 6.98-6.96 (m, 2H), 6.60 (s, 1H), 4.80 (s, 1H), 3.82 - 3.80 (m, 3H), 3.52 - 3.51 (m, 3H), 3.15 - 3.13 (m, 4H), 2.88 - 2.86 (m, 4H), 2.89 (s, 3H), 2.54-2.52 (m, 1H), 2.08 - 2.06 (m, 1H), 1.80 - 1.79 (m, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 409.1$.

Example 10: 3-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-ol



[0301] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2n** (0.16 g, 0.31 mmol, 1.0 equiv) in dioxane (5.0 mL), HCl/dioxane (4 M, 2.0 mL, 25 equiv), for 16 hours. The mixture was concentrated. The residue obtained was purified by prep-HPLC 1 (gradient: 14%-44% over 10 min). The residue was neutralized with SCX (see general protocol). **Example 10** (58 mg, 0.14 mmol, 45% yield, 99% purity) was obtained as a white solid. ^1H NMR (400 MHz, Methanol- d_4) δ (ppm): 7.77 (d, $J = 8.8$ Hz, 2H), 7.10 - 7.00 (m, 3H), 6.48 (s, 1H), 3.99 - 3.82 (m, 2H), 3.81 - 3.66 (m, 2H), 3.26 - 3.16 (m, 4H), 3.03 - 2.95 (m, 4H), 2.58 (d, $J = 0.80$ Hz, 3H), 2.12 - 1.96 (m, 2H), 1.48 (s, 3H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 409.2$.

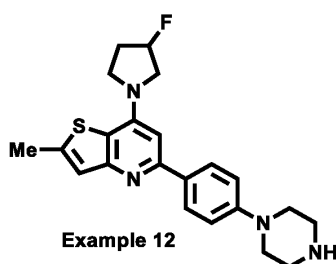
Example 11: 2-methyl-7-(3-methylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



[0302] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2w** (0.18 g, 0.37 mmol, 1.0 equiv), HCl/MeOH (4 M, 2.0 mL, 22 equiv), no dioxane. The reaction mixture was filtered and concentrated under reduced pressure to give the residue. The residue obtained was

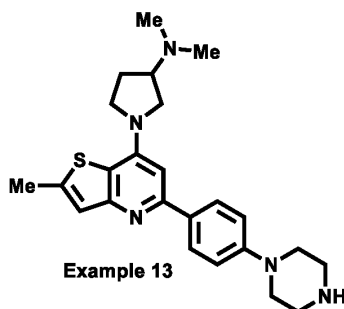
purified by prep-HPLC **1** (gradient: 21%-51% over 10 min). The eluent was lyophilized to give **Example 11** (25 mg, 64 μ mol, 17% yield, 100% purity) as an off-white solid. Compound was neutralized with SCX (see general protocol). ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.01 - 7.86 (m, 2H), 7.11 - 7.06 (m, 1H), 7.02 - 6.94 (m, 2H), 6.62 - 6.55 (m, 1H), 4.03 - 3.54 (m, 4H), 3.21 - 3.14 (m, 4H), 3.01 - 2.89 (m, 4H), 2.54 - 2.53 (m, 3H), 2.38 - 2.30 (m, 1H), 2.20 - 2.06 (m, 1H), 1.71 - 1.56 (m, 1H), 1.14 - 1.09 (m, 3H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 393.2$.

Example 12: 7-(3-fluoropyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-*b*]pyridine



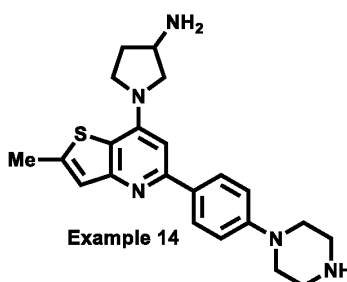
[0303] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2c** (0.30 g, 0.60 mmol, 1.0 equiv), HCl/MeOH (2 M, 10 mL, 33 equiv), for 4 hours. The reaction mixture was concentrated. The residue obtained was purified by prep-HPLC **1** (gradient: 16%-46% over 10 min). After prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give **Example 12** (24 mg, 60 μ mol, 10% yield, 100% purity) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.96 (d, $J = 8.8$ Hz, 2H), 7.13 (s, 1H), 6.98 (br d, $J = 8.6$ Hz, 2H), 6.68 (s, 1H), 5.63 - 5.38 (m, 1H), 4.00 (br d, $J = 3.5$ Hz, 1H), 3.97 - 3.93 (m, 1H), 3.86 - 3.77 (m, 1H), 3.40 (br d, $J = 1.0$ Hz, 2H), 3.20 - 3.06 (m, 4H), 2.85 (br d, $J = 4.3$ Hz, 4H), 2.56 (s, 3H), 2.36 - 2.26 (m, 2H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 397.2$.

Example 13: *N,N*-dimethyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-*b*] pyridin-7-yl) pyrrolidin-3-amine



[0304] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2r** (0.22 g, 0.34 mmol, 1.0 equiv) in MeOH (3.0 mL), HCl/MeOH (4 M, 1.0 mL), for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 2 (gradient: 1%-12% over 10 min) to give a residue. The residue obtained was purified by prep-TLC (EtOAc/MeOH = 0:1) to give **Example 13** (38 mg, 90 μ mol, 84% yield, 100% purity) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.95 (d, J = 8.8 Hz, 2H), 7.09 (s, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.63 (s, 1H), 3.97 - 3.81 (m, 2H), 3.75 - 3.65 (m, 1H), 3.46 (t, J = 8.4 Hz, 1H), 3.16 - 3.11 (m, 4H), 2.90 - 2.84 (m, 4H), 2.83 (s, 1H), 2.54 (s, 3H), 2.24 (s, 6H), 2.18 (s, 1H), 1.92 - 1.79 (m, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 422.2$.

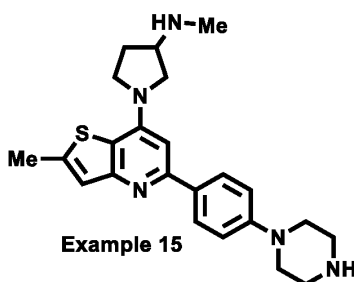
Example 14: 1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-*b*] pyridin-7-yl) pyrrolidin-3-amine



[0305] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1b** (0.18 g, 0.30 mmol, 1.0 equiv) in MeOH (1 mL), HCl/MeOH (4 M, 1 mL), for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 2 (gradient: 1%-12% over 10 min) to give a residue. Then residue was purified with SCX (see general protocol). **Example 14** (26 mg, 65 μ mol, 21% yield, 98% purity) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.92 (d, J = 8.0 Hz, 2H), 7.09 (s,

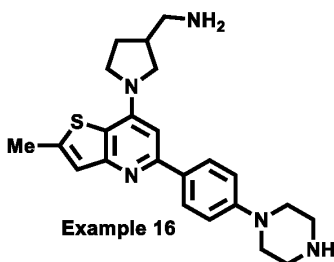
1H), 6.97 (d, $J = 8.4$ Hz, 2H), 6.58 (s, 1H), 3.95 - 3.76 (m, 2H), 3.74 - 3.59 (m, 2H), 3.49 - 3.41 (m, 1H), 3.13 (s, 4H), 2.87 (s, 4H), 2.54 (s, 3H), 2.18 - 2.03 (m, 1H), 1.87 - 1.72 (m, 1H). MS m/z (ESI) $[M+H]^+ = 394.2$.

Example 15: *N*-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-*b*] pyridin-7-yl) pyrrolidin-3-amine



[0306] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1a** (0.24 g, 0.39 mmol, 1.0 equiv) in MeOH (0.50 mL), HCl/MeOH (4 M, 2.0 mL, 20 equiv). The reaction mixture was concentrated. The filter liquor was purified by Prep-HPLC 3' (gradient: 0%-30% over 10 min). The elute was directly lyophilized and then neutralized with SCX (see general protocol). **Example 15** (18 mg, 44 μ mol, 16% yield, 99% purity) as off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.93 (d, $J = 8.9$ Hz, 2H), 7.08 (d, $J = 1.3$ Hz, 1H), 6.97 (d, $J = 8.9$ Hz, 2H), 6.59 (s, 1H), 3.88 - 3.82 (m, 1H), 3.80 - 3.74 (m, 1H), 3.73 - 3.66 (m, 1H), 3.50 (br dd, $J = 4.3, 9.6$ Hz, 1H), 3.15 - 3.11 (m, 4H), 2.90 - 2.84 (m, 4H), 2.68 - 2.66 (m, 1H), 2.54 (br d, $J = 0.90$ Hz, 3H), 2.33 (s, 3H), 2.11 (br dd, $J = 5.6, 12.6$ Hz, 1H), 1.91 - 1.83 (m, 1H). MS m/z (ESI) $[M+H]^+ = 408.2$.

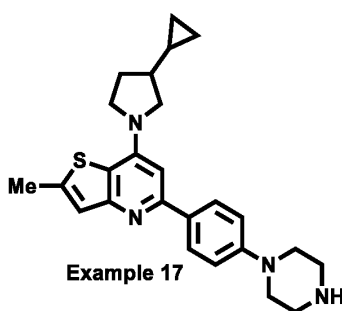
Example 16: (1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-*b*] pyridin-7-yl) pyrrolidin-3-yl) methanamine



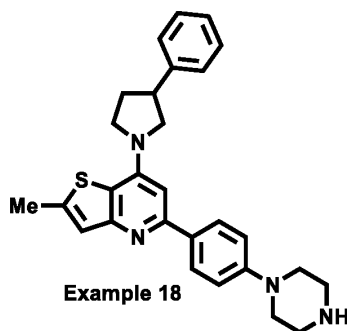
[0307] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1c** (0.21 g, 0.35 mmol, 1.0 equiv) in MeOH (1.0 mL), HCl/MeOH (4 M, 1.0 mL, 12 equiv), for 12 hours. The reaction

mixture was concentrated. The filter liquor was purified by Prep-HPLC 3' (gradient:5%-35% over 10 min). The elute was directly lyophilized then neutralized with SCX (see general protocol). **Example 16** (18 mg, 44 μ mol, 16% yield, 98% purity) as white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.92 (d, J = 8.8 Hz, 2H), 7.08 (s, 1H), 6.99 - 6.94 (m, 2H), 6.61 - 6.57 (m, 1H), 3.85 - 3.76 (m, 2H), 3.73 - 3.67 (m, 1H), 3.49 - 3.42 (m, 2H), 3.13 - 3.09 (m, 4H), 2.87 - 2.82 (m, 4H), 2.67 (br t, J = 7.2 Hz, 3H), 2.38 - 2.30 (m, 2H), 2.14 - 2.06 (m, 1H), 1.82 - 1.72 (m, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 408.2$.

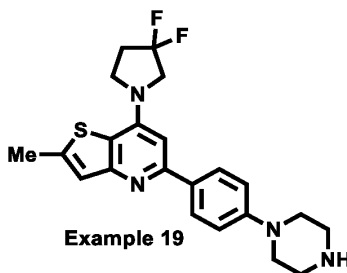
Example 17: 7-(3-cyclopropylpyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



[0308] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2s** (0.25 g, 0.48 mmol, 1.0 equiv) in dioxane (2.0 mL), HCl/dioxane (4 M, 2.0 mL). The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 2 (gradient: 12%-42% over 10 min) to give **Example 17** (0.10 g, 0.21 mmol, 44% yield, 96% purity, HCl) 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): 7.94 (d, J = 8.7 Hz, 2H), 7.08 (s, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.60 (s, 1H), 3.90 - 3.79 (m, 2H), 3.69 - 3.62 (m, 1H), 3.48 - 3.43 (m, 2H), 3.16 (s, 4H), 2.91 (s, 4H), 2.54 (s, 3H), 2.11 (d, J = 3.8 Hz, 1H), 1.83 - 1.70 (m, 2H), 0.81 (td, J = 4.8, 7.8 Hz, 1H), 0.46 (d, J = 7.7 Hz, 2H), 0.21 (d, J = 4.2 Hz, 2H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 419.2$.

Example 18: 2-methyl-7-(3-phenylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine

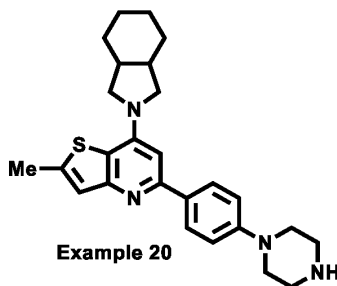
[0309] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2t** (0.10 g, 0.18 mmol, 1.0 eq) in dioxane (2.0 mL), HCl/dioxane (4 M, 2.0 mL). The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 2 (gradient: 10%-40% over 10 min) to give **Example 18** (50 mg, 0.10 mmol, 56% yield, 99% purity, HCl) was obtained as a yellow solid. Then the crude product was purified with SCX (see general protocol). ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.96 (d, J = 8.6 Hz, 2H), 7.43 - 7.32 (m, 4H), 7.30 - 7.24 (m, 1H), 7.10 (s, 1H), 6.97 (d, J = 8.7 Hz, 2H), 6.68 (s, 1H), 4.17 (t, J = 7.8 Hz, 1H), 3.95 (t, J = 7.8 Hz, 1H), 3.88 - 3.79 (m, 1H), 3.70 - 3.64 (m, 1H), 3.58 - 3.53 (m, 1H), 3.17 (s, 4H), 2.92 (s, 4H), 2.53 (s, 3H), 2.45 - 2.37 (m, 2H), 2.20 - 2.10 (m, 1H). MS m/z (ESI) $[M+H]^+ = 455.2$.

Example 19: 7-(3,3-difluoropyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine

[0310] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2u** (0.30 g, 0.58 mmol, 1.0 equiv, 69% purity) in HCl/dioxane (10 mL, 4 M), for 0.5 hours. The reaction mixture was concentrated *in vacuo* to give a crude product. The crude product was purified by preparative HPLC 2 (gradient: 0%-30% over 10 minutes) and then neutralized by SCX (see general protocol). **Example 19** (83 mg, 56% yield, 93% purity) was obtained as a brown solid. ¹H

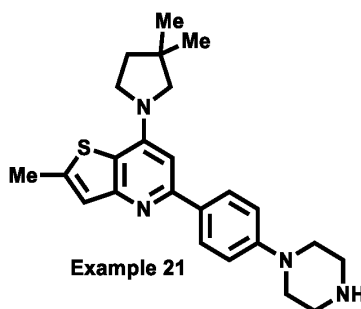
NMR (400 MHz, DMSO- d_6) δ (ppm): 7.97 (d, J = 8.8 Hz, 2H), 7.14 (s, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.72 (s, 1H), 4.11 (t, J = 12.8 Hz, 2H), 3.98 (t, J = 7.2 Hz, 2H), 3.12 (t, J = 4.4 Hz, 4H), 2.85 (t, J = 4.4 Hz, 4H), 2.81-2.58 (m, 2H), 2.56 (s, 3H). MS m/z (ESI) $[M+H]^+ = 415.1$.

Example 20: 2-methyl-7-((cis)-octahydro-2H-isoindol-2-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



[0311] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2v** (0.12 g, 0.23 mmol, 1.0 equiv) in dioxane (2.0 mL), HCl/dioxane (4 M, 2.0 mL, 36 equiv). The reaction mixture was concentrated under reduced pressure to give **Example 20** (90 mg, 0.19 mmol, 85% yield, 100% purity, HCl) 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): 7.93 (d, J = 8.9 Hz, 2H), 7.08 (d, J = 1.1 Hz, 1H), 6.97 (d, J = 8.9 Hz, 2H), 6.59 (s, 1H), 3.77 - 3.71 (m, 2H), 3.60 (dd, J = 4.6, 9.1 Hz, 2H), 3.18 - 3.14 (m, 4H), 2.91 (d, J = 4.5 Hz, 4H), 2.55 - 2.52 (m, 3H), 2.35 (s, 1H), 1.67 - 1.32 (m, 10H). MS m/z (ESI) $[M+H]^+ = 433.2$.

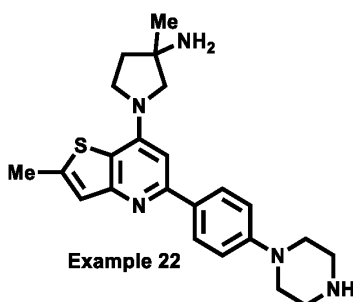
Example 21: 7-(3,3-dimethylpyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



[0312] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2x** (0.22 g, 0.30 mmol, 1.0 equiv) in MeOH (2.0 mL), HCl/MeOH (4 M, 1.0 mL). The reaction mixture was

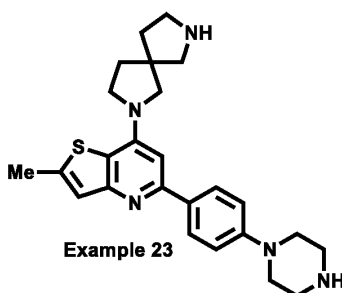
concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 3 (gradient: 25%-55% over 9 min) and neutralized with SCX (see general protocol). **Example 21** (16 mg, 39 μ mol, 13% yield, 98% purity) as a yellow solid. ^1H NMR (400 MHz, Methanol- d_4) δ (ppm): 7.86 - 7.73 (m, 2H), 7.20 - 7.06 (m, 3H), 6.56 (s, 1H), 3.96 (t, J = 6.0 Hz, 2H), 3.63 (s, 2H), 3.38 (d, J = 4.0 Hz, 4H), 3.17 (s, 4H), 2.63 (s, 3H), 1.93 (t, J = 6.0 Hz, 2H), 1.22 (d, J = 1.6 Hz, 6H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 407.2$.

Example 22: 3-methyl-1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-3-amine



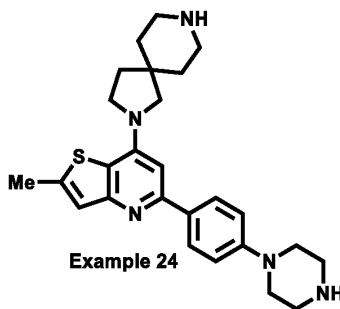
[0313] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1n** (0.20 g, 0.33 mmol, 1.0 equiv) in MeOH (2.0 mL), HCl/MeOH (4 M, 1.0 mL), for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 2 (gradient: 1%-14% over 10 min) and neutralized with SCX (see general protocol). **Example 22** (18 mg, 43 μ mol, 13% yield, 97% purity) as an off-white solid. ^1H NMR (400 MHz, Methanol- d_4) δ (ppm): 7.79 (d, J = 8.8 Hz, 2H), 7.14 - 7.00 (m, 3H), 6.52 (s, 1H), 4.04 - 3.94 (m, 1H), 3.92 - 3.81 (m, 1H), 3.70 (s, 2H), 3.27 - 3.20 (m, 4H), 3.04 - 2.98 (m, 4H), 2.59 (s, 3H), 2.06 - 1.99 (m, 2H), 1.40 (s, 3H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 408.2$.

Example 23: 2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,7-diazaspiro [4.4] nonan-2-yl) thieno[3,2-b] pyridine



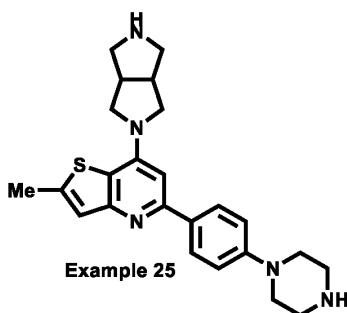
[0314] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1d** (0.10 g, 0.16 mmol, 1 equiv) in dioxane (1.5 mL), HCl/dioxane (4 M, 1.0 mL, 25 equiv), for 0.5 hours. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL, three times). The organic phase was washed with brine (60 mL, three times), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated. The residue obtained was purified by prep-HPLC 1 (gradient: 9%-39% over 10 min) and neutralized with SCX (see general protocol). **Example 23** (28 mg, 60 μ mol, 38% yield, 95% purity) was obtained as an off-white solid. ^1H NMR (400 MHz, Methanol- d_4) δ (ppm): 7.80 (d, J = 8.8 Hz, 2H), 7.14 - 7.04 (m, 3H), 6.54 (s, 1H), 3.94 - 3.85 (m, 2H), 3.78 - 3.68 (m, 2H), 3.27 - 3.21 (m, 4H), 3.07 (t, J = 7.2 Hz, 2H), 3.04 - 2.99 (m, 4H), 2.98 - 2.86 (m, 2H), 2.60 (s, 3H), 2.08 (br t, J = 6.8 Hz, 2H), 1.99 - 1.83 (m, 2H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 434.2$.

Example 24: 2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,8-diazaspiro [4.5] decan-2-yl) thieno[3,2-b] pyridine



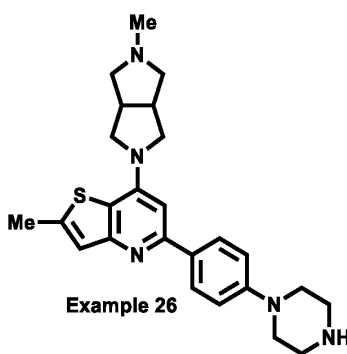
[0315] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1e** (80 mg, 0.12 mmol, 1.0 equiv) in dioxane (1.0 mL), HCl/dioxane (4 M, 1.0 mL, 32 equiv), for 0.5 hours. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL, three times). The organic phase was washed with brine (60 mL, three times), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated. Then the crude product was neutralized with SCX (see general protocol). The residue was then purified by prep-HPLC 1 (gradient: 10%-40% over 10 min). **Example 24** (36 mg, 78 μ mol, 63% yield, 98% purity) was obtained as a white solid. ^1H NMR (400 MHz, Methanol- d_4) δ (ppm): 7.81 (br d, J = 8.8 Hz, 2H), 7.16 - 7.04 (m, 3H), 6.58 (s, 1H), 3.95 (br t, J = 6.8 Hz, 2H), 3.71 (s, 2H), 3.35 (br s, 4H), 3.19 (br t, J = 6.0 Hz, 4H), 3.14 - 3.06 (m, 4H), 2.60 (s, 3H), 2.07 (br t, J = 6.8 Hz, 2H), 1.91 - 1.79 (m, 4H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 448.2$.

Example 25: 7-((cis)-hexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



[0316] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1f** (0.40 g, 0.65 mmol, 1.0 equiv), HCl/MeOH (4 M, 2.0 mL, 12 equiv). The reaction mixture was filtered and concentrated under reduced pressure to give the residue. The residue obtained was purified by prep-HPLC 1 (gradient: 2%-32% over 10 min). The eluent was lyophilized to give **Example 25** (47 mg, 0.11 mmol, 17% yield, 100% purity) as an off-white solid. Then the crude product was purified with SCX (see general protocol). ¹H NMR (400 MHz, DMSO-*d*₆) *d* (ppm): 7.95 - 7.92 (m, 2H), 7.12 - 7.10 (m, 1H), 6.99 - 6.95 (m, 2H), 6.71 - 6.66 (m, 1H), 3.91 - 3.84 (m, 2H), 3.51 - 3.46 (m, 2H), 3.13 - 3.10 (m, 4H), 2.99 - 2.94 (m, 2H), 2.91 - 2.86 (m, 2H), 2.86 - 2.83 (m, 4H), 2.73 - 2.68 (m, 2H), 2.55 - 2.54 (m, 3H). MS *m/z* (ESI) [*M*+*H*]⁺ = 420.2.

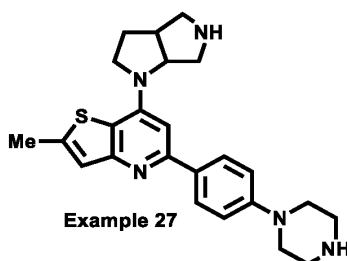
Example 26: 2-methyl-7-((cis)-5-methylhexahydropyrrolo[3,4-c] pyrrol-2(1H)-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



[0317] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2y** (0.27 g, 0.51 mmol, 1.0 equiv), HCl/MeOH (4 M, 2.0 mL, 16 equiv). The reaction mixture was filtered and concentrated under reduced pressure to give the residue. The residue obtained was purified by prep-HPLC 1 (gradient: 2%-32% over 10 min). The eluent was lyophilized to give **Example 26** (46 mg, 0.11 mmol, 21% yield, 100% purity) as an off-white solid. Then the crude product

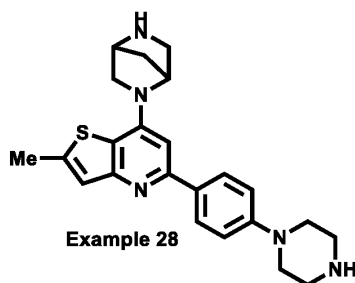
was purified with SCX (see general protocol). ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.98 - 7.91 (m, 2H), 7.14 - 7.08 (m, 1H), 7.00 - 6.93 (m, 2H), 6.73 - 6.68 (m, 1H), 3.88 - 3.80 (m, 2H), 3.56 - 3.50 (m, 2H), 3.30 - 3.29 (m, 3H), 3.15 - 3.09 (m, 4H), 2.97 - 2.91 (m, 2H), 2.88 - 2.84 (m, 4H), 2.55 - 2.54 (m, 2H), 2.52 (br s, 2H), 2.25 - 2.21 (m, 3H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 434.2$.

Example 27: 7-((cis)-hexahydropyrrolo[3,4-b] pyrrol-1(2H)-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



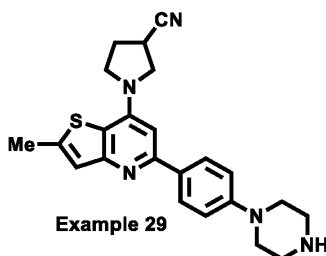
[0318] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1g** (0.23 g, 0.37 mmol, 1.0 equiv) in methanol (1.0 mL), HCl/dioxane (4 M, 93 μL), for 0.5 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified with SCX (see general protocol). **Example 27** (0.11 g, 0.25 mmol, 68% yield, 100% purity) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.92 (d, $J = 8.8$ Hz, 2H), 7.11 (s, 1H), 6.97 (d, $J = 8.9$ Hz, 2H), 6.66 (s, 1H), 4.60 (t, $J = 4.8$ Hz, 1H), 3.67 - 3.87 (m, 2H), 3.10 - 3.16 (m, 4H), 2.82 - 2.98 (m, 7H), 2.66 - 2.75 (m, 2H), 2.55 (s, 3H), 2.03 - 2.18 (m, 1H), 1.78 - 1.95 (m, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 420.1$.

Example 28: 7-(2,5-diazabicyclo [2.2.1] heptan-2-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



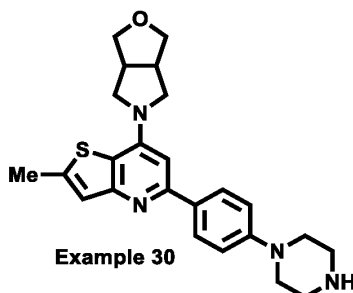
[0319] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1h** (0.23 g, 0.38 mmol, 1.0 eq) in methanol (1.0 mL), HCl/dioxane (4 M, 95 μ L), for 0.5 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified with SCX (see general protocol). **Example 28** (0.12 g, 0.30 mmol, 78% yield, 97% purity) was obtained as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.93 (d, J = 8.9 Hz, 2H), 7.09 (s, 1H), 6.97 (d, J = 8.9 Hz, 2H), 6.68 (s, 1H), 4.77 (s, 1H), 3.84 (dd, J = 8.3, 1.8 Hz, 1H), 3.70 (s, 1H), 3.51 - 3.52 (m, 1H), 3.09 - 3.15 (m, 4H), 2.93 - 3.01 (m, 2H), 2.79 - 2.89 (m, 4H), 2.54 (s, 3H), 1.88 (d, J = 8.4 Hz, 1H) 1.74 (d, J = 9.2 Hz, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 406.1$.

Example 29: 1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidine-3-carbonitrile



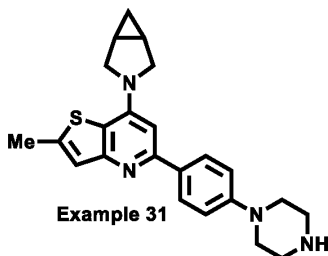
[0320] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2d** (0.15 g, 0.30 mmol, 1.0 equiv), HCl/MeOH (2 M, 0.15 mL, 1.0 equiv), for 4 hours. The reaction mixture was concentrated. The residue obtained was purified by prep-HPLC 2 (gradient: 0%-30% over 10 min). After lyophilization **Example 29** (21 mg, 51 μ mol, 17% yield, 97% purity) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.97 (d, J = 8.9 Hz, 2H), 7.16 - 7.08 (m, 1H), 6.98 (br d, J = 8.9 Hz, 2H), 6.74 - 6.68 (m, 1H), 4.06 - 3.97 (m, 1H), 3.94 - 3.88 (m, 2H), 3.85 - 3.79 (m, 1H), 3.66 - 3.61 (m, 1H), 3.15 (br d, J = 4.4 Hz, 4H), 2.90 (br s, 4H), 2.56 (s, 3H), 2.46 - 2.41 (m, 1H), 2.33 (br dd, J = 1.9, 3.8 Hz, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 404.2$.

Example 30: (cis)-5-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) hexahydro-1H-furo[3,4-c] pyrrole



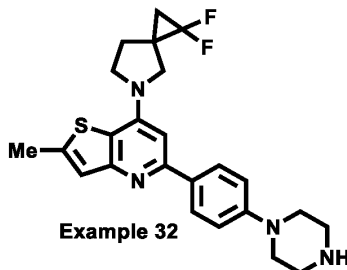
[0321] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2z** (0.26 g, 0.50 mmol, 1.0 equiv), HCl/MeOH (2 M, 2.0 mL, 8.0 equiv). The reaction mixture was concentrated. The residue obtained was purified by prep-HPLC 1 (gradient: 14%-44% over 10 min). After lyophilization **Example 30** (46 mg, 0.11 mmol, 22% yield, 100% purity) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) *d* (ppm): 7.95 (d, *J* = 8.9 Hz, 2H), 7.13 (d, *J* = 1.0 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.72 (s, 1H), 3.91 - 3.83 (m, 4H), 3.68 - 3.61 (m, 4H), 3.19 - 3.12 (m, 4H), 3.08 (br d, *J* = 2.8 Hz, 2H), 2.93 - 2.87 (m, 4H), 2.56 (s, 3H). MS *m/z* (ESI) [*M*+*H*]⁺ = 421.2.

Example 31: 7-((cis)-3-azabicyclo [3.1.0] hexan-3-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



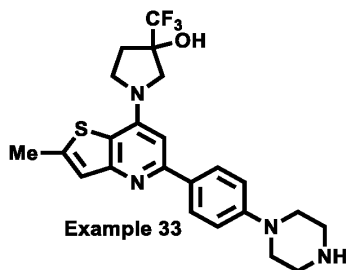
[0322] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2aa** (0.26 g, 0.53 mmol, 1.0 equiv), HCl/MeOH (2 M, 2.0 mL, 7.6 equiv). The reaction mixture was concentrated. The residue obtained was purified by prep-HPLC 4 (gradient: 43%-63%, 10 min). After lyophilization **Example 31** (18 mg, 43 μmol, 8.2% yield, 96% purity) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) *d* (ppm): 7.94 (d, *J* = 8.6 Hz, 2H), 7.11 (s, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.64 (s, 1H), 3.96 (d, *J* = 9.4 Hz, 2H), 3.69 (br d, *J* = 7.9 Hz, 2H), 3.19 - 3.13 (m, 4H), 2.94 - 2.89 (m, 4H), 2.55 (s, 3H), 1.80 - 1.74 (m, 2H), 0.79 (br d, *J* = 4.9 Hz, 1H), 0.31 (br d, *J* = 4.1 Hz, 1H). MS *m/z* (ESI) [*M*+*H*]⁺ = 391.2.

Example 32: 7-(1,1-difluoro-5-azaspiro [2.4] heptan-5-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



[0323] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2e** (0.11 g, 0.20 mmol, 1.0 equiv) in EtOAc (1.0 mL), HCl/EtOAc (4 M, 4.0 mL, 79 equiv), for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 1 (gradient: 2-10 min 25-55%). Compound was neutralized with SCX (see general protocol). **Example 32** (30 mg, 68 μ mol, 46% yield) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.96-7.94 (m, 2H), 7.13 (s, 1H), 6.98-6.96 (m, 2H), 6.68 (s, 1H), 3.94 – 3.92 (m, 4H), 3.11 - 3.10 (m, 4H), 2.85 -2.83 (m, 4H), 2.56 (s, 3H), 2.17 - 2.15 (m, 2H), 1.70 - 1.68 (m, 2H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 441.1$.

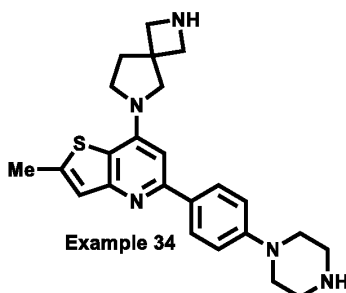
Example 33: 1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl)-3-(trifluoromethyl) pyrrolidin-3-ol



[0324] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2ab** (0.12 g, 0.21 mmol, 1.0 equiv) in EtOAc (1.0 mL), HCl/EtOAc (4 M, 5.0 mL, 94 equiv), for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 1 (gradient: 2-10 min 21-51%). Compound was neutralized with SCX (see general protocol) and **Example 33** (89 mg, 0.19 mmol, 91% yield) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.98-7.96 (m, 2H), 7.13 (s, 1H), 6.98-6.96 (m, 2H), 6.69 - 6.64 (m, 2H), 4.03 - 4.00 (m, 2H), 3.95 - 3.88 (m, 2H), 3.11 - 3.10 (m,

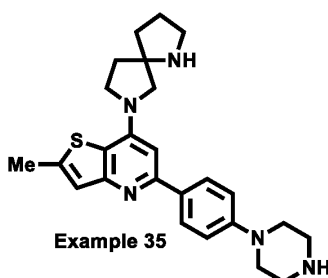
4H), 2.85 - 2.83 (m, 4H), 2.56 (s, 3H), 2.35 - 2.33 (m, 1H), 2.19 - 2.16 (m, 1H). MS m/z (ESI) $[M+H]^+ = 463.1$.

Example 34: 2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,6-diazaspiro [3.4] octan-6-yl) thieno[3,2-b] pyridine



[0325] According to Scheme 3 Step 2: Conditions 2 TFA. **C.1i** (0.25 g, 0.40 mmol, 1.0 eq) in DCM (3.0 mL), TFA (0.92 g, 8.1 mmol, 0.60 mL, 20 equiv) for 2 hours. The mixture was concentrated under reduced pressure to give residue. The residue obtained was purified by prep-HPLC **2** (gradient: 1%-30% over 10 min) to give pure product. The residue obtained was purified with SCX (see general protocol). **Example 34** (87 mg, 0.21 mmol, 51% yield, 99% purity) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.93 (d, $J = 8.8$ Hz, 2H), 7.10 (s, 1H), 6.97 (d, $J = 8.8$ Hz, 2H), 6.61 (s, 1H), 3.88 (s, 2H), 3.61 (s, 6H), 3.12 (d, $J = 4.8$ Hz, 4H), 2.86 (s, 4H), 2.55 (s, 3H), 2.21 (t, $J = 6.8$ Hz, 2H). MS m/z (ESI) $[M+H]^+ = 420.2$.

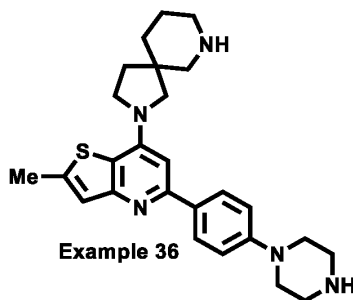
Example 35: 2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(1,7-diazaspiro [4.4] nonan-7-yl) thieno[3,2-b] pyridine



[0326] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1j** (0.30 g, 0.47 mmol, 1.0 equiv) in dioxane (2.0 mL), HCl/dioxane (4 M, 2.0 mL, 17 equiv), for 16 hours. The reaction mixture was concentrated under reduced pressure to give **Example 35** (0.12 g, 0.25 mmol, 54% yield, 99% purity, HCl) was obtained as a yellow solid. Then the crude product was

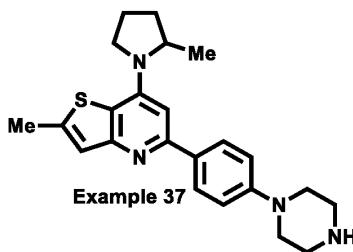
purified with SCX (see general protocol). ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.92 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 1.0 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 6.57 (s, 1H), 3.84 - 3.72 (m, 2H), 3.66 - 3.57 (m, 2H), 3.14 - 3.09 (m, 4H), 2.91 - 2.82 (m, 6H), 2.54 (s, 3H), 1.98 - 1.91 (m, 2H), 1.81 - 1.67 (m, 4H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 434.2$.

Example 36: 2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2,7-diazaspiro [4.5] decan-2-yl) thieno[3,2-b] pyridine



[0327] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1k** (0.22 g, 0.32 mmol, 1.0 equiv, HCl) in MeOH (2.0 mL), HCl/MeOH (4 M, 2.0 mL, 25 equiv), for 16 hours. The reaction mixture was concentrated under reduced pressure to give a residue to give **Example 36** (0.12 g, 0.25 mmol, 77% yield, 100% purity, HCl) 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): 7.93 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 0.9 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 6.59 (s, 1H), 3.82 - 3.69 (m, 3H), 3.44 (d, J = 9.5 Hz, 1H), 3.15 - 3.08 (m, 4H), 2.86 (d, J = 4.4 Hz, 4H), 2.76 - 2.56 (m, 4H), 2.54 (s, 3H), 2.02 - 1.91 (m, 1H), 1.76 (td, J = 8.1, 12.2 Hz, 1H), 1.64 - 1.44 (m, 4H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 448.2$.

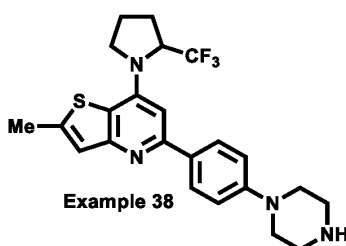
Example 37: 2-methyl-7-(2-methylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



[0328] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2ac** (80 mg, 0.16 mmol, 1.0 equiv), HCl/dioxane (4 M, 1.0 mL, 25 equiv), for 0.5 hours. The mixture was concentrated.

The residue obtained was purified by prep-HPLC 1 (gradient: 20%-50% over 10 min). Then the crude product was purified with SCX (see general protocol). **Example 37** (30 mg, 75 μ mol, 46% yield, 99% purity) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.92 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 1.2 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.67 (s, 1H), 4.44 (td, J = 6.0, 2.0 Hz, 1H), 3.84 (td, J = 8.8, 4.0 Hz, 1H), 3.71 - 3.61 (m, 1H), 3.17 - 3.07 (m, 4H), 2.91 - 2.83 (m, 4H), 2.55 (d, J = 0.80 Hz, 3H), 2.20 - 2.06 (m, 2H), 2.05 - 1.93 (m, 1H), 1.79 - 1.68 (m, 1H), 1.21 (d, J = 6.0 Hz, 3H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 393.1$.

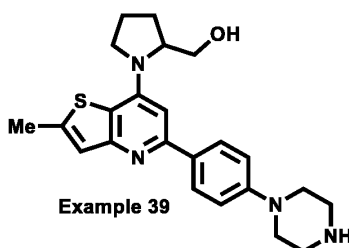
Example 38: 2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(trifluoromethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine



[0329] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2ad** (80 mg, 0.15 mmol, 1.0 equiv) in dioxane (1.0 mL), HCl/dioxane (4 M, 1.0 mL, 27 equiv), for 0.5 hours. The mixture was concentrated. The residue obtained was purified by prep-HPLC 1 (gradient: 20%-50% over 10 min). Then the crude product was purified with SCX (see general protocol).

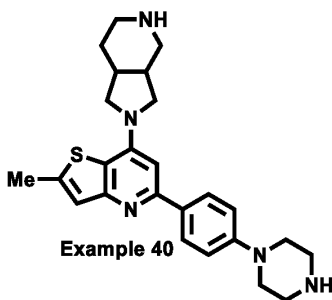
Example 38 (12 mg, 27 μ mol, 18% yield, 99% purity) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.00 (d, J = 8.8 Hz, 2H), 7.19 - 7.10 (m, 2H), 7.01 (d, J = 8.8 Hz, 2H), 5.34 (quin, J = 6.4 Hz, 1H), 4.16 - 4.04 (m, 1H), 3.85 - 3.72 (m, 1H), 3.24 - 3.17 (m, 4H), 3.03 - 2.93 (m, 4H), 2.56 (br d, J = 1.0 Hz, 3H), 2.53 (br d, J = 2.0 Hz, 2H), 2.31 - 2.23 (m, 1H), 2.09 (br s, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 447.1$.

Example 39: (1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-2-yl) methanol



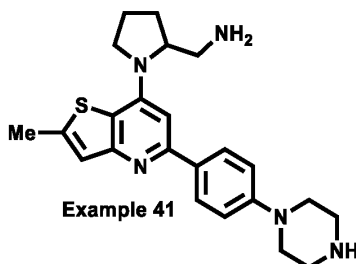
[0330] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2ae** (0.30 g, 0.59 mmol, 1.0 equiv), HCl/MeOH (4 M, 2.0 mL, 14 equiv), for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give the residue. The residue obtained was purified by prep-HPLC 1 (gradient: 14%-44% over 10 min). The eluent was lyophilized to give **Example 39** (40 mg, 99 μ mol, 17% yield, 100% purity) as a yellow solid. Then the crude product was purified with SCX (see general protocol). ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.93 - 7.89 (m, 2H), 7.10 - 7.07 (m, 1H), 7.00 - 6.96 (m, 2H), 6.74 - 6.71 (m, 1H), 5.00 - 4.83 (m, 1H), 4.30 - 4.25 (m, 1H), 3.89 - 3.83 (m, 1H), 3.67 - 3.57 (m, 2H), 3.15 - 3.12 (m, 4H), 2.89 - 2.86 (m, 4H), 2.70 - 2.63 (m, 1H), 2.54 (s, 3H), 2.20 - 1.80 (m, 5H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 409.2$.

Example 40: 2-methyl-7-((cis)-octahydro-2H-pyrrolo[3,4-c] pyridin-2-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



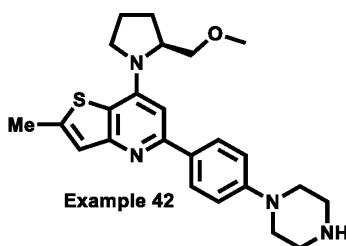
[0331] According to Scheme 3 Step 2: Conditions 1 HCl. **C.11** (0.10 g, 0.16 mmol, 1.0 equiv) in MeOH (2.0 mL), HCl/MeOH (4 M, 2.0 mL), for 16 hours. The reaction mixture was concentrated under reduced pressure to give a residue to give **Example 40** (50 mg, 0.11 mmol, 67% yield, 100% purity, HCl) as a yellow solid. The residue obtained was purified by prep-HPLC 1 (gradient: 9%-39% over 10 min) and neutralized with SCX (see general protocol). ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.92 (d, $J = 8.9$ Hz, 2H), 7.08 (d, $J = 1.0$ Hz, 1H), 6.96 (d, $J = 8.9$ Hz, 2H), 6.58 (s, 1H), 3.81 - 3.67 (m, 3H), 3.60 (br dd, $J = 3.3, 9.3$ Hz, 1H), 3.14 - 3.09 (m, 4H), 2.89 - 2.80 (m, 6H), 2.79 - 2.73 (m, 1H), 2.61 - 2.56 (m, 1H), 2.54 (s, 3H), 2.40 - 2.33 (m, 2H), 1.68 - 1.58 (m, 1H), 1.47 - 1.34 (m, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 434.2$.

Example 41: (1-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl) pyrrolidin-2-yl) methanamine



[0332] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1m** (0.21 g, 0.35 mmol, 1.0 equiv), HCl/MeOH (4 M, 2.0 mL, 23 equiv), for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give the residue. The residue obtained was purified by prep-HPLC 1 (gradient: 9%-39% over 10 min) to give **Example 41** (15 mg, 37 μ mol, 11% yield, 97% purity) as a light-yellow solid. Neutralization was done with SCX (see general protocol). ^1H NMR (400 MHz, Methanol- d_4) δ (ppm): 7.83 - 7.78 (m, 2H), 7.12 - 7.10 (m, 1H), 7.09 - 7.04 (m, 2H), 6.71 - 6.64 (m, 1H), 4.82 - 4.81 (m, 1H), 4.41 - 4.29 (m, 1H), 4.03 - 3.92 (m, 1H), 3.84 - 3.70 (m, 1H), 3.25 (br d, J = 5.0 Hz, 4H), 3.06 - 3.02 (m, 4H), 2.73 - 2.64 (m, 1H), 2.61 - 2.58 (m, 3H), 2.20 - 2.09 (m, 4H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 408.2$.

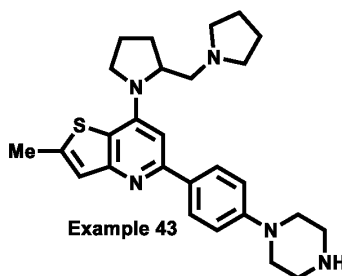
Example 42: (S)-7-(2-(methoxymethyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



[0333] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2af** (0.23 g, 0.43 mmol, 1.0 equiv) in methanol (1.0 mL), HCl/MeOH (4 M, 5.0 mL). The residue obtained was purified with SCX (see general protocol). **Example 42** (110 mg, 0.260 mmol, 64.2% yield, 100% purity) was obtained as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.89 (d, J = 8.8 Hz, 2H), 7.20 (s, 1H) 7.00 (d, J = 8.8 Hz, 2H), 6.66 (s, 1H), 4.46 (s, 1H), 3.95 - 3.85 (m, 1H), 3.76 - 3.66 (m, 1H), 3.63 (dd, J = 9.6, 3.2 Hz, 1H), 3.38 (s, 3H), 3.32 (t, J = 8.8 Hz, 1H), 3.26

- 3.18 (m, 4H) 3.10 - 3.02 (m, 4H), 2.58 (s, 3H), 2.15 - 2.04 (m, 4H). MS m/z (ESI) $[M+H]^+$ = 423.2.

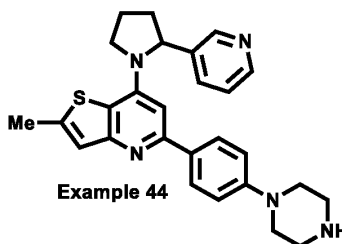
Example 43: 2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyrrolidin-1-ylmethyl) pyrrolidin-1-yl) thieno[3,2-b] pyridine



[0334] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2ag** (0.20 g, 0.352 mol, 1.0 equiv) in MeOH (6.0 mL), HCl/MeOH (4 M, 6.0 mL), for 12 hours. The reaction mixture was concentrated under reduced pressure and neutralized with SCX (see general protocol).

Example 43 (0.10 g, 0.22 mmol, 61% yield, 100% purity) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.90 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 1.1 Hz, 1H), 6.98 (d, J = 8.9 Hz, 2H), 6.76 (s, 1H), 4.30 (d, J = 5.2 Hz, 1H), 3.94 - 3.85 (m, 1H), 3.75 - 3.66 (m, 1H), 3.46 - 3.32 (m, 2H), 3.23 - 3.12 (m, 4H), 2.93 (d, J = 4.5 Hz, 4H), 2.59 (d, J = 7.2 Hz, 2H), 2.53 (s, 3H), 2.52 (s, 2H), 2.10 - 1.92 (m, 4H), 1.70 (s, 4H). MS m/z (ESI) $[M+H]^+$ = 462.2.

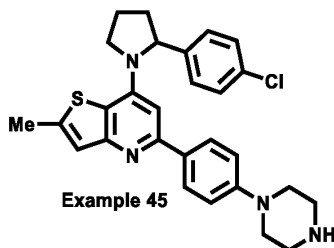
Example 44: 2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyridin-3-yl) pyrrolidin-1-yl) thieno[3,2-b] pyridine



[0335] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2f** (0.20 g, 0.36 mmol, 1.0 equiv) in EtOAc (1.0 mL), HCl/EtOAc (4 M, 5.0 mL, 56 equiv), for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 1 (gradient: 2-10 min 11-41%) and neutralized with SCX (see general protocol). **Example 44** (82 mg, 0.18 mmol, 59% yield, 100% purity) was obtained as a light-yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.59-8.58 (m, 1H), 8.44- 8.43 (m,

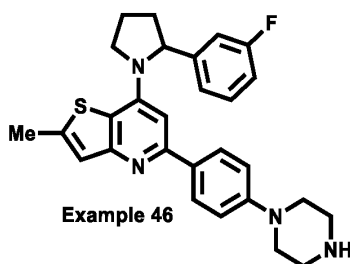
1H), 7.75- 7.73 (m, 2H), 7.70- 7.68 (m, 1H), 7.34- 7.33 (m, 1H), 7.08- 7.07 (m, 1H), 6.97- 6.95 (m, 2H), 6.52 (s, 1H), 5.43- 5.41 (m, 1H), 4.27- 4.25 (m, 1H), 3.98- 3.96 (m, 1H), 3.26- 3.23 (m, 4H), 3.02- 3.00 (m, 4H), 2.51 (s, 3H), 2.47- 2.45 (m, 1H), 2.01- 1.98 (m, 2H), 1.96- 1.94 (m, 1H). MS m/z (ESI) $[M+H]^+ = 456.2$.

Example 45: 7-(2-(4-chlorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



[0336] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2g** (0.20 g, 0.34 mmol, 1.0 equiv), HCl/dioxane (4 M, 1.0 mL), for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 1 (gradient: 25%-55% over 10 min) to give a residue. Then residue was purified with SCX (see general protocol). **Example 45** (35 mg, 72 μ mol, 63% yield, 100% purity) was obtained as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.72 (d, $J = 8.8$ Hz, 2H), 7.41 - 7.26 (m, 4H), 7.05 (d, $J = 0.92$ Hz, 1H), 6.92 (d, $J = 8.8$ Hz, 2H), 6.49 (s, 1H), 5.34 (dd, $J = 3.2, 7.2$ Hz, 1H), 4.28 - 4.15 (m, 1H), 4.03 - 3.88 (m, 1H), 3.16 - 3.05 (m, 4H), 2.89 - 2.80 (m, 4H), 2.50 - 2.48 (m, 3H), 2.48 - 2.36 (m, 1H), 2.08 - 1.90 (m, 2H), 1.89 - 1.78 (m, 1H). MS m/z (ESI) $[M+H]^+ = 489.2$.

Example 46: 7-(2-(3-fluorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



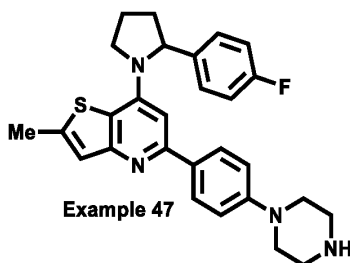
[0337] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2h** (0.20 g, 0.35 mmol, 1.0 equiv), HCl/dioxane (4 M, 1.0 mL), for 12 hours. The reaction mixture was concentrated

under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 1 (gradient: 23%-53% over 10 min). Neutralization was done with SCX (see general protocol).

Example 46 (35 mg, 74 μ mol, 63% yield, 100% purity) was obtained as an off-white solid.

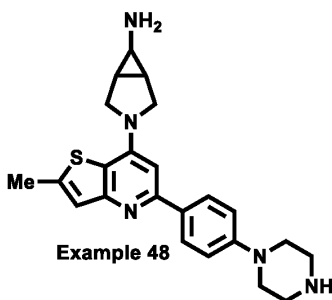
^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.71 (d, $J = 8.8$ Hz, 2H), 7.43 - 7.30 (m, 1H), 7.21 - 7.10 (m, 2H), 7.09 - 6.99 (m, 2H), 6.91 (d, $J = 8.8$ Hz, 2H), 6.49 (s, 1H), 5.34 (dd, $J = 3.2$, 7.2 Hz, 1H), 4.31 - 4.18 (m, 1H), 4.02 - 3.90 (m, 1H), 3.13 - 3.06 (m, 4H), 2.88 - 2.79 (m, 4H), 2.49 - 2.49 (m, 3H), 2.47 - 2.39 (m, 1H), 2.08 - 1.94 (m, 2H), 1.93 - 1.82 (m, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 473.2$.

Example 47: 7-(2-(4-fluorophenyl) pyrrolidin-1-yl)-2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine



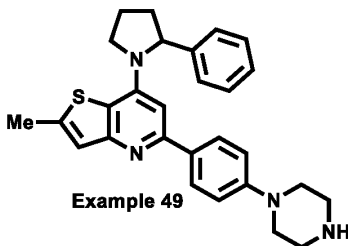
[0338] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2i** (0.15 g, 0.26 mmol, 1.0 equiv), HCl/dioxane (4 M, 5.0 mL, 76 equiv), for 12 hours. The reaction mixture was concentrated. The residue obtained was purified by prep-HPLC 2 (gradient: 12%-42% over 10 min). After lyophilization, **Example 47** (0.10 g, 0.21 mmol, 81% yield) was obtained as a white solid. Then the solid was purified with SCX (see general protocol). ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 8.22 (s, 1H), 7.73 (d, $J = 8.9$ Hz, 1H), 7.35 (dd, $J = 5.4$, 8.6 Hz, 1H), 7.13 (t, $J = 8.9$ Hz, 1H), 7.06 (d, $J = 1.1$ Hz, 1H), 6.97 (d, $J = 8.9$ Hz, 1H), 6.49 (s, 1H), 5.34 (br dd, $J = 3.4$, 6.9 Hz, 1H), 4.23 (dt, $J = 4.8$, 8.0 Hz, 1H), 4.02 - 3.93 (m, 1H), 3.29 (br s, 4H), 3.22 - 2.82 (m, 4H), 2.14 - 1.93 (m, 1H), 1.92 - 1.80 (m, 1H), 1.76 - 1.76 (m, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 473.2$.

Example 48: (cis)-3-(2-methyl-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridin-7-yl)-3-azabicyclo [3.1.0] hexan-6-amine



[0339] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2j** (60 mg, 99 μ mol, 1.0 equiv) in dioxane (1.0 mL), HCl/dioxane (4 M, 25 μ L, 1.0 equiv), for 4 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 1 (gradient: 7%-37% over 10 min) to give **Example 48** (17 mg, 38 μ mol, 39% yield, 100% purity, HCl) was obtained as a yellow solid. Then the crude product was purified with SCX (see general protocol). ^1H NMR (400 MHz, Methanol- d_4) δ (ppm): 7.76 (d, J = 8.3 Hz, 2H), 7.11 - 7.00 (m, 3H), 6.53 - 6.44 (m, 1H), 4.01 - 3.91 (m, 2H), 3.71 (d, J = 9.2 Hz, 2H), 3.23 (s, 4H), 3.01 (s, 4H), 2.57 (s, 3H), 2.16 (s, 1H), 1.87 - 1.69 (m, 2H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 406.1$.

Example 49: 2-methyl-7-(2-phenylpyrrolidin-1-yl)-5-(4-(piperazin-1-yl) phenyl) thieno[3,2-b] pyridine

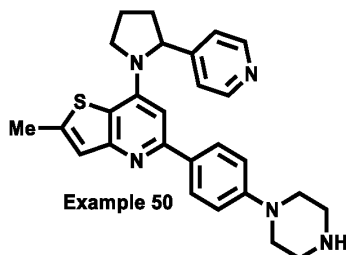


[0340] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2k** (0.18 g, 0.32 mmol, 1.0 equiv) in dioxane (2.0 mL), HCl/dioxane (4 M, 2.0 mL, 25 equiv), for 1 hour. The mixture was concentrated. The residue obtained was purified by prep-HPLC 1 (gradient: 25%-55% over 10 min). Then the crude product was purified with SCX (see general protocol).

Example 49 (18 mg, 39 μ mol, 45% yield, 100% purity) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.69 (br d, J = 8.0 Hz, 2H), 7.38 - 7.29 (m, 4H), 7.22 (br d, J = 3.2 Hz, 1H), 7.06 (s, 1H), 6.92 (br d, J = 8.4 Hz, 2H), 6.50 (s, 1H), 5.36 - 5.27 (m,

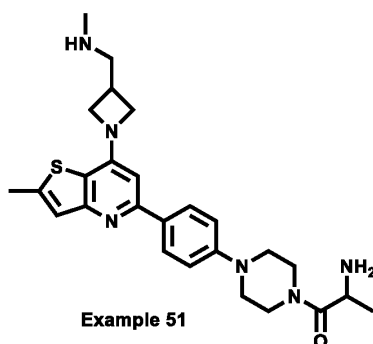
1H), 4.29 - 4.19 (m, 1H), 4.0 (q, $J = 7.2$ Hz, 1H), 3.19 - 3.06 (m, 4H), 2.87 (br s, 4H), 2.50 - 2.37 (m, 3H), 2.10 - 1.74 (m, 4H). MS m/z (ESI) $[M+H]^+ = 455.2$.

Example 50: 2-methyl-5-(4-(piperazin-1-yl) phenyl)-7-(2-(pyridin-4-yl) pyrrolidin-1-yl) thieno[3,2-b] pyridine



[0341] According to Scheme 2 Step 3: Conditions 1 HCl. **B.21** (0.20 g, 0.36 mmol, 1.0 equiv) was added to HCl/dioxane (4 M, 10 mL, 111 equiv), for 12 hours. The reaction mixture was concentrated. The residue obtained was purified by prep-HPLC 2 (gradient: 0%-30% over 10 min). After lyophilization **Example 50** (0.10 g, 0.22 mmol, 61% yield) was obtained as a white solid and was neutralized with SCX (see general protocol). ^1H NMR (400 MHz, Methanol- d_4) δ (ppm): 8.47 (d, $J = 5.4$ Hz, 2H), 7.56 (br d, $J = 8.5$ Hz, 2H), 7.38 (br d, $J = 5.5$ Hz, 2H), 7.08 (s, 1H), 6.98 (br d, $J = 8.6$ Hz, 2H), 6.39 (s, 1H), 5.41 - 5.33 (m, 1H), 4.35 - 4.23 (m, 1H), 4.13 - 4.01 (m, 1H), 3.26 - 3.16 (m, 4H), 3.07 - 2.94 (m, 4H), 2.60 (br d, $J = 8.4$ Hz, 1H), 2.55 (s, 3H), 2.16 - 1.96 (m, 3H). MS m/z (ESI) $[M+H]^+ = 456.2$.

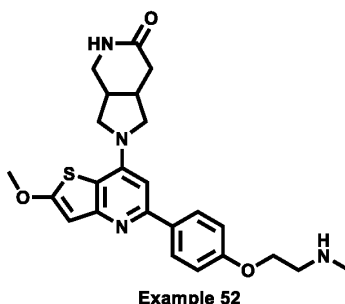
Example 51: 2-amino-1-[4-[4-[2-methyl-7-[3-(methylaminomethyl) vazetidin-1-yl] thieno[3,2-b] pyridin-5-yl] phenyl] piperazin-1-yl] propan-1-one



[0342] According to Scheme 3 Step 2: Conditions 2 TFA. **C.1o** (0.15 g, 0.22 mmol, 1.0 equiv) in DCM (1.0 mL) was added TFA (2.3 g, 20 mmol, 1.5 mL, 91 equiv) at 25 °C. The mixture was stirred at 25 °C for 12 hours. The reaction mixture was concentrated under

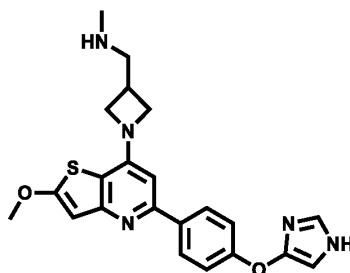
reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 3 (gradient: 5%-35% over 10 min). The residue was neutralized with SCX (see general protocol) to give **Example 51** (40 mg, 84 μ mol, 38% yield, 100% purity) was obtained as a light yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.95 (d, J = 8.8 Hz, 2H), 7.11 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.52 (s, 1H), 4.28 (t, J = 7.7 Hz, 2H), 3.95 - 3.89 (m, 2H), 3.82 (q, J = 6.7 Hz, 1H), 3.70 - 3.58 (m, 4H), 3.25 - 3.18 (m, 4H), 2.89 - 2.83 (m, 1H), 2.75 (d, J = 7.1 Hz, 2H), 2.56 (s, 3H), 2.31 (s, 3H), 1.11 (d, J = 6.7 Hz, 3H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 479.4$.

Example 52: (cis)-2-[2-methoxy-5-[4-[2-(methylamino)ethoxy]phenyl]thieno[3,2-b]pyridin-7-yl]-3,3a,4,5,7,7a-hexahydro-1H-pyrrolo[3,4-c]pyridin-6-one



[0343] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2ah** (20 mg, 36 μ mol, 1.0 equiv) in MeOH (0.20 mL) was added HCl/dioxane (2 M, 18 μ L, 1.0 equiv) at 25 °C. After stirring at 25 °C for 0.5 h, the reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 8 (gradient: 5%-35% over 10 min) to give **Example 52** (14 mg, 28 μ mol, 77% yield, 97% purity, HCl) as a light pink solid. ^1H NMR (400 MHz, D_2O) δ (ppm): 7.63 (d, J = 8.7 Hz, 2H) 7.08 (d, J = 8.7 Hz, 2H) 6.36 (s, 1H) 6.26 (s, 1H) 4.31 (t, J = 4.7 Hz, 2H) 3.91 (s, 3H) 3.63 - 3.87 (m, 2H) 3.30 - 3.58 (m, 5H) 3.00 (dd, J = 14, 6.0 Hz, 1H) 2.77 (s, 3H) 2.57 - 2.72 (m, 2H) 2.51 (dd, J = 18, 7.6 Hz, 1H) 2.05 (dd, J = 18, 5.0 Hz, 1H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 453.2$.

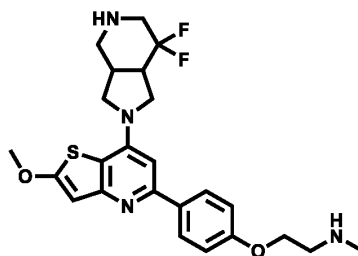
Example 53: 1-[1-[5-[4-(1H-imidazol-4-yloxy) phenyl]-2-methoxy-thieno[3,2-b] pyridin-7-yl] azetidin-3-yl]-N-methyl-methanamine



Example 53

[0344] According to Scheme 3 Step 2: Conditions 2 TFA. **C.1p** (60 mg, 92 μ mol, 1.0 equiv) in DCM (0.5 mL) was added TFA (0.78 g, 6.7 mmol, 0.50 mL, 73 equiv) at 25 °C. The mixture was stirred at 25 °C for 2 hours. The mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 7 (gradient: 30%-50% over 8 min) and prep-HPLC 2 (gradient: 0%-28% over 10 min) to give **Example 53** (20 mg, 41 μ mol, 44% yield, 95% purity, FA) as yellow gum. ^1H NMR (400 MHz, methanol- d_4) δ (ppm): 8.50 (s, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 1.1 Hz, 1H), 7.13 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 1.1 Hz, 1H), 6.59 (s, 1H), 6.40 (s, 1H), 4.54 (t, J = 7.9 Hz, 2H), 4.21 (s, 2H), 4.07 (s, 3H), 3.36 (d, J = 6.6 Hz, 2H), 3.22 (s, 1H), 2.74 (s, 3H). MS m/z (ESI) $[\text{M}+\text{H}]^+ = 422.2$.

Example 54: 2-[4-[7-((cis)-7,7-difluoro-3,3a,4,5,6,7a-hexahydro-1H-pyrrolo[3,4-c] pyridin-2-yl)-2-methoxy-thieno[3,2-b] pyridin-5-yl] phenoxy]-N-methyl-ethanamine

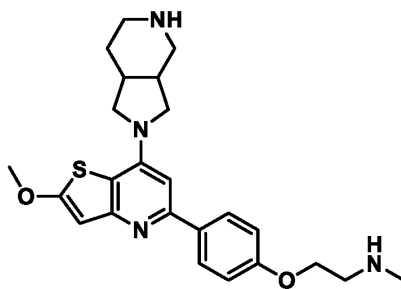


Example 54

[0345] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1r** (30 mg, 44 μ mol, 1.0 equiv) in dioxane (0.20 mL) was added HCl/dioxane (2 M, 0.75 mL) at 25 °C. The mixture was stirred at 25 °C for 2 hours. The mixture was concentrated under reduced pressure to give residue. The residue obtained was purified by prep-HPLC 2 (gradient: 0%-25% over 10 min) to give **Example 54** (7.1 mg, 15 μ mol, 34% yield, 100% purity) as yellow oil. ^1H NMR (400

MHz, methanol- d_4) δ (ppm): 7.92 (d, $J = 8.8$ Hz, 2H), 7.28 (d, $J = 8.8$ Hz, 2H), 6.80 (s, 1H), 6.74 (s, 1H), 4.43 - 4.40 (m, 2H), 4.32 - 4.20 (m, 2H), 4.16 (s, 3H), 4.10 - 3.99 (m, 1H), 3.75 - 3.41 (m, 7H), 3.29 - 3.23 (m, 1H), 3.18 - 3.10 (m, 1H), 2.83 (s, 3H). MS m/z (ESI) $[M+H]^+ = 475.1$.

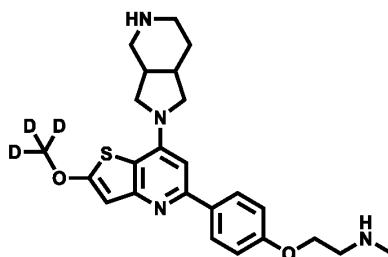
Example 55: 2-(4-(2-methoxy-7-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-5-yl)phenoxy)-N-methylethan-1-amine



Example 55

[0346] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1s** (88 mg, 137.75 μ mol, 1 eq) and HCl/dioxane (2 M, 2 mL, 29.04 eq) were stirred at 25 °C for 2 hours. The mixture was concentrated under reduced pressure to give residue. The residue obtained was purified by prep-HPLC 2 (gradient: 2%-25% over 10 min) to give **Example 55** (27.55 mg, 62.82 μ mol, 45.60% yield, 100% purity) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 14.42 - 14.23 (m, 1H), 9.53 - 9.40 (m, 1H), 9.39 - 9.23 (m, 3H), 8.09 - 7.99 (m, 2H), 7.26 - 7.19 (m, 2H), 7.06 - 7.02 (m, 1H), 6.74 - 6.60 (m, 1H), 4.45 - 4.37 (m, 2H), 4.10 (s, 3H), 3.85 - 3.75 (m, 1H), 3.38 - 3.32 (m, 2H), 3.25 - 2.99 (m, 4H), 2.85 - 2.74 (m, 1H), 2.66 (br s, 4H), 2.52 - 2.51 (m, 3H), 2.04 - 1.88 (m, 1H), 1.84 - 1.65 (m, 1H). MS m/z (ESI) $[M+H]^+ = 439.2$.

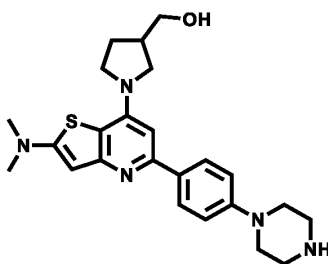
Example 56: 2-(4-(2-(methoxy- d_3)-7-((cis)-octahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridin-5-yl)phenoxy)-N-methylethan-1-amine



Example 56

[0347] According to Scheme 3 Step 2: Conditions 1 HCl. **C.1q** (0.12 g, 0.18 mmol, 1.0 equiv) in dioxane (3.0 mL) was added hydrochloric acid/dioxane (2 M, 3.0 mL) at 25 °C. The mixture was stirred at 25 °C for 16 h, the reaction mixture was concentrated under reduced pressure to give a residue. The residue obtained was purified by prep-HPLC 8 (gradient: 0%-30% over 9 min) to give product (hydrochloric acid salt) as a yellow solid. The hydrochloric acid salt product was purified by SCX (see general protocol) to give **Example 56** (40 mg, 0.09 mmol, 50% yield, 98% purity) as yellow gum. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.98 (d, *J* = 8.76 Hz, 2H), 6.99 (d, *J* = 8.76 Hz, 2H), 6.64 - 6.51 (m, 2H), 4.06 (t, *J* = 5.56 Hz, 2H), 3.78 - 3.62 (m, 3H), 3.54 (dd, *J* = 9.01, 3.00 Hz, 1H), 2.88 - 2.70 (m, 5H), 2.59 - 2.51 (m, 1H), 2.35 (s, 5H), 1.60 (d, *J* = 9.88 Hz, 1H), 1.47 - 1.33 (m, 1H). MS *m/z* (ESI) [*M*+*H*]⁺ = 442.3.

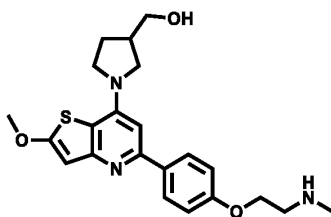
Example 57: [1-[2-(dimethylamino)-5-(4-piperazin-1-ylphenyl) thieno[3,2-b] pyridin-7- yl] pyrrolidin-3-yl] methanol



Example 57

[0348] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2aj** (0.22 g, 0.3 μmol, 1.0 equiv) in dioxane (2.0 mL) was added chlorine hydride / dioxane (2 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 a residue. The residue obtained was purified by prep-HPLC 2 (gradient: 10%-40% over 9 min) to give product (HCl salt) as a yellow solid, the HCl salt product was neutralized by SCX (see general protocol) to give **Example 57** (50.0 mg, 0.114 mmol, 38.3% yield, 100% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.88, (d, *J* = 8.9 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.45 (s, 1H), 6.07 (s, 1H), 4.86 - 4.68 (m, 1H), 3.81 - 3.75 (m, 1H), 3.74 - 3.61 (m, 2H), 3.51 - 3.45 (m, 4H), 3.20 - 3.16 (m, 4H), 2.98 (s, 6H), 2.96 - 2.90 (m, 4H), 2.47 - 2.40 (m, 1H), 2.09 - 2.00 (m, 1H), 1.82 - 1.71 (m, 1H). MS *m/z* (ESI) [*M*+*H*]⁺ = 438.3 .

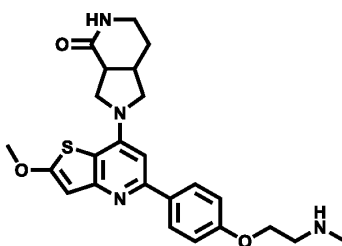
Example 63: [1-[2-methoxy-5-[4-[2-(methylamino)ethoxy]phenyl]thieno[3,2-b]pyridin-7-yl]pyrrolidin-3-yl]methanol



Example 63

[0349] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2ai** (75 mg, 0.15 mmol, 1.0 equiv) and HCl/dioxane (2 M, 2.0 mL, 27 equiv) was stirred at 25 °C for 2 hours. The reaction mixture was filtered and concentrated under reduced pressure to give the residue. The residue obtained was purified by prep-HPLC 8 (gradient: 5%-35% over 9 min). The eluent was lyophilized to give **Example 63** (19 mg, 45 µmol, 31% yield, 100% purity) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 1.81 - 1.93 (m, 1H) 2.06 - 2.17 (m, 1H) 2.52 - 2.57 (m, 1H) 2.62 (t, *J* = 5.4 Hz, 3H) 3.32 - 3.38 (m, 2H) 3.43 - 3.53 (m, 2H) 3.71 - 3.83 (m, 4H) 4.08 - 4.11 (m, 3H) 4.37 - 4.44 (m, 2H) 6.66 - 6.73 (m, 1H) 6.98 - 7.04 (m, 1H) 7.21 (d, *J* = 8.9 Hz, 2H) 8.04 (d, *J* = 8.9 Hz, 2H) 9.23 - 9.39 (m, 2H) 14.07 - 14.30 (m, 1H). MS *m/z* (ESI) [*M*+*H*]⁺ = 414.2.

Example 64: (cis)-2-(2-methoxy-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yl)octahydro-4H-pyrrolo[3,4-c]pyridin-4-one

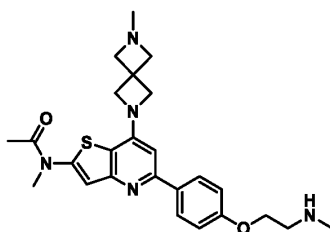


Example 64

[0350] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2ak** (95 mg, 0.17 mmol, 1.0 equiv) in dioxane (2.0 mL) was added HCl/dioxane (4 M, 1.0 mL, 23 equiv), then the resulting mixture was stirred at 25 °C for 1 hour. The reaction mixture was filtered and evaporated under reduced pressure to give the crude product. The crude product was purified by prep-HPLC 8 (gradient: 3%-33% over 9 min) to give **Example 64** (24 mg, 53 µmol, 31% yield, 100% purity) as a white solid. ¹H NMR (400 MHz, methanol-*d*₄) δ (ppm): 7.91 (s, 1H),

7.89 (s, 1H), 7.93 - 7.87 (m, 1H), 7.31 - 7.27 (m, 2H), 6.75 (s, 1H), 6.71 (s, 1H), 4.44 - 4.41 (m, 2H), 4.35 - 4.19 (m, 2H), 4.17 (s, 3H), 4.02 - 3.82 (m, 1H), 3.56 - 3.52 (m, 2H), 3.48 - 3.40 (m, 2H), 3.32 - 3.27 (m, 2H), 3.01 - 2.93 (m, 1H), 2.85 (s, 2H), 2.86 - 2.84 (m, 1H), 2.10 - 2.03 (m, 1H), 1.85 (q, $J = 5.0, 9.3$ Hz, 1H). MS m/z (ESI) $[M+H]^+ = 453.1$.

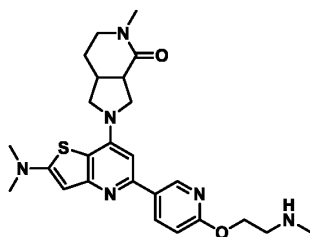
Example 66: N-methyl-N-(7-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-2-yl)acetamide



Example 66

[0351] According to Scheme 2 Step 3: Conditions 2 TFA. **B.2al** (250 mg, 0.301 mmol, 1.00 eq) in DCM (5.00 mL) was added TFA (1.30 g, 11.44 mmol, 38.1 eq) at 20 °C. The mixture was stirred at 20 °C for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm*10um; mobile phase: [water (TFA)-ACN]; gradient: 3%-33% B over 12 min) to give trifluoroacetic acid salt product as a yellow solid. The salt was basified by strong cation exchange resin (CNWBOND SCX, SPE Cartridge). 1/ Wash resin with deionized water 20.0 mL. 2/ Wash resin with the salt in MeOH (4.0 mL) (target was adsorbed to the resin. 3/ Wash resin with deionized water (20.0 mL) until the pH of the solution is neutral. 4/ Wash resin with $NH_3.H_2O/MeOH=1/10$ (21 mL), target was cleaved from the resin. 5/ Concentration and lyophilization give **Example 66** (92.0 mg, 0.196 mmol, 65.2% yield, 99.2% purity) as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm = 7.92 (d, $J = 8.68$ Hz, 2 H), 7.00 (d, $J = 8.68$ Hz, 2 H), 6.94 (s, 1 H), 6.46 (s, 1 H), 4.26 (s, 4 H), 4.05 (t, $J = 5.44$ Hz, 2 H), 3.50 (s, 3 H), 3.32 (s, 4 H), 2.82 (t, $J = 5.44$ Hz, 2 H), 2.40 - 2.27 (m, 6 H), 2.18 (s, 3 H). MS (ESI) m/z $[M+H]^+ = 466.3$.

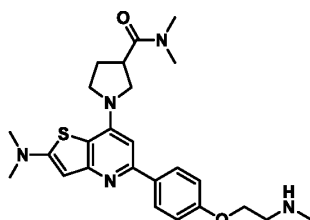
Example 67: (cis)-2-(2-(dimethylamino)-5-(6-(2-(methylamino)ethoxy)pyridin-3-yl)thieno[3,2-b]pyridin-7-yl)-5-methyloctahydro-4H-pyrrolo[3,4-c]pyridin-4-one



Example 67

[0352] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2am** (250 mg, 430.49 μmol , 1 *eq*) was added to HCl/dioxane (2 M, 2 mL, 9.29 *eq*). The reaction solution was stirred at 25 °C for 1 hour. The reaction solution was concentrated under vacuum. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5 μm ; mobile phase: [water(FA)-ACN]; gradient: 4%-34% B over 10 min). After Prep-HPLC purification, the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give a product. The product was basified with SCX cation exchange resin). 1/ Wash resin with deionized water 20.0 mL. 2/ Wash resin with the salt in MeOH (4.0 mL) (target was adsorbed to the resin. 3/ Wash resin with deionized water (20.0 mL) until the pH of the solution is neutral. 4/ Wash resin with $\text{NH}_3 \cdot \text{H}_2\text{O}/\text{MeOH}=1/10$ (21 mL), target was cleaved from the resin. 5/ Concentration and lyophilization give **Example 67** (80 mg, 153.80 μmol , 35.73% yield, 92.4% purity) as a yellow solid. ^1H NMR (400 MHz, $\text{METHANOL}-d_4$) δ = 8.59 (d, J = 2.1 Hz, 1H), 8.14 (dd, J = 2.4, 8.6 Hz, 1H), 6.92 (d, J = 8.7 Hz, 1H), 6.41 (s, 1H), 6.10 (s, 1H), 4.47 (t, J = 5.3 Hz, 2H), 4.14 (t, J = 9.4 Hz, 1H), 4.01 - 3.90 (m, 2H), 3.69 (dd, J = 3.4, 9.7 Hz, 1H), 3.54 - 3.42 (m, 2H), 3.22 - 3.16 (m, 1H), 3.08 - 3.01 (m, 8H), 3.00 (s, 3H), 2.87 - 2.78 (m, 1H), 2.49 (s, 3H), 2.07 - 1.96 (m, 1H), 1.89 (dt, J = 4.6, 9.3 Hz, 1H). MS (ESI) m/z $[\text{M}+\text{H}]^+ = 481.3$.

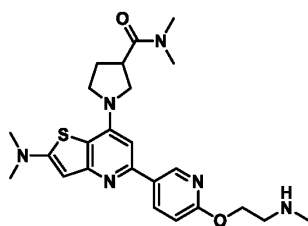
Example 68: 1-(2-(dimethylamino)-5-(4-(2-(methylamino)ethoxy)phenyl)thieno[3,2-b]pyridin-7-yl)-N,N-dimethylpyrrolidine-3-carboxamide



Example 68

[0353] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2an** (200 mg, 352.27 μmol , 1 eq) in dioxane (2 mL) was added HCl/dioxane (2 M, 3 mL) at 25°C. The mixture was stirred at 25 °C for 12 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm*10um; mobile phase: [water (TFA)-ACN]; gradient: 3%-33% B over 12 min) to give trifluoroacetic acid salt product as a yellow solid. The salt was basified by strong cation exchange resin (CNWBOND SCX, SPE Cartridge). 1/ Wash resin with deionized water 20.0 mL. 2/ Wash resin with the salt in MeOH (4.0 mL) (target was adsorbed to the resin. 3/ Wash resin with deionized water (20.0 mL) until the pH of the solution is neutral. 4/ Wash resin with $\text{NH}_3 \cdot \text{H}_2\text{O}/\text{MeOH}=1/10$ (21 mL), target was cleaved from the resin. 5/ Concentration and lyophilization give **Example 68** (100 mg, 202.73 μmol , 57.55% yield, 94.8% purity) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 7.97 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 6.50 (s, 1H), 6.08 (s, 1H), 4.06 (t, J = 5.6 Hz, 2H), 3.93 - 3.84 (m, 1H), 3.80 - 3.68 (m, 3H), 3.59 - 3.52 (m, 1H), 3.09 (s, 3H), 2.99 (s, 6H), 2.89 - 2.84 (m, 5H), 2.36 (s, 3H), 2.28 - 2.16 (m, 1H), 2.06 (J = 7.8, 12.0 Hz, 1H). MS (ESI) m/z $[\text{M}+\text{H}]^+ = 468.2$.

Example 69: 1-(2-(dimethylamino)-5-(6-(2-(methylamino)ethoxy)pyridin-3-yl)thieno[3,2-b]pyridin-7-yl)-N,N-dimethylpyrrolidine-3-carboxamide

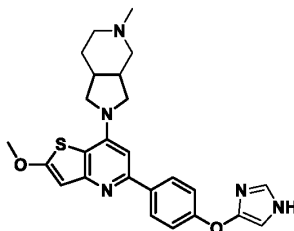


Example 69

[0354] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2ao** (240 mg, 421.99 μmol , 1 eq) in HCl/dioxane (3 mL, 2M) was stirred at 25 °C for 1 hour. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(HCl)-ACN]; gradient: 0%-30% B over 10 min). The eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give a product. The product was basified by SCX cation exchange resin to give **Example 69** (87 mg, 185.65 μmol , 43.99% yield, 100% purity) as a light yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 8.79 (d, J = 2.3 Hz, 1H), 8.32 (dd, J = 2.5, 8.6 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 6.54 (s, 1H), 6.08 (s, 1H), 4.35 (t, J = 5.8 Hz, 2H), 3.95 - 3.85

(m, 1H), 3.82 - 3.65 (m, 3H), 3.60 - 3.50 (m, 1H), 3.09 (s, 3H), 2.99 (s, 6H), 2.91 - 2.83 (m, 5H), 2.35 (s, 3H), 2.28 - 2.16 (m, 1H), 2.12 - 2.00 (m, 1H). MS (ESI) m/z $[M + H]^+ = 469.2$.

Example 70: (cis)-5-(4-((1H-imidazol-4-yl)oxy)phenyl)-2-methoxy-7-(5-methyloctahydro-2H-pyrrolo[3,4-c]pyridin-2-yl)thieno[3,2-b]pyridine



Example 70

[0355] According to Scheme 2 Step 3: Conditions 1 HCl. **B.2ap** (260 mg, 439.31 μ mol, 1 eq) in TFA (0.6 mL) and DCM (3 mL) was stirred at 25 °C for 12 hours. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*40mm*15 μ m; mobile phase: [water(HCl)-ACN]; gradient: 0%-26% B over 10 min), the eluent was concentrated to remove organic solvents. The residual aqueous solution was lyophilized to give a crude product. The crude product was purified by prep-TLC (DCM/MeOH 10/1, 1% $\text{NH}_3 \cdot \text{H}_2\text{O}$, $R_f = 0.3$) to give a solid. This solid was purified by prep-HPLC (column: Phenomenex luna C18 150*40mm* 15 μ m; mobile phase: [water(HCl)-ACN]; gradient: 0%-26% B over 10 min). The eluent was concentrated to remove organic solvents to give **Example 70** (45.17 mg, 90.70 μ mol, 20.65% yield, 100% purity, HCl) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 14.76 - 14.45 (m, 1H), 11.31 - 11.01 (m, 1H), 8.69 (br d, $J = 7.6$ Hz, 1H), 8.21 - 8.02 (m, 2H), 7.42 (br d, $J = 1.3$ Hz, 1H), 7.39 - 7.30 (m, 2H), 7.15 - 7.05 (m, 1H), 6.76 - 6.58 (m, 1H), 4.09 (s, 3H), 4.06 - 3.45 (m, 5H), 3.43 - 3.12 (m, 3H), 3.02 - 2.82 (m, 2H), 2.76 - 2.67 (m, 3H), 2.34 - 1.73 (m, 2H). MS (ESI) m/z $[M + H]^+ = 462.2$.

Biological Examples

[0356] 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

[0357] 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.

[0358] 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

[0359] 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 hours 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 hours 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 hour 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)

[0360] 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.

[0361] Stress and compound treatment in iPSC-MNs were administered as described above in “iPSC-derived motor neuron condensate assay”. Following 24 hours 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: AGCTGTCCATGCTGTCAGTG

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/3IABkFQ/)

[0362] The above procedure was performed for the compounds in Table B-3, for which the results are provided. The symbol “****” indicates a EC_{50} or IC_{50} less than or equal to 0.10 μM . The symbol “***” indicates an EC_{50} or IC_{50} greater than 0.10 μM and less than or equal to 0.50 μM . The symbol “**” indicates an EC_{50} or IC_{50} greater than 0.50 μM and less than or equal to 1.0 μM . The symbol “*” indicates a EC_{50} or IC_{50} greater than 1.0 μM and less than or equal to 5.0 μM . The symbol “NA” indicates no activity. The symbol “-” indicates no data is available.

Table B-3.

Ex. No.	<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	NA	NA	-
3	NA	-	-

Ex. No.	<i>POLDIP3</i> Puromycin Stress qPCR Assay EC ₅₀ (μ M)	<i>STMN2</i> Puromycin Stress qPCR Assay EC ₅₀ (μ M)	Puromycin Stress Imaging Assay IC ₅₀ (μ M)
4	*	*	**
5	**	*	-
6	**	-	**
7	**	-	***
8	*	NA	*
9	*	-	-
10	**	*	*
11	-	-	**
12	-	-	*
13	-	*	***
14	***	*	**
15	***	-	-
16	***	-	-
17	-	-	**
18	NA	-	**
19	-	> 5.0 mM	*
20	-	> 5.0 mM	**
21	***	-	**
22	**	*	**
23	***	*	*
24	***	-	-
25	***	*	*
26	*	> 5.0 mM	-
27	**	*	**
28	*	*	***
29	-	> 5.0 mM	*
30	*	*	**
31	NA	-	*
32	NA	> 5.0 mM	**
33	NA	-	*
34	**	*	-
35	***	-	-
36	***	*	**
37	NA	-	*
38	-	> 5.0 mM	*
39	-	> 5.0 mM	*
40	***	**	***
41	**	-	**
42	*	*	-
43	**	-	-
44	*	> 5.0 mM	-
45	*	*	-
46	*	*	-
47	NA	*	-
48	**	> 5.0 mM	-

Ex. No.	<i>POLDIP3</i> Puromycin Stress qPCR Assay EC ₅₀ (μ M)	<i>STMN2</i> Puromycin Stress qPCR Assay EC ₅₀ (μ M)	Puromycin Stress Imaging Assay IC ₅₀ (μ M)
49	-	*	-
50	-	> 5.0 mM	-
51	**	**	***
52	**	*	**
53	***	*	***
54	***	*	***
55	***	***	***
56	***	**	***
57	***	**	***
58	-	-	-
59	***	**	***
60	**	*	**
61	***	**	***
62	***	**	***
63	***	*	***
64	***	*	***
65	***	***	***
66	****	**	****
67	***	*	****
68	***	**	****
69	***	**	****
70	***	*	***

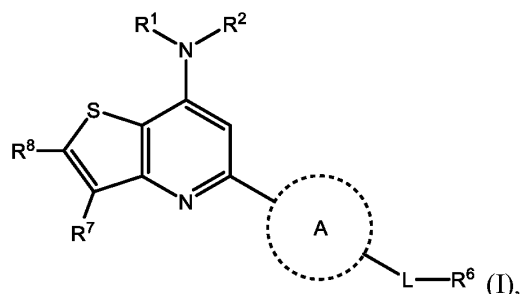
[0363] All publication, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entireties, to the same extent as if each were incorporated by reference individually.

[0364] 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 H or C_{1-6} alkyl;

R^2 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein

the C_{1-6} alkyl or C_{3-6} cycloalkyl of R^2 is optionally substituted with one or more -OH or -N(R^x)(R^y),

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

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

each R^3 is independently halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, -OR¹⁰, -SR¹⁰, -SF₅, -N(R^x)(R^y), -NO₂, -CN, -N(R^{11})C(=O)R¹², -N(R^{11})C(=O)N(R^{11})R¹², -N(R^{11})C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R^{11})R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R^{11})(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R^{11})R¹², -C(=NR¹³)OR¹², -N(R^{11})S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R^{11})R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R^{11})R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², -S(=O)₂N(R^{11})(R¹²), C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl, wherein

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

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

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

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

Ring A is phenyl or 5- to 6-membered heteroaryl, wherein

the phenyl or 5- to 6-membered heteroaryl of Ring A is optionally substituted by one or more R⁴, and

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

each R⁴ is independently halo, C₁₋₆alkyl, or -OR¹⁰;

L is a bond, C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)-, wherein

the C₁₋₆alkyl, -O-(C₁₋₆alkyl)-, -S-(C₁₋₆alkyl)-, or -N(R⁵)(C₁₋₆alkyl)- is optionally substituted by one or more R^L;

each R^L is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 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;

R⁵ is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -C(=O)R¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), or C₃₋₈cycloalkyl, wherein

the C₁₋₆alkyl of R⁵ is optionally substituted with one or more halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹¹)R¹², -S(=NR¹³)OR¹³, -S(=O)₂R¹², or -S(=O)₂N(R¹¹)(R¹²), and the C₃₋₈cycloalkyl is optionally substituted with one or more R^{5b};

R⁶ is H, -OR⁹, -OR¹⁰, -N(R^x)(R^y), -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b}, -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), or -C(=O)OR¹²;

R⁷ is H;

R⁸ is halo, C₁₋₆alkyl, C₁₋₆haloalkyl, -OR⁹, -OR¹⁰, -N(R^x)(R^y), -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², 3- to 8-membered heterocyclyl, wherein

the 3- to 8-membered heterocyclyl of R⁸ is optionally substituted with one or more R^{7b}, and

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

each R^{1a}, R^{3a}, R^{4a}, R^{6a}, or R^{7a} is independently halo, -N(R^x)(R^y), -OR¹⁰, -SR¹⁰, -SF₅, -NO₂, -CN, -N(R¹¹)C(=O)R¹², -N(R¹¹)C(=O)N(R¹¹)R¹², -N(R¹¹)C(=O)OR¹², -OC(=O)R¹², -OC(=O)N(R¹¹)R¹², -OC(=O)OR¹², -C(=O)R¹², -C(=O)N(R¹¹)(R¹²), -C(=O)OR¹², -C(=NR¹³)R¹², -C(=NOR¹²)R¹², -C(=NR¹³)N(R¹¹)R¹², -C(=NR¹³)OR¹², -N(R¹¹)S(=O)₂R¹², -S(=O)R¹², -S(=O)N(R¹¹)R¹², -S(=O)OR¹², -S(=NR¹³)R¹², -S(=NR¹³)N(R¹³)R¹², -S(=NR¹³)OR¹², -S(=O)₂R¹², -S(=O)₂N(R¹¹)(R¹²), 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^{3a}, R^{4a}, R^{6a}, or R^{7a} is optionally substituted with one or more R^{1b}, and

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

each R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is independently halo, C₁₋₆alkyl, -OR⁹, -N(R^x)(R^y), oxo, -CN, C₃₋₈cycloalkyl, or 3- to 8-membered heterocyclyl, wherein

the C₁₋₆alkyl of R^{1b}, R^{3b}, R^{4b}, R^{5b}, R^{6b}, or R^{7b} is optionally substituted by -OR¹², -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 of R⁹ 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 R^9 is optionally substituted with halo, C_{1-3} alkyl, C_{1-3} alkoxy, $-N(R^x)(R^y)$, or 3- to 12-membered heterocyclyl;

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

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

each R^{11} is independently H, C_{1-6} alkyl, or C_{3-8} cycloalkyl;

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

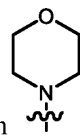
the C_{1-6} alkyl of R^{12} is optionally substituted by one or more halo, $-OH$, $-O(C_{1-6}$ alkyl), $-N(R^x)(R^y)$, C_{3-8} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl, and

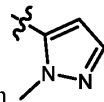
the C_{3-8} cycloalkyl, phenyl, 5- to 6-membered heteroaryl, or 3- to 12-membered heterocyclyl of R^{12} is optionally substituted with halo, C_{1-6} alkyl, or $-N(R^x)(R^y)$;

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

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

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

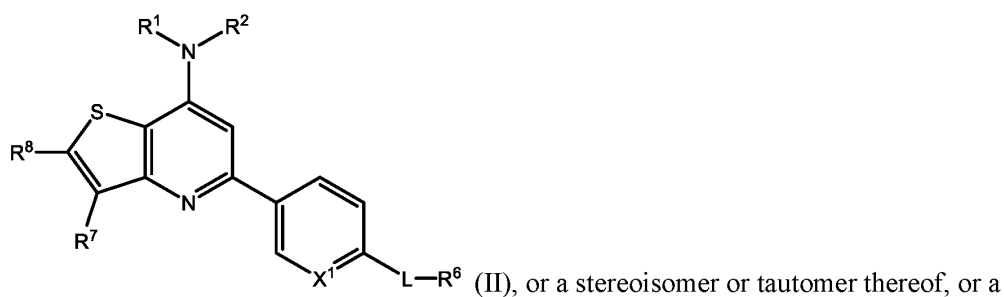
(i) when R^1 and R^2 are taken together with the N to which they are attached to form , $-(Ring\ A)-L-R^6$ are not taken together to form a pyrazolyl substituted by Br; and

(ii) when $-(Ring\ A)-L-R^6$ are taken together to form , R^1 is H, and R^2 is $-CH_3$, R^8 is not $-CH_3$.

2. The compound of claim 1, wherein Ring A is phenyl or 6-membered heteroaryl, wherein

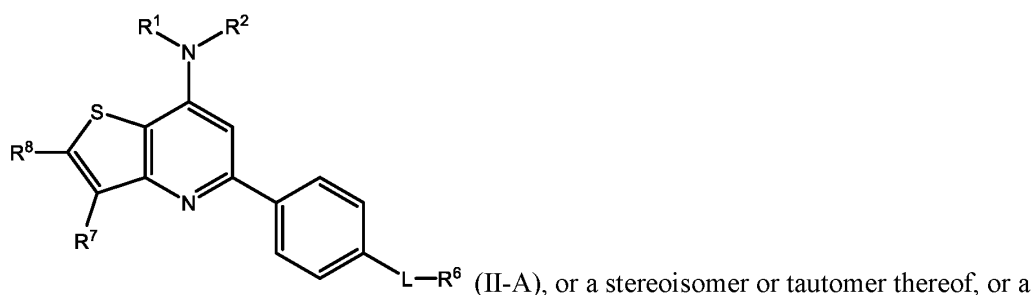
the phenyl or 6-membered heteroaryl is optionally substituted by one or more R^4 , and the 5- to 6-membered heteroaryl of Ring A comprises 1, 2, or 3 atoms selected from the group consisting of N, O, and S.

3. The compound of claim 1 or 2, wherein the compound is a compound of Formula (II)



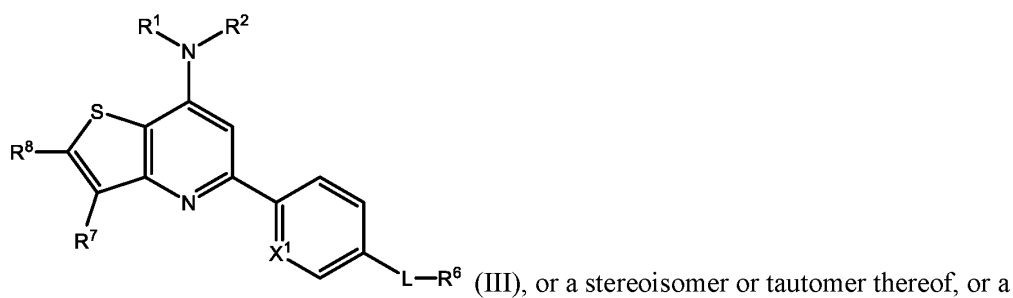
pharmaceutically acceptable salt of any of the foregoing, wherein X^1 is CH or N.

4. The compound of any of claims 1-3, wherein the compound is a compound of Formula (II-A)



pharmaceutically acceptable salt of any of the foregoing.

5. The compound of claim 1 or 2, wherein the compound is a compound of Formula (III)



pharmaceutically acceptable salt of any of the foregoing.

6. The compound of any of claims 1-5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is H or C_{1-6} alkyl.

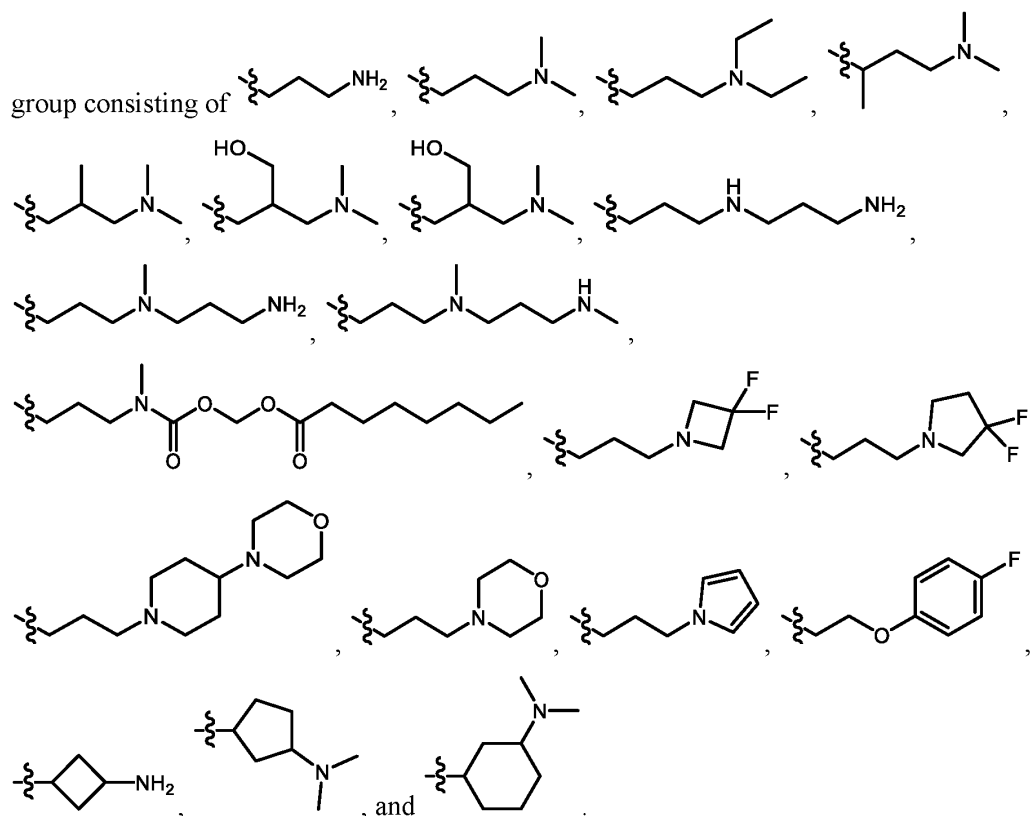
7. The compound of any of claims 1-6, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is H.

8. The compound of any of claims 1-7, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6} alkyl or C_{3-6} cycloalkyl, wherein

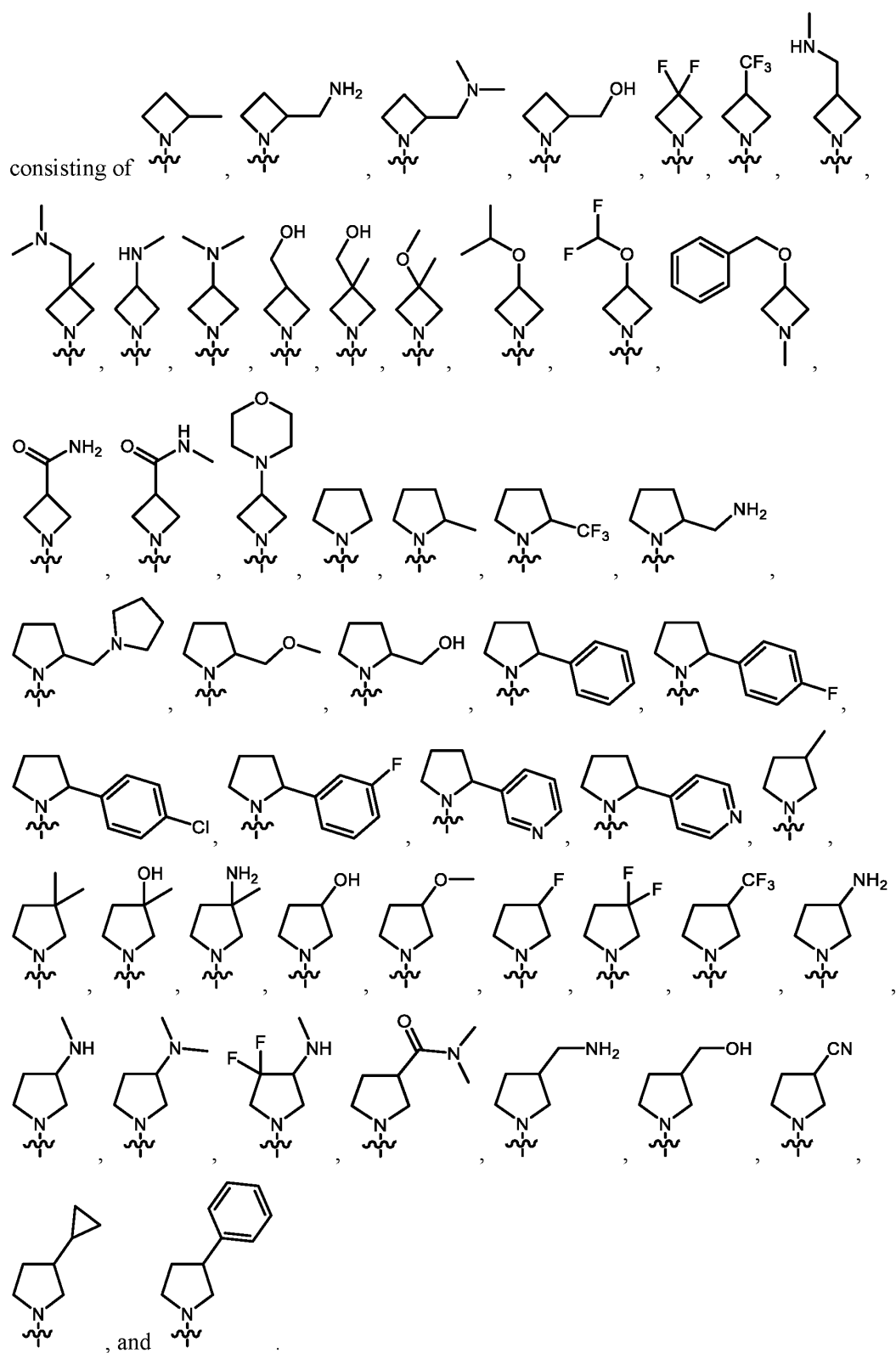
the C_{1-6} alkyl or C_{3-6} cycloalkyl of R^2 is optionally substituted with one or more -OH or -N(R^x)(R^y).

9. The compound of any of claims 1-8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is -(C_{1-6} alkyl)NH₂, -(C_{1-6} alkyl)N(C_{1-6} alkyl)(C_{1-6} alkyl), -(C_{1-6} alkyl)NH(C_{1-6} alkyl-NH₂), or -(C_{3-6} cycloalkyl)NH₂.

10. The compound of any of claims 1-9, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is selected from the

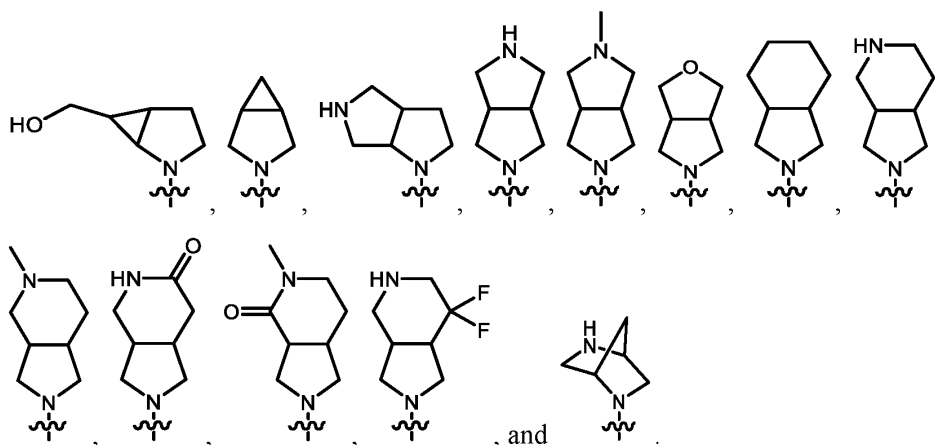


11. The compound of any of claims 1-5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein
- R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3 .
12. The compound of any of claims 1-5 or 11, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a 3- to 12-membered heterocyclyl optionally substituted with one or more R^3 , wherein
- the 3- to 12-membered heterocyclyl comprises a 3- to 8-membered monocyclic heterocyclyl, a 5- to 12-membered fused heterocyclyl, or a 6- to 12-membered spirocyclic heterocyclyl.
13. The compound of claim 12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a 4- to 12-membered heterocyclyl optionally substituted with one or more R^3 .
14. The compound of claim 13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a saturated 3- to 10-membered heterocyclyl optionally substituted with one or more R^3 .
15. The compound of claim 14, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a saturated 4- to 6-membered monocyclic heterocyclyl optionally substituted with one or more R^3 .
16. The compound claim 15, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form an azetidiny or pyrrolidinyl, wherein the azetidiny or pyrrolidinyl is optionally substituted with one or more R^3 .
17. The compound of any of claims 13-16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a heterocyclyl selected from the group



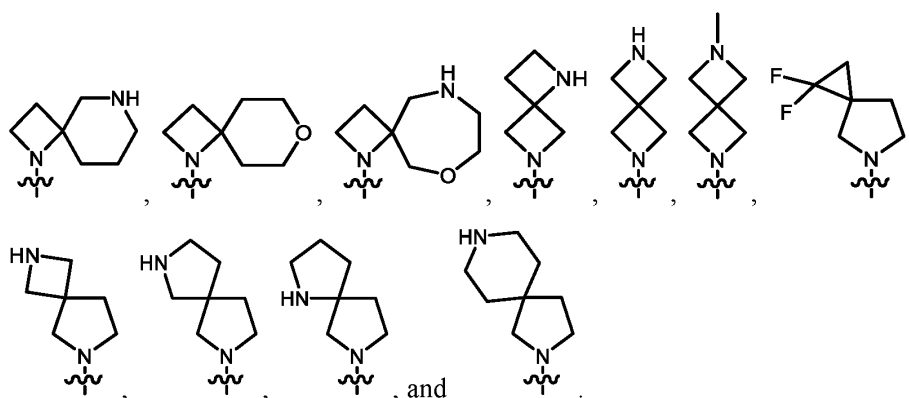
18. The compound of claim 13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a saturated 6- to 10-membered fused or bridged heterocyclyl optionally substituted with one or more R^3 .

19. The compound claim 18, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a group selected from the group consisting of



20. The compound of claim 14, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a saturated 7- to 10-membered spirocyclic heterocyclyl optionally substituted with one or more R^3 .

21. The compound of claim 20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 and R^2 are taken together with the N to which they are attached to form a group selected from the group consisting of



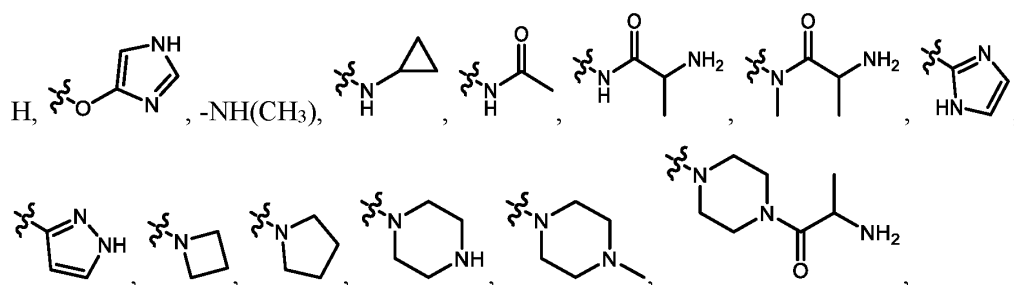
22. The compound of any of claims 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is H, $-OR^9$, $-OR^{10}$, $-N(R^x)(R^y)$, $-N(R^{11})C(=O)R^{12}$, 5- to 6-membered heteroaryl, or 3- to 8-membered heterocyclyl, wherein

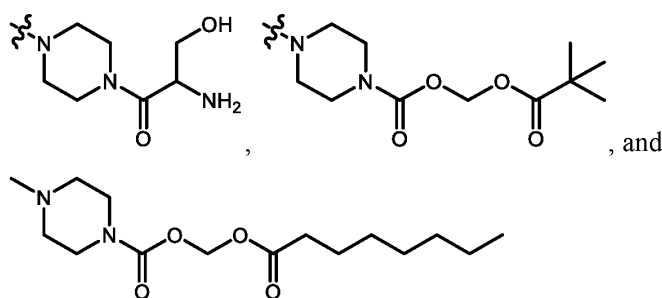
the 3- to 8-membered heterocyclyl is optionally substituted with one or more R^{6b} .

23. The compound of any of claims 1-22, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is H, $-O(5\text{- to }6\text{-membered heteroaryl})$, $-NH(C_{1-6}\text{alkyl})$, $-NH(C_{3-6}\text{cycloalkyl})$, $-NHC(O)(C_{1-6}\text{alkyl})$, $-NHC(O)(C_{1-6}\text{alkyl})NH_2$, $-N(C_{1-6}\text{alkyl})C(O)(C_{1-6}\text{alkyl})NH_2$, 5-membered heteroaryl, or 4- to 6-membered N-containing heterocyclyl, wherein

the 4- to 6-membered N-containing heterocyclyl is optionally substituted with one or more R^{6b} , $-C(=O)R^{12}$, $-C(=O)N(R^{11})(R^{12})$, or $-C(=O)OR^{12}$.

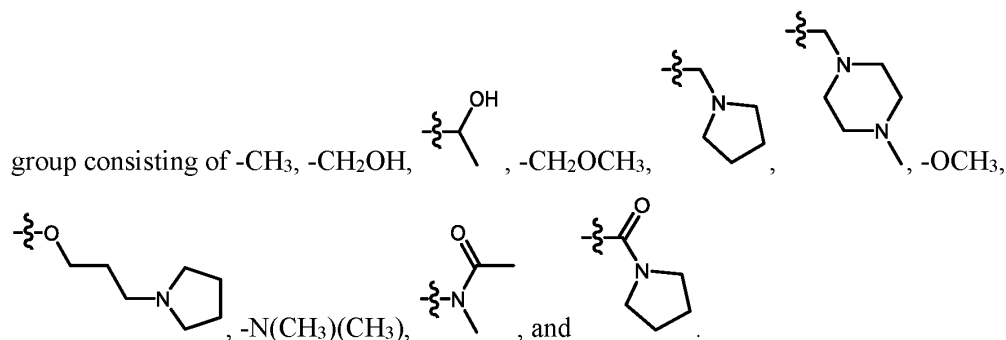
24. The compound of any of claims 1-23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is selected from the group consisting of





25. The compound of any of claims 1-24, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^8 is C_{1-6} alkyl, $-(C_{1-6}$ alkyl)OH, $-C_{1-6}$ alkyl- $O(C_{1-6}$ alkyl), $-(C_{1-6}$ alkyl)(4- to 7-membered heterocyclyl), $-O(C_{1-6}$ alkyl), $-O(C_{1-6}$ alkyl)(4- to 7-membered heterocyclyl), $-N(C_{1-6}$ alkyl)(C_{1-6} alkyl), or $-C(O)(4-$ to 7-membered heterocyclyl), wherein each 4- to 7-membered heterocyclyl is optionally substituted by C_{1-6} alkyl.

26. The compound of any of claims 1-25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^8 is selected from the



27. The compound of claim 1 or 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein

L is a bond or $-O(C_{1-6}$ alkyl)-; and

R^3 is H, $-N(R^x)(R^y)$, or 4- to 12-membered heterocyclyl optionally substituted with one or more R^{3a} .

28. The compound of claim 1 or 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein

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

L is a bond; and

- R^6 is 4- to 12-membered heterocyclyl optionally substituted with one or more R^{6b} , - $C(=O)R^{12}$, - $C(=O)N(R^{11})(R^{12})$, or - $C(=O)OR^{12}$.
29. The compound of claim 28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^6 is piperazinyl optionally substituted with one or more R^{6b} , - $C(=O)R^{12}$, - $C(=O)N(R^{11})(R^{12})$, or - $C(=O)OR^{12}$.
30. The compound of any of claims 1, 2, or 27, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein
L is -O(C₁₋₆alkyl)-; and
 R^6 is H or -N(R^x)(R^y).
31. The compound of claim 1 or 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or 31, wherein
Ring A is phenyl; and
 R^6 is C₁₋₆alkyl.
32. The compound of claim 1 or 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is selected from Table 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.
33. The compound of claim 1 or 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is selected from compounds 1 to 65 of Table 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.
34. A pharmaceutical composition comprising a compound of any of claims 1-33, 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.
35. 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 1-33, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 34.
36. The method of claim 35, wherein said disease or condition mediated by TDP-43 is a neurological disease or condition.

37. The method of claim 36, 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).
38. The method of claim 36 or 37, wherein the neurological disease or condition is traumatic brain injury (TBI).
39. The method of claim 36 or 37, wherein the neurological disease or condition is frontotemporal dementia (FTD).
40. The method of claim 36 or 37, wherein the neurological disease or condition is amyotrophic lateral sclerosis (ALS).
41. The method of any of claims 36, 37, or 40, wherein the neurological disease or condition is sporadic amyotrophic lateral sclerosis or C9ORF72 amyotrophic lateral sclerosis.
42. The method of any of claims 35-41, wherein the individual is a human.
43. A method of modulating TDP-43, comprising contacting a cell with an effective amount of a compound of any of claims 1-33, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 34, 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.
44. 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 1-33, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 34.
45. The method of claim 44, wherein the gene expression levels are for *STMN2*.
46. The method of claim 44, wherein the gene expression levels are for *POLDIP3*.
47. The compound of any of claims 1-33, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 34 for use in the treatment of a TDP-43 mediated disease or disorder.

48. Use of a compound of any of claims 1-33, 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.

49. A kit, comprising (i) a compound of any one of claims 1-33, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or the pharmaceutical composition of claim 34 and (ii) instructions for use in treating a TDP-43 mediated disease or condition in an individual in need thereof.